Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR CELLULAR IMMUNOTHERAPY FOR CANCER
Salt Lake City, UT
Sunday, April 24, 2022, 6:30 AM – 8:15 AM

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1. Introduction

a. Minutes and Overview Plan from February 2021 meeting (Attachment 1)
b. Introduction of new upcoming Chair Sairah Ahmed, MD (MD Anderson Cancer) and assistant Scientific Director Amy Moskop, MD, MS
c. Instructions for sign-in and voting

2. Accrual summary (Attachment 2)

3. Presentations, published or submitted papers

a. **CT19-01** Shadman M, Pasquini MC, Ahn KW, Chen Y, Turtle CJ, Hematti P, Cohen JB, Khimani F, Ganguly S, Merryman RW, Yared JA, Locke FL, Ahmed N, Munshi P, Beitinjaneh A, Reagan P, Herrera AF, Sauter CS, Kharfan-Dabaja MA, Hamadani M. Autologous transplant versus chimeric antigen receptor T-cell therapy for relapsed DLBCL in partial remission. Blood. doi:10.1182/blood.2021013289. Epub 2021 Sep 27.
b. **AC17-01** Park J, Nikiforow S, Kim S, Hu ZH, Moskop , Ahmed S, Abid MB, Badar T, Bredeson C, Brown V, Cairo MS, Díaz M, Dholaria B, Ganguly S, Grover NS, Hanna R, Hematti P, Kohorst MA, Lazarus HM, Lekakis L, Locke FL, Murthy HS, Mussetti A, Pulsipher MA, Qayed M, Reshef R, Rizzieri DA, Salas MQ, Savani BB, Sharma A, Schultz KR, Thakar M, Turtle C, Yared JA, Wagner JL, Qiu X, Pasquini MC, Perales MA. Impact of Allogeneic Hematopoietic Cell Transplantation (HCT) As

Consolidation Following CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy for Treatment of Relapsed Acute Lymphoblastic Leukemia (ALL). ***Poster presentation, ASH 2021.***

c. **SC17-08** Samuel John, Michael A. Pulsipher, Amy Moskop, Zhen-Huan Hu, Christine L. Phillips, Erin Marie Hall, Steven P. Margossian, Sarah Nikiforow, Paul L. Martin, Benjamin Oshrine, Amy K. Keating, Rayne H. Rouce, Ranjan Tiwari, Santiago Redondo, Jennifer Willert, Abhijit Agarwal, Marcelo C Pasquini, and Stephan A. Grupp. Real-World Outcomes for Pediatric and Young Adult Patients with Relapsed or Refractory (R/R) B-Cell Acute Lymphoblastic Leukemia (ALL) Treated with Tisagenlecleucel: Update from the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry. ***Oral presentation, ASH 2021.***

d. **SC17-08** Daniel J Landsburg, Matthew J. Frigault, Zhen-Huan Hu, Samantha Jaglowski, Frederick L. Locke, Christine Ho, Miguel-Angel Perales, Caron Jacobson, Brian T. Hill, Stephen Ronan Foley, Peter A. Riedell, Ranjan Tiwari, Aisha Masood, Stephen Lim, Marta Majdan, Marcelo C Pasquini, and Cameron J. Turtle. Real-World Efficacy and Safety Outcomes for Patients with Relapsed or Refractory (R/R) Aggressive B-Cell Non-Hodgkin's Lymphoma (aBNHL) Treated with Commercial Tisagenlecleucel: Update from the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry. ***Oral presentation, ASH 2021.***

e. **SC17-07** Frederick L. Locke, Caron Jacobson, Long Ma, Hua Dong, Zhen-Huan Hu, Tanya Siddiqi, Sairah Ahmed, Armin Ghobadi, David B. Miklos, Yi Lin, Miguel-Angel Perales, Matthew A. Lunning, Megan M. Herr, Brian T. Hill, Siddhartha Ganguly, Abu-Sayeef Mirza, Sarah Nikiforow, Hairong Xu, and Marcelo C Pasquini. Real-World Outcomes of Axicabtagene Ciloleucel (Axi-cel) for the Treatment of Large B-Cell Lymphoma (LBCL): Impact of Age and Specific Organ Dysfunction. ***Oral presentation, ASH 2021.***

f. **SC17-07** Caron A. Jacobson, Frederick L. Locke, Zhen-Huan Hu, Tanya Siddiqi, Sairah Ahmed, Armin Ghobadi, David B. Miklos, Yi Lin, Miguel-Angel Perales, Matthew A. Lunning, Megan Herr, Brian T. Hill, Siddhartha Ganguly, Hua Dong, Sarah Nikiforow, Jing Xie, Hairong Xu, Michele Hooper, Jun Kawashima, Marcelo C. Pasquini. Real-world evidence of axicabtagene ciloleucel (Axi-cel) for the treatment of large B-cell lymphoma (LBCL) in the United States (US). ***Poster presentation, ASCO 2021.***

4. Studies in progress (Attachment 3)

a. **AC16-01** Pattern of use and outcomes with donor lymphocyte infusion after HLA-haploidentical allogeneic hematopoietic stem cell transplant **Manuscript prep**
b. **AC17-01** CAR-T with or without subsequent HCT for ALL **Manuscript prep/ Accepted ASH Abstract**
c. **AC18-01** Effect of stem cell boost and donor lymphocyte infusion on the incidence of GVHD **Protocol Development**
d. **CT19-02** Prolonged cytopenia following CAR-T for DLBCL **Manuscript Prep**
e. **CT20-01** Comparison of commercial CAR T cells for DLBCL **Analysis**
f. **CT20-02** Health Resource utilization in CAR T cells **Data file prep**
g. **CT20-03** Determinants of outcomes after CAR T cells for Lymphoma **Analysis**
h. **CT20-04** Determinants of outcomes after CAR T cells for ALL **Protocol Development**
i. **CT21-01** Outcomes of elderly patients receiving CAR-T for DLBCL **Protocol Development**

5. Future/proposed studies

a. **PROP 2110-246** Myelodysplastic Syndrome / Acute Myelogenous Leukemia after Autologous Chimeric Antigen Receptor T-cell Immunotherapy for Non-Hodgkin Lymphoma (Dean) (Attachment 4)

b. **PROP 2110-271** Utilization Pattern of Subsequent Non-allogeneic Hematopoietic Cell Transplantation Interventions after Chimeric Antigen Receptor T-cell therapy for B-cell Acute Lymphoblastic Leukemia: CIBMTR analysis (Murthy) **and PROP 2110-292** Outcomes of Second or Subsequent CAR-T infusion after relapse from prior CAR-T cell therapy (Mirza, Gowda) **and PROP 2110-68** Safety and Efficacy of CD19 CAR T Cell Reinfusion in Pediatric Patients with B Lineage Acute Lymphoblastic Leukemia who have Disease Recurrence Following Previous Infusion (Appell, Sharma) **and PROP 2110-264** Clinical Impact of first-line therapy after CAR T cell failure (Alarcon Tomas, Perales) **and PROP 2110-197** Real world practice pattern and clinical outcomes of subsequent therapy after CAR-T treatment in patients with lymphoma (Bezerra, Lin) (Attachment 5)

c. **PROP 2110-333** Composite end point of toxicity-free and progression-free survival (TPFS) after CD19 CAR T cell therapy for large B-cell lymphoma (Lazaryan) (Attachment 6)

d. **PROP 2110-35** Potential for G-CSF in preventing infections in CAR-T recipients (Abid) (Attachment 7)

e. **PROP 2110-151** Effect of renal dysfunction on outcomes in Chimeric Antigen Receptor T-Cell Therapy (Murthy, Iqbal) **and PROP 2110-242** Chimeric Antigen Receptor T- cell therapy in patients with hematological malignancy and chronic kidney disease (Ahmed, Strati) (Attachment 8)

f. **PROP 2110-34** Pre-emptive and early tocilizumab usage and risk of infections in patients receiving CAR-T therapy (Abid) **and PROP 2110-173** Impact of Prophylactic Anti-epileptics on Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) in Recipients of CAR T-cell Therapy (Wang, Metheny) (Attachment 9)

g. **PROP 2110-237** Impact of obesity on outcomes in CD19-directed CAR-T patients (Shah, Janakiram) (Attachment 10)

h. **PROP 2109-01** Machine learning for predicting toxicity and clinical outcomes in DLBCL and B-ALL patients treated with Yescarta and Kymriah cell products in the real-world setting: an analysis of the CIBMTR registry. (Mosquera Orgueira, Nastoupil) **and PROP 2110-130** Predicting Response and Toxicity to CART in Patients with DLBCL Using Artificial Intelligence (AI) (Vuyyala, Farhan) **and PROP 2110-62** Machine learning to determine Clinical predictors of response and toxicity following CD-19 directed Chimeric Antigen Receptor T-cell therapy in patients with Diffuse Large B-cell Lymphoma (Hossain) **and PROP 2110-63** Determining long term outcomes of CD19 directed autologous Chimeric Antigen Receptor T-cell therapy in patients with B-cell Acute Lymphoblastic Leukemia and Diffuse Large B-cell Lymphoma using an ensemble stack of machine learning models (Hossain) (Attachment 11)

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

i. **PROP 2110-37** Center-specific differences in utilization of CAR T-cell therapy and its implications on outcomes (Patel, Dholaria) (Attachment 12)

Proposed studies; not accepted for consideration at this time

j. **PROP 2109-14** Central Nervous System (CNS) Relapse After Anti-CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy in B-Cell Lymphoma and acute lymphoblastic leukemia (ALL)

k. **PROP 2110-32** Incidence of hypogammaglobulinemia following CD19-directed CAR-T therapy and its impact on CAR-T persistence and outcomes
l. **PROP 2110-39** Outcomes of chimeric antigen receptor T-cell treatment for B-cell malignancies relapsing after allogeneic hematopoietic cell transplantation.
m. **PROP 2110-62** Machine learning to determine Clinical predictors of response and toxicity following CD-19 directed Chimeric Antigen Receptor T-cell therapy in patients with Diffuse Large B-cell Lymphoma
n. **PROP 2110-63** Determining long term outcomes of CD19 directed autologous Chimeric Antigen Receptor T-cell therapy in patients with B-cell Acute Lymphoblastic Leukemia and Diffuse Large B-cell Lymphoma using an ensemble stack of machine learning models
o. **PROP 2110-69** Impact of donor lymphocyte infusion (DLI) on mixed chimerism and minimal residual disease (MRD) and association with the CD3+ cell dose.
p. **PROP 2110-108** Use and Outcomes of Allogeneic Hematopoietic Cell Transplantation after chimeric-antigen receptor T-cell (CAR-T) Therapy
q. **PROP 2110-130** Predicting Response and Toxicity to CART in Patients with DLBCL Using Artificial Intelligence (AI)
r. **PROP 2110-135** Cytopenias and infections after treatment with anti-B cell maturation antigen (BCMA) chimeric antigen receptor (CAR) T-cell therapy
s. **PROP 2110-148** Outcomes of elderly patients receiving B-Cell Maturation Antigen (BCMA) directed Chimeric Antigen Receptor (CAR) T cell Therapy in the standard of care setting
t. **PROP 2110-150** Impact of obesity on outcomes following B-Cell Maturation Antigen (BCMA) directed Chimeric Antigen Receptor (CAR) T cell therapy in the standard of care setting
u. **PROP 2110-173** Impact of Prophylactic Anti-epileptics on Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) in Recipients of CAR T-cell Therapy
v. **PROP 2110-202** Risk factors and prognostic impact of prolonged cytopenia in BCMA-directed CAR-T patients
w. **PROP 2110-242** Chimeric Antigen Receptor T- cell therapy in patients with hematological malignancy and chronic kidney disease
x. **PROP 2110-243** Impact of post-transplantation cyclophosphamide (PTCy) on graft-versus-host disease and relapse after subsequent donor lymphocyte infusion
y. **PROP 2110-263** Effect of Age, Performance Status, and Comorbidities on CAR T-cell Induced Toxicities and Outcomes
z. **PROP 2110-268** Comparative outcomes analysis of patients with aggressive B-cell lymphoma treated with axicabtagene ciloleucel vs. lisocabtagene maraleucel
aa. **PROP 2110-271** Utilization Pattern of Subsequent Non-allogeneic Hematopoietic Cell Transplantation Interventions after Chimeric Antigen Receptor T-cell therapy for B-cell Acute Lymphoblastic Leukemia: CIBMTR analysis
ab. **PROP 2110-281** Outcomes of patients with early relapse and /or progression after Chimeric Antigen Receptor (CAR) T-Cell therapy in Diffuse Large B-Cell Lymphoma (DLBCL)
ac. **PROP 2110-292** Outcomes of Second or Subsequent CAR-T infusion after relapse from prior CAR-T cell therapy
ad. **PROP 2110-295** Outcomes of B- Acute Lymphoblastic Leukemia Patients Receiving CD19 CAR-T with Prior Exposure to Blinatumomab.
ae. **PROP 2110-303** Predictors of relapse post CAR-T cell therapy for lymphoid and plasma cell disorders and Outcomes of Salvage Therapies
af. **PROP 2110-322** Predictors of relapse post CAR-T cell therapy for lymphoid and plasma cell disorders and Outcomes with Salvage Therapies.
ag. **PROP 2110-336** Efficacy of CD19-directed chimeric antigen receptor T-cell therapy for double/triple hit lymphoma: the CIBMTR experience

ah. **PROP 2110-343** Comparative outcomes of patients with B cell lymphomas treated with Lisocabtagene maraleucel (liso-cel) compared to Axicabtagene ciloleucel (axi-cel) and Tisagenlecleucel (tisa-cel)

ai. **PROP 2110-344** Cytopenias post BCMA-directed CAR-T cell therapy for multiple myeloma

6. Other business

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

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

INTRODUCTION:

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

GENERAL REMINDERS:

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

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

PRESENTATIONS:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CLOSING:

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

APPENDICES:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

chemotherapy as a confounder in the time delay?

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

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

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

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

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

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

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

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

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

Accrual Summary of patients who received Cellular therapy after 2016 reported to the CIBMTR through CTED

Characteristic	N(%)
No. of patients	6411
No. of centers	174
Patient related	
Age at infusion, by category - no. (%)	
Median (min-max)	60 (0-91)
0-9	326 (5)
10-17	383 (6)
18-29	439 (7)
30-39	276 (4)
40-49	495 (8)
50-59	1218 (19)
60-69	1932 (30)
>= 70	1342 (21)
Recipient Sex - no. (%)	
Male	3983 (62)
Female	2424 (38)
Missing	4 (0)
Disease/Indication - no. (%)	
Relapsed, persistent or progressive disease	60 (1)
Suboptimal donor chimerism	2 (0)
Immune reconstitution	4 (0)
Prevent disease relapse	23 (0)
Solid tumor	13 (0)

Characteristic	N(%)
Malignant hematologic disorder	6307 (98)
Non-malignant disorder	2 (0)
Breakdown of Malignant Hematologic Disorders - no. (%)	
Acute myeloid leukemia (AML)	25 (0)
Acute lymphoblastic leukemia (ALL)	991 (16)
Other leukemia (including CLL/PLL)	24 (0)
Chronic myeloid leukemia (CML)	1 (0)
Myelodysplastic/myeloproliferative diseases (MDS/MPN)	3 (0)
Acute leukemia of ambiguous lineage and other myeloid neoplasms	5 (0)
Non-Hodgkin lymphoma (NHL)	4699 (75)
Hodgkin lymphoma (HD)	14 (0)
Plasma cell disorder/multiple myeloma (PCD/MM)	442 (7)
Solid tumor	2 (0)
Missing	101 (2)
Types of prior HCTs - no. (%)	
No prior HCT	4303 (67)
Prior allo-HCT	382 (6)
Prior auto-HCT	1540 (24)
Prior auto and allo-HCT	31 (0)
Missing	155 (2)
Year of CT - no. (%)	
2016	97 (2)
2017	174 (3)
2018	953 (15)

Characteristic	N(%)
2019	1625 (25)
2020	1804 (28)
2021	1758 (27)

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Cellular Immunotherapy for Cancer Working Committee Members

FROM: Marcelo Pasquini, MD, MS; Scientific Director of CICWC

RE: Studies in Progress Summary

AC16-01: Pattern of use and outcomes with donor lymphocyte infusion (DLI) after HLA-haploidentical allogeneic hematopoietic stem cell (Vivek Roy and James Foran)
The purpose of the study is to:

1. To describe the frequency of use of DLI, CD3 cell dose, and the efficacy and toxicity of DLI after HLA haploidentical T-replete HCT.
2. To explore the specific characteristics associated with outcomes (remission / restoration of full donor chimerism/ or GVHD).

This study is currently in manuscript preparation. The plan is to submit for publication by the Summer of 2022.

AC17-01: Impact of hematopoietic cell transplantation as consolidation following CD19 CAR T cells for the treatment of acute lymphoblastic leukemia. (Jae Park, Miguel-Angel Perales, Sarah Nikiforow)
The purpose of the study is to:

1. To assess the impact of alloHCT consolidation on long-term outcomes of patients with ALL treated with CD19-targeted CAR T-cells.
2. To describe the patterns of alloHCT after CAR T cell for treatment of ALL. AlloHCT as a consolidation or as treatment for post CAR T cell relapse will be assessed.
3. The primary outcome of interest is the event free survival (EFS) of patients who underwent post-CAR alloHCT consolidation versus those who did not.

This study is currently in manuscript preparation. The plan is to submit for publication by the Summer of 2022.

AC18-01: Effect of stem cell boost and donor lymphocyte infusion on the incidence of GVHD (Edmund K. Waller and James J. Yoon)
The purpose of this study is to:

1. To describe the patterns of alloHCT after CAR T cell for treatment of ALL. AlloHCT as a consolidation or as treatment for post CAR T cell relapse will be assessed.

This study is currently being re-assessed for feasibility. The plan is to finalize data set and decide about proceeding with the study by Summer 2022.

CT19-02: Prolonged Cytopenia Following CD-19 Targeted CAR-Therapy for Diffuse Large B-Cell Lymphoma (DLBCL) (Mazyar Shadman)
The purpose of this study is to:

1. To evaluate the incidence and severity of cytopenia and delayed count recovery after treatment with FDA approved CD19 targeted CAR-T product, Axi-cel for large cell lymphoma.
2. To determine the rate and grade of thrombocytopenia and neutropenia at 3, 6 and 12 months after CAR-T therapy, including cytopenias that occur after the initial recovery.
3. To determine pre- and post- CAR-T treatment factors that may be associated with prolonged cytopenia after CAR-T therapy. Evaluate the impact of prolonged cytopenia on overall survival.

This study is currently in manuscript preparation. The plan is to submit for publication by the Summer of 2022.

CT20-01: Analysis of commercial CAR-T of patients with relapsed/refractory Aggressive Large B Cell Lymphoma in the real world setting (Martina Pennisi, Alberto Mussetti, Miguel-Angel Perales, Brian T. Hill, Taiga Nishihori, Michael Jain, Frederick Locke)
The purpose of this study is to:

1. To compare the progression free survival (PFS) of patients with R/R LBCL treated with tisagenlecleucel or axicabtagene ciloleucel.
2. To compare in patients with R/R LBCL treated with tisagenlecleucel vs. axicabtagene ciloleucel: Overall survival (OS), Overall response rate (ORR), complete remission (CR) and partial remission (PR), Duration of response (DOR), and others.

This study is currently in analysis. The plan is to move to manuscript preparation by Summer 2022.

CT20-02: Real World Experience of Costs and Healthcare Utilization associated with Chimeric Antigen Receptor T-cell (CAR-T) Therapy (Caleb J. Scheckel, Minoo Battiwalla, Shahrukh Hashmi, Yi Lin, Jeremy Pantin, Hemalatha Rangarajan, Prakash Satwani, Mustaqeem Siddiqui)
The purpose of this study is to:

1. To determine “real world” costs and HCRU incurred during CAR-T therapy for NHL and pediatric ALL patients. Investigate differences in HCRU (and variance) of CAR-T therapy across demographic groups (age, gender, disease type, obesity, agent, cancer type).
2. To evaluate differences in HCRU and costs between centers that perform CAR-T inpatient vs outpatient in the treatment of relapsed or refractory (R/R) lymphoma
3. To identify variables associated with increased HCRU and associated costs
4. To compare the HCRU and costs incurred by Kymriah treated pediatric (</=21 years) patients with that of pediatric patients who underwent allo HCT between 2016 -2019.

This study is currently in data file preparation. The plan is to move to finalize the population, perform the matching with claims database and move to analysis by July 2022.

CT20-03: Comorbidities, Toxicities and Efficacy Outcomes after Chimeric Antigen Receptor T-cell Therapy in B cell Lymphoma (Sairah Ahmed, Mohamed Sorror, Merav Bar, Uri Greenbaum, Amanda L. Olson, Elizabeth J. Shpall, Partow Kabriae, Mahmoud Elsawy, Hamza Hashmi, Michael Jain, Taiga Nishihori, Frederick Locke, Christopher Strouse, Umar Farooq, Margardia Magalhaes-Silverman, Roni Shouval, Martina Pennisi, Miguel Angel Perales, Elena Mead, Kitsada Wudhikarn, Praveen Ramakrishnan, Farrukh Awan, Anusha Vallurupalli, Siddhartha Ganguly)
The purpose of this study is to:

1. To describe incidence of CRS and ICANS after CAR T-cell therapy for NHL, grading, timing of toxicity, treatment, trends over time and risk factors.
2. To evaluate the impact of toxicities (timing, overlap and severity on overall survival)
3. To describe comorbidity burden in recipients of CAR T-cell therapy for NHL
4. To study associations between individual comorbidities and toxicities and survival.
5. To develop a comprehensive comorbidity model that predicts severe (grade III-V) toxicities and mortality after CAR T-cell therapy.
6. To describe NHL-specific effectiveness outcomes (ORR, event free survival, overall survival, relapse) after CAR T-cell therapy
7. To study the impact of disease and patient-related factors on treatment efficacy after CAR T-cell therapy.
8. Study best-practice decision-making style using the three analyses above
9. Study how to use the three developed models (comorbidity index, toxicity predictive index, and treatment efficacy developed index) to make the best decision about choice of CAR T-cells for different patients.

This study is currently in analysis. The plan is to submit for publication by July 2022.

CT20-04: Outcomes of acute lymphoblastic leukemia post chimeric antigen receptor T-cell therapy (Prajwal Dhakal, Dristhi Ragoonanan, Liora Michal Schultz, Abu-Sayeef Mirza, Nirav Shah, Vijaya Raj Bhatt, Kris Mahadeo, Partow Kebriaei, Lori Muffly, Hany Elmariah, Julio Chavez, Parmeswaran Hari)
The primary purpose of this study is:

1. To describe efficacy outcomes including response rates, overall survival, event-free survival, non-relapse mortality, duration of response, and B cell aplasia in patients with ALL following CAR T-cell therapy
2. To study the impact of patient and disease factors on these outcomes
3. To describe the incidence of CRS and ICANS after CAR T-cell therapy
4. To describe the incidence of prolonged cytopenias after CAR T-cell therapy
5. To study associations between patient and disease factors and severe toxicities after CAR T-cell therapy
6. To evaluate the impact of severe toxicities on overall survival

The secondary purpose of this study is:

1. To describe the use of HCT following CAR T-cell therapy and analyze efficacy outcomes in this cohort
2. To describe the details of timing, patterns (marrow, CNS, other extramedullary site), CD19 status, and B cell aplasia in patients who relapse after CAR T-cell therapy

This study is currently in data file preparation. The plan is to move to analysis by the Summer of 2022.

CT21-01: Outcomes of elderly patients receiving CD-19 directed Car-T Therapy for B-cell lymphomas
(Sayeef Mirza, Chitra Hosing, Francine Foss, Lohith Gowda)

The purpose of this study is:

1. Evaluate cumulative incidence, grades, duration and median time to onset of CRS and CRES/ICANS in patients > 65 versus < 65 years of age receiving CD-19 directed CAR-T therapy.
2. Secondary outcomes of interest among elderly patients who receive CAR T-cells:
    - Evaluate progress free survival (PFS) at 6 and 12 months in elderly adults
    - Evaluate OS in elderly adults
    - Overall Response rate (ORR) in elderly adults
    - Cumulative incidence of relapse (RI) in elderly adults
    - Identify patterns of end organ damage, duration of hospital stay, need for intensive care/intubation, pre-infusion comorbidity burden between elderly adults and younger cohort
    - Causes of death and cumulative incidence of non-relapse mortality
    - Burden of post infusion cytopenias, secondary neoplasms (including MDS, AML etc;) and infections with immune reconstitution data if available.
    - Identifies differences in disease biology (prevalence of double hit or triple hit, TP 53 mutation status) between the 2 groups and their contribution to PFS and OS
    - Identify pre-transfusion predictive markers for toxicity, best responses and survival in the elderly compared to younger peers.

This study is currently in protocol development. The plan is to move to finalize the dataset and move to analysis by July of 2022.

Response Summary:

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

Q1. Study Title

Myelodysplastic Syndrome / Acute Myelogenous Leukemia after Autologous Chimeric Antigen Receptor T-cell Immunotherapy for Non-Hodgkin Lymphoma

Q2. Key Words

CAR T-cell
Immunotherapy
Late effects

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Robert Dean, MD
Email address:	deanr@ccf.org
Institution name:	Cleveland Clinic
Academic rank:	Assistant Professor

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

- No

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	N/A
Email address:	N/A
Institution name:	N/A
Academic rank:	N/A

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

N/A

Q8. Do you identify as an underrepresented/minority?

N/A

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

N/A

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

N/A

LETTER OF COMMITMENT:

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

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

N/A

Q13. PROPOSED WORKING COMMITTEE:

- Cellular Immunotherapy for Cancer

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

- No

Q15. RESEARCH QUESTION:

What are the risks of and factors associated with the development of myelodysplastic syndrome or acute myelogenous leukemia (MDS/AML) after autologous chimeric antigen receptor (CAR) T-cell therapy for non-Hodgkin lymphoma?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that the real-world risk of myelodysplastic syndrome or acute myelogenous leukemia (MDS/AML) after autologous CAR T-cell therapy for DLBCL and MCL is higher than that reported in the registration trials for these treatments.

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

Suggested word limit of 200 words:

1. To characterize the risks of MDS/AML in patients with DLBCL and MCL who underwent autologous CAR T-cell therapy.
2. To identify potential clinical and biological factors associated with subsequent MDS/AML in these patients

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

Identification of risk factors for MDS/AML after autologous CAR T-cell therapy in patients with NHL could:
1) inform treatment decisions for individual patients when autologous CAR T-cell therapy is being considered;
2) provide evidence to help determine the optimal sequencing of autologous CAR T-cell therapy among other treatment strategies; and
3) support the development of novel clinical trials designed to minimize the risks of MDS/AML while preserving the benefits of these treatments.
Identifying a cohort of patients with MDS/AML after autologous CAR T-cell therapy for NHL could facilitate collaboration among participating centers to study additional factors beyond the scope of the CIBMTR database. For example, it would be of interest to conduct next-generation sequencing (NGS) studies on stored bone marrow or peripheral blood samples to determine if clonal hematopoiesis before autologous CAR T-cell therapy predicted the subsequent development of MDS/AML in affected patients.

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

New myeloid neoplasms such as MDS/AML are a serious late effect of lymphoma therapy, the risks of which are well-documented after high-dose chemotherapy and autologous stem cell transplantation. Severe and prolonged cytopenias after autologous CAR T-cell therapy are common, but reports of MDS/AML in the pivotal trials of these agents for DLBCL and MCL were rare [1-3]. Anecdotal experience suggests that these published data may underestimate the risk of MDS/AML after autologous CAR T-cell therapy in treating these patients in a standard-of-care setting. The CIBMTR database provides an opportunity to evaluate this risk in a broader cohort of patients that is more representative of the treated population as a whole.

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

N/A

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

Adult patients undergoing autologous CAR T-cell therapy for DLBCL or MCL

Q21. Does this study include pediatric patients?

- No

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

CAR T-cell therapy is not currently FDA approved for pediatric patients.

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

Form 4000, Pre-Cellular Therapy Essential Data
Form 4003, Cellular Therapy Product
Form 4006, Cellular Therapy Infusion
Form 4100, Cellular Therapy Essential Data Follow-Up Form
Form 3500, Subsequent Neoplasms

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

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

N/A

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

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

N/A

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

N/A

Q26. REFERENCES:

1. Locke, F.L., et al., Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol, 2019. 20(1): p. 31-42.
2. Schuster, S.J., et al., Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med, 2019. 380(1): p. 45-56.
3. Abramson, J.S., et al., Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet, 2020. 396(10254): p. 839-852.

Q27. **CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:**

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

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

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

N/A

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

Embedded Data:

N/A

2110-246: Adult patients undergoing 1st commercial CAR T-cell therapy for DLBCL or MCL

Characteristic	N(%)
No. of patients	3551
No. of centers	116
Patient related	
Age at infusion, by category - no. (%)	
Median (min-max)	64 (18-91)
18-29	94 (3)
30-39	182 (5)
40-49	302 (9)
50-59	774 (22)
60-69	1289 (36)
>= 70	910 (26)
Recipient Sex - no. (%)	
Male	2264 (64)
Female	1287 (36)
Recipient race - no. (%)	
White	2801 (79)
African-American	176 (5)
Asian	155 (4)
Pacific Islander	6 (0)
Native American	13 (0)
More than one race	23 (1)
Unknown	168 (5)
Missing	209 (6)

Characteristic	**N(%)**
Recipient ethnicity - no. (%)	
Hispanic or Latino	343 (10)
Non Hispanic or non-Latino	2861 (81)
Non-resident of the U.S.	218 (6)
Unknown	123 (3)
Missing	6 (0)
Performance score prior to CT - no. (%)	
90-100	1400 (39)
=80	1053 (30)
< 80	703 (20)
Missing	395 (11)
ECOG performance status prior to CT - no. (%)	
0 - Asymptomatic	1400 (39)
1 - Symptomatic but completely ambulatory	1605 (45)
2 - Symptomatic, < 50% in bed during the day	140 (4)
3 - Symptomatic, > 50% in bed, but not bedbound	8 (0)
4 - Bedbound	3 (0)
Missing	395 (11)
CT-CI - no. (%)	
0	1097 (31)
1	672 (19)
2	443 (12)
3+	1269 (36)
TBD	14 (0)
Missing	56 (2)

Characteristic	**N(%)**
Disease related	
Disease classification - no. (%)	
NHL diffuse, large B-cell	802 (23)
Burkitt lym/Burkitt cell leukemia	7 (0)
NHL mantle cell	253 (7)
T-cell / histiocytic rich large B-cell lymphoma	49 (1)
Primary mediastinal large B-cell	82 (2)
Other B-cell	11 (0)
Diffuse, large B-cell lymphoma- Germinal center B-cell type	1133 (32)
Diffuse, large B-cell lymphoma- Activated B-cell type	784 (22)
Primary cutaneous DLBCL, leg type	4 (0)
EBV+ DLBCL, NOS	24 (1)
DLBCL associated with chronic inflammation	1 (0)
High-grade B-cell lymphoma, NOS	62 (2)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	337 (9)
Burkitt-like lymphoma with 11q aberration	2 (0)
IPI at initial diagnosis of the primary disease - no. (%)	
Low	98 (3)
Low intermediate	163 (5)
High intermediate	193 (5)
High	216 (6)
Missing	2881 (81)
Stage of organ involvement at initial diagnosis of the primary disease - no. (%)	
I	240 (7)
II	378 (11)

Characteristic	N(%)
III	671 (19)
IV	1270 (36)
Unknown	496 (14)
Missing	496 (14)
Disease status at CT - no. (%)	
CR	151 (4)
PR	768 (22)
Resistant	2292 (65)
Untreated	208 (6)
Unknown	127 (4)
Missing	5 (0)
Prior lines of therapies - no. (%)	
No	3 (0)
Yes	3290 (93)
1	2394 (67)
2	81 (2)
>= 3	643 (18)
Missing	172 (5)
Missing	258 (7)
Prior radiation therapy - no. (%)	
No	2161 (61)
Yes	1047 (29)
Missing	343 (10)
Prior HCT - no. (%)	
No	2578 (73)

Characteristic	N(%)
Yes	909 (26)
Prior allo-HCT	46 (1)
Prior auto-HCT	834 (23)
Prior auto and allo-HCT	13 (0)
Missing	16 (0)
Missing	64 (2)
Time from HCT to CT, months - median (min-max)	16 (2-315)
CAR-T cell related	
Year of CT - no. (%)	
2017	5 (0)
2018	487 (14)
2019	944 (27)
2020	1153 (32)
2021	962 (27)
Product - no. (%)	
Kymriah	942 (27)
Yescarta	2367 (67)
Tecartus	242 (7)
Time from diagnosis to CT - no. (%)	
Median (min-max)	15 (1-447)
0-6 months	355 (10)
6-12 months	1006 (28)
1-2 years	1002 (28)
2-3 years	1187 (33)
Missing	1 (0)

Characteristic	N(%)
Bridging therapy - no. (%)	
No	2269 (64)
Yes	761 (21)
Systemic therapy	570 (16)
Intrathecal therapy	30 (1)
Intraocular therapy	1 (0)
Radiation therapy	239 (7)
Surgery	1 (0)
Not reported	521 (15)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)	
No	12 (0)
Yes	3538 (100)
Bendamustine only	135 (4)
Flu+Cy only	3318 (93)
Other	78 (2)
None selected	7 (0)
Missing	1 (0)
None selected	1 (0)
Subsequent AML - no. (%)	
No	101 (3)
Yes	8 (0)
Missing	3442 (97)
Subsequent MDS - no. (%)	
No	74 (2)
Yes	35 (1)

Characteristic	**N(%)**
Missing	3442 (97)
Follow-up, in months - median (range)	12 (1-41)

CIBMTR Combined Study Proposal

Study Title: CD19-CAR-T therapy failure: Impact of subsequent therapy in patients with B-cell malignancies

Keywords

ALL	Reinfusion
Lymphoma	Pediatric patients
CAR T cell therapy	Immune modulatory therapies
Relapse	Response rates
Progression	Outcomes

Name: Ana, Alarcon Tomas Degree(s): MD Academic Rank: Visiting Investigator. 2nd year Research fellow Institution: MSKCC Email: alarcona@mskcc.org	Name: Lauren Appell Degree(s): MD Academic Rank: Clinical fellow Institution: Arkansas Children Hospital, AK Email: LEAppell@uams.edu	Name: Evandro Bezerra Degree(s): MD Academic Rank: Clinical Fellow Institution: Mayo clinic email: bezerra.evandro@mayo.edu	Name: Abu-Sayeef Mirza Degree(s): MD Academic Rank: Clinical fellow Institution: Yale Cancer center Email: Abu-Sayeef.mirza@yale.edu
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Name: Guru Subramanian Guru Murthy Degree: MD, MS Academic Rank: Assistant professor. Institution: Medical College of Wisconsin Email: gmurthy@mcw.edu			

Research question

What are the best treatment strategies (including subsequent Cell therapies) and subsequent outcomes after CD19 CAR T therapy for B cell malignancies?

Research Hypotheses:

1. Infusion of 2nd or subsequent CD19-CAR-T cells is safe and offers higher response rates in adult and pediatric patients with B-cell malignancies.
2. Patients with relapsed/refractory B-cell malignancies who received subsequent therapies after CAR T cell therapy have better outcomes than those who didn't receive further treatment. In patients with relapsed/refractory large B cell lymphoma (R/R LBCL) in this setting, we hypothesized that immune modulatory therapies achieve higher response rates and better OS.

Primary endpoints:

1. To describe clinical outcomes (OS and PFS) and real-world utilization patterns of subsequent treatment after CAR-T cell therapy for patients with CD19+ hematologic neoplasms, including 2nd infusion of CD19 CAR T cells.

Secondary endpoints:

1. To describe toxicities (including CRS, ICANS and NRM) associated with different subsequent treatment strategies.
2. To compare characteristics and clinical outcomes (OS and PFS) of those who received subsequent therapy compared to those who didn't.
3. To determine the association between initial disease response post CAR-T therapy and the utilization of subsequent non-transplant interventions.
4. To compare clinical characteristics and outcomes (ORR, OS and PFS) among the different subsequent treatment strategies.
5. To compare ORR, OS and PFS stratified by commercial CAR T products and early or late relapse (before and after day 100).
6. To Identify factors that may predict best response to 2nd or subsequent dose of CAR-T therapy.

Scientific Impact:

Although CD19 CAR T cell therapy has resulted in unprecedented response rates in adult and pediatric patients with B cell malignancies, many patients still experience relapse or progression of their disease after receiving a CD19 directed CAR T cell product. There is a critical need to determine the mechanisms of relapse after CAR T cell therapy and explore treatment strategies that could mitigate these events.

We propose exploring the impact of subsequent therapies including subsequent CAR T infusions in patients who have previously received a CD19 directed CAR T cell product. A large registry based CIBMTR study will allow clinicians to better understand and adequately guide the management of patients who relapse after CAR T cell therapy. Knowing these practice patterns would be important to understand their impact on outcomes and to inform opportunities to design prospective studies to formally study management options in this patient population.

Scientific Justification:

Chimeric antigen receptor (CAR) T cell therapy has improved outcomes of patients with relapsed/ refractory B-ALL and NHL [1-5]. Given the rapid advancement and successful application of CAR-T cell immunotherapy, the number of patients who receive CAR-T cell therapy continues to increase each year (Figure A). Although CD19 CAR T cell therapy has achieved a striking curative effect in B-cell hematological

malignancies, many patients still experience disease relapse [6-17]. These patients are then treated using a variety of subsequent therapies, including reinfusions of CAR T cells. Data guiding the management of this difficult-to-treat population are lacking. Additionally, the factors associated with receiving subsequent therapies are not yet well established.

In clinical practice of patients with r/r B-ALL who have progressed/relapsed after CAR-T, agents such as blinatumomab, inotuzumab, BCR-ABL tyrosine kinase inhibitors, systemic chemotherapy and second CAR-T therapy are available as possible options for managing the disease after CAR T-cell therapy. Long term follow-up data from prior clinical studies suggest variability in the management of patients post CAR-T therapy [7, 18]. A recent follow-up study from MSKCC showed that 79% of patients who relapsed or progressed after CD19 CAR T cell therapy received various salvage therapies including multiagent chemotherapy, blinatumomab, inotuzumab and reinfusion of CAR T-cells with a median remission duration of 4.5 months, event free survival of 5.8 months and OS of 7.5 months [18]. Other authors have reported promising results with consolidation of allogeneic transplant after CAR-T [19]. However, many patients may not be able to undergo subsequent allo-HCT for varying reasons and are likely to utilize non-transplant therapies in the interim.

In patients needing subsequent therapy after failure of a first CAR T cell infusion, one option is retreatment with a second infusion of CD19 CAR T cells. However, the feasibility and efficacy of these subsequent infusions are unknown. A phase 1/2 trial studying 44 adult patients (ALL, CLL, and NHL) demonstrated a higher 2nd dose infusion of CAR-T may improve overall outcomes [20], Figure B. In another phase I clinical trial of HuCART19 at the Children's Hospital of Philadelphia (CHOP), 33 pediatric patients received reinfusion of the CD19 CAR T cell product for partial or no response to prior infusion, CD19+ relapse, or loss of B cell aplasia within 6 months of the initial infusion. The overall response rate in the retreatment cohort was 64% at 1-month post infusion. This cohort of patients had a higher rate of loss of CAR T cell persistence at 6 months, with a 48% probability of losing the cell product at 6 months. Of the 21 patients who achieved a complete response and retained B cell aplasia, relapse free survival (RFS) was 74% at 12 months and 58% at 12 months [21]. Given subsequent CARs in the same patient is safe, tolerable, and responses may be improved, further study with a high-powered analysis of real-world data is warranted.

Other options after CAR T failure in R/R LBCL include Immune checkpoint inhibitors, lenalidomide, bi-specific antibodies, and allogeneic hematopoietic cell transplantation. Polatuzumab, tafasitamab represent recently FDA approved options. However, it is unclear how these therapies should be sequenced after CAR-T therapy [22]. Several groups have reported their experience treating relapses after CAR-T cell therapy [13-17]; however, treatments were heterogeneous and sample sizes were limited. An observational study by MSKCC, Subsequent anti-cancer treatment was administered in 135/183 patients failing CAR-T treatment. Median overall survival (OS) from post-CAR-T treatment was eight months (95% CI 5.6-11). Polatuzumab (n=29), standard chemotherapy (n=17), and lenalidomide (n=15)-based treatments were the most common systemic approaches. Complete remissions (CR) were not observed with conventional chemotherapy, while rates exceeding 30% were noted following polatuzumab- or lenalidomide-based therapies. In a multivariable Cox-regression model, lenalidomide-based treatment was associated with better OS than chemotherapy (HR 0.25 [0.07-0.85]; 1-year OS 69% [48-100] vs. 25%). To conclude, in this largest analysis of patients with LBCL who progressed or relapsed after CAR-T, outcomes are poor. However, novel agents result in favorable response and survival rates and should be further studied [23].

Several options exist for managing the disease after CAR T-cell therapy, however, the current practice pattern of utilizing other non-transplant interventions after CAR-T cell therapy is unknown. Identifying the optimal time to intervene and clinical characteristics that could inform rational selection of subsequent therapy is an unmet need and we think a registry study is the best way to address this question.

Patient Eligibility Population:

Inclusion criteria

1. Any patient (any age) with the diagnosis of any B-cell malignancy (B-ALL and any indolent or aggressive lymphoma) receiving CD19 CAR-T cell product
2. We will include patients from inception until Dec 2021.

Exclusion criteria

- Patients who received CAR T therapy under clinical trial.

Exclusion criteria

Data Requirements:
This proposed study will require no supplemental data to be collected. The current data is included in the CIBMTR collection forms for pre-cellular therapy and post-cellular therapy.

Disease-patient related	**CAR T related**	**Subsequent cellular treatment**	**Subsequent non-cellular therapy**
Age at CAR T cell	Apheresis date	Time from CAR T to next line treatment	Time from CAR T to next line treatment
Gender: Male VS Female	Status at apheresis	CAR-T product	Treatment after CAR T cell: type, start and termination dates.
Ethnicity	Bridging treatment	Date from disease relapse to CART apheresis.	Best Response to Treatment after CAR T cell
Diagnosis: DLBCL, primary mediastinal B cell lymphoma, transformed Follicular MZL, MCL, Double Hit Lymphoma, B-cell ALL	Type of bridging treatment	Time for apheresis to CART infusion	Last contact
Disease risk index	Response to Bridging treatment	Cell dose	Status at last contact
High risk cytogenetics: yes vs.no	Disease status at CAR T cell	Disease status at time of infusion	Live/Death Status at last contact

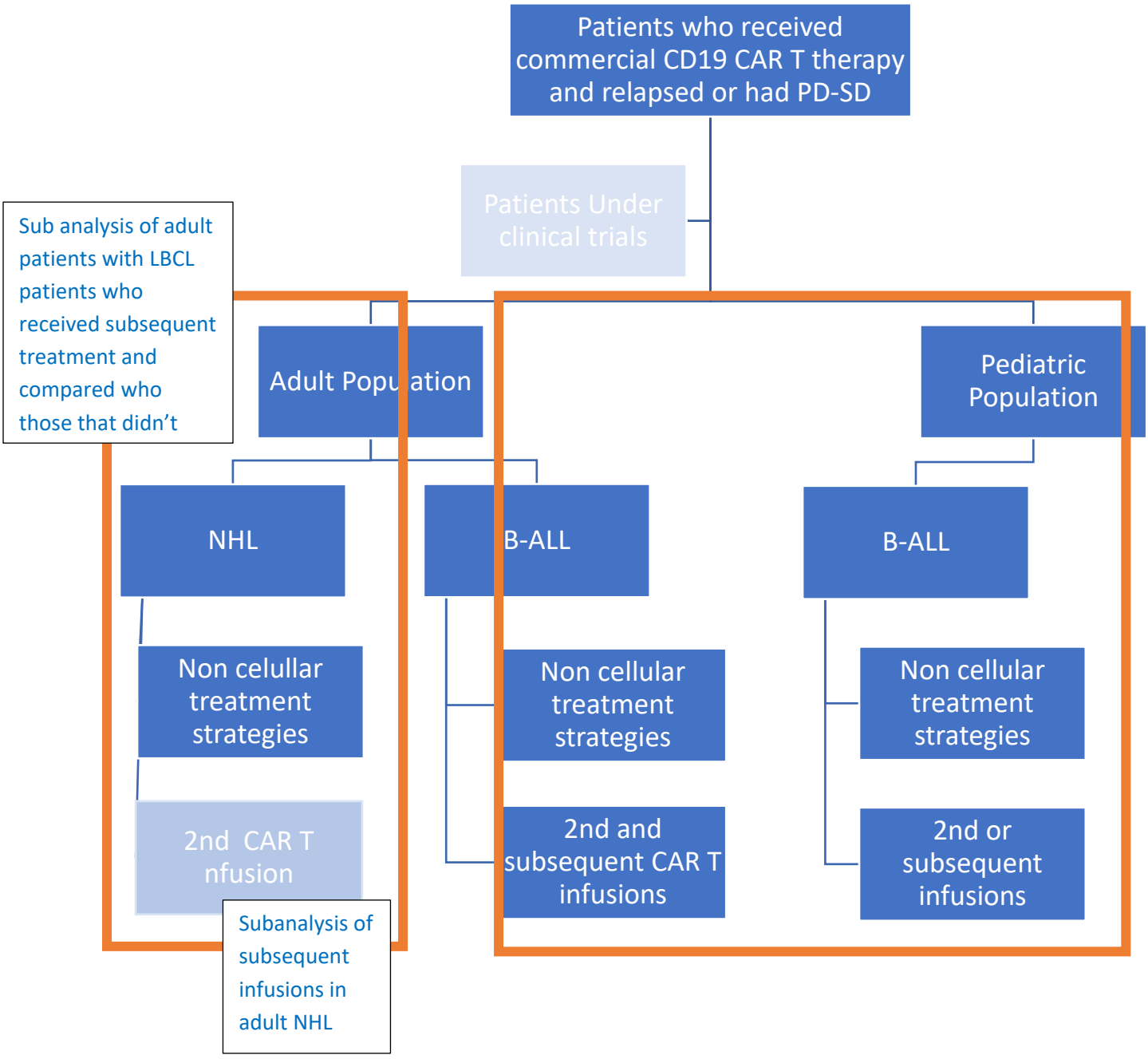
Number of prior therapies (before transplant): 1 vs. 2 vs. ≥ 3	Stage of disease at CAR T cell	CRP and Ferritin at infusion	Cause of death
Dose/fraction of radiation (2 Gy vs 3-Gy vs 4-Gy vs other)	IPI at CAR T cell	lymphodepletion prior to 2nd CAR-T (Y/N) what were the regimens and dose	Disease status at the time of initiation of subsequent therapy
Field of radiation	Lymphodepletion regimen	Response to 2nd CAR-T	
Sites of radiation	Karnofsky Performance Status	CRS (Y/N and grade) and duration	
Timing of radiation prior to apheresis	Hematopoietic Cell Transplant Comorbidity Index	CRES/Neurotoxicity (Y/N and grade)	
Extramedullary disease	CRS: Yes vs No. Grading per ASTCT consensus	Cytopenias	
Prior allogeneic transplant	ICANs: Yes vs No. Grading per ASTCT consensus	Infectious complications	
Prior autologous transplant	Grade 4 organ toxicity (yes/no)		
MRD status	Best response to CAR T cell		
Extramedullary disease	Disease relapse or progression and date		
	Relapse site		

Sample Requirements: No biologic or serologic data are required with this proposal.

Non-CIBMTR Data Source: Not required

Study design

We propose that the analysis be split into at least 2 cohorts, a cohort with B-ALL and another with NHL. Furthermore, if enough patients with NHL receive a 2nd CAR T infusion, that could be a third analysis focusing specifically on those patients where safety and efficacy are reported**.**


Patients who received commercial CD19 CAR T therapy and relapsed or had PD-SD
Patients Under clinical trials
Sub analysis of adult patients with LBCL patients who received subsequent treatment and compared who those that didn't
Adult Population
Pediatric Population
NHL
B-ALL
B-ALL
Non celullar treatment strategies
Non cellular treatment strategies
Non cellular treatment strategies
2nd CAR T nfusion
2nd and subsequent CAR T infusions
2nd or subsequent infusions
Subanalysis of subsequent infusions in adult NHL

Characteristic	ALL	NHL
No. of patients	476	3315
No. of centers	82	116
Patient related		
Age at infusion, by category - no. (%)		
Median (min-max)	15 (1-38)	63 (0-91)
0-9	122 (26)	1 (0)
10-17	191 (40)	1 (0)
18-29	162 (34)	93 (3)
30-39	1 (0)	178 (5)
40-49	0 (0)	297 (9)
50-59	0 (0)	731 (22)
60-69	0 (0)	1185 (36)
>= 70	0 (0)	829 (25)
Recipient Sex - no. (%)		
Male	300 (63)	2077 (63)
Female	176 (37)	1238 (37)
Recipient race - no. (%)		
White	348 (73)	2601 (78)
African-American	19 (4)	161 (5)
Asian	13 (3)	154 (5)
Pacific Islander	0 (0)	7 (0)
Native American	2 (0)	12 (0)
More than one race	16 (3)	21 (1)
Unknown	50 (11)	155 (5)
Missing	28 (6)	204 (6)
Recipient ethnicity - no. (%)		
Hispanic or Latino	207 (43)	320 (10)
Non Hispanic or non-Latino	221 (46)	2657 (80)
Non-resident of the U.S.	27 (6)	217 (7)
Unknown	21 (4)	116 (3)
Missing	0 (0)	5 (0)
Performance score prior to CT - no. (%)		
90-100	304 (64)	1312 (40)
=80	81 (17)	969 (29)
< 80	66 (14)	649 (20)

Characteristic	ALL	NHL
Missing	25 (5)	385 (12)
ECOG performance status prior to CT - no. (%)		
0 - Asymptomatic	304 (64)	1312 (40)
1 - Symptomatic but completely ambulatory	127 (27)	1484 (45)
2 - Symptomatic, < 50% in bed during the day	17 (4)	126 (4)
3 - Symptomatic, > 50% in bed, but not bedbound	3 (1)	6 (0)
4 - Bedbound	0 (0)	2 (0)
Missing	25 (5)	385 (12)
CT-CI - no. (%)		
0	196 (41)	1026 (31)
1	97 (20)	610 (18)
2	57 (12)	415 (13)
3+	122 (26)	1194 (36)
TBD	0 (0)	13 (0)
NA (not collected for these cases)	1 (0)	0 (0)
Missing	3 (1)	57 (2)
Disease related		
Disease classification - no. (%)		
Acute lymphoblastic leukemia (ALL)		
B-lymphoblastic leukemia / lymphoma, BCR-ABL1-like	40 (8)	0 (0)
B-lymphoblastic leukemia / lymphoma, with iAMP21	15 (3)	0 (0)
precursor B-cell ALL	421 (88)	0 (0)
Non-Hodgkin lymphoma (NHL)		
NHL diffuse, large B-cell	0 (0)	803 (24)
T-cell / histiocytic rich large B-cell lymphoma	0 (0)	49 (1)
Nodal marginal zone B-cell	0 (0)	3 (0)
Splenic marginal zone B-cell	0 (0)	1 (0)
Primary mediastinal large B-cell	0 (0)	82 (2)
Other B-cell	0 (0)	18 (1)
Intravascular large B-cell lymphoma	0 (0)	3 (0)
B-cell unclass. between DLBCL and hodgkin	0 (0)	10 (0)
Diffuse, large B-cell lymphoma- Germinal center B-cell type	0 (0)	1133 (34)
Diffuse, large B-cell lymphoma- Activated B-cell type	0 (0)	785 (24)
Primary cutaneous DLBCL, leg type	0 (0)	4 (0)
EBV+ DLBCL, NOS	0 (0)	24 (1)

Characteristic	ALL	NHL
High-grade B-cell lymphoma, NOS	0 (0)	62 (2)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	0 (0)	337 (10)
Large B-cell lymphoma with IRF4 rearrangement	0 (0)	1 (0)
Did the recipient have CNS leukemia anytime prior to preparative regimen / infusion? - no. (%)		
No	228 (48)	0 (0)
Yes	241 (51)	0 (0)
Missing	7 (1)	3315 (100)
Disease status at CT (ALL) - no. (%)		
Primary induction failure	59 (12)	0 (0)
1st complete remission	46 (10)	0 (0)
2nd complete remission	62 (13)	0 (0)
>= 3rd complete remission	69 (14)	0 (0)
1st relapse	118 (25)	0 (0)
2nd relapse	87 (18)	0 (0)
>= 3rd relapse	35 (7)	0 (0)
Missing	0 (0)	3315 (100)
Prior lines of therapies - no. (%)		
No	5 (1)	3 (0)
Yes	442 (93)	3081 (93)
1	334 (70)	2254 (68)
2	25 (5)	74 (2)
>= 3	74 (16)	592 (18)
Missing	9 (2)	161 (5)
Missing	29 (6)	231 (7)
Prior radiation therapy - no. (%)		
No	362 (76)	2021 (61)
Yes	69 (14)	987 (30)
Missing	45 (9)	307 (9)
Prior HCT - no. (%)		
No	348 (73)	2414 (73)
Yes	112 (24)	839 (25)

Characteristic	ALL	NHL
Prior allo-HCT	110 (23)	43 (1)
Prior auto-HCT	1 (0)	771 (23)
Prior auto and allo-HCT	1 (0)	9 (0)
Missing	0 (0)	16 (0)
Missing	16 (3)	62 (2)
Time from HCT to CT, months - median (min-max)	15 (1-176)	15 (2-315)
WBC count prior to LD (billion/L) - median (min-max)	3 (0-131)	5 (0-61)
MRD positive/negative CR prior to CT - no. (%)		
MRD negative	101 (21)	0 (0)
MRD positive	69 (14)	101 (3)
Not tested	2 (0)	2388 (72)
N/A - Not in CR	299 (63)	0 (0)
Missing	5 (1)	826 (25)
CAR-T cell related		
Year of CT - no. (%)		
2017	8 (2)	6 (0)
2018	107 (22)	491 (15)
2019	138 (29)	944 (28)
2020	122 (26)	1090 (33)
2021	101 (21)	784 (24)
Product - no. (%)		
Kymriah	476 (100)	940 (28)
Yescarta	0 (0)	2374 (72)
Tecartus	0 (0)	1 (0)
Time from diagnosis to CT - no. (%)		
Median (min-max)	33 (1-243)	15 (1-447)
0-6 months	70 (15)	351 (11)
6-12 months	57 (12)	976 (29)
1-2 years	74 (16)	951 (29)
2-3 years	275 (58)	1036 (31)
Missing	0 (0)	1 (0)
Bridging therapy - no. (%)		

Characteristic	ALL	NHL
No	236 (50)	2112 (64)
Yes	126 (26)	726 (22)
Systemic therapy	118 (25)	546 (16)
Intrathecal therapy	0 (0)	28 (1)
Intraocular therapy	0 (0)	1 (0)
Radiation therapy	16 (3)	224 (7)
Surgery	0 (0)	1 (0)
Not reported	114 (24)	477 (14)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)		
No	2 (0)	12 (0)
Yes	474 (100)	3302 (100)
Bendamustine only	0 (0)	126 (4)
Flu+Cy only	467 (98)	3097 (93)
Other	7 (1)	72 (2)
None selected	0 (0)	7 (0)
Missing	0 (0)	1 (0)
None selected	0 (0)	1 (0)
Subsequent therapies-ALL only		
Subsequent Blinotumomab Reported - no. (%)		
No	457 (96)	
Yes	19 (4)	
Subsequent Inotozumab Reported - no. (%)		
No	420 (88)	
Yes	56 (12)	
Subsequent CT Reported - no. (%)		
No	394 (83)	
Yes	82 (17)	
Subsequent HCT Reported - no. (%)		
No	380 (80)	
Yes	96 (20)	
Other subsequent therapy Reported - no. (%)		
No	450 (95)	
Yes	26 (5)	

Characteristic	ALL	NHL
Subsequent therapies-NHL only		
Subsequent Radiation Reported - no. (%)		
No		3155 (95)
Yes		160 (5)
Subsequent CT Reported - no. (%)		
No		3293 (99)
Yes		22 (1)
Subsequent HCT Reported - no. (%)		
No		3244 (98)
Yes		71 (2)
Subsequent Gemcitabine Reported - no. (%)		
No		3246 (98)
Yes		69 (2)
Subsequent Rituximab Reported - no. (%)		
No		2899 (87)
Yes		416 (13)
Subsequent Ibrutinib Reported - no. (%)		
No		3215 (97)
Yes		100 (3)
Subsequent Pembrolizumab Reported - no. (%)		
No		3195 (96)
Yes		120 (4)
Subsequent Nivolumab Reported - no. (%)		
No		3251 (98)
Yes		64 (2)
Subsequent Lenalidomide Reported - no. (%)		
No		3088 (93)
Yes		227 (7)
Subsequent Bendamustine Reported - no. (%)		
No		3080 (93)
Yes		235 (7)
Subsequent Polatuzamab Reported - no. (%)		
No		3299 (100)
Yes		16 (0)

Characteristic	ALL	NHL
Subsequent Tafasitamab Reported - no. (%)		
No		3314 (100)
Yes		1 (0)
Subsequent Altezolizumab Reported - no. (%)		
No		3314 (100)
Yes		1 (0)
Subsequent Durvalumab Reported - no. (%)		
No		3314 (100)
Yes		1 (0)
Subsequent Mosunetuzumab Reported - no. (%)		
No		3314 (100)
Yes		1 (0)
Other subsequent therapy Reported - no. (%)		
No		3246 (98)
Yes		69 (2)
Follow-up, in months - median (range)	16 (2-42)	13 (1-41)

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Conflicts of Interest:

1. Miguel Perales, MD: Yes, as reported below
2. Akshay Sharma, MBBS, Yes, as reported below

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

Dr. Perales reports honoraria from Abbvie, Bellicum, Bristol-Myers Squibb, Incyte, Merck, Novartis, Nektar Therapeutics, Omeros, and Takeda. He serves on DSMBs for Servier and Medigene and the scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead, and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of the American Society for Transplantation and Cellular Therapy (ASTCT) and Be The Match (National Marrow Donor Program, NMDP), as well as on the CIBMTR Cellular Immunotherapy Data Resource (CIDR) Committee.

Dr. Sharma is the site principal investigator of clinical trials for genome editing of sickle cell disease sponsored by Vertex Pharmaceuticals/CRISPR Therapeutics (NCT03745287) and by Novartis (NCT04443907). The industry sponsors provide funding for the clinical trial, which includes salary support paid to Dr. Sharma's institution. Dr. Sharma has received consultant fee from Spotlight Therapeutics, Medexus Inc. and Vertex Pharmaceuticals. He has also received research funding from CRISPR Therapeutics and honoraria from Vindico Medical Education.

The other PIs have no conflict of interest to disclose

CD19-CAR-T failure: Impact of subsequent therapies in patients with B malignancies

There is a critical need to determine the mechanisms of relapse and strategies to mitigate these events

Figure A. Patients treated with CAR T-cells in the US reported to the CIBMTR (2016 -2021)

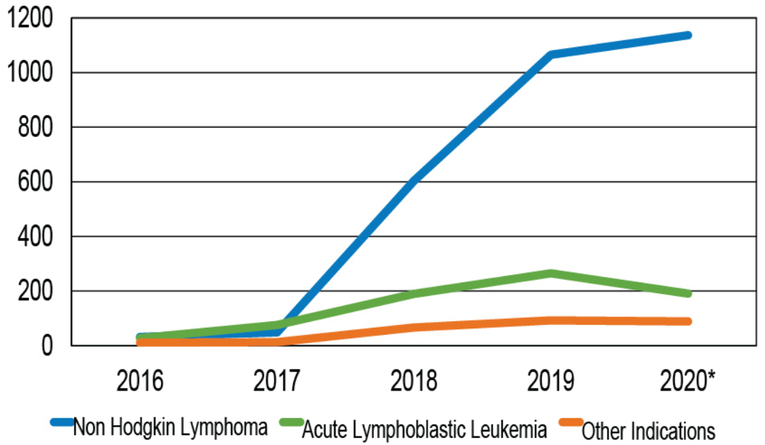


Figure B. Response rates after 2nd CAR T for ALL, CLL and NHL.

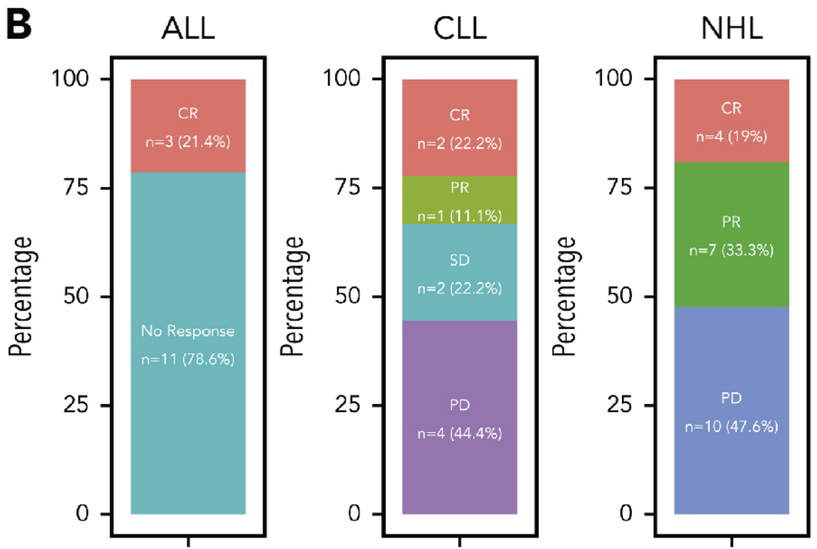
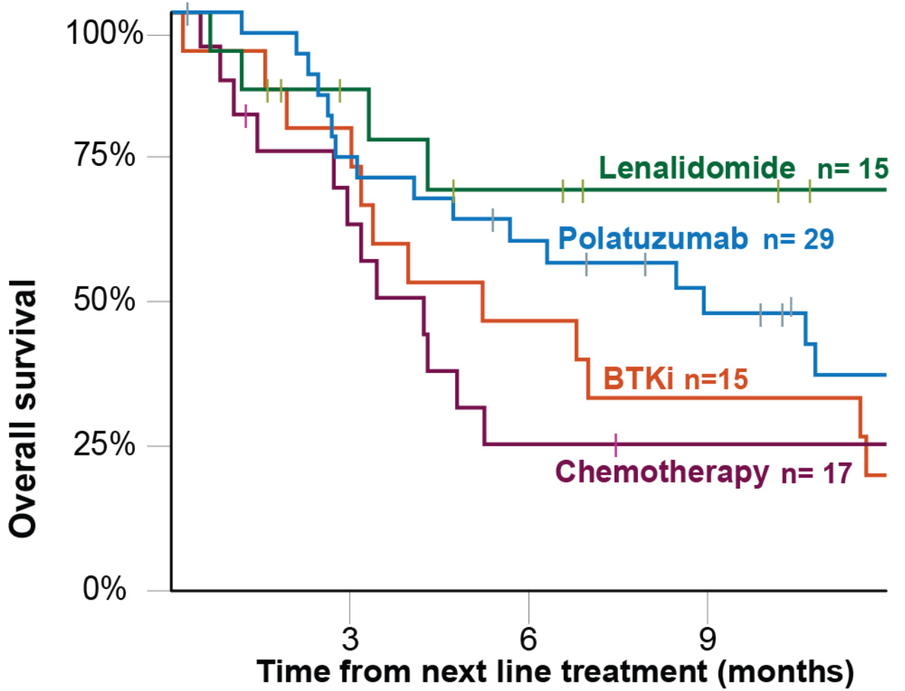


Figure C. increased OS in patients treated with Lenalidomide as first line treatment post CAR T therapy



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Gauthier J, Bezerra ED, Hirayama AV, Fiorenza S, Sheih A, Chou CK, Kimble EL, Pender BS, Hawkins RM, Vakil A, Phi TD,Steinmetz RN, Jamieson AW, Bar M, Cassaday RD, Chapuis AG, Cowan AJ, Green DJ, Kiem HP, Milano F, Shadman M, Till BG, Riddell SR, Maloney DG, Turtle CJ. Factors associated with outcomes after a second CD19-targeted CAR T-cell infusion for refractory B-cell malignancies. Blood. 2021 Jan 21;137(3):323-335.

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Response Summary:

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

Q1. Study Title

Composite end point of toxicity-free and progression-free survival (TPFS) after CD19 CAR T cell therapy for large B-cell lymphoma.

Q2. Key Words

CD19 CAR T, composite endpoint, toxicity-free and progression-free survival

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Aleksandr Lazaryan MD MPH PhD
Email address:	aleksandr.lazaryan@moffitt.org
Institution name:	Moffitt Cancer Center
Academic rank:	Associate member

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

- No

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	N/A
Email address:	N/A
Institution name:	N/A
Academic rank:	N/A

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

N/A

Q8. Do you identify as an underrepresented/minority?

N/A

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

N/A

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

N/A

LETTER OF COMMITMENT:

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

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

active writing member of multiple committees; led 2 prior CIBMTR studies (both published in Heamatologica)

Q13. PROPOSED WORKING COMMITTEE:

- Cellular Immunotherapy for Cancer

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

- No

Q15. RESEARCH QUESTION:

Clinical benefit of major FDA-approved CAR T cell products for large B-cell lymphoma as assessed by novel composite end point of 6-month toxicity-free and progression-free survival (TPFS) and what factors determine superior TPFS.

Q16. RESEARCH HYPOTHESIS:

A novel composite endpoint of toxicity-free and progression-free survival (TPFS) represents an ideal recovery assessment tool following CAR T cell therapy as it measures initial success (at 6 months) without progression, major morbidity and mortality.

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

Suggested word limit of 200 words:

Primary Objectives:
- Define TPFS as a novel composite endpoint in CAR T cell therapy based on Gr3+ CRS- and ICANS-free, progression-free (CR/PR) survival within first 6 month after infusion of CAR T product
- Estimate TPFS for all 3 FDA-approved CAR T cell products (axi-cel, tosa-cel, and liso-cel)

Secondary Objectives:
- Assess factors associated with TPFS at 6 months
- Assess if TPFS at 6 month is prognostic for 1- and 2-year overall survival
- Assess pre-transfusion prognostic markers for severe Gr3+ toxicity, disease progression and non-relapse mortality at 6 months

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

Development of this novel composite endpoint would be of significant interest for the CAR T research community as many current and future investigational agents have potentially dual action of mitigating toxicities of CAR T cell therapy while also potentially modifying its efficacy (e.g. JAK-, GM-CSF, BTK-, TKI-inhibitors etc.). Thus the use of the composite endpoint is expected to capture their net effect as reflected by most optimal outcomes following CAR T therapy.

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

Immunotherapy in the form of CD19 directed chimeric antigen receptor (CAR) T cells has transformed the treatment outcomes for patients with relapsed and refractory large B-cell lymphoma (LBCL) and acute lymphoblastic leukemia (ALL). Durable responses in the range of 40% have been observed with FDA-approved axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and lisocabtagene maraleucel (liso-cel) (Neelapu et al., NEJM 2017; Shuster et al., NEJM 2017; Abramson et al., Lancet 2020). Despite encouraging efficacy, major toxicities of CAR T cell therapy continue to include Cytokine Release Syndrome (CRS) and Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) which are both the major sources of morbidity and mortality in a fraction of patients. Severe toxicities (Grade 3+), disease progression, and non-relapse mortality across all 3 FDA-approved CAR T products are summarized in Table 1.

Ongoing investigational CAR T cell therapy efforts are directed towards novel strategies of toxicity mitigation and efficacy enhancement. Even outside of the clinical trials, toxicity management practices evolve constantly by including the use of pre-emptive strategies of earlier administration of corticosteroids and/or tocilizumab which on a large scale may influence established outcomes reported in pivotal clinical trials. These and other core differences in reported toxicity and efficacy profiles of 3 FDA-approved CAR T cell products challenge their large-scale comparison.

Importance of major severe toxicities of CD19 CAR T therapies and their efficacy can be captured by composite end point in observational and future clinical trials. Such novel endpoint may allow for leveled and more comprehensive comparison between CAR T cell constructs and their major outcomes. Our proposed toxicity-free and progression-free survival (TPFS) composite endpoint is defined as absence of severe (Grade 3+) CRS, ICANS, progression and non-relapse mortality within 6 months after CAR T cell infusion. Since each of these TPFS components is clinically meaningful, TPFS may represent an ideal recovery outcome after CAR T cell therapy (at 6 months) and also a measure of initial success without progression, major morbidity and mortality.

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

[Click here]

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

Inclusion criteria: Adult patients (age ≥ 18) with the diagnosis of large B-cell lymphoma and its variants who underwent autologous CD19 CAR T cell therapy with axi-cel, tisa-cel, or liso-cel.

Q21. Does this study include pediatric patients?

- No

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

very low incidence of LBCL in pediatric patients and FDA approval labels

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

Data will be captured through relevant CIBMTR collection forms and will include:
- Age at CAR T (categorical by decade)
- Gender
- Performance status (KPS)
- HCT comorbidity index prior to CAR T (categorized as 0-2 vs. 3+)
- Race (Caucasian vs African American vs Hispanic vs Asian/Pacific vs Other)
- LBCL features (double-hit, THL.)
- Remission status prior to CAR T
- Number and prior lines of therapy
- Prior radiation therapy status
- Use of bridging therapy and specific regimen
- Prior HCT status
- Secondary CNS involvement status
- Stage at relapse and if EN involvement • Type of product used (axi-cel, tisa-cel, or liso-cel)
- Date of apheresis
- Date of CAR T product infusion
- Conditioning regimen
- Severe Gr3+ CRS and date of onset and duration (max score)
- Severe Gr3+ ICANS and date of onset and duration (max score)
- Use of tocilizumab and/or steroids
- Treatment failure/LBCL progression within 6 months after infusion of CAR T
- Non-relapse mortality within 6 months
- Best overall response within 6 months
- Infections post CAR-T within 6 months
- Time from disease relapse to CAR-T apheresis
- Time from apheresis to CAR-T infusion
- CAR-T Cell dose
- Absolute lymphocyte count pre and post CAR-T cell infusion
- Baseline and peak CRP, ferritin, and LDH
- Length of hospitalization(s) including ICU stay
- Use of anakinra, siltuximab, pulse steroids and their duration
- Length of hospitalization(s) including ICU stay
- Cardiovascular and cardiopulmonary complications

This study will capture only data reported routinely to CIBMTR

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

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

Not required

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

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

Not required

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

N/A

Q26. **REFERENCES:**

N/A

Q27. **CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:**

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

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

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

N/A

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

Embedded Data:

N/A

Table 1. Severe toxicities across 3 FDA-approved CAR T cell therapies for LBCL

CAR T product	Gr3-4 CRS	Gr3-4 ICANS	Progression*	NRM**
Axi-cel				
Locke et al.	11%	32%	~55%	3%
Nastoupil et al.#	7%	31%	~45%	4.4%
Tisa-cel				
Shuster et al.	23%	12%	~60%	3%
Iacoboni et al.#	5%	1%	~60%	4%
Liso-cel				
Abramson et al.	2%	10%	~50%	3%

*At approximately 6 mos; **Total non-relapse mortality as reported in each study; #Real-world experience

4. 2110-333: Patients undergoing 1st axi-cel or tisa-cel treatment for large B-cell lymphoma and its variants, 2016-present

Characteristic	N(%)
No. of patients	3297
No. of centers	115
Patient related	
Age at infusion, by category - no. (%)	
Median (min-max)	63 (18-91)
18-29	94 (3)
30-39	178 (5)
40-49	296 (9)
50-59	726 (22)
60-69	1177 (36)
>= 70	826 (25)
Recipient Sex - no. (%)	
Male	2064 (63)
Female	1233 (37)
Recipient race - no. (%)	
White	2585 (78)
African-American	162 (5)
Asian	152 (5)
Pacific Islander	6 (0)
Native American	12 (0)
More than one race	21 (1)
Unknown	156 (5)
Missing	203 (6)

Characteristic	**N(%)**
Recipient ethnicity - no. (%)	
Hispanic or Latino	321 (10)
Non Hispanic or non-Latino	2641 (80)
Non-resident of the U.S.	215 (7)
Unknown	115 (3)
Missing	5 (0)
Performance score prior to CT - no. (%)	
90-100	1304 (40)
=80	967 (29)
< 80	647 (20)
Missing	379 (11)
ECOG performance status prior to CT - no. (%)	
0 - Asymptomatic	1304 (40)
1 - Symptomatic but completely ambulatory	1480 (45)
2 - Symptomatic, < 50% in bed during the day	126 (4)
3 - Symptomatic, > 50% in bed, but not bedbound	6 (0)
4 - Bedbound	2 (0)
Missing	379 (11)
CT-CI - no. (%)	
0	1025 (31)
1	608 (18)
2	412 (12)
3+	1184 (36)
TBD	13 (0)
Missing	55 (2)

Characteristic	N(%)
Disease related	
Disease classification - no. (%)	
NHL diffuse, large B-cell	802 (24)
Burkitt lym/Burkitt cell leukemia	7 (0)
T-cell / histiocytic rich large B-cell lymphoma	49 (1)
Primary mediastinal large B-cell	82 (2)
Other B-cell	11 (0)
Diffuse, large B-cell lymphoma- Germinal center B-cell type	1132 (34)
Diffuse, large B-cell lymphoma- Activated B-cell type	784 (24)
Primary cutaneous DLBCL, leg type	4 (0)
EBV+ DLBCL, NOS	24 (1)
DLBCL associated with chronic inflammation	1 (0)
High-grade B-cell lymphoma, NOS	62 (2)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	337 (10)
Burkitt-like lymphoma with 11q aberration	2 (0)
IPI at initial diagnosis of the primary disease - no. (%)	
Low	90 (3)
Low intermediate	144 (4)
High intermediate	175 (5)
High	189 (6)
Missing	2699 (82)
Stage of organ involvement at initial diagnosis of the primary disease - no. (%)	
I	235 (7)
II	368 (11)
III	644 (20)

Characteristic	N(%)
IV	1138 (35)
Unknown	468 (14)
Missing	444 (13)
Disease status at CT - no. (%)	
CR	138 (4)
PR	708 (21)
Resistant	2132 (65)
Untreated	198 (6)
Unknown	116 (4)
Missing	5 (0)
c-MYC based on IHC stains at diagnosis - no. (%)	
Negative	377 (11)
Positive	797 (24)
Missing	2123 (64)
c-MYC rearrangement based on FISH at diagnosis - no. (%)	
No	568 (17)
Yes	344 (10)
Not done	104 (3)
Missing	2281 (69)
c-MYC amplification based on FISH at diagnosis - no. (%)	
No	454 (14)
Yes	143 (4)
Not done	417 (13)
Missing	2283 (69)
c-MYC lymphoma at initial diagnosis of the primary disease - no. (%)	

Characteristic	N(%)
Negative	657 (20)
Positive	1164 (35)
Not done	116 (4)
Missing	1360 (41)
Elevated LDH at initial diagnosis of the primary disease - no. (%)	
No	385 (12)
Yes	832 (25)
Missing	2080 (63)
Prior lines of therapies - no. (%)	
No	3 (0)
Yes	3066 (93)
1	2244 (68)
2	75 (2)
>= 3	587 (18)
Missing	160 (5)
Missing	228 (7)
Prior radiation therapy - no. (%)	
No	2011 (61)
Yes	982 (30)
Missing	304 (9)
Prior HCT - no. (%)	
No	2401 (73)
Yes	834 (25)
Prior allo-HCT	41 (1)
Prior auto-HCT	768 (23)

Characteristic	N(%)
Prior auto and allo-HCT	9 (0)
Missing	16 (0)
Missing	62 (2)
Time from HCT to CT, months - median (min-max)	15 (2-315)
CAR-T cell related	
Year of CT - no. (%)	
2017	5 (0)
2018	486 (15)
2019	943 (29)
2020	1085 (33)
2021	778 (24)
Product - no. (%)	
Kymriah	940 (29)
Yescarta	2357 (71)
Time from diagnosis to CT - no. (%)	
Median (min-max)	14 (1-447)
0-6 months	349 (11)
6-12 months	975 (30)
1-2 years	947 (29)
2-3 years	1025 (31)
Missing	1 (0)
Bridging therapy - no. (%)	
No	2103 (64)
Yes	723 (22)
Systemic therapy	543 (16)

Characteristic	N(%)
Intrathecal therapy	29 (1)
Intraocular therapy	1 (0)
Radiation therapy	224 (7)
Surgery	1 (0)
Not reported	471 (14)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)	
No	12 (0)
Yes	3284 (100)
Bendamustine only	126 (4)
Flu+Cy only	3079 (93)
Other	72 (2)
None selected	7 (0)
Missing	1 (0)
None selected	1 (0)
Follow-up, in months - median (range)	13 (1-41)

Response Summary:

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

Q1. Study Title

Potential for G-CSF in preventing infections in CAR-T recipients

Q2. Key Words

G-CSF; infections; CAR-T; CRS

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Muhammad Bilal Abid, MD
Email address:	mabid@mcw.edu
Institution name:	Medical College of Wisconsin
Academic rank:	Assistant Professor of Medicine

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Marcelo Pasquini, MD
Email address:	mpasquini@mcw.edu
Institution name:	Medical College of Wisconsin
Academic rank:	Professor of Medicine

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

- No

Q8. Do you identify as an underrepresented/minority?

- No

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

Marcelo Pasquini, MD

Q10. 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

LETTER OF COMMITMENT:

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

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

I contribute to select CIBMTR studies that are related to infections and CAR-T.

Q13. PROPOSED WORKING COMMITTEE:

- Cellular Immunotherapy for Cancer

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

- Yes

Q14a. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Marcelo Pasquini, MD

Q15. RESEARCH QUESTION:

Does G-CSF worsen immune-mediated toxicities in CAR-T recipients?

Q16. RESEARCH HYPOTHESIS:

With an expansion in the usage of recombinant G-CSF to hasten neutrophil recovery and prevent infections after CAR-T therapy, we hypothesize that myeloid growth factors increase the incidence and/or severity of CRS and ICANS via induction of proinflammatory cytokine secretion from monocytes and macrophages.

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

Suggested word limit of 200 words:

Primary outcome: Cumulative incidence of CRS and ICANS and severity as graded per ASTCT criteria.
Secondary outcomes:
-clinically significant infections and infections density of overall, bacterial, viral, and fungal infections at D+30, and D+100.
-Length of hospital stay.

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

CRS development is directly related to in vivo T-cell expansion and massive production of T-cell effector cytokines, including IL-6, IFN-γ, and granulocyte-macrophage colony-stimulating factor [GM-CSF]). Preclinical data have shown that IL-6, a key cytokine in CRS development, is predominantly produced by monocytes and macrophages. However, clinical data on the utilization of granulocyte-colony stimulating factor (G-CSF) is limited and conflicting in CAR-T therapy. G-CSF drives myeloid precursor proliferation and differentiation and functionally activates phagocytosis through induction of the IgG receptor FcγRI. Recombinant G-CSF is used to hasten neutrophil recovery and prevent infections after allogeneic HCT. However, in the CAR-T setting, myeloid growth factors can potentially increase the incidence and/or severity of CRS and ICANS via induction of proinflammatory cytokine secretion from monocytes and macrophages.
A large dataset such as CIBMTR registry data provides a platform to examine the timely and clinically relevant questions such as GCSF usage in the CAR-T setting.

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

CRS development is directly related to in vivo T-cell expansion and massive production of T-cell effector cytokines, including IL-6, IFN-γ, and granulocyte-macrophage colony-stimulating factor [GM-CSF]). Preclinical data have shown that IL-6, a key cytokine in CRS development, is predominantly produced by monocytes and macrophages. However, clinical data on the utilization of granulocyte-colony stimulating factor (G-CSF) is limited and conflicting in CAR-T therapy. G-CSF drives myeloid precursor proliferation and differentiation and functionally activates phagocytosis through induction of the IgG receptor FcγRI. Recombinant G-CSF is used to hasten neutrophil recovery and prevent infections after allogeneic HCT. However, in CAR-T setting, myeloid growth factors can potentially increase the incidence and/or severity of CRS and ICANS via induction of proinflammatory cytokine secretion from monocytes and macrophages.
To that end, a small single-center study examined the impact of G-CSF in axi-cel recipients with R/R DLBCL. Seven patients (31.8%) received G-CSF upon physician discretion. While the median duration of neutropenia, after LD chemotherapy, was significantly shorter for patients who received G-CSF (5 vs. 15 days, P=0.016), there was no difference in the incidence and severity of infection based on G-CSF use. Interestingly, while there was no significant difference in the incidence of developing CRS or ICANS between the 2 groups, there was a significant increase in CRS severity for patients that received filgrastim compared to those that did not (P=0.042).
In another single-center study examining 70 axi-cel and tisa-cel recipients with R/R DLBCL, 42 (60%) received prophylactic G-CSF and 28 (40%) did not receive G-CSF. While there was no difference between the 2 groups in terms of duration of neutropenia and infections, the patients in the G-CSF group were older (63 vs 50 years, P=0.002), and had lower neutrophil count at day+0 as well as at day+5. Most patients in the study experienced grades 1-2 CRS, and there was no difference between the 2 groups in terms of incidence and severity of CRS. Similarly, 30% of patients experienced ICANS with no significant difference between the 2 groups.
Overall, the role of recombinant G-CSF to aid neutrophil recovery in CAR-T setting remain unexplored. Larger registry data such as CIBMTR affords an opportunity of comparing the efficacy, in preventing infections, and toxicity, in G-CSF potential to worsen the on-target-off-tumor CAR-T effects, in homogeneous patient cohorts.

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

N/A

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

All adult axi-cel recipients. Divide into 2 groups and compare outcomes:
1) GCSF recipients.
2) Non-GCSF recipients.

Q21. Does this study include pediatric patients?

- No

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

Different disease, disease biology, immune status, and toxicity profiles.

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

N/A

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

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

N/A

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

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

N/A

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

N/A

Q26. REFERENCES:

1. Meir J, Abid MA, Abid MB. STATE OF THE CAR-T: Risk of Infections with CAR-T Therapy and Determinants of SARS-CoV-2 Vaccine Responses. Transplant Cell Ther 2021.
2. Giavridis T, van der Stegen SJC, Eyquem J, Hamieh M, Piersigilli A, Sadelain M. CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. Nat Med 2018; 24:731-738.
3. Norelli M, Camisa B, Barbiera Get al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. Nat Med 2018; 24:739-748.
4. Sterner RM, Sakemura R, Cox MJet al. GM-CSF inhibition reduces cytokine release syndrome and neuroinflammation but enhances CAR-T cell function in xenografts. Blood 2019; 133:697-709.
5. Sachdeva M, Duchateau P, Depil S, Poirot L, Valton J. Granulocyte-macrophage colony-stimulating factor inactivation in CAR T-cells prevents monocyte-dependent release of key cytokine release syndrome mediators. J Biol Chem 2019; 294:5430-5437.
6. Mehta HM, Malandra M, Corey SJ. G-CSF and GM-CSF in Neutropenia. J Immunol 2015; 195:1341-1349.
7. Battiwalla M, McCarthy PL. Filgrastim support in allogeneic HSCT for myeloid malignancies: a review of the role of G-CSF and the implications for current practice. Bone Marrow Transplant 2009; 43:351-356.
8. Smith TJ, Bohlke K, Lyman GHet al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015; 33:3199-3212.
9. Gaut D, Tang K, Sim MS, Duong T, Young P, Sasine J. Filgrastim associations with CAR T-cell therapy. Int J Cancer 2021; 148:1192-1196.
10. Galli E, Allain V, Di Blasi Ret al. G-CSF does not worsen toxicities and efficacy of CAR-T cells in refractory/relapsed B-cell lymphoma. Bone Marrow Transplantation 2020; 55:2347-2349.

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

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

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

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

N/A

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

Embedded Data:

N/A

2110-35: Adult patients undergoing 1st Axi-Cel infusion, 2016-present

Characteristic	N(%)
No. of patients	2556
No. of centers	105
Patient related	
Age at infusion, by category - no. (%)	
Median (min-max)	62 (18-91)
18-29	72 (3)
30-39	159 (6)
40-49	258 (10)
50-59	621 (24)
60-69	942 (37)
>= 70	504 (20)
Recipient Sex - no. (%)	
Male	1608 (63)
Female	948 (37)
Recipient race - no. (%)	
White	2025 (79)
African-American	131 (5)
Asian	138 (5)
Pacific Islander	8 (0)
Native American	12 (0)
More than one race	20 (1)
Unknown	122 (5)
Missing	100 (4)

Characteristic	N(%)
Recipient ethnicity - no. (%)	
Hispanic or Latino	280 (11)
Non Hispanic or non-Latino	2102 (82)
Non-resident of the U.S.	87 (3)
Unknown	84 (3)
Missing	3 (0)
Performance score prior to CT - no. (%)	
90-100	1063 (42)
=80	749 (29)
< 80	467 (18)
Missing	277 (11)
ECOG performance status prior to CT - no. (%)	
0 - Asymptomatic	1063 (42)
1 - Symptomatic but completely ambulatory	1115 (44)
2 - Symptomatic, < 50% in bed during the day	94 (4)
3 - Symptomatic, > 50% in bed, but not bedbound	7 (0)
Missing	277 (11)
CT-CI - no. (%)	
0	797 (31)
1	488 (19)
2	326 (13)
3+	880 (34)
TBD	11 (0)
Missing	54 (2)
Disease related	

Characteristic	**N(%)**
Disease classification - no. (%)	
NHL follicular,predominantly small cleaved cell	18 (1)
NHL follicular,mixed,small cleaved and large cell	47 (2)
NHL diffuse, large B-cell	531 (21)
Burkitt lym/Burkitt cell leukemia	3 (0)
NHL mantle cell	10 (0)
Primary CNS lymphoma	2 (0)
T-cell / histiocytic rich large B-cell lymphoma	34 (1)
Nodal marginal zone B-cell	3 (0)
Splenic marginal zone B-cell	1 (0)
Primary mediastinal large B-cell	70 (3)
Other B-cell	15 (1)
Intravascular large B-cell lymphoma	3 (0)
B-cell unclass. between DLBCL and hodgkin	8 (0)
Follicular, predominantly large cell Grade IIIA	29 (1)
Follicular, predominantly large cell Grade IIIB	12 (0)
Follicular unknown grade	21 (1)
Follicular, predominantly large cell (Grade IIIA vs IIIB not specified)	4 (0)
Diffuse, large B-cell lymphoma- Germinal center B-cell type	850 (33)
Diffuse, large B-cell lymphoma- Activated B-cell type	562 (22)
Primary cutaneous DLBCL, leg type	2 (0)
EBV+ DLBCL, NOS	17 (1)
DLBCL associated with chronic inflammation	1 (0)
High-grade B-cell lymphoma, NOS	44 (2)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	233 (9)

Characteristic	N(%)
Large B-cell lymphoma with IRF4 rearrangement	1 (0)
Burkitt-like lymphoma with 11q aberration	2 (0)
Plasmablastic lymphoma	3 (0)
Polymorphic PTLD	1 (0)
Monomorphic PTLD (B- and T- / NK-cell types)	5 (0)
Missing	24 (1)
IPI at initial diagnosis of the primary disease - no. (%)	
Low	67 (3)
Low intermediate	117 (5)
High intermediate	134 (5)
High	135 (5)
Missing	2103 (82)
Stage of organ involvement at initial diagnosis of the primary disease - no. (%)	
I	179 (7)
II	284 (11)
III	477 (19)
IV	924 (36)
Unknown	359 (14)
Missing	333 (13)
Disease status at CT - no. (%)	
CR	81 (3)
PR	532 (21)
Resistant	1669 (65)
Untreated	163 (6)
Unknown	82 (3)

Characteristic	N(%)
Missing	29 (1)
Prior radiation therapy - no. (%)	
No	1580 (62)
Yes	750 (29)
Missing	226 (9)
Prior HCT - no. (%)	
No	1853 (72)
Yes	655 (26)
Prior allo-HCT	33 (1)
Prior auto-HCT	604 (24)
Prior auto and allo-HCT	7 (0)
Missing	11 (0)
Missing	48 (2)
Time from HCT to CT, months - median (min-max)	15 (0-315)
CAR-T cell related	
Prior lines of therapies - no. (%)	
No	2 (0)
Yes	2382 (93)
1	1737 (68)
2	46 (2)
>= 3	490 (19)
Missing	109 (4)
Missing	172 (7)
Year of CT - no. (%)	
2017	6 (0)

Characteristic	N(%)
2018	445 (17)
2019	727 (28)
2020	752 (29)
2021	626 (24)
Product - no. (%)	
Yescarta	2556 (100)
Time from diagnosis to CT - no. (%)	
Median (min-max)	15 (1-447)
0-6 months	266 (10)
6-12 months	735 (29)
1-2 years	713 (28)
2-3 years	818 (32)
Missing	24 (1)
Bridging therapy - no. (%)	
No	1698 (66)
Yes	507 (20)
Systemic therapy	386 (15)
Intrathecal therapy	17 (1)
Intraocular therapy	1 (0)
Radiation therapy	155 (6)
Surgery	1 (0)
Not reported	351 (14)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)	
No	7 (0)
Yes	2549 (100)

Characteristic	**N(%)**
Bendamustine only	9 (0)
Flu+Cy only	2504 (98)
Other	33 (1)
None selected	3 (0)
Follow-up, in months - median (range)	13 (1-41)

Response Summary:

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

Q1. Study Title

Effect of renal dysfunction on outcomes in Chimeric Antigen Receptor T-Cell Therapy

Q2. Key Words

CAR-T
Renal dysfunction
eGFR

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Hemant Murthy
Email address:	murthy.hemant@mayo.edu
Institution name:	Mayo Clinic Florida
Academic rank:	Associate Professor of Medicine

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

- No

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Madiha Iqbal
Email address:	Iqbal.madiha@mayo.edu
Institution name:	Mayo Clinic Florida
Academic rank:	Assistant Prof of Medicine

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

- Yes

Q8. Do you identify as an underrepresented/minority?

- No

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

Hemant Murthy

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

N/A

LETTER OF COMMITMENT:

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

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

Hemant Murthy
CK 19-01
LK 19-01
LK 20-03
Madiha Iqbal
LK 20-03

Q13. PROPOSED WORKING COMMITTEE:

- Cellular Immunotherapy for Cancer

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

- No

Q15. RESEARCH QUESTION:

what is the Effect of renal dysfunction on outcomes in Chimeric Antigen Receptor T-Cell Therapy

Q16. RESEARCH HYPOTHESIS:

Estimated GFR (eGFR) is predictive of toxicities and outcomes in CAR-T recipients

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

Suggested word limit of 200 words:

1. To assess the impact of renal dysfunction as measured by eGFR on survival of recipients of CAR-T therapy
2. To assess the impact of renal dysfunction as measured by eGFR on toxicities and complications of recipients of CAR-T therapy including CRS, ICANS and post CAR-T cytopenias

OUTCOMES:

• Primary outcome

o Overall survival (OS): time to death of any cause will be an event for this outcome. Patients will be censored at time of last follow up.

• Secondary outcomes:

o CAR-T toxicity

• CRS: Grades II-IV and Grades III-IV CRS according to ASTCT criteria will be the events for this outcome.

• Immune effector cell-associated neurotoxicity syndrome (ICANS): Grades II-IV and III-IV ICANS according to ASTCT criteria will be the events for this outcome.

o Hematologic recovery and cytopenias after CAR T

Neutrophil recovery: The event is defined according to the time to initial ANC recovery (>500/mm3). Death without initial neutrophil recovery is a competing event.

Platelet recovery: The event is defined according to the time to initial platelet recovery (≥20 x 109/L). Death without initial platelet recovery is a competing event.

Prevalence of neutropenia at 90 days and 180 days.

Prevalence of thrombocytopenia at 90 days and 180 days

o Clinical Outcomes

• Overall Response Rate:

• Progression Free Survival

• Relapse rate

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

Given the increasing utilization of CAR-T in real world scenarios and lack of patients with renal dysfunction enrolled in registration studies, the need to better refine and predict for toxicities based on pre-CAR-T comorbidities and risk of fludarabine toxicities in patients with renal dysfunction, we propose this study to be conducted through the CIBMTR. The CIBMTR is well positioned to perform such a study given the recent efforts in investigating effect of eGFR on outcomes of allo-HCT. The impact of this proposal will help with optimizing prediction of transplant related toxicities and outcomes in CAR-T recipients with renal dysfunction receiving Flu containing. The hope with such a study may provide guidance in treatment of patients with renal dysfunction being considered for CAR-T therapy and potentially for Flu conditioning dosing in CAR-T recipients with renal insufficiency.

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

CAR-T therapy has been a transformative treatment modality for patients with relapsed/refractory hematological malignancies including various subtypes of non-Hodgkin lymphoma and acute lymphoblastic leukemia(1–4). CAR-T therapy is associated with its unique toxicities such as cytokine release syndrome (CRS) and immune effector associated cell neurotoxicity (ICANS). As CAR-T usage increases and FDA indication increase, there exists a need to examine predictors of CAR-T toxicities and survival, notably prior to CAR-T infusion.

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). However, the use of Cr is not ideal as a true assessment of renal dysfunction. Recently a large CIBMTR analysis demonstrated that degree of renal dysfunction defined by eGFR, independently predicted both overall survival and treatment related mortality in those who received Allo-HCT(5).

The purine analog fludarabine (Flu) is immunosuppressive and has activity against many hematological malignancies. It is widely utilized with cyclophosphamide as the lymphodepletion regimen administered prior to CAR-T infusion. Flu is a prodrug that is rapidly dephosphorylated to the free nucleoside 9-β-Darabinosyl-2-fluoroadenine (F-ara-A) in erythrocytes and endothelial cells. Flu has a half-life of about 20 hours and it is largely eliminated by renal excretion (60% during first 24 hours). A CALGB study, suggested that reduced creatinine clearance is a risk factor for Flu toxicity(6) however it is also reported that flu can be safely used in CKD if the dose is adjusted for creatinine clearance(7). Flu toxicities, have been reported in the literature(8,9). Neurologic toxicities notably have been attributed to Flu based conditioning. 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 (ATL), other leukoencephalopathy (OL) and posterior reversible encephalopathy syndrome (PRES). Risk factors identified include older age, poor renal function, Flu dose, and previously treated central nervous system (CNS) disease(9).

Given the increasing utilization of CAR-T in real world scenarios and lack of patients with renal dysfunction enrolled in registration studies, the need to better refine and predict for toxicities based on pre-CAR-T comorbidities and risk of fludarabine toxicities in patients with renal dysfunction, we propose this study to be conducted through the CIBMTR.

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

[Click here]

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

all car-t recipients captured through CIBMTR

Q21. Does this study include pediatric patients?

- Yes

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

Patient-related:
- Age at receipt of CAR-T therapy: continuous & by age group: decades
- Patient sex: male vs. female
- Karnofsky performance status at transplant: ≥ 90 vs. < 90 vs. missing
- Race: Caucasian vs. others vs. missing
- Body mass index
- eGFR (eGFR ≥ 90ml/min (to be used as reference), eGFR 60-90ml/min, eGFR 45-59ml/min and eGFR <45ml/min)

Disease-related:
- Disease subtype: Lymphoma (Large-B-cell lymphoma, follicular lymphoma, mantle cell lymphoma) vs. Multiple Myeloma vs. acute lymphoblastic leukemia
- Number of prior lines of therapy prior to CAR-T
- Disease stage at CAR-T
- Disease status at time of transplant: CR vs PR vs SD vs PD
- Chemorefractory disease at the time of CAR-T (Y vs. N)
- Bridging therapy pre-CAR T
- Hematopoietic cell transplant pre-CAR-T (autologous vs. allogeneic)

CAR-T related:
- Axi-cel vs. tisa-cel vs. liso-cel vs.brexu-cel vs. ida-cel
- Fludarabine dose (mg/m2) as part of lymphodepletion regimen
- Maximum grade of CRS
- Number of doses of tocilizumab prescribed for CRS
- Steroid requirement for the management of CRS
- Maximum grade of ICANS
- Steroids prescribed 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

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

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

N/A

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

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

N/A

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

N/A

Q26. REFERENCES:

1. 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 Dec 28;377(26):2531–2544.
2. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020 Sep 19;396(10254):839–852.
3. 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 Jan 3;380(1):45–56.
4. Shah BD, Ghobadi A, Oluwole OO, Logan AC, Boissel N, Cassaday RD, 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 Jun 3;
5. Farhadfar N, Dias A, Wang T, Fretham C, Chhabra S, Murthy HS, et al. Impact of Pretransplantation Renal Dysfunction on Outcomes after Allogeneic Hematopoietic Cell Transplantation. Transplantation and Cellular Therapy. 2021 May;27(5):410–422.
6. Martell RE, Peterson BL, Cohen HJ, Petros WP, Rai KR, Morrison VA, et al. Analysis of age, estimated creatinine clearance and pretreatment hematologic parameters as predictors of fludarabine toxicity in patients treated for chronic lymphocytic leukemia: a CALGB (9011) coordinated intergroup study. Cancer Chemother Pharmacol. 2002 Jul;50(1):37–45.
7. Lichtman SM, Etcubanas E, Budman DR, Eisenberg P, Zervos G, D'Amico P, et al. The pharmacokinetics and pharmacodynamics of fludarabine phosphate in patients with renal impairment: a prospective dose adjustment study. Cancer Invest. 2002;20(7-8):904–913.
8. Navarro CE, Rodríguez PJ, Espitia OM. Fludarabine-Induced Posterior Reversible Encephalopathy Syndrome in a Pediatric Patient With β-Thalassemia: Case Report and Literature Review. Clin Neuropharmacol. 2018;41(6):224–229.
9. Beitinjaneh A, McKinney AM, Cao Q, Weisdorf DJ. Toxic leukoencephalopathy following fludarabine-associated hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2011 Mar;17(3):300–308.

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

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

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

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

N/A

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

Embedded Data:

N/A

Response Summary:

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

Q1. Study Title

Chimeric Antigen Receptor T- cell therapy in patients with hematological malignancy and chronic kidney disease

Q2. Key Words

CART, real world experience, chronic kidney disease, CKD

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	sairah ahmed MD
Email address:	sahmed3@mdanderson.org
Institution name:	MD Anderson Cancer Center
Academic rank:	associate professor

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

- No

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Paolo Strati MD
Email address:	pstrati@mdanderson.org
Institution name:	MDACC
Academic rank:	assistant professor

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

- Yes

Q8. Do you identify as an underrepresented/minority?

- No

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

sairah ahmed

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

N/A

LETTER OF COMMITMENT:

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

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

co-PI for BPDCN analysis

Q13. PROPOSED WORKING COMMITTEE:

- Cellular Immunotherapy for Cancer

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

- No

Q15. RESEARCH QUESTION:

- Evaluate the overall safety and efficacy of CAR-T cell in patients with chronic kidney disease.

Q16. RESEARCH HYPOTHESIS:

Chimeric antigen receptor (CAR) T-cell was approved by FDA in 2017 for treatment of relapsed or refractory large B cell lymphoma (r/r LBCL), however patients treated on clinical trial were required to have normal renal function. To date there is no published data regarding the use of CAR T-cell therapy in patients with reduced kidney function despite the prevalence of chronic kidney disease in lymphoma patients.
The research hypothesis would be that safety and efficacy of CAR T-cell therapy in LBCL patients with decreased kidney function will be similar to those patients who have normal kidney function and potentially dose reduction may lead to change in outcomes. There may be an impact on toxicity and NRM for patients with CKD who receive CART

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

Suggested word limit of 200 words:

Primary objective:
Evaluate the impact of conditioning chemotherapy dose and CKD stage on OS and PFS in patients receiving commercial CART cell therapy for LBCL
Secondary Objective:
Evaluate treatment related toxicity including prolonged cytopenias, mortality, and degree of progression of renal dysfunction in patients who have pre-existing CKD
Neutrophil and platelet engraftment: Neutrophil recovery defined as the first of 3 successive days with absolute neutrophil count (ANC) ≥500/µL after post-infusion nadir. Platelet recovery defined as achieving platelet counts ≥20,000/µL for at least 7 days, unsupported by transfusion. For neutrophil and platelet recovery, death without the event is considered a competing risk.
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.
Relapse/progression: Progressive disease or recurrences of disease would be counted as events. NRM will be considered competing event.
Overall response rate: Complete response or partial response per Lugano criteria (ref: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014; 32: 3059–68.)
Progression-free survival (PFS): Survival without recurrence or tumor progression. Recurrence or progression of disease or death would be counted as events.
Overall survival (OS): Time to death. Death from any cause will be considered an event.
Prolonged Cytopenias: count recovery at 15 days, 30 days, 3 months and 6 months post infusion of CART cell therapy

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

potentially would affect dosing of lymphodepletion chemotherapy

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

CAR-T cell therapy was FDA approved in 2017 for treatment of relapsed or refractory large B cell lymphoma (r/r LBCL) after two or more lines of systemic therapy. Enrolled patients in the trial had adequate kidney function, defined as serum creatinine ≤1.5 mg/dl or creatinine clearance ≥ 60 ml/min/1.73 m2. To improve CAR-T cell efficacy, conditioning lymphodepleting chemotherapy is given prior to cells infusion. This regimen includes chemotherapy agents generally composed of fludarabine and cytarabine . As their clearance is strongly correlated with creatinine clearance, a dose reduction is generally recommended in patients with kidney insufficiency to avoid high exposure. Prior reports have associated high exposure to fludarabine with increased toxicity and treatment related mortality.
Over the past 3 years CAR-T cell therapy utilization was expanded into moderate CKD population with r/r LBCL, however the data in this population is limited by small sample size. To date, no published reports evaluated the toxicity and clinical outcome in lymphoma and leukemia patients with moderate CKD who received standard vs. reduced dose of conditioning chemotherapy and CAR-T cell therapy.

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

N/A

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

Male or female patients greater than 18 years of age who have been treated from January 01, 2015 to March 15, 2021 and received CAR-T cell therapy (tisagenlecleucel, lisocabtagene maraleucel, axicabtagene ciloleucel, or brexucabtagene) for the diagnosis of large B cell lymphoma (LBCL), acute lymphoblastic leukemia (ALL), follicular lymphoma, or mantle cell lymphoma

Q21. Does this study include pediatric patients?

- No

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

CKD is rare in pediatric patients

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

Patient-related:
- Age at CART infusion
- Gender: male or female
- Karnofsky performance status at CART infusion: < 80% vs. ≥ 80%
- HCT comorbidity index at CART cell infusion 0, 1, 2, and ≥ 3
- Charleston comorbidity index variables
- Additional markers
o LDH,
o baseline inflammatory markers (IL-6, IL-2, serum ferritin, interferon gamma, C reactive protein)
o thrombocytopenia
o neutropenia
o lymphopenia
o anemia
o history of CNS disease
o history of neurological disorder

Disease-related:
- Prior autologous HCT (yes vs. no)
- Primary refractory vs. relapsed disease
- Number of prior therapy (before transplant): 2-3 vs. >3
- Dosage of the conditioning chemotherapy
- Disease status at the time of CART: chemoresponsive vs. non-responsive/refractory
- Bridging therapy prior to CART (yes/no)
- Extra nodal involvement at the time of prior relapse or PD (yes / no)
- Length of prior CR1 (<= 12 vs. >12 months)
- B symptoms at the time of prior relapse or PD (yes / no)
- Volume of disease generally defined as bulk (>10cm yes or no)

Disease treatment-related:
- Complications related to CAR-T cell therapy CRS, ICANS (ASTCT grading system)
- Side effects related to conditioning chemotherapy (sepsis, any other organ dysfunction beyond expected for CART (respiratory, cardiac, hepatic,etc)
- Duration of hospitalization post CAR-T cell therapy
- Prolonged cytopenia
- Disease status

Chronic kidney disease-related:
- Serum creatinine 1 to 4 weeks prior to receiving the conditioning chemotherapy.
- Serum creatinine level weekly for 4 weeks post CAR-T cell infusion
- Estimated glomerular filtration rate.
- Etiology for CKD
- hx of Hypertension

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

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

NA

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

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

NA

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

NA

Q26. REFERENCES:

References

Ubukata et al. Prevalence and mortality of chronic kidney disease in lymphoma patients: A large retrospective cohort study. Medicine. 2018;97(2): e9615.

Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017; 377:2531-2544.

Gutgarts et al. Acute kidney injury after CAR-T cell therapy: low incidence and rapid recovery. Biol Blood Marrow Transplant. 2020; 26: 1071-1076

Long-Boyle et al. High fludarabine exposure and relationship with treatment-related mortality after nonmyeloablative hematopoietic cell transplantation. Bone Marrow Transplant. 2011 Jan; 46(1): 20–26.

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

1. Employment (such as an independent contractor, consultant or providing expert testimony)?

2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?

3. Ownership (such as equity, ownership or financial interests)?

4. Transactions (such as honoraria, patents, royalties and licenses)?

5. Legal (such as pending or current arbitration or legal proceedings)?

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

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

N/A

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

Embedded Data:

N/A

2110-151 & 2110-242: Patients undergoing 1st commercial CAR-T with Renal Comorbidity, 2016-present

Characteristic	N(%)
Number of patients with Renal Comorbidity since 2016	86
No. of centers	40
Total Number of patients since 2016	4458
Patient related	
Age at infusion, by category - no. (%)	
Median (min-max)	65 (23-83)
18-29	1 (1)
30-39	5 (6)
40-49	9 (10)
50-59	17 (20)
60-69	26 (30)
>= 70	28 (33)
Recipient Sex - no. (%)	
Male	66 (77)
Female	20 (23)
Recipient race - no. (%)	
White	65 (76)
African-American	7 (8)
Asian	3 (3)
Pacific Islander	1 (1)
More than one race	1 (1)
Unknown	2 (2)
Missing	7 (8)

Characteristic	N(%)
Recipient ethnicity - no. (%)	
Hispanic or Latino	7 (8)
Non Hispanic or non-Latino	72 (84)
Non-resident of the U.S.	7 (8)
Performance score prior to CT - no. (%)	
90-100	26 (30)
=80	21 (24)
< 80	23 (27)
Missing	16 (19)
ECOG performance status prior to CT - no. (%)	
0 - Asymptomatic	26 (30)
1 - Symptomatic but completely ambulatory	38 (44)
2 - Symptomatic, < 50% in bed during the day	3 (3)
3 - Symptomatic, > 50% in bed, but not bedbound	1 (1)
4 - Bedbound	2 (2)
Missing	16 (19)
CT-CI - no. (%)	
2	9 (10)
3+	77 (90)
Disease related	
Disease - no. (%)	
Non-Hodgkin lymphoma (NHL)	86 (100)
Elevated LDH at initial diagnosis of the primary disease - no. (%)	
No	11 (13)
Yes	25 (29)

Characteristic	N(%)
Missing	50 (58)
IPI at initial diagnosis of the primary disease - no. (%)	
Low	1 (1)
Low intermediate	5 (6)
High intermediate	8 (9)
High	6 (7)
Missing	66 (77)
Prior lines of therapies - no. (%)	
Yes	79 (92)
1	66 (77)
2	1 (1)
>= 3	7 (8)
Missing	5 (6)
Missing	7 (8)
Prior radiation therapy - no. (%)	
No	55 (64)
Yes	22 (26)
Missing	9 (10)
Prior HCT - no. (%)	
No	71 (83)
Yes	14 (16)
Prior auto-HCT	14 (16)
Missing	1 (1)
Time from HCT to CT, months - median (min-max)	26 (9-97)
CAR-T cell related	

Characteristic	**N(%)**
Year of CT - no. (%)	
2018	7 (8)
2019	24 (28)
2020	32 (37)
2021	23 (27)
Product - no. (%)	
Kymriah	27 (31)
Yescarta	55 (64)
Tecartus	4 (5)
CRS Prophylaxis - no. (%)	
No:	28 (33)
Yes:	3 (3)
Tocilizumab	1 (1)
Other	1 (1)
Not reported	55 (64)
Time from diagnosis to CT - no. (%)	
Median (min-max)	15 (2-131)
0-6 months	13 (15)
6-12 months	20 (23)
1-2 years	27 (31)
2-3 years	26 (30)
Bridging therapy - no. (%)	
No	57 (66)
Yes	17 (20)
Systemic therapy	15 (17)

Characteristic	**N(%)**
Intrathecal therapy	1 (1)
Radiation therapy	3 (3)
Not reported	12 (14)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)	
Yes	86 (100)
Bendamustine only	3 (3)
Flu+Cy only	77 (90)
Other	5 (6)
None selected	1 (1)
Follow-up, in months - median (range)	12 (1-34)

Response Summary:

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

Q1. Study Title

Pre-emptive and early tocilizumab usage and risk of infections in patients receiving CAR-T therapy

Q2. Key Words

Tocilizumab; IL-6 blockade; CAR-T; infections

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Muhammad Bilal Abid, MD
Email address:	mabid@mcw.edu
Institution name:	Medical College of Wisconsin
Academic rank:	Assistant Professor of Medicine

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Marcelo Pasquini, MD
Email address:	mpasquini@mcw.edu
Institution name:	Medical College of Wisconsin
Academic rank:	Professor of Medicine

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

- No

Q8. Do you identify as an underrepresented/minority?

- No

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

Marcelo Pasquini, MD

Q10. 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

LETTER OF COMMITMENT:

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

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

I contribute to select CIBMTR studies that are related to infections and CAR-T.

Q13. PROPOSED WORKING COMMITTEE:

- Cellular Immunotherapy for Cancer

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

- Yes

Q14a. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Marcelo Pasquini, MD

Q15. RESEARCH QUESTION:

Does tocilizumab usage increase the risk of infections in patients receiving CAR-T therapy?

Q16. RESEARCH HYPOTHESIS:

With an expansion in the usage of cytokine-directed biologics and ongoing trials, we hypothesize that tocilizumab usage for CRS grade 1 as well as for prophylaxis is associated with an increased risk of infections.

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

Suggested word limit of 200 words:

Primary: Cumulative incidence of clinically significant infections and infections density of overall, bacterial, viral, and fungal infections at D+30, and D+100.

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

The safety endpoints in ongoing immunotherapy trials needs re-evaluation. Whether early or preemptive corticosteroids and immunomodulators should continue to be used to mitigate chimeric antigen receptor T-cells (CAR-T) toxicities when this is associated with increased risk of infections and diminished vaccine responses, remain a timely question and likely needs a balancing. While the earlier CIBMTR study did show an association between tocilizumab usage and infections, the analysis was limited by small numbers and highly select patients with grade 1 CRS. Systematic examination of infection risks conferred by tocilizumab, in a larger sample, will allow estimation of the real risk and will aid in adapting to the morphing pandemic.

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

The safety endpoints in ongoing immunotherapy trials needs re-evaluation. Whether early or preemptive corticosteroids and immunomodulators should continue to be used to mitigate chimeric antigen receptor T-cells (CAR-T) toxicities when this is associated with increased risk of infections and diminished vaccine responses, remain a timely question and likely needs a balancing act. To that end, several pivotal clinical trials and ongoing studies are examining the effectiveness of preemptive administration of corticosteroids and tocilizumab in reducing the incidence of CAR-T-related toxicities. Evolving studies are further demonstrating that early corticosteroid and tocilizumab usage may not impact the expansion, persistence, and efficacy of CAR T-cells.

On the other hand, extensive data demonstrate a heightened risk of infections with CAR T-cell therapy. While this risk is dependent upon several factors, including CRS severity, the use of corticosteroids and tocilizumab have independently been shown to confer an increased risk of infections. The association of the cumulative dose and duration of corticosteroids and increased risk of infections has been demonstrated in several studies examining CD19-directed CAR T-cells. This is important to consider as infections are among the commonest causes of mortality in CAR-T recipients, second only to relapse of the underlying disease.

In the era of an ongoing pandemic and continuous emergence of variants of concern, CAR-T research and clinical care need redirection. As B-cell aphasia is used as a clinical surrogate of CAR-T persistence and durability, the primary focus of designing sophisticated and durable CARs may not be a clinically meaningful goal when patients are, by design, predisposed to infections for prolonged durations. The unexplored complication of prolonged cytopenia further compounds the toxicity profile and brings the durability endpoint into question.

Further, immunocompromised patients are at a higher risk for the shedding of the replication-incompetent virus. Prolonged usage of corticosteroids has been shown to impact viral kinetics in a similar manner. Importantly, evolving data related to vaccine responses in cancer patients suggest that humoral immune responses may be significantly blunted in CAR-T recipients. The response rates reported so far have ranged between 14% - 36% in CD19+CAR-T recipients. And cellular responses to the COVID-19 vaccine remain to be elucidated. Corticosteroid usage, again, is being identified as one of the key culprits of diminished vaccine responses in CAR-T patients.

Since the previous CIBMTR analysis was limited in terms of sample size and highly select population with grade 1 CRS, a revised analysis is imperative with a larger sample. This will allow estimation of the real risk and will aid in adapting to the morphing pandemic. This will also allow appropriate prophylactic and surveillance guidelines leading to improved patient outcomes.

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

N/A

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

All adult CAR-T recipients. May consider including only those patients who developed grade 1 CRS as there might be few patients with grade ≥2 CRS who did not receive tocilizumab, and most also received other immune-suppressive agents, such as corticosteroids, which could confound the analysis.

Q21. Does this study include pediatric patients?

- No

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

Different disease, disease biology, immune status, and toxicity profiles.

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

N/A

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

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

N/A

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

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

N/A

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

N/A

Q26. REFERENCES:

1. Frigault MJ, Nikiforow S, Mansour MK, et al. Tocilizumab not associated with increased infection risk after CAR T-cell therapy: implications for COVID-19?. Blood. 2020;136(1):137-139. doi:10.1182/blood.2020006216.
2. Abid MB, Mughal M, Abid MA. Coronavirus Disease 2019 (COVID-19) and Immune-Engaging Cancer Treatment. JAMA Oncol 2020.
2. Topp MS, van Meerten T, Houot Ret al. Earlier corticosteroid use for adverse event management in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol 2021.
3. Gardner RA, Ceppi F, Rivers Jet al. Preemptive mitigation of CD19 CAR T-cell cytokine release syndrome without attenuation of antileukemic efficacy. Blood 2019; 134:2149-2158.
4. Caimi PF, Ahmed N, Rojas Pet al. Prophylactic tocilizumab before CD3/4-1bb anti-CD19 car-T cell infusion decreases incidence of severe crs without increased risk of neurotoxicity. Cytotherapy 2020; 22:S16-S17.
5. Liu S, Deng B, Yin Zet al. Corticosteroids do not influence the efficacy and kinetics of CAR-T cells for B-cell acute lymphoblastic leukemia. Blood cancer journal 2020; 10:15-15.
6. Sun Z, Xun R, Liu M, Wu X, Qu H. The Association Between Glucocorticoid Administration and the Risk of Impaired Efficacy of Axicabtagene Ciloleucel Treatment: A Systematic Review. Frontiers in Immunology 2021; 12.
7. Meir J, Abid MA, Abid MB. STATE OF THE CAR-T: Risk of Infections with CAR-T Therapy and Determinants of SARS-CoV-2 Vaccine Responses. Transplant Cell Ther 2021.
8. Kambhampati S, Fakhri B, Sheng Yet al. Infectious Complications of BCMA-Targeted and CD19-Targeted Chimeric Antigen Receptor T-Cell Immunotherapy. Blood 2020; 136:4-5.
9. Abid MA, Nunley L, Abid MB. Could Coronavirus Disease 2019 (COVID-19) Render Natural Immunity to Re-infections? A Spotlight on the Therapeutic Pipeline. Front Immunol 2020; 11:1294.
10. Aydillo T, Gonzalez-Reiche AS, Aslam Set al. Shedding of Viable SARS-CoV-2 after Immunosuppressive Therapy for Cancer. N Engl J Med 2020; 383:2586-2588.
11. Abid MB, Chhabra S, Buchan Bet al. Bronchoalveolar lavage-based COVID-19 testing in patients with cancer. Hematol Oncol Stem Cell Ther 2020.
12. Vormehr M, Lehar S, Kranz LMet al. Dexamethasone premedication suppresses vaccine-induced immune responses against cancer. Oncoimmunology 2020; 9:1758004.
13. Dhakal B, Abedin SM, Fenske TSet al. Response to SARS-CoV-2 vaccination in patients after hematopoietic cell transplantation and CAR-T cell therapy. Blood 2021.
14. Ram R, Hagin D, Kikozashvilli Net al. Safety and Immunogenicity of the BNT162b2 mRNA COVID-19 Vaccine in Patients after Allogeneic HCT or CD19-based CART therapy-A Single-Center Prospective Cohort Study. Transplant Cell Ther 2021.
15. Ranganathan R, Shou P, Ahn Set al. CAR T cells Targeting Human Immunoglobulin Light Chains Eradicate Mature B-cell Malignancies While Sparing a Subset of Normal B Cells. Clinical Cancer Research 2021.

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

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

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

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

N/A

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

Embedded Data:

N/A

Response Summary:

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

Q1. Study Title

Impact of Prophylactic Anti-epileptics on Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) in Recipients of CAR T-cell Therapy

Q2. Key Words

Anti-epileptic medications, Levetiracetam, ICANS, neurotoxicity, CAR T-cell therapy

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Jiasheng Wang, MD
Email address:	jxw1170@case.edu
Institution name:	University Hospitals Cleveland Medical Center/ Case Western Reserve University
Academic rank:	Hematology/ Oncology Fellow

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Leland Metheny, MD
Email address:	Leland.Metheny@UHhospitals.org
Institution name:	University Hospitals Cleveland Medical Center/ Case Western Reserve University
Academic rank:	Assistant Professor of Medicine

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

- No

Q8. Do you identify as an underrepresented/minority?

- No

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

Jiasheng Wang, MD

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

N/A

LETTER OF COMMITMENT:

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

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

None

Q13. PROPOSED WORKING COMMITTEE:

- Cellular Immunotherapy for Cancer

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

- No

Q15. RESEARCH QUESTION:

Will the use of prophylactic anti-epileptics reduce the incidence and severity of ICANS following CAR T-cell infusion?

Q16. RESEARCH HYPOTHESIS:

Prophylactic use of anti-epileptics is associated with fewer and less severe ICANS following CAR T-cell infusion.

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

Suggested word limit of 200 words:

Primary Aim
1. Compare the incidence and severity of ICANS based on whether patients have received prophylactic anti-epileptics.
Secondary aims
1. Describe the manifestations, onset and resolution time, and management methods of ICANS following CAR T-cell infusion based on whether patients have received prophylactic anti-epileptics.
2. Compare the incidence of seizure following CAR T-cell infusion based on whether patients have received prophylactic anti-epileptics.
3. Compare the incidence and severity of ICANS based on whether patients have received prophylactic anti-epileptics in subgroups of patients with B-cell lymphoma and acute lymphoblastic leukemia.
4. Compare overall response rate and progression-free survival based on whether patients have received prophylactic anti-epileptics.

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

ICANS is a common and serious adverse effect after CAR T-cell infusion without effective prophylactic treatments. Anti-epileptics, specifically levetiracetam, is used in some institutions for prevention of seizure and ICANS without much evidence. This retrospective analysis will investigate the efficacy of this practice and provide evidence for potential randomized trials.

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

Immune effector cell-associated neurotoxicity syndrome (ICANS) is an acute/subacute adverse effect following CD19-targeted chimeric antigen receptor (CAR) T-cell infusion, with rates ranging from 23-67% for patients with lymphoma, and 40-62% for those with leukemia.(1, 2) The incidence and severity of ICANS vary depending on CAR targets, CAR constructs, disease types, disease burden prior to CAR T-cell infusion, and the use of high-dose lymphodepleting chemotherapy; after CAR T-cell infusion, peak CAR T-cell expansion and cytokine level were also associated with the severity of ICANS.(3) The American Society for Transplantation and Cellular Therapy (ASTCT) recommended grading ICANS based on common manifestations, including toxic encephalopathy (such as change of orientation, naming, following commands, writing, and attention), depressed level of consciousness, seizure, motor weakness, and elevated intracranial pressure.(4) Among them, seizure and elevated intracranial pressure are associated with dismal outcomes.(5) However, our understanding of the pathogenesis of ICANS is still evolving. Animal model and autopsy results have suggested that endothelial cell activation, blood-brain barrier (BBB) disruption, and glial cell injury were associated with occurrence of ICANS.(6, 7)

Despite its frequent occurrence, effective treatment and prophylactic medications are limited. Recently, prophylactic use of anti-epileptic medications (AEDs) has been adopted in some institutions for the prevention of seizure and ICANS. In a survey conducted by the ASTCT Pharmacy Special Interest Group in 2018, levetiracetam was the agent of choice for AED in all survey responders; among them, 65% of centers offer universal levetiracetam prophylaxis, 20% never offer levetiracetam prophylaxis, while the remaining 15% provide levetiracetam in a case-by-case manner.(8) Multiple animal studies have shown that levetiracetam was able to preserve the BBB integrity under various insults(9-11) and was associated with reduced inflammatory cytokines in the brain(12, 13). Therefore, levetiracetam may not only be effective at preventing seizure, but also reducing in the incidence and severity of ICANS. However, there has been no evidence to support this clinical practice. Indeed, the European Society for Blood and Marrow Transplantation (EBMT) currently recommends against routine use of levetiracetam due to lack of evidence.(14)

Prophylactic use of AEDs for the prevention of ICANS has recently been added to the data collection form at CIBMTR (Form 4000 R8.0, question 87). By retrospectively comparing the incidence and severity of ICANS between patients who received prophylactic AEDs and those who did not, the study will provide evidence to support this clinical practice and provide evidence for potential randomized trials in the future.

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

N/A

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

Inclusion criteria:

1. Adult patients (≥ 18 years) with a diagnosis of B-cell lymphoma or B-cell acute lymphoblastic leukemia.
2. Patients received commercial CAR T-cell products between 2016 and 2021.

Exclusion Criteria:

1. Patients received medications other than anti-epileptics for ICANS prevention.
2. Patients received CAR T-cell product with target other than CD19.

Q21. Does this study include pediatric patients?

- No

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

Provide a more homogeneous population.

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

- Age
- Gender
- Race
- ECOG performance status
- Primary disease for cellular therapy
- Lines of prior therapies
- Blast count prior to CAR T-cell infusion for patients with B-ALL
- Disease stage prior to CAR T-cell infusion for patients with B-cell lymphoma
- LDH prior to CAR T-cell infusion
- Platelet count prior to CAR T-cell infusion
- Lymphodepleting therapy prior to cellular therapy
- Name of CAR T-cell product
- Date of CAR T-cell infusion
- Dose of CAR T-cell infusion
- Therapy given for the prevention of CRS
- Therapy given for the prevention of neurotoxicity (ICANS)
- Date of CRS diagnosis
- Therapy given for CRS
- Symptoms of CRS
- Date of ICANS onset
- Therapy given for ICANS
- Cognitive assessment performed (CARTOX or ICE) and its lowest score
- Symptoms of ICANS
- Date ICANS resolved
- Best response to CAR T-cell therapy
- Progression-free survival

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

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

None

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

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

None

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

None

Q26. REFERENCES:

1. Westin JR, Kersten MJ, Salles G, Abramson JS, Schuster SJ, Locke FL, et al. Efficacy and safety of CD19-directed CAR-T cell therapies in patients with relapsed/refractory aggressive B-cell lymphomas: Observations from the JULIET, ZUMA-1, and TRANSCEND trials. Am J Hematol. 2021;96(10):1295-312.
2. Sheth VS, Gauthier J. Taming the beast: CRS and ICANS after CAR T-cell therapy for ALL. Bone Marrow Transplant. 2021;56(3):552-66.
3. Gust J, Taraseviciute A, Turtle CJ. Neurotoxicity Associated with CD19-Targeted CAR-T Cell Therapies. CNS Drugs. 2018;32(12):1091-101.
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6. Gust J, Hay KA, Hanafi LA, Li D, Myerson D, Gonzalez-Cuyar LF, et al. Endothelial Activation and Blood-Brain Barrier Disruption in Neurotoxicity after Adoptive Immunotherapy with CD19 CAR-T Cells. Cancer Discov. 2017;7(12):1404-19.
7. Gust J, Finney OC, Li D, Brakke HM, Hicks RM, Futrell RB, et al. Glial injury in neurotoxicity after pediatric CD19-directed chimeric antigen receptor T cell therapy. Ann Neurol. 2019;86(1):42-54.
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9. Itoh K, Ishihara Y, Komori R, Nochi H, Taniguchi R, Chiba Y, et al. Levetiracetam treatment influences blood-brain barrier failure associated with angiogenesis and inflammatory responses in the acute phase of epileptogenesis in post-status epilepticus mice. Brain Res. 2016;1652:1-13.
10. Shetty AK. Prospects of levetiracetam as a neuroprotective drug against status epilepticus, traumatic brain injury, and stroke. Front Neurol. 2013;4:172.
11. Ahishali B, Kaya M, Orhan N, Arican N, Ekizoglu O, Elmas I, et al. Effects of levetiracetam on blood-brain barrier disturbances following hyperthermia-induced seizures in rats with cortical dysplasia. Life Sci. 2010;87(19-22):609-19.
12. Itoh K, Taniguchi R, Matsuo T, Oguro A, Vogel CFA, Yamazaki T, et al. Suppressive effects of levetiracetam on neuroinflammation and phagocytic microglia: A comparative study of levetiracetam, valproate and carbamazepine. Neurosci Lett. 2019;708:134363.
13. Stienen MN, Haghikia A, Dambach H, Thone J, Wiemann M, Gold R, et al. Anti-inflammatory effects of the anticonvulsant drug levetiracetam on electrophysiological properties of astroglia are mediated via TGFbeta1 regulation. Br J Pharmacol. 2011;162(2):491-507.
14. Yakoub-Agha I, Chabannon C, Bader P, Basak GW, Bonig H, Ciceri F, et al. Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). Haematologica. 2020;105(2):297-316.

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

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

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

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

N/A

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

Embedded Data:

N/A

8. 2110-34 & 2110-173: Patients undergoing 1st commercial CAR-T, 2016-present

Characteristic	**N(%)**
No. of patients	4458
No. of centers	159
Patient related	
Age at infusion, by category - no. (%)	
Median (min-max)	61 (0-91)
0-9	212 (5)
10-17	250 (6)
18-29	303 (7)
30-39	197 (4)
40-49	329 (7)
50-59	846 (19)
60-69	1375 (31)
>= 70	946 (21)
Recipient Sex - no. (%)	
Male	2815 (63)
Female	1643 (37)
Recipient race - no. (%)	
White	3456 (78)
African-American	225 (5)
Asian	191 (4)
Pacific Islander	8 (0)
Native American	17 (0)
More than one race	49 (1)

Characteristic	**N(%)**
Unknown	237 (5)
Missing	275 (6)
Recipient ethnicity - no. (%)	
Hispanic or Latino	614 (14)
Non Hispanic or non-Latino	3378 (76)
Non-resident of the U.S.	299 (7)
Unknown	161 (4)
Missing	6 (0)
Performance score prior to CT - no. (%)	
90-100	1942 (44)
=80	1218 (27)
< 80	837 (19)
Missing	461 (10)
ECOG performance status prior to CT - no. (%)	
0 - Asymptomatic	1942 (44)
1 - Symptomatic but completely ambulatory	1863 (42)
2 - Symptomatic, < 50% in bed during the day	175 (4)
3 - Symptomatic, > 50% in bed, but not bedbound	13 (0)
4 - Bedbound	4 (0)
Missing	461 (10)
CT-CI - no. (%)	
0	1465 (33)
1	860 (19)
2	551 (12)
3+	1496 (34)

Characteristic	N(%)
TBD	18 (0)
NA (not collected for these cases)	2 (0)
Missing	66 (1)
Disease related	
Disease - no. (%)	
Acute lymphoblastic leukemia (ALL)	649 (15)
Non-Hodgkin lymphoma (NHL)	3753 (84)
Missing	56 (1)
Blasts in Blood at diagnosis (% WBC) - median (min-max)	61 (0-100)
Blasts in Bone Marrow at diagnosis (% WBC) - median (min-max)	90 (0-100)
IPI at initial diagnosis of the primary disease - no. (%)	
Low	104 (2)
Low intermediate	174 (4)
High intermediate	201 (5)
High	223 (5)
Missing	3756 (84)
Prior radiation therapy - no. (%)	
No	2789 (63)
Yes	1169 (26)
Missing	500 (11)
Time from HCT to CT, months - median (min-max)	17 (0-315)
CAR-T cell related	
CRS Prophylaxis - no. (%)	
No:	1315 (29)
Yes:	155 (3)

Characteristic	N(%)
Tocilizumab	110 (2)
Other	39 (1)
Not reported	2988 (67)
ICANS Prophylaxis - no. (%)	
No:	838 (19)
Yes:	632 (14)
Anti-Epileptics	591 (13)
Other	13 (0)
Not reported	2988 (67)
Prior lines of therapies - no. (%)	
No	8 (0)
Yes	4075 (91)
1	2977 (67)
2	117 (3)
>= 3	774 (17)
Missing	207 (5)
Missing	375 (8)
Year of CT - no. (%)	
2017	18 (0)
2018	645 (14)
2019	1167 (26)
2020	1375 (31)
2021	1253 (28)
Product - no. (%)	
Kymriah	1658 (37)

Characteristic	N(%)
Yescarta	2556 (57)
Tecartus	244 (5)
Time from diagnosis to CT - no. (%)	
Median (min-max)	17 (1-447)
0-6 months	463 (10)
6-12 months	1098 (25)
1-2 years	1155 (26)
2-3 years	1685 (38)
Missing	57 (1)
Bridging therapy - no. (%)	
No	2717 (61)
Yes	962 (22)
Systemic therapy	758 (17)
Intrathecal therapy	31 (1)
Intraocular therapy	1 (0)
Radiation therapy	261 (6)
Surgery	1 (0)
Not reported	779 (17)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)	
No	15 (0)
Yes	4442 (100)
Bendamustine only	141 (3)
Flu+Cy only	4196 (94)
Other	95 (2)
None selected	10 (0)

Characteristic	**N(%)**
Missing	1 (0)
None selected	1 (0)
Follow-up, in months - median (range)	13 (1-43)

Response Summary:

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

Q1. Study Title

Impact of obesity on outcomes in CD19-directed CAR-T patients

Q2. Key Words

N/A

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Nishi Shah
Email address:	nisshah@montefiore.org
Institution name:	Montefiore Medical Center
Academic rank:	Assistant Professor

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Murali Janakiram
Email address:	mjanakiram@coh.org
Institution name:	City of Hope Comprehensive cancer center
Academic rank:	Assistant Professor

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

- Yes

Q8. Do you identify as an underrepresented/minority?

- Yes

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

nisshah@montefiore.org

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

N/A

LETTER OF COMMITMENT:

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

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

N/A

Q13. PROPOSED WORKING COMMITTEE:

- Cellular Immunotherapy for Cancer

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

- No

Q15. RESEARCH QUESTION:

Impact of obesity on outcomes in CD19-directed CAR-T patients

Q16. RESEARCH HYPOTHESIS:

The efficacy, adverse effect profile of CD-19 directed CAR-T cell therapy is similar between obese and non-obese patients.
There is no difference in outcomes for CD-19 directed CAR-T cell therapy between obese and non-obese patients.

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

Suggested word limit of 200 words:

To evaluate the rates of toxicities and survival outcomes in obese patients who receive CD-19 directed CAR-T cell therapy

To compare the outcomes for CAR-T cell therapy in obese vs non-obese patients

STUDY OUTCOMES

• Primary outcome

o Clinical outcomes

Response Rate: overall response includes complete and partial remission as best responses post CAR T cell.

PFS: Composite endpoint with disease relapse and death of any cause.

OS: Time to death of any cause will be an event for this outcome. Patients will be censored at time of last follow up.

• Secondary outcomes:

o Hematologic recovery and cytopenia after CAR T

Neutrophil recovery: The event is defined according to the time to initial ANC recovery (>500/mm3). Death without initial neutrophil recovery is a competing event.

Platelet recovery: The event is defined according to the time to initial platelet recovery (≥20 x 109/L). Death without initial platelet recovery is a competing event.

Prevalence of neutropenia at 30 days and 90 days: the event is defined based on the neutrophil count at these different timepoints. Patients with neutropenia will be categorized by severity according to CTCAE criteria: grade 2 (ANC 1000-1500/mm3) grade 3 (ANC 500-1000/mm3) and grade 4 (ANC < 500/mm3). Only patients alive and without disease progression will be evaluated for this outcome.

Prevalence of thrombocytopenia at 30 days and 90 days: the event is defined based on the platelet count at these, different timepoints. Patients with thrombocytopenia will be categorized by severity according to the CTCAE criteria: grade 2 (50-<75 x 109/L), grade 3 (25-<50 x 109/L), and grade 4 (<25 x 109/L). Only patients alive and without disease progression will be evaluated for this outcome.

o Rate of transfusions: Proportion of patents receiving transfusions at time points

Rate of RBC transfusions within 3, 6 and 12 months

Rate of platelet transfusions within 3, 6 and 12 months

• CAR-T toxicity

• CRS: Grades II-IV and Grades III-IV CRS according to ASTCT criteria will be the events for this outcome.

• Immune effector cell-associated neurotoxicity syndrome (ICANS): Grades II-IV and III-IV ICANS according to ASTCT criteria will be the events for this outcome.

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

Estimated prevalence of obesity in adults within the United States was 42.4% in 2017-18. Prior literature suggests that obesity could have an impact on the dose of chemotherapy, immune function and response to immunotherapy. Barring a single institutional study, prior studies have not evaluated the impact of obesity on safety and efficacy of CD-19 directed CAR-T cells. As CD-19 directed CAR-t cells are increasingly being utilized throughout the US, it would be important to critically evaluate this select group of patients. This study will provide us

1. Better understanding of the proportion of obese patients who receive CD-19 directed CAR-T therapy.
2. Clinical evidence and insight about patient outcomes after CAR T cell therapy in this patient population.

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

CD19 Chimeric Antigen Receptor T cell therapy has changed the treatment landscape for aggressive NHLs that have relapsed after and are refractory to chemotherapy. There are currently three FDA approved CART products that are indispensable for the treatment of these aggressive B-cell malignancies. While numerous studies have described the outcomes for patients receiving CD-19 directed CAR-T cell therapy, there is no significant data on whether obesity is a prognostic factor for CAR-T therapy. Obesity leads to a state of chronic inflammation and immune dysregulation. It may thus have an important role in response to CAR-T cell therapy. With this study, we would like to evaluate whether obesity is an important factor that predicts response to CAR-T cell therapy. We would also like to play the role of lymphodepleting chemotherapy dosed by ideal body weight vs actual body weight in response to this therapy for this patient population. Lastly, the study results may potentially be utilized in future clinical trial designs for CAR-T cell therapy.

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

N/A

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

Inclusion criteria:
• Patients with high grade lymphoma who received commercial CD-19 directed CAR-T cell therapy
• Patients who have at least 3 months of follow-up data

Q21. Does this study include pediatric patients?

- No

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

This study is intended for adult patients with lymphoma who are treated with CD-19 directed CAR-T cell therapy

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

- Gender: male vs. female
- Body mass index: <30, 30-35, >35
- Height and weight of the patient at the time of lymphodepleting chemotherapy.
- Race: White vs. African American vs. Asian vs. more than one race
- Comorbid conditions prior to CAR T cells according to HCT-CI: 0 vs. 1-2 vs. ≥3 vs. missing
- Performance score at CAR T cell infusion: < 80% vs. 80-90% vs. 90-100%
- Diagnosis
- Lymphoma: De novo vs Transformed
- Disease status at CAR T cell
- Stage of disease at CAR T cell
- IPI at CAR T cell
- Number of prior lines of treatments including transplantation
- Type of transplant if transplants before CAR T cell: Auto, Allo
- If allotransplant before CAR T cell: Matched sib, unrelated, haplo, cord
- Karnofsky Performance Status: 0-2 VS 3-4
- Hematopoietic Cell Transplant Comorbidity Index: 0-2 VS >3
- Bridging therapy before CAR T cell
- Last date of treatment
- Bridging therapy regimen:Yes, no details of therapy
- Baseline CBC (WBC, ANC, ALC) before starting lymphodepletion
- Baseline IgG, IgA before starting lymphodepletion (if available)
- Baseline CRP, IL-6, Ferritin before lymphodepletion
- Pre-CAR T cells pulmonary function and echocardiogram results
- Lymphodepletion Regimen prior to CAR T cell therapy
- Type of CAR T cell product
- CAR T cell dose
- Time to Neutrophil Engraftment
- ANC and ALC at 14 days and 1 month
- IgG level at 1 month and 3 months
- CAR T Related Complication
- CRS: Yes vs No. Grading per ASTCT consensus
- ICANs: Yes vs No. Grading per ASTCT consensus
- Graft Versus Host Disease
- Peak Cytokine level: Peak IL-6 level, Peak Ferritin, Peak CRP (including date of peak level for all cytokines)
- Steroid: Type, date of first dose, dose, date of last dose
- Tocilizumab: date of first dose, number of doses, date of last dose
- Antimicrobial prophylaxis given (Antibiotic, antiviral, antifungal): Yes or No. (Duration if available)
- IVIG replacement given
- Growth factor given
- Disease status after CAR-T
- Last contact
- Live/Death Status at last contact
- Cause of death

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

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

This study does not require patient reported outcome

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

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

This study has no sample requirements

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

Non-CIBMTR data source is not required

Q26. REFERENCES:

1. W. Bouleftour, B. Mery, E. Chanal, E. Rowinski, A. Viard, F. Forges, P. Fournel & R. Rivoirard (2019) Obesity and chemotherapy administration: between empiric and mathematic method review, Acta Oncologica, 58:6, 880-887, DOI: 10.1080/0284186X.2019.1585942
2. Aguilar EG, Murphy WJ. Obesity induced T cell dysfunction and implications for cancer immunotherapy. Curr Opin Immunol. 2018;51:181–6.
3. Woodall MJ, Neumann S, Campbell K, Pattison ST, Young SL. The effects of obesity on anti-cancer immunity and cancer immunotherapy. Cancers. 2020;12:1230–33.
4. Wudhikarn, K., Bansal, R., Khurana, A. et al. The impact of obesity and body weight on the outcome of patients with relapsed/refractory large B-cell lymphoma treated with axicabtagene ciloleucel. Blood Cancer J. 11, 124 (2021). https://doi.org/10.1038/s41408-021-00515-2
5. FDA Approves First Cell-Based Gene Therapy For Adult Patients with Relapsed or Refractory MCL [cited 2020 July 24]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-cell-based-gene-therapy-adult-patients-relapsed-or-refractory-mcl
6. FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma [Internet]. 2017; 10/18/2017
7. FDA approves tisagenlecleucel for adults with relapsed or refractory large B-cell lymphoma [Internet]. 2018; 5/3/2018
8. Wang Z, Aguilar EG, Luna JI et al. Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. Nat Med. 2019 Jan;25(1):141-151. doi: 10.1038/s41591-018-0221-5. Epub 2018 Nov 12. PMID: 30420753; PMCID: PMC6324991.

Q27. **CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:**

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

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

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

N/A

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

Embedded Data:

N/A

2110-237: Adult Patients undergoing 1st commercial CD-19 directed CAR-T for high-grade Lymphoma with 100-days FU, 2016-present

Characteristic	N(%)
No. of patients	2773
No. of centers	108
Patient related	
Age at infusion, by category - no. (%)	
Median (min-max)	64 (18-91)
18-29	50 (2)
30-39	128 (5)
40-49	248 (9)
50-59	624 (23)
60-69	1024 (37)
>= 70	699 (25)
Recipient Sex - no. (%)	
Male	1753 (63)
Female	1020 (37)
Recipient race - no. (%)	
White	2203 (79)
African-American	134 (5)
Asian	123 (4)
Pacific Islander	6 (0)
Native American	8 (0)
More than one race	15 (1)
Unknown	126 (5)
Missing	158 (6)

Characteristic	N(%)
Recipient ethnicity - no. (%)	
Hispanic or Latino	268 (10)
Non Hispanic or non-Latino	2242 (81)
Non-resident of the U.S.	160 (6)
Unknown	99 (4)
Missing	4 (0)
Performance score prior to CT - no. (%)	
90-100	1086 (39)
=80	801 (29)
< 80	551 (20)
Missing	335 (12)
ECOG performance status prior to CT - no. (%)	
0 - Asymptomatic	1086 (39)
1 - Symptomatic but completely ambulatory	1237 (45)
2 - Symptomatic, < 50% in bed during the day	108 (4)
3 - Symptomatic, > 50% in bed, but not bedbound	5 (0)
4 - Bedbound	2 (0)
Missing	335 (12)
CT-CI - no. (%)	
0	857 (31)
1	495 (18)
2	343 (12)
3+	1017 (37)
TBD	9 (0)
Missing	52 (2)

Characteristic	N(%)
Body Mass Index - no. (%)	
Median (min-max)	27 (10-88)
BMI < 25	775 (28)
25 <= BMI < 30	742 (27)
30 <= BMI < 35	357 (13)
35 <= BMI	218 (8)
Missing	681 (25)
Disease related	
Disease classification - no. (%)	
NHL diffuse, large B-cell	712 (26)
T-cell / histiocytic rich large B-cell lymphoma	43 (2)
Other B-cell	9 (0)
Diffuse, large B-cell lymphoma- Germinal center B-cell type	979 (35)
Diffuse, large B-cell lymphoma- Activated B-cell type	672 (24)
Primary cutaneous DLBCL, leg type	3 (0)
EBV+ DLBCL, NOS	19 (1)
DLBCL associated with chronic inflammation	1 (0)
High-grade B-cell lymphoma, NOS	52 (2)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	283 (10)
IPI at initial diagnosis of the primary disease - no. (%)	
Low	66 (2)
Low intermediate	122 (4)
High intermediate	153 (6)
High	164 (6)
Missing	2268 (82)

Characteristic	N(%)
Prior radiation therapy - no. (%)	
No	1779 (64)
Yes	837 (30)
Missing	157 (6)
Time from HCT to CT, months - median (min-max)	14 (2-269)
CAR-T cell related	
Prior lines of therapies - no. (%)	
No	2 (0)
Yes	2664 (96)
1	1916 (69)
2	69 (2)
>= 3	550 (20)
Missing	129 (5)
Missing	107 (4)
Year of CT - no. (%)	
2017	5 (0)
2018	465 (17)
2019	910 (33)
2020	1037 (37)
2021	356 (13)
Product - no. (%)	
Kymriah	756 (27)
Yescarta	2017 (73)
Time from diagnosis to CT - no. (%)	
Median (min-max)	15 (1-447)

Characteristic	N(%)
0-6 months	284 (10)
6-12 months	804 (29)
1-2 years	789 (28)
2-3 years	895 (32)
Missing	1 (0)
Bridging therapy - no. (%)	
No	1850 (67)
Yes	639 (23)
Systemic therapy	490 (18)
Intrathecal therapy	24 (1)
Intraocular therapy	1 (0)
Radiation therapy	186 (7)
Surgery	1 (0)
Not reported	284 (10)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)	
No	10 (0)
Yes	2762 (100)
Bendamustine only	89 (3)
Flu+Cy only	2606 (94)
Other	63 (2)
None selected	4 (0)
Missing	1 (0)
None selected	1 (0)
Follow-up, in months - median (range)	13 (1-41)

Response Summary:

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

Q1. Study Title

Machine learning for predicting toxicity and clinical outcomes in DLBCL and B-ALL patients treated with Yescarta and Kymriah cell products in the real-world setting: an analysis of the CIBMTR registry.

Q2. Key Words

CAR-T, Machine Learning, Patient Selection

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Adrian Mosquera Orgueira
Email address:	adrian.mosquera.orgeira@sergas.es
Institution name:	University Hospital of Santiago de Compostela
Academic rank:	Hematology MD

Q30. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- Yes

Q29. Do you identify as an underrepresented/minority?

- No

Q28. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Loretta J. Nastoupil
Email address:	LNastoupil@mdanderson.org
Institution name:	MD Anderson Cancer Center
Academic rank:	Hematology MD

Q27. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q26. Do you identify as an underrepresented/minority?

- No

Q31. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

N/A

Q4. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

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

Q6. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

N/A

Q7. PROPOSED WORKING COMMITTEE:

- Cellular Immunotherapy for Cancer

Q8. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- No

Q10. RESEARCH QUESTION:

Patients with Acute Lymphoblastic Leukemia (ALL) and Diffuse Large B-cell Lymphoma (DLBCL) who are treated with CAR-T cells exhibit a variety of adverse events and heterogeneous responses. Machine learning-analysis of basal characteristics can help model final outcomes and thus improve patient selection in a rational basis.

Q11. RESEARCH HYPOTHESIS:

To create machine learning models for personalized predictions of patient survival, disease response, severe toxicity development, time to hematological recovery and optimal CAR-T product selection based on real world data of DLBCL and B-ALL patients treated with tisagenlecleucel and axicabtagene ciloleucel.

Q12. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

1. Primary objective: to create personalized predictors of progression-free survival and overall survival for DLBCL patients treated with CAR-T cells by integrating baseline variables included in the CIBMTR registry of tisagenlecleucel and axicabtagene ciloleucel.
2. Secondary Objective: to develop a model for predicting the best CAR-T cell product for each DLBCL patient in terms of progression free survival and overall survival.
3. Primary Objective: to create personalized predictors of progression-free survival and overall survival for B-ALL patients treated with tisagenlecleucel by using baseline variables included in the RWE CIBMTR registry.
4. Secondary Objective: to create predictions of best disease response for DLBCL and B-ALL patients after treatment with either tisagenlecleucel or axicabtagene ciloleucel.
5. Secondary Objective: to create individualized drug-specific predictions about the development of severe (Grade 3-4) toxicity and the duration of severe cytopenias after CAR-T cell administration in DLBCL and B-ALL patients.

Q13. 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 results of this study will facilitate the application of personalized medicine in the CAR-T cell therapy sector. As a growing number of anti-CD19 CAR-T cell products are in development for DLBCL and B-ALL, there is a need to optimize the use of these expensive drugs and predict severe toxicities (cytokine storm syndrome and neurotoxicity) that will facilitate patient selection, prophylactic treatment and CAR-T drug selection. Our models will include variables that are available for most patients in real practice, so we expect that these will facilitate their incorporation in daily practice.

Additionally, since numerous CAR-T cell products are being developed for different indications (i.e., multiple myeloma, Hodgkin lymphoma…) the results of our pioneering project might anticipate the incorporation of machine learning tools in the current development of these new drugs.

Q14. 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.

The JULIET [1] and ZUMA-1 [2] trials evaluated the security and efficacy of the anti-CD19 CAR-T cell products tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) in patients with relapsed & refractory diffuse large B-cell lymphoma (DLBCL). In the Juliet trial, tisagenlecleucel reached overall response rates of 52%, and median overall survival among infused patients was 12 months. 23% of patients experienced severe (grade ≥ 3) cytokine storm syndrome. Similarly, the ZUMA-1 trial evidenced an 82% overall response rate and an 18-month survival rate of 52%. Axicabtagene ciloleucel produced more seve (grade ≥ 3) neurotoxic events (ICANS) than other products (31%), which were reversible in most cases. Fast track approval for both drugs were granted by the Food And Drug Administration (FDA) and the European Medicine Agency (EMA). Accumulated real-world evidence (RWE) with these drugs confirmed the efficacy of these CAR-T cell products observed in the registry trials [3, 4] and has made possible the identification of a few predictive biomarkers of response and survival [5].

Additionally, tisagenlecleucel safety and efficacy for children, adolescents and young adults with relapsed and refractory B-cell acute lymphoblastic leukemia (B-ALL) was tested in the ELIANA trial [6]. After 3 months of infusion, overall remission rate was 81% with undetectable minimal residual disease (uMRD) in all responding patients. The rates of event-free survival and overall survival were 73% and 90%, respectively, at 6 months and 50% (95% CI, 35 to 64) and 76% (95% CI, 63 to 86) at 12 months. Grade ≥ 3 adverse events related to tisagenlecleucel were observed in 73% of patients. After fast track approval of tisagenlecleucel, RWE collected by the CIBMTR confirmed these promising results [7]. Predictive factors of disease relapse (prior blinatumomab exposure, high disease burden) and severe cytokine release syndrome (age ≥ 10 and high tumor burden) have been described [8], but evidence in this line is still very limited and no predictive scores are available.

There is a need to integrate real-world data into predictive models for use in the real world practice of CAR-T cell patients. Machine Learning (ML) has brought new expectations to different medical fields. ML is a field of artificial intelligence that performs outcome prediction based on complex interactions between multiple variables. ML makes no assumption about the relationship between the dependent and independent variables, and models are created with examples and not programmed with human-made rules [9, 10]. The implementation of ML-based survival models is becoming popular in order to provide patient-centered risk information. Kim et al. (2019) recently published a deep-learning model that predicts survival of oral cancer patients [11], and Biccler et al. (2018) used ML to predict overall survival of DLBCL patients based solely on clinical and laboratory data, reaching a high performance [12]. By applying ML tools to RWE data of CAR-T cell products, we expect to derive reproducible and fully personalized models of survival, disease response and toxicity risk. We expect that our results will assist clinicians in order to improve patient selection, reduce the risk of adverse events and, in the case of DLBCL, select the optimal CAR-T cell product for each patient.

For this purpose, RWE data from patients treated with tisagenlecleucel and axicabtagene ciloleucel in the CIBMTR will be used to create ML models of survival. Machine learning algorithms will be applied in order to select the optimal variables and create predictive personalized models. Models will be validated in a geographically independent test set within the CIBMTR registry. Cross-validation will be used to compare model results within the training set, and concordance indexes (c-index) will be calculated to assess model's predictability in the test set. In the case of DLBCL patients, we will use baseline data before CAR-T cell infusion in order to: 1) predict overall and progression free survival, 2) predict the probability of achieving a complete response at 3 and 18 months, 3) identify patients at high risk of severe adverse events and late hematological recovery, and 4) identify which patients benefit the most from either CAR-T cell product. In the case of B-ALL patients treated with tisagenlecleucel, we will use baseline data to model 1) patient overall and progression free survival, 2) probability of achieving a complete response with uMRD at 3 and 18 months; and 3) developing severe adverse events and late hematological recovery. For each patient, baseline clinical, biochemical, histological, cytogenetic and treatment data will be recovered from B-ALL and DLBCL data. Different machine learning models will be studied.

Inferring sample size for machine learning studies is not an easy task, as these are based on non-linear complex interactions between variables, and therefore no a priori power calculation is possible.

Q16. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

1) Age: all available ages
2) Disease: DLBCL and B-ALL
3) Disease stage: relapsed & refractory
4) CAR-T cell treatment: RWE from Tisagenlecleucel and Axicabtagene Ciloleucel patients.

Q17. Does this study include pediatric patients?

- Yes

Q19. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

• CIBMTR data collection forms: 2402, 4000, 4003, 4006, 4100 for DLBCL and B-ALL patients treated with tisagenlecleucel and axicabtagene ciloleucel.
• Our study will not require collection of supplemental data.
• The proposed study doesn't involve combining CIBMTR data with data from another group.
• List of variables that need to be analyzed, and desired outcome variables:
1. Collection Form 2402: Key Fields, Primary Disease for HCT/Cellular Therapy, Acute Lymphoblastic Leukemia (ALL) and Hodgkin and Non-Hodgkin Lymphoma.
2. Collection Form 4000: Key Fields, Recipient Data, Cellular Therapy and HCT history, Product Identification, Indication for Cellular Therapy, Diseases Assessment at Last Evaluation Prior to Cellular Therapy, Systemic Therapy Prior to Cellular Therapy, Functional Status and Comorbid Conditions.
3. Collection Form 4003: Key Fields, Cellular Therapy Product Identification, Cell Product Source, Collection Procedure, Cell Product Manipulation and Cell Product Analysis.
4. Collection Form 4006: Key Fields, Product Infusion and Concomitant Therapy.
5. Collection Form 4100 (desired outcome variables): Key Fields, Product, Survival, Best Response to Cellular Therapy, Peripheral Blood Count Recovery, Disease Relapse or Progression, Current Hematologic Findings, Persistence of Cells, Toxicities and Infection.

Q20. PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.

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

N/A

Q21. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

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

This study doesn't require biologic samples from the NMDP Repository.

Q22. **NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.**

N/A

Q23. REFERENCES:

1. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019;380(1):45-56. doi:10.1056/NEJMoa1804980
2. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017;377(26):2531-2544. doi:10.1056/NEJMoa1707447
3. Jacobson CA, Hunter B, Armand P, et al. Aggressive lymphoma (diffuse large B-cell and other aggressive B-cell Non-Hodgkin lymphomas)—results from retrospective/observational studies: outcomes with CD19 CAR T therapy and checkpoint blockade in the real-world setting. In: Proceedings from the American Society of Hematology; December 1-3, 2018; San Diego, CA. Abstract 92.
4. Jaglowski S., 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 [abstract]. In: The 61st ASH Annual Meeting.; December 7-10; Orlando, Florida.
5. Vercellino L, Di Blasi R, Kanoun S, et al. Predictive factors of early progression after CAR T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma. Blood Adv. 2020;4(22):5607-5615. doi:10.1182/bloodadvances.2020003001
6. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018;378(5):439-448. doi:10.1056/NEJMoa1709866
7. Grupp S, Hu ZH, Zhang Y et al. Tisagenlecleucel Chimeric Antigen Receptor (CAR) T-Cell Therapy for Relapsed/Refractory Children and Young Adults with Acute Lymphoblastic Leukemia (ALL): Real World Experience from the Center for International Blood and Marrow Transplant Research (CIBMTR) and Cellular Therapy (CT) Registry. Blood (2019) 134 (Supplement_1): 2619. https://doi.org/10.1182/blood-2019-129279
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9. Bender R. Introduction to the use of regression models in epidemiology. Methods Mol Biol. 2009;471:179-95. doi: 10.1007/978-1-59745-416-2_9. PubMed PMID: 19109780.
10. Rajkomar A, Dean J, Kohane I. Machine Learning in Medicine. N Engl J Med. 2019 Apr 4;380(14):1347-1358. doi: 10.1056/NEJMra1814259. Review. PubMed PMID: 30943338.
11. Kim DW, Lee S, Kwon S, Nam W, Cha IH, Kim HJ. Deep learning-based survival prediction of oral cancer patients. Sci Rep. 2019 May 6;9(1):6994. doi: 10.1038/s41598-019-43372-7. PubMed PMID: 31061433; PubMed Central PMCID: PMC6502856.
12. Biccler JL et al. Optimizing Outcome Prediction in Diffuse Large B-Cell Lymphoma by Use of Machine Learning and Nationwide Lymphoma Registries: A Nordic Lymphoma Group Study. JCO Clin Cancer Inform. 2018 Dec;2:1-13. doi: 10.1200/CCI.18.00025. PubMed PMID: 30652603.

Q24. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

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

- Yes, I have conflicts of interest pertinent to this proposal

Q32. 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.

No >$5000 remuneration

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

Embedded Data:

N/A

Response Summary:

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

Q1. Study Title

Machine learning to determine Clinical predictors of response and toxicity following CD-19 directed Chimeric Antigen Receptor T-cell therapy in patients with Diffuse Large B-cell Lymphoma

Q2. Key Words

Machine learning, CD19 CAR T cell, Lymphoma

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Nasheed M Hossain MD
Email address:	nmh1022@gmail.com
Institution name:	Loyola University Chicago - Stritch School of Med
Academic rank:	Assistant Professor

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	N/A
Email address:	N/A
Institution name:	N/A
Academic rank:	N/A

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

N/A

Q8. Do you identify as an underrepresented/minority?

N/A

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

N/A

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

- Yes, I am a junior investigator and would like assistance identifying a senior mentor for my project

LETTER OF COMMITMENT:

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

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

GV18-01a - participated in reviewing concept and manuscript
LK19-02 - protocol review
GV18-02 - protocol review and data analysis
GV20-01 - protocol review
MM20-03 - protocol review
MM20-01- protocol review
MM19-02 - participated in reviewing concept, data analysis and manuscript prep
CK18-03- participated in reviewing concept, data analysis and manuscript prep
CK20-01 - protocol development
LK20-04- participated in reviewing concept, data analysis and manuscript prep
CK19-01a- participated in reviewing concept, data analysis and manuscript prep

Q13. PROPOSED WORKING COMMITTEE:

- Cellular Immunotherapy for Cancer

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

- No

Q15. RESEARCH QUESTION:

Can machine learning algorithms help to identify clinical factors that predict response and toxicity after CAR therapy in DLBCL patients

Q16. RESEARCH HYPOTHESIS:

Machine algorithms may successfully identify key clinical predictors of response and toxicity following CD-19 directed Chimeric Antigen Receptor T-cell therapy in patients with Diffuse Large B-cell Lymphoma

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

Suggested word limit of 200 words:

Clinical predictors of response and toxicity following CD-19 directed Chimeric Antigen Receptor T-cell therapy in patients with Diffuse Large B-cell Lymphoma

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

Provide clinicians with an objective approach to determining which patients are suitable for CAR-T therapy by helping to determine who has the highest chance of a response. At the same time this may help to identify more accurately who is at greatest risk of toxicity following CAR-T therapy.

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

Provide clinicians with an objective approach to determining which patients are suitable for CAR-T therapy by helping to determine who has the highest chance of a response. At the same time this may help to identify more accurately who is at greatest risk of toxicity following CAR-T therapy.
This retrospective study will compile the above-mentioned clinical parameters for each DLBCL patient who has undergone CD19 directed CAR-T therapy. The study will aim to identify variables which may predict efficacy and risk of toxicity from CAR-T therapy in DLBLC patients. The pre-treatment clinical parameters will be compiled into tabular data for univariate, multivariate analysis, and machine learning algorithm generation.
Three different machine learning algorithms will be generated using pre- and post-treatment variables. One model will be a single-class classification model to predict response to CD19 directed CAR-T therapy at day 28 of therapy. If sufficient data is available a regression model will be generated to predict response at different time points throughout treatment (3 months, 6 months, 9 months, and 12 months). Regression models include Boosted ARIMA, Boosted Trees, Bagged MARS, linear regression, neural network, K-nearest neighbor, Poisson Regression, and Support Vector Machines. The second model will be a multi-classification model to predict toxicities, including severe CRS, neurotoxicity, and prolonged cytopenia, associated with CAR-T therapy. Classification models include XGBoost, Random Forest, Neural Net, Support Vector Machines, Elastic Net, Naïve Bayes, Multivariate Regression Splines, and C 5.0 Rule Based. The last model will be generated using time-series data. This will compile different lab values and markers across time points to predict improvement of response or risk of relapsed disease. Time series models include Boosted Auto ARIMA, Exponential Smoothing, Prophet, Linear Regression, and Multivariate Regression Splines. In all models, multiple machine learning models will be stacked together, creating an ensemble. The method of stacking machine learning models together is the most powerful method today in predicting outcomes – it combines the strengths of different algorithms while limiting the bias and variance that is often associated with machine learning models.

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

N/A

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

This retrospective study will compile the above-mentioned clinical parameters for each DLBCL patient who has undergone CD19 directed CAR-T therapy. The study will aim to identify variables which may predict efficacy and risk of toxicity from CAR-T therapy in DLBLC patients. The pre-treatment clinical parameters will be compiled into tabular data for univariate, multivariate analysis, and machine learning algorithm generation.
Three different machine learning algorithms will be generated using pre- and post-treatment variables. One model will be a single-class classification model to predict response to CD19 directed CAR-T therapy at day 28 of therapy. If sufficient data is available a regression model will be generated to predict response at different time points throughout treatment (3 months, 6 months, 9 months, and 12 months). Regression models include Boosted ARIMA, Boosted Trees, Bagged MARS, linear regression, neural network, K-nearest neighbor, Poisson Regression, and Support Vector Machines. The second model will be a multi-classification model to predict toxicities, including severe CRS, neurotoxicity, and prolonged cytopenia, associated with CAR-T therapy. Classification models include XGBoost, Random Forest, Neural Net, Support Vector Machines, Elastic Net, Naïve Bayes, Multivariate Regression Splines, and C 5.0 Rule Based. The last model will be generated using time-series data. This will compile different lab values and markers across time points to predict improvement of response or risk of relapsed disease. Time series models include Boosted Auto ARIMA, Exponential Smoothing, Prophet, Linear Regression, and Multivariate Regression Splines. In all models, multiple machine learning models will be stacked together, creating an ensemble. The method of stacking machine learning models together is the most powerful method today in predicting outcomes – it combines the strengths of different algorithms while limiting the bias and variance that is often associated with machine learning models.

Q21. Does this study include pediatric patients?

- No

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

given the rare incidence of DLBLC in pediatric population and lack of an FDA approved CAR for this population the study will focus on the adult population of DLBCL patients

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

Diagnosis (r/r DLBCL, transformed DLBCL, PMLBCL)
Age
Gender
Stage at Diagnosis
IPI score at diagnosis
Presence of bulky disease (at diagnosis and at time of CAR-T)
Disease status at CAR-T treatment
Prior History of Auto or AlloSCT
CART product received
Type of CART product (CD28 co-stim versus 4-1bb co-stim)
LDH, Ferritin, CRP at time of CAR-T treatment at each follow up date
Blood counts at treatment (WBC, Platelets, Hemoglobin, ANA, ALC) and at each subsequent follow up date when response assessed
D28 Response
D90 Response
D120 Response
Month 6 Response
Month 9 Response
Month 12 Response
Maximum grade of CRS
Maximum grade of Neurotoxity
Duration of cytopenias
Proceed to Auto or AlloSCT?
Timing of disease relapse

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

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

N/A

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

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

N/A

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

N/A

Q26. REFERENCES:

1. Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. Blood. 2015;125(1):22-32. doi:10.1182/blood-2014-05-577189.
2. Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. Hematol Am Soc Hematol Educ Progr. 2011;2011:498-505. doi:10.1182/asheducation-2011.1.498.
3. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. August 2017. doi:10.1182/blood-2017-03-769620.
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5. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371(16):1507-17.
6. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. December 2017. doi:10.1056/NEJMoa1707447.
7. Abramson JS, Siddiqi T, Palomba ML, Gordon LI, Lunning MA, Arnason JE, Wang M, Forero-Torres A, Albertson T, Dehner C, Garcia J, Li Daniel, Xie B MD. R/R Aggressive B-NHL (TRANSCEND NHL 001 Study): A Defined Composition CD19-Directed CAR T Cell Product with Potential for Outpatient Administration. In: 2018 BMT Tandem Meetings. ; 2018.
8. Rubin DB, Al Jarrah A, Li K, et al. Clinical predictors of neurotoxicity after chimeric antigen receptor T-cell therapy. JAMA Neurol. Published online August 10, 2020. doi:10.1001/jamaneurol.2020.2703

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

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

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

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

N/A

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

Embedded Data:

N/A

Response Summary:

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

Q1. Study Title

Determining long term outcomes of CD19 directed autologous Chimeric Antigen Receptor T-cell therapy in patients with B-cell Acute Lymphoblastic Leukemia and Diffuse Large B-cell Lymphoma using an ensemble stack of machine learning models

Q2. Key Words

Machine Learning, ALL, DLBCL, CAR T cell therapy

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Nasheed Hossain MD
Email address:	nmh1022@gmail.com
Institution name:	Loyola University Chicago
Academic rank:	Asst Professor of Medicine

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Reid Shaw
Email address:	reid.shaw@lumc.edu
Institution name:	Loyola University Chicago
Academic rank:	PGY1, Internal Medicine

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

- Yes

Q8. Do you identify as an underrepresented/minority?

- No

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

Nasheed Hossain

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

N/A

LETTER OF COMMITMENT:

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

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

GV18-01a - participated in reviewing concept and manuscript
LK19-02 - protocol review
GV18-02 - protocol review and data analysis
GV20-01 - protocol review
MM20-03 - protocol review
MM20-01- protocol review
MM19-02 - participated in reviewing concept, data analysis and manuscript prep
CK18-03- participated in reviewing concept, data analysis and manuscript prep
CK20-01 - protocol development
LK20-04- participated in reviewing concept, data analysis and manuscript prep
CK19-01a- participated in reviewing concept, data analysis and manuscript prep

Q13. PROPOSED WORKING COMMITTEE:

- Cellular Immunotherapy for Cancer

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

- No

Q15. RESEARCH QUESTION:

Can machine algorithms identify long term consequences of CAR T cell therapy in B-ALL and DLBCL?

Q16. RESEARCH HYPOTHESIS:

Machine learning algorithms can identify and predict long term consequences of CAR T cell therapy in B-ALL and DLBCL patients

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

Suggested word limit of 200 words:

1. Identify the long-term (>90days from CAR T-cell infusion) complications of patients who undergo CD19 CAR-T cell therapy
a. Recurrent Infections
b. Cytopenias
c. Hypogammaglobulinemia
d. Neurotoxicity/Psychiatric complications
e. GvHD in patients who had previously undergone an allogeneic stem cell transplant
f. Secondary Malignancies – solid organ and hematologic
g. Cardiac complications (MI, arrhythmias, heart failure)
2. Delineate if there are differences in long-term complications between patients who achieve a CR vs PR vs SD/PD at Day 90 after CAR infusion
3. Identify factors that may predict risk of long-term complications, including pre-CAR infusion characteristics
4. For patients who lose their response to CAR, assess the persistence of the complications listed in AIM 1 beyond Day 90 following CAR infusion

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

This study will help provide clinicians with an objective approach overview of the possible long-term complications of CAR T-cell therapy. It will help in the effort to formulate the approach to long-term care of this patient population including the types of complication to screen for in patients after they undergo CAR T-cell therapy.

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

This study will help provide clinicians with an objective approach overview of the possible long-term complications of CAR T-cell therapy. It will help in the effort to formulate the approach to long-term care of this patient population including the types of complication to screen for in patients after they undergo CAR T-cell therapy.
This retrospective study will compile the above-mentioned clinical parameters for each ALL or DLBCL patient who has undergone CD19 directed CAR-T therapy. The study will aim to identify the rates of late-onset (beyond Day 90) complications for patients who have had at least 6 months of follow-up, regardless of their initial response. Complications to focus on will include recurrent infections, hypogammaglobinemia, cytopenias, neurologic/psychiatric complications, recurrent GVHD, secondary malignancies and cardiac events (new Heart Failure, Elevated Troponin, Arrhythmias). The pre- and post-treatment clinical parameters will be compiled into tabular data for univariate, and multivariate analysis.
To identify factors that may predict risk of long-term complications, a classification model will be generated using machine learning. To briefly summarize, the data will be split into a 3:1 training to testing dataset. Depending on the sample size, the training data will be further partitioned, using k-fold cross validation or bootstrap-resampling for robust model training. Using a repeated measure ANOVA model, an XGBoost and Support Vector Machine model will be fit to the training dataset across a variety of model-specific hyperparameters. Then, variable importance will be computed across 10,000 pseudo-random model fits. Principal component analysis (PCA) will also be performed using all variables. Combining PCA and variable importance with univariate analysis will provide a clear understanding of the most important clinical parameters in predicting long-term complication.
These variables will then be used to build an ensemble stack of machine learning models to predict long term complications. Multiple classification machine learning models, including XGBoost, Random Forest, Neural Net, Support Vector Machines, Elastic Net, Naïve Bayes, Multivariate Adaptive Regression Splines, and C 5.0 Rule Based will be fit with the selected clinical parameters. Each algorithm will be tuned across their respective hyperparameters using a repeated measure ANOVA model or Bayes optimization. The results from of the machine learning models will then be compiled into an Ensemble Stack using LASSO regression across multiple different penalties. The final model will then be applied to the testing dataset. Sensitivity, specificity, positive predictive value, negative predictive value, and area under the receiver operator curve will be calculated for the final model and its individual components.

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

N/A

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

This retrospective study will compile the above-mentioned clinical parameters for each ALL or DLBCL patient who has undergone CD19 directed CAR-T therapy. The study will aim to identify the rates of late-onset (beyond Day 90) complications for patients who have had at least 6 months of follow-up, regardless of their initial response. Complications to focus on will include recurrent infections, hypogammaglobinemia, cytopenias, neurologic/psychiatric complications, recurrent GVHD, secondary malignancies and cardiac events (new Heart Failure, Elevated Troponin, Arrhythmias). The pre- and post-treatment clinical parameters will be compiled into tabular data for univariate, and multivariate analysis.

To identify factors that may predict risk of long-term complications, a classification model will be generated using machine learning. To briefly summarize, the data will be split into a 3:1 training to testing dataset. Depending on the sample size, the training data will be further partitioned, using k-fold cross validation or bootstrap-resampling for robust model training. Using a repeated measure ANOVA model, an XGBoost and Support Vector Machine model will be fit to the training dataset across a variety of model-specific hyperparameters. Then, variable importance will be computed across 10,000 pseudo-random model fits. Principal component analysis (PCA) will also be performed using all variables. Combining PCA and variable importance with univariate analysis will provide a clear understanding of the most important clinical parameters in predicting long-term complication.

These variables will then be used to build an ensemble stack of machine learning models to predict long term complications. Multiple classification machine learning models, including XGBoost, Random Forest, Neural Net, Support Vector Machines, Elastic Net, Naïve Bayes, Multivariate Adaptive Regression Splines, and C 5.0 Rule Based will be fit with the selected clinical parameters. Each algorithm will be tuned across their respective hyperparameters using a repeated measure ANOVA model or Bayes optimization. The results from of the machine learning models will then be compiled into an Ensemble Stack using LASSO regression across multiple different penalties. The final model will then be applied to the testing dataset. Sensitivity, specificity, positive predictive value, negative predictive value, and area under the receiver operator curve will be calculated for the final model and its individual components.

Q21. Does this study include pediatric patients?

- No

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

given variable incidence and ready availability of CAR for pediatric ALL and DLBCL, this will be a study focused on the adult population

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

Diagnosis (r/r DLBCL, transformed DLBCL, PMLBCL, ALL)
Age
Gender
Stage at Diagnosis
IPI score at diagnosis
Presence of bulky disease (at diagnosis and at time of CAR-T)
Disease status at CAR-T treatment
MRD status at time of CAR infusion
Prior History of Auto or AlloSCT
CART product received
Type of CART product (CD28 co-stim versus 4-1bb costimulatory)
LDH,Ferritin, CRP at time of CAR-T treatment at each follow up date
Blood counts at treatment (WBC, Platelets, Hemoglobin, ANC, ALC) and at each subsequent follow up date when response assessed
Presence or absence of fevers at time of CAR infusion
D28 Response
D90 Response
D120 Response
Month 6 Response
Month 9 Response
Month 12 Response
Maximum grade of CRS
Maximum grade of Neurotoxity
Presence of Cytopenias beyond Day 90
Presence of Hypogammaglobinemia after Day 90
Report of infections (including type) beyond Day 90
Report of GvHD after Day 90 following CAR infusion
New diagnosis of a secondary malignancy after CAR infusion – type of malignancy, time to diagnosis from time of CAR infusion
Neurologic Complications beyond Day 90
Psychiatric complications beyond Day 90
Timing of disease relapse
Elevated Troponin post CAR (Pre, D1- 30, D30-60, D60-90, D90+)
Reduced LV Ejection Fraction (Pre, D1- 30, D30-60, D60-90, D90+)
New clinically significant Arrhythmias ((Pre, D1- 30, D30-60, D60-90, D90+)

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

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

N/A

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

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

N/A

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

N/A

Q26. REFERENCES:

1. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371(16):1507-17.
2. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. December 2017. doi:10.1056/NEJMoa1707447.
3. Locke FL, Ghobadi A, Jacobson, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019 Jan;20(1):31-42. doi: 10.1016/S1470-2045(18)30864-7.
4. Nastoupil LJ, Jain MD, Spiegel JY et al. Axicabtagene Ciloleucel (Axi-cel) CD19 Chimeric Antigen Receptor (CAR) T-cell Therapy for Relapsed/Refractory Large B-cell Lymphoma:
Real World Experience. Presented at: the 60th ASH Annual Meeting and Exposition; December 1-4, 2018; San Diego, CA. Abstract 91.
5. Jacobson CA, Hunter B, Armand P. et al. Axicabtagene Ciloleucel in the Real World: Outcomes and Predictors of Response, Resistance and Toxicity. Presented at: the 60th ASH Annual Meeting and Exposition; December 1-4, 2018; San Diego, CA. Abstract 92.
6. Cordeiro A, Bezerra ED, Hirayama AV. Et al. Late events after treatment with CD19-Targeted Chimeric Antigen Receptor Modified T-cells. Biol Blood Marrow Transplant. 2019 Aug 13. pii: S1083-8791(19)30517-8. doi: 10.1016/j.bbmt.2019.08.003.
7. Alvi RM, Frigualt MJ, Fradley MG et al. Cardiovascular Events Among Adults Treated With Chimeric Antigen Receptor T-Cells (CAR-T). Journal of the American College of Cardiology, ISSN: 0735-1097, Vol: 74, Issue: 25, Page: 3099-3108

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

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

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

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

N/A

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

Embedded Data:

N/A

Response Summary:

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

Q1. Study Title

Predicting Response and Toxicity to CART in Patients with DLBCL Using Artificial Intelligence (AI)

Q2. Key Words

CART , AI

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	SOWJANYA VUYYALA
Email address:	SVUYYAL1@HFHS.ORG
Institution name:	henry ford
Academic rank:	HEM ON FELLOW INTERESTED IN SCT

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

N/A

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Shatha farhan
Email address:	sfarhan1@hfhs.org
Institution name:	henry ford
Academic rank:	clinical assistant professor

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

- No

Q8. Do you identify as an underrepresented/minority?

- Yes

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

shatha farhan

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

N/A

LETTER OF COMMITMENT:

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

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

N/A

Q13. PROPOSED WORKING COMMITTEE:

- Lymphoma

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

- No

Q15. RESEARCH QUESTION:

N/A

Q16. RESEARCH HYPOTHESIS:

We hypothesize that the data routinely collected for patients with DLBCL as part of the CIBMTR reporting contains predictive information which can be used to
a. Build predictive statistical and machine learning models, and
b. Develop a prototype clinical decision support tool,
which can be used to provide patients and providers with more precise information regarding their likelihood of CART failure and toxicity

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

Suggested word limit of 200 words:

Use statistical methods to identify significant patient, disease and CART factors that can inform machine learning models to predict the risk of :

- Early Relapse <6 months
- Late relapse >6 months
- CRS grade III & IV
- ICAN grade III & IV
- Late cytopenias > 3 months post CART

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

N/A

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

Chimeric antigen receptor (CAR) T cell therapy has been used in the treatment of relapsed/ refractory Diffuse Large B Cell Lymphoma (DLBCL) and produce a durable response in 40% of the patients (1). Patient are selected for treatment based on assessment of multiple patient and disease related factors including age, comorbidities and aggressiveness of the disease. Studies evaluating relapse have noted high tumor burden (LDH, total metabolic tumor volume), more than 2 extra nodal sites involvement, increased CRP to be associated with early relapse (2). ECOG Performance status of 2-4, elevated LDH, baseline CRP, prior treatment is associate with lack of response and shorter PS and OS (1,3). CAR T cell therapy carries a high burden of early and late toxicities. Cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS) have early and highly heterogenous presentation. Ferritin, absolute lymphocyte count, CRP, prior autologous transplant are associated with CRS, ICANS (1). Previous stem cell transplant and higher CRS grade were noted to be associated with late cytopenia(4). Given the highly heterogenous and multiple factors involved, prognosticating and predicting response to treatment is highly complex and no standarized prediction tool exists currently to help support the treatment decisions.

Artificial intelligence (AI) can help analyze the multiple patient data collected with CAR T cell therapy and help in predicting the response as well the patient at risk for toxicities. AI is being used in many solid tumors including breast cancer, gastric cancer to help in predicting the prognosis (5,6,7).

The patient and disease related data collected for CAR T cell therapy patients can be used to build statistical and machine learning models which can help predict the response to the treatment and also assist in developing a prototype clinical decision support tool to help guide the physician and patients

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

N/A

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

N/A

Q21. Does this study include pediatric patients?

- No

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

N/A

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

Predictive Variables
Recipient: Age at CART, age at diagnosis, gender, ethnicity, race, zip code, marital status, occupation, employment work status, education, health insurance, income, smoking/chewing history, smoking in last year, clinically significant co-existing diseases, prior solid tumor, prior hematologic malignancy, performance status, ABO Rh, HCT-CI, weight, height, pre-CART laboratory values and organ function testing (CBC and differential, chemistries, ferritin, liver enzymes, lung function testing, LDH, left ventricular ejection fraction, CRP, platelets), CMV antibodies, mechanical ventilation history, prior autologous HCT, history of infection, time from infection to CART, prior viral exposure/infection categorized, PS at CART age at CART , others if available : IL6,IL15, VWF , Ang-2
Disease: DLBCL classification (GC , non GC, transformed), time from diagnosis toCART, recurrent genetic abnormalities, prior disease if treatment related, prior therapy if treatment related, time from prior disease to CART, cytogenetic abnormalities (FISH/Karyotype) at diagnosis, molecular abnormalities at diagnosis, disease risk index, extra-nodal disease at diagnosis, bone marrow involvement at diagnosis, WBC at diagnosis, central nervous system (CNS) involvement pre-CART, time from last evaluation to CART, disease status at CART, time to achieve complete remission, PET positivity at CART and tumor burden , extra nodal disease at time of CART , baseline SUV and at time of CART,
Cellular Product and T cell dose
Bridging Regimen: radiation received, total radiation dose, number of radiation fractions, dose per fraction, chemotherapy medications, total
Lymphodepleting chemo : doses
Post CART : dose and time to use of toci , dose and time to use steroids , PET at 1 month
Outcome Variables
• Early Relapse <6 months
• Late relapse >6 months
• CRS grade III & IV
• ICAN grade III & IV
• Late cytopenias > 3 months post CART
Transplant Related Mortality: Time from transplant to death, cause of death

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

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N/A

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N/A

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

N/A

Q26. REFERENCES:

References
1 Axicabtagene Ciloleucel in the Real World: Outcomes and Predictors of Response, Resistance and Toxicity
Caron A.Jacobson MD
2. Predictive factors of early progression after CAR T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma
Laetitia Vercellino
3. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: Results from the US lymphoma CAR T consortium
Loretta J. Nastoupil
4. Late Effects after Chimeric Antigen Receptor T cell Therapy for Lymphoid Malignancies
Rajshekhar Chakraborty
5. Artificial intelligence in cancer diagnosis and prognosis: Opportunities and challenges
Shigao Huang
6. Artificial intelligence in gastric cancer: Application and future perspectives
Peng-Hui Niu
7. Breast cancer: The translation of big genomic data to cancer precision medicine
Siew-Kee Low,

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

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

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

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

N/A

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

Embedded Data:

N/A

2109-01, 2110-130, 2110-62, 2110-63: Patients undergoing 1st commercial CAR-T for DLBCL or ALL, 2016-present

Characteristic	N(%)
No. of patients	3950
No. of centers	152
Patient related	
Age at infusion, by category - no. (%)	
Median (min-max)	60 (0-91)
0-9	207 (5)
10-17	242 (6)
18-29	296 (7)
30-39	179 (5)
40-49	296 (7)
50-59	726 (18)
60-69	1178 (30)
>= 70	826 (21)
Recipient Sex - no. (%)	
Male	2458 (62)
Female	1492 (38)
Recipient race - no. (%)	
White	3050 (77)
African-American	199 (5)
Asian	171 (4)
Pacific Islander	6 (0)
Native American	15 (0)
More than one race	47 (1)

Characteristic	N(%)
Unknown	217 (5)
Missing	245 (6)
Recipient ethnicity - no. (%)	
Hispanic or Latino	569 (14)
Non Hispanic or non-Latino	2969 (75)
Non-resident of the U.S.	266 (7)
Unknown	141 (4)
Missing	5 (0)
Performance score prior to CT - no. (%)	
90-100	1717 (43)
=80	1070 (27)
< 80	744 (19)
Missing	419 (11)
ECOG performance status prior to CT - no. (%)	
0 - Asymptomatic	1717 (43)
1 - Symptomatic but completely ambulatory	1645 (42)
2 - Symptomatic, < 50% in bed during the day	157 (4)
3 - Symptomatic, > 50% in bed, but not bedbound	9 (0)
4 - Bedbound	3 (0)
Missing	419 (11)
CT-CI - no. (%)	
0	1304 (33)
1	748 (19)
2	481 (12)
3+	1341 (34)

Characteristic	N(%)
TBD	15 (0)
NA (not collected for these cases)	2 (0)
Missing	59 (1)
Disease related	
Disease classification - no. (%)	
t(5;14) (q31;q32); IL3-IGH	2 (0)
B-lymphoblastic leukemia / lymphoma with Hyperdiploidy (51-65 chromosomes)	39 (1)
B-lymphoblastic leukemia / lymphoma with Hypodiploidy (<46 chromosomes)	18 (0)
B-lymphoblastic leukemia / lymphoma, BCR-ABL1-like	40 (1)
B-lymphoblastic leukemia / lymphoma, with iAMP21	15 (0)
Early T-cell precursor lymphoblastic leukemia	1 (0)
NHL diffuse, large B-cell	803 (20)
Burkitt lym/Burkitt cell leukemia	8 (0)
T-cell / histiocytic rich large B-cell lymphoma	49 (1)
Primary mediastinal large B-cell	82 (2)
Other B-cell	11 (0)
precursor B-cell ALL	421 (11)
t(9;22)(q34;q11); BCR/ABL+	30 (1)
t(v;11q23); MLL rearranged	52 (1)
t(1;19)(q23;p13) E2A/PBX1	8 (0)
t(12;21)(p12;q22) ETV/CBFa	23 (1)
Diffuse, large B-cell lymphoma- Germinal center B-cell type	1133 (29)
Diffuse, large B-cell lymphoma- Activated B-cell type	785 (20)
Primary cutaneous DLBCL, leg type	4 (0)
EBV+ DLBCL, NOS	24 (1)

Characteristic	**N(%)**
DLBCL associated with chronic inflammation	1 (0)
High-grade B-cell lymphoma, NOS	62 (2)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	337 (9)
Burkitt-like lymphoma with 11q aberration	2 (0)
IPI at initial diagnosis of the primary disease - no. (%)	
Low	90 (2)
Low intermediate	144 (4)
High intermediate	175 (4)
High	190 (5)
Missing	3351 (85)
Stage of organ involvement at initial diagnosis of the primary disease - no. (%)	
I	235 (6)
II	369 (9)
III	645 (16)
IV	1139 (29)
Unknown	468 (12)
Missing	1094 (28)
Disease status at CT - no. (%)	
CR	138 (3)
PR	710 (18)
Resistant	2134 (54)
Untreated	198 (5)
Unknown	116 (3)
Missing	654 (17)
Prior lines of therapies - no. (%)	

Characteristic	N(%)
No	8 (0)
Yes	3671 (93)
1	2702 (68)
2	107 (3)
>= 3	685 (17)
Missing	177 (4)
Missing	271 (7)
Prior radiation therapy - no. (%)	
No	2518 (64)
Yes	1062 (27)
Missing	370 (9)
Prior HCT - no. (%)	
No	2880 (73)
Yes	986 (25)
Prior allo-HCT	191 (5)
Prior auto-HCT	769 (19)
Prior auto and allo-HCT	10 (0)
Missing	16 (0)
Missing	84 (2)
Time from HCT to CT, months - median (min-max)	15 (1-315)
CAR-T cell related	
Year of CT - no. (%)	
2017	17 (0)
2018	628 (16)
2019	1131 (29)

Characteristic	N(%)
2020	1262 (32)
2021	912 (23)
Product - no. (%)	
Kymriah	1592 (40)
Yescarta	2357 (60)
Tecartus	1 (0)
Time from diagnosis to CT - no. (%)	
Median (min-max)	16 (1-447)
0-6 months	448 (11)
6-12 months	1051 (27)
1-2 years	1058 (27)
2-3 years	1392 (35)
Missing	1 (0)
Bridging therapy - no. (%)	
No	2424 (61)
Yes	903 (23)
Systemic therapy	714 (18)
Intrathecal therapy	29 (1)
Intraocular therapy	1 (0)
Radiation therapy	242 (6)
Surgery	1 (0)
Not reported	623 (16)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)	
No	15 (0)
Yes	3934 (100)

Characteristic	**N(%)**
Bendamustine only	126 (3)
Flu+Cy only	3716 (94)
Other	84 (2)
None selected	8 (0)
Missing	1 (0)
None selected	1 (0)
Follow-up, in months - median (range)	13 (1-43)

Response Summary:

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

Q1. Study Title

Center-specific differences in utilization of CAR T-cell therapy and its implications on outcomes

Q2. Key Words

CAR T-cell therapy, B-cell lymphoma, Resource utilization

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Ameet Patel, MD, MMHC
Email address:	ameet.patel@vumc.org
Institution name:	Vanderbilt University Medical Center
Academic rank:	Clinical Fellow

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Bhagirathbhai, Dholaria, MBBS
Email address:	Bhagirathbhai.r.dholaria@vumc.org
Institution name:	Vanderbilt University Medical Center
Academic rank:	Assistant professor

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

- Yes

Q8. Do you identify as an underrepresented/minority?

- No

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

Ameet Patel

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

N/A

LETTER OF COMMITMENT:

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

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

none currently

Q13. PROPOSED WORKING COMMITTEE:

- Cellular Immunotherapy for Cancer

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

- Yes

Q14a. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Dr. Pasquini

Q15. RESEARCH QUESTION:

Are differences in institution or center-specific variables influence outcomes in CAR T-cell therapy?

Q16. RESEARCH HYPOTHESIS:

Center-specific variables have a significant impact on the outcomes of CAR T cell therapy

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

Suggested word limit of 200 words:

1. Identify if there are differences in clinical outcomes based on centers accredited to administer CAR T-cell therapy
2. Evaluate if center-specific characteristics explain variation in results of aim one

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

Understanding the nature of center-specific differences that influence CAR T-cell therapy outcomes will be important to identify potential factors or proxies for quality measures to monitor in the future.

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

Chimeric antigen receptor (CAR) T-cell therapy is a novel and rapidly developing treatment modality in the use of relapsed/refractory non-hodgkin's lymphoma. Five CAR T agents that are FDA approved include Axicabtagene ciloleucel, Brexucabtagene autoleucel (brexu-cel), Lisocabtagene maraleucel (liso-cel) and Tisagenlecleucel (tisa-cel), and more recently Idecabtagene vicleucel (ide-cel). All cellular products have demonstrated dramatic response with a subset of patients having durable remissions (1-5). Many more CAR T therapies are under investigation. With the abundance of approvals, international collaborations have set standards for administration and management of CAR T-cell therapy (7, 8).

Despite this, there have been significant concerns regarding cost and payment structures for CAR T-cell therapy in the U.S (9-11). Moreover, the collection and manufacture process of CAR T-cell therapy remain heterogenous with speculative concern that this may alter efficacy or toxicities of therapy. With both cost, manufacturing, and biological differences in cellular products, this invariably leads to unique strategies institutions may adopt to provide CAR T-cell therapy to patients (12, 13). These strategies for successful implementation are varied and include (but not limited to) the adoption of and specialty specific intensive care units, structures of care delivery (inpatient vs outpatient), utilization of infrastructure built for allogeneic transplantation, survivorship services, use of more than one cellular product, center volume of treatment, or in-house manufacturing (12, 14, 15).

It remains unknown whether presence of these center-specific and/or cellular product characteristics influence the outcomes for patients receiving CAR T-cell therapy.

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

N/A

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

Adult patients with history of non-Hodgkin lymphoma who received CAR T cell therapy between 2017 to 2021.

Q21. Does this study include pediatric patients?

- No

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

Current FDA approved therapies for B-cell lymphomas are mostly limited to adult patients.

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

Institution-specific descriptors
A) Center characteristics:
Proxy or Presence of:
-FACT accreditation (binary)
-HSCT center (binary)

Relevant forms: CIBMTR as applicable from institutional form submissions (e,g, 2006)
B) Volume
# of CAR T-cell therapies done over specified time interval per institution
# of allogeneic/autologous transplants done each year per institution
---
Relevant forms: CIBMTR as applicable from institutional form submissions
Patient clinical descriptors
C) Demographic characteristics
Age, gender, performance status

Relevant forms: 4000
D) Hematologic characteristics:
Patients with NHL
Presence & date of remission prior to CAR T-cell therapy
Prior lines of therapy
History of autologous/allogeneic stem cell transplant
Use of bridging therapy

Relevant forms: 4000
E) Organ function
Presence of comorbidities

Relevant forms: 4000
F) Cellular therapy product characteristics
Type of product used (axi-cel, tisa-cel, liso-cel, brexu-cel)
Date of cell collection
Mobilization events: 1 or >1
Cell product manipulation: yes/no, all or portion

Methods of manipulation: culture, differentiation, selection (+/- or antigen based)
Transfection vector: lenti or retrovirus
Cell viability testing done: yes/no, date, % viability, method of testing
Product persistence testing (binary, yes/no)
Cryopreserved (binary, yes/no)

Relevant forms: 4003 / 4006 /4100
G) CAR T specific characteristics
Date of infusion
Documented best response post CAR T-cell therapy
Presence of CRS and Neurotoxicity & max score
Presence of seizures or cerebral edema
Date of relapse
Date of cytopenias
Date of hypogammaglobulinemia, treatment and if resolved
Maximum grade toxicity of any organ
Development of a second malignancy

Relevant forms: 4100 / 3500
Primary Endpoints
H) Overall Survival / Relapse Free survival
Based on date and last survey of relevant form. Months from day of CAR T infusion
Relapse free survival will be included: Months from day of CAR T infusion
---
Relevant forms: 4100
I) CAR T Toxicities
Presence of:
CRS (binary), & maximum grade (quantitative)
Neurotoxicity & related sequelae (e.g. seizures) (binary) & maximum grade
Infections post – treatment (binary) & hypogammaglobulinemia (binary)&
Cytopenia beyond D+30 (binary)

Relevant forms: 4100 / 3500

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

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

N/A

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

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

n/a

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

n/a

Q26. REFERENCES:

References:
1. F. L. Locke et al., Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. The lancet oncology 20, 31-42 (2019).
2. S. J. Schuster et al., Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. New England Journal of Medicine 380, 45-56 (2019).
3. P. Jain et al., Outcomes and management of patients with mantle cell lymphoma after progression on brexucabtagene autoleucel therapy. British journal of haematology, (2020).
4. N. C. Munshi et al. (American Society of Clinical Oncology, 2020).
5. J. S. Abramson et al., Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. The Lancet 396, 839-852 (2020).
6. C. Jacobson, in 62nd ASH Annual Meeting and Exposition. (ASH, 2020).
7. Foundation for the Accreditation of Cellular Therapy, University of Nebraska Medical Center, March 2018.
8. A. S. Kanate et al., Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant 26, 1247-1256 (2020).
9. A. E. Hay, M. C. Cheung, CAR T-cells: costs, comparisons, and commentary. J Med Econ 22, 613-615 (2019).
10. J. K. Lin et al., Cost Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Multiply Relapsed or Refractory Adult Large B-Cell Lymphoma. J Clin Oncol 37, 2105-2119 (2019).
11. P. Petrou, Is it a Chimera? A systematic review of the economic evaluations of CAR-T cell therapy. Expert Rev Pharmacoecon Outcomes Res 19, 529-536 (2019).
12. O. L. Reddy, D. F. Stroncek, S. R. Panch, Improving CAR T cell therapy by optimizing critical quality attributes. Semin Hematol 57, 33-38 (2020).
13. S. A. Tuazon et al., Factors affecting lymphocyte collection efficiency for the manufacture of chimeric antigen receptor T cells in adults with B-cell malignancies. Transfusion 59, 1773-1780 (2019).
14. G. L. Shah, N. Majhail, N. Khera, S. Giralt, Value-Based Care in Hematopoietic Cell Transplantation and Cellular Therapy: Challenges and Opportunities. Curr Hematol Malig Rep 13, 125-134 (2018).
15. S. Sievers, G. Watson, S. Johncy, S. Adkins, Recognizing and Grading CAR T-Cell Toxicities: An Advanced Practitioner Perspective. Front Oncol 10, 885 (2020).

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

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

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

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

N/A

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

Embedded Data:

N/A

2110-37: Patients undergoing 1st commercial CAR-T for NHL or ALL in the US, 2017-present

Characteristic	N(%)
No. of patients	4166
No. of centers	135
Patient related	
Age at infusion, by category - no. (%)	
Median (min-max)	61 (0-91)
0-9	197 (5)
10-17	226 (5)
18-29	283 (7)
30-39	181 (4)
40-49	311 (7)
50-59	796 (19)
60-69	1289 (31)
>= 70	883 (21)
Recipient Sex - no. (%)	
Male	2645 (63)
Female	1521 (37)
Recipient race - no. (%)	
White	3358 (81)
African-American	224 (5)
Asian	182 (4)
Pacific Islander	8 (0)
Native American	17 (0)
More than one race	48 (1)

Characteristic	N(%)
Unknown	228 (5)
Missing	101 (2)
Recipient ethnicity - no. (%)	
Hispanic or Latino	610 (15)
Non Hispanic or non-Latino	3340 (80)
Non-resident of the U.S.	60 (1)
Unknown	154 (4)
Missing	2 (0)
Performance score prior to CT - no. (%)	
90-100	1801 (43)
=80	1163 (28)
< 80	804 (19)
Missing	398 (10)
ECOG performance status prior to CT - no. (%)	
0 - Asymptomatic	1801 (43)
1 - Symptomatic but completely ambulatory	1782 (43)
2 - Symptomatic, < 50% in bed during the day	170 (4)
3 - Symptomatic, > 50% in bed, but not bedbound	12 (0)
4 - Bedbound	3 (0)
Missing	398 (10)
CT-CI - no. (%)	
0	1338 (32)
1	811 (19)
2	513 (12)
3+	1424 (34)

Characteristic	N(%)
TBD	17 (0)
NA (not collected for these cases)	2 (0)
Missing	61 (1)
Disease related	
Disease classification - no. (%)	
t(5;14) (q31;q32); IL3-IGH	2 (0)
B-lymphoblastic leukemia / lymphoma with Hyperdiploidy (51-65 chromosomes)	30 (1)
B-lymphoblastic leukemia / lymphoma with Hypodiploidy (<46 chromosomes)	17 (0)
B-lymphoblastic leukemia / lymphoma, BCR-ABL1-like	39 (1)
B-lymphoblastic leukemia / lymphoma, with iAMP21	14 (0)
Early T-cell precursor lymphoblastic leukemia	1 (0)
NHL follicular,predominantly small cleaved cell	18 (0)
NHL follicular,mixed,small cleaved and large cell	47 (1)
NHL diffuse, large B-cell	731 (18)
Burkitt lym/Burkitt cell leukemia	8 (0)
NHL mantle cell	250 (6)
Primary CNS lymphoma	17 (0)
T-cell / histiocytic rich large B-cell lymphoma	48 (1)
Extranodal marginal zone B-cell of MALT	1 (0)
Nodal marginal zone B-cell	3 (0)
Splenic marginal zone B-cell	1 (0)
Primary mediastinal large B-cell	72 (2)
Other B-cell	14 (0)
Intravascular large B-cell lymphoma	3 (0)
B-cell unclass. between DLBCL and hodgkin	10 (0)

Characteristic	N(%)
Follicular, predominantly large cell Grade IIIA	33 (1)
Follicular, predominantly large cell Grade IIIB	13 (0)
Follicular unknown grade	22 (1)
precursor B-cell ALL	406 (10)
t(9;22)(q34;q11); BCR/ABL+	28 (1)
t(v;11q23); MLL rearranged	50 (1)
t(1;19)(q23;p13) E2A/PBX1	7 (0)
t(12;21)(p12;q22) ETV/CBFa	20 (0)
Follicular, predominantly large cell (Grade IIIA vs IIIB not specified)	5 (0)
Diffuse, large B-cell lymphoma- Germinal center B-cell type	1085 (26)
Diffuse, large B-cell lymphoma- Activated B-cell type	746 (18)
Primary cutaneous DLBCL, leg type	4 (0)
EBV+ DLBCL, NOS	23 (1)
DLBCL associated with chronic inflammation	1 (0)
High-grade B-cell lymphoma, NOS	59 (1)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	324 (8)
Large B-cell lymphoma with IRF4 rearrangement	1 (0)
Burkitt-like lymphoma with 11q aberration	2 (0)
Plasmablastic lymphoma	4 (0)
Polymorphic PTLD	1 (0)
Monomorphic PTLD (B- and T- / NK-cell types)	6 (0)
IPI at initial diagnosis of the primary disease - no. (%)	
Low	100 (2)
Low intermediate	166 (4)
High intermediate	198 (5)

Characteristic	N(%)
High	211 (5)
Missing	3491 (84)
Stage of organ involvement at initial diagnosis of the primary disease - no. (%)	
I	254 (6)
II	385 (9)
III	670 (16)
IV	1298 (31)
Unknown	481 (12)
Missing	1078 (26)
Disease status at CT - no. (%)	
CR	150 (4)
PR	775 (19)
Resistant	2294 (55)
Untreated	205 (5)
Unknown	122 (3)
Missing	620 (15)
Prior lines of therapies - no. (%)	
No	7 (0)
Yes	3882 (93)
1	2869 (69)
2	105 (3)
>= 3	766 (18)
Missing	142 (3)
Missing	277 (7)
Prior radiation therapy - no. (%)	

Characteristic	N(%)
No	2679 (64)
Yes	1125 (27)
Missing	362 (9)
Prior HCT - no. (%)	
No	3067 (74)
Yes	1029 (25)
Prior allo-HCT	186 (4)
Prior auto-HCT	819 (20)
Prior auto and allo-HCT	14 (0)
Missing	10 (0)
Missing	70 (2)
Time from HCT to CT, months - median (min-max)	17 (1-315)
CAR-T cell related	
Year of CT - no. (%)	
2017	18 (0)
2018	645 (15)
2019	1136 (27)
2020	1272 (31)
2021	1095 (26)
Product - no. (%)	
Kymriah	1451 (35)
Yescarta	2475 (59)
Tecartus	240 (6)
Time from diagnosis to CT - no. (%)	
Median (min-max)	17 (1-447)

Characteristic	N(%)
0-6 months	440 (11)
6-12 months	1044 (25)
1-2 years	1092 (26)
2-3 years	1590 (38)
Bridging therapy - no. (%)	
No	2615 (63)
Yes	935 (22)
Systemic therapy	743 (18)
Intrathecal therapy	30 (1)
Intraocular therapy	1 (0)
Radiation therapy	247 (6)
Surgery	1 (0)
Not reported	616 (15)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)	
No	12 (0)
Yes	3538 (100)
Bendamustine only	135 (4)
Flu+Cy only	3318 (93)
Other	78 (2)
None selected	7 (0)
Missing	1 (0)
None selected	1 (0)
Follow-up, in months - median (range)	12 (1-41)
Centers of patients undergoing 1st CAR-T for NHL or ALL US, 2017-present	
No. of centers with pediatric infusions	58

Characteristic	**N(%)**
Center Volume (pediatric infusions since 2016) - no. (%)	
Median (min-max)	5 (1-43)
1-2	18 (31)
3-7	17 (29)
8-14	11 (19)
15-131	12 (21)
No. of centers with adult infusions	129
Center Volume (adult infusions since 2016) - no. (%)	
Median (min-max)	15 (1-232)
1-5	39 (30)
6-18	29 (22)
19-44	40 (31)
45-289	21 (16)