Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR CELLULAR IMMUNOTHERAPY FOR CANCER
Orlando, FL
Friday, February 17, 2023, 12:00 p.m. – 2:00 p.m. (EST)

Co-Chair:	**Peiman Hematti, MD; University of Wisconsin Hospitals and Clinics, Madison, WI; E-mail: pxh@medicine.wisc.edu**
Co-Chair:	**Sairah Ahmed, MD, PhD; M.D. Anderson Cancer Center; E-mail: sahmed3@mdanderson.org**
Co-Chair:	**Cameron Turtle, MBBS, PhD; Fred Hutchinson Cancer Research Center, Seattle, WA; E-mail: cturtle@fredhutch.org**
Scientific Director:	**Amy Moskop MD, MS; CIBMTR Statistical Center, Milwaukee, WI; E-mail: amoskop@mcw.edu**
Scientific Director:	**Marcelo Pasquini, MD, MS; CIBMTR Statistical Center, Milwaukee, WI; E-mail: mpasquini@mcw.edu**
Statistical Director:	**Soyoung Kim, PhD; CIBMTR Statistical Center, Milwaukee, WI; E-mail: skim@mcw.edu**
Statistician:	**Matthew Bye, MPH; CIBMTR Statistical Center, Milwaukee, WI; E-mail: mabye@mcw.edu**

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1. **Introduction**

   a. **Minutes and Overview Plan from February 2022 meeting** (Attachment 1)
   b. **Introduction of new upcoming Chair:** Christine Phillips, MD (Cincinnati Children's)
   c. **Instructions for sign-in and voting**

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

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

   a. **CT21-01** Mirza A, Hosing C, Foss F, Kim S, Moskop A, Oloyede T, Ahmed S, Hematti P, Turtle C J, Pasquini M C, Gowda L. Impact of Age on Outcomes after CD19 directed CAR T cell therapy for Large B Cell Lymphomas: Real Word Experience from the Center for International Blood & Marrow Transplant Research (CIBMTR). ***Poster Presentation, ASH 2022.***
   b. **CT20-03** Greenbaum U, Hashmi H, Elsawy M, Kim S, Moskop A, Awan F, Farooq U, Ganguly S, Hematti P, Jain M, Kabriaei P, Locke F, Mead E, Nishihori T, Olson A, Pennisi M, Perales M A, Ramakrishnan P, Shouval R, Shpall E J, Magalhaes-Silverman M, Strouse C, Turtle C, Vallurupalli A, Wudhikarn K, Pasquini M C, Ahmed S, Sorror M. Prognostic Impact of Comorbidities on Outcomes of Patients (pts) with Relapsed or Refractory Large B-cell Lymphoma (r/r LBCL) Treated with Chimeric Antigen Receptor T-cell Therapy (CART). ***Poster Presentation, ASH 2022.***

c. **SC17-07** Jacobson CA, Locke FL, Ma L, Asubonteng J, Hu ZH, Siddiqi T, Ahmed S, Ghobadi A, Miklos DB, Lin Y, Perales MA, Lunning MA, Herr MM, Hill BT, Ganguly S, Dong H, Nikiforow S, Hooper M, Kawashima J, Xu H, Pasquini MC. Real-world evidence of axicabtagene ciloleucel for the treatment of large B cell lymphoma in the United States. ***Transplantation and Cellular Therapy. 2022 Sep 1; 28(9):581.e1-581.e8. doi:10.1016/j.jtct.2022.05.026. Epub 2022 May 21. PMC9427701.***

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 Preparation.**
b. **AC17-01** CAR-T with or without subsequent HCT for ALL **Manuscript Submitted.**
c. **AC18-01** Effect of stem cell boost and donor lymphocyte infusion on the incidence of GVHD **Data File Preparation.**
d. **CT19-02** Prolonged cytopenia following CAR-T for DLBCL **Manuscript Preparation.**
e. **CT20-01** Comparison of commercial CAR T cells for DLBCL **Manuscript Preparation/Submitted.**
f. **CT20-02** Health Resource utilization in CAR T cells **Data File Preparation.**
g. **CT20-03** Determinants of outcomes after CAR T cells for Lymphoma **Manuscript Preparation.**
h. **CT20-04** Determinants of outcomes after CAR T cells for ALL **Data File Preparation.**
i. **CT21-01** Outcomes of elderly patients receiving CAR-T for DLBCL **Manuscript Preparation.**
CT22-01 CD19-CAR-T therapy failure: Impact of subsequent therapy in patients with B-cell malignancies **Protocol Development.**
j. **CT 22-02** Machine learning for predicting toxicity and early clinical outcomes in DLBCL and B-ALL patients treated with commercial CAR T products in the real-world setting: an analysis of the CIBMTR registry **Protocol Development.**

5. Future/Proposed Studies

a. Outcomes of CD19 CAR-T in patients who received lymphodepleting chemotherapy using fludarabine-containing versus other regimens (combined from the following proposals):
    i. **PROP 2207-02** Fludarabine alternatives in CAR-T therapy (R Kamble) (Attachment 4a)
    ii. **PROP 2209-05** Outcomes of CD19 CAR-T in patients with r/r B cell lymphoma who received lymphodepleting chemotherapy using fludarabine-containing versus other regimens (N Ahmed, S Ganguly) (Attachment 4b)
    iii. **PROP 2210-89** What is the influence of conditioning regimen on the efficacy of CAR T cell therapy (A Sieg, C Strouse) (Attachment 4c)
    iv. **PROP 2210-114** Patterns of conditioning before CAR T-cell therapy for large B-cell lymphoma and the effect on clinical outcomes (A Ali, C Rodriguez-Bonilla) (Attachment 4d)
    v. **PROP 2210-252** Impact of lymphodepleting agents on the outcomes of Chimeric Antigen Receptor T-cell therapies (K Nadiminti, P Pophali) (Attachment 4e)
    vi. **PROP 2210-264** Alternative lymphodepletion before CAR-T cell therapy (S Mirza, L Gowda) (Attachment 4f)
b. Impact of prophylactic steroids and tocilizumab on incidence of CRS and ICANS in patients undergoing treatment with CAR T-cell therapy (Attachment 5) (combined from the following proposals):
    i. **PROP 2207-01** Impact of prophylactic steroids and tocilizumab on incidence of CRS and ICANS in patients undergoing treatment with axicabtagene ciloleucel for lymphoma (O Oluwole, S Bhaskar)

ii. **PROP 2210-01** Explore the Efficacy and Safety of Three Prophylactic Measures to Mitigate the Toxicities in Chimeric Antigen Receptor (CAR) T-cell Therapy (J Wang, L Metheny)

iii. **PROP 2210-77** Impact of prophylactic steroids and tocilizumab on incidence of CRS and ICANS in patients undergoing treatment with axicabtagene ciloleucel for lymphoma (O Oluwole, S Bhaskar)

c. **PROP 2209-13** Comparative Outcomes Analysis of Patients with Aggressive B-Cell Lymphoma Treated With Axicabtagene CiloleucelI vs. LisocabtageneI Maraleucel (A Mian, B Hill) (Attachment 6)

d. **PROP 2210-28** Comparative Outcomes Analysis of Outpatient and Inpatient Administration of Chimeric Antigen Receptor (CAR) T-cell Therapy for Aggressive B Cell Lymphomas (V Patel, O Oluwole) (Attachment 7)

e. **PROP 2210-194** Antibiotics exposure correlates of response and toxicity following anti-CD19 CAR T cell therapy (C Elgarten, R Myers) (Attachment 8)

f. **PROP 2210-15** Effect of Delayed Cell Infusion on Outcomes in Patients with Large B-cell Lymphoma Receiving Chimeric Antigen Receptor (CAR) T-cell Therapy (A Jallouk, P Strati) (Attachment 9)

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

a. Prolonged Cytopenia Following anti-B Cell Maturation Antigen (BCMA) CAR T-cell Therapy for Relapsed/Refractory Multiple Myeloma (RRMM) (Combined from the following proposals):

i. **PROP2210-69** Prolonged Cytopenia Following anti-B Cell Maturation Antigen (BCMA) Chimeric Antigen Receptor (CAR) T-cell Therapy for Relapsed/Refractory Multiple Myeloma (RRMM) (J Logue, D Hansen) (Attachment 10a)

ii. **PROP 2210-79** Prolonged Cytopenia Following CAR-T Therapy for Multiple Myeloma (M Janakiram, G Kaur) (Attachment 10b)

b. **PROP 2210-293** Temporal Trends in Outcomes after CAR T-Cell Therapy for relapsed or refractory B-cell Lymphoma (O Agbedia, P Strati) (Attachment 11)

Proposed studies; not accepted for consideration at this time

a. **PROP 2210-02** Explore the Efficacy of CAR T-cell Therapy in Uncommon Types of Large B-cell Lymphomas

b. **PROP 2210-29** Toxicity and Outcomes of patients with B-cell acute lymphoblastic leukemia with negative measurable residual disease at the time of CD19 CAR T-cells therapy

c. **PROP 2210-33** Characterizing differences in clinical outcomes of CAR T-cell therapy for relapsed/refractory ALL and LBCL based on gender

d. **PROP 2210-35** Pre-emptive and early tocilizumab usage and risk of infections in patients receiving CAR-T therapy

e. **PROP 2210-38** Potential for granulocyte-colony stimulating factor in preventing infections in CAR-T recipients without worsening immune-related toxicities

f. **PROP 2210-45** Outcomes of CAR T-cell-associated HLH Toxicities in B-ALL, NHL, and Multiple Myeloma

g. **PROP 2210-83** Assessing safety and efficacy of allogeneic stem cell transplant after CD19-targeted chimeric antigen receptor T-cell therapy

h. **PROP 2210-138** Outcomes of CD19 chimeric antigen receptor (CAR) T cell therapy post targeted immunotherapy in relapsed/refractory (R/R) diffuse large B cell lymphoma (DLBCL), B-cell acute lymphoblastic leukemia (B-ALL) and Multiple Myeloma (MM)
i. **PROP 2210-178** Fludarabine Lymphodepletion Exposure As A Driver of Clinical Outcomes After CAR-T
j. **PROP 2210-184** The impact of pre-therapy vitamin D status on outcomes of patients with large B-cell lymphoma treated with CD19-directed chimeric antigen receptor T-cell therapy
k. **PROP 2210-220** Outcomes of CAR-T therapy in adult patients with relapsed or refractory (R/R) B-ALL
l. **PROP 2210-267** Outcomes of chimeric antigen receptor T-cell treatment for B-cell malignancies relapsing after allogeneic hematopoietic cell transplantation.
m. **PROP 2210-268** Impact of HLA-B leader peptide dimorphism on outcomes of patients treated with CAR T therapy for lymphoid malignancies
n. **PROP 2210-274** CAR T cell therapy in Adults with B-cell Acute lymphoblastic leukemia (B-ALL): Clinical Predictors of Toxicity and Efficacy.
o. **PROP 2210-275** Outcomes of Anti-CD19 CAR T-cell therapy for Relapsed Refractory Mantle cell lymphoma
p. **PROP 2210-292** Outcomes of CAR T Therapy Among Patients with Hematologic Malignancies who Relapse After Allogeneic Hematopoietic Cell Transplantation
q. **PROP 2210-295** Outcomes of patients with B-cell lymphomas relapsing following CD19 directed Chimeric Antigen Receptor (CAR) T-cell therapy: Real-World Data from the Center for International Blood and Marrow Transplant Research (CIBMTR)
r. **PROP 2210-300** Impact of obesity on outcomes in CD19-directed CAR-T patients

6. Other Business

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR CELLULAR IMMUNOTHERAPY FOR CANCER
Salt Lake City, UT
Sunday, April 24, 2022, 6:30 AM – 8:15 AM MDT

Co-Chair:	**Sarah Nikiforow, MD, PhD; Dana Faber Cancer Institute; E-mail: snikiforow@partners.org**
Co-Chair:	**Peiman Hematti, MD; University of Wisconsin Hospitals and Clinics; E-mail: pxh@medicine.wisc.edu**
Co-Chair:	**Cameron Turtle, MBBS, PhD; Fred Hutchinson Cancer Research Center; E-mail: cturtle@fredhutch.org**
Scientific Director:	**Marcelo Pasquini, MD, MS; CIBMTR Statistical Center, Milwaukee, WI; E-mail: mpasquini@mcw.edu**
Scientific Director:	**Amy Moskop MD, MS; CIBMTR Statistical Center, Milwaukee, WI; E-mail: amoskop@mcw.edu**
Statistical Director:	**Soyoung Kim, PhD; CIBMTR Statistical Center, Milwaukee, WI; E-mail: skim@mcw.edu**
Statistician:	**Benjamin Jacobs, MS; CIBMTR Statistical Center, Milwaukee, WI; E-mail: bjacobs@mcw.edu**

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

Dr. Sarah Nikiforow opened the meeting and introduced the chairs and staff of the CICWC. She then explained the procedure of the proposals: there was 5 minutes for presentation and 5 for questions for each proposal. She also reviewed the proposals submitted this year related to cellular therapy.
Dr. Marcelo Pasquini then reviewed the welcome slides. He thanked out-going chair Dr. Nikiforow for her service and gave her a gift on behalf of the committee. He introduced Dr. Amy Moskop as the committee's new scientific director. He also introduced the new upcoming Chair, Dr. Sairah Ahmed, MD, from MD Anderson Cancer Center. Dr. Pasquini explained the purpose of the new collaborative session. He then explained the voting procedures and the new authorship rules.

2. Accrual summary (Attachment 2)

Dr. Pasquini reviewed the accrual of the cell therapy registry. There are now over 6000 cellular therapy infusions with new and increasing numbers of indications. There were over 100 proposals submitted this year were related to CAR T-cell therapies across all working committees. There proposals were divided up among CICWC as well as Lymphoma, Plasma Cell disorders, Health Services, and Infection and Immune reconstitution Working committees based on PI's submitted requested WC and scientific director review. Reasons for dropped studies were overlap with current studies or due to feasibility or needing supplemental information or longer follow up. Please refer to the "CICWC Dropped proposed studies" and "Studies Transferred to Other Working Committees" section below for full list.

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)

Dr. Pasquini briefly reviewed the committee's 9 active studies, 4 of which are in manuscript preparation.

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

Dr. Pasquini reviewed the scoring process for the proposals being presented. He also reviewed the collaborative session and one of the CICWC studies being presented at that time. This session will be held on April 25th, at 2 pm MST. This study will still be voted on within the CICWC.

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

Dr. Dean from the Cleveland Clinic presented 'Myelodysplastic Syndrome / Acute Myelogenous Leukemia after Autologous Chimeric Antigen Receptor T-Cell Immunotherapy for Non-Hodgkin Lymphoma.'

Background: MDS/AML are a known life-threatening complication after autoHCT. But what about after CAR-T? MDS/AML were rarely reported in the NHL CAR-T registration trials.

Hypothesis: The real-world risk of MDS/AML after auto CAR-T is higher than reported in registration trials.

Objectives: To characterize risk of MDS/AML after CAR-T for DLBCL and MCL and to identify potential risk factors for subsequent MDS/AML.

Impacts: This could inform treatment decisions and optimal sequencing of autoCAR-T, support development of novel clinical trials to minimize MDS/AML risk after autoCAR-T and facilitate collaboration among centers to study additional factors.
Data: All required data is on standard CIBMTR forms; 8 AML and 35 MDS cases were found in the preliminary data. Majority did not have prior HCT; this is surprising to the presenter.

- *Dr. Nikiforow asked whether the missing data for subsequent malignancy in the database would lead to follow up bias?*
    - *Dr. Pasquini was of the opinion that there are enough cases. Subsequent neoplasm is the primary endpoint of PASS, so it's a matter of follow-up. The question may be whether to wait another year.*
- *From the audience, as CAR-T becomes a front-line therapy, would you consider looking at the exact prior therapies? Form 2018 wasn't listed in the list of forms to be used.*
    - *Dr. Dean agreed, one limitation is the exact number of prior therapies. He thought that proper treatment for patients with chemo-resistant disease could be helped to be answered by this study. Exclusion of form 2018 was an oversight on his part.*
- *From the audience: one concern is inclusion of both MCL and DLBCL; maybe just include one to make it cleaner. Would be hard to tease out malignancy caused by chemo vs. caused by CAR-T. Also, ZUMA-1 also had a low utilization of prior HCT in its population, so this is not far off.*
- *Dr. Fred Locke suggested to rephrase the hypothesis, and to wait to collect more cases. The real question is: does CRS and the resultant hypocellularity accelerate MDS?*
    - *Dr. Dean agreed attribution of MDS/AML will be tricky, we won't have an easy time attributing it to autoCAR-T as opposed to prior therapies.*

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)

Dr. Ana Alarcon Tomas from MSKCC presented "CD19-CAR-T cell therapy failure: Impact of subsequent therapy in patients with B-cell malignancies."

Background: CAR-T therapies are increasing in use, resulting in higher response rates in r/r LBCL, but many patients still experience relapse. Their question is: what are the best treatment strategies after CD19 CAR-T therapy? A registry study may be the only way to answer this question.

Hypothesis: Patients with r/r B-cell malignancies who receive subsequent therapies after CAR T-cell therapy have better outcomes than those who don't receive further treatment; immune modulatory therapies used after CAR-T have higher response rates and better OS; infusion of 2nd or subsequent CD-19 CAR-T cells is safe and offers higher response rates in both adult and pediatric patients with B-cell malignancies.
Aims: describe toxicities, identify predictors for outcomes; compare characteristics and outcomes for patients who received subsequent therapy and those who didn't, compare ORR, OS, and PFS among different subsequent strategies; explore impact of prior exposure to CD19 targeting drugs to post CAR-T treatments and outcomes.

Primary endpoints: ORR, OS, and PFS and real-world utilization patterns of subsequent treatments after CAR-T cell therapy.

- *Comment from the audience: it would be important to evaluate the characteristics of the relapse, whether the patient retains CD19—is that something in the dataset?*
    - *Dr. Alarcon said that this is something we would need to collect.*
    - *Dr. Moskop said it will be added to the forms, we're in the process of going back to get that.*
    - *Dr. Nikiforow commented that for the transplants after ALL, some are for relapse, some are for consolidation: is that something you have access to?*
    - *Dr. Alarcon said that there is an ongoing project looking at that, we do not want to overlap.*
    - *Dr. Moskop said that we do not collect indication, but we can look at events in-between such as relapse.*
- *From the audience, there was a concern that this data is so big and heterogenous that it will be hard to analyze. Also, there are already a lot of other people looking at this problem. There are other limitations to doing this project here, such as remission, and having patient-level data. What is the advantage of doing this at CIBMTR?*
    - *Dr. Alarcon said she was aware of sample size limitations. It will be difficult, but CIBMTR accrual numbers will go up, and will open the possibility of future prospective studies.*
- *Dr. Hematti asked whether they will compare treatment to number of previous lines.*
    - *Dr. Alarcon said that they thought about this and included the number of previous lines of therapy as a variable to be analyzed.*
- *Question from the chat: do you have plans to aggregate treatments into groups?*
    - *Dr. Alarcon replied that they would probably group by main drug (lenalidomide-based, etc.)*
- *From the chat: do we have data whether the therapy is treatment or maintenance?*
    - *Dr. Alarcon stated that PR/CR is collected on the forms.*
    - *Dr. Moskop confirmed that we collect it by indication.*

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)

Dr. Alex Lazaryan from Moffitt Cancer presented "Composite end point of toxicity-free and progression-free survival (TPFS) after CD19 CAR T cell therapy for large B-cell lymphoma.'

Background: success of CAR-T is due to efficacy and low rate of toxicities. CRS and ICANS are major sources of morbidity and mortality. Research is ongoing in solving this.

Hypothesis: TPFS is an ideal endpoint of CAR-T, as it measures initial success (at 6 months) without progression, major toxicities/morbidities, and mortality.

More background: TPFS is the absence of III-IV CRS, III-IV ICANS, Progression, NRM.
Objectives: define TPFS and estimate for all 3 FDA approved CAR-T cell products. Then assess factors associated with TPFS at 6 months and assess whether TPFS at 6 months is prognostic for 1- and 2-year survival.

Scientific Impact: The novel endpoint would be useful for evaluating new drugs/treatments (such as JAK-, GM-CSF, and TKI-inhibitors) which may mitigate CAR-T toxicities while also modifying its efficacy. TPFS would capture their net effect.

Data: No non-standard data needed.

- *From the audience, someone noted that the study is limited to 18 and older patients: would you consider including pediatric patients?*
  - *Dr. Lazaryan agreed that is a good point. This is just a starting point; we need to start somewhere; we may consider that for a future study.*
- *Dr. Sarah Nikiforow asks why to restrict to grades III-IV as opposed to other complications which are important to clinical outcomes.*
  - *Dr. Lazaryan said that for composite endpoints, each component must be meaningful and equally judged. Less than grade 3 is not as severe as relapse. Other complications would go into the NRM bucket.*
- *From the online Q&A: someone suggested to include duration, as this impacts whether the treatment must be in-patient or out-patient.*
  - *Dr. Lazaryan agreed this was an excellent point. Duration is meaningful for patients, especially older patients.*

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

Dr. Muhammad Abid from MCW presented "Role of G-CSF in preventing infections in CAR-T recipients without worsening immune-related toxicities."

Background: Clinical data on C-CSF utilization is limited and unclear in the CAR-T; G-CSF could exacerbate CRS and ICAN; there is evidence that G-CSF may decrease infection, but significantly increased severity of CRS, and its duration.

Hypothesis: G-CSF use shortens duration of neutropenia; is associated with increased incidence, severity, and duration of CRS and ICANS; G-CSF use after CAR-T infusion does not impact 1-year response rates and OS.

Endpoints: CRS II-IV and III-IV and ICANS II-IV and III-IV per ASTCT criteria; incidence of neutropenia, time to ANC, cumulative incidence, and density of infections; OS, PFS, NRM, DOR

Data needs: majority of data is in CTED forms; need to acquire G-CSF usage in first 30 days including type/formulation of growth factor, dosage, and duration

- *Dr. Nikiforow asked Dr. Pasquini to comment on the viability of collecting supplemental data. Also at her center, they tend to give Neulasta after LD chemo.*
    - Dr. Pasquini believed it was doable. We got 70% of the CBC data when we collected supplemental data for the cytopenia study. Also, if the question is important, we may add it to the form in the future.
- From the audience: context matters for G-CSF utilization. How do you plan to handle planned use vs in response to an infection?
    - Dr. Abid said that the aim is to study G-CSF in the first 30 days, not in response to infections after that point.
    - The audience member clarified this question applies to the first 30 days.
    - Dr. Abid replied that we don't have that data, but we can collect it; this moves the registry forward; it is up to the leadership's discretion.
- From the audience: is 30 days too early a cutoff for looking at G-CSF?
- Dr. Doug Rizzo commented that if planned use then we could just ask centers to see how they use G-CSF. If ad hoc use is the interest, then that is a different issue, and very different data needs. Not a criticism, just a suggestion to revise the question.
- From the audience: is another end point better, such as number of days with ANC less than 500?
    - This is not currently the plan.

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)

Dr. Madhia Iqbal from the Mayo Clinic presented "Effect of Renal Comorbidity on Outcomes in Chimeric Antigen Receptor T-cell Therapy in B Cell Lymphoma."

Background: Renal disfunction is a known risk factor for mortality in patients receiving alloHCT and is a component of the HCT-CI. Adequate kidney function was a requirement of enrollment on pivotal clinical trials for CAR-T. Fludarabine is a common lymphodepletion regiment for CAR-T, but poor renal function is predictive of fludarabine toxicity. In real world, patients with poor renal function receive CAR-T, but we don't know its impact.

Hypothesis: Renal insufficiency predicts inferior survival and increased toxicities in recipients of CAR-T therapy for B cell lymphoma.

Objectives: Identify risk factors for relapse and survival in patients with renal insufficiency; look at the impact of dose reduction of fludarabine on toxicities and disease outcomes in CAR-T patients with renal insufficiency

Inclusion: 18 or older, who have received first CAR-T infusion for treatment of B-cell lymphoma.

Scientific Impact: Outcomes of CAR-T for patients with renal dysfunction is a knowledge gap; this study will help guide treatment of these patients, especially fludarabine dosage.

- *From the audience, for Dr. Pasquini: Is there overlap with another study (CT20-03, which looks at HCT-CI for CAR-T)?*
    - *Dr. Pasquini explained that the other study is looking at HCT-CI for all patients; this would be a sub-population study. There is overlap, but this study is more specific and brings a different perspective to the problem.*
- *From the audience: Why not include ALL patients? It's good to focus on specific populations, but this question is equally applicable to ALL patients.*
    - *Dr. Iqbal agreed that more patients would make the study stronger; it is equally applicable.*
- *From the audience: The hypothesis is confusing: finding optimal dosing is a different question than*

impact of renal insufficiency on CAR-T.
    - *Dr. Iqbal agreed these are different questions.*
- *From the same person: Do we have PK for fludarabine?*
    - *Dr. Iqbal said we have dose but not PK.*
- *Sr. Nikiforow commented that it would be nice to have these variables and the timeline of creatinine.*
    - *Dr. Iqbal agreed that having longitudinal data would be good.*
- *Dr. Sarah Nikiforow suggested to look at dose reduction over time to assess practice patterns; asked Dr. Pasquini if that sounded reasonable.*
- *From the audience, there was a suggestion to make this a dynamic study, since kidney function changes between leukapheresis, lymphodepletion, and infusion.*
    - *Dr. Iqbal agreed this would make a stronger study; it depends on what timepoints we have creatinine for.*
- *Dr. Miguel Perales commented that we should balance the perfect study against a study that will get done: a dynamic study will not happen, we should focus on the main question, namely, the decision to dose adjust fludarabine based on creatinine.*

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)

Dr. Jason Wang from University Hospitals Seidman Cancer Center presented 'Explore the Efficacy and Safety of Prophylactic Use of Tocilizumab and Anti-epileptic Medications in CAR T-cell Therapy Recipients.'

Background: Tocilizumab is beginning to be used to for prophylaxis of CRS, not just for pre-emption of CRS; efficacy of the two approaches is unclear; may lead to increased risk of infections. Previous CIBMTR research into this was inconclusive. Anti-epileptic medications (AEDs) are widely used for preventing ICANS and seizures.

Hypothesis: prophylactic and pre-emptive use of tocilizumab in patients with B-cell malignancies receiving CAR-T therapy is associated with an increased risk of clinically significant infections, less severe CRS, without affecting ICANS and clinical efficacy. Prophylactic use of AEDs is associated with less severe ICANS.

Endpoints: clinically significant infections at day 30 and day 100; incidence, severity, and duration of CRS; incidence of neutropenia at day 300, time to neutrophil recovery, subsequent treatment for CRS, severity of ICANS, ORR, PFS, OS; incidence, severity, and duration of ICANS; seizure incidence, subsequent treatment for ICANS

Data: question about prophylactic use of Tocilizumab and AEDs was only added in 2020, so the numbers are small.

Scientific Impact: If efficacy and safety of prophylactic use of tocilizumab and AEDs is shown, future randomized controlled studies may be needed to confirm benefit; if no clear benefit is seen in this retrospective study, the practice will be brought into question.

- *Dr. Pasquini commented that the numbers are small because of recent changes to the forms. The question of prophylactic vs. Treatment use is a recent addition. Before we did not specify prophylactic vs. other use.*
- *Dr. Perales was going to ask about feasibility, but it is answered now.*
- *Dr. Nikiforow asked what 'pre-emptive' means, how is it different than prophylaxis? We may not be able to use this distinction, as we don't collect timing.*
    - *Dr. Wang replied that in the form we collect dynamics of developing CRS over time, but timing of tocilizumab is not given, does not know if there's a way to define pre-emptive use. Dr. Moskop confirmed we don't collect timing of tocilizumab usage.*

- *From the chat: a question about patients also receiving steroids, Dr. Hematti assumed they mean prophylactic use of steroids.*
    - *Dr. Wang said that it if the patient received steroids, it may be collected in the 'other' field on the forms.*
- *Dr. Tania Jain, via the chat, commented on the need to be cautious about collecting data, and whether prophylactic use of tocilizumab has changed recently due to recent publications.*
- *Dr. Pasquini commented that we are seeing a variety of agents for prophylaxis on the forms, and an impact of earlier and earlier therapies.*
- *From the audience: are you considering the co-stimulating agent?*

    Dr. Wang agreed that this is an important risk factor.

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

Dr. Nishi Shah from Montefiore Medical Center and Albert Einstein College of Medicine presented "Impact of obesity on outcomes of CD-19 directed CAR-T therapy in lymphoma patients."

Background: There are currently three FDA-approved CAR-T products for lymphoma; they differ in their manufacturing, efficacy, and risks. The approval trials did not consider patients' obesity. Studies have suggested that obesity leads to immune dis-regulation. Recent studies imply this is a subset which needs to be studied further.

Aim: to evaluate rates of toxicities and OS in obese CAR-T patients.

Outcomes: Overall response, including complete and partial remission post CAR-T cell therapy. PFS and OS.

Scientific impact: better understanding of obese CAR-T patients and their outcomes. Data generated from this study could form the basis for a prospective study.

- *Dr. Perales asked if we collect dosing of each of the agents? Also, you may need to separate out different agents.*
    - *Dr. Moskop clarified that we collect dosing.*
- *Dr. Peiman Hematti had a question about whether this study can answer the effect of the obesity on the outcome versus the effect of the obesity on the dosing of the LD chemo drugs; the obesity may affect that decision and affect the outcomes that way rather than directly.*
- *Someone from the audience suggested looking at leukemia and lymphoma.*
- *Someone from the audience suggested that since the dosing is often capped, we could use this to study where to cap.*
    - *Dr. Pasquini said that the Kite group did a study at ASCO last year, which looked at this a little bit. We will have data issues for Yescarta.*
- *Someone from the audience commented that it is important to look at pediatric patients, but to be aware that BMI does not define obesity for pediatric patients. Also, it's known that obese patients have worse toxicities from chemotherapy, so they may be coming in with pre-existing comorbidities. Can this be controlled for?*
- *Someone from the audience commented that weight is just one part of a larger biological picture, but weight is still interesting to look at regardless of the other factors, which CIBMTR might not be able to look at.*
- *Dr. Lazaryan asked whether it is possible to look at association with inflammatory markers. Dr. Hematti thought it would be possible to look at that.*
- *Dr. Nikiforow asked about the comorbidity paper that is being worked on.*

Dr. Pasquini said that that paper is looking to build a co-morbidity score; this study would be more specific.

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)

There were two presenters for 'Machine learning for predicting toxicity and early clinical outcomes in DLBCL and C-ALL patients treated with commercial CAR-T in the real-world setting: an analysis of the CIBMTR registry.'

Background: The presenters gave a brief overview of machine learning: supervised learning has an outcome it is predicting; unsupervised learning is trying to group things without a pre-specified outcome. Classification has a discrete response; regression has a continuous response. They explained the concept of 'stacking' or 'ensembling' machine learning algorithms to combine different algorithms. Current prognostic scores do not fully capture the nuances of CAR-T therapy; machine learning algorithms can provide better accuracy than traditional methods.

Objectives: to identify predictors of toxicities including CRS, ICANS, and day 30 cytopenias; identify predictors of complete response at 3 and 6 months; to identify homogenous patient subgroups from baseline data using unsupervised machine learning tools, and correlate these with outcomes.

Methods: split data 3-to-1 training to testing datasets. A binary classification model to predict response at 3 and 6 months. A second model for multi-class classification of toxicities, severe CRS, severe ICANS, and day 30 cytopenias. A third model to 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 relapse. All models will involve ensembling.

- *There was a comment that investigating the time series with machine learning would be novel, not sure that machine learning will help with the other objectives or add anything valuable. Also, can you use neural nets?*
    - *The presenter replied that the stacking approach is novel and tends to outperform other machine learning methods. We can do neural nets.*
- *Dr. Pasquini commented on an ongoing study (CT20-03) whose dataset we could use for this study as well. Our statistics group thought it would be good to compare machine learning to traditional statistical methods, and we should invite the CT20-03 team to participate if this study goes forward.*
- *From the audience, someone asked how do they decide which effects are spurious/noise, and which are real? In some machine learning projects they have found ZIP code to be meaningful, for instance.*
    - *The presenter said that the answer is to use feature analysis, feature selection, and domain expertise. Additional statistical analysis could help answer it.*
- *Dr. Nikiforow asked about the clinical relevance of this work, and if we have enough data for what they are proposing.*
    - *The presenter said that he was impressed with the amount of data CIBMTR has, there is plenty of data to do this work. They could also use bootstrapping and cross-validation to augment the numbers, but they have plenty.*

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

The meeting adjourned at 8:15 AM MST.

Working Committee Overview Plan for 2022-2023		
Study Number and Title	**Current Status**	**Chairs Priority**
AC16-01: Pattern of use and outcomes with donor lymphocyte infusion after HLA-haploidentical allogeneic hematopoietic stem cell transplant	Manuscript Preparation	2
AC17-01: CAR-T with or without subsequent HCT for ALL	Manuscript Preparation	1
AC18-01: Effect of stem cell boost and donor lymphocyte infusion on the incidence of GVHD	Protocol Development	2
CT19-02: Prolonged cytopenia following CAR-T for DLBCL	Manuscript Preparation	1
CT20-01: Comparison of commercial CAR T cells for DLBCL	Analysis	1
CT20-02: Health Resource utilization in CAR T cells	Data File Preparation	2
CT20-03: Determinants of outcomes after CAR T cells for Lymphoma	Analysis	2
CT20-04: Determinants of outcomes after CAR T cells for ALL	Protocol Development	2
CT21-01: Outcomes of elderly patients receiving CAR-T for DLBCL	Protocol Development	3
CT22-01: CD18-CAR-T therapy failure: Impact of subsequent therapy in patients with B-cell malignancies	Protocol Pending	3
CT22-02: Machine learning for predicting toxicity and early clinical outcomes in DLBCL and B-ALL patients treated with commercial CAR T products in the real-world setting: an analysis of the CIBMTR registry	Protocol Pending	3

Patients who received CAR after 2016

Characteristic	Commercial Car-T	Noncommercial Car-T	Total
No. of patients	8059	1408	9467
No. of centers	181	123	189
CT infusion counting number - no. (%)			
1	8059 (100)	1408 (100)	9467
Age at infusion, by category - no. (%)			
Median (min-max)	62 (0-91)	58 (1-89)	61 (0-91)
0-9	298 (4)	108 (8)	406 (4)
10-19	474 (6)	149 (11)	623 (7)
20-29	368 (5)	79 (6)	447 (5)
30-39	335 (4)	56 (4)	391 (4)
40-49	597 (7)	127 (9)	724 (8)
50-59	1532 (19)	256 (18)	1788 (19)
60-69	2552 (32)	373 (26)	2925 (31)
70+	1903 (24)	260 (18)	2163 (23)
Primary disease - no. (%)			
ALL	1062 (13)	334 (24)	1396 (15)
NHL	6226 (77)	603 (43)	6829 (72)
MM/PCD	771 (10)	347 (25)	1118 (12)
Other	0 (0)	124 (9)	124 (1)
NHL disease classification - no. (%)			
Follicular	365 (5)	51 (4)	416 (4)
DLBCL	5281 (66)	448 (32)	5729 (61)
MCL	500 (6)	47 (3)	547 (6)

Characteristic	Commercial Car-T	Noncommercial Car-T	Total
Other	80 (1)	57 (4)	137 (1)
N/A, other disease	1833 (23)	805 (57)	2638 (28)
Age at infusion, by category #2 - no. (%)			
0-17	669 (8)	225 (16)	894 (9)
1-39	806 (10)	167 (12)	973 (10)
40-65	3320 (41)	574 (41)	3894 (41)
65+	3264 (41)	442 (31)	3706 (39)
Age at infusion, by category #3 - no. (%)			
0-64	4795 (59)	966 (69)	5761 (61)
65+	3264 (41)	442 (31)	3706 (39)
Gender - no. (%)			
Male	5062 (63)	856 (61)	5918 (63)
Female	2988 (37)	551 (39)	3539 (37)
Not Reported	9 (0)	1 (0)	10 (0)
Recipient race - no. (%)			
White	6235 (77)	1052 (75)	7287 (77)
Black or African American	497 (6)	112 (8)	609 (6)
Asian	370 (5)	60 (4)	430 (5)
Native Hawaiian or other Pacific Islander	13 (0)	5 (0)	18 (0)
American Indian or Alaska Native	27 (0)	6 (0)	33 (0)
Other	70 (1)	12 (1)	82 (1)
More than one race	437 (5)	91 (6)	528 (6)
Missing	410 (5)	70 (5)	480 (5)
Recipient ethnicity - no. (%)			
Hispanic or Latino	1076 (13)	216 (15)	1292 (14)

Characteristic	Commercial Car-T	Noncommercial Car-T	Total
Not Hispanic or Latino	6229 (77)	1048 (74)	7277 (77)
Non-resident of the U.S.	509 (6)	69 (5)	578 (6)
Unknown	244 (3)	52 (4)	296 (3)
99	1 (0)	23 (2)	24 (0)
Country - no. (%)			
US	7612 (94)	1356 (96)	8968 (95)
Non-US	447 (6)	52 (4)	499 (5)
Disease - no. (%)			
Acute myeloid leukemia (AML)	0 (0)	33 (2)	33 (0)
Acute lymphoblastic leukemia (ALL)	1062 (13)	334 (24)	1396 (15)
Acute leukemia of ambiguous lineage and other myeloid neoplasms	0 (0)	6 (0)	6 (0)
Chronic myeloid leukemia (CML)	0 (0)	4 (0)	4 (0)
Myelodysplastic/myeloproliferative diseases (MDS/MPN)	0 (0)	3 (0)	3 (0)
Other leukemia (including CLL/PLL)	0 (0)	33 (2)	33 (0)
Non-Hodgkin lymphoma (NHL)	6226 (77)	603 (43)	6829 (72)
Hodgkin lymphoma (HD)	0 (0)	24 (2)	24 (0)
Plasma cell disorder/multiple myeloma (PCD/MM)	771 (10)	347 (25)	1118 (12)
Solid tumor	0 (0)	20 (1)	20 (0)
Other indication	0 (0)	1 (0)	1 (0)
Lymphodepleting regimen - no. (%)			
Yes	8034 (100)	1368 (97)	9402 (99)
Lymphodepleting chemotherapy: bendamustine	395 (5)	7 (0)	402 (4)
Lymphodepleting chemotherapy: bendamustine + Lymphodepleting chemotherapy: cyclophosphamide	1 (0)	0 (0)	1 (0)
Lymphodepleting chemotherapy: bendamustine + Lymphodepleting chemotherapy: cyclophosphamide + Lymphodepleting chemotherapy: fludarabine	2 (0)	0 (0)	2 (0)

Characteristic	Commercial Car-T	Noncommercial Car-T	Total
Lymphodepleting chemotherapy: bendamustine + Lymphodepleting chemotherapy: cytarabine	1 (0)	0 (0)	1 (0)
Lymphodepleting chemotherapy: bendamustine + Lymphodepleting chemotherapy: fludarabine	0 (0)	8 (1)	8 (0)
Lymphodepleting chemotherapy: bendamustine + Lymphodepleting chemotherapy: other	6 (0)	0 (0)	6 (0)
Lymphodepleting chemotherapy: carboplatin + Lymphodepleting chemotherapy: fludarabine	2 (0)	0 (0)	2 (0)
Lymphodepleting chemotherapy: clofarabine + Lymphodepleting chemotherapy: cyclophosphamide	1 (0)	0 (0)	1 (0)
Lymphodepleting chemotherapy: clofarabine + Lymphodepleting chemotherapy: fludarabine	1 (0)	0 (0)	1 (0)
Lymphodepleting chemotherapy: cyclophosphamide	43 (1)	5 (0)	48 (1)
Lymphodepleting chemotherapy: cyclophosphamide + Lymphodepleting chemotherapy: cytarabine + Lymphodepleting chemotherapy: etoposide + Lymphodepleting chemotherapy: fludarabine	1 (0)	0 (0)	1 (0)
Lymphodepleting chemotherapy: cyclophosphamide + Lymphodepleting chemotherapy: cytarabine + Lymphodepleting chemotherapy: fludarabine	3 (0)	1 (0)	4 (0)
Lymphodepleting chemotherapy: cyclophosphamide + Lymphodepleting chemotherapy: etoposide	0 (0)	1 (0)	1 (0)
Lymphodepleting chemotherapy: cyclophosphamide + Lymphodepleting chemotherapy: fludarabine	7479 (93)	1248 (89)	8727 (92)
Lymphodepleting chemotherapy: cyclophosphamide + Lymphodepleting chemotherapy: fludarabine + Lymphodepleting chemotherapy: other	18 (0)	16 (1)	34 (0)
Lymphodepleting chemotherapy: cyclophosphamide + Lymphodepleting chemotherapy: other	12 (0)	0 (0)	12 (0)
Lymphodepleting chemotherapy: cyclophosphamide + Lymphodepleting chemotherapy: thiotepa	1 (0)	1 (0)	2 (0)

Characteristic	Commercial Car-T	Noncommercial Car-T	Total
Lymphodepleting chemotherapy: cytarabine	1 (0)	0 (0)	1 (0)
Lymphodepleting chemotherapy: cytarabine + Lymphodepleting chemotherapy: etoposide	2 (0)	1 (0)	3 (0)
Lymphodepleting chemotherapy: cytarabine + Lymphodepleting chemotherapy: fludarabine	15 (0)	1 (0)	16 (0)
Lymphodepleting chemotherapy: etoposide + Lymphodepleting chemotherapy: other	1 (0)	0 (0)	1 (0)
Lymphodepleting chemotherapy: fludarabine	33 (0)	7 (0)	40 (0)
Lymphodepleting chemotherapy: other	0 (0)	1 (0)	1 (0)
None specified	16 (0)	71 (5)	87 (1)
No	24 (0)	37 (3)	61 (1)
99	1 (0)	3 (0)	4 (0)
Clinical trial - no. (%)			
No	7918 (98)	40 (3)	7958 (84)
Yes	141 (2)	1368 (97)	1509 (16)
Product - no. (%)			
Kymriah	2309 (29)	0 (0)	2309 (24)
Yescarta	4017 (50)	0 (0)	4017 (42)
Tecartus	609 (8)	0 (0)	609 (6)
Breyanzi	353 (4)	0 (0)	353 (4)
Abecma	653 (8)	0 (0)	653 (7)
Carvykti	118 (1)	0 (0)	118 (1)
Other	0 (0)	1408 (100)	1408 (15)
Types of prior HCTs - no. (%)			
No prior HCT	5601 (69)	712 (51)	6313 (67)
Prior allo-HCT	329 (4)	163 (12)	492 (5)
Prior auto-HCT	2007 (25)	499 (35)	2506 (26)
Prior auto and allo-HCT	33 (0)	12 (1)	45 (0)

Characteristic	Commercial Car-T	Noncommercial Car-T	Total
99	89 (1)	22 (2)	111 (1)
Year of CT - no. (%)			
2016	0 (0)	94 (7)	94 (1)
2017	20 (0)	146 (10)	166 (2)
2018	716 (9)	228 (16)	944 (10)
2019	1297 (16)	312 (22)	1609 (17)
2020	1515 (19)	292 (21)	1807 (19)
2021	2246 (28)	202 (14)	2448 (26)
2022	2265 (28)	134 (10)	2399 (25)
Time from receiving H4000 baseline form to infusion, days - median (min-max)	28 (-33-1568)	115 (-5-1876)	33 (-33-1876)
No. of patients with follow-up	6732	1311	8043
Follow-up - median (range)	13 (0-54)	24 (1-76)	13 (0-76)

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TO: Cellular Immunotherapy for Cancer Working Committee Members

FROM: Amy Moskop, 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 (Akshay Sharma, Neel S Bhatt, Gunjan Shah, Lowith Gowda, Muhammad Bilal Abid)
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 2023.

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 manuscript was submitted Winter 2022

AC18-01: Effect of stem cell boost and donor lymphocyte infusion on the incidence of GVHD (Edmund K. Waller)
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 March 2023.

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 Spring of 2023.

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 manuscript preparation. The plan is to submit for publication by the Spring 2023.

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 protocol development. The plan is to finalize data set by the Summer of 2023.

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 manuscript preparation. The plan is to submit for publication by Summer 2023. We will also begin analysis of the toxicity and efficacy aims

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 2023.

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 manuscript preparation. The plan is to submit for publication by Summer 2023.

CT22-01: CD19-CAR-T therapy failure: Impact of subsequent therapy in patients with B-cell malignancies (Ana, Alarcon Tomas, Lauren Appell, Evandro Bezerra, Abu-Sayeef Mirza, Miguel-Angel Perales, Akshay Sharma, Yi Lin, Lohith Gowda, Guru Subramanian Guru Murthy)

The primary purpose of this study is:

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

The secondary purpose of this study is:

1. To describe toxicities (CRS, ICANS, and NRM) associated with different subsequent treatment strategies and identify factors that may predict the best response to those strategies.
2. To compare characteristics and clinical outcomes (OS and PFS) of those who received subsequent therapy with those who didn't
3. To compare ORR, OS and PFS among the different subsequent strategies stratified by commercial CAR T products and early or late relapse (before and after day 100) including comparisons for those that received treatment while in ongoing CR/PR with those in SD/PD.
4. To explore the impact of prior exposure to CD19 targeting drugs to post CAR-T treatments/outcomes in ALL patients.

This study is currently in protocol development. The plan is to finalize data set by Summer 2023.

CT22-02 Machine learning for predicting toxicity and early clinical outcomes in DLBCL and B-ALL patients treated with commercial CAR T products in the real-world setting: an analysis of the CIBMTR registry (Adrian Mosquera Orgueira, Loretta J. Nastoupil, Sowjanya Vuyyala, Shatha Farhan, Nasheed M Hossain, Reid Shaw)

The primary purpose of this study is:

1. To identify predictors of early toxicities, including severe CRS, neurotoxicity, and day 30 cytopenia associated with CAR-T therapy.

2. To identify predictors of complete response at 3 months and 6 month for B-ALL patients treated with Tisagenlecleucel
3. To identify predictors for complete response at 3 months and 6 months for DLBCL patients treated with anti-CD19 CAR-T cells
4. To identify homogeneous patient subgroups from baseline data using unsupervised machine learning tools, and correlate these with disease response and drug-specific toxicity with disease outcomes

This study is currently in protocol development. The plan is to finalize data set by Summer 2023.

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

Fludarabine alternatives in CAR-T therapy

Q2. Key Words

CAR-T, Fludarabine, CD19, Lymphoma

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Rammurti Kamble, MD
Email address:	Kamble@sbcglobal.net
Institution name:	Baylor College of Medicine
Academic rank:	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):	na
Email address:	na
Institution name:	na
Academic rank:	na

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:

NA

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.

Several CIBMTR analyses

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:

Alternatives to fludarabine and outcomes of CD-19 or BCMA CAR-T

Q16. RESEARCH HYPOTHESIS:

Alternatives to fludarabine provides non-inferior outcomes of CD-19 or BCMA CAR-T

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

Suggested word limit of 200 words:

Primary end points: Relapse free survival at 30 days, 100 days, 1- year and 2 years.
Secondary end points:
1. Regimen related toxicity
3. CRS
3. ICANS

Since fludarabine is not readily available, clinicians are struggling to find its alternative. Recently, bendamustine has been used but other agents are also receiving attention. Several contenders are listed here along with their respective elimination half life.

Current Agent	Elimination Half-life
Fludarabine	20 hours
CY	3-12 hours
Alternative agents	Elimination half life
Nelarabine	20 minutes
Pentostatin	6 hours
Clofarabine	5 hours

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.

CIBMTR analyses will provide outcomes of fludarabine alternates that will facilitate treatment decisions

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.

Ghilardi et al reported outcomes for bendamustine. They compared the safety and efficacy of lymphodepletion using either fludarabine/cyclophosphamide (n = 42) or bendamustine (n = 90) before tisagenlecleucel in two cohorts of patients with relapsed or refractory large B-cell lymphomas treated consecutively at three academic institutions in the United States (University of Pennsylvania, n = 90; Oregon Health & Science University, n = 35) and Europe (University of Vienna, n = 7). Response was assessed using the Lugano 2014 criteria and toxicities were assessed by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and, when possible, the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading.
Fludarabine/cyclophosphamide led to more profound lymphocytopenia after tisagenlecleucel infusion compared with bendamustine, although the efficacy of tisagenlecleucel was similar between the two groups. We observed significant differences, however, in the frequency and severity of adverse events. In particular, patients treated with bendamustine had lower rates of cytokine release syndrome and neurotoxicity. In addition, higher rates of hematological toxicities were observed in patients receiving fludarabine/cyclophosphamide. Bendamustine-treated patients had higher nadir neutrophil counts, hemoglobin levels, and platelet counts, as well as a shorter time to blood count recovery, and received fewer platelet and red cell transfusions. Fewer episodes of infection, neutropenic fever, and post-infusion hospitalization were observed in the bendamustine cohort compared with patients receiving fludarabine/cyclophosphamide.
There is lack of information on any other agent.

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 CD-19 and BCMA CAR-T patients will be included. Patients will be divided in to Fludarabine cohort and non-fludarabine cohort

Q21. Does this study include pediatric patients?

- No

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

Safety of alternate agents not known 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.

Standard data collection form will be used

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 needed

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.

Not needed

Q26. REFERENCES:

G.Ghilard E.A.Chong J.Svoboda et al. Bendamustine is safe and effective for lymphodepletion before tisagenlecleucel in patients with refractory or relapsed large B-cell lymphomas. Annals of Oncol 2022 Jun 9;S0923-7534(22)01722-7

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.

NA

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

Outcomes of CD19 CAR-T in patients with r/r B cell lymphoma who received lymphodepleting chemotherapy using fludarabine- containing versus other regimens

Q2. Key Words

chimeric antigen receptor T cell (CART), lymphoma, fludarabine shortage, bendamustine

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Nausheen Ahmed, MD
Email address:	nahmed5@kumc.edu
Institution name:	University of Kansas 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):	Siddhartha Ganguly, MD FACP
Email address:	sganguly@houstonmethodist.org
Institution name:	Houston Methodist Hospital and Cancer Center
Academic rank:	Professor; Chief, Division of Hematology

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:

Nausheen Ahmed, 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 have reviewed and suggested edits to several proposals and manuscripts in the process. I am an active participant in several CIBMTR working committees. I also serve on the ASTCT survivorship SIG

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:

Optimization of conditioning chemotherapy is critical to the activity of CAR T-cell therapies. Intermediate dose fludarabine-based regimen has emerged as a popular option to enhance the expansion and persistence of infused cells, while reducing the immunogenicity of transgene products[1]. The most widely used lymphodepleting (LD) regimen with CD19 CAR-T cell therapy, including axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) and lisocabtagene maraleucel (liso-cel), is the combination of fludarabine (25-30mg/m 2) and cyclophosphamide (250-500mg/m 2) administered daily over 3 days[2-4]. However, fludarabine-cyclophosphamide (Flu/Cy) is associated with a significant risk of hematologic toxicity that may preclude administration or result in prolonged cytopenia in pts with pre-existing cytopenia. Bendamustine (Benda) combines both alkylating-agent and purine-analog activities and has potent anti-tumor efficacy in lymphoid malignancies. Importantly, compared to Flu/Cy, Benda typically has less hematologic toxicity, which may reduce the risk of infections. Benda 90 mg/m2 on T-4 and T-3 has been used as an alternative LD regimen for some pts receiving tisa-cel[5]. Given the recent critical shortage of fludarabine in 2022, several institutions had to switch to bendamustine-containing regimens[6]. While small studies suggest no differences in outcomes, there is an unmet need to compare the safety and efficacy of flu/cy versus benda- containing LD regimens[7].

Q16. RESEARCH HYPOTHESIS:

Outcomes of CD19 CAR-T therapy conditioning with Flu/Cy regimen versus benda- containing versus other regimens are similar.

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

Suggested word limit of 200 words:

- Safety: To compare CRS, neurotoxicity and hematologic toxicity of Flu/Cy versus benda- containing versus other LD
- Efficacy: To compare ORR, PFS and OS of r/r LBCL pts

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.

There has been a recent drug supply shortage of fludarabine. While this is the is the widely adopted lymphodepleting regimen as standard of care for both axi-cel and tisa-cel, alternate and novel methods have to be explored. Benda conditioning has been used as an alternate lymphodepleting therapy. Given the supply chain of fludarabine, it is important to study the safety and efficacy profile of benda as a lymphodepleting agent in patients with lymphoma who receive 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.

• Lymphodepleting (LD) chemotherapy prior to CAR-T infusion can effectively prolong the persistence of infused cellular therapy product and is associated with durable remissions in patients with lymphoma[1]. Early studies used and compared different LD regimens. In these studies, fludarabine and cyclophosphamide (Flu/Cy) for lymphodepletion, compared with patients who received cyclophosphamide alone or cyclophosphamide and etoposide, led to improved CAR-T expansion and persistence and higher response rates[8].The most widely used LD regimen, therefore, is the combination of fludarabine (25-30mg/m 2) and cyclophosphamide (250-500mg/m 2) administered daily over 3 days. The addition of fludarabine to the conditioning regimen has been associated with improved survival in early CD19 CAR-T studies [9]. In the ZUMA-1 trial, patients received lymphodepletion chemotherapy with cyclophosphamide and fludarabine[10]. However, Flu/Cy is associated with a significant risk of hematologic toxicity that may preclude administration or result in prolonged cytopenia in pts with pre-existing cytopenia. Benda combines both alkylating-agent and purine-analog activities and has potent anti-tumor efficacy in lymphoid malignancies. Importantly, compared to Flu/Cy, Benda typically has less hematologic toxicity, which may reduce the risk of infections. Therefore, because of its safety profile and lymphocytotoxic activity, benda 90 mg/m2 for 2 days has been used as an alternative LD regimen for some pts receiving tisagenlecleucel (tisa-cel)[5]. In the JULIET trial, most patients (73%) received Flu/Cy, whereas 19% received benda, and 8% did not receive any because the white blood count was already ≤1000 cells/μL[7] Benda was administered as LD for patients who had grade 4 hemorrhagic cystitis with cyclophosphoide or were resistant to prior regimens with cyclophosphamide. No differences in clinical responses were noted between patients who received Flu/Cy versus benda[7]. Since benda is an accepted alternate LD regimen and given the recent challenges with the critical supply chain deficits of fludarabine, necessitating increased utilization of bendamustine-containing or other alternate regimens, we propose to study and compare efficacy and safety of Flu/Cy and benda-containing LD regimens

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:
- All patients who received CD19 CAR-T therapy for r/r NHL
- Treated with any CD19 CART therapy on trial or commercial product

Exclusion:
- Age < 18 yrs.
- No lymphodepletion
- No consent for research

Q21. Does this study include pediatric patients?

- No

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

CAR-T therapy is approved in r/r NHL in adults and is not approved in the pediatric 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.

Patient related
• Patient age at CART in decades starting at 18 y
• Patient sex (M/F)
• Patient ethnicity (Hispanic/Non-Hispanic/Other)
• Race: (White/Black/Other)
• Karnofsky performance at CAR T: 90% vs. ≥90%
• HCT CMI score:
Disease/CAR T Related
• Year of diagnosis:
• Lymphoma (Diffuse large B cell lymphoma- NOS, transformed follicular lymphoma, indolent follicular lymphoma)
Mantle cell
• Lines of therapy:
• Pre-Lymphodepletion LDH: (median, range)
• Extra nodal involvement (yes/no)
• Prior autologous stem cell transplant (yes/no)
• Prior allogeneic stem cell transplant (yes/ no)
• Marrow involvement
• Types of CAR T: Axi vs Liso vs Tisa vs Brex
•
CRS
• CRS any grade (yes/no)
• Day of onset of CRS ___
• Maximum grade (I, II, III, IV)
• Number of doses of tocilizumab used : (num)
• Febrile neutropenia (yes/no)
• Day of onset of febrile neutropenia __
Neurotoxicity:
• ICANS any grade (yes/no)
• Maximum grade (I, II, III, IV)
• Day of onset of ICANS __
Prolonged Cytopenia:
• Neutropenia at Day 30 (yes/no)
• Neutropenia at Day 100 (yes/no)
Outcomes:
100-day Outcomes
• Alive (yes/no)
• Best response (CCR, CR, PR, No response, PD)
6 mo. Outcomes
• Alive (yes/no)
• Best response (CCR, CR, PR, No response, PD)
1-year Outcomes
• Alive (yes/no)
• Best response (CCR, CR, PR, No response, PD)

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, S.S., CAR-T efficacy: is conditioning the key? Blood, 2019. 133(17): p. 1799-1800.
2. Schuster, S.J., et al., Global pivotal phase 2 trial of the CD19-targeted therapy CTL019 in adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)-an interim analysis. Hematological oncology. Conference: 14th international conference on malignant lymphoma palazzo dei congressi. Switzerland, 2017. 35: p. 27.
3. Abramson, J.S., et al., Pivotal safety and efficacy results from transcend NHL 001, a multicenter phase 1 study of lisocabtagene maraleucel (liso-cel) in relapsed/refractory (R/R) large B cell lymphomas. Blood, 2019. 134.
4. Locke, F.L., et al., Durability of response in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients (Pts) with refractory large B-cell lymphoma. Journal of Clinical Oncology, 2018. 36(15_suppl): p. 3003-3003.
5. Ghilardi, G., et al., Bendamustine Is a Safe and Effective Regimen for Lymphodepletion before Tisagenlecleucel in Patients with Large B-Cell Lymphomas. Blood, 2021. 138: p. 1438.
6. Maziarz, R.T., et al., Perspective: An International Fludarabine Shortage: Supply Chain Issues Impacting Transplantation and Immune Effector Cell Therapy Delivery. Transplantation and Cellular Therapy, 2022.
7. Schuster, S.J., et al., Chimeric antigen receptor T cells in refractory B-cell lymphomas. New England Journal of Medicine, 2017. 377(26): p. 2545-2554.
8. Turtle, C.J., et al., Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor–modified T cells. Science translational medicine, 2016. 8(355): p. 355ra116-355ra116.
9. Hay, K.A., et al., Factors associated with durable EFS in adult B-cell ALL patients achieving MRD-negative CR after CD19 CAR T-cell therapy. Blood, 2019. 133(15): p. 1652-1663.
10. Neelapu, S.S., et al., Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. New England Journal of Medicine, 2017. 377(26): p. 2531-2544.

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

N/A

Q2. Key Words

CAR-T Therapy; Lymphodepleting Conditioning; Fludarabine-Cyclophosphamide; Bendamustine

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Alex Sieg, MD MS
Email address:	alex-sieg@uiowa.edu
Institution name:	University of Iowa
Academic rank:	Fellow (PGY-5)

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):	Chris Strouse, MD
Email address:	christopher-strouse@uiowa.edu
Institution name:	University of Iowa
Academic rank:	Clinical 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:

Alex Sieg

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.

Dr Strouse: CT 20-03, SC 21-01 - Mentor

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 influence of conditioning regimen on the efficacy of CAR T cell therapy

Q16. RESEARCH HYPOTHESIS:

Use of fludarabine and cyclophosphamide for pre-CAR T conditioning is associated with superior clinical outcomes compared to use of bendamustine or other conditioning regimens

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

Suggested word limit of 200 words:

Primary:
1) Compare Overall Response Rate of patients receiving Flu/Cy conditioning compared to bendamustine conditioning vs other conditioning
2) Compare progression free survival rate of patients receiving Flu/Cy conditioning compared to bendamustine conditioning vs other conditioning
Secondary:
3) Compare CRS rate of patients receiving Flu/Cy conditioning compared to bendamustine conditioning vs other conditioning
4) Compare ICANS rate of patients receiving Flu/Cy conditioning compared to bendamustine conditioning vs other conditioning
5) Compare rate of prolonged cytopenias of patients receiving Flu/Cy conditioning compared to bendamustine conditioning vs other conditioning
- Prolonged neutropenia (lasting > 90 days)
- Prolonged thrombocytopenia (lasting > 90 days)
6) Compare rate infection of patients receiving Flu/Cy conditioning compared to bendamustine conditioning vs other conditioning within 2 years of CAR T 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.

Conditioning regimen significantly impacts the efficacy of CAR T cell therapy. However, the optimal conditioning regimen choice remains unresolved. This analysis will provide data to inform clinicians' decision-making regarding conditioning regimen.

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 conditioning regimen given prior to CAR T cell therapy influences patients' cytokine profile and promotes CAR T cell expansion, resulting in modulation of the CR and PFS rate [1]. In early investigations with CD19 CAR-T constructs, Turtle et al showed that the addition of fludarabine to Cytoxan resulted in higher response rates compared to Cytoxan alone (ORR 72 vs 50% and CR 50 vs 8%) [2]. Based on these findings, Flu/Cy conditioning has become the standard approach for conditioning prior to CAR-T cell infusion. More recently, nationwide shortages in fludarabine have raised concerns especially given the increasing numbers of CAR-T procedures. Thus, identification of alternative methods of effective lymphodepletion prior to CAR-T infusion would be beneficial.
Bendamustine has been used for conditioning for CAR T treatments with comparable results. In a recently reported retrospective study of 132 patients treated at three institutions, Ghilardi et al demonstrated comparable ORR and PFS in patients treated with Flu/Cy or Bendamustine conditioning with the latter showing lower rates of CRS and ICANS [3]. While these findings are intriguing, it should be noted that the decision on conditioning regimen was per treating physician discretion and results should be confirmed with the aid of a prospective randomized control trial.

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 and pediatric patients (age > 13)
2. Treatment with tisagenlecleucel, axicabtagene, brexucabtagene lisocabtagene, idecabtagene, ciltacabtagene

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 Factors:
1. Age
2. HCT-CI
3. Sex
4. Renal Function (Normal vs eGFR < 60)
5. ECOG (0/1 vs >1)

Disease Related Factors:
1. Diagnosis:
a) Diffuse Large B-cell Lymphoma
b) Mantle Cell lymphoma
c) B-ALL
d) Follicular Lymphoma
e) Multiple Myeloma
2. # of prior treatment lines
3. Prior ASCT (yes vs no)
4. Bridging Therapy (Yes vs No)
5. LDH > ULN (Yes vs No)
6. Pre-lymphodepletion ferritin > ULN (yes vs no)
7. Pre-lymphodepletion CRP > ULN (yes vs no)
8. Bulky Disease > 10-cm (for patients with lymphoma)

Treatment Related Factors:
1. Conditioning Regimen Used
2. Cell Dose

Outcomes:
1. Best overall Response (less than PR vs PR+CR)
2. Progression free survival
3. Highest grade CRS
4. Highest grade ICANS
5. Time to neutrophil recovery
6. Time to platelet recovery
7. Incidence of grade 3+ infection

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

No PROs 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

No samples 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.

No non-CIBMTR data sources will be used

Q26. REFERENCES:

[1] Neelapu SS (2019) CAR-T efficacy: is conditioning the key? Blood 133(17):1799-1800
[2] Turtle et al (2016) Immunotherapy of non-Hodgkin lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor modified T cells Sci Transl Med 8(355):355ra116
[3] Ghilardi et al (2022) Bendamustine is safe and effective for lymphodepletion before tisagenlecleucel in patients with refractory or relapsed large B-cell lymphomas Ann Oncol 33(9):916-928

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

Patterns of conditioning before CAR T-cell therapy for large B-cell lymphoma and the effect on clinical outcomes

Q2. Key Words

CAR T-cell therapy, LBCL, conditioning regimens, lymphodepletion

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Alaa Ali, MD
Email address:	alaa.ali@gunet.georgetown.edu
Institution name:	Georgetown University
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):	Carlos Rodriguez-Bonilla
Email address:	carlos.a.rodriguez-bonilla@medstar.net
Institution name:	N/A
Academic rank:	Fellow

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:

Alaa Ali, 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.

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.

- Yes

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

Dr. Amy Moskop and Dr. Marcelo Pasquini

Q15. RESEARCH QUESTION:

What are the patterns of conditioning (agents used, dosing, timing) utilized prior to CAR T-cell therapy for large B cell lymphoma (LBCL)? How frequently is conditioning omitted in the real world and why? What are the efficacy and toxicity outcomes of each conditioning approach (particularly, FluCy vs bendamustine) and how do they compare with each other?

Q16. RESEARCH HYPOTHESIS:

Different conditioning regimens (Flu/Cy vs bendamustine vs no conditioning vs other) before CAR T-cell for LBCL produce different efficacy and toxicity outcomes. Higher intensity of conditioning regimens does not correlate with improvement of CAR T-cell efficacy and may increase toxicity (CRS, ICANS, hematological toxicity and infection). Kinetics of absolute lymphocyte count (ALC) before and after CAR T-cell infusion may serve as a surrogate marker for the pharmacodynamic effect of conditioning and correlate with efficacy

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

Suggested word limit of 200 words:

Primary: Identify the conditioning patterns (agents, dosing, timing) used before different CAR T-cell products (tisagenlecleucel, axicabtagene ciloleucel, lisocabtagene maraleucel) for LBCL (DLBCL not otherwise specified (DLBCL-NOS), primary mediastinal large B cell lymphoma (PMLBL), high grade B cell lymphoma(HGBL), and DLBCL arising from FL). Compare the efficacy outcomes between these regimens (ORR, CR, PFS)
Secondary:
- Compare the different conditioning regimens in terms of:
- Effect on toxicity (CRS, ICANS, hematological toxicities, infection, hypogammaglobulinemia)
- Persistence of cells (if data is available)
- Days of inpatient admission
- Identify the percentage of patients that receive CAR T-cells without conditioning in the real world and their outcomes. Attempt to identify the reasons for not giving conditioning (cytopenia, lymphopenia, toxicity, age etc)
- Study the kinetics and recovery of ALC with different conditioning approaches and whether there is any correlation with efficacy outcomes

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.

If the aim of the project is completed, it will provide a significant insight into the conditioning and lymphodepletion patterns utilized before CAR T-cell for LBCL in the real world and into the interplay between these conditioning regimens and both potential toxicities and clinical outcomes. Additionally, in light of the recent fludarabine shortage, such a study will help treating clinicians choose alternative regimens (such as bendamustine) with a higher level of confidence. Finally, identifying regimens with safer toxicity profiles could help expand the use of CAR T-cells to older patients and patients with comorbidities

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.

Studies showed that lymphodepleting conditioning enhances CAR T-cell expansion, persistence and clinical activity via a variety of mechanisms such as enhancing the production of homeostatic cytokines and eradicating immune immunoregulatory cells (1,2, 3, 4). Nevertheless, the best conditioning approach is not known. Compared to cyclophosphamide alone, cyclophosphamide plus fludarabine (Flu/Cy) induced higher response rates and improved expansion and persistence of CART-cells (5). This combination was used for conditioning in most pivotal CAR T-cell trials although the timing and the dosing varied between studies (6,7,8). This combination is also given to the majority of patients outside of clinical trials. Although lower-dose regimen of Flu/Cy may reduce the risk of infection, neutropenia and possibly CRS and neurotoxicities (9,10,11,12), it is less likely to induce favorable cytokine profiles in these patients (13).

Other conditioning approaches have also been used. For example, JULIET study allowed patients with cyclophosphamide-resistant disease and/or history of grade 4 hemorrhagic cystitis to be conditioned with bendamustine (6). Subsequently, tisagenlecleucel was approved without lymphodepletion for patients with white blood cell counts of ≤1×10^9 /l at 1 week prior to infusion. Long-term follow-up of the trial reported a longer PFS with Flu/Cy than bendamustine lymphodepletion although the analysis was not adjusted for differences in patient characteristics (14). Recently, the safety and efficacy of lymphodepletion using either Flu/Cy (n=42) or bendamustine (n=90) before tisagenlecleucel were retrospectively compared at 3 centers (15). Bendamustine lymphodepletion had similar efficacy as Flu/Cy in terms of ORRs and PFS but with reduced toxicities, including CRS, neurotoxicity, infections and hematological toxicities. Nevertheless, because of the sample size and the limited analysis to one product (tisagenlecleucel), this limits the conclusions that can be drawn from this comparison. Furthermore, It is unclear whether bendamustine is safer in the setting of CD28-based CAR products (axicabtagene ciloleucel) or other 4-1BB co-stimulated products (lisocabtagene maraleucel).

These studies highlight the need for both large retrospective and prospective studies to compare conditioning approaches and study the interplay between lymphodepletion dose and timing with both toxicities and clinical 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.

Inclusion criteria:
- LBCL patients (DLBCL, NOS; PMLBL; HGBCL; and DLBCL transformed from FL) who received CAR T-cell products (tisagenlecleucel, axicabtagene ciloleucel, lisocabtagene maraleucel) in second or third line
- Treated outside a clinical trial
- Age 18 or older
- First time treated with CAR T-cell

Exclusion criteria:
- Other types of lymphoma such as indolent lymphoma or mantle cell lymphoma
- Age younger than 18
- Second time treated with CAR T-cell

Q21. Does this study include pediatric patients?

- No

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

Tisagenlecleucel, axicabtagene ciloleucel and lisocabtagene maraleucel are approved in adult patients with large B cell lymphoma

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.

Forms: 2000, 2018, 2118, 4000, 4100, 2900
Form 2000, 2400
o Is the recipient an adult (18 years of age or older) or emancipated minor?
o Date of birth:
o Sex
Form 2018
o Disease assessment at Diagnosis
Type of lymphoma: DLBCL, NOS vs PMBCL vs HGBCL vs LBCL transformed from FL or other iNHL
Subtype: GCB vs non-GCB
P53 mutation or deletion 17p
Ki-67 percent
LDH
Stage of organ involvement
Extranodal involvement
ECOG score
o Number of prior systemic therapy regimens
o Pre-HCT or Pre-infusion therapy
Systemic therapy, yes or no
Number of cycles
Specify regimen
Specify other systemic therapy (if not listed)
Intrathecal therapy, yes or no
Radiation therapy, yes or no
Best response to line of therapy by CT criteria
Best response to line of therapy by PET criteria
Did disease relapse/progress following this line of therapy?
Number of prior therapies
Form 2118
o Disease response at the time of best response to therapy
What was the best response by CT (radiographic) criteria to HCT or cellular therapy since the date of the last report?
What was the best response by PET (metabolic) criteria to HCT or cellular therapy since the date of the last report?
Was therapy given since the date of the last report for reasons other than relapse or progressive disease? (Include any maintenance and consolidation therapy and therapy for persistent disease.) yes or no
Did the recipient experience a relapse or progression since the date of the last report? Yes or no
Form 4000
o Age
o Gender
o Race
o Is this the first time the recipient is being treated using a cellular therapy? yes or no
o Has the recipient ever had a prior HCT? yes or no

o Specify the HSC source(s) for the prior HCT (check all that apply)
o Name of cellular therapy product
o Was lymphodepleting therapy given prior to the infusion?
o Lymphodepleting drug
Total prescribed dose:
Date started:
o Therapy given for the prevention of CRS
o Therapy given for the prevention of neurotoxicity (ICANS)?
o Hematologic markers prior to lymphodepleting therapy and on day of infusion
WBC, ANC, ALC, Hgb and PLT prior to lymphodepleting therapy
LDH, ferritin, CRP
o Karnofsky Scale (recipient age ≥ 16 years) Prior to cellular therapy
o Were there any co¬existing diseases or organ impairment present according to the HCT comorbidity index (HCT¬CI)?
o Specify co¬existing diseases or organ impairment
o Was recipient on dialysis immediately prior to the start of systemic therapy
o Specify prior malignancy (check all that apply)
Form 4100
o Specify the recipient's survival status at the date of last contact , Alive or dead
o Was the recipient admitted to the hospital post infusion?
o What was the best response to the cellular therapy?
o Peripheral Blood Count Recovery
Was there evidence of initial recovery?
Date ANC ≥ 500/mm3
Following the initial recovery, was there subsequent decline in ANC to < 500/mm3 for ≥ 3 days since the date of last report?
Date of decline in ANC to < 500/mm3 for ≥ 3 days: (first of 3 days that the ANC declined)
Did recipient recover and maintain ANC ≥ 500/mm3 following the decline?
Date of ANC recovery:
Was an initial platelet count ≥ 20 x 109/L achieved?
o Disease relapse or progression
Was a disease relapse or progression detected since the date of last report?
Date of relapse or progression:
• Were tests performed to detect persistence of the cellular product since the date of last report?
• Was persistence evaluated by molecular assay? (e.g. PCR)
o Date sample collected:
o Were the infused cells detected?
• Was persistence evaluated by flow cytometry testing?
o Date sample collected:
o Specify the cell source
o Were the infused cells detected?
• Was persistence evaluated by another method?
o Specify other method:
o Date sample collected:
o Specify the cell source
o Were the infused cells detected?
• Were B-¬cell counts monitored after infusion?
o Was there B-¬cell recovery?
o Date of B-¬cell recovery:
• CRS? Yes vs no
o Hypotension requiring therapy? Yes vs no
o Pressors needed? Yes vs no. If yes, 1 or 2 pressors?
o Hypoxia requiring oxygen? Yes vs no
o FIO2<40%? Yes vs no
o Positive pressure support needed? Yes vs no
• Therapy for CRS? Yes vs no
o Steroids given for CRS? Yes vs no
o Agents other than tocilizumab or steroids given for CRS? Yes vs no
o 2 doses of Tocilizumab given? Yes vs no
• CRS resolved? Yes vs no. Number of days before resolution.
• ICANS? Yes vs no
o Lowest CARTOX or ICE score
o Cerebral edema occurred? Yes vs no
o Seizure occurred? Yes vs no
o The most severe level of depressed level of consciousness
• Therapy for ICANS? Yes vs no

• Second line therapy needed for ICANS (agents other than steroids)? Yes vs no
• MAS/HLH? Yes vs no
• Hypogammaglobulinemia? Yes vs no
• Immunoglobulin replacement therapy? Yes vs no
• Grade 3 or 4 organ toxicity? Yes vs no. If yes, what organ? Did it resolve?
• Maximum CRP and ferritin.
• Clinically significant infection? Yes vs no
• If yes, what organism and site?
• WBC, ANC, ALC, Hgb and PLT at different time points post infusion (2 weeks, 4 weeks, 12 weeks etc)
Form 2900
• Primary cause of death
• Contributing 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

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. Hirayama AV, Gauthier J, Hay KA, et al. The response to lymphodepletion impacts PFS in patients with aggressive non-Hodgkin lymphoma treated with CD19 CAR T cells. Blood. 2019;133:1876-1887
2. Geyer MB, Rivière I, Sénéchal B, et al. Safety and tolerability of conditioning chemotherapy followed by CD19-targeted CAR T cells for relapsed/refractory CLL. JCI Insight. 2019;5:e122627.
3. Kochenderfer, J. N. et al. Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. J. Clin. Oncol. 35, 1803–1813 (2017).
4. Wrzesinski, C. et al. Increased intensity lymphodepletion enhances tumor treatment efficacy of adoptively transferred tumor-specific T cells. J. Immunother. 33, 1–7 (2010).
5.Turtle, C. J. et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor–modified T cells. Sci. Transl. Med. 8, 355ra116 (2016)
6. Chuster, S. J. et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N. Engl. J. Med. 380, 45–56 (2019).
7. Neelapu, S. S. et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N. Engl. J. Med. 377, 2531–2544 (2017)
8. 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 396, 839–852 (2020)
9. Hill, J. A. et al. Infectious complications of CD19- targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood 131, 121–130 (2018).
10. Kochenderfer, J. N. et al. Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. J. Clin. Oncol. 35, 1803–1813 (2017)
11. Gust, J. et al. Endothelial activation and blood–brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T Cells. Cancer Discov. 7, 1404–1419 (2017). 118.
12. Hay, K. A. et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. Blood 130, 2295–2306 (2017).
13. Ninomiya, S. et al. Tumor indoleamine 2,3-dioxygenase (IDO) inhibits CD19-CAR T cells and is downregulated by lymphodepleting drugs. Blood 125, 3905–3916 (2015)
14. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study Lancet Oncol, 22 (2021), pp. 1403-1415
15. Bendamustine is safe and effective for lymphodepletion before tisagenlecleucel in patients with refractory or relapsed large B-cell lymphomas. Ann Oncol 2022 Sep;33(9):916-928. doi: 10.1016/j.annonc.2022.05.521

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 lymphodepleting agents on the outcomes of Chimeric Antigen Receptor T-cell therapies

Q2. Key Words

CART, Non-Hodgkin Lymphoma, B-lymphoblastic leukemia, Multiple Myeloma, lymphodepletion, bendamustine, fludarabine

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Kalyan Nadiminti, MD
Email address:	nadiminti@wisc.edu
Institution name:	University of Wisconsin
Academic rank:	Assistant professor of medicine, hematology

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):	Priyanka Pophali, MD
Email address:	pophali@wisc.edu
Institution name:	University of Wisconsin
Academic rank:	Assistant professor of medicine, hematology

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:

Kalyan Nadiminti

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.

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.

- Yes

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

Peiman Hematti

Q15. RESEARCH QUESTION:

Are CART related outcomes influenced by the choice of lymphodepleting (LD) agents?
Compare the outcomes between Fludarabine/cyclophosphamide (Flu/Cy) versus Bendamustine based LD for Diffuse large B-cell lymphoma (DLBCL), B-lymphoblastic leukemia (B-ALL) and Multiple Myeloma (MM).

Q16. RESEARCH HYPOTHESIS:

There is limited published data about safety and efficacy of using alternate LD agents, such as bendamustine, in adults receiving CART therapy for approved hematologic conditions. We hypothesize that bendamustine would be a safe alternate effective approach for LD for DLBCL and other hematologic malignancies.

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

Suggested word limit of 200 words:

Primary Outcome:
- Response rates at D100 post-CART following LD with Bendamustine based regimen

Secondary outcomes:
- Response rates at 6 months and 1-year post-CART following bendamustine based LD
- Progression free survival
- Overall survival
- Rates of CART-related morbidity (CRS, ICANS) and mortality in first 30 days

Specific aims:
1. To describe the primary and secondary outcomes for DLBCL, MM and B-ALL patients
2. To compare the primary and secondary outcomes between Flu/Cy and Bendamustine based LD regimens

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.

Flu/Cy has been the standard LD regimen used in all the registration clinical trials for CART therapies and hence the most used regimen for all commercial products. However, efficacy of Bendamutine as an alternate LD agent for various CART products is unknown.

This proposed project aims to describe the safety and efficacy of bendamustine as an LD agent prior to treatment with approved products of CART for DLBCL, B-ALL and MM, in a larger patient dataset with CIBMTR. Additionally, we would like to compare these results with the historical cohort of CART patients who were treated with the standard Flu/Cy LD regimen.

This project has the potential to inform and impact the current and future practice using appropriate LD regimens for CART patients with hematologic malignancies.

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.

There are currently 6 FDA approved CART products in the USA.
Three CART products (Axi-cel, Tisa-cel, Liso-cel) were approved for treatment of large-B cell lymphoma that is relapsed or refractory(R/R) to at least 2 systemic therapies, whereas recently Axi-cel and Liso-cel have also been approved for disease refractory to first line chemoimmunotherapy.
Axi-cel is also approved for treatment of follicular lymphoma that is refractory to 2 lines of therapy, and brexucabtagene is approved for adults with R/R mantle cell lymphoma and R/R B-ALL.
Idecabtagene and Ciltacabtagene have been approved for MM that is R/R after four prior lines of therapy.
The registration clinical trials that led to the approval of these CART products exclusively used Flu/Cy as the LD regimen, which informs the current clinical practice.
Lympohodepletion is an essential and key determinant of the CART therapy outcome. Several studies demonstrated the importance of exposure of Fludarabine, and directly correlates with the duration of B-cell aplasia, relapse risks and PFS. 1–3 Additionally, LD agents also one of the factors that influences the cytokine profile which in turn impacting disease control as well as the development of cytokine release syndrome (CRS) or neurotoxicity. 3,4
Therefore, modification with LD regimen must be very cautiously undertaken.
Due to an expected and unprecedented shortage of fludarabine supply in the recent months, many centers across the nation and globally had to adopt alternate LD agents, prominently bendamustine, extrapolating from the published experience showing bendamustine as a potentially effective LD agent with Tisa-cel for DLBCL, and a CD30 targeted CART for Hodgkin lymphoma. 4–7 A recent perspective editorial provides further insight and guidance to navigate the current situation of global fludarabine shortage.7 The study by Ghilardi et al further demonstrated not only comparable efficacy of bendamustine to Flu/Cy LD, but also better tolerability with reduced rates of CRS, and neurotoxicity, and re-hospitalizations.4
However, the safety and efficacy of bendamustine with other CART constructs and products needs to be studied and established systematically. It is imperative to urgently describe and establish the efficacy of bendamustine as LD agent, from the evolving and accumulating data from the global cellular therapy centers, using a larger dataset from CIBMTR.
Finally, it would be necessary to compare these results with the available historical and contemporary cohort of patients who received CART therapy using the standard Flu/Cy LD regimen.

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:
Investigational cohort: All adult patients who received LD chemotherapy with bendamustine based regimen and CART therapy for the following diagnoses, included int eh CIBMTR
- B-cell lymphoma
- Follicular Lymphoma and Mantle cell lymphoma
- R/R B-ALL
- Multiple Myeloma

Comparison cohort: all adult patients who received standard LD chemotherapy with Flu/Cy regimen and CART therapy for the following diagnoses, included in the CIBMTR
- B-cell lymphoma
- Follicular Lymphoma and Mantle cell lymphoma
- R/R B-ALL
- Multiple Myeloma

Exclusion criteria:
Treatment with more than one CART or multiple LD agents
Treatment with LD chemotherapy other than bendamustine or Flu/Cy

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 ASCT or CAR-T treatment
- Sex (Form 2400/2)
- Race (Form 2400/4)
- Ethnicity (Form 2400/3)
- ECOG performance status/Karnofsky performance status (Form 2018/80-81)
- HCT-CI (with component comorbidities where available)

Disease related:
- Diagnosis by WHO classification
- Date of diagnosis and relapse
- LDH at diagnosis (Form 2018/67-68) and pre-CART/ASCT – autologous or allogeneic
- Extranodal involvement (Form 2018/75-76) for lymphoma
- Prior lines of therapy (Form 2018/166-222) including prior SCT (autologous and allogeneic)

CART related:
- Date of ASCT/CAR-T
- Date of apheresis for CART
- Conditioning regimen for ASCT
- Disease status at CART: CR vs PR vs SD vs PD (lymphoma), CR Vs PR Vs VGPR Vs refractory (MM), CR Vs MRD + Vs residual/refractory disease (B-ALL)
- CAR-T product (clinical trial/SOC; within/outside specification; cell dose)
- Bridging therapy pre-CART: yes/no
- Lymphodepleting drugs and dose
- Any concomitant therapy with CART

Follow-up
- Patient status at D100, 6 months, 1 year and last contact
- Best objective response (CR/PR/SD/PD)
- Time to neutrophil recovery (ANC 500)
- Time to platelet recovery (PLT 50)
- ALC recovery and kinetics
- Maximum CRS grade (CAR-T only)
- Maximum ICANS grade (CAR-T only)
- Number of toci doses (CAR T only)
- Dex dose received (CAR T only)
- Date of disease relapse /progression
- Time to next treatment
- Details of next treatment
- Date of 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.**

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. Hirayama A v., Gauthier J, Hay KA, et al. The response to lymphodepletion impacts PFS in patients with aggressive non-Hodgkin lymphoma treated with CD19 CAR T cells. Blood. 2019;133(17):1876–1887.
2. Dekker L, Calkoen FG, Jiang Y, et al. Fludarabine exposure predicts outcome after CD19 CAR T-cell therapy in children and young adults with acute leukemia. Blood Adv. 2022;6(7):1969–1976.
3. Fabrizio VA, Boelens JJ, Mauguen A, et al. Optimal fludarabine lymphodepletion is associated with improved outcomes after CAR T-cell therapy. Blood Adv. 2022;6(7):1961–1968.
4. Ghilardi G, Chong EA, Svoboda J, et al. Bendamustine is safe and effective for lymphodepletion before tisagenlecleucel in patients with refractory or relapsed large B-cell lymphomas. 2022;
5. Chong EA, Ruella M, Schuster SJ. Five-Year Outcomes for Refractory B-Cell Lymphomas with CAR T-Cell Therapy. New England Journal of Medicine. 2021;384(7):673–674.
6. Ramos CA, Grover NS, Beaven AW, et al. Anti-CD30 CAR-T Cell Therapy in Relapsed and Refractory Hodgkin Lymphoma. J Clin Oncol. 2020;38:3794–3804.
7. Maziarz RT, Diaz A, Miklos DB, Shah NN. Perspective: An International Fludarabine Shortage: Supply Chain Issues Impacting Transplantation and Immune Effector Cell Therapy Delivery. Transplant Cell Ther. 2022;

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

Alternative lymphodepletion before CAR-T cell therapy

Q2. Key Words

conditioning, chemotherapy, lymphodepletion, cellular therapy, CAR-T, lymphoma, myeloma

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Sayeef Mirza
Email address:	Abu-Sayeef.mirza@yale.edu
Institution name:	Yale Cancer Center
Academic rank:	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):	Lohith Gowda
Email address:	lohith.gowda@yale.edu
Institution name:	Yale 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?

- No

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

N/A

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

- 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.

CT20-04: co-PI
CT21-01: PI
CT22-01: co-PI
P2110-109: co-PI

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:

How does non-fludarabine-based lymphodepletion regimens impact post-CAR-T outcomes?

Q16. RESEARCH HYPOTHESIS:

1. We hypothesize that non-fludarabine-based lymphodepletion regimens are safe and do not compromise post-CAR-T outcomes.

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

Suggested word limit of 200 words:

1. Primary aim: Evaluate progression-free survival (PFS) after CAR T cell therapy when alternative lymphodepletion (LD) chemotherapy (i.e. non-fludarabine conditioning regimens) are utilized.
2. Secondary aims:
a. Overall Survival (OS)
b. Overall Response rate (ORR)
c. Cumulative incidence of relapse (RI)
d. Incidence of cytokine release syndrome (CRS) and immune effector cell associated neurologic syndromes (Different grades, low vs high grade)
e. Causes of death
f. Identify prognostic markers that may predict best response to non-fludarabine-based LD 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.

Although there are several CAR-T products for both lymphoma and myeloma, they all use the same 2 agents for lymphodepletion (LD). There is currently a fludarabine shortage and institutions have been forced to use alternative agents despite strong evidence favoring any one alternative. Extrapolating from prior clinical trials, alternative agents such as bendamustine, clofarabine and pentostatin may be equally efficacious for response rates and the duration of response. With limited time to run randomized trials during pandemics in order to identify the best LD regimens, physicians have been forced to make some quick decisions. The CIBMTR registry is the best way to provide statistically significant answers to this current shortage dilemma. As more cellular therapy is utilized, more options for LD should be available and better understood in a highly unpredictable world prone to drug shortages.

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 had dramatic responses in certain hematologic malignancies.1 Although CD-19 targeted CAR T-cell therapy has yielded success for patients with certain types of relapsed/refractory lymphomas, much of its applications are still in its developmental and evolving stage; hence, there are many clinical questions surrounding its management and outcomes.2-4 Over the last few years, pivotal clinical trials (ZUMA-1 and Juliet) have led to the FDA approval of different CAR-T products for relapsed/refractory DLBCL.5-7 Axi-cel, studied in ZUMA-1 uses a CD28 co-stimulatory domain whereas tisa-cel (studied in JULIET) use 4-1BB as the co-stimulatory domain, which may explain differences in expansion and persistence among other postulated ramifications.8 The newest CAR-T product studied in TRANSCEND utilizes 4-1BB and has shown good efficacy in aggressive types of lymphoma (including double hit).5,9 In the TRANSCEND trial, 59% of patients received bridging therapy (0 and 55% in ZUMA and JULIET), 38% had bulky disease (16%-ZUMA and 31%- JULIET) and more older patients (median age of 63 years) were included in liso-cel (upper range 86 years), highlighting the benefits of its use in a high risk cohort.5-7 The median OS at 12 months was not reached in ZUMA-1, 11.1 months with JULIET and 21 months with TRANSCEND.5-7

One of the prerequisites prior to CAR-T infusion is the need for lymphodepletion which facilitates subsequent T cell activation, expansion, and effector function. Majority of our current knowledge on lymphodepletion comes from a series of trials with allogeneic stem cell transplant in bone marrow failure states and with clonal disorders. We have experimented with different doses of radiation, cyclophosphamide, fludarabine, clofarabine, and bendamustine to achieve lymphodepletion and or immune-ablation. In contrast, our experience in the CAR-T setting with non-fludarabine-based regimens is limited. All the registration trials utilized fludarabine and cyclophosphamide as LD therapy. Prior experimental trials, demonstrated efficacy when a range of LD agents and dosing schedules were used other than fludarabine and cyclophosphamide, including bendamustine, interleukin-2, total body irradiation, and pentostatin.10 All of these LD regimens accomplish the same goal of naïve T cell depletion and allowing for greater CAR-T cell expansion after infusion.

In light of the pandemic and logistical barriers, many institutions have experienced a fludarabine shortage leading to questions in the community about which is the best alternative agent.11 A limited study on only B-ALL revealed bendamustine-based LD was associated with lower rates of CRS and ICANS, with less future cytopenias, shorter time to count recovery, and fewer transfusions. This also resulted in fewer infections, neutropenic fevers, and post-infusion hospitalizations.12

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.

1. Any patient (any age) with the diagnosis of large B-cell lymphoid or plasma cell malignancy receiving commercially available, FDA-approved CD-19 or BCMA CAR-T cell product (axi-, tisa-, liso-cel, cilta-cel, ide-cel) up until December 2022. We would broadly want 2 groups of patients- those who received fludarabine based vs those who did not receive fludarabine-based regimens.

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.

Data will be captured through CIBMTR collection forms. The following variables of interest will be studied:
ORR = CR + PR
Relapse/progression: Progressive disease or recurrence of disease would be counted as an event. Treatment-related death, defined as death without relapse or progression, is the competing event. Those who survive without recurrence or progression would be censored at the time of last contact.
Progression-free survival (PFS): Survival without recurrence or tumor progression. Recurrence of progression of disease and death would be counted as events. Those who survive without recurrence or progression would be censored at the time of last contact.
Overall survival (OS): Time to death. Death from any cause will be considered an event. Surviving patients will be censored at the time of last follow-up.
Non-relapse mortality (NRM): Death without relapse or progression, where relapse or progression would be competing risks. Those who survive without recurrence or progression would be censored at the time of last contact.
Patient-related:
- Age at transplant/CAR-T
- Gender
- Karnofsky performance status at transplant: < 90% vs. ≥ 90%
- HCT comorbidity index at transplant 0, 1, 2, and ≥ 3
- ABO blood group
- CMV status

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

- Immunoglobulin and light chain data
- Bone marrow plasma cell counts
- CD19 expression (bright/dim etc;)
- BCMA expression and serum levels
- Bridging therapy

CAR-T cell therapy:
- CAR-T product
- cell dose
- Date from disease relapse to CART apheresis.
- Time for apheresis to CART infusion
- Cell dose
- Disease status at time of infusion
- CRP and Ferritin at infusion
- lymphodepletion prior to CAR-T (Y/N)
- LD agent and dose
- Bridging therapy
- Response to CAR-T
- CRS (Y/N and grade) and duration
- CRS treatment or prevention drugs – Y/N
- B cell and T cell recovery markers at D 100, 180 and 365
- CRES/Neurotoxicity (Y/N and grade)
- Cytopenias
- Infectious complications

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. Davila ML, Brentjens RJ. CD19-Targeted CAR T cells as novel cancer immunotherapy for relapsed or refractory B-cell acute lymphoblastic leukemia. Clin Adv Hematol Oncol. 2016;14(10):802-808.
2. Brentjens R, Davila ML. CAR T cells, immunologic and cellular therapies in hematologic malignancies. Best Pract Res Clin Haematol. 2018;31(2):115-116.
3. Davila ML, Sadelain M. Biology and clinical application of CAR T cells for B cell malignancies. Int J Hematol. 2016;104(1):6-17.
4. Zhao Z, Chen Y, Francisco NM, Zhang Y, Wu M. The application of CAR-T cell therapy in hematological malignancies: advantages and challenges. Acta Pharm Sin B. 2018;8(4):539-551.
5. Abramson JS, Palomba ML, Gordon LI, 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):839-852.
6. Locke FL, Ghobadi A, Jacobson CA, 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):31-42.
7. 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.
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Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

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

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

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

N/A

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

Embedded Data:

N/A

2207-02, 2209-05, 2210-89, 2210-114, 2210-252, 2210-264, Fludarabine - Patients with DLBCL, MCL, FL, ALL, or MM

Characteristic	Non-fludarabine containing	Fludarabine containing
No. of patients	554	6820
No. of centers	71	174
Patient related		
Age at infusion, yrs		
Mean (SD)	62 (14.0)	56 (20.0)
Age at infusion, by category - no. (%)		
0-9 Years Old	4 (1)	275 (4)
10-17 Years Old	6 (1)	326 (5)
18-29 Years Old	15 (3)	429 (6)
30-39 Years Old	15 (3)	281 (4)
40-49 Years Old	45 (8)	490 (7)
50-59 Years Old	106 (19)	1259 (18)
60-69 Years Old	214 (39)	2130 (31)
70 or more Years Old	149 (27)	1630 (24)
Recipient sex - no. (%)		
Male	361 (65)	4289 (63)
Female	193 (35)	2523 (37)
Missing	0 (0)	8 (0)
Recipient race - no. (%)		
White	432 (78)	5264 (77)
Black or African American	37 (7)	414 (6)
Asian	26 (5)	303 (4)
Native Hawaiian or other Pacific Islander	0 (0)	11 (0)
American Indian or Alaska Native	1 (0)	26 (0)
Other	4 (1)	66 (1)
More than one race	45 (8)	347 (5)
Missing	9 (2)	389 (6)
Recipient ethnicity - no. (%)		
Hispanic or Latino	52 (9)	949 (14)
Non Hispanic or non-Latino	466 (84)	5182 (76)
Non-resident of the U.S.	12 (2)	470 (7)
Unknown	23 (4)	211 (3)
Missing	1 (0)	8 (0)
Performance score prior to CT - no. (%)		

Characteristic	Non-fludarabine containing	Fludarabine containing
90-100%	188 (34)	2912 (43)
80%	160 (29)	2026 (30)
<80%	134 (24)	1278 (19)
Missing	72 (13)	604 (9)
ECOG performance status prior to CT - no. (%)		
Asymptomatic	188 (34)	2912 (43)
Symptomatic but completely ambulatory	249 (45)	3010 (44)
Symptomatic, < 50% in bed during the day	40 (7)	270 (4)
Symptomatic, > 50% in bed, but not bedbound	4 (1)	20 (0)
Bedbound	1 (0)	4 (0)
Missing	72 (13)	604 (9)
HCT-CI - no. (%)		
0	172 (31)	2126 (31)
1	104 (19)	1349 (20)
2	76 (14)	895 (13)
3+	195 (35)	2359 (35)
TBD	2 (0)	35 (1)
NA (not collected for these cases)	0 (0)	2 (0)
Missing	5 (1)	54 (1)
Disease related		
Disease - no. (%)		
Acute lymphoblastic leukemia (ALL)	19 (3)	990 (15)
Non-Hodgkin lymphoma (NHL)	440 (79)	5100 (75)
Plasma cell disorder/multiple myeloma (PCD/MM)	95 (17)	730 (11)
MRD positive/negative CR prior to CT (ALL only) - no. (%)		
MRD negative	7 (37)	219 (22)
MRD positive	0 (0)	134 (14)
Not tested	1 (5)	11 (1)
N/A, ALL not in CR	11 (58)	610 (62)
Missing	0 (0)	16 (2)
Disease status at CT (NHL only) - no. (%)		
CR	41 (9)	241 (5)
PR	133 (30)	1121 (22)
Resistant	230 (52)	3293 (65)
Missing	36 (8)	445 (9)
IPI at initial diagnosis of the primary disease - no. (%)		
Low	9 (2)	173 (3)

Characteristic	Non-fludarabine containing	Fludarabine containing
Low intermediate	22 (4)	284 (4)
High intermediate	21 (4)	339 (5)
High	31 (6)	369 (5)
Missing	471 (85)	5655 (83)
Prior lines of therapies - no. (%)		
No	1 (0)	27 (0)
Yes	457 (82)	6337 (93)
1	314 (57)	4441 (65)
2	14 (3)	151 (2)
>=3	76 (14)	1367 (20)
Missing	53 (10)	378 (6)
Missing	96 (17)	456 (7)
Prior radiation therapy - no. (%)		
No	264 (48)	4170 (61)
Yes	148 (27)	1941 (28)
Missing	142 (26)	709 (10)
Prior HCT - no. (%)		
No	385 (69)	4609 (68)
Yes	144 (26)	1917 (28)
Prior allo-HCT	11 (2)	271 (4)
Prior auto-HCT	131 (24)	1577 (23)
Prior auto and allo-HCT	1 (0)	31 (0)
Missing	1 (0)	38 (1)
Missing	25 (5)	294 (4)
Time from HCT to CT, months - median (min-max)	52 (4-230)	32 (1-315)
CAR-T cell related		
Year of CT - no. (%)		
2017	0 (0)	17 (0)
2018	17 (3)	615 (9)
2019	50 (9)	1091 (16)
2020	77 (14)	1280 (19)
2021	78 (14)	1820 (27)
2022	332 (60)	1997 (29)
Time from diagnosis to CT - no. (%)		
Median (min-max)	19 (1-322)	18 (0-447)
Less than 6 months	51 (9)	664 (10)
6-11 months	127 (23)	1627 (24)

Characteristic	Non-fludarabine containing	Fludarabine containing
12-17 months	124 (22)	1655 (24)
24-36 months	54 (10)	678 (10)
More than 36 months	198 (36)	2190 (32)
Missing	0 (0)	6 (0)
Bridging therapy - no. (%)		
No	249 (45)	4120 (60)
Yes	124 (22)	1602 (23)
Systemic therapy	86 (16)	1269 (19)
Intrathecal therapy	4 (1)	45 (1)
Intraocular therapy	0 (0)	1 (0)
Radiation therapy	49 (9)	431 (6)
Surgery	0 (0)	3 (0)
Not reported	181 (33)	1098 (16)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)		
No	22 (4)	0 (0)
Yes	531 (96)	6820 (100)
Bendamustine only	406 (73)	0 (0)
Flu+Cy only	0 (0)	6752 (99)
Other	110 (20)	68 (1)
Not reported	15 (3)	0 (0)
Missing	1 (0)	0 (0)
Lymphodepleting chemotherapy - no. (%)		
Bendamustine	406 (73)	0 (0)
Bendamustine + Cyclophosphamide (Cytoxan)	1 (0)	0 (0)
Bendamustine + Cyclophosphamide (Cytoxan) + Fludarabine (Fludara)	0 (0)	2 (0)
Bendamustine + Cytarabine (Ara-C)	1 (0)	0 (0)
Bendamustine + Other	14 (3)	0 (0)
Carboplatin + Fludarabine (Fludara)	0 (0)	2 (0)
Clofarabine + Cyclophosphamide (Cytoxan)	1 (0)	0 (0)
Clofarabine + Fludarabine (Fludara)	0 (0)	1 (0)
Cyclophosphamide (Cytoxan)	46 (8)	0 (0)
Cyclophosphamide (Cytoxan) + Cytarabine (Ara-C) + Etoposide (VP-16, VePesid) + Fludarabine (Fludara)	0 (0)	1 (0)
Cyclophosphamide (Cytoxan) + Cytarabine (Ara-C) + Fludarabine (Fludara)	0 (0)	3 (0)

Characteristic	Non-fludarabine containing	Fludarabine containing
Cyclophosphamide (Cytoxan) + Fludarabine (Fludara)	0 (0)	6752 (99)
Cyclophosphamide (Cytoxan) + Fludarabine (Fludara) + Other	0 (0)	15 (0)
Cyclophosphamide (Cytoxan) + Gemcitabine	1 (0)	0 (0)
Cyclophosphamide (Cytoxan) + Other	19 (3)	0 (0)
Cyclophosphamide (Cytoxan) + Thiotepa	1 (0)	0 (0)
Cytarabine (Ara-C) + Etoposide (VP-16, VePesid)	1 (0)	0 (0)
Cytarabine (Ara-C) + Fludarabine (Fludara)	0 (0)	13 (0)
Etoposide (VP-16, VePesid) + Other	1 (0)	0 (0)
Fludarabine (Fludara)	0 (0)	31 (0)
Other	24 (4)	0 (0)
None specified	38 (7)	0 (0)
Follow-up, in months - median (range)	13 (1-51)	13 (0-54)

CT Extract December 2022

Title:

Impact of Toxicity Prophylactic Medications on Outcomes of Chimeric Antigen Receptor T-cell Therapy

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Research Hypothesis

1. Prophylactic administration of tocilizumab and steroids are associated with fewer and less severe cytokine release syndrome (CRS) and/or immune-effector cell-associated neurotoxicity syndrome (ICANS) without impacting response rate or overall survival.
2. Prophylactic use of anti-epileptic medications (AEDs) is associated with fewer and less severe ICANS.

Objectives/Outcomes

Primary outcomes

1. Incidence of all-grade CRS and ICANS
2. Incidence of grade 3 or higher CRS and ICANS

Secondary outcomes

1. Duration of CRS and ICANS
2. Subsequent treatment for CRS and ICANS
3. Overall response rate
4. Complete response rate
5. Infection
6. Progression-free survival
7. Overall survival

Scientific Impact

The development of CRS and ICANS, and particularly grade 3 or higher CRS and ICANS, remains a challenge in CAR T-cell therapy. Prophylactic tocilizumab and steroids, as well as anti-epileptics have been adopted in some centers to mitigate these toxicities despite weak evidence. The proposed study would provide further evidence regarding the efficacy of these three prophylactic methods and pave the way for potential randomized trials.

Scientific Justification

Cytokine release syndrome (CRS) and immune-effector cell associated neurotoxicity syndrome (ICANS) are specific and serious adverse effects following CAR T-cell therapy. CRS is defined by clinical criteria of fever, hypotension, and hypoxia, and is graded on a scale from 1 to 4 using a grading system proposed by the American Society for Transplantation and Cellular Therapy (ASTCT).(1) Similarly, ICANS is characterized by changes in the level of consciousness, motor findings, seizures, and raised intracranial pressure and is also graded by a system developed by ASTCT.(1) The incidence of CRS and ICANS varied in different clinical trials. In the ZUMA-1 study of axicabtagene ciloleucel (axi-cel) in relapsed/refractory B-NHL, grade 3 or higher CRS occurred in 13% and grade 3 or higher ICANS occurred in 28% of all patients.(2) Although the majority of CRS or ICANS are low grade, severe CRS and ICANS which are grade 3 or higher can be debilitating and even fatal. Therefore, developing optimal strategies to prevent and mitigate these adverse effects are of great importance.

Glucocorticoids are commonly used in the treatment of CRS and ICANS. In Cohort 6 of the ZUMA-1 trial, 40 patients universally received prophylactic dexamethasone for 3 days; none developed grade 3 or higher CRS, and overall CRS severity and duration were significantly lower than propensity-matched cohorts without prophylaxis.(3) Moreover, the duration of ICANS was also shorter in patients who received prophylaxis. Notably, the overall response rate (ORR) and complete response (CR) rate were not significantly different from patients without prophylaxis. These results have led to FDA amending toxicity management recommendations to include prophylactic corticosteroids across all indications for axi-cel. However, steroids prophylaxis has not been widely adopted due to concerns regarding CAR T-cell efficacy. Moreover, in the prophylactic cohort, there were 3 (8%) patients with grade 3 and 2 (5%) patients with grade 4 ICANS, raising concern for a possible association between prophylactic steroids and more severe ICANS.(4) Therefore, retrospective analysis is needed to provide more information regarding the efficacy and safety of this practice.

Tocilizumab, an antagonist of IL-6 receptor, was recommended by the FDA for the treatment of severe or life-threatening CRS. Additionally, it has also been increasingly used prophylactically before the onset of CRS, which is administered as a premedication with CAR T-cell infusion. However, limited data exist to support this practice. In the Cohort 3 of ZUMA-1 study, tocilizumab was given on Day 2 after axi-cel infusion regardless of CRS onset; this cohort was found to have less severe CRS (grade 3 or higher) comparing to other cohorts in the study (3% vs 13%).(5) In another single-arm study of prophylactic tocilizumab use in 20 patients with non-Hodgkin lymphoma, no patients experienced grade 3 or higher CRS.(6) Therefore, more evidence is needed to support its routine use.

Anti-epileptic medications (AEDs) such as levetiracetam have 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, 65% of centers offered universal levetiracetam prophylaxis, 20% never offer AED prophylaxis, while the remaining 15% provide levetiracetam in a case-by-case manner.(7) Multiple animal studies have shown that levetiracetam was able to preserve the BBB integrity under various insults(8-10) and was associated with reduced inflammatory cytokines in the brain(11, 12). Therefore, levetiracetam may not only be effective at preventing seizure, but also reducing in the incidence and severity of ICANS. However, there has been little 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.(13)

Prophylactic use of tocilizumab, steroids, and anti-epileptics have been added to the data collection form at CIBMTR (Form 4000 R8.0, question 87) since 2020. The study proposed here would compare a much larger sample of patients receiving prophylactic medications for CRS or ICANS to matched controls. The study would evaluate the incidence, severity, and duration of CRS and ICANS, as well as outcomes in terms of response rate, infection, and survival between these two groups. We expect that the findings from a larger sample will further validate the findings in previous smaller cohort, add to the body of medical knowledge on mitigating CAR T toxicity, and provide more convincing arguments for wider adoption of prophylactic medications.

Study Population

Inclusion criteria:

1. Adult patients (≥ 18 years) with a diagnosis of large B-cell lymphoma (LBCL).
2. Received first-time commercial CAR T-cell products between 2016 and 2021.

Exclusion Criteria:

1. Received steroids, tocilizumab, or AEDs for other conditions prior to CAR T-cell infusion
2. Received other immunosuppressive medications prior to CAR T-cell infusion
3. Received medications other than tocilizumab or steroids for CRS prevention
4. Received medications other than anti-epileptics for ICANS prevention
5. Received CAR T-cell product with target other than CD19

Study Design

Data will be retrospectively collected from the CIBMTR and CIDR databases. Patients who received prophylactic steroids, tocilizumab, or AEDs will be included in the study cohort; patients who never received any prophylactic medications will be included in the control group. A propensity score matching method will be applied, incorporating baseline characteristics as well as known covariates associated with the severity of CRS and/or ICANS, including CAR T-cell products, lymphodepleting regimen intensity, baseline platelet count, and tumor burden (using baseline LDH as a surrogate). CRS will be graded according to the ASTCT grading criteria. ICANS will be graded per the ICE-score based on the ASTCT grading criteria.

For primary outcomes, descriptive methods will be used to compare the composition of different grades of CRS/ICANS. Odds of non-CRS/ICANS, mild CRS/ICANS (grade 1 or 2), and severe CRS/ICANS (grade 3 or higher) will be compared using *Chi*-squared test. The hazard ratio of severe CRS/ICANS will be calculated using Cox regression. For secondary outcomes, onset day of CRS/ICANS, duration of CRS/ICANS, the maximum value of CRS markers (IL2/6, ferritin, CRP), and the highest ICE score will be compared using the Mann-Whitney *U*-test. Subsequent treatments for CRS/ICANS will be compared using descriptive methods. Response rate and infection rate will be compared using the *Chi*-squared test. Progression-free survival and overall survival will be compared using the Kaplan-Meier method.

Variables to be Analyzed

Type of data/Form	**Data point**	**Specific data/questionnaire#**
Patient related	Demographics	Age, gender
Disease at infusion (Form 2402 R6.0)	Disease	Primary disease and date of dx (1-2)
	NHL	Histology (379-381) Disease status at infusion (388-394) Lines of previous treatment (385)
	Recipient data	Ethnicity (1), race (2), clinical trial (16), prior CAR T therapy (18), prior HCT history (27-32)
Disease at infusion (Form 2018 R6.0)	NHL	Nodal involvement and largest size (283-285) Extranodal involvement (286-288)
CAR T-cell therapy pre-infusion (Form 4000 R8.0)	Cellular therapy product	Cellular therapy product (52, 53)
	Lymphodepleting therapy	Lymphodepleting given or not (78) Drug, dose, date of start (81-84)
	Toxicity prophylaxis	CRS and ICANS prophylaxis (85-88)
	Pre-infusion characteristics	Indication for CAR T (58), date of disease diagnosis (59) Comorbidities: neurologic (65), COVID-19 infection history and vaccine history (106-115), co-existing disease (118)

		Laboratory findings: CBC (89-99), LDH (100-102) Functional status (103-105)
CAR T-cell therapy infusion (Form 4006 R5.0)	Infusion characteristics	Date of infusion (6) Total number of cells administered (14-15)
CAR T-cell therapy post-infusion (Form 4100 R7.0)	Best response	Best response and date of achievement (9-11)
	Toxicities	CRS (80-109) ICANS (110-128) Grade 3 toxicities (148-154) Grade 4 toxicities (155-161) CRS markers: CRP, IL-2/6, ferritin (162-170)
	Infection	Infection (171-175)
	Progression and survival	Survival (2-3) Disease relapse or progression (21-22) Subsequent cellular infusions (4-8)
Recipient death data (Form 2900)	Recipient death data	

Non-CIBMTR Data Source

None

Conflicts of interest

None

Reference

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2207-01,2210-77,2210-01, PPX - Patients treated with CAR T for Leukemia and Lymphoma

Characteristic	N (%)
No. of patients	6690
No. of centers	173
Patient related	
Age at infusion, yrs	
Mean (SD)	56 (19.3)
Age at infusion, by category - no. (%)	
0-9 Years Old	221 (3)
10-17 Years Old	282 (4)
18-29 Years Old	378 (6)
30-39 Years Old	292 (4)
40-49 Years Old	518 (8)
50-59 Years Old	1259 (19)
60-69 Years Old	2104 (31)
70 or more Years Old	1636 (24)
Recipient sex - no. (%)	
Male	4247 (63)
Female	2441 (36)
Missing	2 (0)
Recipient race - no. (%)	
White	5184 (77)
Black or African American	343 (5)
Asian	316 (5)
Native Hawaiian or other Pacific Islander	11 (0)
American Indian or Alaska Native	26 (0)
Other	55 (1)
More than one race	373 (6)
Missing	382 (6)
Recipient ethnicity - no. (%)	
Hispanic or Latino	911 (14)
Non Hispanic or non-Latino	5078 (76)
Non-resident of the U.S.	470 (7)
Unknown	222 (3)
Missing	9 (0)
Performance score prior to CT - no. (%)	
90-100%	2874 (43)
80%	1941 (29)

Characteristic	N (%)
<80%	1248 (19)
Missing	627 (9)
ECOG performance status prior to CT - no. (%)	
Asymptomatic	2874 (43)
Symptomatic but completely ambulatory	2903 (43)
Symptomatic, < 50% in bed during the day	260 (4)
Symptomatic, > 50% in bed, but not bedbound	22 (0)
Bedbound	4 (0)
Missing	627 (9)
HCT-CI - no. (%)	
0	2128 (32)
1	1347 (20)
2	867 (13)
3+	2264 (34)
TBD	29 (0)
NA (not collected for these cases)	1 (0)
Missing	54 (1)
Disease related	
Disease - no. (%)	
Acute lymphoblastic leukemia (ALL)	799 (12)
Non-Hodgkin lymphoma (NHL)	5891 (88)
MRD positive/negative CR prior to CT (ALL only) - no. (%)	
MRD negative	171 (21)
MRD positive	113 (14)
Not tested	8 (1)
N/A, ALL not in CR	493 (62)
Missing	14 (2)
Disease status at CT (NHL only) - no. (%)	
CR	292 (5)
PR	1316 (22)
Resistant	3751 (64)
Missing	532 (9)
IPI at initial diagnosis of the primary disease - no. (%)	
Low	195 (3)
Low intermediate	327 (5)
High intermediate	374 (6)
High	414 (6)
Missing	5380 (80)

Characteristic	N (%)
Prior lines of therapies - no. (%)	
No	30 (0)
Yes	6115 (91)
1	4958 (74)
2	79 (1)
>=3	848 (13)
Missing	230 (3)
Missing	545 (8)
Prior radiation therapy - no. (%)	
No	4186 (63)
Yes	1830 (27)
Missing	674 (10)
Prior HCT - no. (%)	
No	5233 (78)
Yes	1176 (18)
Prior auto-HCT	1144 (17)
Missing	32 (0)
Missing	281 (4)
Time from HCT to CT, months - median (min-max)	21 (2-315)
CAR-T cell related	
Year of CT - no. (%)	
2017	14 (0)
2018	576 (9)
2019	1101 (16)
2020	1326 (20)
2021	1763 (26)
2022	1910 (29)
Product - no. (%)	
Kymriah	1990 (30)
Yescarta	3796 (57)
Tecartus	563 (8)
Breyanzi	341 (5)
CRS Therapy - no. (%)	
Tocilizumab only	1703 (25)
Tocilizumab + Corticosteroids	926 (14)
Corticosteroids only	84 (1)
Anakinra + Tocilizumab + Corticosteroids	56 (1)
Anakinra + Tocilizumab	29 (0)

Characteristic	N (%)
Anakinra	13 (0)
Siltuximab	12 (0)
Other	80 (1)
Not Specified	3787 (57)
ICANS Therapy - no. (%)	
Corticosteroids	760 (11)
Corticosteroids + Anti Epileptics	377 (6)
Corticosteroids + Tocilizumab	203 (3)
Anti Epileptics	156 (2)
Corticosteroids + Tocilizumab + Anti Epileptics	107 (2)
Tocilizumab	64 (1)
Corticosteroids + Anakinra + Anti Epileptics	56 (1)
Corticosteroids + Anakinra	40 (1)
Corticosteroids + Anakinra + Tocilizumab + Anti Epileptics	25 (0)
Anakinra	11 (0)
Siltuximab	2 (0)
Other	111 (2)
Not Specified	4778 (71)
CRS Prophylaxis - no. (%)	
No:	3420 (51)
Yes:	419 (6)
Tocilizumab	265 (4)
Corticosteroids	75 (1)
Other	88 (1)
Not reported	2851 (43)
ICANS Prophylaxis - no. (%)	
No:	1866 (28)
Yes:	1973 (29)
Anti-Epileptics	1938 (29)
Corticosteroids	46 (1)
Other	70 (1)
Not reported	2851 (43)
Time from diagnosis to CT - no. (%)	
Median (min-max)	16 (1-447)
Less than 6 months	714 (11)
6-11 months	1765 (26)
12-17 months	1751 (26)
24-36 months	674 (10)

Characteristic	N (%)
More than 36 months	1780 (27)
Missing	6 (0)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)	
No	19 (0)
Yes	6670 (100)
Bendamustine only	384 (6)
Flu+Cy only	6136 (92)
Other	137 (2)
Not reported	13 (0)
Missing	1 (0)
Lymphodepleting chemotherapy - no. (%)	
Bendamustine	384 (6)
Bendamustine + Cyclophosphamide (Cytoxan)	1 (0)
Bendamustine + Cyclophosphamide (Cytoxan) + Fludarabine (Fludara)	2 (0)
Bendamustine + Cytarabine (Ara-C)	1 (0)
Bendamustine + Other	18 (0)
Carboplatin + Fludarabine (Fludara)	2 (0)
Clofarabine + Cyclophosphamide (Cytoxan)	1 (0)
Clofarabine + Fludarabine (Fludara)	1 (0)
Cyclophosphamide (Cytoxan)	24 (0)
Cyclophosphamide (Cytoxan) + Cytarabine (Ara-C) + Fludarabine (Fludara)	3 (0)
Cyclophosphamide (Cytoxan) + Fludarabine (Fludara)	6136 (92)
Cyclophosphamide (Cytoxan) + Fludarabine (Fludara) + Other	15 (0)
Cytarabine (Ara-C) + Etoposide (VP-16, VePesid)	1 (0)
Cytarabine (Ara-C) + Fludarabine (Fludara)	13 (0)
Etoposide (VP-16, VePesid) + Other	1 (0)
Fludarabine (Fludara)	31 (0)
Other	23 (0)
None specified	33 (0)
Follow-up, in months - median (range)	13 (0-52)

CT Extract December 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

COMPARATIVE OUTCOMES ANALYSIS OF PATIENTS WITH AGGRESSIVE B-CELL LYMPHOMA TREATED WITH AXICABTAGENE CILOLEUCEL VS. LISOCABTAGENE MARALEUCEL

Q2. Key Words

axi-cel, liso-cel, CAR T-cell therapy

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Agrima Mian, MD
Email address:	miana@ccf.org
Institution name:	Cleveland Clinic
Academic rank:	PGY3, Internal 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):	Brian T. Hill, MD, PhD.
Email address:	hillb2@ccf.org
Institution name:	Cleveland Clinic
Academic rank:	Associate Professor (Case Western Reserve University School 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:

Brian T. Hill

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.

Agrima Mian has no ongoing projects with CIBMTR. Brian T. Hill proposed, and is involved in study number CT20-01.

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:

In patients with relapsed or refractory aggressive B-cell lymphoma, is there a significant difference between the comparative survival outcomes and toxicities in those treated with axicabtagene ciloleucel (axi-cel) versus lisocabtagene maraleucel (liso-cel)?

Q16. RESEARCH HYPOTHESIS:

Currently, axi-cel and liso-cel share essentially the same indications for treatment of relapsed or refractory (r/r) large B-cell lymphoma, and no direct comparison of these products has been performed so far. The hypothesis of this study is that patients with r/r aggressive B-cell lymphoma have similar rates of durable remissions when treated with anti-CD19 directed chimeric antigen receptor (CAR) T-cell using axi-cel or liso-cel.

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

Suggested word limit of 200 words:

Primary Outcome

• To compare Progression free survival (PFS) assessed at 6 months in patients with r/r LBCL treated with axi-cel vs. liso-cel.

(As shown in the two pivotal trials ZUMA-1 and TRANSCEND NHL 001 (1,2), for patients treated with both axi-cel and liso-cel, the PFS curves reach a plateau at 6 months, indicating that majority of patients who are free from progression/relapse at 6 months will not eventually relapse/progress.)

Secondary Outcomes

• To compare the overall survival (OS) in patients with r/r LBCL treated with axi-cel vs. liso-cel.

• To compare the best objective response rate (ORR), complete remission (CR), partial remission (PR) rates and incidence of relapse/progression in patients with r/r LBCL treated with axi-cel vs. liso-cel.

• To compare the incidence and severity of cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS) in patients with r/r LBCL treated with axi-cel vs. liso-cel.

• To compare treatment-related mortality (TRM) and primary cause of death in patients with r/r LBCL treated with axi-cel vs. liso-cel.

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.

Results of this study will immediately inform clinical practice as currently all approved anti-CD19 CAR T-cell therapies essentially share the same indication for use in r/r LBCL population, and the selection of the type of product is based on institutional preference, manufacturing availability and/or perceived efficacy and tolerability of these agents.

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.

Although diffuse large B-cell lymphoma (DLBCL) is a curable illness, approximately 30-40% patients experience relapse or may fail initial therapy. Fewer than 50% of patients with relapsed or refractory (r/r) LBCL achieve a response to subsequent treatment after second line salvage regimens and autologous stem cell transplant (ASCT) (3,4). Particularly worse outcomes are seen in those with chemotherapy refractory disease, early relapse (<1 year) or those who relapse after ASCT (median overall survival of 6 months) (5).

At present, three anti-CD19 directed chimeric antigen receptor (CAR) T-cell therapy products are commercially available for patients with r/r LBCL, who have failed prior systemic therapy or transplant. These have remarkable clinical activity and can potentially achieve durable remissions. In a single center, retrospective, study of 215 patients with r/r LBCL, outcomes of those treated with (any) anti-CD19 CAR T-cell therapy compared with a historical population treated with alternate therapies, demonstrated a superior CR rate (52% vs 22%; P<0.001), median PFS (5.2 vs 2.3 months; P=0.1), and median OS (19.3 vs 6.5 months; P=0.006), irrespective of number of lines of prior therapy (6).

Two seminal studies lead to the FDA approval of axi-cel and tisagenlecleucel for this patient population (1,7). More recently, lisocabtagene maraleucel (liso-cel), a novel anti-CD19 CAR T-cell (with a 4-1BB co-stimulatory domain administered as sequential infusions of equal target doses of CD8 and CD4 CAR T-cells) received FDA approval for r/r LBCL and follicular lymphoma grade 3b, after results from the TRANSCEND NHL 001 study (2). Compared to the seminal CAR T-cell studies, this study enrolled a broad range of patients with diverse histological features and other high-risk features such as low creatinine clearance, poor cardiac function and secondary CNS involvement.

At present, there is paucity of data on comparative efficacy and toxicity of the three commercial CAR T-cell products in the real-world scenario. There are limited reports, but no conclusive evidence, to suggest that axi-cel may have superior disease control and higher toxicity, than tisa-cel (8,9). Recently, a matching-adjusted indirect comparison of the patient population in the JULIET vs. TRANSCEND NHL-001 study indicated no differences in the OS, PFS and CR rate between patients treated with tisa-cel vs liso-cel (10). Our previously proposed CIBMTR study to compare outcomes of patients treated with axi-cel vs. tisa-cel is currently in progress. With the recent FDA approval of liso-cel, which essentially shares the same indication for treatment as the prior two CAR T-cell products, “real-world” data to compare their efficacy and toxicity is warranted. A CIBMTR study is the most reasonable methodology to address this clinical question, since head-to-head comparison in randomized controlled trials seems unlikely in the near 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

• Patients ≥ 18 years who have undergone treatment with axi-cel or liso-cel at a CIBMTR center between 2018-2022.

• Patients with the following diagnosis: DLBCL with or without transformation from indolent lymphoma, high-grade B-cell lymphoma (including double-hit or triple-hit lymphoma) and primary mediastinal B-cell lymphoma.

Exclusion Criteria

• Patients with follicular lymphoma Grade 3b will be excluded.

• Patients who have received prior cellular therapy (for any indication) will be excluded.

Q21. Does this study include pediatric patients?

- No

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

Axi-cel and liso-cel are both approved only for adult patients with r/r DLBCL.

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 captured in the baseline demographics will include gender, age of diagnosis, performance status, time from diagnosis to relapse, response to most recent therapy (chemosensitive or chemoresistant), disease status at the last evaluation prior to CAR-T cell therapy and hematopoietic cell transplantation comorbidity index (HCT-CI).
• Details (and number) of prior treatments will include systemic chemotherapies (including bridging therapy), monoclonal antibodies or check point inhibitor therapy and prior hematopoietic stem cell transplant.
• Details of response and survival outcomes will include best response, time to best response, time to relapse/progression and overall survival.
• Details of toxicities will include severity of CRS and ICANS (using ASTCT consensus grading), specific therapies given for treatment of CRS and ICANS, peripheral blood cytopenia, hypogammaglobinemia, tumor lysis syndrome, clinically significant infections, subsequent malignancies or other Grade ¾ toxicities.
• These data will be procured from CIBMTR data collection forms: 4000 (Pre-Cellular Therapy Essential Data), 4003 (Cell Therapy Product), 4006 (Cellular Therapy Infusion) and 4100 (Cellular Therapy Essential Data Follow-Up Form)
• No supplemental data form will be required.

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

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:

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 28;377(26):2531–44.
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):839–52.
3. Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010 Sep 20;28(27):4184–90.
4. Van Den Neste E, Schmitz N, Mounier N, Gill D, Linch D, Trneny M, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant. 2016 Jan;51(1):51–7.
5. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017 19;130(16):1800–8.
6. Sermer D, Batlevi C, Palomba ML, Shah G, Lin RJ, Perales M-A, et al. Outcomes in patients with DLBCL treated with commercial CAR T cells compared with alternate therapies. Blood Advances. 2020 Oct 1;4(19):4669–78.
7. 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 03;380(1):45–56.
8. Riedell PA, Walling C, Nastoupil LJ, Pennisi M, Maziarz RT, McGuirk JP, et al. A Multicenter Retrospective Analysis of Clinical Outcomes, Toxicities, and Patterns of Use in Institutions Utilizing Commercial Axicabtagene Ciloleucel and Tisagenlecleucel for Relapsed/Refractory Aggressive B-Cell Lymphomas. Blood. 2019 Nov 13;134(Supplement_1):1599–1599.
9. Nastoupil LJ, Jain MD, Feng L, Spiegel JY, Ghobadi A, Lin Y, et al. Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium. J Clin Oncol. 2020 Sep 20;38(27):3119–28.
10. Schuster SJ, Zhang J, Yang H, Agarwal A, Tang W, Martinez-Prieto M, et al. Comparative efficacy of tisagenlecleucel (tisa-cel) and lisocabtagene maraleucel (liso-cel) in patients with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). JCO. 2021 May 20;39(15_suppl):7535–7535.

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)?

- Yes, I have 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.

Brian T. Hill has received research funding from Kite Pharma (a Gilead Company) and has served as a consultant to Kite Pharma as well as Novartis and Juno Therapeutics (a Celgene/Bristol-Myers Squibb Company). Agrima Mian is supported by the ASH HONORS Grant for the year 2022-2023.

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

2209-13, Breyanzi vs yescarta - Adults treated with Breyanzi or Yescarta for DLBCL

Characteristic	Yescarta	Breyanzi
No. of patients	3480	332
No. of centers	117	56
Patient related		
Age at infusion, yrs		
Mean (SD)	60 (12.9)	67 (11.6)
Age at infusion, by category - no. (%)		
18-29 Years Old	115 (3)	2 (1)
30-39 Years Old	208 (6)	11 (3)
40-49 Years Old	355 (10)	20 (6)
50-59 Years Old	804 (23)	43 (13)
60-69 Years Old	1257 (36)	105 (32)
70 or more Years Old	741 (21)	151 (45)
Recipient sex - no. (%)		
Male	2219 (64)	207 (62)
Female	1260 (36)	125 (38)
Missing	1 (0)	0 (0)
Recipient race - no. (%)		
White	2710 (78)	291 (88)
Black or African American	191 (5)	11 (3)
Asian	191 (5)	20 (6)
Native Hawaiian or other Pacific Islander	8 (0)	0 (0)
American Indian or Alaska Native	17 (0)	0 (0)
Other	25 (1)	3 (1)
More than one race	175 (5)	6 (2)
Missing	163 (5)	1 (0)
Recipient ethnicity - no. (%)		
Hispanic or Latino	412 (12)	22 (7)
Non Hispanic or non-Latino	2776 (80)	302 (91)
Non-resident of the U.S.	181 (5)	0 (0)
Unknown	106 (3)	8 (2)
Missing	5 (0)	0 (0)
Performance score prior to CT - no. (%)		
90-100%	1431 (41)	114 (34)
80%	1067 (31)	99 (30)
<80%	650 (19)	87 (26)
Missing	332 (10)	32 (10)

Characteristic	Yescarta	Breyanzi
ECOG performance status prior to CT - no. (%)		
Asymptomatic	1431 (41)	114 (34)
Symptomatic but completely ambulatory	1574 (45)	168 (51)
Symptomatic, < 50% in bed during the day	134 (4)	16 (5)
Symptomatic, > 50% in bed, but not bedbound	8 (0)	2 (1)
Bedbound	1 (0)	0 (0)
Missing	332 (10)	32 (10)
HCT-CI - no. (%)		
0	1078 (31)	88 (27)
1	698 (20)	51 (15)
2	465 (13)	47 (14)
3+	1178 (34)	142 (43)
TBD	16 (0)	4 (1)
Missing	45 (1)	0 (0)
Disease related		
Disease classification - no. (%)		
Non-Hodgkin lymphoma (NHL)		
NHL diffuse, large B-cell:	697 (20)	61 (18)
Burkitt lym/Burkitt cell leukemia:	9 (0)	3 (1)
T-cell / histiocytic rich large B-cell lymphoma:	54 (2)	4 (1)
Primary mediastinal large B-cell (095CORE):	106 (3)	2 (1)
Other B-cell, spec:	10 (0)	1 (0)
B-cell unclass. between DLBCL and hodgkin:	1 (0)	0 (0)
Diffuse, large B-cell lymphoma- Germinal center B-cell type	1184 (34)	112 (34)
Diffuse, large B-cell lymphoma- Activated B-cell type	830 (24)	105 (32)
Primary cutaneous DLBCL, leg type (1822)	5 (0)	1 (0)
EBV+ DLBCL, NOS (1823)	38 (1)	3 (1)
DLBCL associated with chronic inflammation (1825)	1 (0)	0 (0)
HHV8+ DLBCL, NOS (1826)	1 (0)	0 (0)
High-grade B-cell lymphoma, NOS	71 (2)	5 (2)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	472 (14)	35 (11)
Burkitt-like lymphoma with 11q aberration (1834)	1 (0)	0 (0)
Disease status at CT - no. (%)		
CR	144 (4)	29 (9)
PR	771 (22)	80 (24)
Resistant	2249 (65)	202 (61)
Missing	316 (9)	21 (6)

Characteristic	Yescarta	Breyanzi
IPI at initial diagnosis of the primary disease - no. (%)		
Low	113 (3)	17 (5)
Low intermediate	182 (5)	26 (8)
High intermediate	225 (6)	24 (7)
High	231 (7)	29 (9)
Missing	2729 (78)	236 (71)
Prior lines of therapies - no. (%)		
No	11 (0)	0 (0)
Yes	3237 (93)	298 (90)
1	2516 (72)	262 (79)
2	43 (1)	4 (1)
>=3	549 (16)	27 (8)
Missing	129 (4)	5 (2)
Missing	232 (7)	34 (10)
Prior radiation therapy - no. (%)		
No	2116 (61)	184 (55)
Yes	1067 (31)	114 (34)
Missing	297 (9)	34 (10)
Prior HCT - no. (%)		
No	2624 (75)	276 (83)
Yes	733 (21)	36 (11)
Prior allo-HCT	38 (1)	3 (1)
Prior auto-HCT	667 (19)	31 (9)
Prior auto and allo-HCT	8 (0)	0 (0)
Missing	20 (1)	2 (1)
Missing	123 (4)	20 (6)
Time from HCT to CT, months - median (min-max)	16 (2-315)	47 (5-230)
CAR-T cell related		
Year of CT - no. (%)		
2018	429 (12)	0 (0)
2019	718 (21)	0 (0)
2020	743 (21)	0 (0)
2021	656 (19)	130 (39)
2022	934 (27)	202 (61)
Time from diagnosis to CT - no. (%)		
Median (min-max)	13 (0-447)	16 (2-356)
Less than 6 months	398 (11)	28 (8)
6-11 months	1128 (32)	93 (28)

Characteristic	Yescarta	Breyanzi
12-17 months	999 (29)	93 (28)
24-36 months	314 (9)	37 (11)
More than 36 months	640 (18)	81 (24)
Missing	1 (0)	0 (0)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)		
No	8 (0)	0 (0)
Yes	3472 (100)	332 (100)
Bendamustine only	141 (4)	24 (7)
Flu+Cy only	3275 (94)	302 (91)
Other	53 (2)	6 (2)
Not reported	3 (0)	0 (0)
Lymphodepleting chemotherapy - no. (%)		
Bendamustine	141 (4)	24 (7)
Bendamustine + Cyclophosphamide (Cytoxan)	1 (0)	0 (0)
Bendamustine + Other	12 (0)	1 (0)
Carboplatin + Fludarabine (Fludara)	1 (0)	0 (0)
Cyclophosphamide (Cytoxan)	5 (0)	1 (0)
Cyclophosphamide (Cytoxan) + Fludarabine (Fludara)	3275 (94)	302 (91)
Cyclophosphamide (Cytoxan) + Fludarabine (Fludara) + Other	14 (0)	0 (0)
Cytarabine (Ara-C) + Fludarabine (Fludara)	5 (0)	1 (0)
Etoposide (VP-16, VePesid) + Other	1 (0)	0 (0)
Fludarabine (Fludara)	12 (0)	3 (1)
Other	2 (0)	0 (0)
None specified	11 (0)	0 (0)
Follow-up, in months - median (range)	18 (1-52)	6 (1-17)

CT Extract December 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

Compartive Outcomes Analysis of Outpatient and Inpatient Administration of Chimeric Antigen Receptor (CAR) T-cell Therapy for Agressive B Cell Lymphomas

Q2. Key Words

CAR-T, Large B cell lymphoma, refractory lymphoma, relapsed lymphoma, ICANS, CRS

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Vivek Patel MD
Email address:	vivek.g.patel@vumc.org
Institution name:	Vanderbilt University Medical Center
Academic rank:	Fellow

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):	Olalekan Oluwole MD
Email address:	N/A
Institution name:	Vanderbilt University Medical Center
Academic rank:	Associate 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:

Olalekan Oluwole

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:

What are the differences in safety outcomes, efficacy outcomes, and resource utilization of outpatient compared to inpatient administration of CAR-T therapy for patients with aggressive B Cell Lymphomas?

Q16. RESEARCH HYPOTHESIS:

There will be no significant difference in response and survival outcomes between the cohorts. There will be similar rates and severity of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity (ICANS). Inpatient resource utilization will be lower in the outpatient cohort compared to the inpatient cohort.

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

Suggested word limit of 200 words:

Primary objective
• Compare overall survival outcomes for patients with aggressive B Cell lymphomas treated with outpatient CAR-T compared to inpatient CAR-T
Secondary Objective
• Determine incidence, maximum severity, and duration of CRS
• Determine incidence, maximum severity, and duration of ICANS
• Compare differences in use of steroids and anti IL-6 therapy for toxicity management
• Compare differences in need for pressors and positive pressure ventilation for CRS
• Compare progression free survival outcomes
• Compare inpatient hospital length of 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.

It is unknown whether outpatient administration of CAR-T yields similar safety and efficacy outcomes as inpatient administration for patients with aggressive B cell lymphoma. Understanding differences in safety, efficacy, and resource utilization comparing outpatient and inpatient administration of CAR-T therapy will be critical to potentially enhance patient quality of life and improve cost savings. In addition, this analysis can provide insight into potential patient selection criteria for successful outpatient 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.

Chimeric antigen receptor T-cell (CAR-T) therapies have changed the treatment landscape for relapsed or refractory large B-cell lymphoma (LBCL), follicular lymphoma, and mantle cell lymphoma (MCL). Given risk of toxicities including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), registrational trials for axicabtagene ciloleucel (axi-cel) and brexucabtagene autoleucel (brexu-cel) required hospitalization for close monitoring. In the TRANSCEND trial studying the use of lisocabtagene maraleucel (liso-cel), only 9% of patients received treatment in the outpatient setting. The rate of hospitalization for these patients was 72% for toxicity management. As a result, outpatient experience with CAR-T therapies has been limited.
Over the past few years, the toxicity management process has improved with earlier administration of corticosteroids and tocilizumab resulting in lower rates of acute high-grade toxicities while preserving efficacy outcomes. The ongoing evolution of CAR-T management guidelines calls into question whether inpatient therapy with its higher financial burden is necessary for all CAR-T recipients. There have only been a few published single center reports on feasibility of outpatient CAR-T therapy. These reports were limited by small sample size and a lack of comparison to inpatient controls. We propose to conduct an analysis on safety outcomes, efficacy outcomes, and resource utilization of outpatient compared to inpatient administration of CAR-T therapy for patients with aggressive B Cell Lymphomas.

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: Adult patient age >18 years old, receiving CAR-T for treatment of any type of B cell lymphoma
Exclusion Criteria: Exclude patients with acute lymphoblastic lymphoma (ALL)

Q21. Does this study include pediatric patients?

- No

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

Determination of outpatient outcomes for adult patients recieving CAR-T therapy. Pediatric population requires different monitoring strategies and supportive care that may not be amenable to outpatient administration.

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 Inclusion:
Cellular Therapy Essential Data Pre-infusion:
-Age, gender
-Prior HCT
-Prior HCT type
-Indication for cellular therapy
-Therapy for prevention of CRS
-Therapy for prevention of ICANS
-WBC, platelets before LD chemotherapy
-LDH, ferritin, CRP before LD therapy
-Karnofsky performance status
-Date of product collection
Cellular Therapy Product:
-Type of product
Cellular Therapy Infusion:
-Date of product infusion
-Concomitant therapy
-Type
Cellular therapy essential data follow up:
-Survival
-Hospital admission date, discharge date
-Best response to cellular therapy
-Development of CRS, ICNANS
-Severity of CRS, ICANS
-Date of development
-Therapy given for CRS, ICANS
-Symptoms of CRS, ICANS
-Resolution of CRS, ICANS

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;377(26):2531–44.
2. Shah BD, Ghobadi A, Oluwole OO, Logan AC, Boissel N, Cassaday RD, et al. KTE-X19 for relapsed or refractory adult B-cell acute lym-phoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. Lancet. 2021;398(10299):491– 502.
3. Jacobson C, Chavez JC, Sehgal AR, William BM, Munoz J, Salles G, et al. Primary analysis of Zuma-5: a phase 2 study of Axicabtagene Ciloleucel (Axi-Cel) in patients with relapsed/refractory (R/R) indo-lent non-Hodgkin lymphoma (iNHL). Blood. 2020;136(Supplement 1):4 0 – 1.
4. Sengsayadeth S, Savani B, Oluwole O, Dholaria B. Overview of ap-proved CAR-T therapies, ongoing clinical trials, and its impact on clinical practice. eJHaem. 2021;3:6–10.
5. Sengsayadeth SM, Dholaria BR, Savani BN, Oluwole OO. Chimeric antigen receptor-T cell therapies: the changing landscape. eJHaem. 2022;3(S1):3– 5.
6. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with re-lapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839– 52.
7. Borogovac A, Keruakous A, Bycko M, Holter Chakrabarty J, Ibrahimi S, Khawandanah M, et al. Safety and feasibility of outpatient chime-ric antigen receptor (CAR) T-cell therapy: experience from a tertiary care center. Bone Marrow Transplant. 2022;57:1025–7.
8. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASBMT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625–38.
9. Oluwole OO, Bouabdallah K, Muñoz J, De Guibert S, Vose JM, Bartlett NL, et al. Prophylactic corticosteroid use in patients receiv-ing axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol. 2021;194(4):690 – 700.
10. Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2020;382(14):1331–42.
11. Gatwood KS, Dholaria B, Lucena M, Baer B, Savani B, Oluwole O. Chimeric antigen receptor T-cell therapy: challenges and framework of outpatient administration. eJHaem. 2022;3(Suppl. 1):54–60.
12. Borogovac, A., Keruakous, A., Bycko, M. et al. Safety and feasibility of outpatient chimeric antigen receptor (CAR) T-cell therapy: experience from a tertiary care center. Bone Marrow Transplant 57, 1025–1027 (2022).

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

2210-28, Inpatient vs outpatient - Patients treated with CAR T

Characteristic	In-patient	Out-patient
No. of patients	5268	1083
No. of centers	167	75
Patient related		
Age at infusion, yrs		
Mean (SD)	58 (18.3)	53 (22.5)
Age at infusion, by category - no. (%)		
0-9 Years Old	141 (3)	66 (6)
10-17 Years Old	174 (3)	84 (8)
18-29 Years Old	282 (5)	76 (7)
30-39 Years Old	214 (4)	38 (4)
40-49 Years Old	383 (7)	71 (7)
50-59 Years Old	1023 (19)	179 (17)
60-69 Years Old	1721 (33)	314 (29)
70 or more Years Old	1330 (25)	255 (24)
Recipient sex - no. (%)		
Male	3322 (63)	668 (62)
Female	1940 (37)	413 (38)
Missing	6 (0)	2 (0)
Recipient race - no. (%)		
White	3990 (76)	848 (78)
Black or African American	349 (7)	52 (5)
Asian	250 (5)	39 (4)
Native Hawaiian or other Pacific Islander	8 (0)	1 (0)
American Indian or Alaska Native	21 (0)	3 (0)
Other	40 (1)	20 (2)
More than one race	287 (5)	76 (7)
Missing	323 (6)	44 (4)
Recipient ethnicity - no. (%)		
Hispanic or Latino	724 (14)	133 (12)
Non Hispanic or non-Latino	3959 (75)	855 (79)
Non-resident of the U.S.	415 (8)	49 (5)
Unknown	162 (3)	46 (4)
Missing	8 (0)	0 (0)
Performance score prior to CT - no. (%)		
90-100%	2158 (41)	521 (48)
80%	1639 (31)	277 (26)

Characteristic	In-patient	Out-patient
<80%	1036 (20)	168 (16)
Missing	435 (8)	117 (11)
ECOG performance status prior to CT - no. (%)		
Asymptomatic	2158 (41)	521 (48)
Symptomatic but completely ambulatory	2424 (46)	419 (39)
Symptomatic, < 50% in bed during the day	226 (4)	25 (2)
Symptomatic, > 50% in bed, but not bedbound	20 (0)	1 (0)
Bedbound	5 (0)	0 (0)
Missing	435 (8)	117 (11)
HCT-CI - no. (%)		
0	1619 (31)	369 (34)
1	1055 (20)	213 (20)
2	715 (14)	149 (14)
3+	1833 (35)	341 (31)
TBD	33 (1)	5 (0)
NA (not collected for these cases)	0 (0)	1 (0)
Missing	13 (0)	5 (0)
Disease related		
Disease - no. (%)		
Acute lymphoblastic leukemia (ALL)	580 (11)	224 (21)
Non-Hodgkin lymphoma (NHL)	3976 (75)	736 (68)
Plasma cell disorder/multiple myeloma (PCD/MM)	712 (14)	123 (11)
MRD positive/negative CR prior to CT (ALL only) - no. (%)		
MRD negative	149 (26)	60 (27)
MRD positive	55 (9)	32 (14)
Not tested	5 (1)	8 (4)
N/A, ALL not in CR	358 (62)	123 (55)
Missing	13 (2)	1 (0)
Disease status at CT (NHL only) - no. (%)		
CR	219 (6)	45 (6)
PR	906 (23)	184 (25)
Resistant	2538 (64)	423 (57)
Missing	313 (8)	84 (11)
IPI at initial diagnosis of the primary disease - no. (%)		
Low	139 (3)	30 (3)
Low intermediate	224 (4)	48 (4)
High intermediate	273 (5)	42 (4)
High	299 (6)	39 (4)

Characteristic	In-patient	Out-patient
Missing	4333 (82)	924 (85)
Prior lines of therapies - no. (%)		
No	27 (1)	3 (0)
Yes	4750 (90)	988 (91)
1	3369 (64)	693 (64)
2	105 (2)	21 (2)
>=3	943 (18)	215 (20)
Missing	333 (6)	59 (5)
Missing	491 (9)	92 (8)
Prior radiation therapy - no. (%)		
No	3081 (58)	617 (57)
Yes	1445 (27)	322 (30)
Missing	742 (14)	144 (13)
Prior HCT - no. (%)		
No	3618 (69)	701 (65)
Yes	1397 (27)	300 (28)
Prior allo-HCT	149 (3)	63 (6)
Prior auto-HCT	1194 (23)	227 (21)
Prior auto and allo-HCT	20 (0)	4 (0)
Missing	34 (1)	6 (1)
Missing	253 (5)	82 (8)
Time from HCT to CT, months - median (min-max)	41 (2-315)	36 (4-251)
CAR-T cell related		
Year of CT - no. (%)		
2018	33 (1)	13 (1)
2019	253 (5)	68 (6)
2020	1098 (21)	227 (21)
2021	1769 (34)	343 (32)
2022	2115 (40)	432 (40)
Product - no. (%)		
Kymriah	1236 (23)	530 (49)
Yescarta	2517 (48)	265 (24)
Tecartus	559 (11)	63 (6)
Breyanzi	244 (5)	102 (9)
Abecma	587 (11)	94 (9)
Carvykti	125 (2)	29 (3)
Time from diagnosis to CT - no. (%)		
Median (min-max)	20 (0-447)	22 (0-324)

Characteristic	In-patient	Out-patient
Less than 6 months	468 (9)	118 (11)
6-11 months	1184 (22)	214 (20)
12-17 months	1217 (23)	234 (22)
24-36 months	509 (10)	109 (10)
More than 36 months	1884 (36)	408 (38)
Missing	6 (0)	0 (0)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)		
No	20 (0)	2 (0)
Yes	5248 (100)	1080 (100)
Bendamustine only	276 (5)	162 (15)
Flu+Cy only	4848 (92)	886 (82)
Other	121 (2)	26 (2)
Not reported	3 (0)	6 (1)
Missing	0 (0)	1 (0)
Lymphodepleting chemotherapy - no. (%)		
Bendamustine	276 (5)	162 (15)
Bendamustine + Cyclophosphamide (Cytoxan)	0 (0)	1 (0)
Bendamustine + Cyclophosphamide (Cytoxan) + Fludarabine (Fludara)	2 (0)	0 (0)
Bendamustine + Cytarabine (Ara-C)	1 (0)	0 (0)
Bendamustine + Other	10 (0)	8 (1)
Carboplatin + Fludarabine (Fludara)	1 (0)	1 (0)
Clofarabine + Cyclophosphamide (Cytoxan)	1 (0)	0 (0)
Clofarabine + Fludarabine (Fludara)	1 (0)	0 (0)
Cyclophosphamide (Cytoxan)	44 (1)	4 (0)
Cyclophosphamide (Cytoxan) + Cytarabine (Ara-C) + Fludarabine (Fludara)	0 (0)	1 (0)
Cyclophosphamide (Cytoxan) + Etoposide (VP-16, VePesid)	0 (0)	1 (0)
Cyclophosphamide (Cytoxan) + Fludarabine (Fludara)	4848 (92)	886 (82)
Cyclophosphamide (Cytoxan) + Fludarabine (Fludara) + Other	2 (0)	0 (0)
Cyclophosphamide (Cytoxan) + Gemcitabine	1 (0)	0 (0)
Cyclophosphamide (Cytoxan) + Other	16 (0)	3 (0)
Cyclophosphamide (Cytoxan) + Thiotepa	1 (0)	0 (0)
Cytarabine (Ara-C) + Etoposide (VP-16, VePesid)	1 (0)	0 (0)
Cytarabine (Ara-C) + Fludarabine (Fludara)	8 (0)	4 (0)
Etoposide (VP-16, VePesid) + Other	1 (0)	0 (0)
Fludarabine (Fludara)	31 (1)	3 (0)
None specified	23 (0)	9 (1)
Follow-up, in months - median (range)	12 (0-49)	12 (2-45)

Characteristic	In-patient	Out-patient

CT Extract December 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

Antibiotics exposure correlates of response and toxicity following anti-CD19 CAR T cell therapy

Q2. Key Words

Antibiotics, pediatric, b-ALL, CD19 CAR

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Caitlin W. Elgarten, MD, MSCE
Email address:	elgartenc@chop.edu
Institution name:	Children's Hospital of Philadelphia
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):	Regina M. Myers, MD
Email address:	myersRM@chop.edu
Institution name:	Children's Hospital Of Philadelphia
Academic rank:	Instructor

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:

Elgarten

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.

Elgarten - Currently a Co-I on HS20-01; participant in the Infection and Immune Reconstitution, Pediatric Cancer working committees
Myers - No active studies at present, but a participant in the Cellular Immunotherapy for Cancer, Pediatric Cancer, and Late Effects and Quality of Life working committees

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:

Amy Moskop, MD

Q15. RESEARCH QUESTION:

To determine the independent association of antibiotics commonly administered for neutropenic fever with toxicities and outcomes after CD19-directed CAR T-cell therapy (CD19 CAR) in children, adolescents, and young adults with ALL.

Q16. RESEARCH HYPOTHESIS:

The efficacy and toxicity of CD19 CAR will be differential based on exposure to antibiotics immediately pre- and post-CAR infusion.

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.) *Suggested word limit of 200 words:*

This study will investigate the association of antibiotics with the following key clinically relevant outcomes:
(1) Overall survival
(2) Relapse-free survival
(3) Duration of B-cell aplasia
(4) CRS and ICANS severity

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 proposal will elucidate if there is an association between specific classes of antibiotic exposure in the pre- and post-CD19 CAR period with clinically relevant toxicities and outcomes, including survival, CRS and ICANS. Exposure to antibiotics in children with relapsed/refractory ALL is ubiquitous. Frequent antibiotic exposures – especially those that target anaerobic commensal microorganisms – cause dramatic alterations in the composition of the intestinal microbiome.1,2 Because the microbiome plays a critical role in regulating T cell immune responses and has been implicated in response to immunotherapies,3-5, we hypothesize that certain antibiotic exposures in the immediate post-CAR or pre-CAR period may alter efficacy and/or toxicity of CD19 CAR. Identification of differential outcomes by antibiotic exposure could impact supportive care guidelines for this patient population and direct future study of microbiome modulation to improve CD19 CAR outcomes.

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 CAR has transformed the treatment landscape for patients with relapsed or refractory CD19+ hematologic malignancies. Despite remarkable initial response rates, approximately 30-50% of patients experience a subsequent disease relapse, and another small proportion do not achieve a complete response.6-9 CD19 CAR also portends a risk of unique toxicities including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Multiple studies have shown that high bone marrow disease burden pre-infusion and higher CAR T cell doses are associated with the development of severe toxicities.10-12 More recently, collaborative groups have established aggregate datasets to evaluate clinical variables that are also associated with CD19 CAR efficacy. These studies demonstrated that high bone marrow disease burden, prior poor response to the CD3-CD19 bispecific antibody blinatumomab, greater number of lines of prior chemotherapy, active extramedullary disease at CD19 CAR infusion, suboptimal fludarabine exposure, and lower CAR T cell doses may be associated with worse clinical efficacy.7,9,13-15 However, these factors fail to predict with precision which patients will develop toxicities and to what degree or which patients will achieve long-term remissions. This raises the possibility that other variables contribute to the function of CAR T cells in vivo both with respect to their antitumor function and their propensity to cause toxicity.

The microbiota of the human gut play an important role in the inhibition of potentially pathogenic microbes and stimulation of the gut immune system. Accumulating data suggest that the intestinal microbiome can regulate immunity in cancer, including the anti-tumor immune response to chemotherapy,16 radiation,17 check point blockade,18-21 allogeneic stem cell therapy3 and adoptive cellular therapies.4,5,22,23 However, the interaction between the gut microbiome and CAR T cells is not yet understood. Because the gut microbiota is a uniquely accessible target for modulation, it holds potential promise as an emerging strategy for modifying CAR T-cell response and toxicity. As drivers of microbiome change,24 antibiotics may represent an additional target for modification to improve outcomes after immunotherapies. Indeed, exposure to specific classes of antibiotics have been associated with worse outcomes after immune-based therapies including check point blockade and stem cell transplantation.18,25-27

Antibiotics are frequently given to patients before and after CAR T cell infusions, as febrile neutropenia, infection, and CRS are all common.28,29 The current pediatric fever and neutropenia guidelines support a variety of anti-pseudomonal beta-lactam or carbapenem agents as first-line empiric therapy. Although these antibiotics are considered similar in their effectiveness for managing fever and neutropenia, they vary considerably in their activity against anaerobic commensal organisms and therefore in their potential to alter the gut microbiota. It is thus reasonable to hypothesize that certain antibiotic exposures in the immediate post-CAR or pre-CAR period may alter efficacy and toxicity of CD19 CAR. In a recent study, Smith et al. demonstrated that exposure to antibiotics, particularly piperacillin/tazobactam, meropenem and imipenem/cilastin, in the month prior to CD19 CAR infusion was associated with worse survival and increased neurotoxicity.22 However, this study was limited in that the cohort only included adult patients at two centers and the vast majority of patients (95.8%) received CD19 CAR for lymphoma. More research is needed to assess the differential impact of antibiotic choice outcomes of CD19 CAR in pediatrics where the microbiome, the immune system and CAR T-cell therapy are all distinct from their adult counterparts and to further define how antibiotics can serve as a modifiable target to enhance efficacy or reduce toxicity after CD19 CAR in pediatric leukemia.

It is critical to examine questions of antibiotic utilization in a multicenter study in order to leverage variability in antibiotic practice by center and minimize confounding by indication. No single database exists that contains extensive information on CD19 CAR outcomes, as well as health care resource utilization. However, we have previously successfully merged the high quality transplant and outcomes data available through CIBMTR with daily pharmacy utilization available through the Pediatric Health Information Systems (PHIS) in order to evaluate the association of antibiotic exposures with risk of graft-versus-host disease after transplant (GV17-01).25 The proposed study will build on our experience using these two databases in tandem to define the association of antibiotics and outcomes of CD19 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.

This cohort will include patients 0-25 years old who received a CD19 CAR T cell product for treatment of acute lymphoblastic leukemia from 2017 through 2022.

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.

We propose to use data elements from the following forms in the CIBMTR database:
• Pre-Cellular Therapy Essential Data (4000)
• Cellular Therapy Product (4003)
• Cellular Therapy Infusion (4006)
• Cellular Therapy Essential Data Follow-up Form (4100)
Data elements from these forms will be used to compile outcome data including:
- Best response to cellular therapy
- Disease relapse/progression
- Survival
- Cell persistence/B cell recovery
- CRS and ICANS
We will also collect the following covariates for potential inclusion in a multivariable regression model:
• Demographic information: Age at CD19 CAR infusion
• Diagnostic information: Indication for CD19 CAR, cancer cytogenetics
• Disease burden at CD19 CAR infusion
• Admission to the hospital post-infusion
• CAR-related variables: Product, lymphodepleting chemotherapy regimen

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.

The Pediatric Health Information System (PHIS) database is a comparative pediatric database that includes clinical and resource utilization data for inpatient, emergency department and observation unit patient encounters for over 50 freestanding pediatric hospitals across the United States, including at least 30 centers that administer CD19 CAR. Data elements in the PHIS database include demographics, dates of admission and discharge, discharge diagnosis and procedures codes, length of stay and adjusted hospital charges. The PHIS data also contain billing data corresponding to specific resources utilized including inpatient pharmaceutical agents with medication name and route of administration. Our research group has extensive experience with the PHIS database and has applied this data to explore resource utilization and infectious complications in pediatric oncology patients.30-37 The group has also successfully merged this data with other databases,38-42 including with data from Center for International Blood and Marrow Transplant Research (CIBMTR), the most comprehensive database of clinical information on transplanted patients. We have successfully leveraged this merged data source to examine the association between antibiotic exposure and graft-versus-host disease after transplantation for acute leukemia (GV17-01).25 The use of PHIS and CIBMTR in tandem – pharmacy utilization data from PHIS and clinical outcome data from CIBMTR – will be applied in an analogous manner to assess the association antibiotic utilization and outcomes after CART.

Q26. REFERENCES:

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

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

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

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

N/A

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

Embedded Data:

N/A

2210-194, Antibiotics exposure - Patients 25 and under with ALL

Characteristic	N (%)
No. of patients	981
No. of centers	104
Patient related	
Age at infusion, yrs	
Mean (SD)	13 (6.5)
Age Group (by decade) - no. (%)	
0-9 Years Old	321 (33)
10-17 Years Old	387 (39)
18-25 Years Old	273 (28)
Recipient sex - no. (%)	
Male	590 (60)
Female	391 (40)
Recipient race - no. (%)	
White	680 (69)
Black or African American	48 (5)
Asian	40 (4)
Native Hawaiian or other Pacific Islander	1 (0)
American Indian or Alaska Native	5 (1)
Other	37 (4)
More than one race	106 (11)
Missing	64 (7)
Recipient ethnicity - no. (%)	
Hispanic or Latino	385 (39)
Non Hispanic or non-Latino	481 (49)
Non-resident of the U.S.	82 (8)
Unknown	33 (3)
Performance score prior to CT - no. (%)	
90-100%	655 (67)
80%	134 (14)
<80%	122 (12)
Missing	70 (7)
ECOG performance status prior to CT - no. (%)	
Asymptomatic	655 (67)
Symptomatic but completely ambulatory	213 (22)
Symptomatic, < 50% in bed during the day	41 (4)
Symptomatic, > 50% in bed, but not bedbound	2 (0)

Characteristic	N (%)
Missing	70 (7)
HCT-CI - no. (%)	
0	435 (44)
1	221 (23)
2	99 (10)
3+	217 (22)
TBD	2 (0)
NA (not collected for these cases)	2 (0)
Missing	5 (1)
Disease related	
Disease classification - no. (%)	
Acute lymphoblastic leukemia (ALL)	
t(5;14) (q31;q32); IL3-IGH:	3 (0)
B-lymphoblastic leukemia / lymphoma with Hyperdiploidy (51-65 chromosomes)	67 (7)
B-lymphoblastic leukemia / lymphoma with Hypodiploidy (<46 chromosomes)	31 (3)
B-lymphoblastic leukemia / lymphoma, BCR-ABL1-like	76 (8)
B-lymphoblastic leukemia / lymphoma, with iAMP21	24 (2)
Early T-cell precursor lymphoblastic leukemia	1 (0)
precursor B-cell ALL:	600 (61)
t(9;22)(q34;q11); BCR/ABL+:	45 (5)
t(v;11q23); MLL rearranged:	78 (8)
t(1;19)(q23;p13) E2A/PBX1:	16 (2)
t(12;21)(p12;q22) ETV/CBFa:	40 (4)
MRD positive/negative CR prior to CT - no. (%)	
MRD negative	256 (26)
MRD positive	139 (14)
Not tested	10 (1)
N/A, ALL not in CR	566 (58)
Missing	10 (1)
Prior lines of therapies - no. (%)	
No	9 (1)
Yes	908 (93)
1	706 (72)
2	36 (4)
>=3	144 (15)
Missing	22 (2)
Missing	64 (7)
Prior radiation therapy - no. (%)	

Characteristic	N (%)
No	769 (78)
Yes	119 (12)
Missing	93 (9)
Prior HCT - no. (%)	
No	709 (72)
Yes	206 (21)
Prior allo-HCT	200 (20)
Prior auto-HCT	1 (0)
Prior auto and allo-HCT	1 (0)
Missing	4 (0)
Missing	66 (7)
Time from HCT to CT, months - median (min-max)	16 (1-176)
CAR-T cell related	
Year of CT - no. (%)	
2017	10 (1)
2018	149 (15)
2019	217 (22)
2020	216 (22)
2021	214 (22)
2022	175 (18)
Product - no. (%)	
Kymriah	973 (99)
Tecartus	8 (1)
Time from diagnosis to CT - no. (%)	
Median (min-max)	32 (0-243)
Less than 6 months	132 (13)
6-11 months	116 (12)
12-17 months	165 (17)
24-36 months	122 (12)
More than 36 months	445 (45)
Missing	1 (0)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)	
No	11 (1)
Yes	970 (99)
Flu+Cy only	948 (97)
Other	19 (2)
Not reported	3 (0)
Lymphodepleting chemotherapy - no. (%)	

Characteristic	N (%)
Clofarabine + Cyclophosphamide (Cytoxan)	1 (0)
Clofarabine + Fludarabine (Fludara)	1 (0)
Cyclophosphamide (Cytoxan)	2 (0)
Cyclophosphamide (Cytoxan) + Cytarabine (Ara-C) + Etoposide (VP-16, VePesid) + Fludarabine (Fludara)	2 (0)
Cyclophosphamide (Cytoxan) + Cytarabine (Ara-C) + Fludarabine (Fludara)	2 (0)
Cyclophosphamide (Cytoxan) + Fludarabine (Fludara)	948 (97)
Cyclophosphamide (Cytoxan) + Fludarabine (Fludara) + Other	1 (0)
Cyclophosphamide (Cytoxan) + Gemcitabine	1 (0)
Cytarabine (Ara-C) + Etoposide (VP-16, VePesid)	1 (0)
Cytarabine (Ara-C) + Fludarabine (Fludara)	2 (0)
Fludarabine (Fludara)	6 (1)
None specified	14 (1)
Follow-up, in months - median (range)	17 (0-54)

CT Extract December 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

Effect of Delayed Cell Infusion on Outcomes in Patients with Large B-cell Lymphoma Receiving Chimeric Antigen Receptor (CAR) T-cell Therapy

Q2. Key Words

Delayed cell infusion; large B-cell lymphoma; CAR T-cell therapy

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Andrew Jallouk, M.D., Ph.D.
Email address:	apjallouk@mdanderson.org
Institution name:	University of Texas MD Anderson Cancer Center
Academic rank:	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):	Paolo Strati
Email address:	pstrati@mdanderson.org
Institution name:	University of Texas MD Anderson 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?

- 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:

Paolo Strati

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.

Dr. Strati is currently a member of the Cellular Therapy working group

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:

Sairah Ahmed

Q15. RESEARCH QUESTION:

Does delaying cell infusion following the initiation of lymphodepleting chemotherapy (LDC) impact outcomes in patients with large B-cell lymphoma receiving CAR T-cell therapy?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that patients with large B-cell lymphoma receiving CAR T-cell therapy who have delayed cell infusion (> 5 days after initiation of LDC) will have inferior outcomes compared to patients with on-time infusion (≤ 5 days after initiation of LDC).

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

Suggested word limit of 200 words:

1. Primary: Compare the day 30 complete response (CR) rate, day 100 CR rate, progression-free survival (PFS) and overall survival (OS) of patients receiving delayed CAR T-cell infusion to those of patients receiving on-time infusion.
2. Secondary:

• Compare the onset, grade and duration of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), as well as the rates of persistent cytopenias and immune effector cell-associated hemophagocytic lymphohistiocytosis (IEC-HLH) in these patients.

• Describe variables associated with delayed cell infusion, including: age, gender, performance status, International Prognostic Index (IPI) score, pre-lymphodepletion laboratory values (hemoglobin, white blood count, absolute neutrophil count, absolute lymphocyte count, platelets, LDH, etc.), type/dose of LDC, the time from initiation of LDC to cell infusion, number of prior therapies and the rates of infection prior to LDC and prior to cell 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.

The pivotal trials for all currently available CAR T-cell products specified that cell infusion take place within a certain time period after LDC. However, the recommended time period varies substantially across products, with the Food and Drug Administration (FDA) package label recommending infusion of axicabtagene ciloleucel (axi-cel) on the third day following completion of LDC (1), while infusions of lisocabtagene maraleucel (liso-cel) and tisagenlecleucel (tisa-cel) may be given 2-7 days and 2-11 days respectively after completion of a similar LDC regimen. (2,3) No data are currently available to justify these differences or to guide the timing of cell infusion within the ranges provided. Furthermore, in real-world practice, cell infusions may be unavoidably delayed for a variety of reasons, including clinical and logistical complications. The impact of these delays on patient outcomes is not well-characterized. Our study seeks to determine how the timing of cell infusion relative to LDC affects CAR T-cell efficacy and toxicity. Our findings will inform providers who are attempting to select the optimal time for cell infusion and, in the case of unavoidable delay, could suggest the need for alternative strategies, such as additional delay with repeat LDC upon count recovery to allow for on-time infusion.

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 use of a lymphodepleting conditioning regimen prior to CAR T-cell infusion has been shown to improve CAR T-cell expansion, persistence and clinical efficacy. (4-6) While its mechanism is not entirely clear, it likely involves changes in both cytokine levels and the tumor microenvironment which enhance CAR T-cell function. (7-9) Of the three CAR T-cell products currently approved by the Food and Drug Administration for treatment of large B-cell lymphoma, the timing of cell infusion is most stringent for axi-cel, with infusion recommended to occur on the third day following completion of a three-day LDC regimen consisting of fludarabine and cyclophosphamide. (1) In contrast, liso-cel and tisa-cel may be given 2-7 days and 2-11 days respectively after completion of a similar lymphodepleting regimen. (2,3) No data are available to support these particular ranges and data to indicate whether the timing of infusion relative to LDC impacts outcomes are strongly needed.

In a retrospective analysis of 240 patients at our institution treated with standard-of-care axi-cel, we found that 16.7% of patients received delayed cell infusion, defined as cell infusion occurring > 5 days after initiation of LDC (unpublished data). These patients had a significantly lower day 30 overall response rate (59.0% vs. 79.4%; $p = 0.008$) and shorter median PFS (3.5 vs. 8.2 months; $p = 0.02$) and OS (7.8 vs. 26.4 months; $p = 0.046$) compared to those with on-time infusion. An association between extent of delay and survival was observed, with significantly shorter median PFS in patients who had delay of 2-5 days (1.8 vs. 8.2 months; $p = 0.002$) and >5 days (4.6 vs. 8.2 months; $p = 0.040$) but no significant difference in median PFS for patients with a delay of 1 day (5.4 vs. 8.2 months; $p = 0.240$) compared to those with on-time infusion.

Although these findings are thought-provoking, our study was limited by its small size, single-center nature, and restriction to a single CAR T-cell product. Herein, we propose to expand this analysis to a larger multi-institutional cohort using the CIBMTR database to better understand the impact of delayed CAR T-cell infusion on clinical outcomes in patients with large B-cell lymphoma.

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 (age ≥ 18) with large B-cell lymphoma, defined as: diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high grade B-cell lymphoma (HGBCL) and transformed follicular lymphoma (tFL).
2. Patients must have received a standard-of-care CAR T-cell therapy from 2018 onwards. These include any FDA-approved CAR T-cell product (e.g., axi-cel, tisa-cel, liso-cel) given in the second-line setting or beyond.

Exclusion criteria:

1. Patients receiving experimental CAR T-cell therapy or CAR T-cells in the context of a clinical trial
2. Patients receiving out-of-specification CAR T-cells
3. Patients without clearly documented start date of LDC and date of cell infusion

Q21. Does this study include pediatric patients?

- No

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

This study focuses on the use of standard-of-care CAR T-cell therapies for the treatment of large B-cell lymphoma. All current FDA approvals for this indication are for adults.

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 CIBMTR collection forms.
Outcome variables to be analyzed:
- CR rates at day 30 and day 100
- Progression-free survival: Time from cell infusion to disease progression or death
- Overall survival: Time from cell infusion to death
- CRS onset, maximum grade and duration
- ICANS onset, maximum grade and duration
- Rates of grade 3-4 cytopenias (neutropenia, anemia, thrombocytopenia) at day 30
- Rates of IEC-HLH

Variables to be included in multivariate analyses:
Infusion-related:
- Time from initiation of LDC to cell infusion (main analysis)
- Type of cell therapy product: axi-cel vs. tisa-cel vs. liso-cel
- Dose and type of LDC

Patient-related:
- Age at time of CAR T-cell therapy
- Gender: Male or female
- Race
- Karnofsky performance status: <80% vs. ≥80%
- Laboratory values at initiation of LDC
o White blood count
o Absolute neutrophil count
o Absolute lymphocyte count
o Hemoglobin
o Platelet count
o LDH
o Additional inflammatory markers (e.g., ferritin, C-reactive protein, etc.) if available
o Creatinine
o Liver function tests
o Evidence of infection or on antibiotics

Disease-related:
- Stage
- International Prognostic Index (IPI) score
- Subtype of large B-cell lymphoma: DLBCL vs. PMBCL vs. HGBCL vs. tFL
- Number of extranodal sites
- CNS involvement: yes/no
- Number of prior therapies
- Disease status at time of CAR T: chemoresponsive vs. non-responsive/refractory
- Bridging therapy prior to CAR T: yes vs. no and type of bridging therapy
- Prior autologous SCT: yes vs. no and time since SCT
- Prior allogeneic SCT: yes vs. no and time since SCT and whether patient remains on immunosuppression

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 PRO data.

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 does not require samples from the CIBMTR repository.

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.

Data obtained from the CIBMTR will not be linked to an external source.

Q26. REFERENCES:

1. YESCARTA (axicabtagene ciloleucel) [package insert]. Kite Pharma; 2022.
2. BREYANZI (lisocabtagene maraleucel) [package insert]. Juno Therapeutics, Inc; 2022.
3. KYMRIAH (tisagenlecleucel) [package insert]. Novartis Pharmaceuticals Corporation; 2022.
4. Hirayama AV, Gauthier J, Hay KA, et al. The response to lymphodepletion impacts PFS in patients with aggressive non-Hodgkin lymphoma treated with CD19 CAR T cells. Blood. 2019;133(17):1876-1887.
5. Fabrizio VA, Boelens JJ, Mauguen A, et al. Optimal fludarabine lymphodepletion is associated with improved outcomes following CAR T-cell Therapy. Blood Advances. 2021.
6. Amini L, Silbert SK, Maude SL, et al. Preparing for CAR T cell therapy: patient selection, bridging therapies and lymphodepletion. Nature Reviews Clinical Oncology. 2022;19(5):342-355.
7. Ninomiya S, Narala N, Huye L, et al. Tumor indoleamine 2,3-dioxygenase (IDO) inhibits CD19-CAR T cells and is downregulated by lymphodepleting drugs. Blood. 2015;125(25):3905-3916.
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9. Jain MD, Zhao H, Wang X, et al. Tumor interferon signaling and suppressive myeloid cells are associated with CAR T-cell failure in large B-cell lymphoma. Blood. 2021;137(19):2621-2633.

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)?

- Yes, I have 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.

Dr. Jallouk has no conflicts of interest to declare.
Dr. Strati is a consultant for Kite-Gilead, Roche-Genentech, Hutchinson MediPharma, ADC Therapeutics, Incyte Morphosis and TG Therapeutics; and received research funds from Sobi Pharmaceuticals, Astrazeneca-Acerta, ALX Oncology and ADC Therapeutics.

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

2210-15, delayed cell infusion - Adults with LBCL

Characteristic	N (%)
No. of patients	3730
No. of centers	124
Patient related	
Age at infusion, yrs	
Mean (SD)	61 (12.9)
Age at infusion, by category - no. (%)	
18-29 Years Old	103 (3)
30-39 Years Old	199 (5)
40-49 Years Old	339 (9)
50-59 Years Old	803 (22)
60-69 Years Old	1316 (35)
70 or more Years Old	970 (26)
Recipient sex - no. (%)	
Male	2332 (63)
Female	1398 (37)
Recipient race - no. (%)	
White	2929 (79)
Black or African American	180 (5)
Asian	176 (5)
Native Hawaiian or other Pacific Islander	6 (0)
American Indian or Alaska Native	13 (0)
Other	24 (1)
More than one race	176 (5)
Missing	226 (6)
Recipient ethnicity - no. (%)	
Hispanic or Latino	350 (9)
Non Hispanic or non-Latino	2981 (80)
Non-resident of the U.S.	262 (7)
Unknown	132 (4)
Missing	5 (0)
Performance score prior to CT - no. (%)	
90-100%	1489 (40)
80%	1103 (30)
<80%	734 (20)
Missing	404 (11)
ECOG performance status prior to CT - no. (%)	

Characteristic	N (%)
Asymptomatic	1489 (40)
Symptomatic but completely ambulatory	1679 (45)
Symptomatic, < 50% in bed during the day	145 (4)
Symptomatic, > 50% in bed, but not bedbound	11 (0)
Bedbound	2 (0)
Missing	404 (11)
HCT-CI - no. (%)	
0	1144 (31)
1	699 (19)
2	475 (13)
3+	1348 (36)
TBD	17 (0)
Missing	47 (1)
Disease related	
Disease classification - no. (%)	
Non-Hodgkin lymphoma (NHL)	
NHL diffuse, large B-cell:	853 (23)
T-cell / histiocytic rich large B-cell lymphoma:	55 (1)
Primary mediastinal large B-cell (095CORE):	94 (3)
Other B-cell, spec:	14 (0)
Diffuse, large B-cell lymphoma- Germinal center B-cell type	1210 (32)
Diffuse, large B-cell lymphoma- Activated B-cell type	905 (24)
Primary cutaneous DLBCL, leg type (1822)	4 (0)
EBV+ DLBCL, NOS (1823)	28 (1)
DLBCL associated with chronic inflammation (1825)	1 (0)
High-grade B-cell lymphoma, NOS	71 (2)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	495 (13)
Disease status at CT - no. (%)	
CR	151 (4)
PR	815 (22)
Resistant	2424 (65)
Missing	340 (9)
IPI at initial diagnosis of the primary disease - no. (%)	
Low	115 (3)
Low intermediate	191 (5)
High intermediate	221 (6)
High	234 (6)
Missing	2969 (80)

Characteristic	N (%)
Prior lines of therapies - no. (%)	
No	8 (0)
Yes	3576 (96)
1	2681 (72)
2	73 (2)
>=3	664 (18)
Missing	158 (4)
Missing	146 (4)
Prior radiation therapy - no. (%)	
No	2335 (63)
Yes	1177 (32)
Missing	218 (6)
Prior HCT - no. (%)	
No	2729 (73)
Yes	908 (24)
Prior allo-HCT	55 (1)
Prior auto-HCT	829 (22)
Prior auto and allo-HCT	8 (0)
Missing	16 (0)
Missing	93 (2)
Time from HCT to CT, months - median (min-max)	15 (2-315)
CAR-T cell related	
Year of CT - no. (%)	
2018	490 (13)
2019	954 (26)
2020	1110 (30)
2021	1176 (32)
Time from start of LD chemo to CT infusion - no. (%)	
Less than or equal to 5 days	218 (6)
5 days	3033 (81)
Greater than 5 days	479 (13)
Product - no. (%)	
Kymriah	1059 (28)
Yescarta	2540 (68)
Tecartus	3 (0)
Breyanzi	128 (3)
Time from diagnosis to CT - no. (%)	
Median (min-max)	14 (0-447)

Characteristic	N (%)
Less than 6 months	395 (11)
6-11 months	1111 (30)
12-17 months	1052 (28)
24-36 months	381 (10)
More than 36 months	790 (21)
Missing	1 (0)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)	
No	15 (0)
Yes	3714 (100)
Bendamustine only	135 (4)
Flu+Cy only	3492 (94)
Other	77 (2)
Not reported	10 (0)
Missing	1 (0)
Lymphodepleting chemotherapy - no. (%)	
Bendamustine	135 (4)
Bendamustine + Cyclophosphamide (Cytoxan) + Fludarabine (Fludara)	1 (0)
Bendamustine + Cytarabine (Ara-C)	1 (0)
Carboplatin + Fludarabine (Fludara)	2 (0)
Cyclophosphamide (Cytoxan)	10 (0)
Cyclophosphamide (Cytoxan) + Cytarabine (Ara-C) + Fludarabine (Fludara)	1 (0)
Cyclophosphamide (Cytoxan) + Fludarabine (Fludara)	3492 (94)
Cyclophosphamide (Cytoxan) + Fludarabine (Fludara) + Other	14 (0)
Cytarabine (Ara-C) + Fludarabine (Fludara)	6 (0)
Etoposide (VP-16, VePesid) + Other	1 (0)
Fludarabine (Fludara)	16 (0)
Other	25 (1)
None specified	26 (1)
Follow-up, in months - median (range)	20 (0-52)

CT Extract December 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

Prolonged Cytopenia Following anti-B Cell Maturation Antigen (BCMA) Chimeric Antigen Receptor (CAR) T-cell Therapy for Relapsed/Refractory Multiple Myeloma (RRMM)

Q2. Key Words

Cytopenia, Infection, CAR-T, BCMA, Myeloma

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Jennifer M. Logue, MD
Email address:	Jennifer.Logue@moffitt.org
Institution name:	Moffitt Malignant Hematology & Cellular Therapy at Memorial Healthcare System
Academic rank:	Assistant Member

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):	Doris K. Hansen, MD
Email address:	Doris.Hansen@moffitt.org
Institution name:	H. Lee Moffitt Cancer Center & Research Institute
Academic rank:	Assistant Member

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:

Jennifer M. Logue, 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.

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 patients are at increased risk grade ≥3 cytopenia beyond 30 days after treatment with anti-BCMA CAR T-cell therapy and how should they be managed?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that grade ≥3 cytopenia beyond 30 days after treatment with anti-BCMA CAR T-cell therapy is associated with a baseline inflammatory state, leads to increased toxicity and infection, and requires supportive care measures to decrease complications.

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

Suggested word limit of 200 words:

Primary Aim:

• To quantify the prevalence of grade ≥3 cytopenia at 3, 6, and 12 months after treatment with FDA-approved anti-BCMA CAR T-cell therapy with idecabtagene vicleucel (ide-cel) or ciltacabtagene autoleucel (cilta-cel)

Secondary Aims:

• To identify the association of prolonged grade ≥3 cytopenia >30 days with patient baseline characteristics (comorbidities, disease biology, inflammatory markers, prior anti-myeloma therapies), CAR-T related toxicities (cytokine release syndrome and neurotoxicity) and their management, and outcomes (overall response rate, complete response rate, very good partial response, partial response, clearance of minimal residual disease)

• To identify the rate and timing of infection post-CAR

• To evaluate the association of infection with cytopenia, patient baseline characteristics, CAR-T related toxicities and their management, and outcomes

• To evaluate the impact of prolonged cytopenia on progression free survival (PFS), overall survival (OS), and non-relapse mortality (NRM)

• To determine the median time to sustained recovery to grade <3 and grade 0 neutropenia, anemia, and thrombocytopenia

• To evaluate the time to transfusion independence

• To quantify the use and duration of granulocyte colony stimulating factor (G-CSF), thrombopoietin receptor (TPO) agonist, and intravenous immunoglobulin (IVIG) support

• To identify the use and impact of CD34+ stem cell boost

• To identify cause of death, stratified by cytopenia and infection

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.

Results from this study will inform on appropriate management of hematologic toxicity and will reveal the factors associated with severe and prolonged cytopenias in patients treated with commercial anti-BCMA CAR T-cell therapy for relapsed/refractory multiple myeloma. A large cohort of patients treated in the standard of care setting will provide validation for use of supportive therapies including prophylactic antibiotics, G-CSF, transfusion, TPO agonist, intravenous immunoglobulin (IVIG), and CD34+ stem cell boost. This study will also help create predictive models to identify patients at highest risk of toxicity, in order to guide earlier intervention with supportive strategies. Though fludarabine and cyclophosphamide lymphodepletion is a commonality shared among FDA-approved CAR-T therapies, the long-term effects of BCMA targeting by CAR-T are unknown. We remain optimistic that our study will be important to understand similarities and differences in hematotoxicity for CAR-T therapy targeting BCMA versus CD19.

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.

Idecabtagene vicleucel (ide-cel, Abecma®) (1) and ciltacabtagene autoleucel (cilta-cel, Carvykti™) (2) are FDA approved autologous BCMA-directed CAR T-cell therapies for the treatment of adults with relapsed or refractory multiple myeloma (RRMM). In the pivotal KarMMa trial, patients who received ide-cel commonly experienced CTCAE grade ≥3 neutropenia (89%), anemia (60%), thrombocytopenia (52%), and infections (22%) (3). Patients who received cilta-cel in the CARTITUDE-1 trial showed even higher rates of grade ≥3 hematologic toxicity including neutropenia (95%), anemia (68%), and thrombocytopenia (60%), but similar rates of grade ≥3 infections (20%) (4). While "prolonged" cytopenias beyond day 30 have been seen with both products (3-6), the timeline of expected count recovery after BCMA CAR T-cell therapy has yet to be clearly delineated. Additionally, the factors which contribute to cytopenias and infections and possible mitigation strategies for these toxicities remain to be fully explored.

We recently published real-world data on prolonged cytopenias and infections after ide-cel (7). In our retrospective, multi-center study, 52 patients received commercial ide-cel and 47 reached day 90 follow-up. Grade ≥3 cytopenia was present among 65% of patients at day 30 and 40% of patients at day 90, particularly thrombocytopenia (40%). Prevalence of grade ≥3 cytopenias over time is shown graphically in Figure 1. G-CSF was administered to 88%, packed red blood cell (pRBC) transfusions to 63%, platelet transfusions to 42%, TPO agonists to 21%, IVIG to 13%, and CD34+ stem cell boosts to 8%. At day 100, 19% and 13% of patients had ongoing use of TPO agonists and G-CSF, respectively. Infections occurred in 54% of patients and were grade ≥3 in 23%. Earlier infections in the first 30 days were typically bacterial (68%) and severe (50%). Later infections between days 31 – 100 were 50% bacterial and 42% viral; only 13% were grade ≥3. Cumulative incidence of first infection by infection type (viral, bacterial, and fungal) is shown in Figure 2.

Immediate hematotoxicity in the first 30 days post-CAR-T has been attributed to fludarabine and cyclophosphamide lymphodepleting chemotherapy (4-5,8); however, the prolonged and biphasic nature of cytopenias observed post-antiCD19 CAR T-cell therapy (9-12) has called into question what other risk factors might be involved. Our study showed on univariate analysis that at both days 30 and 90, any grade ≥3 cytopenia was associated with high pre-CAR-T marrow myeloma burden (≥50%) (P=0.002 at day 30; P<0.001 at day 90), circulating plasma cells at pre-lymphodepletion (LD) (P=0.042; P=0.003), and grade ≥3 anemia at pre-LD (P=0.004; P=0.009). Although limited due to small patient numbers, high baseline marrow burden was a significant risk factor for grade ≥3 cytopenia at day 90 on multivariable analysis (P=0.02). Longer time from last bridging treatment to LD was the only significant risk factor for infection (P=0.04).

The CAR-HEMATOTOX (HT) model is a validated risk-stratification tool for hematotoxicity after anti-CD19 CAR-T in relapsed/refractory large B-cell lymphoma (12). Patients treated with standard of care axicabtagene ciloleucel (axi-cel) or tisagenlecleucel (tisa-cel) were found to be at increased risk of prolonged neutropenia, severe thrombocytopenia, and anemia in the first four months after treatment based on markers of impaired hematopoietic reserve (platelet count, hemoglobin, absolute neutrophil count) and baseline inflammation (C-reactive protein and ferritin). Preliminary data by our group has provided validation of the CAR-HEMATOTOX score in 102 patients receiving BCMA-directed CAR-T for multiple myeloma, including 95 patients who received ide-cel and 7 who received cilta-cel (13). Moreover, patients with high HT score more frequently exhibited marrow plasma cell infiltration (P=0.05).

To better characterize risk factors and patterns of cytopenia after BCMA CAR-T cell therapy, further studies from larger multi-centered cohorts are warranted. In this study, we aim to describe the association of cytopenia with BCMA CAR-T cell therapy efficacy and immune-mediated toxicities, and to identify opportunities for supportive care measures to ameliorate these common complications.

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: Any patient with a diagnosis of Multiple Myeloma receiving any anti-BCMA CAR-T cell commercial product.

Exclusion Criteria: None

Q21. Does this study include pediatric patients?

- No

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

Ide-cel and cilta-cel are FDA approved for the treatment of adult patients only.

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.

This study would assess the outcomes of all patients with multiple myeloma who receive an FDA approved anti-BCMA CAR-T cell product. The study will follow a retrospective registry-based descriptive analysis design. Descriptive tables of patient, disease-, and CAR-T-related factors will be created. The primary endpoint will be cumulative incidence of cytopenia and infection after treatment with anti-BMCA CAR T-cells, with characterization of cellular and humoral reconstitution post-CART. We would additionally like to assess need for prolonged hospitalization, intensive care and interventions practiced. Patient, disease, CAR-T related variables will list median and range for continuous variables and percent of total for categorical variables. Probabilities of relapse/progression, OS and PFS following CAR-T will be calculated using the Kaplan-Meier estimator. Post CAR-T relapse therapies will be summarized, and outcomes further defined by Kaplan Meier Survival curves. Values for other endpoints will be generated using cumulative incidence estimates to account for competing risks. Multivariate analysis will be performed using Cox proportional hazards models for various outcomes. A stepwise model building approach will then be used to identify the significant risk factors associated with the outcomes. A backward stepwise model selection approach will be used to identify all significant risk factors. Factors which are significant at a 5% level will be kept in the final model. The potential interactions between main effect and all significant risk factors will be tested. Multivariate analysis with adjustment of covariates such as pre-CAR-T factors (lines of therapy, response status etc) will be performed. A propensity matched pair analysis for different outcomes of interest between patients with and without severe cytopenias or infections will be pursued.
Data will be captured through CIBMTR collection forms. The following variables will be analyzed:
Patient-Related:
• Age at CAR-T: continuous and categorical by decade
• Gender: male vs female
• Race: Caucasian vs African American vs Hispanic vs Asian/Pacific vs other
• Karnofsky performance status at CAR-T infusion (< 90% vs ^{3} 90%)
• HCT comorbidity index pre infusion (0, 1, 2 and ^{3} 3)
• Secondary malignancies
Disease-Related:
• Heavy and light chain subtypes
• Disease status: ISS, and/or R-ISS
• High risk cytogenetics: yes vs. no including high risk: del 17p, t(4;14), t(14;16), t(14;20)
• Number of prior antimyeloma therapies
• Types of prior therapies (chemotherapy vs. radiation vs. other)
• Best response to each line of therapy as per IMWG response criteria
• Previous autologous hematopoietic stem-cell transplant: yes vs. no; > 1 transplant: yes vs. no
• Extramedullary disease: yes vs. no
• Bone marrow involvement prior to CAR-T (% CD138 positive plasma cells as a continuous variable)

• Time from diagnosis to CAR-T (continuous variable)
• Time from autologous transplant CAR-T (continuous variable)
• Time from last cytotoxic chemotherapy to CAR-T (continuous variable)
• Presence of cytopenias prior to CAR-T: yes vs no
• Transfusion dependence prior to CAR-T: yes vs no
• Disease status at the time of CAR-T: relapsed vs refractory
• CNS involvement at diagnosis and prior to CAR-T infusion: yes vs no
• Chemotherapy exposed vs refractory status: identify status to immunomodulatory agent, proteasome inhibitor, anti-CD38 monoclonal antibody; identify if double-refractory, triple-refractory, or penta-refractory or exposed

CAR-T Related:
• Specific BCMA CAR-T product
• Time from disease relapse to CAR-T apheresis (continuous variable)
• Time from apheresis to CAR-T infusion (continuous variable)
• Details regarding apheresis and collection efficiency: cell counts at time of apheresis, patient weight and body mass index (BMI) at apheresis, collection time, collection volume, whole blood processed, total blood volume processed, access type (peripheral vs central, tunneled vs non-tunneled)
• CAR-T cell dose (bags, volume, cells)
• Bridging therapy: yes vs no, if yes then type
• Hematologic recovery (white blood cells/ANC, Hb, Plt)
• Baseline and peak CRP, ferritin, and LDH
• CRS (yes vs. no), maximum grade, and duration
• Neurotoxicity (ICANS and ICE) (yes vs. no), maximum grade, and duration
• Response to CAR-T therapy
• Infections post-CAR-T
• Bone marrow biopsy results after CAR-T
• Use of IVIG support
• Use of G-CSF and TPO agonist support
• Transfusion requirements
• Length of hospitalization(s) including ICU stay
• Toxicity management including utilization of tocilizumab (yes v no), corticosteroids (yes vs no), and anakinra (yes vs no)

Outcomes:
• ORR, CR, sCR, VGPR, PR, and clearance of MRD: as defined by the International Myeloma Working Group (IMWG) response criteria
• OS: Time from CAR-T to death due to any cause. Surviving patients will be censored at the time of last follow up
• PFS: Time from CAR-T to death or relapse. Patients will be censored at the time of last follow up
• Relapse/ Progression: Progressive or recurrent disease as defined by the IMWG be counted as an event. Those who survive without recurrence or progression to be censored at the date of last follow-up
• 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
• Duration of cytopenias

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

No biologic samples are required for this proposed study.

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. Package insert: ABECMA (idecabtagene vicleucel), suspension for intravenous infusion. Initial U.S. Approval: 2021. 2021. https://www.fda.gov/media/147055/download. Accessed 9 May 2022.
2. Package Insert: CARVYKTI™ (ciltacabtagene autoleucel), suspension for intravenous infusion. Initial U.S. Approval: 2022. 2022. https://www.fda.gov/media/156560/download. Accessed 13 May 2022.
3. Munshi NC, Anderson LD, Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med. 2021;384(8):705-16.
4. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021;398:314-24.
5. Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2019 May;380(18):1726-37.
6. Zhao WH, Liu J, Wang BY, et al. A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with relapsed or refractory multiple myeloma. J Hematol Oncol. 2018 Dec;11(1):141.
7. Logue JM, Peres LC, Hashmi H, et al. Early cytopenias and infections after standard of care idecabtagene vicleucel in relapsed or refractory multiple myeloma. Blood Adv. 2022 Aug. Online ahead of print.
8. Ysebaert L, Gross E, Kühlein E, et al. Immune recovery after fludarabine-cyclophosphamide-rituximab treatment in B-chronic lymphocytic leukemia: implication for maintenance immunotherapy. Leukemia. 2010;24(7):1310-1316.
9. Logue JM, Zucchetti E, Bachmeier CA, et al. Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma. Haematologica. 2021;106(4):978-986.
10. Fried S, Avigdor A, Bielorai B, et al. Early and late hematologic toxicity following CD19 CAR-T cells. Bone Marrow Transplant. 2019;54(10):1643-1650.
11. 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. 2020;26(1):26-33.
12. Rejeski K, Perez AP, Sesques P, et al. CAR-HEMATOTOX: A model for CAR T-cell related hematological toxicity in relapsed/refractory large B-cell lymphoma. Blood. 2021 Dec;138(24):2499-2513.
13. Rejeski K, Hansen DK, Bansal R, et al. The CAR-HEMATOTOX Score as a Prognostic Model of Toxicity and Response in Patients Receiving BCMA-Directed CAR-T for Relapsed/Refractory Multiple Myeloma. [Abstract] ASH 2022.

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

Figures:

Figure 1. Prevalence of grade ≥3 cytopenias before and after ide-cel

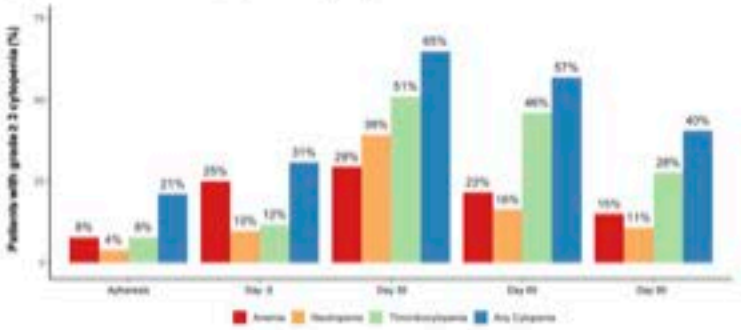

Figure 2. Cumulative incidence of first infection

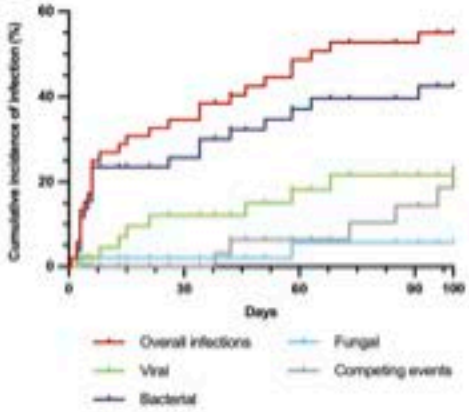

Table 1. Patient baseline and treatment characteristics by grade ≥ 3 cytopenia at day 90

Characteristic	Grade ≥ 3 cytopenia at day 90		P-value
	No, N = 28	Yes, N = 19	
Age (years) – median (range)	64.5 (46 – 78)	68 (43 – 73)	>0.9
≥ 65 – n (%)	14 (50%)	12 (63%)	0.4
Male sex – n (%)	11 (39%)	10 (53%)	0.4
Extramedullary disease – n (%)	20 (71%)	8 (42%)	**0.044**
High baseline marrow burden (≥ 50%) – n (%)	4 (14%)	12 (63%)	**< 0.001**
Circulating plasma cells at pre-LD – n (%)	0 (0%)	6 (32%)	**0.003**
ECOG performance status at pre-LD – n (%)			0.3
0-1	26 (93%)	14 (74%)	
≥2	2 (7%)	5 (26%)	
R-ISS stage at CAR T-cell infusion – n (%)			0.3
I	7 (26%)	1 (6%)	
II	16 (59%)	14 (78%)	
III	4 (15%)	3 (17%)	
Unknown	1	1	
High-risk cytogenetics – n (%)	7 (29%)	9 (50%)	0.2
Unknown	4	1	
Prior lines of therapy – median (range)	6 (4 – 10)	6 (4 – 13)	>0.9
> 4 prior lines of therapy – n (%)	24 (86%)	15 (79%)	0.7
Prior autoSCT – n (%)	21 (75%)	17 (89%)	0.3
Prior BCMA-directed therapy – n (%)	3 (11%)	1 (5%)	0.6
Bridging therapy – n (%)	22 (79%)	14 (74%)	0.7
Alkylating bridging therapy – n (%)	12 (43%)	7 (37%)	0.7
Days from last treatment to LD – median (range)	21 (3 – 48)	31 (6 – 48)	0.2
Refractory status – n (%)			
Double-refractory disease	26 (93%)	18 (95%)	>0.9
Triple-refractory disease	24 (86%)	17 (89%)	>0.9
Penta-refractory disease	15 (54%)	7 (37%)	0.3
Eligible for KarMMa trial at apheresis – n (%)	11 (39%)	2 (11%)	**0.031**
Any cytopenia at day -5 – n (%)	24 (86%)	19 (100%)	0.14
Any grade neutropenia at day -5	9 (32%)	9 (47%)	0.3
Any grade anemia at day -5	22 (79%)	19 (100%)	0.068
Any grade thrombocytopenia at day -5	13 (46%)	14 (74%)	0.064
Grade ≥ 3 cytopenia at day -5 – n (%)	3 (11%)	10 (53%)	**0.002**
Grade ≥ 3 neutropenia at day -5	0 (0%)	4 (21%)	**0.022**
Grade ≥ 3 anemia at day -5	2 (7%)	8 (42%)	**0.009**
Grade ≥ 3 thrombocytopenia at day -5	1 (4%)	5 (26%)	**0.033**
Day 90 bone marrow % cellularity – median (range)	30 (5 – 65)	30 (5 – 95)	>0.9
Not evaluable	7	4	

Double-refractory disease: Refractory to an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI). Triple-refractory disease: Refractory to an IMiD, PI and daratumumab. Penta-refractory disease: Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab.

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

PROLONGED CYTOPENIA FOLLOWING CAR-T THERAPY FOR MULTIPLE MYELOMA

Q2. Key Words

CART MYELOMA CYTOPENIA

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	MURALI JANAKIRAM
Email address:	mjanakiram@coh.org
Institution name:	CITY OF HOPE
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):	GURBAKHASH KAUR
Email address:	Gurbakhash.Kaur@UTSouthwestern.edu
Institution name:	UNIVERSITY OF TEXAS
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:

MURALII JANAKIRAM

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:

What is the prevalence of cytopenias post CART and risk factors for prolonged cytopenias as defined by platelets of <50, ANC <1000 after D100 of CART therapy for myeloma?
This proposal was submitted last year and the advice from the committee was to resubmit this proposal this year due to lack of numbers.

Q16. RESEARCH HYPOTHESIS:

We hypothesize that prolonged cytopenia is not an infrequent complication after CAR T-cell therapy for myeloma and pre- (prior treatments, baseline cytopenia) and post-treatment factors (>=Grade 2 CRS, >=Grade 2 ICANS) associated with this complication

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

Suggested word limit of 200 words:

• Primary outcome:
Incidence of prolonged cytopenia: the event for this outcome is lack of neutrophil (ANC < 1000/mm3) and or platelet recovery (platelet < 50 x 109/L) at D100 post CAR T cell. This outcome will specify prolonged neutropenia, prolonged thrombocytopenia and combined neutropenia and thrombocytopenia. Patients who never dropped their respective counts will be input to reach these outcomes at Day+1 post CAR T cell infusion.
• Secondary outcomes:
-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 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

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.

There is no real world data on post CART cytopenias at different time points. This study will identify risk factors, prevalence and course of post CART cytopenias in myeloma

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.

Idecabtagene (Ide-cel) and ciltacabtagene (Cilta-cel) are approved for the treatment of multiple myeloma with high response rates. From the safety standpoint, the main focus has been on immediate toxicities, namely cytokine-release syndrome (CRS) and neurotoxicity. In practice, however, prolonged cytopenia is a common clinical finding in patients receiving CAR-T cell therapy, including MM patients. Prolonged cytopenia limits treatment options for patients with relapsed or refractory disease after CAR-T. Understanding the incidence, severity, and risk factors of prolonged cytopenia can lead to interventional studies to address the problem. This is especially important as patients relapse after short or long remissions after CAR-T therapy and subsequent treatments mainly clinical trials are needed for these patients, but the presence of cytopenia could make patients ineligible for trials.

Cytopenias are common after CART and can be triphasic. In a study by Rejeski et al cytopenias were classified as y, (1) quick recovery: sustained neutrophil recovery without a second dip below ANC < 1000 cells/microL; (2) intermittent recovery: neutrophil recovery with ANC > 1000 cells/microL followed by second dip with ANC < 1000 cells/microL after day+21; or (3) aplastic: severe neutropenia (ANC < 500 cells/microL) for ≥14 days). In this analysis, intermittent recovery was seen in about 50% of cases, whereas 25% developed quick recovery and 25% aplastic phenotype. Grade 3 or more thrombocytopenia is reported in 52% of patients 30 days after receiving axi-cel.10 There is limited published data from the clinical trials on the incidence and severity of cytopenia beyond day 30 after treatment. This has also been seen in CART for lymphomas where there is a significant percentage of short and long term cytopenia. In order to design interventional trials to overcome cytopenia, an understanding of the actual burden of the problem is needed, and in this study, we aim to establish a benchmark for cytopenia with a focus on thrombocytopenia and neutropenia at D30, 3, 6, and 12 months after treatment with CART for myeloma.

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.

Patient-related:
• Age (continuous)
• Gender: male vs. female
• Body mass index: <30, 30-35, >35
• 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%
Disease Related
• Disease classification: Multiple myeloma
• Prior autoHCT: yes or no
• Type of prior HCT: alloHCT vs. autoHCT vs. both vs. none
• Time from prior HCT to CAR T cell infusion: months
• Prior lines of therapies (including HCT): 1-2 vs. 3-4 vs. >4, details of therapies
• Disease status prior to CAR-T: CR1 vs. CR2 vs. CR3+ vs. relapse, 1st vs. relapse, other vs. PIF/Untreated
• Disease status at CAR-T: CR vs. PR vs. Resistant
Disease-related:
Serum monoclonal immunoglobulin
Immunochemical subtype: IgG vs. IgA vs. light chain vs. others (CRF-only)
Involved serum free light chain at diagnosis, continuous; (Kappa vs. Lambda) (CRF-only)
Serum creatinine at any time prior to transplant, mg/dl: ≥2 vs. <2 vs missing
LDH
Baseline Hb, ANC, Plts
Cytogenetics:
o High risk: t(4:14), t(14:16), t(14:20), 17p deletion, hypodiploid, + 1q, 1p del, ≥2 HR
o Standard risk
o Test not done/Unknown.
o Missing
Bone marrow plasma cells prior to CART: <10% vs ≥10% (CRF-only)
Bone marrow plasma cells prior to transplant: <10% vs ≥10% (CRF-only)
HCT-CI score
Cellular Therapy Related
• Time from diagnosis to CAR-T: 0-6 months vs. 6-12 months vs. 1-2 years vs. 2-3 years
• Lymphodepleting (LD) chemotherapy: Flu/Cy, Bendamustine, other
o standard dose vs. dose reduced
• Bridging chemotherapy: yes vs. No, details of therapy

Q21. Does this study include pediatric patients?

- No

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

Since myeloma is not a disease of the pediatric population we have not included this

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:**

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

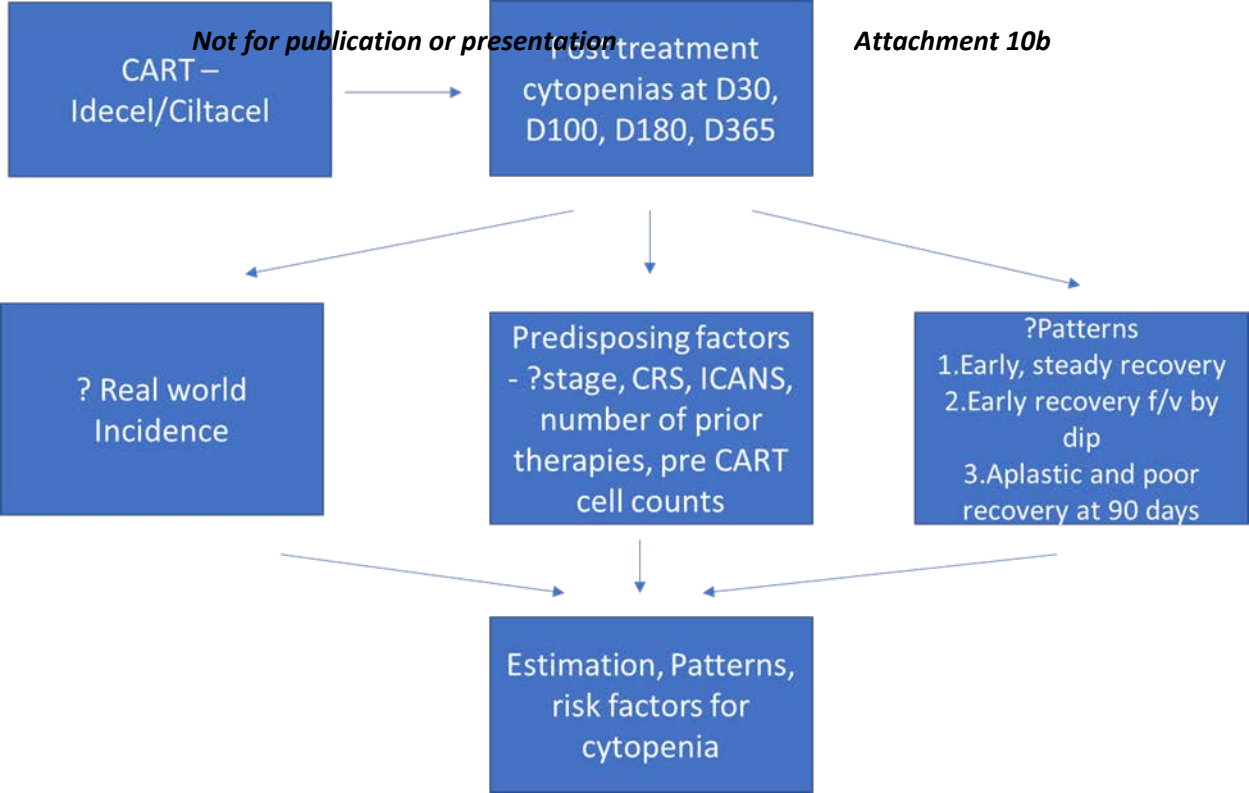
CART – Idecel/Ciltacel
Post treatment cytopenias at D30, D100, D180, D365
? Real world Incidence
Predisposing factors - ?stage, CRS, ICANS, number of prior therapies, pre CART cell counts
?Patterns
1.Early, steady recovery
2.Early recovery f/v by dip
3.Aplastic and poor recovery at 90 days
Estimation, Patterns, risk factors for cytopenia

Table. Patients who received first CAR-T infusion between 2016 - 2022 for Multiple Myeloma, with follow-up reported to CIBMTR

Characteristic	N (%)
No. of patients[1]	786
No. of centers	73
Age at infusion, yrs - median (min-max)	64 (29-86)
Age at infusion, by category #1 - no. (%)	
20 - 29 years	2 (0)
30 - 39 years	13 (2)
40 - 49 years	58 (7)
50 - 59 years	200 (25)
60 - 69 years	330 (42)
70+ years	183 (23)
Age at infusion, by category #2 - no. (%)	
18 - 39	15 (2)
40 - 65	407 (52)
65+	364 (46)
Age at Infusion, by category #3 - no. (%)	
>=18 years	786 (100)
Age at infusion, by category #4 - no. (%)	
0 - 64	422 (54)
65+	364 (46)
Gender - no. (%)	
Male	468 (60)
Female	314 (40)
Not reported	4 (1)
Recipient race - no. (%)	
White	624 (79)
Black or African American	102 (13)
Asian	20 (3)
Native Hawaiian or other Pacific Islander	1 (0)
American Indian or Alaska Native	3 (0)
Other	5 (1)
More than one race	11 (1)
Not reported	20 (3)
Recipient ethnicity - no. (%)	
Hispanic or Latino	51 (6)
Not Hispanic or Latino	710 (90)

Characteristic	N (%)
Non-resident of the U.S.	12 (2)
Unknown	13 (2)
Country - no. (%)	
US	765 (97)
Other	21 (3)
Karnofsky performance score prior to CT - no. (%)	
90-100	291 (37)
80	268 (34)
< 80	147 (19)
Not reported	80 (10)
ECOG performance status prior to CT - no. (%)	
0 - Asymptomatic	291 (37)
1 - Symptomatic but completely ambulatory	382 (49)
2 - Symptomatic, < 50% in bed during the day	29 (4)
3 - Symptomatic, > 50% in bed, but not bedbound	3 (0)
4 - Bedbound	1 (0)
Not reported	80 (10)
Body mass index (BMI) category at infusion - no. (%)	
< 18.5 - Underweight	14 (2)
>= 18.5 to < 25 - Normal	224 (28)
>= 25 to < 30 - Overweight	288 (37)
>= 30 - Obese	238 (30)
Not reported	22 (3)
Sub-disease for CT - no. (%)	
Multiple myeloma, NOS	501 (64)
Plasma cell leukemia	11 (1)
Multiple myeloma - IgG	54 (7)
Multiple myeloma - IgA	23 (3)
Multiple myeloma - light chain only	180 (23)
Multiple myeloma - non-secretory	17 (2)
Diagnosis	
Age at initial diagnosis - median (min-max)	57 (25-85)
ISS stage at diagnosis - no. (%)	
1 (beta2-mic < 3.5, albumin >= 3.5)	202 (26)
2 (Not fitting stage 1 or 3)	170 (22)
3 (beta2-mic >= 5.5, regardless of albumin)	160 (20)
Not reported	254 (32)
R-ISS stage at diagnosis - no. (%)	

Characteristic	N (%)
1 (ISS stage I and standard-risk abnormalities by iFISH and normal LDH)	62 (8)
2 (Not R-ISS stage I or III)	188 (24)
3 (ISS stage III and either high-risk chromosomal abnormalities by iFISH or high LDH)	78 (10)
Not reported	458 (58)
Serum creatinine at diagnosis, value - median (min-max)	1 (0-1493)
Time from initial diagnosis to CT - no. (%)	
Median (min-max)	66 (0-324)
>= 0 to < 12 months	39 (5)
>= 12 to < 36 months	131 (17)
>= 36 to < 60 months	185 (24)
>= 60 months	431 (55)
Lymphodepleting regimen - no. (%)	
Yes	779 (99)
Lymphodepleting chemotherapy: bendamustine	3 (0)
Lymphodepleting chemotherapy: cyclophosphamide	3 (0)
Lymphodepleting chemotherapy: cyclophosphamide + Lymphodepleting chemotherapy: cytarabine + Lymphodepleting chemotherapy: fludarabine	1 (0)
Lymphodepleting chemotherapy: cyclophosphamide + Lymphodepleting chemotherapy: fludarabine	761 (97)
Lymphodepleting chemotherapy: cyclophosphamide + Lymphodepleting chemotherapy: fludarabine + Lymphodepleting chemotherapy: other	4 (1)
Lymphodepleting chemotherapy: cyclophosphamide + Lymphodepleting chemotherapy: thiotepa	1 (0)
Lymphodepleting chemotherapy: fludarabine	3 (0)
Lymphodepleting chemotherapy: other	1 (0)
None specified	2 (0)
No	7 (1)
Commercial vs. noncommercial CAR-T product - no. (%)	

Characteristic	N (%)
Commercial	501 (64)
Noncommercial	285 (36)
Clinical trial - no. (%)	
No	499 (63)
Yes	287 (37)
CAR-T Product type (Other - specify) - no. (%)	
Abecma	468 (60)
Carvykti	33 (4)
Other	285 (36)
Non-commercial Idecabtagene vicleucel	84 (11)
Non-commercial Ciltacabtagene autoleucel	14 (2)
Non-commercial Orvacabtagene autoleucel	1 (0)
Non-commercial - No product name	9 (1)
Non-commercial - Other product	94 (12)
Non-commercial - Product name not reported	83 (11)
Prior transplants and therapies	
Types of prior HCTs - no. (%)	
No	78 (10)
Yes	707 (90)
Prior allo-HCT	8 (1)
Prior auto-HCT	668 (85)
Prior auto and allo-HCT	23 (3)
Not reported	8 (1)
Unknown	1 (0)
Total number of prior HCTs - no. (%)	
0	78 (10)
1	508 (65)
2	139 (18)
3	17 (2)
4	1 (0)
Not reported	43 (5)
Prior CT - no. (%)	
No	766 (97)
Yes	20 (3)
CT infusion counting number - no. (%)	
1	777 (99)
2	8 (1)
3	1 (0)

Characteristic	N (%)
Time from prior HCT to CT, months - median (min-max)	
No prior HCT	NE
Prior allo-HCT	36 (9-176)
Prior auto-HCT	46 (0-250)
Prior auto and allo-HCT	51 (5-159)
Time from the latest prior HCT to current CT, days - median (min-max)	1407 (14-7601)
Clinically significant co-existing diseases or organ impairment	
Clinically significant comorbidity prior to CT - no. (%)	
No	256 (33)
Yes	526 (67)
Comorbidity: Arrhythmia, any history	83 (11)
Comorbidity: Cardiac, any history	94 (12)
Comorbidity: Cerebrovascular disease, any history	23 (3)
Comorbidity: Diabetes requiring non-diet treatment, in the last 4 week	93 (12)
Comorbidity: Heart valve disease	19 (2)
Comorbidity: Hepatic disease (mild), any history or at the time of infusion	38 (5)
Comorbidity: Hepatic disease (moderate/severe), any history or at the time of infusion	12 (2)
Comorbidity: Infection requiring antimicrobial treatment, continuation after day 0	36 (5)
Comorbidity: Inflammatory bowel disease, any history	2 (0)
Comorbidity: Obesity, during pre-infusion work-up period	86 (11)
Comorbidity: Peptic ulcer, any history	11 (1)
Comorbidity: Psychiatric disturbance requiring consult/treatment, in the last 4 weeks	124 (16)
Comorbidity: Pulmonary disease (moderate), at the time of infusion	127 (16)
Comorbidity: Pulmonary disease (severe), at the time of infusion	80 (10)

Characteristic	N (%)
Comorbidity: Renal disease (moderate/severe), at the time of infusion or prior renal transplant	31 (4)
Comorbidity: Rheumatologic disease, any history	10 (1)
Comorbidity: Prior malignancy, treated at any time in the past	116 (15)
Comorbidity: Breast cancer	22 (3)
Comorbidity: Central nervous system malignancy	1 (0)
Comorbidity: Genitourinary malignancy	36 (5)
Comorbidity: Leukemia (including acute or chronic leukemia)	4 (1)
Comorbidity: Lung cancer	1 (0)
Comorbidity: Lymphoma (including Hodgkin & non-Hodgkin lymphoma)	1 (0)
Comorbidity: MDS/MPN	1 (0)
Comorbidity: Melanoma	11 (1)
Comorbidity: Multiple myeloma/plasma cell disorder (PCD)	4 (1)
Comorbidity: Oropharyngeal cancer	1 (0)
Comorbidity: Sarcoma	2 (0)
Comorbidity: Thyroid cancer	6 (1)
Comorbidity: Other skin malignancy (basal cell, squamous)	38 (5)
Comorbidity: Other solid tumor	1 (0)
Not reported	4 (1)
Disease/indication - no. (%)	
Malignant hematologic disorder	786 (100)
Disease status prior to infusion - no. (%)	
Stringent complete response	3 (0)
Complete response (CR)	8 (1)
Very good partial response (VGPR)	53 (7)
Partial response (PR)	84 (11)
No response (NR) / stable disease (SD)	124 (16)
Progressive disease (PD)	493 (63)
Relapse from CR (Rel) (untreated)	14 (2)
Not reported	7 (1)
Year of CT - no. (%)	

Characteristic	N (%)
2016	1 (0)
2017	3 (0)
2018	59 (8)
2019	72 (9)
2020	91 (12)
2021	331 (42)
2022	229 (29)
Serum creatinine at the time of best response since infusion, value - median (min-max)	1 (0-8)
Time from receiving H4000 baseline form to infusion, days - median (min-max)	29 (-5-1116)
No. of patients with follow-up	786
Follow-up - median (range)	9 (1-53)

[1] Note: Excluded cases with Amyloidosis, Solitary plasmacytoma, Light chain deposition disease, Smoldering myeloma, Plasma cell myeloma, Plasma cell proliferative disorder, and missing sub-disease data (n=22)

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

Temporal Trends in Outcomes after CAR T-Cell Therapy for relapsed or refractory B-cell Lymphoma

Q2. Key Words

Cellular therapy; CAR T; Large B cell lymphoma, Follicular Lymphoma, Mantle Cell Lymphoma

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Owhofasa Agbedia, MD, MPH
Email address:	ooagbedia@mdanderson.org
Institution name:	UT. MD Anderson Cancer Center
Academic rank:	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?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Paolo Strati, MD
Email address:	pstrati@mdanderson.org
Institution name:	UT. MD Anderson 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?

- 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:

Owhofasa Agbedia, MD, MPH

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.

- 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:

Evaluate yearly outcomes over time for patients with relapsed or refractory B-cell Lymphoma since the first CAR T-cell therapy was approved by the US FDA in 2017

Q16. RESEARCH HYPOTHESIS:

Four autologous CAR T-cell therapy products, all targeting CD19 have been approved for the treatment of patients with relapsed or refractory (r/r/) large B-cell lymphoma (LBCL), mantle cell lymphoma (MCL), and follicular lymphoma (FL). Axicabtagene ciloleucel received approval in 2017, tisagenlecleucel in 2018, brexucabtagene autoleucel in 2020, and lisocabtagene maraleucel in 2021. These advances have the potential to result in durable remission in up to 40% of patients. However, there is little information on the yearly outcome with the CAR T therapy since 2018, a period marked by increased referral of patients for commercial CAR T-cell therapy. The research hypothesis is that efficacy and safety outcomes have progressively improved overtime (from 2018 to 2022) for patients who received CAR T-cell therapy for r/r B-cell Lymphoma.

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.) *Suggested word limit of 200 words:*

Primary objective:
Evaluate trends in efficacy (overall response rate and complete response rate per Lugano criteria) in patients receiving commercial CAR T-cell therapy for r/r B-cell Lymphoma during the period since FDA approval of CAR T-cell therapy, comparing year 1(2018) to year 2,3,4 (2019, 2020, 2021 respectively).
Secondary objectives:
Evaluate trends in survival (progression free survival and overall survival) in patients receiving commercial CAR T-cell therapy for r/r B-cell Lymphoma during the period 2018-2021
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.
Evaluate treatment related toxicity including rates of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), prolonged cytopenias.
CRS and ICANS defined in the ASTCT consensus grading for CRS and ICANS
Prolonged Cytopenias: incomplete count recovery at 15 days, 30 days, 3 months and 6 months post infusion of CAR T-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.

The results of this analysis will impact referral patterns for CAR T-cell therapy and will inform practice if it shows that patient outcomes have improved during the time period (2018-2021).

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-engineered (CAR) T-cell therapy has demonstrated significant efficacy for patients with r/r B-cell Lymphoma after at least two lines of therapy. While these therapies induce very high complete response (CR) rates and long-term remissions are observed in a substantial proportion of patients, approximately 60-65% of patients with r/r B-cell Lymphoma relapse after CD19 CAR T-cell therapy. Pretreatment disease characteristics such as number of lines of therapy, need for bridging therapy which reflects higher tumor burden or more rapidly progressive disease, ECOG ≥2, elevated lactate dehydrogenase (LDH) and large tumor volume at the time of conditioning have been associated with inferior outcomes after CAR T-cell therapy. It is unclear if outcomes after commercial CAR T for patients with B-cell Lymphoma have changed since CAR-T cell therapy was FDA approved in 2017. Prior reports have shown that the safety and efficacy of currently approved CAR T-cell products in the standard-of-care (SOC) setting is comparable to outcomes in the registrational trials. Over the past 4 years, CAR T-cell therapy utilization has expanded with outpatient administration, use in older patients and patients with organ dysfunction. Despite this increased use, there is limited information on temporal outcomes. This study will provide insight regarding the longitudinal trend in efficacy and safety outcomes after 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 who have been treated from January 01, 2018 to December 31, 2021 and received commercial CAR-T cell therapy products (axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel or tisagenlecleucel) for the diagnosis of r/r B-cell lymphomas including LBCL, MCL, and FL.

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 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
• LDH, o baseline inflammatory markers (IL-6, IL-2, serum ferritin, interferon gamma, C reactive protein)
• thrombocytopenia
• neutropenia
• lymphopenia
• anemia
• history of CNS disease
• 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
• best response to the cellular therapy
• date of best response to the cellular therapy
• was a disease relapse or progression detected since the date of last report
• date of relapse or progression

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

Samples are not required for this study

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.

No external data is required

Q26. REFERENCES:

1. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. Dec 28 2017;377(26):2531-2544.
2. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. Jan 3 2019;380(1):45-56.
3. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. Sep 19 2020;396(10254):839-852.
4. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med. Apr 2 2020;382(14):1331-1342.
5. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. Jan 2022;23(1):91-103.
6. Nastoupil LJ, Jain MD, Feng L, et al. Journal of Clinical Oncology 2020 38:27, 3119-3128

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

2210-293, Temporal trends - Patients treated with CD-19 CAR T

Characteristic	N (%)
No. of patients	5197
No. of centers	164
Patient related	
Age at infusion, yrs	
Mean (SD)	53 (21.3)
Age at infusion, by category - no. (%)	
0-9 Years Old	275 (5)
10-17 Years Old	327 (6)
18-29 Years Old	366 (7)
30-39 Years Old	224 (4)
40-49 Years Old	380 (7)
50-59 Years Old	949 (18)
60-69 Years Old	1548 (30)
70 or more Years Old	1128 (22)
Recipient sex - no. (%)	
Male	3276 (63)
Female	1920 (37)
Missing	1 (0)
Recipient race - no. (%)	
White	4033 (78)
Black or African American	258 (5)
Asian	222 (4)
Native Hawaiian or other Pacific Islander	8 (0)
American Indian or Alaska Native	18 (0)
Other	61 (1)
More than one race	290 (6)
Missing	307 (6)
Recipient ethnicity - no. (%)	
Hispanic or Latino	722 (14)
Non Hispanic or non-Latino	3926 (76)
Non-resident of the U.S.	359 (7)
Unknown	183 (4)
Missing	7 (0)
Performance score prior to CT - no. (%)	
90-100%	2306 (44)
80%	1411 (27)

Characteristic	N (%)
<80%	949 (18)
Missing	531 (10)
ECOG performance status prior to CT - no. (%)	
Asymptomatic	2306 (44)
Symptomatic but completely ambulatory	2137 (41)
Symptomatic, < 50% in bed during the day	203 (4)
Symptomatic, > 50% in bed, but not bedbound	17 (0)
Bedbound	3 (0)
Missing	531 (10)
HCT-CI - no. (%)	
0	1709 (33)
1	1036 (20)
2	639 (12)
3+	1732 (33)
TBD	22 (0)
NA (not collected for these cases)	3 (0)
Missing	56 (1)
Disease related	
Disease - no. (%)	
Acute lymphoblastic leukemia (ALL)	858 (17)
Non-Hodgkin lymphoma (NHL)	4307 (83)
Missing	32 (1)
MRD positive/negative CR prior to CT (ALL only) - no. (%)	
MRD negative	219 (26)
MRD positive	107 (12)
Not tested	8 (1)
N/A, ALL not in CR	517 (60)
Missing	7 (1)
Disease status at CT (NHL only) - no. (%)	
CR	178 (4)
PR	936 (22)
Resistant	2801 (65)
Missing	392 (9)
IPI at initial diagnosis of the primary disease - no. (%)	
Low	138 (3)
Low intermediate	231 (4)
High intermediate	259 (5)
High	275 (5)

Characteristic	N (%)
Missing	4294 (83)
Prior lines of therapies - no. (%)	
No	17 (0)
Yes	4952 (95)
1	3700 (71)
2	118 (2)
>=3	938 (18)
Missing	196 (4)
Missing	228 (4)
Prior radiation therapy - no. (%)	
No	3410 (66)
Yes	1446 (28)
Missing	341 (7)
Prior HCT - no. (%)	
No	3774 (73)
Yes	1273 (24)
Prior allo-HCT	273 (5)
Prior auto-HCT	966 (19)
Prior auto and allo-HCT	14 (0)
Missing	20 (0)
Missing	150 (3)
Time from HCT to CT, months - median (min-max)	18 (1-315)
CAR-T cell related	
Year of CT - no. (%)	
2017	18 (0)
2018	662 (13)
2019	1218 (23)
2020	1447 (28)
2021	1852 (36)
Product - no. (%)	
Kymriah	1966 (38)
Yescarta	2772 (53)
Tecartus	317 (6)
Breyanzi	142 (3)
Time from diagnosis to CT - no. (%)	
Median (min-max)	17 (0-447)
Less than 6 months	539 (10)
6-11 months	1284 (25)

Characteristic	N (%)
12-17 months	1310 (25)
24-36 months	550 (11)
More than 36 months	1481 (28)
Missing	33 (1)
Was systemic therapy given immediately prior to CT as part of the protocol? - no. (%)	
No	22 (0)
Yes	5174 (100)
Bendamustine only	156 (3)
Flu+Cy only	4903 (94)
Other	101 (2)
Not reported	14 (0)
Missing	1 (0)
Lymphodepleting chemotherapy - no. (%)	
Bendamustine	156 (3)
Bendamustine + Cyclophosphamide (Cytoxan) + Fludarabine (Fludara)	1 (0)
Bendamustine + Cytarabine (Ara-C)	1 (0)
Carboplatin + Fludarabine (Fludara)	2 (0)
Clofarabine + Fludarabine (Fludara)	1 (0)
Cyclophosphamide (Cytoxan)	18 (0)
Cyclophosphamide (Cytoxan) + Cytarabine (Ara-C) + Etoposide (VP-16, VePesid) + Fludarabine (Fludara)	2 (0)
Cyclophosphamide (Cytoxan) + Cytarabine (Ara-C) + Fludarabine (Fludara)	3 (0)
Cyclophosphamide (Cytoxan) + Etoposide (VP-16, VePesid)	1 (0)
Cyclophosphamide (Cytoxan) + Fludarabine (Fludara)	4903 (94)
Cyclophosphamide (Cytoxan) + Fludarabine (Fludara) + Other	14 (0)
Cyclophosphamide (Cytoxan) + Gemcitabine	1 (0)
Cytarabine (Ara-C) + Fludarabine (Fludara)	7 (0)
Etoposide (VP-16, VePesid) + Other	1 (0)
Fludarabine (Fludara)	24 (0)
Other	25 (0)
None specified	37 (1)
Follow-up, in months - median (range)	14 (0-54)

CT Extract December 2022