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