Not for publication or presentation

2021 STATUS REPORT
CELLULAR IMMUNOTHERAPY FOR CANCER WORKING COMMITTEE

Working Committee Leadership	
Co-Chair:	Sarah Nikiforow; Dana Farber Cancer Institute; snikiforow@partners.org
Co-Chair:	Peiman Hematti; University of Wisconsin Hospital and Clinics; pxh@medicine.wisc.edu
Co-Chair:	Cameron Turtle; Fred Hutchinson Cancer Research Center; cturtle@fredhutch.org
Scientific Director:	Marcelo Pasquini; CIBMTR Statistical Center; mpasquini@mcw.edu
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INTRODUCTION

a. Minutes and overview plan from 2020 TCT meeting (Attachment 1)

PROPOSALS MOVING FORWARD FOR SCORING (click here to cast your score)

a. PROP 2010-154 Center-specific differences in CAR T-cell therapy and its implications on outcomes (Ameet Patel/ Olalekan Oluwole/ Bhagirathbhai Dholaria). (Attachment 2)

b. PROP 2010-87; 2010-315 Outcomes of elderly patients receiving CD-19 directed CAR-T therapy for B-cell lymphomas (Sayeef Mirza/ Sreekanth Gattu/ Chitra Hosing/ Francine Foss/ Lohith Gowda). (Attachment 3)

PROPOSALS DROPPED BECAUSE THEY OVERLAP WITH EXISTING STUDIES OR ARE NOT FEASIBLE DUE TO LIMITATIONS OF AVAILABLE PATIENTS OR DATA

a. PROP 2010-14 Late-toxicity in long-term survivor patients treated with CAR-T cell therapies (Maria Queralt Salas/ Rajat Kumar/ Arjun Law).

b. PROP 2010-100 Impact of systemic hyperglycemia on outcomes and toxicities in patients undergoing Chimeric Antigen Receptor Therapy for hematologic malignancies (Nasheed M. Hossain).

c. PROP 2010-103 Determining long term outcomes of CD19 directed autologous Chimeric Antigen Receptor T-cell therapy in patients with B-cell acute lymphoblastic leukemia and diffuse (Nasheed M. Hossain/ Patrick J. Stiff).

d. PROP 2010-118 Hemophagocytic lymphohistiocytosis (HLH)/ macrophage activation syndrome (MAS) as a complication of CD19 directed chimeric antigen receptor (CAR) T-cell therapy (Jennifer M. Logue/ Aleksandr Lazaryan/ Frederick Locke).

e. PROP 2010-119 Impact of tumor biology on chimeric antigen receptor T-Cell therapies outcomes in diffuse large B-Cell lymphoma (Dylan Barth/ Sagar S. Patel).

f. PROP 2010-123 Assessment of prognostic impact of dose, duration and timing of corticosteroid therapy in patients with non-hodgkin lymphoma receiving chimeric antigen receptor T Cell therapy (Sairah Ahmed/ Paolo Strati/ Sattva Neelapu).

g. PROP 2010-129 Impact of body-mass index on outcomes after treatment with CD19 CAR T cells for patients with leukemia or lymphoma (Konstantinos Lontos/ Michael Boyiadzis/ Greg M. Delgoffe).

h. PROP 2010-136 Impact of prior allogeneic hematopoietic cell transplantation (HCT) on outcomes of CD19 chimeric antigen receptor (CAR) T cell therapy for acute lymphoblastic leukemia and non-hodgkin lymphoma (Mark Leick/ Matthew Frigault/ Yi-Bin Chen).

i. PROP 2010-157 Outcomes of CD19 CAR-T in patients who achieve complete remission prior to lymphodepletion in patients with aggressive non-hodgkin's lymphoma (NHL) (Trent Peng Wang/ Antonio Martin Jimenez/ Krishna V. Komanduri).

j. PROP 2010-164 Impact of obesity on outcomes of autologous CD19 CAR T cell therapy in hematologic B cell malignancies (Mahmoud Refat Gaballa/ Sairah Ahmed/ Elizabeth J. Shpall/ Partow Kebriaei).

k. PROP 2010-169 Efficacy and survival of patients with relapsed/refractory non-hodgkin's lymphoma who receive a second CAR T-cell product infusion (Joanna C. Zurko/ Nirav N. Shah).

l. PROP 2010-176 Therapy related myeloid malignancies after chimeric antigen receptor T cell therapy (Rawan Ghassan Faramand/ Aleksander Lazaryan/ Frederick Locke).

m. PROP 2010-190 Use of bridging therapy in patients receiving CD19-directed CAR-T cells for large B Cell lymphoma (Natalie Sophia Grover/ Timothy Voorhees).

n. PROP 2010-221 Impact of G-CSF prophylaxis on the prevention of prolonged neutropenia following CD19 directed CAR-T cell therapy for diffuse large B cell lymphoma (Dipenkumar Modi).

o. PROP 2010-234 Assessment of bridging therapy impact on the outcomes of patients with non-hodgkin lymphoma receiving chimeric antigen receptor T cell therapy (Sairah Ahmed/ Chelsea Pinnix/ Paolo Strati/ Sattva Neelapu).

p. PROP 2010-238 Outcomes of allogeneic hematopoietic cell transplantation after failure of chimeric antigen receptor T-cell (CAR-T) therapy for diffuse large B-cell lymphoma (DLBCL) (Ernesto Ayala/ Mohamed Kharfan-Dabaja/ Madiha Iqbal).

q. PROP 2010-254 Real world practice pattern and clinical outcomes of subsequent therapy after CAR-T treatment in patients with lymphoma (Evandro Bezerra/ Grzegorz Nowakowski/ Shahrukh Hashmi/ Yi Lin).

r. PROP 2010-256 Outcomes of patients with aggressive B-cell lymphomas after CD19 CAR T-cells that required bridging therapy prior to infusion (Evandro Bezerra/ Arushi Khurana/ Yi Lin/ Shahrukh Hashmi).

s. PROP 2010-26 Anti-CD19 chimeric antigen receptor T cells versus autologous stem cell transplant for diffuse large B cell lymphoma patients in partial response after second-line therapy (Alberto Mussetti/ Maria Queralt Salas/ Abraham S Kanate).

t. PROP 2010-267 Chimeric antigen receptor T-cell therapy outcomes in T-cell/histocyte-rich Large B-cell lymphoma and primary mediastinal B-cell lymphoma (Jennifer L. Crombie/ Caron Jacobson).

u. PROP 2010-278 Efficacy of anti-CD19 CAR-T cell therapy given as consolidation for relapsed/refractory aggressive B-cell non-hodgkin's lymphoma without measurable disease at the time of infusion (Joanna C. Zurko/ Nirav N. Shah).

v. PROP 2010-283 The impact of obesity and body weight on immune mediated toxicities and outcomes of patients with relapsed/refractory large B cell lymphoma treated with CD19 CAR T cells (Kitsada Wudhikarn/ Nora Bennani/ Yi Lin/ Shahrukh K. Hashmi).

w. PROP 2010-294 Myelodysplastic syndrome / acute myelogenous leukemia after autologous chimeric antigen receptor T-cell Immunotherapy for non-hodgkin lymphoma (Robert M. Dean).

x. PROP 2010-301 Pulmonary system adverse events CAR T-cell therapy (Roomi Nusrat/ Marcello C. Pasquini/ Mary Horowitz).

y. PROP 2010-306 The effect of moderate cytokine release syndrome (CRS) on clinical outcomes after chimeric antigen receptor T-Cell (CART) therapy (Jonathan Edward Brammer/ Daniel Addison).

z. PROP 210-312 Impact of timing of leukapheresis and CAR-T infusion on DFS and OS in CAR-T therapy for patients with large B cell lymphoma (Muthu Veeraputhiran/ Akash Mukherjee/ Applanaidu Sasapu/ Abhijit Godbole/ Aasiya Matin/ John Dipersio).

aa. PROP 2010-316 Comparative outcomes of patients with B cell lymphomas treated with lisocabtagene maraleucel (liso-cel) compared to axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) (Sayeef Mirza/ Lohith Gowda/ Chitra Hosing/ Stuart Seropian).

ab. PROP 2010-325 Outcomes of allogeneic HCT in patients with B-cell non-hodgkin lymphoma after prior chimeric antigen receptor – T cell (CAR-T) therapy (Farrukh Awan/ Ankit Kansagra/ Praveen Ramakrishnan/ Mehdi Hamadani).

ac. PROP 2010-335 Bridging therapy as a predictor of post CAR-T outcomes (Sayeef Mirza/ Lohith Gowda/ Iris Isufi).

ad. PROP 2010-64 Impact of HCT-CI score of CAR T therapy outcomes (Bhagirathbhai Dholaria/ Bipin Savani).

ae. PROP 2010-75 Outcomes of hematopoietic cell transplantation in non-hodgkin lymphoma after CAR T-cell therapy (Baldeep Wirk).

af. PROP 2010-80 Treatment outcomes of CAR T cell versus allogeneic hematopoietic cell transplant in patients in remission after multiply relapsed diffuse large B-cell lymphoma (Ana Alarcon Tomas/ Parastoo Bahrami Dahi/ Craig S. Sauter/ Miguel-Angel Perales).

ag. PROP 2011-03 CD19 Clinical impact of first-line therapy after CAR T cell failure (Ana Alarcon Tomas/ Miguel-Angel Perales).

ah. PROP 2012-01 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 (Adrián Mosquera Orgueira/ José Luis Bello López).

PROPOSALS NOT ACCEPTED FOR CONSIDERATION AT THIS TIME DUE TO RELATIVE SCIENTIFIC IMPACT COMPARED TO ONGOING STUDIES AND/OR OTHER PROPOSALS

Not applicable

STUDIES IN PROGRESS

a. **AC16-01** Pattern of use and outcomes with donor lymphocyte infusion after human leukocyte antigen haploidentical allogeneic hematopoietic stem cell transplant. Status: Data File Preparation. The study is currently in protocol development/data file prep. Statistician is working on a results memo.
Goal 07-2021: Submitted.

b. **AC17-01** CD-19 chimeric antigen receptor T-cells with or without hematopoietic cell transplantation for treatment of refractory acute lymphocytic leukemia. Status: Data File Preparation. Statistician is finalizing the data file. Goal 07-2021: Manuscript Preparation.

c. **AC18-01** Effect of stem cell boost and donor lymphocyte infusion on the incidence of graft-versus-host disease. Status: Data File Preparation**.** The study is currently in data file prep. The plan is to have a population selected. Goal 07-2021: Manuscript Preparation.

d. **CT19-01** Allogeneic hematopoietic cell transplantation vs chimeric antigen receptor T-cell therapy for diffuse large B-cell lymphoma patients with prior autologous transplant failure or refractory disease. Status: Data File Preparation. Statistician is finalizing the data file. Goal 07-2021: Manuscript Preparation.

e. **CT19-02** Prolonged cytopenia following CD-19 targeted chimeric antigen receptor T therapy for diffuse large B-cell lymphoma. Status: Data File Preparation. Statistician is finalizing the data file. Goal 07-2021: Submitted.

f. **CT19-03** Patient outcomes after chimeric antigen receptor T cells. Status: Manuscript Preparation. Study proposed by the PI. Goal 07-2021: Submitted.

g. **CT20-01** Comparative outcomes analysis of patients with aggressive B-cell lymphoma treated with axicabtagene ciloleucel versus tisagenlecleucel. Status: Protocol Development. Statistician is working on the baseline table. Goal 07-2021: Manuscript Preparation.

h. **CT20-02** Resource utilization with chimeric antigen receptor T cells. Status: Protocol Development. Statistician will work on the baseline table soon. Goal 07-2021: Data File Preparation.

i. **CT20-03** Determinants of outcomes after chimeric antigen receptor T cells for lymphoma. Status: Protocol Development. Statistician will work on the baseline table soon. Goal 07-2021: Manuscript Preparation.

j. **CT20-04** Determinants of outcomes after chimeric antigen receptor T cells for acute lymphoblastic leukemia. Status: Protocol Development. Statistician will work on the baseline table soon. Goal 07-2021: Data File Preparation.

PUBLICATIONS, SUBMITTED PAPERS, PRESENTATIONS

a. **CV20-03** Nikiforow S, Mansour M, Hu Z-H, Horowitz MM, Riches M, Hematti P, Turtle CJ, Zhang M-J, Perales M-A, Pasquini MC, Frigault MJ. Tocilizumab not associated with increased infection risk after CAR T-cell therapy: implications for COVID-19? Blood. 2020 Jul 2; 136(1):137-139. doi:10.1182/blood.2020006216. Epub 2020 May 25. PMC7332891.

b. **SC17-08** Pasquini MC, Hu ZH, Curran K, Laetsch T, Locke F, Rouce R, Pulsipher MA, Phillips CL, Keating A, Frigault MJ, Salzberg D, Jaglowski S, Sasine JP, Rosenthal J, Ghosh M, Landsburg D, Margossian S, Martin PL, Kamdar MK, Hematti P, Nikiforow S, Turtle C, Perales MA, Steinert P, Horowitz MM, Moskop A, Pacaud L, Yi L, Chawla R, Bleickardt E, Grupp S. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. Blood Adv. 2020 Nov 10;4(21):5414-5424. doi: 10.1182/bloodadvances.2020003092. PMID: 33147337; PMCID: PMC7656920.

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR CELLULAR IMMUNOTHERAPY FOR CANCER
Orlando, Florida
Friday, February 21, 2020, 12:15 pm – 3:15 pm (break: 1:30 pm-1:45 pm)

Co-Chair:	**Sarah Nikiforow, MD, PhD, Dana Farber Cancer Institute, Boston, MA**
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1. **Introduction**

   The Committee chairs (Peiman Hematti, MD, Sarah Nikiforow MD) and the Scientific director (Marcelo Pasquini, MD) welcomed the committee and started the meeting at 12:20. After the brief introduction, Dr. Nikiforow talked about CIBMTR industry funding disclosure and CICWC leadership. She announced the incoming chair Cameron Turtle, MBBS, PhD from Fred Hutchinson Cancer Research Center. Then Dr. Nikiforow showed the goals: publishing high impact studies in a timely manner; expectations: providing current status of gonging studies and timelines, and members to assess and select proposals that would have a high impact on the field; and limitations of this working committee: early follow up, and data collected were part of an ongoing prospective study and early data could be embargoed until regulatory review.

   Dr Pasquini introduced the new name of our working committee: Cellular immunotherapy for cancer working committee (CICWC), and some of updates of this working committee. Then he showed the voting process: scientific impact score, key questions, allocation of time, number of proposals that would be accepted and how long of the decision. He reminded committee members on the voting prioritization: scientific impact, priority of studies, and voting.

2. **Accrual Summary**

   Dr. Pasquini mentioned that this year we received many proposals, and we directed 9 to the infection committee and 2 to the lymphoma committee. Then, he briefly discussed the status of data that was available for cellular therapy with a brief overview of the milestones since the launch of the CT registry in the summer of 2016. The graph of number of CAR T cell infusions and CAR T cell indications from 2016 to 2019 was on the website. As January 2020, a total of 2058 CAR T cell recipients and 2217 infusions were reported to the CIBMTR. 79% were commercial CAR T cells, and the span of age was very broad from infants to 91-year-old patients. There are two industry-sponsored projects which are ongoing and target 1500 and 2500 patients as the accrual goal. He addressed the importance of industry collaborations, as without the implementation of these long term post approval studies the cellular therapy registry would not have accrued as many patients as it did to date. The importance having the CIBMTR involvement it to facilitate data collection using a

standard approach that centers are familiar and to have these data in the public domain so future studies can be performed.
Dr. Pasquini mentioned that collection of CAR T cell data remains voluntary as the regulatory requirement is imposed to manufacturer in order to follow patients long term. At the center level, reporting CAR T cells is voluntary which has an implication for the development of studies. It is important to ascertain consecutive reporting in order to minimize any bias on reporting.

3. Cellular Therapy Registry, CIDR and CICWC (M Pasquini)
Dr Pasquini introduced the CIDR, CT registry and CICWC update. The CIDR governance structure outlines the development of a working committee to oversee the utilization of this resource for research purposes. Dr Pasquini then mentioned the new restructure of this working committee, after the launch of the CIDR.

4. Presentations, Published or Submitted Papers

a. **SC17-07** Pasquini M, Locke FL, Herrera AF, Siddiqi T, Ghobadi A, Komanduri KV, Hu Z-H, Dong H, Hematti P, Nikiforow S, Steinert P, Purdum A, Horowitz MM, Hooper M, Kawashima J, Jacobson C. Post-marketing use outcomes of an anti-CD19 CAR T cell therapy, axicabtagene ciloleucel, for the treatment of large B cell lymphoma in the US. ***61st ASH Annual Meeting and Exposition.*** **Oral.**
b. **SC17-08** Jaglowski S, Hu Z-H, Zhang Y, Kamdar M, Ghosh M, Lulla P, Sasine J, Perales M-A, Hematti P, Nikiforow S, Steinert P, Jeschke M, Yi L, Chawla R, Pacaud L, Horowitz MM, Bleikardt E, Pasquini M. Tisagenlecleucel CAR T-cell therapy for adults with diffuse large B-cell lymphoma: real world experience from the CIBMTR Cellular Therapy Registry. ***61st ASH Annual Meeting and Exposition.*** **Oral.**
c. **SC17-08** Grupp S, Hu Z-H, Zhang Y, Keating A, Pulsipher MA, Philips C, Margossian SP, Rosenthal J, Salzberg D, Schiff DE, Yanik G, Curran KJ, Harris AC, Hematti P, Nikiforow S, Steinert P, Yi L, Chawla R, Horowitz MM, Bleikardt E, Pasquini M. Tisagenlecleucel CAR T-cell therapy for relapsed/refractory children and young adults with acute lymphoblastic leukemia: real world experience from the CIBMTR and Cellular Therapy Registry. ***61st ASH Annual Meeting and Exposition*****. Poster.**
d. **SC17-08** Pasquini M, Hu Z-H, Zhang Y, Crupp S, Hematti P, Jaglowski S, Keating A, Nikiforow S, Philips C, Pulsipher M, Shah S, Steinert P, Yanik G, Wang H, Horowitz M, Bleikardt E. Real world experience of tisagenlecleucel CAR T-cells targeting CD19 in patients with acute lymphoblastic leukemia and diffuse large B-cell lymphoma using the CIBMTR Cellular Therapy Registry. ***SOHO 2019 Annual Meeting.*** **2019, Houston, TX. Oral.**

5. Studies in progress

Dr. Pasquini briefly discussed the studies in progress before we started presenting the proposals.

e. **CT13-01** Utility of unmanipulated donor lymphocyte infusion (DLI) for the treatment of infections in allogeneic hematopoietic cell transplantation recipients (G Akpek) **Analysis**
f. **AC16-01** Pattern of use and outcomes with donor lymphocyte infusion (DLI) after HLA-haploidentical allogeneic hematopoietic stem cell transplant (E Gupta/J Foran/V Roy) **Data File Preparation**
g. **AC17-01** CD-19 chimeric antigen receptor T cells with or without hematopoietic cell transplantation for treatment of refractory ALL (S Nikiforow/J Park/M Perales) **Protocol Development.** Dr. Pasquini said that since we didn't have enough data at the beginning, we didn't move forward. However, the data is accumulated, we will work on this this year.
h. **AC18-01** Effect of stem cell boost and donor lymphocyte infusion on the incidence of GVHD (J Yoon/ E Waller) **Protocol Development**

i. **CT19-01** Allogeneic hematopoietic cell transplantation vs. chimeric antigen receptor T-cell therapy for DLBCL patients with a prior autologous transplant failure (M Hamadani/M Pasquini/F Locke/A Gopal) **Protocol Development**. Dr. Pasquini mentioned that this study is also going a little bit slow, since the follow up data is a little shorter of this year.

j. **CT19-02** Prolonged cytopenia following CD-19 targeted CAR-T therapy for diffuse large B-cell lymphoma (M Shadman) **Protocol Development**

6. Future/proposed studies

Dr. Pasquini briefly discussed we received 313 proposals this year and most of them came to cellular therapy. Overall, we have 52 proposals submitted for 2020. 16 proposals were dropped due to overlap with existent studies, due to feasibility or requiring long term follow up or needing supplemental information. Among the drop proposals the themes were comparing of CAR T cell that inpatients vs outpatients, cardiovascular toxicities and assessing the impact of bridging therapy. Updates on the CT forms released January 2020 will help answer these questions in the future. The investigators were invited to propose their studies next year.

Most accepted proposals were merged into 11 studies proposals based on the overlapping themes, which were correlation between CAR T cell manufacturing and outcomes, toxicities, comorbidities, comparisons between commercial CAR T cells or CAR T cells with HCT, health resource utilization, and predictors of disease response (ALL and DLBCL).

k. **PROP 1911-38/PROP 1911-67/PROP 1911-260** Comparative outcomes analysis of patients with aggressive B-cell lymphoma treated with axicabtagene ciloleucel vs. tisagenlecleucel (B Hill), Tisagenlecleucel (Kymriah®) versus axicabtagene ciloleucel (Yescarta®) in patients with relapsed/refractory diffuse large B cell lymphoma (M Pennisi/A Mussetti/M Perales), Comparative analysis of patient characteristics and efficacy of patients with aggressive B-cell lymphoma who received CD19 directed chimeric antigen receptor T-cell therapy (T Nishihori/M Jain/F Locke)
This study was presented by Martina Pennisi who started out by explaining that the hypothesis of this study were that Axi-Cel and Tisa-Cel shared clinical indication, and were considered largely equivalent in efficacy; different products (CD28 vs 41bb) with different response and toxicity rates; no direct comparison reported and randomized clinical trial unlikely. The aims of this study were describing baseline characteristics of patients treated with tisagenlecleucel vs axicabtagene ciloleucel and assessing their impact on the outcomes. There were 816 total patients that met the proposal eligibility criteria which were adults treated with commercially available anti-CD19 CAR T cells; diagnosing of DLBCL w/wo transformation from indolent, R/R after >2 lines of therapy.

l. **PROP 1911-53/PROP 1911-74/PROP 1911-77/PROP 1911-120/PROP 1911-258** Assessment of modified hematopoietic cell transplantation comorbidity index in non-Hodgkin lymphoma patients receiving chimeric antigen receptor T cell therapy (S Ahmed), A modified hematopoietic stem cell transplantation – comorbidity index for recipients of chimeric antigen receptor T cell therapy (M Sorror/M Bar), A model for predicting toxicity using the hematopoietic cell transplantation comorbidity index parameters in patients with toxicity after chimeric antigen receptor T cell therapy (U Greenbaum/A Olson/E Shpall/P Kebriaei), Prognostic impact of comorbidities and on outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma receiving chimeric antigen receptor T cell therapy (M Elsawy), Development of comorbidity scores that could impact the treatment related mortality and overall survival in patients receiving CD19 directed chimeric antigen receptor T-cell therapy (H Hashmi/T Nishihori/F Locke)
Dr. Hamza Hashmi presented this proposal starting with a question: were pre-treatment comorbidities predictive of CAR T cell therapy related toxicities and survival outcomes? This study could improve decision-making process and patient counselling prior to CAR T cell therapy and optimize the design of new clinical trials. The objectives of this study were evaluating the impact of

individual comorbidities on development of severe toxicities after CAR T cell therapy; designing and validating a CAR-T specific comorbidity index. All CAR T recipients in the CIBMTR database was 1187 which included ALL (302) and NHL (885). Dr. Hashmi also mentioned the methods of this study design.

a. **PROP 1911-63/PROP 1911-89/PROP 1911-105** Pre-infusion risk score for incidence of cytokine release syndrome and CAR related encephalopathy syndrome in patients treated with CAR T-cell therapies (C Strouse/U Farooq/M Magalhaes-Silverman), Comprehensive assessment of CAR T cells' toxicities burden in patients with diffuse large B cell lymphoma treated with FDA approved anti-CD19 CAR T cells(axicabtagene ciloleucel or tisagenlecleucel) (M Pennisi/E Mead/M Perales), Development of a prognostic model of CAR-T cell therapy toxicity (R Shouval/M Pennisi/M Perales)
Dr. Roni Shouval presented this proposal, the hypothesis stated that baseline features collected before the time of Anti-CD19 CAR-T cells infusion were predictive of treatment toxicity. A weighted score, considering pre-infusion features, would reliably predict toxicity. The primary aim was developing a risk score for severe CAR T cell toxicity. The second aim were descriptive analysis of toxicities; incidence of CRS and ICANs by grading system; identification of risk factors for toxicities and correlation with duration; association between toxicities and survival/ short-term mortality; prediction of any CRS/ICANs grade. The population was 1024 which included ALL (208) and NHL (816). Then Dr. Shouval talked about the study design which included descriptive analysis of CAR T cell toxicities; Identification of predictors of individual toxicities; Construction of a risk score for composite toxicity; Independent validation. The prediction of severe toxicity would allow for risk stratification, toxicity prevention in high-risk patients, informed consent, adjustment tool in pro/retrospective analyses.

b. **PROP 1910-12** Correlation between CAR-T cell dose, disease response, cytokine release syndrome and acute neurotoxicity (M Salas/A Law/R Kumar)
Dr. Queralt Salas presented this proposal, explaining that CAR T cell was one of the most remarkable advances in cancer therapy in the last decades. However, CAR T cell therapy was associated with significant toxicities (CRS, ICANS), and adequate cell dose was crucial to achieve engraftment in alloHCT. It was reasonable to question if optimum CAR T cell dose range to achieve maximum therapeutic effect, and relation between CAR T cell dose and early toxicity. Then Dr. Salas mentioned the scientific justification that cell dose infused is a factor that can be adjusted to improve survival. This study exploring the impact of key product cellular attributes of tisagenlecleucel on clinical outcomes in patients diagnosed with DLBCL was presented at ASH. This study included 115 patients included in phase 2 JULET trial. The percentage and absolute number of the subpopulation were analyzed and correlated with efficacy and safety. The aim of this study was correlation between CAR T cell dose and overall survival controlled by disease status.

c. **PROP 1911-33/PROP 1911-168/PROP 1911-206/PROP 1911-221** Predictive value of 1-month FDG-PET CT scan post CAR T cell therapy on outcome of aggressive B cell NHL (K Wudhikarn/M Perales/M Pennisi), Outcomes of CD19 CAR T cell therapy for large B cell lymphoma arising from a non-follicular transformation (M Jain/F Locke/T Nishihori), Outcomes in patients with double/ triple hit lymphoma post CAR T treatments (A Vallurupalli/S Ganguly), Analysis of the incidence of immune-effector cell toxicity and outcomes after anti-CD19 CAR-T cell therapy for B-cell lymphomas (P Ramakrishnan/ F Awan)
This study was presented by Kitsada Wudhikarn who started out by explaining that pivotal studies did not show response differences among key underlying characteristics but were underpowered. Early post-treatment PET response may not accurately reflect long term response and outcome. The hypothesis of this study was that disease characteristics determined response, toxicities and outcomes of aggressive large B-NHL patients treated with CAR T cells; immune-mediated toxicities were associated with treatment outcomes; early PET response to CAR T cells was an important surrogate for long-term outcomes. The aims were that Identify underlying lymphoma characteristics which can

predict response and outcomes of aggressive large B-NHL patients treated with CAR T cells; evaluate the association between immune-mediated toxicities and outcomes; Explore prognostic implication of early PET response on long-term outcomes in aggressive large B-NHL treated with CAR T cells. This study included 869 patients who were adult with aggressive large B-NHL. Dr. Pasquini commented that we didn't capture the 30 days past, and we didn't know how the practice varied among different centers. He suggested that if the study moved forward, we could ask the practice of the 30 days past or we only include the centers which have the information.

d. **PROP 1911-145** Real world practice pattern and clinical outcomes of subsequent therapy after CAR-T treatment in patients with lymphoma (E Bezerra/G Nowakowski/Y Lin/S Hashmi)
Dr. Evandro Bezerra presented this proposal starting with the unmet need for NHL patients who don't achieve durable CR after CAR-T therapy. Survival is poor for patients who don't achieve durable CR after CAR-T1-3. The aims are comparing OS between who did and didn't receive subsequent therapies; comparing response rates, PFS and OS among different subsequent therapies; comparing OS between those who did and didn't receive subsequent allo-HCT. The hypothesizes are longer OS in those able to receive further therapies; similar outcomes across different therapies categories; patients not in CR post CAR T that received subsequent allo-HCT will have longer OS. This study included 875 patients, and 255 patients received subsequent systemic therapies.

e. **PROP 1911-41/PROP 1911-148** Assessing the outcomes of CAR T-cell therapy in patients who relapse within a year of autologous stem cell transplantation compared to patients who never undergo autologous stem cell transplantation: A CIBMTR analysis (P Johnson/A EI-Jawahri), Clinical outcomes of CAR-T cell therapy in transplant naïve patients versus CAR-T cell therapy post autologous transplant (N Shah/P Hari)
Dr. Connor Johnson presented this proposal, explaining that the aims were to compare PFS in patients with aggressive NHL receiving CAR-T cell therapy who were transplant naïve versus those who received an autologous HCT prior to CAR-T cell therapy; to characterize other outcomes among patients with aggressive NHL receiving CAR-T cell therapy who were transplant naïve versus those who received an autologous HCT prior to CAR-T cell therapy. The hypothesis was the receipt of autologous HCT would be associated with lower PFS in patients receiving CAR-T cell therapy. Dr. Johnson stated the design of this study which was retrospective multicenter analysis of patients with NHL receiving anti-CD19 CAR T-cell therapy. There were 840 patients undergoing first CAR T for NHL with/without prior autologous transplant from 2016 to 2019.

f. **PROP 1911-149/PROP 1911-261** Patient derived donor origin CAR-T cell therapy for B cell malignancy patients who have relapsed post allogeneic transplant (N Shah/P Hari), Outcomes of CD-19 chimeric antigen receptor T cell therapy after allogeneic hematopoietic cell transplantation for relapsed B-cell lymphoid malignancies (A Mirza/H Elmariah/J Chavez)
This study was presented by Sayeef Mirza who started out by explaining that the background of CAR T cell post allogeneic transplant. Limited studies showed CAR-T cell therapy offers high remission rates for patients with relapsed B-cell malignancies post-transplant. A larger sample size may better assess the safety and efficacy of CAR-T cells against relapsed/refractory B cell malignancies post-allogeneic transplant. The hypothesis was CAR T cell therapy was safe and had improved outcomes in patients with relapsed B-cell malignancies post-transplant compared to other donor lymphocyte infusion/immunotherapy versus chemotherapy versus second transplant. The study design was A retrospective multicenter study utilizing the CIBMTR dataset involving patients with relapsed B-cell malignancies post allogeneic transplant who subsequently received CAR-T cell therapy. There were 133 patients who underwent first CAR T for ALL or NHL with prior allo-HCT.

g. **PROP 1911-110/PROP 1911-159/PROP 1911-216** Determinants of outcomes of acute lymphoblastic leukemia following the receipt of chimeric antigen receptor T-cell therapy (P Dhakal/V Bhatt),

Outcome and prognostic significance of cytogenetic abnormalities in pediatric and adult patients with acute lymphoblastic leukemia post chimeric antigen receptor T-cell therapy (D Ragoonanan/K Mahadeo/P Kebriaei), Clinical features and outcomes in patients with acute lymphoblastic leukemia who relapse post-chimeric antigen receptor therapy (L Schultz/L Muffly)
This study was presented by Dristhi Ragoonanan who started out by explaining that we lack predictors of durable response, relapse, and survival. The hypothesis was that analysis of patient, disease and treatment variables would identify predictors of remission, relapse and survival following CAR T cell therapy. The primary aims were developing a model for predictors of outcomes post CAR T therapy; developing outcomes following CAR T therapy. Dr. Ragoonanan then mentioned the scientific impact of this study: improving risk stratification of patients allowing tailored management; understanding how to integrate CAR T cell therapy into current ALL management algorithms; identifying optimal candidates for CAR T cell therapy; recognizing modulable factors that impact outcomes of CAR T cell therapy; identifying patients who may benefit from consolidation therapy; evaluating long-term outcomes of CAR T-cell therapy. There were 302 patients including 208 commercial products and 94 noncommercial products.

h. **PROP 1911-115/PROP 1911-166/PROP 1911-187** Resource utilization with CAR-T cells (M Battiwalla/J Pantin), Real world experience of costs and healthcare utilization in children and young adults receiving Kymriah for acute lymphoblastic leukemia (H Rangarajan/P Satwani) of resource utilization patterns in adult patients receiving inpatient vs outpatient chimeric antigen receptor therapy for relapsed lymphoma (C Scheckel/ M Siddiqui/Y Lin/S Hashmi)
Dr. Caleb Scheckel presented this proposal starting with the background of CAR T cell therapy: two FDA approved therapies in NHL & ALL; future growth into other malignancies; high cost of therapy; no real-world data analysis on true cost and cost effectiveness. The goal of this study was describing and establishing “real world” cost and resource utilization in CAR-T recipients in first 60 days after infusion. The area of special focus was the cost of savings which included Inflammatory markers and treatment toxicity correlation with resource utilization; comparative CAR-T inpatient and outpatient resource utilization; CAR-T cost-effectiveness compared to other treatment strategies in pediatric ALL. Then Dr. Scheckel stated the methods of this study: currently can access via institutional licenses; critical data needed. The data had 1249 patients which included 302 patients of ALL and 886 patients of NHL.

i. **PROP 1911-92** Not everyone has access to care with CAR T cells for relapsed/refractory Diffuse Large B Cell Lymphoma (M Pennisi/M Pasquini/M Perales)
Dr. Martina Pennisi presented this proposal, showing the graph of socio-demographic disparities. The hypothesis was that there were disparities in access to care with CAR T cells in patients with R/R DLBCL based on varied characteristics. The aim was assessing rate of utilization of CAR T cells for patients with R/R DLBCL after auto-HCT, stratified by socio-economic, geographic and demographic data. There were 229 patients receiving CAR T cells after auto-HCT. The scientific impact of this study was a better definition of rates of utilization could provide important information on how to improve: access to care and health care policy.

Dropped proposed studies

Dr. Pasquini mentioned that the reasons for dropped studies were overlap or due to feasibility or requiring long term follow up or needing supplemental information.

a. **PROP 1909-05** 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. *Dropped due to supplemental data needed.*
b. **PROP 1910-15** Late-toxicity in long-term survivor patients treated with CAR-T cell therapies. *Dropped due to supplemental data needed.*

c. **PROP 1910-16** Comparison between patients who received consolidation with allo-HSCT vs not in acute lymphoblastic leukemia treated with CAR-T cell therapy. *Dropped due to overlap with current study/publication*.
d. **PROP 1911-55** Outcomes of allogeneic stem cell transplantation in patients with relapsed/refractory non-Hodgkin lymphoma after CAR T cell therapy. *Dropped due to small sample size.*
e. **PROP 1911-56** Outcomes of allogeneic stem cell transplantation in patients with relapsed/refractory acute lymphoblastic leukemia after CAR T cell therapy. *Dropped due to overlap with current study/publication.*
f. **PROP 1911-128** The impact of lymphodepletion regimen on CD19 CAR-T cell outcomes in patients with aggressive non-Hodgkin lymphoma. *Dropped due to small sample size.*
g. **PROP 1911-144** Outcomes of patients with aggressive B-cell lymphomas after CD19 CAR T-cells that required bridging therapy prior to infusion. *Dropped due to supplemental data needed.*
h. **PROP 1911-174** Matched-pair analysis of survival in patients with hematologic malignancies treated with haploidentical donor lymphocyte infusions compared to alternative donor lymphocyte infusions. *Dropped due to overlap with current study/publication.*
i. **PROP 1911-178** Age-based outcomes of chimeric antigen T-cell therapy for non-Hodgkin lymphoma. *Dropped due to overlap with current study/publication.*
j. **PROP 1911-199** Cardiovascular toxicity and clinical outcomes following chimeric antigen receptor T-cell infusion for B-cell lymphoid malignancies. *Dropped due to supplemental data needed*.
k. **PROP 1911-201** Outcomes in allogeneic hematopoietic cell transplant recipients with prior exposure to chimeric antigen receptor-T cell therapy for B cell malignancies. *Dropped due to overlap with current study/publication.*
l. **PROP 1911-207** Outcomes of allogeneic hematopoietic cell transplantation after CD-19 chimeric antigen receptor T cell therapy for B-cell acute lymphoblastic leukemia patients. *Dropped due to overlap with current study/publication.*
m. **PROP 1911-248** Outcome of CD-19 directed CAR T cell infusion on patients with secondary CNS lymphoma. *Dropped due to small sample size.*
n. **PROP 1911-251** Outcomes of allogeneic HCT in patients with B-cell non-Hodgkin lymphoma after prior chimeric antigen receptor – T cell therapy. *Dropped due to small sample size.*
o. **PROP 1911-259** Efficacy and safety of CD19 directed CAR T-cell therapy for aggressive non-Hodgkin B-cell lymphomas with secondary central nervous system involvement. *Dropped due to small sample size*.
p. **PROP 1911-264** Impact of prior blinatumomab exposure on efficacy and safety of CD19-targeted chimeric antigen receptor T cells in acute lymphoblastic leukemia. *Dropped due to small sample size.*
q. **PROP 1912-03** Outcomes of long-term survivors of Immune Effector Cell Therapy. *Dropped due to small sample size.*

Transfer to Infection and Immune Reconstitution Working Committee

a. **PROP 1911-34** Infectious disease patterns, clinical impacts and treatment in aggressive B cell non-Hodgkin lymphoma and precursor B acute lymphoblastic leukemia patients treated with CD19 CAR T cell therapy.
b. **PROP 1911-50** Impact of early infection in chimeric antigen receptor T (CAR-T) cell therapy outcomes in the first 100 days post-therapy.
c. **PROP 1911-76** Infectious complications after CAR-T cell immunotherapy in patients with B-cell malignancies.
a. **PROP 1911-155** Infections after CD19-targeted chimeric antigen receptor–modified (CAR) T-cell therapy for non-Hodgkin lymphoma.

b. **PROP 1911-158** Observational study of infectious complications among patients treated with anti-CD19 chimeric antigen receptor T cells (CAR-T cells).
c. **PROP 1911-209** Infectious complications and immune reconstitution following CD19-directed CAR-T cell therapy.
d. **PROP 1911-235** The role of intravenous immune globulins in patients after CAR-T therapy.
e. **PROP 1911-254** Patterns of infections post CD19 directed CAR-T cells infusions.
f. **PROP 1911-266** Risk factors for clinically significant infections following CD19-targeted CAR-T cells therapy for hematological malignancies.

Transfer to Lymphoma Working Committee

a. **PROP 1911-51** CAR-T cell therapy versus autologous transplant in early rituximab failure patients with diffuse large B-cell lymphoma.
b. **PROP 1911-267** Comparison of outcomes of DLBCL patients with partial response after salvage therapy who underwent CAR-T vs. ASCT.

The meeting adjourned at 3:00 pm.

Working Committee Overview Plan for 2020-2021						
Study number and Short title	Current status	Goal with date	Total hours to complete	Hours allocated to 6/30/2020	Hours allocated 7/1/2020-6/30/2021	Total Hours allocated
CT13-01: Utility of unmanipulated donor lymphocyte infusion (DLI) for the treatment of infections in allogeneic hematopoietic cell transplantation recipients	Analysis	Analysis -June 2020	110	0	0	**0**
AC16-01: Pattern of use and outcomes with donor lymphocyte infusion after HLA-haploidentical allogeneic hematopoietic stem cell transplant	Data File Prep	Manuscript Preparation -June 2020	130	60	70	**130**
AC17-01: CD-19 chimeric antigen receptor T Cells with or without hematopoietic cell transplantation for treatment of refractory Acute Lymphocytic Leukemia	Protocol Development	Analysis -June 20	260	130	60	**190**
AC18-01: Effect of stem cell boost and donor lymphocyte infusion on the incidence of GVHD	Protocol Development	Data File Preparation -June 20	330	100	160	**260**
CT19-01: Allogeneic hematopoietic cell transplantation vs chimeric antigen receptor t-cell therapy for dlbcl patients with prior autologous transplant failure or refractory disease	Protocol Development	Analysis -June 20	260	130	60	**190**
CT19-02: Prolonged cytopenia following CD-19 targeted CAR-T therapy for diffuse large b-cell lymphoma	Protocol Development	Manuscript Preparation -June 20	230	160	70	**230**

CT20-01: Comparative outcomes analysis of patients with aggressive B-cell lymphoma treated with axicabtagene ciloleucel vs. tisagenlecleucel	Protocol Pending	Protocol Development -June 20	330	0	260	**260**
CT20-02: Resource utilization with CAR-T cells	Protocol Pending	Protocol Development -June 20	370	0	240	**240**
CT20-03: Determinants of outcomes after CAR T cells for Lymphoma	Protocol Pending	Protocol Development -June 20	330	0	200	**200**
CT20-04: Determinants of outcomes after CAR T cells for ALL	Protocol Pending	Protocol Development -June 20	350	0	100	**100**

Oversight Assignments for Working Committee Leadership March 2020		
Sarah Nikiforow	**AC17-01**	CD19 CAR T cells without HCT for ALL
	CT19-01	ALLO vs CAR T DLBCL with prior Auto or refractory disease
	CT20-01	Comparison of commercial CAR T cells for DLBCL
	CT20-04	Determinants of outcomes after CAR T cells for ALL
Peiman Hematti	**CT13-01**	DLI for viral or fungal Infections in Allo HCT
	AC18-01	Effect of SCB and DLI on GVHD incidence
	AC16-01	DLI After HLA-haploidentical allogeneic transplant
Cameron Turtle	**CT19-02**	Prolonged Cytopenia Following CD-19 CAR-T Therapy for DLBCL
	CT20-02	Resource utilization with CAR-T cells
	CT20-03	Determinants of outcomes after CAR T cells for Lymphoma

Proposal: 2010-154

Title:
Center-specific differences in CAR T-cell therapy and its implications on outcomes

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Research hypothesis:
Center variables have significant impact on the outcomes of CAR T cell therapy

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

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

Scientific justification:
Chimeric antigen receptor (CAR) T-cell therapy is a novel and rapidly developing treatment modality in the use of relapsed/refractory non-hodgkin's lymphoma. Two CAR T agents that are FDA approved include axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel). Both cellular products have demonstrated dramatic response with a subset of patients having durable remissions (*1, 2*).
Though this therapy is new, the FDA approvals for various NHL histologies continue and international collaborations have set standards for administration and management of CAR T-cell therapy.
Despite this, there have been significant concerns regarding cost and future payment structures for CAR T-cell therapy in the U.S (*3-5*). Moreover, the collection and manufacture process of CAR T-cell therapy remain heterogenous with speculative concern that this may alter efficacy or toxicities of therapy. With both cost, manufacturing, and biological differences in cellular products, this invariably leads to unique strategies institutions may adopt to provide CAR T-cell therapy to patients (*6, 7*). These strategies are heterogenous and include (but not limited to) the adoption of and specialty specific intensive care units, structures of care delivery (inpatient vs outpatient), presence of multi-disciplinary care, use of more than one cellular product, center volume of treatment, in-house manufacturing (*6, 8, 9*).
It remains unknown whether presence of these institution-specific or cellular product characteristics influence outcomes for patients receiving CAR T-cell therapy.

Patient eligibility population:
Patients with relapsed with 2 or more prior lines of therapy or primary refractory diffuse large b-cell lymphoma

Data requirements:
Patient and institutional data will be obtained from 1/2018 – 1/2020. The following baseline patient characteristics and primary endpoints will be obtained based on CIBMTR forms noted in Table 1.

The major relevant forms will include: 4000 ,4003, 4100, 3500 Institution specific terms may be supplied from CIBMTR allogeneic transplant related data if applicable.

Sample requirements:
None

Study design:
Patient and center-specific characteristics will be summarized with descriptive statistics (Table 1) Descriptive analysis using Fisher's or Chi square tests for categorical variables and T tests or one way ANOVA for parametric quantitative variables will be used for patient level characteristics (Table1), cancer-type, age, performance score, prior auto HSCT, conditioning regimen, use of bridging therapy and year of transplantation will be recorded and controlled for across institutions. Effects of all center characteristics will be evaluated systematically to minimize the effect of multicollinearity as many center characteristics may have a high degree of correlation.
Regarding Aim 1 and 2: Primary and secondary endpoints are listed below (Table 1). Random effects logistic regression analysis will be used to identify center characteristics important in explaining variation or differences in primary endpoints. Depending on # of institutions available, subgroup analysis will be done on high vs low volume centers (defined by median # of CAR T-cell treatments/annually or allogeneic hematopoietic transplantation volume as a surrogate marker for institutional volume. Greater than 50/year defined as high). Patient characteristics, cancer histology, and treatment history will be adjusted for prior to making cross-center comparisons.
Regarding Aim 3: Logistic regression analysis will be used to identify if cell product characteristics (independent variables, binary) are significant in explaining possible differences or variation in endpoints listed in Table 1 (relapse free survival, OS, CAR-T related toxicities). Further descriptive analysis can be done to assess differences in product characteristics across centers. Correlations can be done to identify relationships between significant product characteristics and low vs high volume centers.
Statistical analysis will identify differences at alpha value 0.05, or p value less than or equal to 0.05. Maximum type I error rate of $p < 0.05$ error rate will be used.

Table 1: descriptive parameters requested & details of endpoints

Institution-specific descriptors	**Characteristics**	**Relevant Forms**
Center characteristics	Presence of: -FACT accreditation (binary) -HSCT center (binary) -allo-HSCT volume (#/annually), quantitative	CIBMTR as applicable from institutional form submissions (e,g, 2006)
Volume	# of CAR T-cell therapies done over specified time interval per institution # of allogeneic transplants done each year per institution	CIBMTR as applicable from institutional form submissions
Patient clinical descriptors	**Characteristics**	**Relevant Forms**
Demographic	Age, gender, performance status	4000

Hematologic	Patients with DLBCL Presence & date of remission prior to CAR T-cell therapy Prior lines of therapy History of autologous stem cell transplant Presence of bridging therapy	4000
Organ function	Presence of comorbidities	4000
Cellular therapy product characteristics	Type of product used (axi-cel, tisa-cel) Date of cell collection Mobilization events: 1 or >1 Cell product manipulation: yes/no, all or portion Methods of manipulation: culture, differentiation, selection (+/- or antigen based) Transfection vector: lenti or retrovirus Cell viability testing done: yes/no, date, % viability, method of testing	4003 4100
CAR T specific	Date of infusion Documented best response post CAR T-cell therapy Presence of CRS and Neurotoxicity & max score Presence of seizures or cerebral edema Date of relapse Date of cytopenias Date of hypogammaglobulinemia, treatment and if resolved Maximum grade toxicity of any organ Development of a new malignancy	4100 3500
Primary Endpoints	**Characteristics**	**Relevant forms**
Overall Survival Relapse free survival	Based on date and last survey of relevant form. date and time since day zero Relapse free survival will be included: date and time since day zero	4100

CAR T toxicities	Presence of: CRS (binary), & maximum grade (quantitative) Neurotoxicity & related sequelae (e.g. seizures) (binary) & maximum grade Infections post – treatment (binary) & hypogammaglobulinemia (binary)	4100 3500

Non-CIBMTR data source:
None

Conflicts of interest:
None

References:
1. F. L. Locke et al., Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. The lancet oncology 20, 31-42 (2019).
2. S. J. Schuster et al., Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. New England Journal of Medicine 380, 45-56 (2019).
3. A. E. Hay, M. C. Cheung, CAR T-cells: costs, comparisons, and commentary. J Med Econ 22, 613-615 (2019).
4. J. K. Lin et al., Cost Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Multiply Relapsed or Refractory Adult Large B-Cell Lymphoma. J Clin Oncol 37, 2105-2119 (2019).
5. P. Petrou, Is it a Chimera? A systematic review of the economic evaluations of CAR-T cell therapy. Expert Rev Pharmacoecon Outcomes Res 19, 529-536 (2019).
6. O. L. Reddy, D. F. Stroncek, S. R. Panch, Improving CAR T cell therapy by optimizing critical quality attributes. Semin Hematol 57, 33-38 (2020).
7. S. A. Tuazon et al., Factors affecting lymphocyte collection efficiency for the manufacture of chimeric antigen receptor T cells in adults with B-cell malignancies. Transfusion 59, 1773-1780 (2019).
8. G. L. Shah, N. Majhail, N. Khera, S. Giralt, Value-Based Care in Hematopoietic Cell Transplantation and Cellular Therapy: Challenges and Opportunities. Curr Hematol Malig Rep 13, 125-134 (2018).
9. S. Sievers, G. Watson, S. Johncy, S. Adkins, Recognizing and Grading CAR T-Cell Toxicities: An Advanced Practitioner Perspective. Front Oncol 10, 885 (2020).

Table 1: Characteristics of patients with DLBCL who received an anti-CD19 CAR-T cell therapy

Characteristic	N (%)
No. of patients	941
No. of centers	77
Patient related	
Age - no. (%)	
Median (min-max)	63.1 (18.5-90.8)
18-29	11 (1.2)
30-39	46 (4.9)
40-49	89 (9.5)
50-59	220 (23.4)
60-69	357 (37.9)
>= 70	218 (23.2)
Gender - no. (%)	
Male	626 (66.5)
Female	315 (33.5)
Recipient race - no. (%)	
White	805 (85.5)
African-American	41 (4.4)
Asian	37 (3.9)
More than one race	5 (0.5)
Unknown	27 (2.9)
Missing	26 (2.8)
Recipient ethnicity - no. (%)	
Hispanic or Latino	86 (9.1)
Non Hispanic or non-Latino	815 (86.6)
Non-resident of the U.S.	10 (1.1)
Unknown	29 (3.1)
Missing	1 (0.1)
Performance score prior to CT - no. (%)	
90-100	336 (35.7)
=80	299 (31.8)
< 80	180 (19.1)
Missing	126 (13.4)
HCT Comorbidity Index - no. (%)	
0	273 (29.0)
1-2	275 (29.2)

Characteristic	N (%)
>=3	336 (35.7)
Missing	57 (6.1)
Clinically significant co-morbidity prior to CT - no. (%)	
No	273 (29.0)
Yes	626 (66.5)
Missing	42 (4.5)
Disease Related	
Disease classification - no. (%)	
Diffuse, large B-cell lymphoma - NOS	268 (28.5)
T-cell/histiocytic rich large B-cell lymphoma	15 (1.6)
Diffuse, large B-cell lymphoma - germinal center B-cell type	301 (32.0)
Diffuse, large B-cell lymphoma - activated B-cell type	207 (22.0)
EBV+ DLBCL, NOS	7 (0.7)
High-grade B-cell lymphoma, NOS	9 (1.0)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	134 (14.2)
c-MYC rearrangement based on FISH at diagnosis - no. (%)	
No	215 (22.8)
Yes	132 (14.0)
Not done	22 (2.3)
Missing	572 (60.8)
BCL-2 rearrangement based on FISH at diagnosis - no. (%)	
No	154 (16.4)
Yes	142 (15.1)
Not done	74 (7.9)
Missing	571 (60.7)
BCL-6 rearrangement based on FISH at diagnosis - no. (%)	
No	237 (25.2)
Yes	98 (10.4)
Not done	33 (3.5)
Missing	573 (60.9)
Double/triple hit at initial diagnosis of the primary disease - no. (%)	
Neither	383 (40.7)
Double/triple hit	134 (14.2)
Missing	424 (45.1)
Stage of organ involvement at initial diagnosis of the primary disease - no. (%)	
I	62 (6.6)
II	106 (11.3)
III	213 (22.6)

Characteristic	N (%)
IV	364 (38.7)
Unknown	106 (11.3)
Missing	90 (9.6)
Extranodal involvement at initial diagnosis of the primary disease - no. (%)	
No	262 (27.8)
Yes	511 (54.3)
adrenal (NHL)	13 (1.4)
bone (NHL)	119 (12.6)
bone marrow (NHL)	90 (9.6)
brain (NHL)	8 (0.9)
cerebrospinal fluid (CSF) (NHL)	2 (0.2)
epidural space (NHL)	5 (0.5)
gastrointestinal (GI) tract (NHL)	89 (9.5)
heart involvement (NHL)	3 (0.3)
kidney (NHL)	35 (3.7)
leptomeningeal (NHL)	1 (0.1)
liver (NHL)	59 (6.3)
lung (NHL)	64 (6.8)
pericardium (NHL)	5 (0.5)
pleura (NHL)	14 (1.5)
skin (NHL)	21 (2.2)
spleen (NHL)	162 (17.2)
other site (NHL)	204 (21.7)
Unknown	75 (8.0)
Not reported	93 (9.9)
>1 extranodal site at initial diagnosis of the primary disease (NHL) - no. (%)	
No	535 (56.9)
Yes	311 (33.0)
Missing	95 (10.1)
IPI at initial diagnosis of the primary disease - no. (%)	
Low	25 (2.7)
Low intermediate	40 (4.3)
High intermediate	66 (7.0)
High	65 (6.9)
Missing	745 (79.2)
Age adjusted IPI at initial diagnosis of the primary disease - no. (%)	
Low	15 (1.6)
Low intermediate	44 (4.7)

Characteristic	N (%)
High intermediate	85 (9.0)
High	16 (1.7)
Missing	781 (83.0)
Types of prior HCTs - no. (%)	
No prior HCT	673 (71.5)
Prior allo-HCT(s)	13 (1.4)
Prior auto-HCT(s)	251 (26.7)
Prior auto and allo-HCT(s)	3 (0.3)
Missing	1 (0.1)
No. of prior HCTs - no. (%)	
0	673 (71.5)
1	263 (27.9)
2	4 (0.4)
Missing	1 (0.1)
Prior HCTs - no. (%)	
No	673 (71.5)
Yes	267 (28.4)
0-6 months	36 (3.8)
6-12 months	77 (8.2)
>= 12 months	154 (16.4)
Missing	1 (0.1)
The size of the largest nodal mass - median (min-max)	9.0 (0.0-450.0)
Cellular Therapy Related	
Product - no. (%)	
Kymriah	156 (16.6)
Yescarta	785 (83.4)
Time from diagnosis to CT - no. (%)	
Median (min-max)	15.2 (0.2-406.3)
0-6 months	98 (10.4)
6-12 months	273 (29.0)
1-2 years	258 (27.4)
2-3 years	312 (33.2)
Disease status prior to CT - no. (%)	
Relapse, 1st	265 (28.2)
Relapse, other	288 (30.6)
PIF/Untreated	388 (41.2)
Disease status at CT - no. (%)	
PR	197 (20.9)

Characteristic	N (%)
Resistant	644 (68.4)
Missing	100 (10.6)
Year of CT - no. (%)	
2017	5 (0.5)
2018	406 (43.1)
2019	530 (56.3)
Prior lines of therapies - no. (%)	
Yes	941 (100)
2	212 (22.5)
>= 3	729 (77.5)
Lymphodepleting chemotherapy - no. (%)	
bendamustine	7 (0.7)
bendamustine + corticosteroids	10 (1.1)
corticosteroids + cyclophosphamide + monoclonal antibody + other drug	1 (0.1)
cyclophosphamide	1 (0.1)
cyclophosphamide + cytarabine + fludarabine + monoclonal antibody	1 (0.1)
cyclophosphamide + fludarabine	917 (97.4)
cyclophosphamide + fludarabine + monoclonal antibody	1 (0.1)
cyclophosphamide + fludarabine + other drug	1 (0.1)
cytarabine + fludarabine + monoclonal antibody	1 (0.1)
None specified	1 (0.1)
Bridging therapy - no. (%)	
No	715 (76.0)
Yes	226 (24.0)
Systemic therapy given as bridging therapy	183 (19.4)
Intrathecal therapy given as bridging therapy	11 (1.2)
Radiation therapy given as bridging therapy	54 (5.7)
Follow-up - median (min-max)	12.1 (0.9-28.5)

Combined Proposal: 2010-87; 2010-315

Title:
Outcomes of Elderly patients receiving CD-19 directed CAR-T therapy for B-cell Lymphomas

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Research hypothesis:
We hypothesize that elderly (age > 65 years) patients have higher rates of neurologic toxicity and cytokine release syndrome (CRS) while achieving similar response rates and overall survival (OS) after receiving CD-19 directed Chimeric Antigen Receptor T (CAR-T) cell therapy for relapsed/refractory B-cell lymphomas compared to younger patients.

Specific aims:
- Primary aim: Evaluate cumulative incidence and median time to onset of CRS and immune effector cell associated neurologic syndrome or encephalopathy syndrome (CRES) in the elderly.
- Secondary aims:
  - 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 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.

Scientific justification:
According to the SCHOLAR-1 study, patients with refractory DLBCL had an ORR of 26% in a heavily pre-treated cohort (complete response in only 7%) with a median OS of 6.3 months and only 20% of patients were alive at 2 years.[1] Chimeric Antigen Receptor (CAR) T-cell therapy for DLBCL and other transformed high grade lymphomas has shown dramatic responses in such historically chemo resistant groups.[2] Although CD-19 targeted CAR T-cell therapy has yielded success for patients with certain types of relapsed/refractory lymphomas, there is a significant under representation of elderly in registration trials (ZUMA-1, ZUMA-2, Juliet and Transcend).[3-5]
Patients with large B cell lymphoma have a median age at diagnosis of 66-70 years with over half of new cases being diagnosed beyond 65 years. Prior reports suggest age to be an important factor in making high intensity treatment decisions with historically poorer outcomes in the elderly compared to younger patients.[6] In addition high dose chemotherapy is difficult with many elderly patients demonstrating resistance due to aggressive tumor biology and toxicity owing to adverse comorbidities.[7] Richter's

transformation which happens in about 5%-10% of CLL is also frequent in elderly (median age 69 years) with median survival of less than 10 months from diagnosis. Median age at diagnosis for mantle cell lymphoma is around 65-70 years and in relapsed refractory stetting post ibrutinib exposure, survival has been dismal. Similarly, median age for diagnosis of follicular lymphoma is 60 years with a varying history of natural progression. In the modern era, follicular lymphoma transformation to high grade lymphoma occurs in about 2%-3% of patients per year with many transformed cases seen frequently among the elderly for whom current pharmacologic agents are suboptimal.
Management of transformed follicular lymphomas, Richter transformed CLL can be challenging due to various reasons.[8] Despite this significance, initial registration trials (ZUMA-1, Juliet), studied a different age epidemiology including less than 25% of patients being over the age of 65.[9,10] In the more recent TRANSCEND trial the median age was 63 years (slightly higher).[11] Similarly in the ZUMA-2 trial on relapsed/refractory mantle cell lymphoma, the median age was 65 years.[12] This likely represents a growing optimism in the field to push the envelope of age limit for this unique niche population who otherwise are ill-served by current available therapies. A limited study using FDA Adverse Events Reporting System has reported differences in patterns of CRS and CRES among patients over > 60 years receiving CAR-T but outcomes, risk factors, and comorbidities were not further studied and its real impact in those beyond 70 years is not well defined.[13] Given that real world data is limited, and there are omnipresent toxicity concerns due to comorbidities in the elderly, our efficacy and toxicity based study seeks to delve deeper to set a new benchmark in the field.

Significance:
Findings from this study will inform appropriate patient selection and preparation for those seeking CAR-T and in management of post CAR-T relapses. With increasing life span in western world, the prevalence of the elderly and with them the incidence of lymphomas continues to rise. Management of aggressive lymphomas in the elderly desperately need novel approaches of which early application of CAR-T (shuffle the Deck of therapies) whose mechanism of action is different from pharmaceutical drugs might be of critical importance. In the unlikely event CAR-T therapy in the elderly is associated with poor survival or enhanced toxicities in our study this will propel further refinement of ongoing trials, design pre-emptive remedies, better patient counselling and initiate mechanistic studies to better understand this phenomenon. We remain optimistic that the findings from our study will help eliminate some current age-based biases that exist in CAR-T trials and clinical practice. In published literature rates of cytopenias and infections are not well defined in this at-risk cohort about which our study will offer further insights. While premature, long term the risk of secondary neoplasms in this cohort may also be pursued and help better prepare for life beyond CAR-T in this underserved but growing population.

Patient eligibility population:
Any patient (any age) with the diagnosis of any B-cell lymphoid malignancy (indolent or aggressive lymphoma) receiving CAR-T cell product (CD19 target)

Data requirements:
Data will be captured through CIBMTR collection forms. The following variables of interest will be studied:

- 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 (< 65, 65-75, 75- 85 and > 85 years)
- Gender
- Karnofsky performance status at transplant: < 90% vs. ≥ 90%
- HCT comorbidity index at transplant 0, 1, 2, and ≥ 3
- Specific past medical cardiovascular and cardiopulmonary diseases
- ABO blood group
- CMV status

Disease-related:

- Diagnosis: DLBCL, primary mediastinal B cell lymphoma, transformed Follicular MZL, Richter's transformation, MCL, Double or triple Hit Lymphoma (TP53 status if available), Other
- Disease risk index
- High risk cytogenetics: yes vs.no
- Number of prior therapies (before transplant): 1 vs. 2 vs. ≥ 3
- Type of prior therapies (chemo vs radiation vs other)
- Sites of disease
- Tumor size/bulk (in cm)
- 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
- Therapies given before HCT/CAR-T
- Remission status prior to HCT/CAR-T
- Chemo sensitive/Chemo resistant

CAR-T related:

- CAR-T product
- 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)
- Response to CAR-T
- CRS (Y/N and grade) and duration
- CRES/Neurotoxicity (Y/N and grade)
- Cytopenias
- Infectious complications

Study design:

This study would assess the outcomes of all patients with B-cell lymphoid malignancies who receive all FDA approved 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 endpoints will be cumulative incidence and severity of CRS and CRES. Median time to CRS and CRES, need for higher level of care and interventions practiced will be described. Patient, disease, treatment 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, with the variance estimated by Greenwood's formula. 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. Subset analyses will be pursued separating different types of lymphoid malignancies receiving potentially different CAR-T products. Outcomes analysis by age stratification (< 65, 65-75, 76-85 and > 85 years old). Burden of infection, cytopenias in elderly will be illustrated. Multivariate analysis with adjustment of covariates such as pre-CAR-T factors (lines of therapy, response status, and burden of disease etc:) will be performed. A propensity matched pair analysis for different outcomes of interest between elderly and younger cohorts will be pursued.

Conflicts of interest:

Dr Gattu is employed by Sandoz/Novartis and a part time student of Master's in advanced Oncology at University of Ulm (Germany). All other authors have no conflict of interest or relevant/non-relevant disclosures.

References:

1. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800-1808.
2. 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.
3. Brentjens R, Davila ML. CAR T cells, immunologic and cellular therapies in hematologic malignancies. Best Pract Res Clin Haematol. 2018;31(2):115-116.
4. Davila ML, Sadelain M. Biology and clinical application of CAR T cells for B cell malignancies. Int J Hematol. 2016;104(1):6-17.
5. 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.
6. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts: NHL - Diffuse Large B-Cell Lymphoma (DLBCL), SEER 21 2012-2016, All Races, Both Sexes. 2020. https://seer.cancer.gov/statfacts/html/dlbcl.html.
7. Thieblemont C, Bernard S, Molina T. Management of aggressive lymphoma in very elderly patients. Hematological oncology. 2017;35 Suppl 1:49-53.
8. Casulo C, Burack WR, Friedberg JW. Transformed follicular non-Hodgkin lymphoma. Blood. 2015;125(1):40-47.
9. Neelapu SS, Jacobson CA, Oluwole OO, et al. Outcomes of older patients in ZUMA-1, a pivotal study of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2020;135(23):2106-2109.
10. 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.
11. Abramson JS, Palomba ML, Gordon LI, 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(Supplement_1):241-241.
12. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. The New England journal of medicine. 2020;382(14):1331-1342.
13. Zettler ME, Feinberg BA, Phillips EG, Jr., Klink AJ, Mehta S, Gajra A. Real-world adverse events associated with CAR T-cell therapy among adults age ≥ 65 years. J Geriatr Oncol. 2020.

Table1: Characteristics of patients with DLBCL who received an anti-CD19 CAR-T cell therapy

Characteristic	N (%)
No. of patients	1046
No. of centers	79
Patient related	
Age - no. (%)	
Median (min-max)	63.1 (18.5-90.8)
<65	612 (58.5)
65-74	348 (33.3)
75-84	81 (7.7)
>=85	5 (0.5)
Gender - no. (%)	
Male	691 (66.1)
Female	355 (33.9)
Recipient race - no. (%)	
White	893 (85.4)
African-American	47 (4.5)
Asian	44 (4.2)
More than one race	6 (0.6)
Unknown	27 (2.6)
Missing	29 (2.8)
Recipient ethnicity - no. (%)	
Hispanic or Latino	95 (9.1)
Non Hispanic or non-Latino	899 (85.9)
Non-resident of the U.S.	16 (1.5)
Unknown	35 (3.3)
Missing	1 (0.1)
Performance score prior to CT - no. (%)	
90-100	384 (36.7)
=80	327 (31.3)
< 80	194 (18.5)
Missing	141 (13.5)
HCT Comorbidity Index - no. (%)	
0	302 (28.9)
1-2	307 (29.3)

Characteristic	N (%)
>=3	374 (35.8)
Missing	63 (6.0)
Disease Related	
Disease classification - no. (%)	
Diffuse, large B-cell lymphoma - NOS	303 (29.0)
T-cell/histiocytic rich large B-cell lymphoma	15 (1.4)
Diffuse, large B-cell lymphoma - germinal center B-cell type	338 (32.3)
Diffuse, large B-cell lymphoma - activated B-cell type	231 (22.1)
EBV+ DLBCL, NOS	7 (0.7)
High-grade B-cell lymphoma, NOS	12 (1.1)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	140 (13.4)
c-MYC rearrangement based on FISH at diagnosis - no. (%)	
No	227 (21.7)
Yes	136 (13.0)
Not done	29 (2.8)
Missing	654 (62.5)
BCL-2 rearrangement based on FISH at diagnosis - no. (%)	
No	161 (15.4)
Yes	151 (14.4)
Not done	81 (7.7)
Missing	653 (62.4)
BCL-6 rearrangement based on FISH at diagnosis - no. (%)	
No	250 (23.9)
Yes	100 (9.6)
Not done	41 (3.9)
Missing	655 (62.6)
Double/triple hit at initial diagnosis of the primary disease - no. (%)	
Neither	408 (39.0)
Double/triple hit	140 (13.4)
Missing	498 (47.6)
Stage of organ involvement at initial diagnosis of the primary disease - no. (%)	
I	72 (6.9)
II	115 (11.0)
III	233 (22.3)
IV	389 (37.2)
Unknown	114 (10.9)

Characteristic	N (%)
Missing	123 (11.8)
Extranodal involvement at initial diagnosis of the primary disease - no. (%)	
No	279 (26.7)
Yes	556 (53.2)
adrenal (NHL)	14 (1.3)
bone (NHL)	126 (12.0)
bone marrow (NHL)	102 (9.8)
brain (NHL)	10 (1.0)
cerebrospinal fluid (CSF) (NHL)	2 (0.2)
epidural space (NHL)	5 (0.5)
gastrointestinal (GI) tract (NHL)	94 (9.0)
heart involvement (NHL)	3 (0.3)
kidney (NHL)	37 (3.5)
leptomeningeal (NHL)	1 (0.1)
liver (NHL)	62 (5.9)
lung (NHL)	70 (6.7)
pericardium (NHL)	5 (0.5)
pleura (NHL)	14 (1.3)
skin (NHL)	22 (2.1)
spleen (NHL)	177 (16.9)
other site (NHL)	218 (20.8)
Unknown	83 (7.9)
Not reported	128 (12.2)
>1 extranodal site at initial diagnosis of the primary disease (NHL) - no. (%)	
No	583 (55.7)
Yes	333 (31.8)
Missing	130 (12.4)
IPI at initial diagnosis of the primary disease - no. (%)	
Low	29 (2.8)
Low intermediate	44 (4.2)
High intermediate	67 (6.4)
High	66 (6.3)
Missing	840 (80.3)
Age adjusted IPI at initial diagnosis of the primary disease - no. (%)	
Low	17 (1.6)
Low intermediate	49 (4.7)

Characteristic	N (%)
High intermediate	88 (8.4)
High	16 (1.5)
Missing	876 (83.7)
Types of prior HCTs - no. (%)	
No prior HCT	705 (67.4)
Prior allo-HCT(s)	17 (1.6)
Prior auto-HCT(s)	304 (29.1)
Prior auto and allo-HCT(s)	6 (0.6)
Missing	14 (1.3)
No. of prior HCTs - no. (%)	
0	705 (67.4)
1	295 (28.2)
2	7 (0.7)
Missing	39 (3.7)
Prior HCTs - no. (%)	
No	705 (67.4)
Yes	340 (32.5)
0-6 months	42 (4.0)
6-12 months	86 (8.2)
>= 12 months	174 (16.6)
Missing	38 (3.6)
Missing	1 (0.1)
Cellular Therapy Related	
Product - no. (%)	
Kymriah	182 (17.4)
Yescarta	864 (82.6)
Time from diagnosis to CT - no. (%)	
Median (min-max)	15.6 (0.2-406.3)
0-6 months	108 (10.3)
6-12 months	286 (27.3)
1-2 years	288 (27.5)
2-3 years	364 (34.8)
Disease status prior to CT - no. (%)	
CR1	4 (0.4)
CR2	13 (1.2)
CR3+	14 (1.3)

Characteristic	N (%)
Relapse, 1st	286 (27.3)
Relapse, other	317 (30.3)
PIF/Untreated	409 (39.1)
Missing	3 (0.3)
Disease status at CT - no. (%)	
CR	31 (3.0)
PR	209 (20.0)
Resistant	691 (66.1)
Missing	115 (11.0)
Year of CT - no. (%)	
2017	5 (0.5)
2018	448 (42.8)
2019	593 (56.7)
Prior lines of therapies - no. (%)	
No	1 (0.1)
Yes	1027 (98.2)
1	9 (0.9)
2	214 (20.5)
>= 3	756 (72.3)
Missing	48 (4.6)
Missing	18 (1.7)
Lymphodepleting chemotherapy - no. (%)	
bendamustine	7 (0.7)
bendamustine + corticosteroids	11 (1.1)
corticosteroids + cyclophosphamide + monoclonal antibody + other drug	1 (0.1)
cyclophosphamide	2 (0.2)
cyclophosphamide + cytarabine + fludarabine + monoclonal antibody	1 (0.1)
cyclophosphamide + fludarabine	1020 (97.5)
cyclophosphamide + fludarabine + monoclonal antibody	1 (0.1)
cyclophosphamide + fludarabine + other drug	1 (0.1)
cytarabine + fludarabine + monoclonal antibody	1 (0.1)
None specified	1 (0.1)
Follow-up - median (min-max)	12.1 (0.9-28.5)