Not for publication or presentation

A G E N D A
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** **Telephone: 617-632-3470; E-mail: snikiforow@partners.org**
Co-Chair:	**Peiman Hematti, MD, University of Wisconsin Hospital and Clinics, Madison, WI** **Telephone: 608-265-0106; E-mail: pxh@medicine.wisc.edu**
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1. **Introduction**
   a. Minutes and Overview Plan from February 2019 meeting (Attachment 1)
   b. Introduction of incoming Co-Chair: **Cameron Turtle, MBBS, PhD;** Fred Hutchinson Cancer Research Center.
   c. Instructions for sign-in and voting
2. **Accrual summary** (Attachment 2)
3. **Cellular Therapy Registry, CIDR and CICWC** (M Pasquini)
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 (Attachment 3)

a. **CT13-01** Utility of unmanipulated donor lymphocyte infusion (DLI) for the treatment of infections in allogeneic hematopoietic cell transplantation recipients (G Akpek) **Analysis**
b. **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**
c. **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**
d. **AC18-01** Effect of stem cell boost and donor lymphocyte infusion on the incidence of GVHD (J Yoon/ E Waller) **Protocol Development**
e. **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**
f. **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

a. **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) (Attachment 4), Tisagenlecleucel (Kymriah®) versus axicabtagene ciloleucel (Yescarta®) in patients with relapsed/refractory diffuse large B cell lymphoma (M Pennisi/A Mussetti/M Perales) (Attachment 5), 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) (Attachment 6)
b. **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) (Attachment 7), A modified hematopoietic stem cell transplantation – comorbidity index for recipients of chimeric antigen receptor T cell therapy (M Sorror/M Bar) (Attachment 8), 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) (Attachment 9), 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) (Attachment 10), 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) (Attachment 11)
c. **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)(Attachment 12), 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) (Attachment 13), Development of a prognostic model of CAR-T cell therapy toxicity (R Shouval/M Pennisi/M Perales) (Attachment 14)

d. **PROP 1910-12** Correlation between CAR-T cell dose, disease response, cytokine release syndrome and acute neurotoxicity (M Salas/A Law/R Kumar) (Attachment 15)
e. **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) (Attachment 16), Outcomes of CD19 CAR T cell therapy for large B cell lymphoma arising from a non-follicular transformation (M Jain/F Locke/T Nishihori) (Attachment 17), Outcomes in patients with double/ triple hit lymphoma post CAR T treatments (A Vallurupalli/S Ganguly) (Attachment 18), 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) (Attachment 19)
f. **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) (Attachment 20)
g. **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) (Attachment 21), Clinical outcomes of CAR-T cell therapy in transplant naïve patients versus CAR-T cell therapy post autologous transplant (N Shah/P Hari) (Attachment 22)
h. **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) (Attachment 23), 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) (Attachment 24)
i. **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) (Attachment 25), 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) (Attachment 26), Clinical features and outcomes in patients with acute lymphoblastic leukemia who relapse post-chimeric antigen receptor therapy (L Schultz/L Muffly) (Attachment 27)
j. **PROP 1911-115/PROP 1911-166/PROP 1911-187** Resource utilization with CAR-T cells (M Battiwalla/J Pantin) (Attachment 28), Real world experience of costs and healthcare utilization in children and young adults receiving Kymriah for acute lymphoblastic leukemia (H Rangarajan/P Satwani) (Attachment 29), Comparison 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) (Attachment 30)
k. **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) (Attachment 31)

Dropped proposed studies

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.

d. **PROP 1911-155** Infections after CD19-targeted chimeric antigen receptor–modified (CAR) T-cell therapy for non-Hodgkin lymphoma.
e. **PROP 1911-158** Observational study of infectious complications among patients treated with anti-CD19 chimeric antigen receptor T cells (CAR-T cells).
f. **PROP 1911-209** Infectious complications and immune reconstitution following CD19-directed CAR-T cell therapy.
g. **PROP 1911-235** The role of intravenous immune globulins in patients after CAR-T therapy.
h. **PROP 1911-254** Patterns of infections post CD19 directed CAR-T cells infusions.
i. **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.

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR AUTOIMMUNE DISEASES AND CELLULAR THERAPIES
Houston, Texas
Friday, February 22, 2019, 12:15 pm – 2:15 pm

Co-Chair:	**Sarah Nikiforow, MD, PhD, Dana Farber Cancer Institute Boston, Massachusetts; Telephone: 6176323470; E-mail: snikiforow@partners.org**
Co-Chair:	**Peiman Hematti, MD, University of Wisconsin Hospital and Clinics, Madison, WI; Telephone: 608-265-0106; E-mail: pxh@medicine.wisc.edu**
Co-Chair:	**Stefanie Sarantopoulos, MD, PhD, Duke University Medical Center, Durham, NC; Telephone: 919-668-4383; E-mail: stefanie.sarantopoulos@duke.edu**
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1. Introduction

The Committee chairs (Peiman Hematti, MD, Sarah Nikiforow MD, and Stefanie Sarantopoulos, MD) and the Scientific director (Marcelo Pasquini, MD) welcomed the committee and started the meeting at 12:17. After the brief introduction, Dr. Nikiforow acknowledged the contributions by the outgoing chair Stephanie Sarantopoulos, MD. Then the minutes from the 2018 meeting in Salt Lake City were then approved by the committee.

Dr. Pasquini then introduced the new incoming working committee co-chair for the Non-Malignant Diseases working committee George Georges, MD from Fred Hutchinson Cancer Research Center.

Dr Pasquini then introduced the Cellular immunotherapy data resources (CIDR) which is part of the cancer moonshot initiative. The initiative involves building outcomes database on cellular immunotherapy to serve as a resource to the community at large. This NCI funded initiative is a program under the Moonshot Initiative to advance cancer research. The CIDR governance structure outlines the development of a working committee to oversee the utilization of this resource for research purposes.

Dr Pasquini then discussed the upcoming restructuring that will affect this working committee, after the launch of the CIDR. As of March 2019, the Autoimmune Diseases and Cellular Therapy working committee will be split based on indication and therapy. The Autoimmune diseases focus will be move to the non-malignant diseases working committee and the cellular therapy will change its focus to cellular immunotherapy for cancer.

2. Accrual Summary (attachment 2)

Dr. Pasquini briefly discussed the status of data that is available for cellular therapy with a brief overview of the milestones since the launch of the CT registry in the summer of 2016. Data in the CT Registry was

operationally divided into three categories, cellular therapy in the context of an HCT, such as donor lymphocyte infusion for prevention or treatment of post transplant complications; cellular immunotherapy for cancer, which includes CAR T-cells and cytotoxic T-cells; and finally regenerative medicine, which includes uses of hematopoietic-derived or other cells for treatment of neurologic, cardiovascular and other illnesses. Additionally, the regenerative medicine group will capture therapies to correct diseases using genetic modified stem cells products. Over 2600 patients who received CT under all categories were reported to the CT registry, mostly receiving DLI after HCT for treatment of disease relapse followed by CAR T cells for treatment of hematologic malignancies. For regenerative medicine, the most common reported indication was for treatment of neurologic diseases. Among CAT-cells, in 2018 the CIBMTR contracted with Kite/Gilead and Novartis to utilize the CT registry infrastructure to capture long term follow up as part of a prospective post approval study to capture long term outcomes on these patients. The introduction of these two products resulted in an increase in the number of reported CAR T cell cases to the CT registry, which now accumulated 646 recipients mostly recipients of a commercial CAR T cell product. The majority of indications mirror the FDA approved indications for these products, including NHL and ALL.

Dr. Pasquini then discussed the accrual of data for the autoimmune disease, which reporting at least from the US remains in low numbers and unchanged, at least since the publication of SCOT trial for SSC and the MIST trial for MS. The CIBMTR worked wit ASBMT on two position statements to assist centers in referencing them to obtain approval from payors.

3. Studies in progress

Dr. Pasquini briefly discussed the studies in progress before we started presenting the proposals. All autoimmune diseases focused studies will be moved to the non-malignant disease working committee.

a. **CT10-01** Donor Leukocyte Infusion versus Second Allogeneic Hematopoietic Stem Cell Transplantation for Disease Relapse after First Allogeneic Stem Cell Transplantation (N Frey/A Loren/D Porter) Manuscript Preparation
b. **CT13-01** Utility of Unmanipulated Donor Lymphocyte Infusion (DLI) for the Treatment of Infections in Allogeneic Hematopoietic Cell Transplantation Recipients (G Akpek, B Omar) Analysis
c. **AC14-01** Long Term Outcomes after Autologous Hematopoietic Cell Transplantation for Rapidly Progressive Systemic Scleroderma (D Farge) Data Collection – deferred
d. **AC16-01** Pattern of use and outcomes with donor lymphocyte infusion (DLI) after HLA-haploidentical allogeneic hematopoietic stem cell transplant (V Roy) Data Collection
e. **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
f. **AC18-01** Effect of stem cell boost and donor lymphocyte infusion on the incidence of GVHD (James Yoon/ Edmund Waller) Deferred for 2019
g. **AC18-02** Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis (George Georges) Deferred for 2019

5. Future/proposed studies

Dr. Pasquini briefly discussed the two autoimmune proposals we received this year. One of which was dropped due to feasibility issues. The committee received 5 Cellular therapy-focused proposals. Dr. Pasquini then explained that the working committee could accept up to two studies this year.

Autoimmune:

a. **PROP 1811-11** To evaluate the outcomes of hematopoietic stem cell transplant with cyclophosphamide and ATG vs total body irradiation conditioning in the treatment of systemic sclerosis (Gul,Khan,Abuali) (Attachment 3)

This study was presented by Zartash Gul who started out by explaining that the hypothesis of this study was that Immune ablation (with cyclophosphamide and ATG) as a conditioning regimen is safer and has better outcomes than TBI based conditioning regimens. There were 112 total patients that met the proposal eligibility criteria most of these cases received either TBI or Cyclophosphamide based conditioning. There were no conflicts of interest to disclose from any of the PI's.

One comment received was regarding how accessible data will be for long term follow up for these cases. Dr. Pasquini mentioned that we will have to retroactively ask sites for follow up data which is always challenging but especially for this study as we will likely need help from rheumatologist at the sites to help in reporting SSC specific outcome data. Dr. George Georges then commented that this hypothesis might not be supported by the current data we have available. The SCOT trial and ASTIS trial have showed that TBI regimen has been superior. Dr. Gul response was that we still need long term follow up data is, so we can answer this question.

Cellular Therapy:

b. **PROP 1809-03** Allogeneic hematopoietic cell transplantation vs chimeric antigen receptor t-cell therapy for DLBCL patients with prior autologous transplant failure or refractory disease (Hamadani, Pasquini, Locke, Gopal) (Attachment 4)

Dr. Hamadani presented this proposal explaining that 40-45% of DLBCL patients relapse after an autologous HCT transplant. The question is are these patients better off with an Allogeneic Transplant or a CAR T cell infusion. The hypothesis is that overall survival in DLBCL patients with a prior autologous HCT failure or refractory disease following CAR-T therapy will be comparable to patients undergoing allogeneic HCT. Dr. Hamadani then explained the data available to study this question based on the accrual summary of patients generated for the proposal. Currently there are 52 CAR-T patients and 446 Allogeneic HCT patients that fit the eligibility criteria for this study. One limitation for this study Dr. Hamadani brought up is that these 52 CAR-T patients may not be available to analyze due to data being embargoed by centers who are using the CIBMTR as a registry for long term follow up. However, if this is the case Dr. Hamadani mentioned that there is the possibility of including cases from other registries that would be willing to collaborate with the CIBMTR for this study. Dr. Hamadani addressed one comment that asked is it fair to compare patients who survived long enough to receive an allogenic transplant against those who received a CAR-T. Dr. Hamadani explained that the same is true though for patients who survived long enough to receive a CAR-T.

c. **PROP 1811-66** 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, Stiff) (Attachment 5)

Dr. Hossain presented this proposal, explaining that he hypothesis is that baseline clinical characteristics of patients impact likelihood of response to CD19 directed CAR-T cell therapy and the risk of associated toxicities. The scientific impact of the proposal will provide clinicians with an objective approach for determining which patients are suitable for CAR-T therapy by identifying who has the highest chance of a response. Also, this study will identify which patient s are at greatest risk of toxicity post CAR-T therapy. Dr. Hossain then discussed the accrual of patients identified for this proposal. There were 214 patients available most of the patients were enrolled in the registry in 2018 so there is limited follow up data for many of these patients. Dr. Nikiforow asked how toxicity

is captured in the CIBMTR follow up forms. Dr. Pasquini explained that this is captured on the 3 month, 6 months and annual follow up forms.

d. **PROP 1811-88** Impact of DLI dose on outcomes of relapsed MDS and AML patients who have had an allogeneic transplant from matched related and unrelated donors (Varadarajan) (Attachment 6)

Dr. Varadarajan presented the proposal, the hypothesis states that the dose of DLI from 0.5x10^7 to 1x 10^7 CD3+ cells correlates with an improved overall survival (OS)and relapse free survival (RFS), in patients who have had relapsed MDS and AML after allogeneic transplants. The primary outcome for this study is to determine the overall survival rate at 1-year post DLI comparing four groups of DLI dose range. 1x10^6cells/kg vs. 1x10^6 - 0.5x10^7 cells/kg vs. 0.5x10^7 – 1x10^7 cells/kg vs. >1x10^7 cells/kg. Secondary outcomes include reporting the incidence of pancytopenia post DLI. Dr. Varadarajan then explained that the CIBMTR is the best database to study this question and this is an important question to study as it could lead to the standardization in dosing of DLI. One question asked how this study would be better than CT10-01 which is very similar in concept to this study. Dr. Pasquini explained that this proposal is looking at a more contemporary cohort and is using the new cellular therapy forms which collects more robust data than the data forms we had for the older study.

e. **PROP 1811-141** Prolonged cytopenia following CD-19 targeted CAR-T therapy for diffuse large b-cell lymphoma (Shadman) (Attachment 7)

Dr. Shadman presented this proposal, Dr. Shadman explained that prolonged cytopenia's are not uncommon in practice but the actual incidence is unknown beyond 30 days post CAR-T therapy. He explained that to design interventional trials to overcome cytopenia a benchmark on the actual burden of the problem is needed. The hypothesis states that at least 50% of patients who receive one of the FDA-approved CD-19 targeted CAR-T products for DLBCL have at least grade 2 thrombocytopenia (platelet < 75,000/mm3) or grade 2 neutropenia (<1,500/mm3) 6 months after treatment. The specific aims of this study are to determine the rate/grade of thrombocytopenia at 6 and 12 months after CAR-T therapy. Also, this study aims to determine the rate/grade of neutropenia at 6 and 12 months after CAR-T therapy as well as determining pre and post treatment factors that may be associated with prolonged cytopenia after CAR-T therapy. Dr. Shadman then highlighted the accrual of patients that met the eligibility criteria of the proposal. There were 189 patients eligible most of the cases were infused in 2018 and there was limited follow up data for survivor as a result. One question received asked what is the status of the embargoed data and should there be concern that this data will not be available for analysis and publication? Dr. Pasquini responded that the CIDR and involving industry partners to participate into the studies. Additionally, once the data is sent and reviewed by regulatory agencies then this data will be available for CIBMTR studies.

f. **PROP 1811-109** CAR-T therapy vs autologous transplant in early rituximab failure in patients with diffuse large b cell lymphoma (Shah, Hamadani) (Attachment 8)

Dr. Hamadani presented this study on behalf of Dr. Shah. The Hypothesis of this study states that CAR-T cell therapy improves OS in patients with early Rituximab failure (<12 months) compared to autologous transplant. Dr. Hamadani explained that the primary outcome will be to compare overall survival among patients who relapse within 1 year of initial diagnosis after first-line rituximab-based chemo-immunotherapy who undergo autologous transplant versus those who receive CAR-T cell therapy against CD19. Secondary outcomes will include relapse rates, and rates of non-relapse mortality. Dr. Hamadani then described the accrued population that matched the eligibility criteria of the proposal 179 patients in the auto cohort and 142 in the CAR-T Cohort. Most of the CAR T cases were infused in 2018 which is a limitation for follow up data.

One comment brought up was the challenge of comparing these two cohorts as the years of patients receiving CAR-T is mostly collected in 2018 and only 18 cases of auto HCT were reported on CRF track in 2017. Dr. Hamadani explained that this is a limitation of this study as we need CRF level data to do this study as not the all the information needed is collected on TED. That said CRF patients are only a subset of the total number of patients that are reported to the CIBMTR. Dr. Hamadani also mentioned that the lack of available for follow up for the CAR-T cohort is also a limitation.

The meeting adjourned at 2:13 pm.

Working Committee Overview Plan for 2019-2020

Study number and Short title	Current status	Goal with date	Total hours to complete	Hours allocated to 6/30/2019	Hours allocated 7/1/2019-6/30/2020	Total Hours allocated
CT10-01: Donor leukocyte infusion versus second allogeneic HCT for disease relapse after first allogeneic HCT	Manuscript prep	Submission – July 19	0	*0*	0	**0**
CT13-01: Utility of donor leukocyte infusion for the treatment of drug-resistant viral or fungal infections in allogeneic HCT recipients: A CIBMTR analysis	Analysis	Published -July 2020	110	110	5	**115**
AC16-01: Pattern of use and outcomes with donor lymphocyte infusion after HLA-haploidentical allogeneic hematopoietic stem cell transplant	Data File Prep	Submitted -July 20	130	80	50	**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	Manuscript Prep -July 20	290	140	80	**220**
AC18-01: Effect of stem cell boost and donor lymphocyte infusion on the incidence of GVHD	Draft protocol	Manuscript Prep -July 20	310	60	180	**240**
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 Pending	Manuscript Prep -July 20	330	0	260	**260**
CT19-02: Prolonged cytopenia following CD-19 targeted CAR-T therapy for diffuse large b-cell lymphoma	Protocol Pending	Manuscript Prep -July 20	330	0	260	**260**

Oversight Assignments for Working Committee Leadership March 2019		
Sarah Nikiforow	**CT10-01**	DLI vs Second Allo HCT for relapse
	AC17-01	CD19 CAR T cells without HCT for ALL
	CT19-01	ALLO vs CAR T DLBCL with prior Auto or refractory disease
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
	CT19-02	Prolonged Cytopenia Following CD-19 CAR-T Therapy for DLBCL

Accrual Summary for the Cellular Immunotherapy for Cancer Working Committee

Baseline characteristics for patients receiving 1st CT (excluding DLIs) after 2016 reported to the CIBMTR CT Registry

Characteristic	N (%)
No. of patients	1958
No. of centers	128
Age at infusion, by category - no. (%)	
Median (min-max)	57.54 (0.37-90.82)
< 10	136 (6.9)
10-19	201 (10.3)
20-29	120 (6.1)
30-39	82 (4.2)
40-49	173 (8.8)
50-59	374 (19.1)
60-69	555 (28.3)
>= 70	317 (16.2)
Gender - no. (%)	
Male	1239 (63.3)
Female	718 (36.7)
Not reported	1 (0.1)
CT type - no. (%)	
CAR-T	1858 (94.9)
Commercial	1469 (75)
Noncommercial	389 (19.9)
Other CT, genetic modified	16 (0.8)
TBD	84 (4.3)
Disease - no. (%)	
Solid tumor	26 (1.3)
Malignant hematologic disorder	1930 (98.6)
AML	8 (0.4)
ALL	409 (20.9)
CLL/PLL	5 (0.3)
MDS	2 (0.1)
NHL	1341 (68.5)
HD	10 (0.5)
PCD/MM	113 (5.8)
Not reported	42 (2.1)
Not reported	2 (0.1)
Prior HCTs - no. (%)	
No	1156 (59)
Yes	792 (40.4)
Prior allo-HCT(s)	202 (10.3)
Prior auto-HCT(s)	548 (28)

Characteristic	N (%)
Prior auto and allo-HCT(s)	14 (0.7)
Not reported	28 (1.4)
Not reported	10 (0.5)
Clinical trial - no. (%)	
No	1366 (69.8)
Yes	591 (30.2)
Not reported	1 (0.1)
Year of CT - no. (%)	
2016	71 (3.6)
2017	130 (6.6)
2018	816 (41.7)
2019	941 (48.1)

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Cellular Immunotherapy for Cancer Working Committee Members

FROM: Marcelo Pasquini, MD, MS; Scientific Director for the Cellular Immunotherapy for Cancer Working Committee

RE: 2019-2020 Studies in Progress Summary

CT13-01 Utility of unmanipulated donor lymphocyte infusion (DLI) for the treatment of infections in allogeneic hematopoietic cell transplantation recipients. (G Akpek) The objectives of the study are: 1) to describe the microbiologic response and clinical outcomes after DLI in allogeneic HCT recipients with drug-resistant infections; 2) to identify variables that are associated with any type of response to DLI. The study is undergone analysis procedure in Jan 2020. The goal of the study is to have the manuscript finalized by June 2020.

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) The primary objectives of the study are: 1) to describe the frequency of use of DLI, CD3 cell dose, and the efficacy and toxicity of DLI after HLA haploidentical T-replete HCT; 2) to explore the specific characteristics associated with outcomes (remission / restoration of full donor chimerism/ or GVHD). The current status of the study in Jan 2020 is under data file preparation. The goal of the study is to have the manuscript finalized by June 2020.

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) The primary aim of the study is to assess the impact of allo-HCT on long-term outcomes of patients with ALL treated with CD19-targetd CAR T cells. The current status of the study in Jan 2020 is under protocol development. The goal of the study is to have manuscript preparation completed by June 2020.

AC18-01 Effect of stem cell boost and donor lymphocyte infusion on the incidence of GVHD. (J Yoon/ E Waller) The primary objectives of the study are: 1) CD34-selected stem cell boost: T cell content < 105 cells/kg; 2) T cells not reduced > 107 cells /kg. The study is currently under protocol development in Jan 2020. The goal of the study is to have protocol development finalized by June 2020.

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) The primary aim of the study is to compare outcomes for DLBCL patients with failed prior autologous HCT undergoing allogeneic HCT vs. immunotherapy with CAR T-cells. The study is currently under protocol development in Jan 2020. The goal of the study is to start analysis by June 2020.

CT19-02 Prolonged cytopenia following CD-19 targeted CAR-T therapy for diffuse large B-cell lymphoma. (M Shadman) The primary objective of the study is to evaluate the incidence and severity of cytopenia after treatment with FDA approved CD19 targeted CAR-T products - axicabtagene ciloleucel (Yescarta) or tisagenlecleucel (Kymriah) for large B-cell lymphoma. The study is currently under protocol development in Jan 2020. The goal of the study is to have the manuscript finalized by June 2020.

Proposal: 1911-38

Title:
COMPARATIVE OUTCOMES ANALYSIS OF PATIENTS WITH AGGRESSIVE B-CELL LYMPHOMA TREATED WITH *AXICABTAGENE CILOLEUCEL* VS. *TISAGENLECLEUCEL*

Brian T. Hill, MD, PhD, hillb2@ccf.org, Taussig Cancer Institute; Cleveland Clinic

Research hypothesis:
The hypothesis of this study is that patients with relapsed or refractory aggressive B-cell lymphoma have higher rates of durable remissions when treated with anti-CD19 directed chimeric antigen receptor (CAR) T-cell using *axicabtagene ciloleucel* (*axi-cel)* when compared to *tisagenlecleucel (tisa-cel)* but higher rates of toxicity.

Specific aims:
Primary aim:
- To compare the overall survival of patients with relapsed/refractory aggressive B-cell lymphoma treated with axi-cel vs. tisa-cel.

Secondary aims:
- To compare the progression-free survival of patients with relapsed/refractory aggressive B-cell lymphoma treated with axi-cel vs. tisa-cel.
- To compare the rate of best overall response rate (ORR), complete remission (CR) and partial remission (PR) rates of patients with relapsed/refractory aggressive B-cell lymphoma treated with axi-cel vs. tisa-cel.
- To compare the incidence and severity of cytokine release syndrome (CRS) and CAR T cell-related encephalopathy syndrome (CRES) in patients with relapsed/refractory aggressive B-cell lymphoma treated with axi-cel vs. tisa-cel.

Scientific impact:
Results of this study will immediately inform clinical practice as currently, the selection of product is based on institutional preference, manufacturing availability and/or perceived tolerability of these agents**.**

Scientific justification:
Aggressive B-cell lymphoma including *de novo* diffuse large B-cell lymphoma (DLBCL) and transformed follicular lymphoma have the potential to cause significant morbidity and mortality if not cured with standard therapy. In the case of relapsed or refractory (r/r) aggressive B-cell lymphoma, traditional chemotherapy often fails to produce sufficient disease control to allow for autologous stem cell transplantation (ASCT).[1, 2] Such patients who are ineligible for ASCT or those who relapse after ASCT have historically had very poor prognosis.[3]
Anti-CD19 directed chimeric antigen receptor (CAR) T-cell therapy has remarkable clinical activity and can potentially achieve durable remission for patients with r/r aggressive B-cell lymphoma. Two seminal studies lead to the FDA approval of *axi-cel and tisa-cel*.[4, 5] Recently a report from 8 US academic centers of 149 patients treated with commercial *axi-cel* was compared with outcomes of 75 patients treated with *tisa-cel.*[6] In this analysis, the 30 day CR rate was 43% vs 44% for *axi-cel* and tisa-cel, respectively, but this was based only 32 response evaluate patients treated with *tisa-cel*. The overall response rate was higher with *axi-cel* than with *tisa-cel* (72% vs 59%, respectively). Of note, in a significantly larger

series of patients treated with *axi-cel* treated at 17 US academic centers, the best ORR and CR rate, among the 277 patients were 81% (N=225) and 57% (N=157), respectively, suggesting that differences in patient characteristics and treatment site may impact outcomes and suggest that *axi-cel* may have superior disease control than *tisa-cel*.[7] In the report by Reidel, *et al*, cytokine release syndrome (CRS) and CAR T cell-related encephalopathy syndrome (CRES) were significantly higher with *axi-cel* vs. *tisa-cel.*

The CIBMTR is the clearinghouse of patient-level data detailing the baseline demographics, outcomes and toxicity of patients treated with CAR-T cell therapy in the United States. These data have been collected for the past 2 years and there are now sufficient cases with adequate follow-up to allow for for the most direct comparison of the efficacy and safety of the two approved CAR-T cell therapies.

Patient eligibility population:

- Patients ≥ 18 years who have undergone treatment with axi-cel or tisa-cel at a CIBMTR center between 2018-2020.
- Diagnosis of DLBCL with or without transformation from indolent NHL. Cases of primary mediastinal B-cell lymphoma will be excluded as this is not an approved indication for tisa-cel.

Data requirements:

- Data captured in the baseline demographics will include gender, age of diagnosis, time from diagnosis to relapse, response to most recent therapy (chemosensitive or chemoresistant), disease status at the last evaluation prior to CAR-T cell therapy and hematopoietic cell transplantation comorbidity index (HCT-CI).
- Outcomes will include severity of cytokine release syndrome (CRS) and neurotoxicity by application of ASBMT CRS Consensus Grading
- No supplemental data form will be required.

Sample requirements

N/A

Study design (scientific plan):

Categorical variables will be compared between *axi-cel* and *tisa-cel* using the Chi-square test. Continuous variables will be compared using the Wilcoxon rank sum test. Relapse and NRM will be estimated with cumulative incidence and compared between treatments using the Gray test; OS and PFS were estimated with Kaplan-Meier and compared using the log-rank test. Univariable prognostic factor analysis will be performed with Fine and Gray regression (relapse, NRM) or Cox proportional hazards analysis (OS, PFS). Multivariable prognostic factors will be identified using a stepwise selection process with a variable entry criterion of $P<0.10$ and a variable retention criterion of $P<0.05$. Results are presented as the hazard ratio (HR) and 95% confidence interval (CI) for HR.

Because there are likely differences in baseline characteristics between patients treated with *axi-cel* and *tisa-Cel*, propensity matching will be used to identify more balanced groups of cohorts. A logistic regression model will be used based on the following variables: gender, age, performance status, number of prior chemotherapy regimens, NHL type (*de novo* vs. transformed DLBLC), time from diagnosis to CAR-T cell therapy, HCT-CI and disease status at the time of CAR-T cell treatment (relapsed vs. refractory)

Data source:

CIBMTR form 4000 - Pre-Cellular Therapy Essential Data

CIBMTR form 4000 - Pre-Cellular Therapy Essential Data

CIBMTR form 4003 - Cell Therapy Product
CIBMTR form 4006 - Cellular Therapy Infusion
CIMBTR form 4100 - Cellular Therapy Essential Data Follow-Up Form

Conflict of interest:
I have received research funding from Kite Pharma (a Gilead Company) and have served as a consultant to Kite Pharma as well as Novartis and Juno Therapeutics (a Celgene/Bristol-Myers Squibb Company).

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Baseline characteristics for patients undergoing 1st commercial CAR-T for NHL

Characteristic	N (%)
No. of patients	816
No. of centers	72
Age at infusion, by category - no. (%)	
Median (min-max)	62.27 (15.02-88.99)
10-19	4 (0.5)
20-29	18 (2.2)
30-39	40 (4.9)
40-49	84 (10.3)
50-59	202 (24.8)
60-69	307 (37.6)
>= 70	161 (19.7)
Gender - no. (%)	
Male	522 (64)
Female	294 (36)
Recipient race - no. (%)	
White	700 (85.8)
African-American	37 (4.5)
Asian	35 (4.3)
Other	1 (0.1)
More than one race	19 (2.3)
Not reported	24 (2.9)
Recipient ethnicity - no. (%)	
Hispanic or Latino	81 (9.9)
Non Hispanic or non-Latino	688 (84.3)
Non-resident of the U.S.	16 (2)
Unknown	31 (3.8)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	308 (37.7)
80	246 (30.1)
< 80	148 (18.1)
Not reported	114 (14)
Disease classification - no. (%)	

Characteristic	N (%)
Follicular, predominantly small cleaved cell	3 (0.4)
Follicular, mixed small cleaved and large cell	6 (0.7)
Diffuse, large B-cell lymphoma - NOS	242 (29.7)
Mantle cell lymphoma	5 (0.6)
Primary diffuse, large B-cell lymphoma of the CNS	2 (0.2)
T-cell/histiocytic rich large B-cell lymphoma	15 (1.8)
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)	1 (0.1)
Nodal marginal zone B-cell lymphoma	2 (0.2)
Primary mediastinal (thymic) large B-cell lymphoma	22 (2.7)
Other B-cell lymphoma	10 (1.2)
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL	3 (0.4)
Follicular, predominantly large cell (grade IIIA)	5 (0.6)
Follicular, predominantly large cell (grade IIIB)	4 (0.5)
Follicular (grade unknown)	6 (0.7)
B-lymphoblastic leukemia, NOS	1 (0.1)
Diffuse, large B-cell lymphoma - germinal center B-cell type	259 (31.7)
Diffuse, large B-cell lymphoma - activated B-cell type	154 (18.9)
EBV+ DLBCL, NOS	6 (0.7)
High-grade B-cell lymphoma, NOS	6 (0.7)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	62 (7.6)
Plasmablastic lymphoma	2 (0.2)
Disease status prior to CT - no. (%)	
CR1	7 (0.9)
CR2	8 (1)
CR3+	11 (1.3)
Relapse, 1st	195 (23.9)
Relapse, other	259 (31.7)
PIF/Untreated	333 (40.8)
Not reported	3 (0.4)
Types of prior HCTs - no. (%)	
No	536 (65.7)
Yes	277 (33.9)
Prior allo-HCT(s)	19 (2.3)

Characteristic	**N (%)**
Prior auto-HCT(s)	242 (29.7)
Prior auto and allo-HCT(s)	3 (0.4)
Not reported	13 (1.6)
Not reported	3 (0.4)
Product - no. (%)	
Kymriah	117 (14.3)
Yescarta	699 (85.7)
Year of CT - no. (%)	
2017	6 (0.7)
2018	505 (61.9)
2019	305 (37.4)

Proposal: 1911-67

Title:
Tisagenlecleucel (kymriah®) versus Axicabtagene ciloleucel (yescarta®) in patients with relapsed/refractory Diffuse Large B Cell Lymphoma

Martina Pennisi, MD, pennisim@mskcc.org/martina.pennisi@unimi.it, Memorial Sloan Kettering Cancer Center; University of Milan
Alberto Mussetti, MD, amussetti@iconcologia.net, Institut Català d'Oncologia
Miguel-Angel Perales, MD, peralesm@mskcc.org, Memorial Sloan Kettering Cancer Center

Hypothesis:
Currently, tisagenlecleucel (Kymriah) or axicabtagene ciloleucel (Yescarta) share the same indication for relapsed/refractory (R/R) Diffuse Large B Cell Lymphoma (DLBCL) and are therefore considered largely equivalent. However, no direct comparison of the two products has been performed so far.

Specific aims:
Our aim is to compare survival outcomes and treatment-related toxicities of patients treated with tisagenlecleucel or axicabtagene ciloleucel for R/R DLBCL.

General outcomes to be examined include:
Primary objective:
Progression free survival (PFS) assessed at 6 months; this endpoint is based on the assumption that majority of patients who are free from progression at 6 months will not eventually relapse/progress, as preliminarily shown in the two pivotal phase 2 trials, ZUMA-1 and JULIET, where for patients treated with both axicabtagene ciloleucel and tisagenlecleucel, PFS curves reach a plateau at 6 months, suggesting the chance of definitive cure for a proportion of patients (30-40%) [1–3]

Secondary objectives:
Overall response rate (ORR)
Overall Survival (OS)
Relapse/progression Incidence (RI)
Treatment- related mortality (TRM)
Cytokine release syndrome (CRS) incidence
Immune effector cells associated neurological syndrome (ICANS)
Primary cause of death

Scientific impact:
The novelty of this study relies on comparing for the first time the results of two different anti-CD19 CAR T cell products which share the same indication, in order to provide more consistent data regarding the best salvage strategy for R/R DLBCL patients. Knowing the therapeutic effects and toxicity profiles related to the different products, and the impact of baseline characteristics of the patients, can be useful in order to guide physicians in the choice of the best CAR T cell option for their patients. Currently, there are no studies supporting the use of one CAR T cell product over the other. In case of absence of significant differences between the two products, the results of the study will be considered significant as they will confirm the actual concept that the two drugs are equivalent.

Scientific justification:
During the last years, two different anti CD19 Chimeric Antigen Receptor (CAR) T cells products have been approved for R/R DLBCL, tisagenlecleucel and axicabtagene ciloleucel.
In the pivotal phase 2 ZUMA-1 trial, axicabtagene ciloleucel showed a complete response (CR) rate of 54%, a progression free survival (PFS) rate at 2 years of 72% for responding patients (CR) and an overall survival (OS) rate at 2 years of 50%. Grade 3-4 cytokine release syndrome (CRS) incidence and neurotoxicity incidence were 12% and 32%, respectively (graded respectively according to Lee 2014 and CTCAE v4.0) [1,2,4].
In the phase 2 JULIET-1 trial, considering only the infused patients, tisagenlecleucel had a 40% CR rate, with a PFS rate for responding patients (CR) of 83% at 1 year. Median OS for the overall population was 12 months, and not reached for patients in CR (1-year OS 90%). Grade 3-4 CRS was 22% (according to UPenn grading scale) and grade 3-4 neurotoxicity was 12% (using CTCAE v4.0) [3,5].
Both trials also show that after 6 months of follow-up both PFS and OS curves reach a plateau, suggesting the preliminary evidence of chance of definitive cure for a proportion of patients (30-40%).
The results of the ZUMA-1 trial have been reproduced by Nastoupil et al., who have reported the outcomes of 274 patients treated with commercially available axicabtagene ciloleucel in the "real worl experience", showing rates of responses and toxicities analogous to the ZUMA-1 trial, but in a larger population (patients) which included also patients with relevant comorbidities and a higher proportion of older patients [6]. However, survival analyses suffered a very short follow-up, which doesn't allow any reliable conclusion. No "real world data" have been reported so far for patients treated with tisagenlecleucel. Currently, the two drugs share essentially the same indications but, however, a formal comparison between tisagenlecleucel and axicabtagene ciloleucel in the setting of R/R DLBCL has not yet been performed. Unfortunately, a randomized prospective trial appears unlikely. For this reason, a registry study is the most reasonable methodology to address this issue. Our study could address for the first time if the type of anti-CD19 CART could affect survival outcomes for patients with R/R DLBCL.

Patient eligibility population:
This study will include adult patients aged $\geq$ 18 (no upper age limit) who received first commercially available anti-CD19 CAR T cells infusion for R/R DLBCL after FDA approval.
Inclusion criteria:
Relapsed/refractory DLBCL (including high grade B cell lymphomas and large B cell lymphomas transformed from indolent diseases) after $\geq$ 2 lines of therapy
Use of tisagenlecleucel or axicabtagene ciloleucel as first CAR T cell therapy

Exclusion criteria:
Histology-proven diagnosis of Primary Mediastinal B cell lymphoma (PMBCL), for which the use of tisagenlecleucel is not approved

Data requirements:
Utilizing data collected by the CIBMTR, from pre- and post- IEC infusion forms, and pre-transplant essential data forms. The parameters to be assessed are outlined in table 1 below.

Table 1 Data requirements:

Type of data	Data point	Specific data
Patient Specific	Patient and disease specific characteristics	Age at infusion (Date of birth) Gender Race/Ethnicity Date of diagnosis

		Disease histology Significant comorbidities (ECOG, Karnofsky) at infusion Comorbidity score at infusion Weight Prior autologous transplant Remission status at CAR T cells infusion (CR1, CR2, etc) Chemorefractory/chemosensitive disease Bridging chemotherapy
Infusion Specific	Date	Lymphoapheresis date Infusion date
	CART type	axicabtagene ciloleucel vs tisagenlecleucel
	Lymphodepletive chemotherapy	Fludarabine/Cyclophosphamide Bendamustine No lymphodepletive chemotherapy
		Time to neutrophil > 500/mcl Time to platelets engraftment >20.000/mmc
	CRS	CRS occurrence (yes vs no, peak grade)
	ICANS	ICANS occurrence (yes vs no, peak grade)
	Mortality	Day +28 and 1-year mortality Treatment-related mortality at day +28 and 1 year Cause of death
	Efficacy and Disease relapse	Response at 6 months Best response after CAR T cells infusion Time to best response Incidence of disease relapse/progression Time to disease relapse/progression

Study design:

A retrospective multicenter study will be conducted utilizing CIBMTR data. Patients included will be stratified according to tisagenlecleucel or axicabtagene ciloleucel treatment, to compare these two approaches and their effects on survival outcomes. Chi-squared or the Wilcoxon statistic will be used to compare patient, disease and infusion specific characteristics between the 2 groups for categorical or continuous variables respectively. PFS and OS will be calculated using the Kaplan-Meier estimator. The probabilities of TRM, RI, CRS and ICANS will be calculated using the cumulative incidence estimator. Data on patients without an event will be censored at last follow up. For univariate analysis, Gray test and log-rank test will be used to identify factors influencing cumulative incidence and survival respectively. The association between treatment groups and outcomes will be studied with multivariate Cox regression models. P values are 2 sided and values < 0.05 will be considered significant and insert in the multivariate model. The treatment group will be included in all steps of model building regardless of level of significance. The other variables tested will be retained in the final multivariate model if the variable will attain the level of significance set for these analyses. Results will be expressed as hazard ratio (HR) with 95% confidence intervals (CI). Possible interactions within the treatment groups and other variables will be tested. All models will be tested regarding proportional hazard of assumptions (PHA). If the assumption will be violated, time dependent covariates will be constructed.

Outcomes definitions:
PFS: survival without relapse/progression or death at 6 months. Relapse or progression of disease and death are events. Those who survive without recurrence or progression are censored at last contact.
OS: time to death. Death from any cause will be considered an event. Surviving patients will be censored at time of last follow-up.
ORR: combined percentage of patients with a complete or partial response at +6 months. Lugano classification will be used as per standard guidelines.
RI: Cumulative incidence of disease relapse/progression with TRM as competing event.
TRM: Cumulative incidence of TRM. TRM is defined as death without preceding disease relapse/progression. Relapse/progression are competing events.
CRS incidence (only descriptive): Cumulative incidence of CRS at day +28. CRS intensity will be reported according to ASTCT grading system. Death without event is the competing event.
ICANS incidence (only descriptive): Cumulative incidence of ICANS at day +28. ICANS intensity will be reported according to ASTCT grading system, or by CTCAEv4.03 if ASTCT data not available. Death without event is the competing event.

Conflicts of interest:
Dr. Pennisi and Dr. Mussetti have no conflict of interest.
Dr. Perales reports honoraria from Abbvie, Bellicum, Celgene, Bristol-Myers Squibb (>$5,000), Incyte, Merck (>$5,000), Novartis (>$5,000), Nektar Therapeutics, Omeros, and Takeda. He serves on DSMBs for Cidara Therapeutics, Servier and Medigene, and the scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of American Society for Transplantation and Cellular Therapy (ASTCT) and Be the Match (National Marrow Donor Program, NMDP), as well as on the CIBMTR Cellular Immunotherapy Data Resource (CIDR) Committee.

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Baseline characteristics for patients undergoing 1st commercial CAR-T for NHL

Characteristic	N (%)
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No. of centers	72
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Median (min-max)	62.27 (15.02-88.99)
10-19	4 (0.5)
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>= 70	161 (19.7)
Gender - no. (%)	
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White	700 (85.8)
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Unknown	31 (3.8)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	308 (37.7)
80	246 (30.1)
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Diffuse, large B-cell lymphoma - activated B-cell type	154 (18.9)
EBV+ DLBCL, NOS	6 (0.7)
High-grade B-cell lymphoma, NOS	6 (0.7)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	62 (7.6)
Plasmablastic lymphoma	2 (0.2)
Disease status prior to CT - no. (%)	
CR1	7 (0.9)
CR2	8 (1)
CR3+	11 (1.3)
Relapse, 1st	195 (23.9)
Relapse, other	259 (31.7)
PIF/Untreated	333 (40.8)
Not reported	3 (0.4)
Types of prior HCTs - no. (%)	
No	536 (65.7)
Yes	277 (33.9)
Prior allo-HCT(s)	19 (2.3)
Prior auto-HCT(s)	242 (29.7)
Prior auto and allo-HCT(s)	3 (0.4)
Not reported	13 (1.6)
Not reported	3 (0.4)
Product - no. (%)	
Kymriah	117 (14.3)
Yescarta	699 (85.7)
Year of CT - no. (%)	
2017	6 (0.7)
2018	505 (61.9)

Characteristic	N (%)
2019	305 (37.4)

-

Proposal: 1911-260

Title:
Comparative analysis of patient characteristics and efficacy of patients with aggressive B-cell lymphoma who received CD19 directed chimeric antigen receptor (CAR) T-cell therapy

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Hypothesis:
Aggressive B-cell lymphomas respond differently to two commercially available CD19-directed CAR T-cell therapy

Specific aims:
To compare patient characteristics, response and survival after commercially available CD19-directed CAR T-cell therapy for aggressive B-cell lymphoma and deepen the understanding of best utilization of CD19-directed CAR T-cell therapy

Scientific impact:
This study will help characterize patient population and disease characteristics best suited for each commercially available CD19-directed CAR T-cell therapy which will provide insights on patient population and practices that may further improve patient outcomes with CAR T-cell therapy.

Scientific justification:
Patients with relapsed/refractory diffuse large B cell lymphoma (DLBCL) and other aggressive B-cell lymphomas have fairly limited prognosis.[1] Autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy with axicabtagene ciloleucel (Axi-Cel) and tisagenlecleucel have shown remarkable results in these refractory patients, changed the natural history of these disorders and revolutionized the immunotherapy options for lymphoma. These therapies hae been approved by the Food and Drug Administration (FDA) for their commercial use.[2,3] For those receiving CD19 CAR-T had the objective response rates (ORR) of 52-82%, complete response (CR) rates of 40-54% with remarkable overall survival (OS)[2,3] In the axicabtagene ciloleucel study, CAR-T cell expansion peaked within 14 days after infusion and its expansion was significantly associated with response after CAR-T infusion. On the other hand, in the tisagenlecleucel study, there was no apparent effect of exposure to tisagenlecleucel and clinical outcomes, and persistent CAR transgene levels were observed up to 2 years after infusion in patients with durable responses.[3] Nonetheless, the longer term survivors with continued remission of these refractory aggressive B-cell lymphomas after CAR T-cell therapy have been reported and the results are simply impressive.[4]
Since the introduction of CD19-directed CAR T-cell therapy, the number of CAR T-cell therapy delivered to these patients is expanding and many centers are gaining experience in caring for CAR T patients. These two commercial CAR T-cell products target the same antigen albeit their CAR constructs and co-stimulatory domain are different. The two different products have different kinetics and the toxicity profile may also be different although the many features are shared. There is a growing interest in understanding the best strategy to utilize these two products and choosing the best option for individual lymphoma patients. For example, in the study of tisagenlecleucel, a bridging therapy was allowed when clinically indicated after leukapheresis, however systemic bridging chemotherapy was not allowed in the axicabtagene ciloleucel. This may resulted in slightly different patient populations between these two

studies. It is also not known whether how much bridging therapy is given prior to these products in real world setting after FDA approval which may have some impact on the CAR T-cell outcomes. It has been postulated that the bridging therapy may select certain patients who may survive to receive CAR T-cell therapy, however, emerging data that are presented at ASH may suggest otherwise which could be in fact due to selecting more aggressive lymphoma with bridging.[5] [6] Additionally, there may be some patient characteristic differences that are found in post approval settings that can only be seen in studies through CIBMTR that may be of interest to understand the application of these two different CD19-directed CAR-T products. Therefore, we propose to evaluate the patient- and disease-characteristics of CD19-directed CAR T-cell therapy and compare the efficacy of these two products. At there are no randomized studies to compare the two products, CIBMTR data serve as the most useful outcomes data repository for such analysis.

Patient eligibility population:
Inclusion criteria:
Adult patients (age ≥ 18) who received CD19 directed CAR T-cell therapy for B-cell NHL (including diffuse large B cell lymphoma, transformed follicular lymphoma and primary mediastinal B cell lymphoma]

Exclusion criteria:
None

Variables to be described: [Bold variables to be included in multivariate analysis]
Patient related:

- **Age at CAR T-cell therapy:** continuous and categorical by decade
- **Gender:** male vs. female
- **Race:** Caucasian vs. African American vs. Asian/Pacific Islander vs. Hispanic vs. Others vs. missing
- **Ethnicity:** Hispanic or Latino vs. Non-Hispanic or non-Latino vs. non-resident of the U.S.
- **ECOG Performance status/Karnofsky performance score**
- Serum creatinine at the start of lymphodepletion:
- Baseline lymphocyte count prior to the initiation of lymphodepleting therapy

Disease-related:

- **Disease histology:** B-cell NHL (diffuse large B cell lymphoma, transformed follicular lymphoma, primary mediastinal B cell NHL vs. others)
- lymphoma
- Disease stage at diagnosis: I-II vs. III-IV
- Refined disease risk index (DRI): low vs. intermediate vs. high vs. very high risk
- International Prognostic Index (IPI) score at diagnosis: 0-3
- **HCT-CI**: 0, 1, 2, 3+
- Presence of CNS disease at diagnosis: yes vs. no
- **Prior lines of chemotherapy**: 0-1, 2, 3, 4+
- Prior radiation therapy: yes vs. no
- **Prior autologous stem cell transplant**: yes vs. no
- **Prior allogeneic stem cell transplant**: yes vs. no
- Disease status prior to CAR T-cell therapy: CR, PR, SD, or PD for NHL
- Baseline markers of inflammation (ferritin, CRP) prior to CAR T-cell infusion: continuous and categorical (to be determined)

CAR T-cell therapy related:

- Time from diagnosis to CAR T-cell therapy
- Time from leukapheresis to CAR T-cell therapy: continuous (days)
- **Use of bridging therapy**: yes vs. no
- Type of bridging therapy
  - Use of radiation therapy as bridging: yes vs. no
  - Use of chemotherapy as bridging: yes vs. no
- **Use of lymphodepleting chemotherapy**: yes vs. no
- Type of lympho-depleting chemotherapy used:
  - Fludarabine/cyclophosphamide
  - Bendamustine
  - Others

Data requirements:
Bridging therapy information may need to be requested to centers.

Sample requirements:
No samples requested.

Study design:
Outcomes:

- Response: Response rates at the day 30, 3 months and 6 months post CAR T-cell therapy based on bone marrow biopsy with morphological and flow cytometry analysis, CT and/or PET-CT
- Cytokine release syndrome (CRS) and neurotoxicity: Occurrence of grade 1-5 CRS and neurotoxicity. Lee criteria or modified Lee criteria will be used for the CRS grading. CTCAE v4 or CARTOX grading will be used for grading of neurotoxicity.
  - The use of tocilizumab and corticosteroids will be described for each grade of CRS and neurotoxicity
- Overall survival (OS): Time from CAR T-cell infusion to death due to any cause. Patients will be censored at the time of last follow up.
- Progression free survival (PFS): Time from CAR T-cell infusion to death or relapse. Patients will be censored at the time of last follow up.
- CAR T-cell treatment-related mortality (TRM): Death due to any cause in the first 28 days or death due to conditions other than disease relapse or progression beyond 28 days. Events will be summarized by the cumulative incidence estimate with relapse as a competing risk.
- Relapse: Development of relapse as defined by the CIBMTR. The event will be summarized by the cumulative incidence estimate. TRM will be a competing risk for this outcome.
- Hemophagocytic lymphohistiocytosis (HLH)/mast cell activation syndrome (MAS): Cumulative incidence of HLH or MAS after CAR T-cell therapy
- Causes of death: causes of death will be summarized

This retrospective study will determine the patient characteristics and outcomes of CAR T-cell therapy in B-cell NHL. Patient-, disease-, and CAR T-cell therapy-related factors will be compared using the Chi-square test for categorical and the Kruskal-Wallis test for continuous variables according to CD19-directed CAR T-cell therapy. OS and PFS probabilities will be estimated by Kaplan-Meier method. Comparison of survival curves will be performed with the log-rank test and point-wise estimates at 3 months, 6 months, 1 year and 2 years. Probabilities of CAR- T-cell related TRM, and disease relapse/progression will be calculated using cumulative incidence curves to accommodate competing risks. Comparison of incidence curves will

be performed using the Fine and Gray method. Causes of death will be descriptive outcomes.
Multivariate analysis of OS, PFS, CAR-T related TRM, CRS and neurotoxicity will be performed using Cox proportional hazards model. Variables tested in the multivariate analysis are listed above and will be tested in a forward stepwise approach. The final model will include covariates associated with the outcome at a level of 0.05. Tests for interactions may be considered. We will also evaluate center effect and center volume. Geographic information on each center may be also considered.

Non-CIBMTR data source:
N/A

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2. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med*. 2017;377(26):2531-2544.
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Baseline characteristics for patients undergoing 1st commercial CAR-T for NHL

Characteristic	N (%)
No. of patients	816
No. of centers	72
Age at infusion, by category - no. (%)	
Median (min-max)	62.27 (15.02-88.99)
10-19	4 (0.5)
20-29	18 (2.2)
30-39	40 (4.9)
40-49	84 (10.3)
50-59	202 (24.8)
60-69	307 (37.6)
>= 70	161 (19.7)
Gender - no. (%)	
Male	522 (64)
Female	294 (36)
Recipient race - no. (%)	
White	700 (85.8)
African-American	37 (4.5)
Asian	35 (4.3)
Other	1 (0.1)
More than one race	19 (2.3)
Not reported	24 (2.9)
Recipient ethnicity - no. (%)	
Hispanic or Latino	81 (9.9)
Non Hispanic or non-Latino	688 (84.3)
Non-resident of the U.S.	16 (2)
Unknown	31 (3.8)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	308 (37.7)
80	246 (30.1)
< 80	148 (18.1)
Not reported	114 (14)
Disease classification - no. (%)	
Follicular, predominantly small cleaved cell	3 (0.4)
Follicular, mixed small cleaved and large cell	6 (0.7)
Diffuse, large B-cell lymphoma - NOS	242 (29.7)

Characteristic	N (%)
Mantle cell lymphoma	5 (0.6)
Primary diffuse, large B-cell lymphoma of the CNS	2 (0.2)
T-cell/histiocytic rich large B-cell lymphoma	15 (1.8)
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)	1 (0.1)
Nodal marginal zone B-cell lymphoma	2 (0.2)
Primary mediastinal (thymic) large B-cell lymphoma	22 (2.7)
Other B-cell lymphoma	10 (1.2)
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL	3 (0.4)
Follicular, predominantly large cell (grade IIIA)	5 (0.6)
Follicular, predominantly large cell (grade IIIB)	4 (0.5)
Follicular (grade unknown)	6 (0.7)
B-lymphoblastic leukemia, NOS	1 (0.1)
Diffuse, large B-cell lymphoma - germinal center B-cell type	259 (31.7)
Diffuse, large B-cell lymphoma - activated B-cell type	154 (18.9)
EBV+ DLBCL, NOS	6 (0.7)
High-grade B-cell lymphoma, NOS	6 (0.7)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	62 (7.6)
Plasmablastic lymphoma	2 (0.2)
Disease status prior to CT - no. (%)	
CR1	7 (0.9)
CR2	8 (1)
CR3+	11 (1.3)
Relapse, 1st	195 (23.9)
Relapse, other	259 (31.7)
PIF/Untreated	333 (40.8)
Not reported	3 (0.4)
Types of prior HCTs - no. (%)	
No	536 (65.7)
Yes	277 (33.9)
Prior allo-HCT(s)	19 (2.3)
Prior auto-HCT(s)	242 (29.7)
Prior auto and allo-HCT(s)	3 (0.4)
Not reported	13 (1.6)
Not reported	3 (0.4)
Product - no. (%)	
Kymriah	117 (14.3)

Characteristic	N (%)
Yescarta	699 (85.7)
Year of CT - no. (%)	
2017	6 (0.7)
2018	505 (61.9)
2019	305 (37.4)

Proposal: 1911-53

Title:
Assessment of Modified Hematopoietic Cell Transplantation Comorbidity Index in Non-Hodgkin Lymphoma Patients Receiving Chimeric Antigen Receptor T Cell Therapy

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Research hypothesis:
We hypothesize that the hematopoietic cell transplantation comorbidity index (HCT-CI) with modification to incorporate factors unique to CD19 directed Chimeric Antigen Receptor T (CART) cell therapy will predict for non-relapse related mortality (NRM) in patients who receive CART cell therapy for aggressive B cell non Hodgkin lymphoma (NHL)

Specific aims:
Primary:
Compare the risk of NRM, progression free survival (PFS) and overall survival (OS), among recipients of CART cell therapy for a diagnosis of NHL using modified HCT-CI score

Secondary:
Assess if variables such as age, gender, disease stage, performance status, history of autologous hematopoietic stem cell transplant (auto-HCT), LDH, baseline inflammatory markers/cytopenias, history of CNS disease or neurological disorder or response prior to CART cell therapy in association to HCT-CI predicts for NRM, PFS or OS

Scientific impact:
The quality and quantity of evidence available to help assess risk of NRM with CART cell therapy are limited. The sparse data reported appears to show that there are risk factors which may portend a higher risk of CRS or ICANS but that does not necessarily translate into the high overall NRM associated with this treatment. Herein, we propose a registry analysis of patients who have received CART cell therapy for a diagnosis of aggressive B cell NHL comparing the HCT-CI with individual comorbidities and disease-related factors relative to their impact on outcomes, with a specific emphasis on OS and NRM.

Scientific justification:
Patients with refractory B cell NHL or disease that has relapsed within 12 months of auto-HCT have very poor outcomes. The SCHOLAR-1 study demonstrated fewer than 10% of patients will have a complete response, to subsequent therapies, and median overall survival (OS) for these patients is disappointingly only 6 months.[1] A minority of these patients will be eligible for an allogeneic hematopoietic cell transplant, a potentially curative option that itself can carry a treatment related mortality risk as high as 30%.[2] As of 2018, 2 anti-CD19 CAR T cell products were commercially approved by the US Food and Drug Administration (FDA) for the treatment of patients with relapsed or refractory aggressive B cell NHL, tisagenlecleucel (t-cel) and axicabtagene ciloleucel (axi-cel), with anticipation that lisocabtagene maraleucel (liso-cel) will soon receive approval. This innovative therapy meets a considerable unmet need for patients who have few treatment options with the promise of long term remission. Axi-cel was approved on the basis of the ZUMA-1 trial, including 111 patients with refractory large B cell lymphoma, and demonstrated an overall response rate (ORR) of 84%, complete response (CR) rate 58% at a median follow-up of 27.1 months while median OS has not been reached.[3,4] These 3 CART products (axi-cel, t-cel, and liso-cel), have shown long-term durable responses in approximately 40% of patients.[5] The high

response rates for CART cell therapy is impressive in a highly refractory patient population for a number of reasons, including the fact that response does not seem to be associated with traditional risk factors for relapse with chemotherapy or HCT such as age, international prognostic index (IPI) score, double hit status, treatment history, or response status at the time of CART cell therapy.[3,5] Current FDA approval for t-cel and axi-cel is for the treatment of diffuse large cell lymphoma (DLBCL), transformed follicular lymphoma [t-FL], and high grade B cell lymphoma after at least two lines of systemic therapy (axi-cel is also approved for primary mediastinal B cell lymphoma [PMBCL] after two lines of therapy).
Toxicity associated with CART cell therapy can range in severity, timing and can be secondary to either the CART cell infusion or be secondary to subsequent immune dysregulation and immunosuppression. Cytokine release syndrome (CRS) is a generalized inflammatory response associated with serum IL-6 levels cells while the mechanism of the immune effector cell (IEC)-associated neurotoxicity syndrome (ICANS) is less well understood but may be associated with CART cell dose, burden of disease, younger age, and lymphodepletion with fludarabine.[6] In clinical trials there the median time to onset of CRS is generally 2-5 days post infusion with earlier symptoms seen with axi-cel as well as increased incidence of grade 3 and higher CRS and ICANS compared to other products. While toxicity can be managed with corticosteroids, anti IL-6 receptor antibody (tocilizumab) and intensive monitoring there is still a significant NRM rate of 15%. Recently at ASCO, Anand et al focused on the FDA adverse event reporting system and described the 636 recipients of anti-CD19 CAR-T therapy in the system: 288 patients received t-cel and 348 patients received axi-cel. Among the 636 patients who received CAR-T, there were 195 deaths, of which 95 were deemed not related to disease progression. The nonrelapse mortality rate for the whole group was 15%; for tisagenlecleucel it was 21% and for axicabtagene ciloleucel it was 10% and among the major toxicities reported were CRS, as well as hematological, cardiovascular, neurological, and infectious disease-related adverse effects.[7]
The hematopoietic cell transplantation comorbidity index (HCT-CI), a weighted index of 17 pretransplantation comorbidities, has been validated in nonmyeloablative and myeloablative allogeneic hematopoietic stem cell transplantation (allo-HCT) studies as well as specifically in patients with lymphoma and a higher HCT-CI score corresponds to higher risk of transplant related mortality (TRM) both at 100 days and at 1 year post allo-HCT.[8]
The quality and quantity of evidence available to help assess risk of NRM with CART cell therapy are limited. The sparse data reported appears to show that there are risk factors which may portend a higher risk of CRS or ICANS but that does not necessarily translate into the high overall NRM associated with this treatment. Herein, we propose a registry analysis of patients who have received CART cell therapy for a diagnosis of aggressive B cell NHL comparing the HCT-CI with individual comorbidities and disease-related factors relative to their impact on outcomes, with a specific emphasis on OS and NRM.

Patient eligibility population:

- Adult patients (age ≥18) who received CART cell therapy for LBCL between 2013-2019
- Eligible diagnosis: DLBCL, t-FL, high grade B cell lymphoma, and PMBCL
- Any lymphodepletion
- CD19 CART cell therapy with either t-cel, axi-cel or liso-cel

Data requirements: Data will be captured through CIBMTR collection forms

Sample requirements: N/A

Study Design:
Outcomes:

- Neutrophil and platelet engraftment: Neutrophil recovery defined as the first of 3 successive days with absolute neutrophil count (ANC) ≥500/µL after post-CART cell therapy nadir. Platelet recovery defined as achieving platelet counts ≥20,000/µL for at least 7 days, unsupported by transfusion. For neutrophil and platelet recovery, death without the event is considered a competing risk.
- Non-relapse mortality (NRM): Death without relapse or progression, where relapse or progression would be competing risks. Those who survive without recurrence or progression would be censored at the time of last contact.
- Relapse/progression: Progressive disease or recurrences of disease would be counted as events. NRM will be considered competing event.
- Progression-free survival (PFS): Survival without recurrence or tumor progression. Recurrence or progression of disease or death would be counted as events.
- Overall survival (OS): Time to death. Death from any cause will be considered an event.

Variables to be analyzed:

Main effect:

- HCT-CI as continuous variable

Patient-related:

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

Disease-related:

- Disease risk index (DRI)
- Prior autologous HCT (yes vs. no)
- Prior allogeneic HCT (yes vs no)
- Primary refractory vs. relapsed disease
- Number of prior therapy (before transplant): 2-3 vs. >3
- Disease status at the time of CART: chemoresponsive vs. non-responsive/refractory
- Bridging therapy prior to CART (yes/no)
- Extranodal involvement at the time of prior relapse or PD (yes / no)
- Length of prior CR1 (<= 12 vs. >12 months)
- B symptoms at the time of prior relapse or PD (yes / no)
- Volume of disease

Study design:
The study aims at assessing the impact of comorbidity evaluation in CART cell therapy recipients with aggressive B cell NHL. The HCT-CI has been integrated in transplantation-related analyses and has demonstrated the importance of risk assessment before HCT or even conventional therapies [8-11] and its utility to better select patients for different regimen intensities.[9,10]
Descriptive tables of patient, disease-, and HCT-CI-related factors will be created. Probabilities of relapse/progression, NRM, OS, and PFS will be calculated using the cumulative incidence or Kaplan-Meier methods, as appropriate. Univariate and multivariate analyses will be performed using Cox proportional hazards models to assess predictors of outcomes. The proportionality of the hazards assumption and potential interactions between the CART cell prodcut type and each factor found to be significant on univariate analysis will be tested and accounted for as indicated in multivariate analysis. A stepwise model selection approach will be used for multivariate analysis. Statistical significance will be set at the 0.1 and 0.05 levels for univariate and multivariate analysis, respectively.

Non-CIBMTR data source:
N/A

Conflicts of interest:
None

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Baseline characteristics for patients undergoing 1st CAR-T for NHL

Characteristic	N (%)
No. of patients	285
No. of centers	65
Age at infusion, by category - no. (%)	
Median (min-max)	62.09 (4.97-82.46)
< 10	1 (0.4)
10-19	1 (0.4)
20-29	5 (1.8)
30-39	13 (4.6)
40-49	28 (9.8)
50-59	75 (26.3)
60-69	116 (40.7)
≥ 70	46 (16.1)
Gender - no. (%)	
Male	194 (68.1)
Female	91 (31.9)
Recipient race - no. (%)	
White	244 (85.6)
African-American	14 (4.9)
Asian	15 (5.3)
More than one race	5 (1.8)
Not reported	7 (2.5)
Recipient ethnicity - no. (%)	
Hispanic or Latino	30 (10.5)
Non Hispanic or non-Latino	242 (84.9)
Non-resident of the U.S.	5 (1.8)
Unknown	8 (2.8)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	129 (45.3)
80	71 (24.9)
< 80	38 (13.3)
Not reported	47 (16.5)
Disease status prior to CT - no. (%)	
CR1	4 (1.4)
CR2	5 (1.8)

Characteristic	N (%)
CR3+	8 (2.8)
Relapse, 1st	72 (25.3)
Relapse, other	168 (58.9)
PIF/Untreated	26 (9.1)
Not reported	2 (0.7)
Types of prior HCTs - no. (%)	
Yes	285
Prior allo-HCT(s)	16 (5.6)
Prior auto-HCT(s)	263 (92.3)
Prior auto and allo-HCT(s)	6 (2.1)
Year of CT - no. (%)	
2016	6 (2.1)
2017	15 (5.3)
2018	180 (63.2)
2019	84 (29.5)
Commercial vs. noncommercial CAR-T product - no. (%)	
Commercial	243 (85.3)
Noncommercial	42 (14.7)
Clinically significant co-morbidity prior to CT - no. (%)	
No	87 (30.5)
Yes	185 (64.9)
Arrhythmia, any history	19 (6.7)
Cardiac, any history	27 (9.5)
Cerebrovascular disease, any history	3 (1.1)
Diabetes requiring non-diet treatment, in the last 4 week	38 (13.3)
Heart valve disease	3 (1.1)
Hepatic (mild), any history or at the time of infusion	23 (8.1)
Hepatic (moderate/severe), any history or at the time of infusion	3 (1.1)
Infection requiring antimicrobial treatment, continuation after day 0	16 (5.6)
Inflammatory bowel disease, any history	3 (1.1)
Obesity, during pre-infusion work-up period	27 (9.5)
Peptic ulcer, any history	2 (0.7)
Psychiatric disturbance requiring consult/treatment, in the last 4 weeks	51 (17.9)
Pulmonary (moderate), at the time of infusion	44 (15.4)
Pulmonary (severe), at the time of infusion	34 (11.9)

Characteristic	N (%)
Renal (moderate/severe), at the time of infusion or prior renal transplant	3 (1.1)
Rheumatologic, any history	5 (1.8)
Solid tumor (except non-melanoma skin cancer), any history	29 (10.2)
Other	23 (8.1)
Not reported	13 (4.6)

Proposal: 1911-74

Title:
A Modified Hematopoietic Stem Cell Transplantation – Comorbidity Index (HCT-CI) for Recipients of Chimeric Antigen Receptor T (CAR-T) Cell Therapy.

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Research hypothesis:
CAR-T cells have shown activity against a number of malignancies. This customized treatment uses the patient's own T lymphocytes, which are genetically modified (transfected) with a gene that encodes a chimeric antigen receptor to direct the patient's T cells against the tumor cells. The T cells are genetically modified ex vivo, expanded in a production facility, and then infused back into the patient as therapy. CAR-T cell therapy is increasingly investigated and used for treatment of hematological and solid tumors, with currently two CD19 targeted CAR-T cell products approved by the United States Food and Drug Administration (FDA).
CAR-T therapy is associated with serious complications, including potentially fatal neurologic events and cytokine release syndrome (CRS), which is a severe systemic response to the proliferation and activation of CAR-T cells. Our understanding of the toxicities following CAR-T therapy is under continued development. Previous research has shown that patient's burden of comorbidities play a large role in the morbidity and mortality seen after allogeneic hematopoietic cell transplantation. These efforts results in development of an HCT-specific comorbidity index (HCT-CI).
We propose her to test the impact of comorbidities within the HCT-CI as well as any other meaningful comorbidity information in regard to their impact on severe toxicities seen after CAR-T therapy. We will attempt to design and validate a CAR-T specific comorbidity index (CAR-T-CI).

Objectives:
- Evaluate the independent impact of individual comorbidities on development of severe toxicities after CAR-T cell therapy.
- If appropriate, assign weights to comorbidities based on their independent impact on development of severe toxicities after CAR-T cell therapy.
- If successful in developing a CAR-T-CI, validate the predictive capacity of the new model both by bootstrapping internal validation as well as in an independent validation cohort.
- Study the impact of comorbidities and/or CAR-T-CI on other outcomes (1-year survival, 1- year disease-free survival and any long-term morbidity) after CAR-T cell therapy.

Scientific justification:
CAR-T cell therapy is increasingly used to treat a number of hematologic and solid malignancies. CRS and neurotoxicity are the most common toxicities after CAR-T cell therapy. In one study using CD19 CAR T cell therapy in acute lymphoblastic leukemia (ALL), CRS of any grade was observed in 85% of patients, and was severe (grade ≥3) in 26%. One patient died with severe CRS and multi-organ failure. Severe neurotoxicity (grade ≥3) occurred in 42% of patients. Patients with higher disease burden had a higher incidence of CRS and neurotoxic events.(1) In a multicenter study (ZUMA-1) targeting patients with relapse/refractory diffuse large B cell lymphoma (DLBCL), 3 patients died during treatment, and 13% and 28%, respectively experienced grade 3-4 CRS and neurotoxicity.(2) In another multicenter study

(JULIET), patients experienced grade 3-4 CRS in 22% and neurotoxicity 12%.(3)
Various factors have been implicated in development of severe CRS including disease burden (antigen load),(4-6) defined as percentage of blast cells in bone marrow before infusion in case of ALL. The dose of CAR-T cells may also affect the severity of CRS.(7) Other contributing factors include the molecular design of the CAR (eg, CD28 versus 4-1BB as the costimulatory domain) and the nature and intensity of lymphodepletion prior to cell infusion.(4-6)
Neurotoxicity can present with various symptoms including tremor, dysgraphia, mild expressive aphasia (impaired naming), impaired attention, apraxia, and mild lethargy. In severe cases, this can progress over hours or days to global aphasia, seizures, motor weakness, incontinence, mental obtundation, increased intracranial pressure, papilledema, and cerebral edema.(8-11)
Comorbidity evaluation was introduced into risk-assessment before allogeneic HCT to improve decision-making.(12, 13) An HCT-CI was developed to accurately capture comorbidity burden before and precisely predict various outcomes after allogeneic transplants.(13-18) The index has been used extensively in risk-assessment before HCT (19-25). Patients with the highest comorbidity scores (≥ 3; about 35% of HCT recipients) were found to experience significant increases in morbidity,(15)mortality,(18, 26, 27) long-term impairments in health-related quality of life (HRQOL),(16) and use of resources(14) compared to patients with lower scores.
Comorbidities have not been tested in the field of CAR-T cell therapy. The potential impact of comorbidities on outcomes of CAR-T cell therapy could be different from that on HCT outcomes given that early toxicities rather than non-relapse mortality are the main sequels of CAR-T cell therapy. Here, we are interested to investigate whether comorbidities can expand our knowledge about the development of CRS and neurotoxicity after CAR T cell therapy. This knowledge could potentially set the stage for novel interventions to reduce the severity of these toxicities.

Study population:
Inclusion criteria:
- Recipients of CAR T-cell therapy
- All ages, diagnoses, lymphodepletion regimens are allowed

Exclusion criteria:
- None

Study outcomes:
- Primary Endpoint – grade 3-5 (where grade 5 indicates death because of toxicity) CRS/neurotoxicity as graded by either the NCI common toxicity criteria (CTC) or the American Society of Transplantation and Cellular Therapy (ASTCT) grading system.(8)
- Secondary endpoints
    - Overall survival
    - Disease-free survival

Variables to be described:
Patient-related variables:
- Recipient Age (0-19, 20-39, 40-49, 50-59, 60-69, 70 or more) years
- Recipient Gender (Male v Female)
- Race (Caucasian v African American v Hispanic v Other v Missing)
- Performance Status (80-100 v < 80 v Missing)
- HCT-CI (0 v 1-2 v ≥3)
- Comorbidities – arrhythmia, cardiac disease, cerebrovascular disease, diabetes, heart valve disease,

hepatic disease, peptic ulcer disease, infection, IBD, obesity, psychiatric disease, pulmonary disease, rheumatologic disease, prior other malignancy, other comorbidities
- History of Mechanical ventilation (yes v no v missing)
- BMI (<18.5, 18.5-30, 30-35, >35)
- Age adjusted BMI based on CDC definition (<5%ile, 5-95%ile, >95%ile)
- Smoking - number of pack years (continuous)
- Alcohol use disorders (if available)
- Disease Categorization
- Markers: C-reactive protein, ferritin, interferon-γ, soluble interleukin-2 receptor, interleukin-6.
- Diagnoses: ALL versus lymphoma/CLL versus solid cancers
- Disease burden (continuous % of blasts in BM for ALL, Deauville score or size of lymph node for lymphoma/CLL)

CAR-T cell related variables:
- CAR T cell dose (continuous)
- CAR-T costimulatory domain (if available)
- Lympho-depletion chemotherapy used

Study design:
Primary endpoint will be determined as the cumulative and added grades 3-5 CRS/neurotoxicity/any other organ toxicity over the first month after infusion of CAR-T cells. Alternatively, we could also look at the time till development of the peak toxicity per patient (whether grade 3, 4, or 5).
Primary endpoint will be determined as the binary outcome of occurrence of the peak toxicity grade (between grades 3-5 where grade 5 indicates mortality not related to primary disease) within the first month after infusion of CAR-T cells.
Descriptive statistics will be presented for the variables noted above. The primary outcome for this study will be any and peak grade 3-5 toxicities as defined by either NCI-CTC or ASTCT grading system. Using the NCI-CTC might add the benefit for accounting for toxicities other than CRS or neurotoxicity. We will attempt designing the model using either of these two outcomes and chose the model that yields the highest power for discrimination of outcomes by boostrapping internal validation. Grade 5 for either grading systems will be equivalent to mortality not related to primary disease. We will start by describing the frequencies of each HCT-CI defining comorbidity in each group of patients. Next, we will perform a stepwise multivariable (logistic for binary outcome or Poisson if counting toxicities) regression model to identify which factors affect primary endpoint accounting for the competing risk of toxicity/mortality from underlying disease.
We will separate patients randomly into a training cohort (2/3 of patients) and a validation cohort (1/3 of patients). We will initially determine the factors to be used for adjustment of impact of comorbidities on primary endpoint. All covariates described above (excluding comorbidities) will be tested in univariate analysis for their impact on primary endpoint. Factors associated with primary endpoint at $p<0.10$ will be used to construct the multivariate hazards model in which the impact of each comorbidity will be adjusted for that of all other comorbidities as well as covariates that survive the initial univariate step. Assuming we find comorbidities with HR of association with primary endpoint of >1.0 and to develop the novel CAR-T-CI we will use actual adjusted hazard ratio (HR) estimates for primary endpoint from the multivariate model. This means that actual HRs (whether 1.2, 1.9, 2.5..etc) will be converted to exactly similar weights. No attention will be made at this stage to p-value or significance as per original method to develop the HCT-CI. The CAR-T-CI Will be the sum of comorbidity weights.

The new model will be validated in an independent set of patients. We will compare the performances of all models by computing the c-statistic(28) for a continuous predictor associated with time to development of peak toxicity. For binary outcomes, we will compute the area under receiver operating characteristic curves (AUC). A value of 1.0 indicates perfect predictive discrimination, whereas a value of 0.5 indicates no ability to discriminate. Standard deviations of the c-statistics and AUCs will be estimated from 50 bootstrap samples. Statistical significance will be determined by paired t-test from the 50 bootstrap samples. Cumulative incidence curves for toxicities as well as Kaplan-Meier curves for 1-year survival will be computed for risk groups defined by the different indices.

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Baseline characteristics for patients undergoing 1st CAR-T for ALL/NHL

Characteristic	ALL	NHL	Total
No. of patients	302	885	1187
No. of centers	56	73	102
Age at infusion, by category - no. (%)			
Median (min-max)	13.58 (0.41-74.63)	62.26 (15.02-88.99)	56.81 (0.41-88.99)
< 10	96 (31.8)	0	96 (8.1)
10-19	140 (46.4)	4 (0.5)	144 (12.1)
20-29	53 (17.5)	20 (2.3)	73 (6.1)
30-39	3 (1)	44 (5)	47 (4)
40-49	2 (0.7)	92 (10.4)	94 (7.9)
50-59	3 (1)	216 (24.4)	219 (18.4)
60-69	3 (1)	335 (37.9)	338 (28.5)
≥ 70	2 (0.7)	174 (19.7)	176 (14.8)
Gender - no. (%)			
Male	179 (59.3)	569 (64.3)	748 (63)
Female	123 (40.7)	316 (35.7)	439 (37)
Recipient race - no. (%)			
White	210 (69.5)	755 (85.3)	965 (81.3)
African-American	18 (6)	43 (4.9)	61 (5.1)
Asian	12 (4)	39 (4.4)	51 (4.3)
Other	4 (1.3)	1 (0.1)	5 (0.4)
More than one race	41 (13.6)	21 (2.4)	62 (5.2)
Not reported	17 (5.6)	26 (2.9)	43 (3.6)
Recipient ethnicity - no. (%)			
Hispanic or Latino	115 (38.1)	91 (10.3)	206 (17.4)
Non Hispanic or non-Latino	158 (52.3)	743 (84)	901 (75.9)
Non-resident of the U.S.	10 (3.3)	17 (1.9)	27 (2.3)
Unknown	19 (6.3)	34 (3.8)	53 (4.5)
Karnofsky/Lansky performance score prior to CT - no. (%)			
90-100	202 (66.9)	349 (39.4)	551 (46.4)
80	49 (16.2)	259 (29.3)	308 (25.9)
< 80	37 (12.3)	158 (17.9)	195 (16.4)
Not reported	14 (4.6)	119 (13.4)	133 (11.2)
Disease status prior to CT - no. (%)			
CR1	22 (7.3)	8 (0.9)	30 (2.5)
CR2	30 (9.9)	8 (0.9)	38 (3.2)
CR3+	45 (14.9)	12 (1.4)	57 (4.8)
Relapse, 1st	76 (25.2)	220 (24.9)	296 (24.9)

Characteristic	ALL	NHL	Total
Relapse, other	80 (26.5)	288 (32.5)	368 (31)
PIF/Untreated	41 (13.6)	346 (39.1)	387 (32.6)
Not reported	8 (2.6)	3 (0.3)	11 (0.9)
Types of prior HCTs - no. (%)			
No	187 (61.9)	560 (63.3)	747 (62.9)
Yes	112 (37.1)	322 (36.4)	434 (36.6)
Prior allo-HCT(s)	101 (33.4)	21 (2.4)	122 (10.3)
Prior auto-HCT(s)	3 (1)	280 (31.6)	283 (23.8)
Prior auto and allo-HCT(s)	1 (0.3)	8 (0.9)	9 (0.8)
Not reported	7 (2.3)	13 (1.5)	20 (1.7)
Not reported	3 (1)	3 (0.3)	6 (0.5)
Year of CT - no. (%)			
2015	3 (1)	0	3 (0.3)
2016	9 (3)	10 (1.1)	19 (1.6)
2017	52 (17.2)	28 (3.2)	80 (6.7)
2018	157 (52)	537 (60.7)	694 (58.5)
2019	81 (26.8)	310 (35)	391 (32.9)
Commercial vs. noncommercial CAR-T product - no. (%)			
Commercial	208 (68.9)	816 (92.2)	1024 (86.3)
Noncommercial	94 (31.1)	69 (7.8)	163 (13.7)
Clinically significant co-morbidity prior to CT - no. (%)			
No	142 (47)	280 (31.6)	422 (35.6)
Yes	137 (45.4)	547 (61.8)	684 (57.6)
Arrhythmia, any history	2 (0.7)	52 (5.9)	54 (4.5)
Cardiac, any history	9 (3)	75 (8.5)	84 (7.1)
Cerebrovascular disease, any history	9 (3)	12 (1.4)	21 (1.8)
Diabetes requiring non-diet treatment, in the last 4 week	5 (1.7)	93 (10.5)	98 (8.3)
Heart valve disease	2 (0.7)	9 (1)	11 (0.9)
Hepatic (mild), any history or at the time of infusion	31 (10.3)	51 (5.8)	82 (6.9)
Hepatic (moderate/severe), any history or at the time of infusion	23 (7.6)	12 (1.4)	35 (2.9)
Infection requiring antimicrobial treatment, continuation after day 0	26 (8.6)	46 (5.2)	72 (6.1)
Inflammatory bowel disease, any history	0	8 (0.9)	8 (0.7)
Obesity, during pre-infusion work-up period	24 (7.9)	75 (8.5)	99 (8.3)
Peptic ulcer, any history	0	7 (0.8)	7 (0.6)

Characteristic	ALL	NHL	Total
Psychiatric disturbance requiring consult/treatment, in the last 4 weeks	31 (10.3)	137 (15.5)	168 (14.2)
Pulmonary (moderate), at the time of infusion	17 (5.6)	129 (14.6)	146 (12.3)
Pulmonary (severe), at the time of infusion	8 (2.6)	98 (11.1)	106 (8.9)
Renal (moderate/severe), at the time of infusion or prior renal transplant	0	14 (1.6)	14 (1.2)
Rheumatologic, any history	0	29 (3.3)	29 (2.4)
Solid tumor (except non-melanoma skin cancer), any history	2 (0.7)	76 (8.6)	78 (6.6)
Other	30 (9.9)	75 (8.5)	105 (8.8)
Not reported	23 (7.6)	58 (6.6)	81 (6.8)

Proposal: 1911-77

Study Title:
A model for predicting toxicity using the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) parameters in patients with toxicity after chimeric antigen receptor (CAR) T cell therapy.

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Research hypothesis:
Cellular therapy patients' comorbidities, such as age, organ dysfunction, and other HCT-CI parameters correlate with treatment related toxicity, specifically cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.

Specific aims:
- To review clinical parameters correlating to treatment related toxicities in chimeric antigen receptor (CAR) T cell recipients for B cell malignancies.
- To formulate a risk stratification system for patients undergoing CAR T therapy.
- To validate the risk stratification system using a large cohort of patients.

Scientific impact:
The development of a risk stratification score for patients undergoing CAR T therapy will enable a better prognostication of these patients, and allow for development of preventative strategies for patients at risk of major treatment related complications.

Scientific justification:
Clinical trials using CAR-T cell therapy in CD19 positive hematological malignancies have shown promising results in heavily pre-treated patient cohorts. However, severe toxicity has been associated with the treatment, manifesting as a cytokine release syndrome (CRS) alone or in combination with Immune effector cell-associated neurotoxicity syndrome (ICANS). CRS is an immune mediated syndrome characterized by fever, hypotension, as well as hypoxia due to a cytokine storm caused by the expansion of the effector cells and secretion of inflammatory cytokines by the T cells and the associated monocytes and macrophages(1). ICANS's mechanism is thought to be linked to endothelial activation and disruption of the blood-brain barrier, correlating with cytokine levels as well as CAR-T cell expansion(2). The clinical picture is a deterioration in neurological functions, ranging from aphasia and difficulty concentrating, and in some cases leading to a depressed level of consciousness, seizures and even raised intracranial pressure(3). Psychiatric disturbances such as delirium have also been described in CD19 directed CAR-T treated patients, as well as encephalopathy(4). Grades $\geq$3 CRS (13 to 46 %)(5-9) and ICANs (12 to 42%)(5-7) have been reported in patients with hematologic cancers treated with CAR-T cells, with a 0-5% mortality rate associated with the toxicities(5-10).
The response rate for older adults receiving CAR-T cell therapy appears to be similar to the younger age group(11) . An abstract looking into the general safety profile of the older adults getting Axicabtagene Ciloleucel, compared to the younger patients- did not show major differences between the 2 groups- with the CRS rates of 82% vs 90.9% for the older and younger cohorts respectively(12). The grade 3 or

higher rates, appear not to differ significantly either, with 18% vs 11% (3 vs 5 patients) respectively. The ICANS rates were - 58.8% vs 70.5% and the grade 3 or higher rates were 29% vs 38.6% respectively. High disease burden and higher cytokine levels have been associated with severe CRS yet the correlation with other comorbidities is still unclear (13, 14). In hematopoietic stem cell transplantation (HCT), a comorbidity index score, HCT comorbidity index (HCT-CI) has been validated as a prognostic tool for transplant morbidity and mortality (15, 16). Age has later been added to the score as an additional prognostic marker (17). However, there is no established mortality or morbidity risk prognostication score for CRS or ICANS in CAR-T patients, rendering their prediction and prevention a difficult task.
Our group is currently studying our local CAR T cohort , and it is our intention to find possible correlations between comorbidities, such as age, organ dysfunction, and other parameters as outlined in the HCT-CI to identify possible predictive markers for severe toxicity, thus formulating and validating a prognostic score for patients undergoing CAR T therapy. Such a score may inform clinicians as to which subset of patients may be able to receive therapy outpatient, or who may benefit from prophylactic therapy to minimize toxicity.

Patient eligibility population:

- All adult patients over the age of 18 who have received FDA approved CAR T therapy for hematological malignancies.

Data requirements:

- Standard demographics
- HCT- CI- Scale parameters prior to transplant (section 253 on collection form 4000).
- Blood tests from30 days prior to transplant- until day 90 post transplant and follow-up : WBC count and differential, including ALC, ANC. Platelets, hemoglobin, Chemistry (including creatinine, liver enzymes, bilirubin, albumin), viral panels, ferritin, CRP, soluble IL2 receptor, triglycerides, cytokine panels taken during hospitalization.
- CSF cell counts, chemistry, and cytokine levels.
- Disease status, MRD data, previous lines of therapy, effector cell dose at transplant, induction chemotherapy, concurrent medications.
- Post Treatment: Response, neuro toxicity- grade and score, length in days, CRS (grade, length), management (medication- Toci, steroids, and cumulative dose), length of hospitalization, progression, death: date and cause of death.

Supplemental data:
N\A

Sample requirements:
N\A

Non-CIBMTR data source:
N\A

Study design:
We plan to develop and validate a model for prediction of CAR T related toxicity using CIBMTR data. The study will divide the patient population into two cohorts- one for prognostic score development and one as a validation cohort for the prognostic score. For model development, endpoints of CRS, ICANS, and

their severity will be used. A pre-transplant multivariable analysis will be done to test for factors predicting for toxicity. The model will then be validated using the second cohort.

Conflicts of Interest:

- Dr. Shpall is on the advisory boards of Magenta, Novartis, Celgene, Adaptimmune, and Zelluna.
- All other PI's do not have any conflict of interests to report.

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Baseline characteristics for patients undergoing 1st CAR-T for ALL/NHL

Characteristic	ALL	NHL	Total
No. of patients	302	885	1187
No. of centers	56	73	102
Age at infusion, by category - no. (%)			
Median (min-max)	13.58 (0.41-74.63)	62.26 (15.02-88.99)	56.81 (0.41-88.99)
< 10	96 (31.8)	0	96 (8.1)
10-19	140 (46.4)	4 (0.5)	144 (12.1)
20-29	53 (17.5)	20 (2.3)	73 (6.1)
30-39	3 (1)	44 (5)	47 (4)
40-49	2 (0.7)	92 (10.4)	94 (7.9)
50-59	3 (1)	216 (24.4)	219 (18.4)
60-69	3 (1)	335 (37.9)	338 (28.5)
≥ 70	2 (0.7)	174 (19.7)	176 (14.8)
Gender - no. (%)			
Male	179 (59.3)	569 (64.3)	748 (63)
Female	123 (40.7)	316 (35.7)	439 (37)
Recipient race - no. (%)			
White	210 (69.5)	755 (85.3)	965 (81.3)
African-American	18 (6)	43 (4.9)	61 (5.1)
Asian	12 (4)	39 (4.4)	51 (4.3)
Other	4 (1.3)	1 (0.1)	5 (0.4)
More than one race	41 (13.6)	21 (2.4)	62 (5.2)
Not reported	17 (5.6)	26 (2.9)	43 (3.6)
Recipient ethnicity - no. (%)			
Hispanic or Latino	115 (38.1)	91 (10.3)	206 (17.4)
Non Hispanic or non-Latino	158 (52.3)	743 (84)	901 (75.9)
Non-resident of the U.S.	10 (3.3)	17 (1.9)	27 (2.3)
Unknown	19 (6.3)	34 (3.8)	53 (4.5)
Karnofsky/Lansky performance score prior to CT - no. (%)			
90-100	202 (66.9)	349 (39.4)	551 (46.4)
80	49 (16.2)	259 (29.3)	308 (25.9)
< 80	37 (12.3)	158 (17.9)	195 (16.4)

Characteristic	ALL	NHL	Total
Not reported	14 (4.6)	119 (13.4)	133 (11.2)
Disease status prior to CT - no. (%)			
CR1	22 (7.3)	8 (0.9)	30 (2.5)
CR2	30 (9.9)	8 (0.9)	38 (3.2)
CR3+	45 (14.9)	12 (1.4)	57 (4.8)
Relapse, 1st	76 (25.2)	220 (24.9)	296 (24.9)
Relapse, other	80 (26.5)	288 (32.5)	368 (31)
PIF/Untreated	41 (13.6)	346 (39.1)	387 (32.6)
Not reported	8 (2.6)	3 (0.3)	11 (0.9)
Types of prior HCTs - no. (%)			
No	187 (61.9)	560 (63.3)	747 (62.9)
Yes	112 (37.1)	322 (36.4)	434 (36.6)
Prior allo-HCT(s)	101 (33.4)	21 (2.4)	122 (10.3)
Prior auto-HCT(s)	3 (1)	280 (31.6)	283 (23.8)
Prior auto and allo-HCT(s)	1 (0.3)	8 (0.9)	9 (0.8)
Not reported	7 (2.3)	13 (1.5)	20 (1.7)
Not reported	3 (1)	3 (0.3)	6 (0.5)
Year of CT - no. (%)			
2015	3 (1)	0	3 (0.3)
2016	9 (3)	10 (1.1)	19 (1.6)
2017	52 (17.2)	28 (3.2)	80 (6.7)
2018	157 (52)	537 (60.7)	694 (58.5)
2019	81 (26.8)	310 (35)	391 (32.9)
Commercial vs. noncommercial CAR-T product - no. (%)			
Commercial	208 (68.9)	816 (92.2)	1024 (86.3)
Noncommercial	94 (31.1)	69 (7.8)	163 (13.7)
Clinically significant co-morbidity prior to CT - no. (%)			
No	142 (47)	280 (31.6)	422 (35.6)
Yes	137 (45.4)	547 (61.8)	684 (57.6)
Arrhythmia, any history	2 (0.7)	52 (5.9)	54 (4.5)
Cardiac, any history	9 (3)	75 (8.5)	84 (7.1)
Cerebrovascular disease, any history	9 (3)	12 (1.4)	21 (1.8)
Diabetes requiring non-diet treatment, in the last 4 week	5 (1.7)	93 (10.5)	98 (8.3)

Characteristic	ALL	NHL	Total
Heart valve disease	2 (0.7)	9 (1)	11 (0.9)
Hepatic (mild), any history or at the time of infusion	31 (10.3)	51 (5.8)	82 (6.9)
Hepatic (moderate/severe), any history or at the time of infusion	23 (7.6)	12 (1.4)	35 (2.9)
Infection requiring antimicrobial treatment, continuation after day 0	26 (8.6)	46 (5.2)	72 (6.1)
Inflammatory bowel disease, any history	0	8 (0.9)	8 (0.7)
Obesity, during pre-infusion work-up period	24 (7.9)	75 (8.5)	99 (8.3)
Peptic ulcer, any history	0	7 (0.8)	7 (0.6)
Psychiatric disturbance requiring consult/treatment, in the last 4 weeks	31 (10.3)	137 (15.5)	168 (14.2)
Pulmonary (moderate), at the time of infusion	17 (5.6)	129 (14.6)	146 (12.3)
Pulmonary (severe), at the time of infusion	8 (2.6)	98 (11.1)	106 (8.9)
Renal (moderate/severe), at the time of infusion or prior renal transplant	0	14 (1.6)	14 (1.2)
Rheumatologic, any history	0	29 (3.3)	29 (2.4)
Solid tumor (except non-melanoma skin cancer), any history	2 (0.7)	76 (8.6)	78 (6.6)
Other	30 (9.9)	75 (8.5)	105 (8.8)
Not reported	23 (7.6)	58 (6.6)	81 (6.8)

Proposal: 1911-120

Title:
Prognostic impact of comorbidities and on outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL) receiving chimeric antigen receptor T (CAR-T) cell therapy

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Research hypothesis:
Do comorbidities as assessed by an augmented comorbidity/age index with the incorporation of other lymphoma specific biomarkers (LDH and CRP) predict morbidity and mortality risks following CAR T-cell therapy for r/r DLBCL?

Specific aims:
Test the association between pretreatment comorbidity burden as assessed by an augmented comorbidity/age index (1)(2), combined with other specific biomarkers; CRP and LDH, and the development, grade, and organ affection of cytokine release syndrome (CRS) and development and grade of neurotoxicity and non-relapse mortality (NRM) incidences and survival following CAR T-cell therapy for r/r DLBCL

Scientific impact:
Specific eligibility criteria for patients with r/r DLBCL to receive CAR T cell therapy are not yet well defined outside of clinical trials. Risk stratification based on patient specific comorbidities is of prime importance given the associated morbidity and mortality risks. Comorbidity assessment may further refine eligibility criteria and risk stratification process particularly with the anticipated growing indications. Additionally, some of the comorbidities could be the target for preemptive pretreatment interventions to alleviate the subsequent adverse events. Moreover, higher comorbidities burden as assessed using the hematopoietic cell transplantation-specific comorbidity index (HCT-CI) scores have been shown to be associated with poor quality of life and patient reported outcomes following allogeneic HCT (3) and whether same is true following CAR T cell therapy is yet to be investigated. This research should provide additional data for proper patient selection and for counseling patients prior considering for this treatment and aid in design of future prospective studies targeting specific comorbid conditions for risk mitigation prior to receiving this therapy. A cutoff score of comorbidity/age index may be set as criterion in future clinical trials to guide proper patient selection based on risk benefit assessment.

Scientific justification:
CAR T-cell therapy is breakthrough treatment modality for patients with relapsed refractory non-Hodgkin lymphoma (4). However this treatment is associated with significant adverse events. Less is known regarding the impact of patient related comorbid conditions as a predictor of toxicity and subsequent morbidity and mortality. The HCT-CI is a validated tool for prognostication of post-allogeneic HCT morbidity and NRM risks (5); however there is currently very limited available data whether it could be of prognostic value for outcomes of recipients of CAR T-cell therapy (6). Recently, an augmented comorbidity/age index incorporating the serum values of 3 biomarkers, albumin, ferritin and platelets, has been shown to better prognosticate for outcomes of allogeneic HCT from alternative donors (2). An additional layer of prognostication could be obtained by the addition of scores for serum values of pretreatment CRP and LDH as lymphoma specific biomarkers to the comorbidity/age index and developing a single model specific for recipients of CAR T-cell therapy.

Patient eligibility population:
All patients aged above 18 years with a diagnosis of r/r DLBCL who received their first CAR T-cell therapy infusion reported to CIBMTR database between FDA approval in August 2017 and December 2019 will be eligible for the purpose of this analysis. A minimum of 200 patients will be essential for detection of significant differences between subgroups of HCT-CI scores as previously published (7).

Data requirements:
All relevant variables will be extracted using forms 2018 (Hodgkin and Non-Hodgkin Lymphoma (LYM) Pre-Infusion Data), 4000 (Cellular Therapy Essential Data Pre-Infusion Form) and 4100 (Cellular Therapy Essential Data Follow-Up Form). Baseline patients and disease specific characteristics will include, age, ECOG status, disease status at time of infusion, number of prior lines of treatment, histologic subtype, previous transplant, comorbidities, with calculation of augmented comorbidity/age score, and serum values of LDH, CRP, albumin, ferritin, platelets.

Sample requirements:
None

Study design:
Data will be retrospectively collected for augmented comorbidity/age index variables and other baseline patients' and lymphoma specific characteristics. The impact of LDH and CRP on NRM will be assessed and scores will be assigned based on hazards of association with NRM as previously described similar to development of the original HCT-CI (5). A CAR T specific comorbidity model that incorporates scores for LDH and CRP values together with the augmented comorbidity/age index will be tested using multivariable models adjusted for baseline variables to assess hazards of higher versus lower model scores on CRS, neurotoxcity, NRM, progression free survival, overall survival. C-statistics estimates for NRM will be utilized to assess the prognostic ability of the augmented comorbidity/age index versus the index incorporating the addition of scores for LDH and CRP.

Non-CIBMTR data source:
None

Conflicts of interest:
Kite/Gilead: advisory board participation
Celgene: advisory board participation

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Baseline characteristics for patients undergoing 1st CAR-T for DLBCL

Characteristic	N (%)
No. of patients	256
No. of centers	62
Age at infusion, by category - no. (%)	
Median (min-max)	62.31 (21.89-82.46)
20-29	5 (2)
30-39	13 (5.1)
40-49	25 (9.8)
50-59	66 (25.8)
60-69	103 (40.2)
≥ 70	44 (17.2)
Gender - no. (%)	
Male	171 (66.8)
Female	85 (33.2)
Recipient race - no. (%)	
White	219 (85.5)
African-American	12 (4.7)
Asian	15 (5.9)
More than one race	4 (1.6)
Not reported	6 (2.3)
Recipient ethnicity - no. (%)	
Hispanic or Latino	27 (10.5)
Non Hispanic or non-Latino	218 (85.2)
Non-resident of the U.S.	5 (2)
Unknown	6 (2.3)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	113 (44.1)
80	66 (25.8)
< 80	37 (14.5)
Not reported	40 (15.6)
Disease status prior to CT - no. (%)	
CR1	3 (1.2)
CR2	4 (1.6)
CR3+	8 (3.1)

Characteristic	N (%)
Relapse, 1st	63 (24.6)
Relapse, other	155 (60.5)
PIF/Untreated	22 (8.6)
Not reported	1 (0.4)
Types of prior HCTs - no. (%)	
Yes	256
Prior allo-HCT(s)	14 (5.5)
Prior auto-HCT(s)	239 (93.4)
Prior auto and allo-HCT(s)	3 (1.2)
Year of CT - no. (%)	
2016	5 (2)
2017	11 (4.3)
2018	162 (63.3)
2019	78 (30.5)
Commercial vs. noncommercial CAR-T product - no. (%)	
Commercial	224 (87.5)
Noncommercial	32 (12.5)
Clinically significant co-morbidity prior to CT - no. (%)	
No	73 (28.5)
Yes	171 (66.8)
Arrhythmia, any history	18 (7)
Cardiac, any history	25 (9.8)
Cerebrovascular disease, any history	3 (1.2)
Diabetes requiring non-diet treatment, in the last 4 week	35 (13.7)
Heart valve disease	3 (1.2)
Hepatic (mild), any history or at the time of infusion	22 (8.6)
Hepatic (moderate/severe), any history or at the time of infusion	2 (0.8)
Infection requiring antimicrobial treatment, continuation after day 0	16 (6.3)
Inflammatory bowel disease, any history	3 (1.2)
Obesity, during pre-infusion work-up period	27 (10.5)
Peptic ulcer, any history	1 (0.4)
Psychiatric disturbance requiring consult/treatment, in the last 4 weeks	47 (18.4)
Pulmonary (moderate), at the time of infusion	42 (16.4)
Pulmonary (severe), at the time of infusion	32 (12.5)
Renal (moderate/severe), at the time of infusion or prior renal transplant	3 (1.2)

Characteristic	N (%)
Rheumatologic, any history	5 (2)
Solid tumor (except non-melanoma skin cancer), any history	26 (10.2)
Other	21 (8.2)
Not reported	12 (4.7)

Proposal: 1911-258

Title:
Development of comoribidity scores that could impact the treatment related mortality and overall survival in patients receiving CD19 directed chimeric antigen receptor (CAR) T-cell therapy

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Hypothesis:
Comorbidities influence treatment related mortality (TRM) and overall survival (OS) in patients receiving CD19 directed CAR T-cell therapy

Specific aims:
To develop the comorbidity scores predictive of TRM and OS in patients receiving CD19 directed CAR T-cell therapy

Scientific impact:
This study will help identify comorbidity scores that may predict TRM and OS in patients receiving CD19 directed CAR T-cell therapy. The CAR-T comorbidity index ("CAR-T-CI") could help select appropriate patients for CAR-T cell therapy and serve as a counseling tool.

Scientific justification:
CAR T-cell therapy has revolutionized the treatment of relapsed/refractory B-cell non-Hodgkin lymphoma (NHL) and acute lymphoblastic leukemia (ALL). Axicabtagene ciloleucel and Tisagenlecleucel are currently approved CAR T-cell therapies by the US Food and Drug Administration (FDA), having demonstrated response rates of about 50-80% [1-3].
Organ dysfunctions and comorbidities have been associated with the outcome of treatment for a given primary disease and in particular cancer [4]. In 2005, a hematopoietic cell transplantation-comorbidity index (HCT-CI) was introduced as a measure of organ dysfunctions that was suited for recipients of HCT [5]. The hematopoietic cell transplantation-comorbidity index (HCT-CI) is a comorbidity index that has been shown to sensitively capture the prevalence and magnitude of severity of various organ impairments before HCT and to provide valuable prognostic information after HCT [6].
Pivotal trials with CAR T-cell therapy for B cell ALL and B cell NHL reported TRM of about 2-10% and did not identify any comorbidities that have a statistically significant impact on the depth or duration of response [1-3]. Although these pivotal clinical trials have only included patients with adequate performance status and organ function, the real world experience with CAR T-cell therapy revealed that more than half of the patients that would have otherwise been excluded in the trial received CAR T-cell therapy, and experienced similar efficacy and toxicity [7]. Thus far, the impact of individual comorbidities on the survival outcomes after CAR-T remains undetermined. In the absence of any clearly defined comorbidity index that predicts TRM from CAR T-cell therapy, there is an unmet clinical need to evaluate the impact of comorbidities on TRM and OS in patients undergoing CAR T-cell therapy. We propose to develop the comorbidity scoring system for the CAR T-cell therapy that could predict TRM and OS. This tool would help with decision making process and appropriate patient selection for CAR T-cell therapy in patients with lymphoid malignancies.

Patient eligibility population:

Inclusion criteria:
All patients (age ≥ 3) who received CD19 directed CAR T-cell therapy for B cell acute Lymphoblastic Leukemia (ALL) and B-cell NHL (including diffuse large B cell lymphoma, transformed follicular lymphoma and primary mediastinal B cell lymphoma]

Exclusion criteria:
None

Variables to be described: [Bold variables to be included in multivariate analysis]
Patient related:

- **Age at CAR T-cell therapy:** continuous and categorical by decade
- **Gender:** male vs. female
- **Race:** Caucasian vs. African American vs. Asian/Pacific Islander vs. Hispanic vs. Others vs. missing
- **Ethnicity:** Hispanic or Latino vs. Non-Hispanic or non-Latino vs. non-resident of the U.S.
- ECOG Performance status / Karnofsky performance score
- Serum creatinine at the start of lymphodepletion:

Disease-related:

- **Disease histology:** B cell ALL vs. B-cell NHL (diffuse large B cell lymphoma, transformed follicular lymphoma and primary mediastinal B cell NHL)
- lymphoma
- Disease stage at diagnosis (for NHL only): I-II vs. III-IV
- Refined disease risk index (DRI): low vs. intermediate vs. high vs. very high risk
- International Prognostic Index (IPI) score at diagnosis: 0-3
- Presence of CNS disease at diagnosis: yes vs. no
- Prior lines of chemotherapy: 0-1, 2, 3, 4+
- Prior radiation therapy: yes vs. no
- **Prior autologous stem cell transplant**: yes vs. no
- **Prior allogeneic stem cell transplant**: yes vs. no
- Disease status prior to CAR T-cell therapy: CR, PR, SD, or PD for NHL; CR, CRi, PR, or PD for ALL
- Baseline markers of inflammation (ferritin, CRP) prior to CAR T-cell infusion: continuous and categorical (to be determined)

Comorbidities:
yes vs. no: HCT-CI score will be used for the initial analysis and individual comorbidities will be analyzed for the development of a new comorbidity score

- **History of arrhythmia**
- **Cardiac disease** [coronary artery disease requiring medical treatment, stent or coronary artery bypass grafting (CABG), congestive heart failure with left ventricular ejection fraction <45%]
- Inflammatory bowel disease [Crohn's disease or ulcerative colitis]
- **Diabetes mellitus**
- **Psychiatric disorders**
- **Neurological disorders** (including cerebrovascular ischemia/hemorrhage, multiple sclerosis, dementia, Parkinsonism)
- **Hepatic dysfunction** [chronic hepatitis/liver cirrhosis]
- **Obesity** [body mass index (BMI) more than 35 kg/m^2]
- **Infection** requiring continuation of antibiotic after day 0 (i.e., CAR-T infusion)

- **Rheumatological disease** [systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), polymyositis, mixed connective tissue disease]
- **Peptic ulcer disease**
- **Renal dysfunction** [serum creatinine greater than 2 mg/dL, on dialysis, or prior renal transplant]
- **Pulmonary dysfunction** [DLCO and/or FEV1 66-80% or dyspnea on slight activity vs DLCO and/or FEV1 <65% or dyspnea at rest or requiring oxygen]
- **Prior solid tumor** excluding non-melanoma skin cancer
- HCT-CI index: 0 vs. 1 vs. 2 vs. 3+

CAR T-cell therapy related:

- Time from diagnosis to CAR T-cell therapy
- **Use of bridging therapy**
- Type of bridging therapy
- **Type of lympho-depleting chemotherapy used**

Data requirements:
No additional data collection requested.

Sample requirements:
No samples requested.

Study Design:
Outcomes:

- Response: Response rates at the day 30, 3 months and 6 months post CAR T-cell therapy based on bone marrow biopsy with morphological and flow cytometry analysis, CT and/or PET-CT
- Cytokine release syndrome (CRS) and neurotoxicity: Occurrence of grade 1-5 CRS and neurotoxicity. Lee criteria or modified Lee criteria will be used for the CRS grading. CTCAE v4 or CARTOX grading will be used for grading of neurotoxicity.
    - The use of tocilizumab and corticosteroids will be described for each grade of CRS and neurotoxicity
- Overall survival (OS): Time from CAR T-cell infusion to death due to any cause. Patients will be censored at the time of last follow up.
- Progression free survival (PFS): Time from CAR T-cell infusion to death or relapse. Patients will be censored at the time of last follow up.
- CAR T-cell treatment-related mortality (TRM): Death due to any cause in the first 28 days or death due to conditions other than disease relapse or progression beyond 28 days. Events will be summarized by the cumulative incidence estimate with relapse as a competing risk.
- Relapse: Development of relapse as defined by the CIBMTR. The event will be summarized by the cumulative incidence estimate. TRM will be a competing risk for this outcome.
- Hemophagocytic lymphohistiocytosis (HLH)/mast cell activation syndrome (MAS): Cumulative incidence of HLH or MAS after CAR T-cell therapy
- Causes of death: causes of death will be summarized

This retrospective study will determine the impact of comorbidities on the outcomes of CAR T-cell therapy in B-cell NHL and ALL. Patient-, disease-, and CAR T-cell therapy-related factors will be compared using the Chi-square test for categorical and the Kruskal-Wallis test for continuous variables according to the historical HCT-CI indices. OS and PFS probabilities will be estimated by Kaplan-Meier method. Comparison of survival curves will be performed with the log-rank test and point-wise estimates at 3

months, 6 months, 1 year and 2 years. Probabilities of CAR- T-cell related TRM, and disease relapse/progression will be calculated using cumulative incidence curves to accommodate competing risks. Comparison of incidence curves will be performed using the Fine and Gray method. Causes of death will be descriptive outcomes.
Multivariate analysis of OS, PFS, CAR-T related TRM, CRS and neurotoxicity will be performed using Cox proportional hazards model. Variables tested in the multivariate analysis are listed above and will be tested in a forward stepwise approach. The final model will include covariates associated with the outcome at a level of 0.05. Tests for interactions may be considered.
In order to develop a new CAR-T related comorbidity index (CAR-CI), the overall study cohort will be randomly divided in half for the training set and the validation set. The multivariate Cox regression models will be built for the discovery cohort for all of the same outcomes but using individual comorbid medical conditions. On the basis of the magnitude of hazard ratios (HRs) associated with variables, a weighted score will be assigned to the factors positively associated with variables for each outcomes in the training set. These results will be confirmed in the validation cohort.

Non-CIBMTR data source:
N/A

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Baseline characteristics for patients undergoing 1st CAR-T for ALL/NHL

Characteristic	ALL	NHL	Total
No. of patients	302	885	1187
No. of centers	56	73	102
Age at infusion, by category - no. (%)			
Median (min-max)	13.58 (0.41-74.63)	62.26 (15.02-88.99)	56.81 (0.41-88.99)
< 10	96 (31.8)	0	96 (8.1)
10-19	140 (46.4)	4 (0.5)	144 (12.1)
20-29	53 (17.5)	20 (2.3)	73 (6.1)
30-39	3 (1)	44 (5)	47 (4)
40-49	2 (0.7)	92 (10.4)	94 (7.9)
50-59	3 (1)	216 (24.4)	219 (18.4)
60-69	3 (1)	335 (37.9)	338 (28.5)
≥ 70	2 (0.7)	174 (19.7)	176 (14.8)
Gender - no. (%)			
Male	179 (59.3)	569 (64.3)	748 (63)
Female	123 (40.7)	316 (35.7)	439 (37)
Recipient race - no. (%)			
White	210 (69.5)	755 (85.3)	965 (81.3)
African-American	18 (6)	43 (4.9)	61 (5.1)
Asian	12 (4)	39 (4.4)	51 (4.3)
Other	4 (1.3)	1 (0.1)	5 (0.4)
More than one race	41 (13.6)	21 (2.4)	62 (5.2)
Not reported	17 (5.6)	26 (2.9)	43 (3.6)
Recipient ethnicity - no. (%)			
Hispanic or Latino	115 (38.1)	91 (10.3)	206 (17.4)
Non Hispanic or non-Latino	158 (52.3)	743 (84)	901 (75.9)
Non-resident of the U.S.	10 (3.3)	17 (1.9)	27 (2.3)
Unknown	19 (6.3)	34 (3.8)	53 (4.5)
Karnofsky/Lansky performance score prior to CT - no. (%)			
90-100	202 (66.9)	349 (39.4)	551 (46.4)
80	49 (16.2)	259 (29.3)	308 (25.9)
< 80	37 (12.3)	158 (17.9)	195 (16.4)

Characteristic	ALL	NHL	Total
Not reported	14 (4.6)	119 (13.4)	133 (11.2)
Disease status prior to CT - no. (%)			
CR1	22 (7.3)	8 (0.9)	30 (2.5)
CR2	30 (9.9)	8 (0.9)	38 (3.2)
CR3+	45 (14.9)	12 (1.4)	57 (4.8)
Relapse, 1st	76 (25.2)	220 (24.9)	296 (24.9)
Relapse, other	80 (26.5)	288 (32.5)	368 (31)
PIF/Untreated	41 (13.6)	346 (39.1)	387 (32.6)
Not reported	8 (2.6)	3 (0.3)	11 (0.9)
Types of prior HCTs - no. (%)			
No	187 (61.9)	560 (63.3)	747 (62.9)
Yes	112 (37.1)	322 (36.4)	434 (36.6)
Prior allo-HCT(s)	101 (33.4)	21 (2.4)	122 (10.3)
Prior auto-HCT(s)	3 (1)	280 (31.6)	283 (23.8)
Prior auto and allo-HCT(s)	1 (0.3)	8 (0.9)	9 (0.8)
Not reported	7 (2.3)	13 (1.5)	20 (1.7)
Not reported	3 (1)	3 (0.3)	6 (0.5)
Year of CT - no. (%)			
2015	3 (1)	0	3 (0.3)
2016	9 (3)	10 (1.1)	19 (1.6)
2017	52 (17.2)	28 (3.2)	80 (6.7)
2018	157 (52)	537 (60.7)	694 (58.5)
2019	81 (26.8)	310 (35)	391 (32.9)
Commercial vs. noncommercial CAR-T product - no. (%)			
Commercial	208 (68.9)	816 (92.2)	1024 (86.3)
Noncommercial	94 (31.1)	69 (7.8)	163 (13.7)
Clinically significant co-morbidity prior to CT - no. (%)			
No	142 (47)	280 (31.6)	422 (35.6)
Yes	137 (45.4)	547 (61.8)	684 (57.6)
Arrhythmia, any history	2 (0.7)	52 (5.9)	54 (4.5)
Cardiac, any history	9 (3)	75 (8.5)	84 (7.1)
Cerebrovascular disease, any history	9 (3)	12 (1.4)	21 (1.8)
Diabetes requiring non-diet treatment, in the last 4 week	5 (1.7)	93 (10.5)	98 (8.3)

Characteristic	ALL	NHL	Total
Heart valve disease	2 (0.7)	9 (1)	11 (0.9)
Hepatic (mild), any history or at the time of infusion	31 (10.3)	51 (5.8)	82 (6.9)
Hepatic (moderate/severe), any history or at the time of infusion	23 (7.6)	12 (1.4)	35 (2.9)
Infection requiring antimicrobial treatment, continuation after day 0	26 (8.6)	46 (5.2)	72 (6.1)
Inflammatory bowel disease, any history	0	8 (0.9)	8 (0.7)
Obesity, during pre-infusion work-up period	24 (7.9)	75 (8.5)	99 (8.3)
Peptic ulcer, any history	0	7 (0.8)	7 (0.6)
Psychiatric disturbance requiring consult/treatment, in the last 4 weeks	31 (10.3)	137 (15.5)	168 (14.2)
Pulmonary (moderate), at the time of infusion	17 (5.6)	129 (14.6)	146 (12.3)
Pulmonary (severe), at the time of infusion	8 (2.6)	98 (11.1)	106 (8.9)
Renal (moderate/severe), at the time of infusion or prior renal transplant	0	14 (1.6)	14 (1.2)
Rheumatologic, any history	0	29 (3.3)	29 (2.4)
Solid tumor (except non-melanoma skin cancer), any history	2 (0.7)	76 (8.6)	78 (6.6)
Other	30 (9.9)	75 (8.5)	105 (8.8)
Not reported	23 (7.6)	58 (6.6)	81 (6.8)

Proposal: 1911-63

Title:
Pre-infusion Risk Score for Incidence of Cytokine Release Syndrome and CAR Related Encephalopathy Syndrome in Patients Treated with CAR T-Cell Therapies

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Research hypothesis:
A risk score utilizing pre-infusion clinical characteristics can estimate patients' risk of developing cytokine release syndrome (CRS) and CAR related encephalopathy syndrome (CRES) following treatment with anti-CD19 chimeric antigen receptor T-cell therapies.

Specific aims:
- Characterize the incidence and severity of cytokine release syndrome and CAR related encephalopathy syndrome among patients treated with CAR T-cell therapies
- Characterize the morbidity and mortality associated with development of cytokine release syndrome and CAR related encephalopathy syndrome
- Identify pre-infusion clinical characteristics which are predictive of development of severe cytokine release syndrome among patients treated with CAR T-cell therapies.
- Identify pre-infusion clinical characteristics which are predictive of development of severe CAR related encephalopathy syndrome among patients treated with CAR T-cell therapies
- Characterize the relative magnitude of risk associated with clinical characteristics identified in aims #3 and #4
- Utilize relative risk magnitudes to create a risk score capable of assigning patients an estimated risk of cytokine release syndrome and CAR related encephalopathy syndrome
- Validate the risk score from #6 using a cohort of patients independent from that used to construct the risk score.
- Identify subsets of patients at low risk, intermediate risk, and high risk for cytokine release syndrome and/or CAR related encephalopathy syndrome

Scientific impact:
A risk score that accurately stratifies patients by likelihood of developing significant CRS and/or CRES would allow clinicians to better individualize treatment and monitoring strategies for patients. This could assist in the patient selection process, pre-infusion treatment strategies, CAR T dosing strategy, or post-infusion monitoring strategy. Additionally, interventional studies to prevent CRS and CRES via prophylactic procedures would greatly benefit from identification of a cohort that is very likely to develop these complications, whereas patients at very low risk would be less likely to benefit from the proposed intervention.

Scientific justification:
Cytokine release syndrome (CRS) and CAR related encephalopathy syndrome (CRES) are consequences of the vigorous generalized immune activation following infusion and in vivo expansion of anti-CD19 CAR T-cells.[1,2] These characteristic sequelae of CAR T-cell therapy are associated with significant morbidity and rarely may result in death.

CRS and CRES are early complications of CAR T-cell therapy, occurring on median at day +1-2, and generally not after 3 weeks.[3-5] Cytokine release syndrome of any grade was common in the ZUMA-1 trial, with overall incidence of 93%. However, the incidence of grade 3 or higher CRS was considerably lower, at 13%.[3] The overall incidence of CRS among patients treated with tisagenlecleucel in the Juliet trial overall was 58%, and was 14% for grade 3 or higher CRS.[4] Among patients treated with axicabtagene, the ZUMA-1 trial reported incidence of 64% for any neurologic complications, and 28% for grade 3 or higher neurologic complications. The rate of any grade neurologic events in patients treated with tisagenlecleucel in the Juliet trial was 21%, and was 7% for grade 3 or higher. It must be noted that the cross trial comparison of incidences is imperfect, as the grading scales used in each trial differed; the UPenn scale was used for the Juliet trial and the Lee criteria was used for the ZUMA-1 trial.[6] Reports of the use of axicabtagene ciloleucel outside the clinical trial context has demonstrated rates of CRS similar to the ZUMA-1 study (7% for grade 3 or higher CRS, and 31% for grade 3 or higher CRES).[7]
The inflammatory cascade causing CRS and CRES appear to begin early in the post-infusion period. Patients with grade 4 or greater CRS had onset of first fever on median 0.35 days from the infusion of CAR T-cells.[8] It may thus be necessary to identify patients at high risk prior to CAR-T infusion to effectively begin prophylactic measures.
Development of CRS and CRES has significant consequences for patients. In terms of mortality, of 636 patients treated with anti-CD19 CAR T-cell therapies reported to the FDA Adverse Events Reporting System (FAERS), 95 experienced non-relapse mortality. The cause of death was CRS related in 32 and was neurological in 47, a substantial portion of which are likely related to CRES.[9] Additionally, development of CRS has been associated with more severe and prolonged cytopenias, increased risk of acute kidney injury (HR 4.9, 95% CI 2.4 to 9.9, p<0.001), increased risk of infectious complications(grade 0 vs 1-3 vs 4-5, HR 3.38, 95% CI 1.99-5.73).[8,10,11] A suggestive association between CRES and subsequent cognitive difficulties has been noted (OR = 3.62, p=0.07).[12]
Known risk factors identifiable prior to CAR T-cell infusion can broadly be categorized into treatment related factors, disease related factors, and patient related factors. Treatment related factors include the rate and extent of CAR T cell in vivo expansion, and the infused CAR T-cell dose,.[8] Differences in co-stimulatory domains (e.g. CD28 vs 4-1BB) may have a significant effect on incidence of CRS/CRES, though a direct comparison has not been made.[3-5] Use of a more intensely lymphodepleting conditioning regimen is also associated with higher risk of CRS/CRES, possibly via facilitation of greater CAR T-cell expansion.[8] Disease related factors include the disease burden, and by proxy the extent of exposure of antigen to the CAR T-cells.[8] Identified patient related factors include younger age or pre-existing neurologic comorbidities (for CRES specifically). Pre-infusion thrombocytopenia may increase the risk of CRS, though it has been suggested that pathophysiologically this may be a reflection of the overall tumor burden.[8]
Though several individual risk factors for CRS/CRES have been identified, aggregating them to estimate an overall risk level for individual patients remains challenging. We thus propose to construct a risk score to estimate patients' risk of CRS/CRES using pre-infusion characteristics. Identification of a population at high risk for CRS or CRES may facilitate focused study and application of prophylactic strategies to mitigate these complications. Additionally, some risk factors, such as conditioning regimen intensity or CAR T-cell dose, are potentially modifiable if risk is found to be unacceptably high. Conversely, identification of a low risk population may permit earlier de-escalation of inpatient monitoring or even outpatient monitoring in the early post CAR T-cell infusion period.

Patient eligibility population:

Inclusion criteria:

- Adult DLBCL undergoing anti CD-19 CAR T-cell therapy between Jan 2012 and July 2019

- Adult and pediatric ALL patients undergoing anti CD-19 CAR T-cell therapy between Jan 2012 and July 2019
- All disease states

Exclusion criteria:
- Patients receiving CRS/CRES prophylaxis

Data requirements:
Patient related factors:
- Age
- Gender
- Ethnicity (form 4000)
- Race (form 4000)
- Prior cellular therapy (form 4000)
- Prior HCT (form 4000)
    - Auto, Allo
- Cardiovascular disease (form 4000)
- Neurologic disease (form 4000)
- Pulmonary disease (form 4000)
- Infection pre-infusion (form 4000 51-57)
- Performance status (form 4000)

Baseline (pre-infusion) biomarkers:
- Ferritin
- C reactive protein
- ESR
- WBC
- LDH
- Absolute neutrophil count
- Absolute lymphocyte count
- Platelet count
- Hgb

Disease related factors:
- Disease / indication for CAR T
    - DLBCL, ALL
- Disease status prior to cellular therapy:: CR vs not in CR (form 4000)
    - For ALL:
        - MRD by PCR assessed? (form 4000)
        - MRD by flow assessed? (form 4000)
        - Detectable disease by radiological assessment? (form 4000)
        - Bone marrow involvement pre-infusion (%)
        - Circulating blast #
        - Site of relapsed disease (form 2011, #55)
            - CNS
                - Parynchema

        - CSF
    - Testes/ovaries
    - Other
- For DLBCL:
    - KI-67 @ diagnosis
    - Disease stage
    - Cytogenetics @ diagnosis:
        - BCL-2 rearrangement
        - C-MYC rearrangement
        - BCL-6 rearrangement
    - Largest tumor size (>7.5 vs <7.5cm if cut-off necessary)
    - Extranodal involvement pre-infusion
        - Number of extranodal sites (per form 2018 #287)
        - Hepatic
        - Splenic
        - CNS involvement
    - Bone marrow involvement pre-infusion (%)

<u>Treatment related factors:</u>

- Pre-HCT therapies
    - # of systemic therapy lines
    - Pre-conditioning bendamustine exposure
    - Pre-conditioning fludarabine exposure
    - Prior anti-PD-L1 or anti-CTLA-4 exposure
    - Prior blinatumomab (for ALL)
    - Prior intrathecal therapy (any)
    - Prior craniospinal or whole brain radiation therapy
- Conditioning Regimen (form 4000)
- Bridging therapy (form 4000)
- Intrathecal therapy(form 4000)
- CAR T construct (Form 4003)
    - CD3z, CD28, 4-1BB
- Transfection efficiency (Form 4003)
- Viability of cells:: % viable (Form 4003)
- Number of planned infusions (Form 4003)
- Cell dose (form 4006)
    - Recipient height/weight used for infusion
    - Lymphocyes administered
    - CD4+ lymphocytes administered
    - CD8+ lymphocytes administered

<u>Outcomes:</u>

- Death (form 4100)
    - Cause of death:: CRS/CRES vs progressive disease vs other non-relapse mortality
- Did the recipient develop CRS (form 4100)
    - Date of CRS (form 4100)
        - Fevers (form 4100)

    - Date of onset
    - Explained entirely by non-CRS cause?
  - Hypoxia (form 4100)
    - Date of onset
    - Requiring minimal supplemental O2
    - Requiring more than minimal supplemental O2
    - MVI required
    - Explained entirely by non-CRS cause?
  - Hypotension (form 4100)
    - Date of onset
      - Requiring IV Fluids
      - Requiring pressors
      - Explained by non-CRS cause?
    - Highest grade of CRS – utilizing ASTCT criteria13
  - Organ toxicity grade ≥ 3
    - By organ system as collected on form 4100 #137 – GI, Heart, Kidney, Liver, Lungs, MSK, other organ
  - Therapy given for CRS (form 4100)
    - Steroids, siltuximab, tocilizumab, other
  - Did CRS resolve (form 4100)
    - Date resolved
- Neurotoxicity (form 4100)
  - Date of neurotoxicity
  - Lowest CARTOX score
  - Symptoms of neurotoxicity
    - Altered mental status
    - Aphasia
    - Hemiparesis
    - Seizure
    - Tremors
    - Visual hallucinations
    - Coma
    - Cerebral edema
  - Highest grade of CRES – utilizing ASTCT criteria13
- Length of hospitalization for CAR T-cell infusion
- Bleeding episodes by day +100
- Number of days of hospitalization by day + 100 and within 1 year
- Development of clinically significant infection by day + 100 and within 1 year

Sample requirements:
No testing of biologic samples is proposed

Study design:
All patients meeting the inclusion criteria should be randomly divided into one of two cohorts: a training cohort and a validation cohort. In the training cohort, we will perform a retrospective analysis of clinical data to identify clinical variables significantly associated with the development of CRS and/or CRES. This will involve univariate and multivariate analysis. Upon identification of significant variable, the

magnitude of the significant clinical factors' hazard ratios can be incorporated into a risk score which will be able to assign a predicted probability of developing CRS and/or CRES for individual patients. The performance of the risk score will then be tested in the validation cohort.

Conflicts of interest:
None

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Baseline characteristics for patients undergoing 1st CAR-T for ALL/NHL

Characteristic	ALL	NHL	Total
No. of patients	302	885	1187
No. of centers	56	73	102
Age at infusion, by category - no. (%)			
Median (min-max)	13.58 (0.41-74.63)	62.26 (15.02-88.99)	56.81 (0.41-88.99)
< 10	96 (31.8)	0	96 (8.1)
10-19	140 (46.4)	4 (0.5)	144 (12.1)
20-29	53 (17.5)	20 (2.3)	73 (6.1)
30-39	3 (1)	44 (5)	47 (4)
40-49	2 (0.7)	92 (10.4)	94 (7.9)
50-59	3 (1)	216 (24.4)	219 (18.4)
60-69	3 (1)	335 (37.9)	338 (28.5)
≥ 70	2 (0.7)	174 (19.7)	176 (14.8)
Gender - no. (%)			
Male	179 (59.3)	569 (64.3)	748 (63)
Female	123 (40.7)	316 (35.7)	439 (37)
Recipient race - no. (%)			
White	210 (69.5)	755 (85.3)	965 (81.3)
African-American	18 (6)	43 (4.9)	61 (5.1)
Asian	12 (4)	39 (4.4)	51 (4.3)
Other	4 (1.3)	1 (0.1)	5 (0.4)
More than one race	41 (13.6)	21 (2.4)	62 (5.2)
Not reported	17 (5.6)	26 (2.9)	43 (3.6)
Recipient ethnicity - no. (%)			
Hispanic or Latino	115 (38.1)	91 (10.3)	206 (17.4)
Non Hispanic or non-Latino	158 (52.3)	743 (84)	901 (75.9)
Non-resident of the U.S.	10 (3.3)	17 (1.9)	27 (2.3)
Unknown	19 (6.3)	34 (3.8)	53 (4.5)
Karnofsky/Lansky performance score prior to CT - no. (%)			
90-100	202 (66.9)	349 (39.4)	551 (46.4)
80	49 (16.2)	259 (29.3)	308 (25.9)
< 80	37 (12.3)	158 (17.9)	195 (16.4)

Characteristic	ALL	NHL	Total
Not reported	14 (4.6)	119 (13.4)	133 (11.2)
Disease status prior to CT - no. (%)			
CR1	22 (7.3)	8 (0.9)	30 (2.5)
CR2	30 (9.9)	8 (0.9)	38 (3.2)
CR3+	45 (14.9)	12 (1.4)	57 (4.8)
Relapse, 1st	76 (25.2)	220 (24.9)	296 (24.9)
Relapse, other	80 (26.5)	288 (32.5)	368 (31)
PIF/Untreated	41 (13.6)	346 (39.1)	387 (32.6)
Not reported	8 (2.6)	3 (0.3)	11 (0.9)
Types of prior HCTs - no. (%)			
No	187 (61.9)	560 (63.3)	747 (62.9)
Yes	112 (37.1)	322 (36.4)	434 (36.6)
Prior allo-HCT(s)	101 (33.4)	21 (2.4)	122 (10.3)
Prior auto-HCT(s)	3 (1)	280 (31.6)	283 (23.8)
Prior auto and allo-HCT(s)	1 (0.3)	8 (0.9)	9 (0.8)
Not reported	7 (2.3)	13 (1.5)	20 (1.7)
Not reported	3 (1)	3 (0.3)	6 (0.5)
Year of CT - no. (%)			
2015	3 (1)	0	3 (0.3)
2016	9 (3)	10 (1.1)	19 (1.6)
2017	52 (17.2)	28 (3.2)	80 (6.7)
2018	157 (52)	537 (60.7)	694 (58.5)
2019	81 (26.8)	310 (35)	391 (32.9)
Commercial vs. noncommercial CAR-T product - no. (%)			
Commercial	208 (68.9)	816 (92.2)	1024 (86.3)
Noncommercial	94 (31.1)	69 (7.8)	163 (13.7)

Proposal: 1911-89

Title:
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)

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Hypothesis:
We hypothesize that Chimeric Antigen Receptor (CAR) T cells products might have different toxicity profiles and might require different toxicity management with possible impact on CAR T cells efficacy.

Specific aims:
We aim to describe the toxicity profiles of FDA approved anti-CD19 CAR T cells (axicabtagene ciloleucel or tisagenlecleucel) in adult patients with relapsed/refractory (R/R) Diffuse Large B Cell Lymphoma (DLBCL). Moreover, we aim to describe management of Cytokine Release Syndrome (CRS) and Immune-Effector-Associated Neurotoxicity Syndrome (ICANS) and their impact on CAR T cells' efficacy, evaluated as response rate at 3 and 6 months.

General Outcomes to be examined include:
Primary objective:
- Incidence of CRS and ICANS for axicabtagene ciloleucel and tisagenlecleucel, graded according to the unified grading system proposed by the American Society for Transplantation and Cellular Therapy (ASTCT);
- Incidence of organ toxicities and cytopenias for axicabtagene ciloleucel and tisagenlecleucel;

Secondary objectives:
- Incidence of CRS for axicabtagene ciloleucel and tisagenlecleucel, graded according to the Lee score and U-Penn score, respectively; incidence of ICANS for axicabtagene ciloleucel and tisagenlecleucel, graded according to CTCAEv4.03
- Treatment Related Mortality;
- Management of CRS and ICANS, for axicabtagene ciloleucel and tisagenlecleucel, including the use of tocilizumab, steroids, siltuximab and other agents;
- Impact of the use of tocilizumab and steroids for the treatment of CRS/ICANS on response to CAR T cells at 3 months and 6 months;
- Response rates at 3 and 6 months for patients who received tocilizumab or steroids for grade 1 CRS/ICANS versus patients who were not treated for grade 1 CRS/ICANS;

Scientific impact:
This study would provide for the first time a comprehensive description of toxicity profiles for axicabtagene ciloleucel and tisagenlecleucel, including CRS and ICANS graded according to the ASTCT grading system, which has already been adopted for common use at many centers. This comparison might help clinicians in choosing one product over the other based on patients' specific characteristics and risk of toxicity. Moreover, a clear relationship between the use of tocilizumab and steroids for the

treatment of CRS and ICANS and CAR T cells efficacy has not been identified, according to the results of a secondary underpowered analysis of one clinical trial. It is possible that assessing this effect on a larger population can identify an impairment of CAR T cells efficacy in terms of CAR T cells response at 3 and 6 months.

Scientific justification:
Anti-CD19 CAR T cell therapies represent a paradigm shift in the treatment of lymphoid malignancies. Two different products are approved by the United States Food and Drug Administration (FDA) and the European Medical Agency for the treatment of R/R DLBCL: axicabtagene ciloleucel (Yescarta, Kite/Gilead) based on results of the ZUMA-1 trial [1,2], and tisagenlecleucel (Kymriah, Novartis Pharmaceuticals), based on results of the JULIET trial [3]. These products are characterized by different manufacturing with the incorporation of two different costimulatory molecules, which are responsible for different expansion and survival patterns of the two products, and possibly different toxicity profiles. CAR T cell therapies have been associated with specific toxicities [4,5], including CRS and ICANS, which have been reported in the pivotal clinical trials according to different grading systems developed at different institutions. However, these distinct grading systems vary slightly in variables included and in definitions of severity [4,6–8]. Therefore, direct comparisons of CRS and ICANS rates associated with the two different products haven't been reported to date. Recently, the ASTCT has proposed a consensus grading system as a unified score applicable to all CAR T cells products and to be used in daily practice and across clinical trial, to have a uniform reporting of these toxicities [9]. Besides CRS and ICANS, other recurrent toxicities, such as prolonged cytopenias and other organ toxicities, have been only described in small populations of patients [10]. Based on the availability of two different products with the same clinical indication (axicabtagene ciloleucel or tisagenlecleucel for R/R DLBCL), physicians often need to select one product over the other. The comprehensive description of the toxicity rates of the two products according to a unified grading system, would be a helpful information to guide physicians' decisions, based on toxicity profiles of the products and on specific patients' factors (age, comorbidities, others).
Moreover, a clear relationship between the use of tocilizumab and steroids, as lympho-toxic agents for the management of these toxicities, and CAR T cells efficacy has not been identified yet. Clinical data are limited to a secondary analysis conducted in the ZUMA-1 trial [1], where treatment with either tocilizumab or steroids did not show an impact on overall response rates. Despite the availability of limited data on the impact of these treatments on CAR T cells efficacy and persistence, in the real world experience a much higher use of tocilizumab and steroids has been reported [11], and clinical trials are investigating the early use of these treatments, in order to prevent high grade toxicities [12].

Patient eligibility population:
Inclusion criteria:
- Age $\geq$ 18
- Treatment with either axicabtagene ciloleucel or tisagenlecleucel after FDA approval
- Diagnosis of: Diffuse Large B cell lymphoma; large B cell lymphoma transformed from indolent lymphomas; Primary mediastinal B cell lymphoma; High grade B cell lymphoma

Exclusion criteria:
- Having received axicabtagene ciloleucel or tisagenlecleucel as part of a clinical trial

Data requirements:
- CIBMTR: Utilizing data from form #2402 #4000 #4003 #4006 #4100 #2118 #2900. The parameters to be assessed are outlined in the table below.

Table for Data Requirements:

Type of data	Data point	Specific data
Patient Specific	Patient specific characteristics	Age Gender Race/Ethnicity Significant Comorbidities Prior autologous transplant Prior allogeneic transplant Prior IEC therapy Disease histology Disease assessment by PET (Deauville Score) Disease status (CR vs no CR) Karnofsky PS at CAR infusion: ≥ 90 vs. < 90 vs. missing
CAR T cell therapy Specific	CAR T cell therapy	Type of product (axicabtagene ciloleucel or tisagenlecleucel) Collection date Infusion date
	Bridging regimen used	Yes/no Type of regimen
	Lymph depletion	Yes/no Type of regimen
Outcome Measures	Response assessment	Best response obtained (date) Response status at 3-6 months (date) Relapse after best response (yes/no)
	For both CRS and ICANS	Occurrence yes/no Date of start Symptoms developed Grade for CRS according to ASTCT, Lee, U-Penn Grade for ICANS according to ASTCT, CTCAEv4.03 Treatment received (including tocilizumab, steroids, siltuximab, other agents, vasopressor, O2 therapy, antiepileptic drugs)
	Other toxicities	- Organ toxicities (yes/no, grade grade by CTCAE) - Cytopenias: anemia, leukopenia, neutropenia, thrombocytopenia (yes/no, grade by CTCAE) o Transfusion/growth factor requirement - Hypogammaglobulinemia (yes/no) o Replacement treatment requirement (yes/no)
	Status at last follow-up	Alive/dead (date) Disease status at last follow-up (date) Cause of death

Study design:

A retrospective study will be conducted utilizing CIBMTR data. Patients included will be stratified according to axicabtagene ciloleucel or tisagenlecleucel treatment. Descriptive tables of patient-, CAR T cell- related factors and outcomes will be created. The tables will list median and range for continuous variables and percent of total for categorical variables. Chi-squared statistics will be used to compare patient and CAR T cell specific characteristics between axicabtagene ciloleucel or tisagenlecleucel treatment for categorical or continuous variables respectively. Cumulative incidence of CRS, ICANS,

cytopenias, hypogammaglobulinemia and organ toxicities will be calculated while accounting for competing events (death without event and progression/relapse of disease). Data on patients without an event will be censored at last follow up. Univariate analysis will be performed to identify factors influencing cumulative incidence of different toxicities. The associations between patient, CAR T cell-related factors and outcomes will be studied with multivariate Cox regression models.

Conflicts of Interest:

- Dr. Pennisi and Dr. Mead have no conflict of interest.
- Dr. Perales reports honoraria from Abbvie, Bellicum, Celgene, Bristol-Myers Squibb (>$5,000), Incyte, Merck (>$5,000), Novartis (>$5,000), Nektar Therapeutics, Omeros, and Takeda. He serves on DSMBs for Cidara Therapeutics, Servier and Medigene, and the scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of American Society for Transplantation and Cellular Therapy (ASTCT) and Be the Match (National Marrow Donor Program, NMDP), as well as on the CIBMTR Cellular Immunotherapy Data Resource (CIDR) Committee.

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Baseline characteristics for patients undergoing 1st commercial CAR-T for NHL

Characteristic	N (%)
No. of patients	816
No. of centers	72
Age at infusion, by category - no. (%)	
Median (min-max)	62.27 (15.02-88.99)
10-19	4 (0.5)
20-29	18 (2.2)
30-39	40 (4.9)
40-49	84 (10.3)
50-59	202 (24.8)
60-69	307 (37.6)
>= 70	161 (19.7)
Gender - no. (%)	
Male	522 (64)
Female	294 (36)
Recipient race - no. (%)	
White	700 (85.8)
African-American	37 (4.5)
Asian	35 (4.3)
Other	1 (0.1)
More than one race	19 (2.3)
Not reported	24 (2.9)
Recipient ethnicity - no. (%)	
Hispanic or Latino	81 (9.9)
Non Hispanic or non-Latino	688 (84.3)
Non-resident of the U.S.	16 (2)
Unknown	31 (3.8)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	308 (37.7)
80	246 (30.1)
< 80	148 (18.1)
Not reported	114 (14)
Disease status prior to CT - no. (%)	
CR1	7 (0.9)
CR2	8 (1)
CR3+	11 (1.3)
Relapse, 1st	195 (23.9)

Characteristic	N (%)
Relapse, other	259 (31.7)
PIF/Untreated	333 (40.8)
Not reported	3 (0.4)
Types of prior HCTs - no. (%)	
No	536 (65.7)
Yes	277 (33.9)
Prior allo-HCT(s)	19 (2.3)
Prior auto-HCT(s)	242 (29.7)
Prior auto and allo-HCT(s)	3 (0.4)
Not reported	13 (1.6)
Not reported	3 (0.4)
Year of CT - no. (%)	
2017	6 (0.7)
2018	505 (61.9)
2019	305 (37.4)
Product - no. (%)	
Kymriah	117 (14.3)
Yescarta	699 (85.7)

Proposal: 1911-105

Title:
Development of a prognostic model of CAR-T cell therapy toxicity

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Research hypothesis:
Anti-CD19 chimeric antigen receptor (CAR) T cell therapy has resulted in unprecedented remission rates following infusion to patients with relapsed and refractory B-cell malignancies [1-5]. However, the treatment is associated with considerable toxicity, with cytokine release syndrome (CRS) and neurotoxicity being leading causes [1-3,5,6]. We hypothesize that baseline features collected before the time of CAR-T cells infusion are predictive of treatment toxicity.

Specific aims:
- Develop a risk score for severe CAR T cell toxicity (composite of grade >=3 CRS or grade>=3 immune effector cell therapy-associated neurotoxicity syndrome [ICANS]).
- Identify risk factors for severe CAR-T cell toxicity (CRS and ICANS, separately)

Scientific impact:
The safety profile of CAR-T cell therapy varies between products and has been associated with multiple independent factors. Here, we propose to aggregate and weight the different factors in order to generate a unified model for prediction of treatment-related toxicity. Such a tool could guide interventions to prevent and mitigate therapy-related adverse events and to inform patients and practitioners regarding the expected course of therapy. Furthermore, it could be used for risk stratification in prospective and retrospective studies.

Scientific justification:
CAR T cell therapy is an effective novel treatment for hematologic malignancies [1-3,5,6]. With two FDA approved indications (i.e., acute lymphoblastic leukemia [ALL] and diffuse large B-cell lymphoma [DLBCL]) and others pending, experience with the commercial CAR-T cell products is expected to rise steeply.
Toxicity, primarily cytokine release syndrome (CRS) and immune effector cell therapy-associated neurotoxicity syndrome (ICANS), is a major barrier for the widespread use of CAR-T cell therapy. We have recently analyzed CAR-T toxicities in a cohort of 102 receiving tisagenlecleucel or axicabtagene ciloleucel at Memorial Sloan Kettering Cancer Center (Pennisi et al., *under review*). Rates if CRS and ICANS were as high as 82% and 50%, respectively (Figure 1).
Several factors have been to be associated with a higher risk of CAR-T cell therapy toxicity. Patient-specific factors include a higher burden disease, baseline thrombocytopenia, and elevated baseline markers of endothelial activation, such as angiopoietin-2 and von Willebrand factor [1-3,7-14]. Treatment-related factors include rapid T-cell expansion, higher cell doses, and conditioning therapy including fludarabine [1,2,8,10-13,15-20]. In addition, a variety of cytokines and inflammatory markers have been correlated with the development of CRS and ICANS [13,21].
While determinants of CAR-T cell therapy toxicity have been explored in multiple trails, cohorts were relatively small and may have been underpowered to detect additional risk factors. Furthermore,

comprehensive models weighing multiple factors affecting toxicity risk are lacking. The CIBMTR cellular therapy registry offers a unique opportunity to address these challenges.
Identification of determinants of CAR-T cell therapy toxicities and combining them to a prognostic model would beneficial for the field, as it will identify patients at a high-risk for complications, opening avenues for preventive interventions. Such a tool could also serve practitioners and investigators involved in CAR-T therapy patient care and research, and
contribute to the dissemination of this potentially life-saving treatment.

Patient eligibility population:
Inclusion criteria:
Pediatric and adult population
Diagnosis of ALL or DLBCL
Commercial anti-CD19 CAR-T cell product (tisagenlecleucel or axicabtagene ciloleucel)
1st CAR T infusion

Exclusion criteria:
Patients receiving immunotherapy to augment CAR-T action

Data requirements:

Recipient	
	age at infusion
	functional status (Karnofsky)
	Comorbidities
	Weight
	Height
	granular baseline laboratory data (including creatinine, liver enzymes, LDH, uric acid, albumin, CRP, ferritin, fibrinogen, CBC with differential) and sequential data (*if available*)
Disease	
	indication for CAR-T
	date of diagnosis
	transformation (lymphoma)
	prior CNS involvement
	disease stage at diagnosis (lymphoma)
	lymphoma and leukemia molecular, genetic, and immunophenotypic markers of risk
	disease assessment at last evaluation before cellular therapy (all fields in the form 4000 R5.0 questions 68-93)
	disease stage (lymphoma) and blast burden (leukemia) before cellular therapy
	bridging therapy between leukapheresis and CAR-T infusion
	prior cellular therapies and dates (Auto-HCT, Allo-HCT, CAR-T)
Treatment	
	clinical trial enrollment
	product
	date of leukapheresis
	date of cells infusion
	number of cells collected

	conditioning
Post infusion/outcomes	
	CRS date of onset and termination, maximal grade, and treatment
	neurotoxicity - date of onset and termination, maximal grade, and treatment
	grade 3-4 organ toxicity
	maximal lab values ferritin and CRP
	best response to cellular therapy
	disease relapse or progression
	survival status at last follow-up
	cause of death

Study design:

This is a retrospective study using the CIBMTR cellular cell therapy registry. The primary outcome is severe CAR-T cell toxicity defined as grade 3-4 CRS or grade 3-4 ICANS. Secondary outcomes include grades 3-4 CRS and grade 3-4 ICANS (separately). The project aims to develop a prognostic model for severe CAR-T cell therapy toxicity. Briefly, we will follow the proposed guidelines set in the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement [22]. To develop and internally validate the model, we will apply an approach previously described by Shouval et al. [23] Logistic regression analysis will be applied as a univariate model for each covariate separately, as well as a unified multivariate model for all covariates, using severe toxicity as the clinical outcome. To provide an easily accessible tool for model calculation, we will generate a nomogram based on the multivariable model. A nomogram is a graphical representation of a mathematical formula or algorithm incorporating several predictors to predict an end-point based on statistical methods, such as multivariable logistic regression and Cox proportional hazards analysis. For the nomogram construction, stepwise backward selection with the P-value criterion of 0.05 will be performed to choose covariates for the final model. The prediction model will be developed and internally validated using bootstrapping. We will also work on obtaining an independent validation data set. Model performance will be evaluated using measures of discrimination (area under the receiver operating characteristic curve) and calibration [22]. Depending on the data complexity, we could also consider non-parametric/machine learning methods, which we have previously used in the setting of allogeneic-hematopoietic stem cell transplantation [24-28].

Figure 1. Incidence of CRS (yellow) and ICANS (blue) according to ASTCT grading system

TOXICITY INCIDENCE BY ASTCT GRADING	CRS						ICANS					
	global	grade by grade					global	grade by grade				
		1	2	3	4	5		1	2	3	4	5
Overall (n=102)	84 (82%)	35 (34%)	29 (28%)	13 (13%)	6 (6%)	1 (1%)	51 (50%)	8 (8%)	7 (7%)	31 (30%)	5 (5%)	0
B-ALL (n=53)	46 (87%)	21 (40%)	10 (19%)	9 (17%	5 (9%)	1 (2%)	29 (55%)	3 (6%)	2 (4%)	21 (40%)	3 (6%)	0
DLBCL (n=49)	38 (77%)	14 (29%)	19 (39%)	4 (8%)	1 (2%)	0	22 (45%)	5 (10%)	5 (10%)	10 (20%)	2 (4%)	0
axi-cel *(n=36)*	*31 (86%)*	*12 (33%)*	*14 (39%)*	*4 (11%)*	*1 (3%)*	*0*	*20 (55%)*	*4 (11%)*	*4 (11%)*	*10 (28%)*	*2 (6%)*	*0*
tisa-cel *(n=13)*	*7 (54%)*	*2 (15%)*	*5 (38%)*	*0*	*0*	*0*	*2 (15%)*	*1 (8%)*	*1 (8%)*	*0*	*0*	*0*

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Baseline characteristics for patients undergoing 1st commercial CAR-T for ALL/NHL

Characteristic	ALL	NHL	Total
No. of patients	208	816	1024
No. of centers	46	72	99
Age at infusion, by category - no. (%)			
Median (min-max)	13.19 (0.41-63.48)	62.27 (15.02-88.99)	58.13 (0.41-88.99)
< 10	70 (33.7)	0	70 (6.8)
10-19	100 (48.1)	4 (0.5)	104 (10.2)
20-29	37 (17.8)	18 (2.2)	55 (5.4)
30-39	0	40 (4.9)	40 (3.9)
40-49	0	84 (10.3)	84 (8.2)
50-59	0	202 (24.8)	202 (19.7)
60-69	1 (0.5)	307 (37.6)	308 (30.1)
>= 70	0	161 (19.7)	161 (15.7)
Gender - no. (%)			
Male	126 (60.6)	522 (64)	648 (63.3)
Female	82 (39.4)	294 (36)	376 (36.7)
Recipient race - no. (%)			
White	150 (72.1)	700 (85.8)	850 (83)
African-American	15 (7.2)	37 (4.5)	52 (5.1)
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Other	4 (1.9)	1 (0.1)	5 (0.5)
More than one race	19 (9.1)	19 (2.3)	38 (3.7)
Not reported	13 (6.3)	24 (2.9)	37 (3.6)
Recipient ethnicity - no. (%)			
Hispanic or Latino	81 (38.9)	81 (9.9)	162 (15.8)
Non Hispanic or non-Latino	114 (54.8)	688 (84.3)	802 (78.3)
Non-resident of the U.S.	7 (3.4)	16 (2)	23 (2.2)
Unknown	6 (2.9)	31 (3.8)	37 (3.6)
Karnofsky/Lansky performance score prior to CT - no. (%)			
90-100	138 (66.3)	308 (37.7)	446 (43.6)
80	34 (16.3)	246 (30.1)	280 (27.3)
< 80	27 (13)	148 (18.1)	175 (17.1)
Not reported	9 (4.3)	114 (14)	123 (12)
Disease status prior to CT - no. (%)			
CR1	19 (9.1)	7 (0.9)	26 (2.5)

Characteristic	ALL	NHL	Total
CR2	22 (10.6)	8 (1)	30 (2.9)
CR3+	31 (14.9)	11 (1.3)	42 (4.1)
Relapse, 1st	53 (25.5)	195 (23.9)	248 (24.2)
Relapse, other	51 (24.5)	259 (31.7)	310 (30.3)
PIF/Untreated	30 (14.4)	333 (40.8)	363 (35.4)
Not reported	2 (1)	3 (0.4)	5 (0.5)
Types of prior HCTs - no. (%)			
No	139 (66.8)	536 (65.7)	675 (65.9)
Yes	66 (31.7)	277 (33.9)	343 (33.5)
Prior allo-HCT(s)	59 (28.4)	19 (2.3)	78 (7.6)
Prior auto-HCT(s)	1 (0.5)	242 (29.7)	243 (23.7)
Prior auto and allo-HCT(s)	1 (0.5)	3 (0.4)	4 (0.4)
Not reported	5 (2.4)	13 (1.6)	18 (1.8)
Not reported	3 (1.4)	3 (0.4)	6 (0.6)
Year of CT - no. (%)			
2017	16 (7.7)	6 (0.7)	22 (2.1)
2018	127 (61.1)	505 (61.9)	632 (61.7)
2019	65 (31.3)	305 (37.4)	370 (36.1)
Commercial vs. noncommercial CAR-T product - no. (%)			
Commercial	208	816	1024

Proposal: 1910-12

Title:
Correlation between CAR-T cell dose, disease response, cytokine release syndrome and acute neurotoxicity

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Hypothesis and scientific justification:
Chimeric antigen receptor (CAR) T-cell therapy is one of the most remarkable advances in cancer therapy in the last decades (1-3). Since 2017, the two CAR T-cell products targeting CD19: Tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®), are approved in the United States and Europe for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) in pediatric and young adult patients, and relapsed or refractory B-cell lymphoma in adults (4-7). The use of CAR-T cell therapies is gradually increasing and more than 300 adoptive T-cell therapy trials are ongoing, which is a testament to the early success and hope engendered by this line of investigation (8).
However, CAR-T cell therapy is associated with significant acute toxicities including cytokine release syndrome (CRS) and neurological toxicity (Immune effector cell-associated neurotoxicity syndrome (ICANS)), that are not typically seen with other anticancer therapies. In addition, later toxicities related to CAR-T-cell therapy have been reported such as prolonged cytopenia and increased risk for opportunistic infections (9).
In allogeneic stem cell transplant, the infusion of an optimal T-cell CD3+ cell dose is crucial to achieve sustained engraftment (10). In addition, the infusion of higher CD3+ cell dose containing grafts has been historically correlated with higher rates of graft versus host disease (GVHD) and worse survival (11). However, in a recent study conducted by the CIBMTR, the CD3+ T cell dose of peripheral blood stem cell products did not influence the risk of GVHD or other transplantation outcomes when using 8/8 matched sibling and unrelated donors (12).
With this rationale, it is reasonable to question if there is an ideal CAR-T cell dose range to achieve maximum therapeutic effect, and if the CAR-T cell dose infused to the patient has an impact in the incidence of CRS and acute neurotoxicity.
The innovation: The correlation between CAR-T cell dose and cytokine release syndrome, neurotoxicity, and disease response has not been explored.
The clinical significance: CAR-T cell therapy is a novel and effective therapy for patients diagnosed with non-Hodgkin lymphoma and acute lymphoblastic leukemia and the use of this approach is significantly increasing over the world. Doses administered to patients treated on and off-trial have been highly variable.

Objectives:
Hypothesis (H0):
The dose of CAR-T cell infused to the patients does not correlate with overall response rates and survival and acute therapy-related toxicity.

Primary objective:
The primary objective is to explore a potential correlation between CAR-T cell dose infused and overall survival

- Correlation between CAR-T cell dose and overall survival e controlled by disease status prior to therapy.

Secondary objectives:

- To explore a potential correlation with CAR-T cell dose and disease response
    - Correlation between CAR-T cell dose and relapse-free survival
    - Correlation between CAR-T cell dose and overall response rate
    - Correlation between CAR-T cell dose and overall response controlled by disease status prior therapy.
- To explore a potential correlation with CAR-T cell dose and cytokine release syndrome.
    - Frequency of cytokine release syndrome
    - Grade of cytokine release syndrome
    - Time of cytokine release syndrome
- To explore a potential correlation with CAR-T cell dose and acute neurotoxicity.
    - Frequency of ICANS
    - Grade of ICANS
    - Time of ICANS

Study population:
Inclusion criteria:

- Patients treated with commercial CAR-T cell therapy (Kite/Gilead and Novartis) will be eligible for the present study.
- Minimum follow-up required for inclusion will be 6 months.
- Pediatric and adult population will be eligible for the study.

Exclusion criteria:

- Patients treated with academic CAR-T cell therapy would not be eligible for the study.
- Follow-up lower than 6 months.

Outcomes:
Main variables of interest will be overall survival (OS), relapse-free survival (RFS), non-relapse mortality (NRM), cumulative incidence of relapse (CIR).

Main definitions:

- OS: Time to death at 1, 2 and 5 years. Death from any cause will be considered an event. Surviving patients will be censored at time of last follow-up.
- RFS: Time to death or relapse at 1, 2 and 5 years. Death from any cause or relapse will be considered as event. Surviving patients will be censored at time of last follow-up.
- TRM: Cumulative incidence of TRM will be estimated at day +100 and 1, 2 and 5 year. TRM is defined as death without preceding disease relapse/progression.
- CIR: Cumulative incidence of relapse will be estimated at 1 and 2 years after HCT is defined as death preceding disease relapse/progression.

- CRS and ICANS would be grade according to the ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells (13).

Data requirements:
Utilizing data collected by the CIBMTR organization from patients treated with CAR-T cell therapy. This proposed study will require no supplemental data to be collected. No biological samples are required for this study. The parameters to be assessed are outlined in **Table 1** below.

Type of data	Data point	Specific data
Patient Specific	Patient specific characteristics	Age at the time of the infusion (Date of birth) Sex Race Country of transplant Significant comorbidities Diagnosis Date of diagnosis CNS involvement at any time CNS involvement prior to CAR-T cell therapy Bulky disease (Lymphoma) ≥30% bone marrow or peripheral blood blasts (ALL) Bridging Therapy (Y/N) Bridging Therapy (Type) Number lines prior to CAR-T cell therapy Interval from diagnosis to CAR-T cell therapy Previous history of anti-PD1 check point inhibitors treatment If yes, time between anti-PD1 and CAR-T cell therapy Disease status prior to CAR-T cell therapy CRP, Ferritin, Albumin, LDH, Platelet count prior to CAR-T cell therapy Karnofsky performance status
CAR-T specific	Infusion date	Date of CAR-T cell infusion
	CAR-T information	Date of collection Time required between processing – infusion of the product Commercial brand of CAR-T product **Number of CAR-T cell infused** Viability Time required to complete the infusion Blood counts at the time of the first infusion
Therapy related complications	Cytokine release syndrome	Yes/No Date of onset Grade at onset, Maximum Grade Treatment required ICU admission Response to treatment (Yes/no)
	Neurotoxicity	Yes/No Date of onset

		Grade at onset, Maximum Grade Late Neurotoxicity (Y/N) Treatment required ICU admission Response to treatment (Yes/no)
Outcome information	Overall response rate	Overall response rate at 3 months, 1 and 2 years Time to assessment of the response Disease status at last follow-up
	Disease relapse	Incidence of disease relapse Time to disease relapse Cumulative incidence of relapse at 1 and 2 year s Relapse free survival at 1 and 2 years
	Mortality	Death yes/no Date of death Cause of death Disease status Overall survival at 1 and 2 years Non-relapse mortality + 100, 1 and 2 years

Study Design:

Study characteristics:

Multicenter, retrospective and observational.

The CIBMTR data base would provide data for the variables of interest. Baseline characteristics will be reported using descriptive statistics (counts and percentages). Main variables of interest will be overall survival (OS), relapse-free survival (RFS), non-relapse mortality (NRM) and cumulative-incidence of relapse (CIR). OS and PFS rates will be calculated using the Kaplan-Meier product-limit method and the impact of variables will be assessed using the Log-rank test. NRM will be estimated using the cumulative incidence method considering relapse as a competing risk. CIR will be estimated using the cumulative incidence method considering relapse as a competing risk. The impact of variables in NRM and CIR will be explored with Fine and Gray method. All P-values will be 2-sided and for the statistical analyses, $P < 0.05$ will be considered to indicate a statistically significant result.

Part 1:

Explore the impact of CAR-T cell dose in survival and treatment response

The impact of CAR-T cell dose would be explored in the entire cohort of patients and according to the commercial brand of the CAR-T product (Kite/Gilead and Novartis), and according to the hematological disorder (NHL and ALL).

The impact of CAR-T cell dose in OS and RFS will be analyzed as a continuous variable with Cox Proportional hazards regression and in NRM and CIR will be explored using Fine and Gray method.

An optimal cut-off of CAR-T cell dose for OS would be explored based on the binary partitioning method for the entire cohort, according to the CAR-T cell commercial brand and according to the hematological diagnosis (NHL and ALL). The impact of other covariates of interest in OS and RFS would be explored with Cox Proportional hazards regression method. To explore the impact of the CAR-T cell dose count a multivariate analysis would be done controlled by those variables found to be significant in the univariate analysis.

Part 2:

Explore the impact of CAR-T cell dose in cytokine release syndrome (CRS) and acute neurotoxicity

The impact of CAR-T cell dose in the cumulative incidence of CRS and acute neurotoxicity would be explored using the cumulative incidence method considering death as competing event and using Fine and Gray method.

Part 3:

To define an ideal CAR-T cell range to achieve maximum survival rates without grade 3-4 acute toxicity (CRS and neurotoxicity).

To estimate an optimal cell dose range controlled by variables found to be significant in the multivariate analysis and try to find a window which provides minimum toxicity (if higher CAR-T cell dose count found to be a significant parameter for higher acute toxicity) and maximum disease response and survival. To attempt to correlate CAR-T cell dose with disease burden.

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Other	4 (1.9)	1 (0.1)	5 (0.5)
More than one race	19 (9.1)	19 (2.3)	38 (3.7)
Not reported	13 (6.3)	24 (2.9)	37 (3.6)
Recipient ethnicity - no. (%)			
Hispanic or Latino	81 (38.9)	81 (9.9)	162 (15.8)
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Non-resident of the U.S.	7 (3.4)	16 (2)	23 (2.2)
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90-100	138 (66.3)	308 (37.7)	446 (43.6)
80	34 (16.3)	246 (30.1)	280 (27.3)
< 80	27 (13)	148 (18.1)	175 (17.1)
Not reported	9 (4.3)	114 (14)	123 (12)
Disease status prior to CT - no. (%)			
CR1	19 (9.1)	7 (0.9)	26 (2.5)
CR2	22 (10.6)	8 (1)	30 (2.9)

Characteristic	ALL	NHL	Total
CR3+	31 (14.9)	11 (1.3)	42 (4.1)
Relapse, 1st	53 (25.5)	195 (23.9)	248 (24.2)
Relapse, other	51 (24.5)	259 (31.7)	310 (30.3)
PIF/Untreated	30 (14.4)	333 (40.8)	363 (35.4)
Not reported	2 (1)	3 (0.4)	5 (0.5)
Types of prior HCTs - no. (%)			
No	139 (66.8)	536 (65.7)	675 (65.9)
Yes	66 (31.7)	277 (33.9)	343 (33.5)
Prior allo-HCT(s)	59 (28.4)	19 (2.3)	78 (7.6)
Prior auto-HCT(s)	1 (0.5)	242 (29.7)	243 (23.7)
Prior auto and allo-HCT(s)	1 (0.5)	3 (0.4)	4 (0.4)
Not reported	5 (2.4)	13 (1.6)	18 (1.8)
Not reported	3 (1.4)	3 (0.4)	6 (0.6)
Year of CT - no. (%)			
2017	16 (7.7)	6 (0.7)	22 (2.1)
2018	127 (61.1)	505 (61.9)	632 (61.7)
2019	65 (31.3)	305 (37.4)	370 (36.1)
Commercial vs. noncommercial CAR-T product - no. (%)			
Commercial	208	816	1024

Proposal: 1911-33

Title:
Predictive value of 1-month FDG-PET CT scan post CAR T cell therapy on outcome of aggressive B cell NHL

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Research hypothesis:
- FDG PET-CT scan at 1-month after CAR T cell therapy is predictive marker for short- and long-term outcome of aggressive B cell non-Hodgkin lymphoma treated with CD19 CAR T cell
- Cytokine release syndrome and immune effector cells associated neurotoxicities may affect the specificity and predictive value of 1-month post CAR T cell FDG PET-CT scan result in aggressive B cell non-Hodgkin lymphoma

Specific aims:
- To assess the sensitivity, specificity and predictive value of FDG PET-CT scan result at 1-month post-CAR T cell therapy on the survival outcomes of aggressive B cell non-Hodgkin lymphoma (as stratified by Deauville score).
    - Progression Free Survival: 3 months, 6 months, 1 year +/- 2 years
    - Overall Survival: 3 months, 6 months, 1 year +/- 2 years
- To explore the parameters which may be associated with positive FDG PET-CT result at 1-month post CAR T cell therapy
- To describe the responsible etiologies of positive FDG PET-CT at 1-month post-CAR T cell therapy

Scientific impact:
Currently, the application of FDG PET-CT scan after CAR T cell therapy is not yet well defined. Current practice is derived from the clinical trial endpoint and based upon the consensus from the expert in the field with no high level of evidence. This study will provide the role of FDG PET-CT scan at the end of treatment. It will help us understand more about the predictive value, potential confounders and appropriate timepoint of end of treatment FDG PET-CT scan in NHL patients who are treated with CD19 directed chimeric antigen receptor T cells.

Scientific justification:
Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET-CT) is a standard tool for end of treatment response evaluation in aggressive B cell non-Hodgkin lymphoma. The end of treatment (EOT) FDG PET-CT scan is strongly associated with outcome of aggressive B cell NHL. Many studies have demonstrated the implication of EOT FDG PET-CT in many circumstances including after first line induction treatment, after salvage systemic therapy (before stem cell transplantation) or post stem cell transplantation. Despite its highly predictive information, FDG-avidity is not specific only to active malignancy but can be results of many different underlying etiologies including infection, treatment induced tumor inflammation or underlying comorbidities (i.e. plasma glucose). In addition, despite that current FD PET-CT interpretation guideline is more uniform using Deauville score based on the Revised Response Criteria for Malignant Lymphoma, some aspects are remained unclear or possess controversial evidence. Current recommendation suggests the appropriate timeline of EOT FDG PET-CT scan to be approximately 6 to 8 weeks, after completion of therapy to minimize confounding factors. However, this recommendation is based on patients who are treated with chemotherapy or radiotherapy but the value

of FDG PET-CT scan has not been validated in CAR T cell treated patients. There are established data of "pseudo-progression" from FDG PET-CT in solid tumor patients treated with immune based treatments. Moreover, there was a report of false positive FDG PET-CT result in aggressive NHL after allogeneic stem cell transplantation. Since one of the unique side effects of CAR T cell therapy is cytokine release syndromes which is the consequence of massive inflammatory cytokine response as a result of immunologic synapse between CAR T cells and malignant lymphoma cells. Currently, it is not known how the extent of this inflammatory response would affect the validity of EOT FDG PET-CT during the initial post CAR T cell therapy. The appropriate timeline of EOT FDG PET-CT in aggressive NHL treated with CAR T cell is not yet described. To date, most CAR T cell research protocols and institutional guidelines have incorporated the EOT FDG PET-CT scan at 1-month post CAR T cell therapy for the response assessment based upon the historical perspective of CAR T cell trial designs. Another potential role of EOT FDG PET-CT scan is to guide the decision about consolidative or maintenance therapy. This key question was evident in aggressive NHL patients with positive EOT FDG PET-CT who would benefit from post-induction radiotherapy consolidation.

According to aforementioned uncertainties, we propose to explore the prognostic implication of EOT FDG PET-CT scan at 1-month post-CAR T cell treatment. In addition, we plan to look at the potential factors which may interfere or affect the result of EOT FDG PET-CT at 1-month post CAR T cell therapy in aggressive B cell NHL. This study will help us to better understand the significance and the clinical inference of EOT FDG PET-CT in NHL patients treated with CAR T cell therapy. It also will guide us to determine appropriate intervention for this high-risk patient subgroup.

Patient eligibility population:

Aggressive B cell NHL patients who underwent FDA-approved CD19 CAR T cell therapy (Axicabtagene ciloleucel and Tisagenlecleucel) between October 2017 and July 2019

Data requirements:

Form 4000, 4003, 4006, 4100, 2018, 2118, 2402, 2900, 2402

- Diagnosis
- De novo vs Transformed
- Age at CAR T cell
- Gender: Male VS Female
- Disease status at CAR T cell
- Stage of disease at CAR T cell
- IPI at CAR T cell
- Pre-treatment PET
- Number of prior lines of treatments including transplantation
- Type of transplant if transplants before CAR T cell: Auto, Allo
- If allotransplant before CAR T cell: Type of transplant - Matched sib, unrelated, haplo, cord
- Eastern Cooperative Oncology Group Performance Status: 0-2 VS 3-4
- Hematopoietic Cell Transplant Comorbidity Index: 0-2 VS $\geq$3
- Bridging therapy before CAR T cell
    - Last date of treatment
    - Bridging therapy regimen
- Conditioning Regimens for CAR T cell
- Type of CAR T cell product
- CAR T cell dose

- Neutrophil and platelet engraftment
- CAR T Related Complication
    - CRS: Yes vs No. Grading per ASTCT consensus
    - ICANs: Yes vs No. Grading per ASTCT consensus
    - Infection during the first month of CAR T cell: Type, onset
    - Graft Versus Host Disease
- Cytokine profile: Peak IL-6 level, Peak Ferritin, Peak CRP (including date of peak level for all cytokines)
- Steroid: Type, date of first dose, dose, date of last dose
- Tocilizumab: date of first dose, number of doses, date of last dose
- Post treatment PET CT response assessment (CR, PR, SD, PD) (If detailed result i.e. Deauville score is available – but if not available, will use C, PR, SD, PD per report)
    - 1 month
    - 3 months
    - 6 months
    - 9 months
    - 1 year
- Pathology confirmation of positive PET finding if available
- Last contact
- Live/Death Status at last contact
- Cause of death

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

Study design:
This study is a retrospective study. The goal of this study is to describe the pattern of EOT FDG PET-CT result at 1-month post CAR T cell therapy and explore its prognostic implication (including specificity, sensitivity, predictive value) on the treatment outcomes of in aggressive NHL patients. In addition to explore the potential factors which could affect the result of EOT FDG PET-CT scan at 1-month post CAR T cell therapy while adjusting for significant patient-, disease-, and CAR T-related variables listed in Section 6.0. Descriptive tables of patient-, disease-, and CAR T cell-related factors will be prepared. These tables will list median and range for continuous variables and percent of total for categorical variables. Patient-, disease- and transplant- related factors will be compared between different CAR T cell products and EOT response using the Chi-square test for categorical variables and the Wilcoxon sample test for continuous variables. The probabilities of progression-free and overall survival at different timepoints will be calculated using the Kaplan-Meier estimator with log rank test comparison between EOT FDG PET-CT result cohort. Cumulative incidence of non-relapse morality (NRM) and relapse risk will be estimated, with relapse as a competing risk for the former and death in remission for the latter. Gray's test will be used to assess the difference between EOT FDG PET-CT result for NRM and relapse rate. Cox proportional hazards models will be used to determine the association between the clinical variables and the outcomes constructing for cumulative incidence of NRM, relapse, and for OS and PFS, using a limited backward selection procedure. Variables considered in the model will be those significant at α=0.20 level from the univariable models. Variables remaining in the final models will be significant at α=0.05 level.

Non-CIBMTR data source:
Not required

Conflicts of interest:

- Kitsada Wudhikarn, MD: No conflict of interest to disclose
- Martina Pennisi, MD: No conflict of interest to disclose
- Miguel Perales, MD: Yes as reported below

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

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Baseline characteristics for patients undergoing 1st commercial CAR-T for NHL

Characteristic	N (%)
No. of patients	804
No. of centers	71
Age at infusion, by category - no. (%)	
Median (min-max)	62.31 (15.02-88.99)
10-19	4 (0.5)
20-29	18 (2.2)
30-39	40 (5)
40-49	82 (10.2)
50-59	196 (24.4)
60-69	305 (37.9)
>= 70	159 (19.8)
Gender - no. (%)	
Male	514 (63.9)
Female	290 (36.1)
Recipient race - no. (%)	
White	689 (85.7)
African-American	37 (4.6)
Asian	35 (4.4)
Other	1 (0.1)
More than one race	18 (2.2)
Not reported	24 (3)
Recipient ethnicity - no. (%)	
Hispanic or Latino	78 (9.7)
Non Hispanic or non-Latino	680 (84.6)
Non-resident of the U.S.	16 (2)
Unknown	30 (3.7)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	303 (37.7)
80	243 (30.2)
< 80	147 (18.3)
Not reported	111 (13.8)
Disease classification - no. (%)	
Follicular, predominantly small cleaved cell	3 (0.4)
Follicular, mixed small cleaved and large cell	6 (0.7)
Diffuse, large B-cell lymphoma - NOS	238 (29.6)

Characteristic	N (%)
Mantle cell lymphoma	5 (0.6)
Primary diffuse, large B-cell lymphoma of the CNS	2 (0.2)
T-cell/histiocytic rich large B-cell lymphoma	15 (1.9)
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)	1 (0.1)
Nodal marginal zone B-cell lymphoma	2 (0.2)
Primary mediastinal (thymic) large B-cell lymphoma	22 (2.7)
Other B-cell lymphoma	9 (1.1)
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL	3 (0.4)
Follicular, predominantly large cell (grade IIIA)	5 (0.6)
Follicular, predominantly large cell (grade IIIB)	4 (0.5)
Follicular (grade unknown)	6 (0.7)
Diffuse, large B-cell lymphoma - germinal center B-cell type	255 (31.7)
Diffuse, large B-cell lymphoma - activated B-cell type	152 (18.9)
EBV+ DLBCL, NOS	6 (0.7)
High-grade B-cell lymphoma, NOS	6 (0.7)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	62 (7.7)
Plasmablastic lymphoma	2 (0.2)
Disease status prior to CT - no. (%)	
CR1	7 (0.9)
CR2	8 (1)
CR3+	11 (1.4)
Relapse, 1st	194 (24.1)
Relapse, other	253 (31.5)
PIF/Untreated	330 (41)
Not reported	1 (0.1)
Types of prior HCTs - no. (%)	
No	530 (65.9)
Yes	271 (33.7)
Prior allo-HCT(s)	18 (2.2)
Prior auto-HCT(s)	237 (29.5)
Prior auto and allo-HCT(s)	3 (0.4)
Not reported	13 (1.6)
Not reported	3 (0.4)
Year of CT - no. (%)	
2017	6 (0.7)
2018	494 (61.4)

Characteristic	N (%)
2019	304 (37.8)
Commercial vs. noncommercial CAR-T product - no. (%)	
Commercial	804
Best response based on PET (at 100-day reporting) (NHL) - no. (%)	
Complete remission (CR)	368 (45.8)
Partial remission (PR)	157 (19.5)
No response (NR)/Stable disease (SD)	48 (6)
Progressive disease (PD)	119 (14.8)
Not assessed	111 (13.8)
Not reported	1 (0.1)

Proposal: 1911-168

Title:
Outcomes of CD19 CAR T cell therapy for large B cell lymphoma arising from a non-follicular transformation.

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Research hypothesis:
Outcomes of non-follicular transformed large B cell lymphoma arising from marginal zone lymphoma or chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) are poorer in terms of efficacy and toxicity compared to transformed follicular lymphoma (TFL) or *de novo* diffuse large B cell lymphoma (DLBCL) after CD19 CAR T cell therapy.

Specific aims:
- Compare the efficacy (PFS, OS) of CD19 CAR T cell therapy between non-follicular transformation and TFL/DLBCL.
- Compare the rates of CAR T toxicity (CRS, ICANS) between non-follicular transformation and TFL/DLBCL.

Scientific impact:
CD19 CAR T cell therapy is FDA approved as axicabtagene ciloleucel (axi-cel) or tisagenlecleucel (tisa-cel) for large B cell lymphoma (LBCL) and variants including transformed follicular lymphoma (TFL), and data on the treatment of these patients as standard of care treatment is captured by CIBMTR. While CAR T therapy leads to durable remissions in many patients, the risk factors for toxicity and relapse after CAR T cell therapy are not well characterized. In particular, little is known about the outcomes of axi-cel or tisa-cel in patients with high risk histologies such as Richter transformation from CLL/SLL or transformed marginal zone lymphoma. Patients with non-follicular transformations are at high risk of death due to lymphoma and understanding the benefit of CAR T in this population is needed for treatment planning and design of future clinical trials

Scientific justification:
Non-follicular transformations are rare high risk variants of LBCL (Godfrey et al. 2018). The outcomes of patients treated with axi-cel or tisa-cel for non-follicular transformations are not well studied as Richter transformation was excluded the pivotal trials ZUMA-1 and JULIET, and marginal zone transformation has not been described from this data (Neelapu, Locke et al. NEJM 2017; Schuster et al NEJM 2019; Locke et al. Lancet Oncology 2019). Richter transformation is sometimes included in CLL trials, but small numbers have been treated overall (Turtle et al. J. Clin. Oncol. 2017). There is reason to believe that the outcomes of non-follicular transformation may be worse overall. For JCAR017, transformations from marginal zone lymphoma and CLL/SLL had poorer outcomes than de novo DLBCL or TFL and were excluded from analysis of the core subset of the TRANSCEND NHL 001 trial (Abramson et al. ASH 2017). At Moffitt we have also noted a higher risk of toxicity and a lower efficacy in non-follicular transformed patients when treated with axi-cel (unpublished data). Transformed CLL/SLL and high risk transformed marginal zone lymphoma patients are often considered for stem cell transplant and understanding the toxicity and durable response rate of CAR T cell therapy may help clinical decisions about transplant timing in these patients.

Patient eligibility population:
Patients treated with CD19 CAR T therapies (axi-cel or tisa-cel) for R/R LBCL as standard of care who are in the CIBMTR database.

Data requirements:
Supplemental data on bridging therapy (as a covariate known to affect OS; Jain, Jacobs et al. ASH abstract 2019) may be required as a query for all retrospective CAR T projects including this one. Required data from CIBMTR is as listed in the "study design".

Sample requirements:
N/A

Study design:
We propose to compare the efficacy (based on PFS and OS) and severe toxicity (grade 3 or higher CRS and neurotoxicity) between patients with the following histologies:

- All aggressive B cell lymphomas (LBCL and variants)
- Transformed follicular lymphoma
- Non-follicular transformed lymphoma (transformed marginal zone or from CLL/SLL).

Patients will be listed as transformed if the histology is listed as such in the database or if a history of any indolent lymphoma is also listed.
Subgroup analysis will look if there is a difference between axi-cel and tisa-cel in this population.

Variables to be described:
<u>Patient related:</u>

- Age at CAR T-cell therapy: continuous and categorical by decade
- Gender: male vs. female
- Race: Caucasian vs. African American vs. Asian/Pacific Islander vs. Hispanic vs. Others vs. missing
- Ethnicity: Hispanic or Latino vs. Non-Hispanic or non-Latino vs. non-resident of the U.S.
- ECOG Performance status/Karnofsky performance score
- Serum creatinine at the start of lymphodepletion:

<u>Disease-related:</u>

- Disease histology: B-cell NHL (diffuse large B cell lymphoma, transformed follicular lymphoma and primary mediastinal B cell NHL) lymphoma, non-follicular transformation (history of chronic lymphocytic leukemia/small lymphocytic lymphoma or marginal zone lymphoma).
- Disease stage at diagnosis: I-II vs. III-IV
- Refined disease risk index (DRI): low vs. intermediate vs. high vs. very high risk
- International Prognostic Index (IPI) score at leukapheresis: 0-3
- HCT-CI: 0, 1, 2, 3+
- Presence of CNS disease at diagnosis: yes vs. no
- Prior lines of chemotherapy: 0-1, 2, 3, 4+
- Prior radiation therapy: yes vs. no
- Prior autologous stem cell transplant: yes vs. no
- Prior allogeneic stem cell transplant: yes vs. no
- Disease status prior to CAR T-cell therapy: CR, PR, SD, or PD for NHL

- Baseline markers of inflammation (ferritin, CRP) prior to CAR T-cell infusion: continuous and categorical (to be determined)
- Baseline LDH (at leukapheresis;, continuous and categorical to be determined).

CAR T-cell therapy related:
- Time from diagnosis to CAR T-cell therapy
- Use of bridging therapy
- Type of bridging therapy
    - Use of radiation therapy as bridging: yes vs. no
    - Use of chemotherapy as bridging: yes vs. no
- Type of lympho-depleting chemotherapy used
- Type of CAR T product used

Outcomes:
Overall survival (OS):
Time from CAR T-cell infusion to death due to any cause. Patients will be censored at the time of last follow up.

Progression free survival (PFS):
Time from CAR T-cell infusion to death or relapse. Patients will be censored at the time of last follow up.

Cytokine release syndrome (CRS) and neurotoxicity:
Occurrence of grade 3-5 CRS and neurotoxicity. Lee criteria or modified Lee criteria will be used for the CRS grading. CTCAE v4 or CARTOX grading will be used for grading of neurotoxicity.

Relapse:
Development of relapse as defined by the CIBMTR. The event will be summarized by the cumulative incidence estimate. TRM will be a competing risk for this outcome.
This retrospective study is designed to compare the outcomes of CD19-directed CAR T-cell therapy between de novo DLBCL, transformed follicular lymphoma and non-follicular transformed lymphoma. Patient-, disease-, and CAR T-cell therapy related factors will be compared using the Chi-square test for categorical and the Kruskal-Wallis test for continuous variables according to the histologies. OS and PFS probabilities will be estimated by Kaplan-Meier method. Comparison of survival curves will be performed with the log-rank test and point-wise estimates at 3 months, 6 months, 1 year and 2 years. Probabilities of disease relapse/progression will be calculated using cumulative incidence curves to accommodate competing risks. Comparison of incidence curves will be performed using the Fine and Gray method.
Multivariate analysis of OS, PFS, CRS, neurotoxicity and relapse/progression will be performed using Cox proportional hazards model. Variables tested in the multivariate analysis are listed above and will be tested in a forward stepwise approach. The final model will include covariates associated with the outcome at a level of 0.05. Tests for interactions may be considered.

Non-CIBMTR data source:
None

Conflicts of interest:
MDJ: Consultancy/advisory: Kite/Gilead under $5000 annually.

FLL: Scientific Advisor: (<5000 within the last 12 months) Kite/Gilead, Novartis, Celgene, Calibr, GammaDelta Therapuetics; Consultancy (>5000 within the last 12 months): Cellular BioMedicine Group Inc.
TN: None

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Baseline characteristics for patients undergoing 1st commercial CAR-T for non-follicular transformed NHL

Characteristic	N (%)
No. of patients	886
No. of centers	73
Age at infusion, by category - no. (%)	
Median (min-max)	62.25 (15.02-88.99)
10-19	4 (0.5)
20-29	20 (2.3)
30-39	44 (5)
40-49	92 (10.4)
50-59	217 (24.5)
60-69	335 (37.8)
>= 70	174 (19.6)
Gender - no. (%)	
Male	570 (64.3)
Female	316 (35.7)
Recipient race - no. (%)	
White	756 (85.3)
African-American	43 (4.9)
Asian	39 (4.4)
Other	1 (0.1)
More than one race	21 (2.4)
Not reported	26 (2.9)
Recipient ethnicity - no. (%)	
Hispanic or Latino	91 (10.3)
Non Hispanic or non-Latino	744 (84)
Non-resident of the U.S.	17 (1.9)
Unknown	34 (3.8)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	349 (39.4)
80	259 (29.2)
< 80	159 (17.9)
Not reported	119 (13.4)
Disease classification - no. (%)	
Follicular, predominantly small cleaved cell	3 (0.3)
Follicular, mixed small cleaved and large cell	7 (0.8)

Characteristic	N (%)
Diffuse, large B-cell lymphoma - NOS	268 (30.2)
Mantle cell lymphoma	14 (1.6)
Primary diffuse, large B-cell lymphoma of the CNS	2 (0.2)
T-cell/histiocytic rich large B-cell lymphoma	15 (1.7)
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)	1 (0.1)
Nodal marginal zone B-cell lymphoma	2 (0.2)
Primary mediastinal (thymic) large B-cell lymphoma	22 (2.5)
Other B-cell lymphoma	11 (1.2)
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL	3 (0.3)
Follicular, predominantly large cell (grade IIIA)	6 (0.7)
Follicular, predominantly large cell (grade IIIB)	4 (0.5)
Follicular (grade unknown)	7 (0.8)
Diffuse, large B-cell lymphoma - germinal center B-cell type	273 (30.8)
Diffuse, large B-cell lymphoma - activated B-cell type	164 (18.5)
EBV+ DLBCL, NOS	6 (0.7)
High-grade B-cell lymphoma, NOS	6 (0.7)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	64 (7.2)
Plasmablastic lymphoma	2 (0.2)
Not reported	6 (0.7)
Original lymphoma histology - no. (%)	
No transformation	651 (73.5)
Transformation from a follicular lymphoma histology	163 (18.4)
Follicular, predominantly small cleaved cell	30 (3.4)
Follicular, mixed small cleaved and large cell	46 (5.2)
Follicular, predominantly large cell (grade IIIA)	36 (4.1)
Follicular, predominantly large cell (grade IIIB)	15 (1.7)
Follicular (grade unknown)	26 (2.9)
Follicular, predominantly large cell (grade IIIA vs IIIB unspecified)	9 (1)
Follicular T-cell lymphoma	1 (0.1)
Transformation from a non-follicular lymphoma histology	51 (5.8)
Diffuse, large B-cell lymphoma - NOS	5 (0.6)
Burkitt lymphoma	1 (0.1)
T-cell/histiocytic rich large B-cell lymphoma	1 (0.1)
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)	5 (0.6)
Nodal marginal zone B-cell lymphoma	6 (0.7)

Characteristic	N (%)
Splenic marginal zone B-cell lymphoma	7 (0.8)
Primary mediastinal (thymic) large B-cell lymphoma	1 (0.1)
Other B-cell lymphoma	7 (0.8)
Peripheral T-cell lymphoma (PTCL), NOS	1 (0.1)
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL	1 (0.1)
Hodgkin lymphoma, NOS	4 (0.5)
Hodgkin lymphoma, nodular lymphocyte predominant	2 (0.2)
Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma	1 (0.1)
Diffuse, large B-cell lymphoma - germinal center B-cell type	2 (0.2)
Diffuse, large B-cell lymphoma - activated B-cell type	2 (0.2)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	1 (0.1)
Not reported	4 (0.5)
Transformation from CLL	18 (2)
Not reported	3 (0.3)
Disease status prior to CT - no. (%)	
CR1	8 (0.9)
CR2	8 (0.9)
CR3+	12 (1.4)
Relapse, 1st	220 (24.8)
Relapse, other	288 (32.5)
PIF/Untreated	346 (39.1)
Not reported	4 (0.5)
Types of prior HCTs - no. (%)	
No	560 (63.2)
Yes	323 (36.5)
Prior allo-HCT(s)	22 (2.5)
Prior auto-HCT(s)	280 (31.6)
Prior auto and allo-HCT(s)	8 (0.9)
Not reported	13 (1.5)
Not reported	3 (0.3)
Year of CT - no. (%)	
2016	10 (1.1)
2017	28 (3.2)
2018	537 (60.6)
2019	311 (35.1)
Commercial vs. noncommercial CAR-T product - no. (%)	

Characteristic	N (%)
Commercial	816 (92.1)
Noncommercial	70 (7.9)

Proposal: 1911-206

Title:
Outcomes in patients with Double/ Triple Hit Lymphoma post Car T treatments

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Research hypothesis:
Long term outcomes in patients with Double/Triple Hit lymphoma that have received Cellular therapy with any of the Car T products. Hypothesis is that these patients will have poor outcomes compared to Diffuse large B Cell Lymphoma (DLBCL) without the C-myc, Bcl-2 and Bcl-6 rearrangements.

Specific aims:
Primary objective of the study are to analyze the long term outcomes in Double/Triple Hit lymphoma patients by evaluating Complete response (CR), Overall response rate (ORR) and duration of response to Car T treatments.

Scientific impact:
Understanding the variability in outcomes of Double/Triple Hit Lymphoma patients will help guide future studies and development combination treatments aimed for better outcomes in this specific subset of patients.

Scientific justification:
There are multiple different subtypes in Diffuse Large B Cell Lymphoma (DLBCL) and historically Double/Triple Hit Lymphomas have the worst prognosis with RCHOP (1,2). Majority of patients relapse within the first year of treatment and are often chemo-refractory. Response rates have improved in upfront setting with using more aggressive regimens such as DA R EPOCH and Hyper CVAD and consideration of autologous stem cell transplant in first Complete Remission (CR) on a case by case basis(1,2). However, outcomes remained dismal in relapsed/refractory patients due to chemo refractory disease and lack of targeted treatments (2,3).
Cellular Therapy with Car T in general have improved the CR rates in DLBCL after the second line setting compared to the historical control from SCHOLAR-1 (4,5). However, we lack data in regards to responses and long term outcomes in this specific sub set of population with Double and Triple hit patients who have high risk for relapse and poor outcomes.

Patient eligibility population:
Patient eligible for this study will need to have a diagnosis of high grade B cell lymphoma with C-myc and Bcl-2 and/or Bcl-6 rearrangements for Florescent InSitu Hybridization (FISH) testing and should have received cellular therapy with any of the Car T products from 2015-2019.

- Age > 18
- Diffuse large B Cell lymphoma or high grade B cell lymphoma with C-myc and Bcl-2 and/or Bcl-6 rearrangements on FISH
- Received cellular therapy with any of the Car T products

Data requirements:
We will be using the information collected through the following Data Collection Forms:

- Form 2018: Hodgkin and Non-Hodgkin Lymphoma Pre-HCT Data

- Form 4000: Pre-Cellular Therapy Essential Data
- Form 4003: Cellular Therapy Product
- Form 4006: Cellular Therapy Infusion
- Form 4100: Cellular Therapy Essential Data Follow-Up Form

Sample requirements:
We do not need biological samples for this study.

Study design:
Patient level data will be collected from the information available through CIBMTR research database based on specific data collection forms mentioned above. Patients must have recived cellular therapy and will need to have Double/Triple Hit based on FISH analysis.
We will be collecting age, sex, prior treatments received, Car T product received, toxicities, response rates and duration of response.
We will also be collecting additional data that may impact results including IPI score, ECOG status, Stage of disease, line of therapy and chemo refractory status.
We will be using pooled analysis method from patient level data that has been obtained. Response rates from the data will be assessed using random effects model. Survival and variables will be assessed by Cox proportional hazards.

Non-CIBMTR data source:
We will be using CIBMTR research Database and are not planning using non CIBMTR data source.

Conflicts of interest:
Anusha Vallurupalli – NO Conflicts of interest.

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Baseline characteristics for patients undergoing 1st CAR-T for double/triple hit NHL

Characteristic	N (%)
No. of patients	293
No. of centers	53
Age at infusion, by category - no. (%)	
Median (min-max)	62.16 (15.02-88.99)
10-19	2 (0.7)
20-29	8 (2.7)
30-39	13 (4.4)
40-49	27 (9.2)
50-59	73 (24.9)
60-69	105 (35.8)
>= 70	65 (22.2)
Gender - no. (%)	
Male	181 (61.8)
Female	112 (38.2)
Recipient race - no. (%)	
White	250 (85.3)
African-American	13 (4.4)
Asian	13 (4.4)
More than one race	11 (3.8)
Not reported	6 (2)
Recipient ethnicity - no. (%)	
Hispanic or Latino	34 (11.6)
Non Hispanic or non-Latino	249 (85)
Non-resident of the U.S.	3 (1)
Unknown	7 (2.4)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	97 (33.1)
80	99 (33.8)
< 80	57 (19.5)
Not reported	40 (13.7)
Disease status prior to CT - no. (%)	
CR1	1 (0.3)
CR2	3 (1)
CR3+	2 (0.7)
Relapse, 1st	70 (23.9)
Relapse, other	69 (23.5)

Characteristic	N (%)
PIF/Untreated	148 (50.5)
Types of prior HCTs - no. (%)	
No	224 (76.5)
Yes	69 (23.5)
Prior allo-HCT(s)	3 (1)
Prior auto-HCT(s)	62 (21.2)
Not reported	4 (1.4)
Year of CT - no. (%)	
2016	1 (0.3)
2017	6 (2)
2018	177 (60.4)
2019	109 (37.2)
Commercial vs. noncommercial CAR-T product - no. (%)	
Commercial	282 (96.2)
Noncommercial	11 (3.8)

Proposal: 1911-221

Title: Analysis of the incidence of immune-effector cell toxicity and outcomes after anti-CD19 CAR-T cell therapy for B-cell lymphomas

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Hypothesis:
Patients who experience immune-effector cell toxicity [cytokine release syndrome (CRS) or immune effector cell–associated neurologic syndrome (ICANS)] after anti-CD19 CAR-T cell therapy for B-cell lymphomas have improved progression-free survival due to reduced relapse rates.

Specific aims:
To compare the outcomes of B-cell lymphoma patients aged ≥18 years who experience any grade of CRS or ICANS after CAR-T cell therapy versus others. The following outcomes will be evaluated:
Primary objective:

- Progression-free survival (PFS)

Secondary objectives:

- Cumulative incidence of disease relapse
- Overall survival (OS)
- Cumulative incidence of non-relapse mortality (NRM)
- Cause of death.

To identify factors predictive of outcomes after anti-CD19 CAR-T cell therapy to treat B-cell lymphomas
To describe and identify biomarkers predictive of immune-cell effector toxicity (CRS and ICANS)

Scientific justification:
Chimeric Antigen Receptor (CAR-T) cell therapy is revolutionizing the treatment of relapsed/ refractory B-cell lymphomas. Two anti-CD19 CAR-T products, tisagenlecleucel and axicabtagene ciloleucel have been approved by the FDA for this indication.[1, 2] These *"living drugs"* are also associated with other *"on-target, off-tumor"* effects and hence a unique toxicity profile. The two common side effects that are seen with this therapy are CRS and ICANS. The CRS rates of any grade range from 37% to 93% and ICANS of any grade range from 23-67% for patients with lymphoma receiving anti-CD19 CAR-T cells. These side effects are usually self-limited, though could be life threatening in certain patients. The pathogenesis of these disorders are being fully elucidated and cytokine release from T-cell activation, endothelial dysfunction and immune mediated neural injury are postulated mechanisms. The type of CAR-T construct, cell dose, disease burden, bridging and conditioning regimens prior to CAR-T therapy used could all potentially impact toxicity occurrence.[3] Despite overall response rates of > 80% seen in trial data, durable responses are only seen in less than half of all CAR-T treated B-cell lymphoma patients. The variability of responses is not clearly explained and is likely multifactorial.[4] In the solid tumor arena with immune check-point inhibition, the occurrence of immune relate adverse events (irAEs) have been shown to be associated with a survival benefit.[5, 6]
Whether the occurrence of CRS/ ICANS influences the outcomes after anti-CD19 CAR-T cell therapy is unclear. We therefore propose a retrospective evaluation of the outcomes of patients undergoing anti-CD19 CAR-T therapy for B-cell lymphomas with respect to occurrence of immune-cell related adverse

events. In addition, we will attempt to evaluate the impact of other variables that could have an impact on outcomes after CAR-T therapy.

Study population:

Inclusion criteria:

- Adults≥ 18 years of age
- Diagnosis of relapsed/ refractory B-cell lymphoma
- Anti-CD19 CAR-T cell therapy during the years January 2017- October 2019

Study outcomes:

Primary outcomes:

- Progression-free survival: Survival following CAR-T cell therapy without relapse or progression. Relapse or progression of disease are considered events.

Secondary outcomes:

- Relapse/progression: Progressive disease or recurrences of disease would be counted as events. 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.
- Overall survival: 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: Cumulative incidence of NRM. NRM is defined as death without preceding disease relapse/progression. Relapse and progression are competing events.

Variables to be described:

*Bolded variables to be included in multivariate analysis

Main Effect: CRS/ICANS grades 1-4 after CAR-T cell therapy: No vs. Yes

Patient-related:

- **Age at CAR-T therapy, Continuous & by age group:decades**
- **Patient sex: male vs. female**
- **R-IPI score: Low vs intermediate vs High**
- **LDH at CAR-T therapy: low vs high**
- **Karnofsky performance status at transplant: ≥ 90 vs. < 90 vs. missing**
- **HCT comorbidity index at CAR-T therapy: 0 vs 1-2vs ≥ 3 vs. missing**
- **Race: Caucasian vs. others vs. missing**

Disease-related:

- **Remission status at HCT: PR vs. PD vs. untreated/unknown**
- **History of autologous transplant: no vs. yes**
- **History of allogeneic transplant: no vs yes**
- **Time from diagnosis to CAR-T therapy: ≥12 months vs.<12 months**
- **Time from prior transplant to CAR-T therapy: ≥12 months vs.<12 months**

CAR-T-related:

- **Bridging therapy used: Yes vs No**
- **Radiation used prior to CAR-T therapy: Yes vs No**
- **Type of conditioning regimen: Flu/Cy based vs Other vs No conditioning**
- **CAR-T cell construct used: CD28 vs 4-1BB vs other**

- **CAR-T cell dose employed**
- **Steroids used to treat CAR-T toxicity: Yes vs No**
- **Anti IL-6 agents used to treat CAR-T toxicity: Yes vs No**
- **Year of CAR-T delivery: Continuous**

Study design:
A retrospective multicenter study will be conducted utilizing CIBMTR dataset. Patients will be eligible if they satisfied the criteria detailed in the "Study population" section. Patients will then be stratified according to occurrence of CRS/ICANS. The objective of this analysis is to compare the effect of occurrence of CRS/ICANS on anti-CD19 CAR-T outcomes in patients with R/R B-cell lymphomas. Descriptive tables of patient, disease-, and transplant-related factors will be created and compared for both cohorts. The tables will list median and range for continuous variables and percent of total for categorical variables. Cumulative incidence of relapse/progression, and NRM will be calculated while accounting for competing events. Probabilities of PFS and OS will be calculated using the Kaplan-Meier estimator. Multivariate analysis will be performed using Cox proportional hazards models for outcomes for relapse/progression, NRM, PFS, and OS. A stepwise model building approach will then be used to identify the significant risk factors associated with the outcomes. Factors which are significant at a 5% level will be kept in the final model. The potential interactions between main effect and all significant risk factors will be tested. The proportional hazards assumption will be checked for the Cox model. If violated, it will be added as time-dependent covariates.

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Baseline characteristics for patients undergoing 1st CAR-T for NHL

Characteristic	N (%)
No. of patients	886
No. of centers	73
Age at infusion, by category - no. (%)	
Median (min-max)	62.25 (15.02-88.99)
10-19	4 (0.5)
20-29	20 (2.3)
30-39	44 (5)
40-49	92 (10.4)
50-59	217 (24.5)
60-69	335 (37.8)
>= 70	174 (19.6)
Gender - no. (%)	
Male	570 (64.3)
Female	316 (35.7)
Recipient race - no. (%)	
White	756 (85.3)
African-American	43 (4.9)
Asian	39 (4.4)
Other	1 (0.1)
More than one race	21 (2.4)
Not reported	26 (2.9)
Recipient ethnicity - no. (%)	
Hispanic or Latino	91 (10.3)
Non Hispanic or non-Latino	744 (84)
Non-resident of the U.S.	17 (1.9)
Unknown	34 (3.8)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	349 (39.4)
80	259 (29.2)
< 80	159 (17.9)
Not reported	119 (13.4)
Disease classification - no. (%)	
Follicular, predominantly small cleaved cell	3 (0.3)
Follicular, mixed small cleaved and large cell	7 (0.8)
Diffuse, large B-cell lymphoma - NOS	268 (30.2)
Mantle cell lymphoma	14 (1.6)

Characteristic	N (%)
Primary diffuse, large B-cell lymphoma of the CNS	2 (0.2)
T-cell/histiocytic rich large B-cell lymphoma	15 (1.7)
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)	1 (0.1)
Nodal marginal zone B-cell lymphoma	2 (0.2)
Primary mediastinal (thymic) large B-cell lymphoma	22 (2.5)
Other B-cell lymphoma	11 (1.2)
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL	3 (0.3)
Follicular, predominantly large cell (grade IIIA)	6 (0.7)
Follicular, predominantly large cell (grade IIIB)	4 (0.5)
Follicular (grade unknown)	7 (0.8)
Diffuse, large B-cell lymphoma - germinal center B-cell type	273 (30.8)
Diffuse, large B-cell lymphoma - activated B-cell type	164 (18.5)
EBV+ DLBCL, NOS	6 (0.7)
High-grade B-cell lymphoma, NOS	6 (0.7)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	64 (7.2)
Plasmablastic lymphoma	2 (0.2)
Not reported	6 (0.7)
Disease status prior to CT - no. (%)	
CR1	8 (0.9)
CR2	8 (0.9)
CR3+	12 (1.4)
Relapse, 1st	220 (24.8)
Relapse, other	288 (32.5)
PIF/Untreated	346 (39.1)
Not reported	4 (0.5)
Types of prior HCTs - no. (%)	
No	560 (63.2)
Yes	323 (36.5)
Prior allo-HCT(s)	22 (2.5)
Prior auto-HCT(s)	280 (31.6)
Prior auto and allo-HCT(s)	8 (0.9)
Not reported	13 (1.5)
Not reported	3 (0.3)
Year of CT - no. (%)	
2016	10 (1.1)
2017	28 (3.2)

Characteristic	N (%)
2018	537 (60.6)
2019	311 (35.1)
Commercial vs. noncommercial CAR-T product - no. (%)	
Commercial	816 (92.1)
Noncommercial	70 (7.9)

Proposal: 1911-145

Title: Real world practice pattern and clinical outcomes of subsequent therapy after CAR-T treatment in patients with lymphoma

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Research hypothesis:
Registration trials demonstrated that outcome for patients who do not achieve durable complete response (CR) with CAR-T therapy are poor (1-3). We hypothesize that patients who receive CART as standard of care (SOC) and do not achieve CR will have better survival if they can receive follow-up therapy. In addition, some therapy may yield better outcome than others. We aim to examine real world patient characteristics and practice patterns of the patients who received subsequent therapy after CAR-T and to identify outcomes with each categories of treatment. This data could be used to inform opportunities to design prospective studies to formally study management options in this patient population.
In addition, question still exist, particularly for patients with highly aggressive, refractory disease prior to CAR-T therapy, whether consolidation with allogeneic stem cell transplant (alloSCT) would offer additional benefit. We hypothesize that patients, who achieve CR, regardless of poor prognostic features, could be observed and do not need consolidation with allogeneic stem cell transplant for prolonged OS. In this proposal, we will examine real world practice patterns for patients who achieve CR and compare clinical outcome for those observed versus those consolidated with alloSCT.

Specific aims:
Aim 1:
- Compare PFS and OS between patients who received subsequent therapy and those who didn't for patients who did not achieve CR at their first assessment after CART infusion.
    - Describe practice pattern for patients with PR, SD, or PD as initial response in terms of period of observation, if any, prior to subsequent therapy and types of subsequent therapy.
    - Compare PFS and OS for patients who receive subsequent therapy versus those who didn't, and compare PFS/OS among the different types of subsequent therapy: immunotherapy, targeted therapy, chemotherapy.

Aim 2:
- Quantify the rate of best CR and PR to subsequent therapy for each category of therapy as described in Aim 1.

Aim 3:
- For patients who achieved CR, compare PFS and OS between those who were observed and those who received allogeneic stem cell transplant while in CR.
    - If sample size permits, analysis will be stratified for known poor prognostic features such as IPI and abnormal CRP/ferritin levels.

Scientific impact:
This practice patterns and outcomes of approved CD19 CART in real world standard of care practice will confirm areas of unmet need and delineate the landscape of future prospective trials. For example the use of allogeneic hematopoietic cell transplant as consolidation versus observation in patients achieving

CR, use of further therapies versus observation in patients that didn't achieve CR and outcomes of this population, as well predictors of ineligibility to receive further therapies.

Scientific justification:
The use of CD19 CAR T-cells is now established as a treatment of option for patients with relapsed and/or refractory (R/R) diffuse large B-cell lymphomas (DLBCL) (1-3). Despite the relative high response rate compared to other salvage therapies and durable survival for patients who achieve CR over a two year follow-up period, best follow-up management remains to be defined (2-3). For patients who achieve CR, overall follow-up is short in the 2 years range. Question remain whether allogeneic stem cell therapy offer any additional survival advantage for those with aggressive, refractory disease.
For patients who don't achieve durable CR, PFS and OS remain poor (1-4). Early reports of real world experience showed that many, close to 50%, of the patients treated with approved CART would not have qualified for registration CART trials (5-7). It is possible that some of these patients with less favorable characteristics would not tolerate subsequent therapy or perform worse with subsequent therapy when they do not respond to CAR-T. Indeed, single center practice experience for all patients with disease progression after CD19 CART showed a median overall survival of 5.3 months (4).
Enrollment in clinical trials was poor due to patient's clinical status. Identifying the optimal time to intervene and clinical characteristics that could inform rational selection of subsequent therapy is an unmet need. For example, while conversion of response to CR has been report, up to 40% in registration trial (1, 3), this is a limited number of patients. Whether similar rate is seen in real world practice where treated patients have different clinical characteristics from those in the registration trial is unknown. Defining current practice pattern for observation versus addition of therapy while the patient is in PR and outcome of the therapy could be hypothesis generating for future prospective study in the clinical characteristic of patients with higher likelihood converting to CR with observation alone and those who would benefit from additional therapy and considerations for therapy selection.

Patient eligibility population:
Patients with aggressive B cell lymphoma treated with Axicabtagene ciloleucel or Tisagenlecleucel as standard of care or through expanded access protocols for products that are out of specification.

Data requirements:
Forms 4000 V4, 4003 V1, 4006 V2 and 4100 V3.

Sample requirements:
None

Data extraction:
will be done from the CIBMTR database for all groups specified above.

Baseline characteristics to be compared among different study subgroups

Gender (female)	Categorical
Age	Ordinal
ECOG	Categorical
Date of diagnosis	
Diagnosis: DLBCL/PMBCL/tFL/High-grade	Categorical
R-IPI	Categorical
LDH at time of CD19 CAR-T cells	Ordinal

Bone marrow involvement at time of CD19 CAR T-cells	Categorical
Bulky disease at time of CD19 CAR T-cells	Categorical
Extra-nodal involvement at time of CD19 CAR T-cells	Categorical
CNS involvement at time of CD19 CAR T-cells	Categorical
Number or previous line of systemic therapies not including transplant	Ordinal
Prior autologous HCT	Categorical
Prior allogeneic HCT	Categorical
Lympho-depleting regimen:	Categorical
Date of infusion	
Cell dose:	Ordinal
Product: Axicabtagene ciloleucel or Tisagenlecleucel	Categorical
Grade Cytokine release syndrome: 0-IV	Categorical
Grade Neurotoxicity: 0-IV	Categorical
Ferritin peak	Ordinal
CRP peak	Ordinal

Follow-up characteristics to be compared among different study subgroups

Time from CD19 CAR T-cells	Ordinal
ECOG	Categorical
Hemoglobin (Hb)	Ordinal
Absolute Neutrophil Count (ANC)	Ordinal
Platelets counts (Plt)	Ordinal
Hypogammaglobinemia	Categorical
Name of the next therapy. Next line of treatment: specific therapies will be grouped into categories for radiation, chemotherapy, immunotherapy, targeted, clinical trials, autologous transplant or allogeneic transplant	Categorical
Date of start of next therapy after CAR-T	
Best response to next line of therapy	Categorical
Date of the stop of next therapy after CAR-T	
Date of progression of disease from next therapy	
Date of death	
Date of last follow-up	

Study design:

Study population:

There two main pts groups for all patients who received regulatory agency approved CART for aggressive lymphoma that will be studied. One main group is patient that didn't achieve CR at first response assessment after CD19 CAR T-cells infusion. This population will be stratified by initial response of PR, SD or PD. For each response category, analysis will be performed for those who did or did not receive subsequent therapies after CD19 CAR T-cells. Subsequent therapies will be grouped into chemotherapy, immunotherapy, radiation and targeted therapy. The other main group is patients who achieved CR and will be stratified among who received or not consolidation with allogeneic HCT.

Outcomes/analysis:

Categorical variables will be compared with chi-square and ordinal variables will be compared with Mann-Whitney U-test. Overall Survival and PFS will be estimated with Kaplan-Meier method and compared with log-rank test. OS is defined as time from infusion of CAR T-cells until death or last follow-up (censoring). For patients who achieved CR as first response to CART, PFS is defined as time from CAR-

T infusion to PD or death or last follow-up (censoring) regardless of whether they received subsequent alloSCT. For patients who did not achieve CR as their initial response, PFS and OS comparison between those who did or did not receive subsequent therapies will use date of CAR-T infusion to each defined event respectively. For comparison of PFS and OS of subsequent therapies, date of initiation of subsequent therapy to the date of defined event respectively will be used.
For patients with PR as first response, the percent of patients with PR as first response that did not receive subsequent therapy versus the percent who received subsequent therapy will be quantified. PFS and OS from the date of CART infusion will be estimated and compared between those who received subsequent therapy and those who didn't. For patients who did not receive subsequent therapy, the median and range of time between date of first response assessment and date of change in response will be calculated. The percent of the patients who converted to CR and the percent that evolved to PD will be calculated. Patient and disease characteristics will be compared for statistically significant difference between those who convert to CR vs those who progressed.
Similarly, for all patients with PR as initial response and who received subsequent therapies, we will define the median and range of time between first response and the start of subsequent therapy. Subsequent therapies will be grouped radiation only, Immunotherapy, targeted therapy or chemotherapy. The number of patients in each category of therapy, the median and range of length of subsequent therapy, and the best response rate for CR and PR will be calculated for each category of subsequent therapy. Wherever sample size allows, multivariate analysis (logistic regression model) will be performed to identify correlative patient and disease specific characteristic associated with CR, PFS and OS from the time of CART infusion will be estimated for each category of treatment and compared.
For patients with SD or PD as 1st response, similar analysis will be performed as described for the PR response population.
For patients who achieved CR as their first response, the number and percent of patients who received subsequent alloSCT will be quantified. PFS and OS will be estimated between those observed after achieving CR and those who received allogeneic HCT. PFS and OS analysis will be stratified by known prognostic features such as IPI, normal vs abnormal baseline CRP, normal versus abnormal baseline Ferritin and compared between those who were observed and those who received allogeneic HCT.

Conflicts of interest:
Evandro Dantas Bezerra: None.
Grzegorz Nowakowski: None.
Yi Lin: research funding from Janssen, Kite/Gilead, Celgene, BlueBird Bio; consultancy with Kite/Gilead, Novartis, Janssen, Legend Biotech, BlueBird Bio, Celgene, JUNO, AlloGene, Gamida Cells. DSMB: Sorrento. Steering Committee: Legend Biotech, Janssen, Celgene. All funds paid to Mayo, no personal compensation.
Shahrukh Hashmi: None.

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Baseline characteristics for patients undergoing 1st commercial CAR-T for NHL

Characteristic	N (%)
No. of patients	875
No. of centers	75
Age at infusion, by category - no. (%)	
Median (min-max)	62.34 (15.02-88.99)
10-19	4 (0.5)
20-29	21 (2.4)
30-39	42 (4.8)
40-49	85 (9.7)
50-59	210 (24)
60-69	338 (38.6)
>= 70	175 (20)
Gender - no. (%)	
Male	566 (64.7)
Female	309 (35.3)
Recipient race - no. (%)	
White	750 (85.7)
African-American	40 (4.6)
Asian	37 (4.2)
Other	1 (0.1)
More than one race	19 (2.2)
Not reported	28 (3.2)
Recipient ethnicity - no. (%)	
Hispanic or Latino	83 (9.5)
Non Hispanic or non-Latino	742 (84.8)
Non-resident of the U.S.	16 (1.8)
Unknown	33 (3.8)
Not reported	1 (0.1)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	337 (38.5)
80	266 (30.4)
< 80	157 (17.9)
Not reported	115 (13.1)
Disease classification - no. (%)	
Follicular, predominantly small cleaved cell	3 (0.3)
Follicular, mixed small cleaved and large cell	7 (0.8)
Diffuse, large B-cell lymphoma - NOS	258 (29.5)
Mantle cell lymphoma	8 (0.9)

Characteristic	N (%)
Primary diffuse, large B-cell lymphoma of the CNS	2 (0.2)
T-cell/histiocytic rich large B-cell lymphoma	15 (1.7)
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)	1 (0.1)
Nodal marginal zone B-cell lymphoma	2 (0.2)
Primary mediastinal (thymic) large B-cell lymphoma	23 (2.6)
Other B-cell lymphoma	9 (1)
Intravascular large B-cell lymphoma	1 (0.1)
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL	3 (0.3)
Follicular, predominantly large cell (grade IIIA)	5 (0.6)
Follicular, predominantly large cell (grade IIIB)	4 (0.5)
Follicular (grade unknown)	8 (0.9)
Follicular, predominantly large cell (grade IIIA vs IIIB unspecified)	1 (0.1)
Diffuse, large B-cell lymphoma - germinal center B-cell type	277 (31.7)
Diffuse, large B-cell lymphoma - activated B-cell type	165 (18.9)
EBV+ DLBCL, NOS	6 (0.7)
High-grade B-cell lymphoma, NOS	6 (0.7)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	69 (7.9)
Plasmablastic lymphoma	2 (0.2)
Disease status prior to CT - no. (%)	
CR1	7 (0.8)
CR2	10 (1.1)
CR3+	13 (1.5)
Relapse, 1st	218 (24.9)
Relapse, other	270 (30.9)
PIF/Untreated	356 (40.7)
Not reported	1 (0.1)
Types of prior HCTs - no. (%)	
No	579 (66.2)
Yes	292 (33.4)
Prior allo-HCT(s)	17 (1.9)
Prior auto-HCT(s)	257 (29.4)
Prior auto and allo-HCT(s)	5 (0.6)
Not reported	13 (1.5)
Not reported	4 (0.5)
Year of CT - no. (%)	
2017	6 (0.7)
2018	516 (59)
2019	353 (40.3)
Commercial vs. noncommercial CAR-T product - no. (%)	

Characteristic	N (%)
Commercial	875
Lymphodepleting chemotherapy - no. (%)	
Bendamustine	6 (0.7)
Bendamustine + Corticosteroids	7 (0.8)
Corticosteroids + Other	1 (0.1)
Cyclophosphamide	2 (0.2)
Cyclophosphamide + Cytarabine + Fludarabine + Monoclonal antibody	1 (0.1)
Cyclophosphamide + Fludarabine	841 (96.1)
Cyclophosphamide + Fludarabine + Monoclonal antibody	1 (0.1)
Cyclophosphamide + Fludarabine + TKI	1 (0.1)
Cytarabine + Fludarabine	1 (0.1)
Cytarabine + Fludarabine + Monoclonal antibody	1 (0.1)
Monoclonal antibody	1 (0.1)
Nitrosourea	1 (0.1)
Other	3 (0.3)
Not reported	8 (0.9)
Therapy given for maintenance or consolidation reported during the follow-up for this CT - no. (%)	
No	814 (93)
Yes	61 (7)
Systemic therapy	50 (5.7)
Radiation therapy	14 (1.6)
Cellular therapy	4 (0.5)
Other therapy	9 (1)
Therapy given for treating relapse, persistent/progressive disease, or MRD reported during the follow-up for this CT - no. (%)	
No	640 (73.1)
Yes	235 (26.9)
Systemic therapy (other than CT/HCT)	205 (23.4)
Intrathecal therapy	13 (1.5)
Radiation therapy	82 (9.4)
Cellular therapy	4 (0.5)
Other therapy	4 (0.5)
Subsequent HCT since the CT infusion - no. (%)	
No	609 (69.6)
Yes	19 (2.2)
Not reported	247 (28.2)

Proposal: 1911-41

Title:
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

Patrick Connor Johnson, MD, Patrick_Johnson@dfci.harvard.edu, Dana-Farber Cancer Institute; Massachusetts General Hospital
Areej El-Jawahri, MD, ael-jawahri@partners.org, Massachusetts General Hospital

Specific aims and hypotheses:
Specific aim 1**:**
To compare PFS and OS at 6 months and one year for patients undergoing CAR T-cell therapy who (a) relapse within one year of autologous stem cell transplantation (SCT) versus (b) those who never received autologous SCT.

- Hypothesis 1.1: Patients undergoing CAR T-cell therapy who never received autologous SCT will have higher PFS and OS at 6 months and one year compared to patients undergoing CART-cell therapy who relapse within one year of autologous SCT.

Specific aim 2:
To compare NRM at 6 months and one year for patients undergoing CAR T-cell therapy who (a) relapse within one year of autologous SCT versus (b) those who never received autologous SCT.

- Hypothesis 2.1: Patients undergoing CAR-T cell therapy who never received autologous SCT will have lower NRM at 6 months and one year compared to patients undergoing CART-cell therapy who relapse within one year of autologous SCT.

Specific aim 3:
To compare rates of CRS and ICANS in patients undergoing CAR T-cell therapy who (a) relapse within one year of autologous SCT versus (b) those who never received autologous SCT.

- Hypothesis 3.1: Rates of CRS and ICANS will not differ statistically among patients undergoing CAR T-cell therapy who relapsed within one year of autologous SCT versus those who never received autologous SCT

Scientific impact:
Our study has the potential to provide unique contributions to the growing CAR-T literature. First, to our knowledge, this is the first study to assess the outcomes of patients receiving CAR T-cell therapy who relapse within one year after autologous SCT versus those that never receive autologous SCT and will offer insight into the impact autologous SCT has on CAR T-cell therapy outcomes. Second, this study will provide important insights regarding the potential for CART-cell therapy in the second-line setting for treatment of lymphomas by enhancing our understanding of how CAR T-cell therapy outcomes are impacted by prior autologous SCT. The role of CAR T-cell therapy in the second-line setting for treatment of lymphomas will only be definitively assessed with randomized controlled trials, but this study will provide valuable information to further our understanding of the optimal sequencing of therapies. Lastly, this study will add to our understanding of the rates of toxicity such as CRS and ICANS in these patient populations receiving CAR T-cell therapy. The use of a large database such as the Center for International Blood and Marrow Transplant (CIBMTR) will allow for a greater understanding of these important research questions.

Scientific justification:
CAR T-cell therapy is a novel treatment that has changed the landscape of treatment options for patients with hematologic malignancies, including large B-cell lymphoma[1,2]. Patients with refractory large B-cell lymphoma or disease relapsing after autologous SCT historically had a dismal prognosis, with a median survival of approximately 6.3 months[3]. In relapsed/refractory large B-cell lymphomas, multiple CAR T-cell products have been investigated and have demonstrated durable remissions in approximately 40% of patients[4,5]. This has revolutionized the treatment options and outcomes for these patients.
Unfortunately, the current second-line therapy options for patients with large B-cell lymphomas are associated with poor outcomes[6,7]. Only about half of patients are able to proceed with autologous SCT, primarily due to poor responses to second-line chemotherapy[6,7]. Therefore, improved second-line therapy options are clearly an unmet need in large B-cell lymphomas.
Given the encouraging results seen with CAR T-cell therapy, the optimal sequencing of high dose chemotherapy and autologous SCT and CAR T-cell therapy for aggressive B-cell lymphomas is a crucial unanswered question. Chemosenstive disease may still benefit from chemotherapy followed by autologous SCT in some patients[6], but chemotherapy may be toxic to patients' T cells and may delay the time to a more effective therapy. Thus, additional research in needed to compare the outcomes of patients receiving CAR T-cell therapy after an autologous SCT versus patients who never undergo autologous SCT in order to augment the understanding of how to best sequence therapies.
To date there has not been a large study assessing the outcomes of patients receiving CAR T-cell therapy after autologous SCT versus those who do not undergo autologous SCT. We hope to better understand the impact of autologous SCT on CAR T-cell therapy clinical outcomes by comparing the NRM, PFS, and OS of patients who relapse within a year of autologous SCT versus those patients who never undergo autologous SCT. Additionally, we hope to characterize the rates of toxicities, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), in these patient populations. In this study, we will control for possible confounders utilizing the CIBMTR database to extract important patient-, disease-, and CAR T-cell-related variables that may impact the relationship of autologous SCT and clinical outcomes. Developing a greater understanding of the relationship of autologous SCT on CAR T-cell therapy outcomes could have critical ramifications for the management of aggressive B-NHL. This data could help guide future research targeted at optimizing the sequencing of therapies in aggressive B-NHL.

Patient eligibility population:
We propose to study all adult ($\geq$18 years of age) patients who received CAR T-cell therapy for a diagnosis of lymphoma from 2008-2018 in the United States who relapsed within one year of autologous SCT or never received autologous SCT.

Data requirements:
- Data collection forms: (1) Recipient Baseline Data, (2) Pre-Cellular Thearpy Essential Data, (3) Post-Cellular Therapy Follow-Up Data, (4) Cellular Therapy Product, (5) Cellular Therapy Infusion
- No supplemental data collection will be required.
- Data variables: Relapse within one year of autologous SCT versus never undergoing autologous SCT, demographic variables (age, gender, race, ethnicity, marital status, education, income, smoking history), diagnosis, stage, double or triple HIT lymphoma (yes or no), number of prior lines of therapy, disease status prior to CAR T-cell therapy, comorbidities, date of infusion, type of CAR T-cell product, lymphodepletion regimen, bridging therapy (yes or no), bridging therapy regimen, region of CAR T-cell therapy center, interval of diagnosis to CAR T-cell infusion, development of CRS, grade of

CRS, development of ICANS, grade of ICANS, date of relapse/progression, date of death, survival status, cause of death, and ECOG performance status.

Sample requirements:
No NMDP samples will be used.

Study design:
The CIBMTR is a prospectively maintained international database that will be used to identify patients who underwent CAR T-cell therapy. Patients will be categorized based on having relapsed within one year of autologous SCT versus never receiving autologous SCT. In univariate analysis, patient-, disease-, CAR T-cell therapy- and toxicity-related variables will be compared between these two patient populations using chi square statistics for categorical variables, and Kruskal-Wallis test for continuous variables. OS and PFS will be estimated using the Kaplan-Meier method with the log-rank test used for univariate comparisons. Probabilities of NRM, CRS, and ICANS will be estimated using cumulative incidence to allow for competing risks.
In the multivariate analyses, we will compare the outcomes of NRM, PFS, and OS using Cox proportional hazard models to adjust for potential imbalance in baseline characteristics between the two patient groups. A model will be built for each primary outcome of interest as a dependent variable and all the relevant exposure variables as explanatory variables. A main effect term of relapse after autologous SCT or no autologous SCT will be forced into the model at each step. Interaction between the main effect term and other significant explanatory variables will be explored. The following variables will be considered in model building: relapse after autologous or no autologous SCT (main effect), patient's demographics (age, gender, race, education, marital status), smoking history, pre-CAR T-cell therapy performance status, lymphoma diagnosis, number of prior lines of therapy, disease status prior to CAR T-cell therapy (stage, presence or absence of double or triple HIT lymphoma), comorbid conditions, type of CAR T-cell product, year of CAR T-cell therapy, region of CAR T-cell therapy center, interval diagnosis of relapse to CAR T-cell therapy treatment, lymphodepletion regimen, bridging therapy (yes vs. no and regimen), post-CAR T-cell infection, development of CRS, maximum overall grade of CRS, development of ICANS, and maximum grade of ICANS.
In a multivariate analysis controlling for significant confounders, we will also compare the incidence of CRS and ICANS among patients who relapse within a year of autologous SCT versus those who never have undergone autologous SCT. We will also compare cause of death among these patient groups undergoing CAR T-cell therapy using chi square statistics and in a multivariate analysis controlling for significant confounders**.**
The findings of this study could add important knowledge about the association of autologous SCT before CAR T-cell therapy with the outcomes of PFS, OS, and NRM for patients with relapsed lymphoma. It can potentially improve the understanding of the optimal sequencing of therapies in relapsed large B-cell lymphomas.

Non-CIBMTR data source:
No external data sources will be used.

Conflicts of interest:
None

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Baseline characteristics for patients undergoing 1st CAR-T for NHL with/without prior auto-HCT

Characteristic	N (%)
No. of patients	840
No. of centers	72
Age at infusion, by category - no. (%)	
Median (min-max)	62.33 (15.02-88.99)
10-19	4 (0.5)
20-29	20 (2.4)
30-39	38 (4.5)
40-49	84 (10)
50-59	206 (24.5)
60-69	314 (37.4)
>= 70	174 (20.7)
Gender - no. (%)	
Male	536 (63.8)
Female	304 (36.2)
Recipient race - no. (%)	
White	718 (85.5)
African-American	41 (4.9)
Asian	36 (4.3)
Other	1 (0.1)
More than one race	20 (2.4)
Not reported	24 (2.9)
Recipient ethnicity - no. (%)	
Hispanic or Latino	85 (10.1)
Non Hispanic or non-Latino	708 (84.3)
Non-resident of the U.S.	13 (1.5)
Unknown	34 (4)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	327 (38.9)
80	250 (29.8)
< 80	153 (18.2)
Not reported	110 (13.1)
Disease classification - no. (%)	

Characteristic	N (%)
Follicular, predominantly small cleaved cell	3 (0.4)
Follicular, mixed small cleaved and large cell	6 (0.7)
Diffuse, large B-cell lymphoma - NOS	253 (30.1)
Mantle cell lymphoma	12 (1.4)
Primary diffuse, large B-cell lymphoma of the CNS	2 (0.2)
T-cell/histiocytic rich large B-cell lymphoma	13 (1.5)
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)	1 (0.1)
Nodal marginal zone B-cell lymphoma	2 (0.2)
Primary mediastinal (thymic) large B-cell lymphoma	21 (2.5)
Other B-cell lymphoma	10 (1.2)
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL	3 (0.4)
Follicular, predominantly large cell (grade IIIA)	6 (0.7)
Follicular, predominantly large cell (grade IIIB)	4 (0.5)
Follicular (grade unknown)	7 (0.8)
Diffuse, large B-cell lymphoma - germinal center B-cell type	262 (31.2)
Diffuse, large B-cell lymphoma - activated B-cell type	157 (18.7)
EBV+ DLBCL, NOS	6 (0.7)
High-grade B-cell lymphoma, NOS	6 (0.7)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	62 (7.4)
Plasmablastic lymphoma	2 (0.2)
Not reported	2 (0.2)
Disease status prior to CT - no. (%)	
CR1	7 (0.8)
CR2	7 (0.8)
CR3+	9 (1.1)
Relapse, 1st	215 (25.6)
Relapse, other	263 (31.3)
PIF/Untreated	337 (40.1)
Not reported	2 (0.2)
Types of prior HCTs - no. (%)	
No	560 (66.7)
Yes	280 (33.3)
Prior auto-HCT(s)	280 (33.3)

Characteristic	N (%)
Year of CT - no. (%)	
2016	10 (1.2)
2017	24 (2.9)
2018	508 (60.5)
2019	298 (35.5)
Commercial vs. noncommercial CAR-T product - no. (%)	
Commercial	778 (92.6)
Noncommercial	62 (7.4)

Proposal: 1911-148

Title:
Clinical Outcomes of CAR-T cell therapy in Transplant Naïve Patients versus CAR-T cell Therapy post Autologous Transplant

Nirav N. Shah MD, MSHP, nishah@mcw.edu, Medical College of Wisconsin
Parameswaran Hari, MD, phari@mcw.edu, Medical College of Wisconsin

Hypothesis:
CAR-T cell therapy improves PFS in patients who are autologous transplant naïve compared to patients previously exposed to transplant

Specific aims:
To evaluate clinical outcomes in terms of progression free and overall survival

- Primary outcome will be to compare progression free survival of anti-CD19 CAR-T cell treated patients with aggressive NHL who are transplant naïve versus those who relapse post-transplant.
- Secondary outcomes will include overall survival, relapse rates, and rates of non-relapse mortality.

Scientific justification:
Diffuse large B-cell lymphoma (DLBCL) is the most common form of aggressive non-Hodgkin lymphoma (NHL) accounting for approximately 30-40% of cases[1]. The standard frontline treatment option generally includes combination chemo-immunotherapy given for 6-8 cycles of which R-CHOP (Rituximab, Cyclophosphamide, Adriamycin, and Prednisone) is considered standard of care for most patients[1, 2]. Despite long-term remissions achieved in approximately 60% of patients, for those with high risk features such as single or double hit lymphoma, primary refractory disease, or early relapse outcomes remain poor [3, 4].
Prior to the advent of CAR-T cell therapy the standard of care for relapsed DLBCL was salvage chemotherapy and in responding patients' consolidation with an autologous stem cell transplant[5]. For those who relapsed post-autoHCT, options were generally limited. With results of pivotal phase II studies, CAR-T cell therapy is now offered in patients who are not auto-transplant candidates[6, 7]. This phenotype of patients is likely different than those who are able to achieve a clinical response and then proceed with autologous transplant. Additionally, CAR-T cell therapy earlier in the course may impact clinical outcomes compared to patients who receive after autologous transplant due to clonal evolution of the tumor.
To better understand the differences in these varying patient populations we are proposing a CIBMTR analysis to compare anti-CD19 CAR-T cell outcomes among aggressive B-cell NHL patients who are auto-transplant naïve vs. those who relapse post-autoHCT.

Patient eligibility population:
Inclusion/exclusion criteria:

- Prior autologous transplant patients
    - Aggressive B-cell NHL subjects>18 years of age at the time of transplant
    - Received CD19 CAR-T after relapse/progression from prior auto-HCT
- Auto-HCT naive
    - Adults>18 years who received anti-CD19 CAR-T cell therapy who have NOT had a prior autologous transplant

Data requirements:

- Data will be captured through CIBMTR collection forms

Demographic/patient level variables to be analyzed:

Main effect:

- Auto-HCT naïve vs Auto-HCT cohort

Patient-related:

- Age at time of transplant or CAR-T treatment, Continuous & decades
- Gender: male or female
- Karnofsky performance status at transplant: < 90% vs. ≥ 90%
- HCT comorbidity index at transplant 0, 1, 2, and ≥ 3

Disease-related:

- Disease stage at diagnosis: I/II vs III/IV
- Chemo-resistant vs Chemo-sensitive disease
- Time from diagnosis to transplant

Study outcomes:

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.

Relapse/progression:

Progressive disease or recurrences of disease would be counted as events. 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.

Study design:

A retrospective multicenter study will be conducted utilizing CIBMTR dataset involving patients who received anti-CD19 CAR-T cell therapy aggressive B-cell NHL stratified by exposure to prior autologous transplant versus no prior transplant. Patients will be eligible if they satisfied the criteria detailed in the patient eligibility section above. The objective of this analysis is report outcomes, survival, and NRM within the two cohorts.

PFS and OS will be calculated using the Kaplan-Meier estimator. For NRM, relapse/progression will be the competing event. For relapse rate, NRM will be the competing event. Data on patients without an event will be censored at last follow up. For univariate analysis, the log-rank test will be used to identify factors influencing survival and to compare survival among CAR-19 patients who received a prior auto-

HCT versus those who are auto-HCT naïve with relapsed DLBCL. The association between treatment groups and outcomes will be studied with multivariate Cox regression models. P values are 2 sided and values < 0.05 will be considered significant.
The other variables tested will be retained in the final multivariate model if the variable will attain the level of significance set for these analyses. Results will be expressed as hazard ratio (HR) with 95% confidence intervals (CI). Possible interactions within the treatment groups and other variables will be tested. All models will be tested regarding proportional hazard of assumptions (PHA). If the assumption will be violated, time dependent covariates will be constructed.

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7. Schuster, S.J., et al., Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med, 2018. 380(1): p. 45-56.

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60-69	314 (37.4)
>= 70	174 (20.7)
Gender - no. (%)	
Male	536 (63.8)
Female	304 (36.2)
Recipient race - no. (%)	
White	718 (85.5)
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Asian	36 (4.3)
Other	1 (0.1)
More than one race	20 (2.4)
Not reported	24 (2.9)
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Hispanic or Latino	85 (10.1)
Non Hispanic or non-Latino	708 (84.3)
Non-resident of the U.S.	13 (1.5)
Unknown	34 (4)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	327 (38.9)
80	250 (29.8)
< 80	153 (18.2)
Not reported	110 (13.1)
Disease classification - no. (%)	
Follicular, predominantly small cleaved cell	3 (0.4)
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Diffuse, large B-cell lymphoma - germinal center B-cell type	262 (31.2)
Diffuse, large B-cell lymphoma - activated B-cell type	157 (18.7)
EBV+ DLBCL, NOS	6 (0.7)
High-grade B-cell lymphoma, NOS	6 (0.7)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	62 (7.4)
Plasmablastic lymphoma	2 (0.2)
Not reported	2 (0.2)
Disease status prior to CT - no. (%)	
CR1	7 (0.8)
CR2	7 (0.8)
CR3+	9 (1.1)
Relapse, 1st	215 (25.6)
Relapse, other	263 (31.3)
PIF/Untreated	337 (40.1)
Not reported	2 (0.2)
Types of prior HCTs - no. (%)	
No	560 (66.7)
Yes	280 (33.3)
Prior auto-HCT(s)	280 (33.3)
Year of CT - no. (%)	
2016	10 (1.2)
2017	24 (2.9)
2018	508 (60.5)
2019	298 (35.5)
Commercial vs. noncommercial CAR-T product - no. (%)	
Commercial	778 (92.6)

Characteristic	N (%)
Noncommercial	62 (7.4)

Proposal: 1911-149

Title:
Patient derived donor origin CAR-T cell therapy for B cell malignancy patients who have Relapsed Post Allogeneic Transplant

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Hypothesis:
CAR-T cell therapy is safe and effective utilizing donor origin autologous T-cells from patients who have established donor hematopoiesis after post-allogeneic transplant.

Specific aims:
To evaluate clinical outcomes in terms of progression free and overall survival

- Primary outcome will be to evaluate TRM, GVHD and special complications among patients who have received anti-CD19 CAR-T cell therapy post-allogeneic transplant for CD19 positive malignancies.
- Secondary outcomes will include OS, PFS, relapse rates, and rates of non-relapse mortality.

Scientific justification:
CAR-T cell therapy has revolutionized the management of relapsed, refractory B-cell malignancies with impressive outcomes in chemorefractory non-Hodgkin lymphoma (NHL) and B-cell ALL patients. For patients with aggressive B-cell NHL CD19 targeted CAR-T cell therapy leads to long-term PFS in the 30-40% range[1, 2]. However, many patients included in pivotal trials for CAR-T cell therapy were excluded if they had a history of prior allogeneic transplant due to concerns that CAR-T cell therapy may lead to adverse outcomes such as graft-versus-host-disease (GVHD) in these patients. However, there are small reports of patients receiving CAR-T post-allogeneic transplant for B-cell malignancies which has demonstrated it to be safe and effective (see below table adapted from Liu et al. JAHO 2017)[3].

Table 1 The results of allogeneic CAR-T cell infusion after allogeneic transplantation in B cell malignancies

Author	No. of patients	Disease	Activation motif of CAR	Dose of infused CAR-T	No. of GVHD	Toxicities	Outcomes
Kochenderfer et al.	10	CLL, DLBCL, and MCL	28	Between 0.4×10^6/kg and 7.8×10^6/kg	No	Fatigue, fever, and hypotension	1 CR, 1 PR, and 6 with stable disease
Cruz et al.	8	CLL and ALL	28	Escalation schedule of $1.5\times10^7/m^2$, $4.5\times10^7/m^2$, and $1.2\times10^8/m^2$	No	No	2 CR(1 remained in CR for 8 months and the other 1 for 8 weeks)
Brudno et al.	20	CLL, DLBCL, MCL, and ALL	28	From 10^6/kg to 10^7/kg	2 (mild chronic GVHD)	Fever, tachycardia, and hypotension	8 of 20 patients obtained remission (6 CR and 2 PR)
Zuo et al.	1	ALL	28, 137, and 27	First dose 10^6/kg and three maintenance (from 0.83×10^6 to 1.65×10^6/kg)	No	Mild or moderate CRS	DFS for 10 months
Grupp et al.	1	ALL	28	1.4×10^6/kg	No	Fever	MRD-negative CR at approximately 1 month and relapse after 2 months

CLL chronic lymphocytic leukemia, *DLBCL* diffuse large B cell lymphoma, *MCL* mantle cell lymphoma, *ALL* acute lymphoblastic leukemia, *CAR* chimeric antigen receptor, *CAR-T* chimeric antigen receptors redirected T cells, *GVHD* graft-versus-host disease, *CRS* cytokine release syndrome, *CR* complete remission, *PR* partial remission, *DFS* disease-free survival, *MRD* minimal residual disease

These above data provide evidence at a small scale that CAR-T cells from patient apheresis products who have underwent allogeneic transplant is a reasonable consideration. To better assess the safety and efficacy of CAR-T cells produced from patients relapsing with NHL or ALL post-allogeneic transplant, a

larger sample size is indicated. Through the CIBMTR registry, patients can be identified who have had a history of an allogeneic transplant and subsequently received commercial CAR-T cell product for management of relapsed disease. These data will be clinically valuable given the limited information for this patient population.

Patient eligibility population:
Inclusion/exclusion criteria:

- Diagnosis of CD19 positive cancer – ALL or B-cell NHL
- Underwent allogeneic transplant prior to CAR-T cell therapy
- Received CD19 directed CAR-T cell therapy for relapse of original malignancy

Data requirements:

- Data will be captured through CIBMTR collection forms

Demographic/patient level variables to be analyzed:
Main effect:

- Anti-CD19 CAR-T cell outcomes among relapsed B-cell malignancy patients who have had a prior allogeneic transplant.

Patient-related:

- Age at time of CAR-T treatment, Continuous & decades
- Gender: male or female
- Karnofsky performance status at transplant: < 90% vs. ≥ 90%
- HCT comorbidity index at transplant 0, 1, 2, and ≥ 3

Disease-related:

- Disease stage at diagnosis: I/II vs III/IV for NHL only

Study outcomes:
Incidence of GVHD or other alloimmune complications:

Acute and chronic GVHD:
Occurrence of grades II, III and/or IV acute GVHD, and limited and extensive chronic GVHD.

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.

Relapse/progression:
Progressive disease or recurrences of disease would be counted as events. 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.

Study design:
A retrospective multicenter study will be conducted utilizing CIBMTR dataset involving patients with history of prior allogeneic transplant for B-cell malignancies who subsequently received anti-CD19 CAR-T cell therapy for management of relapse. Patients will be eligible if they satisfied the criteria detailed in the patient eligibility section above. The objective of this analysis is report complications and safety , outcomes, survival, rates of GVHD, and NRM.
PFS and OS will be calculated using the Kaplan-Meier estimator. For NRM, relapse/progression will be the competing event. For relapse rate, NRM will be the competing event. Data on patients without an event will be censored at last follow up. For univariate analysis, the log-rank test will be used to identify factors influencing survival. The association between variables and outcomes will be studied with multivariate Cox regression models. P values are 2 sided and values < 0.05 will be considered significant. The other variables tested will be retained in the final multivariate model if the variable will attain the level of significance set for these analyses. Results will be expressed as hazard ratio (HR) with 95% confidence intervals (CI). Possible interactions within the treatment groups and other variables will be tested. All models will be tested regarding proportional hazard of assumptions (PHA). If the assumption will be violated, time dependent covariates will be constructed.

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Baseline characteristics for patients undergoing 1st CAR-T for ALL/NHL with/without prior allo-HCT

Characteristic	ALL	NHL	Total
No. of patients	288	582	870
No. of centers	56	65	94
Age at infusion, by category - no. (%)			
Median (min-max)	13.67 (0.41-74.63)	62.41 (15.02-88.99)	54.66 (0.41-88.99)
< 10	90 (31.3)	0	90 (10.3)
10-19	134 (46.5)	4 (0.7)	138 (15.9)
20-29	51 (17.7)	14 (2.4)	65 (7.5)
30-39	3 (1)	30 (5.2)	33 (3.8)
40-49	2 (0.7)	59 (10.1)	61 (7)
50-59	3 (1)	136 (23.4)	139 (16)
60-69	3 (1)	212 (36.4)	215 (24.7)
>= 70	2 (0.7)	127 (21.8)	129 (14.8)
Gender - no. (%)			
Male	168 (58.3)	365 (62.7)	533 (61.3)
Female	120 (41.7)	217 (37.3)	337 (38.7)
Recipient race - no. (%)			
White	201 (69.8)	494 (84.9)	695 (79.9)
African-American	17 (5.9)	27 (4.6)	44 (5.1)
Asian	10 (3.5)	25 (4.3)	35 (4)
Other	4 (1.4)	1 (0.2)	5 (0.6)
More than one race	41 (14.2)	17 (2.9)	58 (6.7)
Not reported	15 (5.2)	18 (3.1)	33 (3.8)
Recipient ethnicity - no. (%)			
Hispanic or Latino	108 (37.5)	61 (10.5)	169 (19.4)
Non Hispanic or non-Latino	153 (53.1)	490 (84.2)	643 (73.9)
Non-resident of the U.S.	9 (3.1)	7 (1.2)	16 (1.8)
Unknown	18 (6.3)	24 (4.1)	42 (4.8)
Karnofsky/Lansky performance score prior to CT - no. (%)			
90-100	191 (66.3)	213 (36.6)	404 (46.4)
80	48 (16.7)	186 (32)	234 (26.9)
< 80	35 (12.2)	117 (20.1)	152 (17.5)
Not reported	14 (4.9)	66 (11.3)	80 (9.2)
Disease status prior to CT - no. (%)			
CR1	21 (7.3)	5 (0.9)	26 (3)
CR2	29 (10.1)	4 (0.7)	33 (3.8)

Characteristic	ALL	NHL	Total
CR3+	43 (14.9)	4 (0.7)	47 (5.4)
Relapse, 1st	75 (26)	148 (25.4)	223 (25.6)
Relapse, other	74 (25.7)	108 (18.6)	182 (20.9)
PIF/Untreated	39 (13.5)	310 (53.3)	349 (40.1)
Not reported	7 (2.4)	3 (0.5)	10 (1.1)
Types of prior HCTs - no. (%)			
No	187 (64.9)	560 (96.2)	747 (85.9)
Yes	101 (35.1)	22 (3.8)	123 (14.1)
Prior allo-HCT(s)	101 (35.1)	22 (3.8)	123 (14.1)
Year of CT - no. (%)			
2015	3 (1)	0	3 (0.3)
2016	8 (2.8)	4 (0.7)	12 (1.4)
2017	51 (17.7)	11 (1.9)	62 (7.1)
2018	149 (51.7)	353 (60.7)	502 (57.7)
2019	77 (26.7)	214 (36.8)	291 (33.4)
Commercial vs. noncommercial CAR-T product - no. (%)			
Commercial	198 (68.8)	555 (95.4)	753 (86.6)
Noncommercial	90 (31.3)	27 (4.6)	117 (13.4)

Proposal: 1911-261

Title:
Outcomes of CD-19 Chimeric Antigen Receptor T cell therapy after allogeneic hematopoietic cell transplantation for relapsed B-cell lymphoid malignancies.

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Research hypothesis:
Chimeric antigen receptor T (CAR-T) cell therapy may offer improved outcomes for patients with B-cell lymphoid malignancies relapsing after allogeneic hematopoietic cell transplantation (allo-HCT).

Specific aims:
Primary aim:
Compare progression free survival (PFS) and overall survival (OS) with CAR-T cell therapy versus donor lymphocyte infusion (DLI)/immunotherapy versus chemotherapy in patients with lymphoid malignancy who have relapsed after allogeneic hematopoietic cell transplant (allo-HCT).

Secondary aims:
Identify prognostic markers that may predict response to CAR-T therapy in patients relapsing after allo-HCT

Scientific impact:
For patients with lymphoid malignancies who relapse after allo-HCT, we seek to compare long term PFS among those who went on to receive CAR-T cell versus other donor lymphocyte infusion/immunotherapy versus chemotherapy. Thus, this study will more clearly delineate the optimal therapeutic approach for treatment of patients with B-cell lymphoid malignancies who relapse after allo-HCT.

Scientific justification:
Relapsed B-cell lymphoid malignancies after allo-HCT are associated with poor outcomes and low rates of remission.[1,2] Post-transplant cellular therapies have been under study to prevent post-transplant relapse, though relapse rates remain ~30% .[3] Past therapies such as donor lymphocyte infusions (DLI) including donor-derived T and natural killer (NK) cells may prevent or treat relapsed disease after allo-HCT through a graft-versus-tumor (GVT) effect but are associated with significant morbidity due to graft-versus-host-disease (GVHD) and other side effects.[4,5]
Chimeric antigen receptor (CAR) T-cell therapy has emerged as a novel therapeutic modality by redirecting T-cell anti-tumor effector responses toward B-lineage hematological malignancies and have demonstrated greater potency and more durable responses than monoclonal antibodies.[6-10] Favorable response in relapsed/refractory acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL) without prior transplant suggest that CAR T-cell therapy may induce remissions after post-transplant relapse.[11-14] CAR-T cell therapy may enhance the GVT response and thus could induce remissions in patients with refractory/relapsed B-cell malignancies.[7-9,15] However, enhancing the GVT effect comes at the expense of possibly inducing GVHD.[16] Therefore, several aspects of CAR-T cell therapy need to be further studied before optimizing this novel therapy for patients with relapsed lymphoid disease after allo-HCT.[17]

Several institutions have described their limited experiences with treating patients with relapsed disease after allo-HCT. Kochenderfer *et al.* described how ten patients with persistent B-cell disease after being treated with allo-HCT and DLI received CD19 directed CAR-T cell therapy and resulted in three patients (30%) with disease regression, one patient with CR, one patient with PR, one patient had tumor lysis syndrome (TLS) as the chronic lymphocytic leukemia (CLL) improved, and no patients developed GVHD.[15] Cruz *et al*. described how two out of eight patients (four with CLL and four with ALL) who relapsed after allo-HCT and received allogeneic CD19-28z-CAR-T cells experienced objective antitumor activity.[18] Further, some studies suggest that CAR-T cell therapy may induce higher remission rates when given to ALL patients who relapsed after transplant as opposed to those who relapsed after chemotherapy without prior transplant.[19] More emerging CAR products such as bispecific CARs targeting CD19 and CD20 have been shown to induce long-term remission in a patient with relapsed/refractory B-ALL after allo-HCT.[20]
Despite the advent of several different immunotherapies from checkpoint inhibition, monoclonal targets, and now CAR-T cell therapy, HCT remains a standard of care for patients with advanced lymphoid diseases, offering potential cure. Thus, adjunctive and sequential therapies combined with transplant may improve overall survival.[21,22] This study hopes to shed light on the utility of CAR-T cell therapy for the treatment of relapse after allo-HCT.

Patient eligibility population:
Any patient (any age) with the diagnosis of any B-cell malignancy (leukemia or lymphoma) who underwent allo-HCT and subsequently relapsed at any year of management in the documented history of this registry.

Data requirements:
Data will be captured through CIBMTR collection forms. Examples of collection forms include (2011) Acute Lymphoblastic Leukemia Pre-HCT Data, (2018) Hodgkin and Non-Hodgkin Lymphoma Pre-HCT Data, (2111) Acute Lymphoblastic Leukemia Post-HCT Data, and (2118) Hodgkin and Non-Hodgkin Lymphoma Post-HCT Data. 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.

Acute and chronic GVHD: Occurrence of grades II, III and/or IV acute GVHD, and limited and extensive chronic GVHD.

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
- Gender
- Karnofsky performance status at transplant: < 90% vs. ≥ 90%
- HCT comorbidity index at transplant 0, 1, 2, and ≥ 3
- ABO blood group
- CMV status

Disease-related:

- Diagnosis: B-cell ALL, DLBCL, Double Hit Lymphoma, Other
- Disease risk index
- High risk cytogenetics: yes vs.no
- For ALL, Philadelphia Chromosome (yes vs. no)
- Number of prior therapies (before transplant): 1 vs. 2 vs. ≥ 3
- Disease status at the time of transplant: complete remission vs partial response vs. stable disease vs progressive disease
- CNS involvement at diagnosis and transplant
- Response to First line therapy
- Therapies given before HCT
- Remission status prior to HCT

Transplant-related:

- Year of transplant
- Time from diagnosis to allogeneic transplantation: months
- Timing of HCT: upfront (after induction), late (>1 line of therapy), unknown
- Disease risk index at transplant
- Mobilization regimen for allo-HCT
- Conditioning regimen: myeloablative vs. reduced-intensity/non-myeloablative (NMA)
- Graft source (PBSCT versus marrow)
- Donor type (matched related, matched unrelated, mismatched related/haploidentical related, mismatched unrelated, cord)
- Neutrophil and platelet engraftment (days)
- GVHD prophylactic regimen
- Donor/Recipient ABO match
- Donor/Recipient CMV match
- Donor age

Post-transplant-related:

- Treatment after transplant
- Response to alternative treatment
- Response to transplant
- Follow-up of survivors (months)
- GVHD after transplant
- 100-day disease status
- 30 and 100-day mortality
- Date of post-transplant relapse

- Date of death
- Cause of death

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)
- Neurotoxicity (Y/N and grade)
- Cytopenias
- Infectious complications

Study design:

This study would assess the outcomes of all patients with B-cell malignancies (leukemia and lymphoma) who relapsed after allo-HCT in order to determine the optimal subsequent line of therapy. The study will follow a retrospective registry-based descriptive analysis design. Descriptive tables of patient, disease-, and transplant-related factors will be created. The primary endpoints will be PFS and OS following salvage therapy after post-allo HCT relapse, comparing outcomes based on type of subsequent treatment: CAR-T cells vs donor lymphocyte infusion/immunotherapy vs chemotherapy. The tables will list median and range for continuous variables and percent of total for categorical variables. Probabilities of relapse/progression, OS and PFS following post-allo salvage therapy will be calculated using the Kaplan-Meier estimator, with the variance estimated by Greenwood's formula. 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. Transplant related outcomes will be tested using Cox proportional hazards models across various disease and transplant related factors. Subset analyses will be pursued separating ALL patients and lymphoma patients.

Conflicts of interest:

All other authors have no conflict of interest or relevant/non-relevant disclosures.

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Baseline characteristics for patients with prior allo-HCT undergoing 1st CAR-T for ALL/NHL

Characteristic	ALL	NHL	Total
No. of patients	103	30	133
No. of centers	40	17	50
Age at infusion, by category - no. (%)			
Median (min-max)	13.9 (1.31-74.63)	58.58 (30.97-69.32)	17.45 (1.31-74.63)
< 10	34 (33)	0	34 (25.6)
10-19	39 (37.9)	0	39 (29.3)
20-29	22 (21.4)	0	22 (16.5)
30-39	2 (1.9)	4 (13.3)	6 (4.5)
40-49	3 (2.9)	5 (16.7)	8 (6)
50-59	1 (1)	7 (23.3)	8 (6)
60-69	1 (1)	14 (46.7)	15 (11.3)
>= 70	1 (1)	0	1 (0.8)
Gender - no. (%)			
Male	58 (56.3)	21 (70)	79 (59.4)
Female	45 (43.7)	9 (30)	54 (40.6)
Recipient race - no. (%)			
White	76 (73.8)	25 (83.3)	101 (75.9)
African-American	8 (7.8)	2 (6.7)	10 (7.5)
Asian	5 (4.9)	2 (6.7)	7 (5.3)
More than one race	7 (6.8)	1 (3.3)	8 (6)
Not reported	7 (6.8)	0	7 (5.3)
Recipient ethnicity - no. (%)			
Hispanic or Latino	36 (35)	4 (13.3)	40 (30.1)
Non Hispanic or non-Latino	59 (57.3)	26 (86.7)	85 (63.9)
Non-resident of the U.S.	5 (4.9)	0	5 (3.8)
Unknown	3 (2.9)	0	3 (2.3)
Karnofsky/Lansky performance score prior to CT - no. (%)			
90-100	67 (65)	15 (50)	82 (61.7)
80	18 (17.5)	6 (20)	24 (18)
< 80	10 (9.7)	4 (13.3)	14 (10.5)
Not reported	8 (7.8)	5 (16.7)	13 (9.8)
Disease status prior to CT - no. (%)			
CR1	2 (1.9)	1 (3.3)	3 (2.3)
CR2	5 (4.9)	1 (3.3)	6 (4.5)
CR3+	26 (25.2)	3 (10)	29 (21.8)
Relapse, 1st	19 (18.4)	4 (13.3)	23 (17.3)
Relapse, other	45 (43.7)	17 (56.7)	62 (46.6)
PIF/Untreated	3 (2.9)	2 (6.7)	5 (3.8)

Characteristic	ALL	NHL	Total
Not reported	3 (2.9)	2 (6.7)	5 (3.8)
Types of prior HCTs - no. (%)			
Yes	103	30	133
Prior allo-HCT(s)	102 (99)	22 (73.3)	124 (93.2)
Prior auto and allo-HCT(s)	1 (1)	8 (26.7)	9 (6.8)
Year of CT - no. (%)			
2015	1 (1)	0	1 (0.8)
2016	5 (4.9)	0	5 (3.8)
2017	25 (24.3)	4 (13.3)	29 (21.8)
2018	54 (52.4)	19 (63.3)	73 (54.9)
2019	18 (17.5)	7 (23.3)	25 (18.8)
Commercial vs. noncommercial CAR-T product - no. (%)			
Commercial	60 (58.3)	22 (73.3)	82 (61.7)
Noncommercial	43 (41.7)	8 (26.7)	51 (38.3)

Proposal: 1911-110

Title:
Determinants of outcomes of acute lymphoblastic leukemia following the receipt of chimeric antigen receptor T-cell therapy

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Research hypothesis:
Disease status, performance status, and comorbidity burden may affect the outcomes of chimeric antigen receptor (CAR) T-cell therapy for relapsed-refractory (R/R) acute lymphoblastic leukemia (ALL).

Specific aims:
Primary aims:
- To identify the determinants of overall survival in patients with ALL undergoing CAR T-cell therapy
- To determine the factors associated with disease-free survival and risk of relapse in patients with ALL undergoing CAR T-cell therapy

Secondary aims:
- To analyze the outcomes of patients receiving CAR T-cell therapy after previous hematopoietic cell transplant
- To determine the rate of hematopoietic cell transplant after CAR T-cell therapy
- To identify the risk factors for infectious and non-infectious complications among recipients of CAR T-cells (if data available)

Scientific impact:
CAR T-cell therapy has revolutionized the treatment of ALL in the last few years. In 2017, tisagenlecleucel, a CD19 directed CAR T-cell therapy, was approved by the Food and Drug Administration (FDA) for treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse. Since approval, CAR T-cell therapy has been used in patients outside of clinical trials. Understanding the determinants of outcomes of CAR T-cell in R/R ALL can provide important prognostic information with potential therapeutic implications.

Scientific justification:
CAR T-cell therapy has emerged as a highly effective treatment options in patients with R/R ALL. In the phase II ELIANA trial with tisagenlecleucel, 81% of patients responded to treatment with complete remission or complete remission with incomplete hematologic recovery (1). In an updated analysis, relapse free survival was 66% and overall survival was 70% at 18 months with a plateau in relapse free survival starting at around 10 months (2). However, almost 1/3rd of patients treated with tisagenlecleucel relapsed after achieving complete remission (1).
The real-world practice data regarding the use of CAR T-cell therapy in R/R ALL is limited. Applying clinical trials' data to the real-world patients is challenging as the outcomes are reported in a carefully selected cohort of patients in a controlled environment and may not always reflect the real-world experience. In clinical practice, patients with poor performance status, other comorbidities and CNS involvement may also have received CAR T-cells. Other factors which may influence outcomes in real-world data but may not be encountered in clinical trials include prior treatment with other novel immunotherapeutic options (3).

No large-scale analysis of different clinical characteristics, laboratory markers and other factors associated with outcomes in R/R ALL after CAR T-cell therapy has been done. A subgroup analysis of clinical trial patients reported low levels of lactate dehydrogenase, no extramedullary disease, and conditioning with cyclophosphamide/fludarabine lymphodepletion as the predictors of longer disease-free survival (4). Effect of prior HCT on outcomes has been debatable; although, a meta-analysis of clinical trials resulted in a statistically insignificant increase in the likelihood of achieving MRD negative status after CAR T-cell therapy in HCT-naïve patients (5). In a study with an investigational CAR T-cell formulation, prior use of blinatumomab did not have any effects on efficacy CAR T-cell therapy (6). Effects of major complications with CAR T-cell therapy such as cytokine release syndrome, neurotoxicity, and infections on relapse and OS have not been studied in detail. Thus, the determinants of outcomes with CAR T-cell therapy need to be analyzed in real-world cohorts to confirm the clinical trial findings. Also, such prognostic information may direct the use of subsequent hematopoietic cell transplant in patients at a higher risk of relapse, or other strategies such as bispecific CAR T-cell immunotherapy or CAR T-cell targeting other antigens (7).
The objective of our study is to identify and understand the determinants of outcomes in recipients of CAR T-cell therapy using the large CIBMTR database. Our results will be helpful, not only for the current CAR T-cell therapy, but also in future as novel and different CAR T-cell therapies continue to develop and be used in ALL patients.

Patient eligibility population:
All patients regardless of age who have received CAR-T cell therapy for ALL.

Data requirements:
Data collection forms: 4000, 4003, 4006, 4100

Patient-related variables:
- Age: <12 vs ≥12 years
- Gender: male or female
- Karnofsky performance score: ≥90 or <90
- Race: White vs. Black vs. Asian/Pacific Islander vs. Hispanics vs Others
- Comorbidities as available

Disease-related variables:
- Disease type: ALL, Philadelphia chromosome positive vs Philadelphia chromosome negative
- Disease status at CAR T-cell therapy including MRD status if available

CAR T-cell therapy-related variables:
- Type of CAR T-cell therapy
- Complications with CAR T-cell therapy as available
- Prior hematopoietic stem cell transplant
- Prior treatments including novel agents if available
- Bridging therapy during CAR T-cell manufacture if available

Outcomes variables:
- Relapse at last follow-up: Yes or no
- Overall survival
- Cause of death, if available

Sample requirements:
No biologic samples will be used.

Study design:
We will perform univariate and multivariate analyses (cox-proportional hazard model or logistic regression model as appropriate) to identify factors associated with relapse, disease-free survival and overall survival in patient who undergo CAR-T cell therapy for ALL. Kaplan Meier or cumulative incidence curves will be plotted for various outcomes with appropriate adjustment for competing risks.
If information is available, descriptive statistics will be used to evaluate the practice patterns of CAR-T cell therapy in ALL.
The CIBMTR statistician will be consulted for final statistical plan

Data source:
CIBMTR Research Database only

Conflicts of interest:
None

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Baseline characteristics for patients undergoing 1st CAR-T for ALL

Characteristic	N (%)
No. of patients	302
No. of centers	56
Age at infusion, by category - no. (%)	
Median (min-max)	13.58 (0.41-74.63)
< 10	96 (31.8)
10-19	140 (46.4)
20-29	53 (17.5)
30-39	3 (1)
40-49	2 (0.7)
50-59	3 (1)
60-69	3 (1)
>= 70	2 (0.7)
Gender - no. (%)	
Male	179 (59.3)
Female	123 (40.7)
Recipient race - no. (%)	
White	210 (69.5)
African-American	18 (6)
Asian	12 (4)
Other	4 (1.3)
More than one race	41 (13.6)
Not reported	17 (5.6)
Recipient ethnicity - no. (%)	
Hispanic or Latino	115 (38.1)
Non Hispanic or non-Latino	158 (52.3)
Non-resident of the U.S.	10 (3.3)
Unknown	19 (6.3)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	202 (66.9)
80	49 (16.2)
< 80	37 (12.3)
Not reported	14 (4.6)
Disease classification - no. (%)	
B-lymphoblastic leukemia, with t(5:14), IL3-IGH	1 (0.3)
B-lymphoblastic leukemia, with hyperdiploidy	17 (5.6)
B-lymphoblastic leukemia, BCR-ABL1-like	6 (2)

Characteristic	N (%)
B-lymphoblastic leukemia, with iAMP21	7 (2.3)
Early T-cell precursor lymphoblastic leukemia	5 (1.7)
B-lymphoblastic leukemia, NOS	197 (65.2)
B-lymphoblastic leukemia, with t(9:22), BCR-ABL1	26 (8.6)
B-lymphoblastic leukemia, with t(v:11q23), KMT2A rearranged	21 (7)
B-lymphoblastic leukemia, with t(1:19), TCF3-PBX1	4 (1.3)
B-lymphoblastic leukemia, with t(12:21), ETV6-RUNX1	10 (3.3)
T-cell lymphoblastic leukemia/lymphoma	1 (0.3)
Not reported	7 (2.3)
Disease status prior to CT - no. (%)	
CR1	22 (7.3)
CR2	30 (9.9)
CR3+	45 (14.9)
Relapse, 1st	76 (25.2)
Relapse, other	80 (26.5)
PIF/Untreated	41 (13.6)
Not reported	8 (2.6)
Types of prior HCTs - no. (%)	
No	187 (61.9)
Yes	112 (37.1)
Prior allo-HCT(s)	101 (33.4)
Prior auto-HCT(s)	3 (1)
Prior auto and allo-HCT(s)	1 (0.3)
Not reported	7 (2.3)
Not reported	3 (1)
Year of CT - no. (%)	
2015	3 (1)
2016	9 (3)
2017	52 (17.2)
2018	157 (52)
2019	81 (26.8)
Commercial vs. noncommercial CAR-T product - no. (%)	
Commercial	208 (68.9)
Noncommercial	94 (31.1)

Proposal: 1911-159

Title:
Outcome and Prognostic Significance of Cytogenetic Abnormalities in Pediatric and Adult Patients with Acute Lymphoblastic Leukemia Post Chimeric Antigen Receptor T-Cell Therapy

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Research hypothesis:
Chimeric Antigen Receptor T-Cell (CAR-T) Therapy can lead to improved outcomes in patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), Philadelphia chromosome like ALL(Ph-like ALL) and ALL patients with the KMT2A fusion gene

Specific aims:
Establish the prevalence of cytogenetic abnormalities in patients receiving tisagenlecleucel (Kymriah) CAR-T therapy
Evaluate the prognostic significance of molecular heterogeneity in patients with ALL and assess the overall survival, relapse free survival and event free survival in these patients
Evaluate the persistence of cells post Kymriah CAR-T therapy in patients with cytogenetic abnormalities and its role in disease outcome
Assess the outcome of continuing maintenance chemotherapy with tyrosine kinase inhibitors in patients with Ph+ ALL post Kymriah CAR-T therapy

Scientific impact:
Cytogenetic risk stratification at diagnosis is a powerful predictor of prognosis in patients with ALL. While cytogenetics at diagnosis of ALL is a key determinant of overall outcome in patients treated with conventional chemotherapy, it was not shown to be an independent predictor of outcomes in adult ALL allo-hematopoietic cellular therapy (HCT) recipients.[1-3] Establishing the outcomes of patients with cytogenetic abnormalities who have received Kymriah CAR-T therapy can delineate the benefits of this therapy and establish expanded indications for its use. Additionally the prognostic significance of patients with minimal residual disease (MRD) positivity and genomic diversity pre -cellular therapy can be further investigated to allow further risk stratification of patients to better allow tailored management. [4, 5 6]

Scientific justification:
Initial cytogenetic risk stratification at diagnosis is a key predictor of prognosis in patients with ALL. Ph+ ALL has been identified as a high risk subtype of B cell ALL has an increased incidence with age occurring in 3-5% of childhood cases and up to 40-50 % in older patients (>50years). [4, 5 6]
While the combinatorial treatment of chemotherapy with tyrosine kinase inhibitors (TKI) has greatly improved the long term survival in patients with Ph+ ALL up to 70%, tyrosine kinase inhibitor (TKI) resistant disease and relapse remains the main cause of treatment failure, resulting in inferior outcomes.[7] Such similar improvement has not been made in patients with other cytogenetic abnormalities such as Ph-like ALL and multiple studies show their inferior prognosis with outcomes inversely related to age where the 5 year overall survival(OS) decreases from 72.8% in childhood to 26%

in ages 21-39.[8]Additionally OS differences exist within ALL subgroups due to molecular heterogeneity and patients with JAK2 and EPOR rearrangements or IKZF1 deletions having worse outcomes.[5]
While CAR-T therapy has been shown to produce remission in patients with refractory Ph+ ALL, there is a need to further critically examine the role of CAR-T therapy in these patients as well as those with other cytogenetic abnormalities and its ability to producing durable remission and possible improved OS. [9, 10] Additionally there is limited data on the persistence of these adoptive T cells post CAR-T therapy, by examining B cell aplasia in these patients its long term effects and prognostic significance can be further explored.

Patient eligibility population
Eligibility:

- All patients ages 0-85 years with a confirmed diagnosis of ALL that received Kymriah CAR-T therapy from January 2017 to present

Data requirements:
Data collection forms that will be required are:
Form 2000: Recipient baseline data
Form 2400: Pre-Transplant Essential data
Form 2402: Disease Classification
Form 2450: Post-Transplant Essential Data
Form 2006: Hematopoietic Stem Cell Transplant (HCT) Infusion
Form 2011: Acute lymphoblastic Pre-HCT Data
Form 2111: Acute lymphoblastic Leukemia Post HCT Data
Form 2900: Recipient Death Data
Form 4000: Pre-cellular Therapy essential Data
Form 4003: Cellular Therapy product
Form 4006: Cellular Therapy Infusion
Form 4100: Cellular therapy Essential data Follow-Up Form
Supplemental data requiring collection will include patient's date of birth to evaluate outcomes specifically according to age. This study will not involve combining CIBMTR data with data from another group.
List of variables from the existing CIBMTR data collection forms that need to be analyzed, and desired outcome variables

Variable to be analyzed	**Desired Outcome Variable**
Cytogenetic abnormalities at diagnosis	Prognostic significance of these abnormalities
Did the patient receive TKI therapy	Incidence of TKI resistant disease and its outcome post CAR-T
Disease status immediately prior to cellular therapy	Outcome of CAR-T therapy based on disease burden
Cellular therapy product used and dose administered	Efficacy of cellular therapy product
What was the best response to cellular therapy	Remission rate
Patient status at 100 day, 6month, 1 year, 2 year and > 2 year follow up	Disease free survival Overall survival Relapse free survival Non Relapse Mortality

Did the patient receive maintenance chemotherapy or radiation post cell therapy	Outcome of CAR-T therapy with concurrent maintenance therapy
Has the recipient developed any grade 3 or 4 organ toxicity post cellular therapy	Incidence of organ toxicity post CAR-T therapy
Did the recipient receive an HCT since the date of the last report	Indications for HCT post CAR-T
Was persistence of the cellular product evaluated in the recipient and by what method	Impact on persistence of cellular product on relapse free survival and overall survival

Sample requirements:
This study will not require biological samples from the NMDP research sample repository

Study design:
This is an exploratory study .Descriptive statistics such as mean, standard deviation, median, range, frequency and confidence interval will be used to summarize patient demographics and clinical characteristics. Overall Survival (OS), Event Free Survival (EFS) and progression free survival (PFS) will be estimated using the Kaplan–Meier method .Chi-squared test, Fisher's exact test and logistic regression will be used to assess the association between genetic factors and outcomes. Statistical analysis will be performed using SPSS Statistics V 24.This study may be limited if insufficiently powered due to a small population of eligible patients

Data source:
The CIBMTR Research Database will be used in this study as the data source. No external data sources will be linked

Conflicts of interest:
There are no conflicts of interest to disclose

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Baseline characteristics for patients undergoing 1st commercial CAR-T for ALL

Characteristic	N (%)
No. of patients	208
No. of centers	46
Age at infusion, by category - no. (%)	
Median (min-max)	13.19 (0.41-63.48)
< 10	70 (33.7)
10-19	100 (48.1)
20-29	37 (17.8)
60-69	1 (0.5)
Gender - no. (%)	
Male	126 (60.6)
Female	82 (39.4)
Recipient race - no. (%)	
White	150 (72.1)
African-American	15 (7.2)
Asian	7 (3.4)
Other	4 (1.9)
More than one race	19 (9.1)
Not reported	13 (6.3)
Recipient ethnicity - no. (%)	
Hispanic or Latino	81 (38.9)
Non Hispanic or non-Latino	114 (54.8)
Non-resident of the U.S.	7 (3.4)
Unknown	6 (2.9)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	138 (66.3)
80	34 (16.3)
< 80	27 (13)
Not reported	9 (4.3)
Disease classification - no. (%)	
B-lymphoblastic leukemia, with t(5:14), IL3-IGH	1 (0.5)
B-lymphoblastic leukemia, with hyperdiploidy	13 (6.3)
B-lymphoblastic leukemia, BCR-ABL1-like	6 (2.9)
B-lymphoblastic leukemia, with iAMP21	6 (2.9)
B-lymphoblastic leukemia, NOS	145 (69.7)
B-lymphoblastic leukemia, with t(9:22), BCR-ABL1	12 (5.8)

Characteristic	N (%)
B-lymphoblastic leukemia, with t(v:11q23), KMT2A rearranged	14 (6.7)
B-lymphoblastic leukemia, with t(1:19), TCF3-PBX1	4 (1.9)
B-lymphoblastic leukemia, with t(12:21), ETV6-RUNX1	5 (2.4)
Not reported	2 (1)
Disease status prior to CT - no. (%)	
CR1	19 (9.1)
CR2	22 (10.6)
CR3+	31 (14.9)
Relapse, 1st	53 (25.5)
Relapse, other	51 (24.5)
PIF/Untreated	30 (14.4)
Not reported	2 (1)
Types of prior HCTs - no. (%)	
No	139 (66.8)
Yes	66 (31.7)
Prior allo-HCT(s)	59 (28.4)
Prior auto-HCT(s)	1 (0.5)
Prior auto and allo-HCT(s)	1 (0.5)
Not reported	5 (2.4)
Not reported	3 (1.4)
Year of CT - no. (%)	
2017	16 (7.7)
2018	127 (61.1)
2019	65 (31.3)
Commercial vs. noncommercial CAR-T product - no. (%)	
Commercial	208

Proposal: 1911-216

Title:
Clinical Features and Outcomes in Patients with Acute Lymphoblastic Leukemia who Relapse Post-Chimeric Antigen Receptor Therapy

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Research hypothesis:
Despite striking early remission rates using chimeric antigen receptor (CAR) T cells in relapsed/refractory B cell ALL, relapse post-CAR has emerged as a common mechanism of failure of CAR T cell therapy. We hypothesize that a retrospective study of longitudinal post-CAR outcomes will establish predictors of relapse and survival outcomes as well as clinical patterns in patients who relapse post-CAR T cell therapy.

Specific aims:
Specific aim 1:
To describe characteristics of ALL patients relapsing post-CAR therapy, evaluate for independent patient, disease, and treatment variables associated with relapse following CAR T cells, and assess overall survival of patients with and without ALL relapse following CAR T cell therapy.
We will describe baseline characteristics of patients who have received CAR T cells for ALL and were reported to the CIBMTR, stratified by post-CAR relapse vs. no relapse. We will report OS for both groups and conduct univariable and multivariable analyses to evaluate for predictors of post-CAR relapse.

Specific aim 2:
To *characterize specific patterns at relapse following CAR therapy, including loss of target antigen expression, B-cell aplasia, and relapse timing in patients with ALL who relapse following CAR T cell therapy.*
Among the cohort of ALL patients relapsing after CAR therapy, we will describe specific patterns at relapse including presence/absence of target antigen expression, presence/absence of B-cell aplasia, and whether relapse occurred early (within 6 months of CAR) or late (after six months of CAR). If feasible based on patient numbers, we will evaluate patient, disease, and treatment level predictors of different patterns at time of relapse.

Scientific impact:
With increased patient experience using CAR T cell therapy in ALL, response rates have been established and toxicities that characterize the early post-CAR period have been well-described. Features that are predictive or associated with failure to achieve durable remissions and relapse have not been well-established. Additionally, the fate of individuals who relapse post-CAR has not been well described. In this large multi-center analysis characterizing clinical features and outcomes of patients who relapse post-CAR therapy, we will investigate variables are predictive of relapse, survival following ALL relapse, and explore distinct clinical patterns at time of relapse. We anticipate this effort will aid in filling significant gaps in population-based knowledge in CAR therapy in ALL and improve predictive models of patient's risk of relapse post-CAR therapy.

Scientific justification:

Chimeric antigen receptor (CAR) T cell therapy has yielded striking responses in patients with B-cell acute lymphoblastic leukemia (ALL) with current published clinical trials reporting complete response (CR) rates of 70%-90% post-infusion of CD19-specific CAR T cells. The FDA has resultantly approved Tisagenlecleucel (Kymriah) for treatment of relapsed/refractory B-cell ALL in patients up to age 25. CAR T cell therapy is now being delivered both in context of investigational studies and as commercialized products. Delivery of commercial products does not come with tight reporting requirements of investigational agents and although early result reporting has been robust from clinical trials, there remains a need to study long-term outcomes following CAR T cell therapy and fate of CAR failures. Relapse with either CD19+ or CD19- disease remains the most common cause of CAR failure to date and efforts to characterize relapse and identify predictors of relapse are vital to advancing the field. Further, B-cell aplasia has been used as a surrogate for CAR persistence with early loss (<6 months post-infusion) concerning for impending relapse, but the utility of this biomarker broadly is unclear. The CIBMTR registry has successfully captured reporting across both investigational and commercial products. Analysis of single institution outcomes will unlikely be powered to yield meaningful data, we therefore propose to use CIBMTR-generated data to collect and analyze population-level data exploring predictors, outcomes, and clinical patterns in ALL patients who relapse following CAR therapy.

Patient eligibility population:

- Diagnosis of acute lymphoblastic leukemia/lymphoblastic lymphoma
- Recipient of CD19-specific CAR T cell therapy
- Minimum of three months f/u time from initial CAR infusion
- Age 0-80 years

Data requirements:

Patient/disease/prior Tx variables:

- Age (<15, 15-25, 26-39, 40+)
- Sex (M, F)
- Race/Ethnicity
- KPS (<90, 90+)
- HCT-CI (0, 1-2, 3+)
- Diagnosis (Date)
- Cytogenetics/Molecular subtype (Ph+, MLL, hypodiploid, Ph-like, other)
- Disease site (BM, CNS, testicular, skin, other extramedullary sites)
- Disease Status at infusion (Refractory, Relapse, CR1, CR2, CR3, CR4+)
- Prior lines of chemotherapy (1, 2, 3, 4, 5, 6+)
- Prior Blinatumumab (Y/N)
- Prior Inotuzumab (Y/N)
- Prior Transplant (Y/N)
- Transplant Donor Source

CAR T variables:

- Product
- Cell Dose
- Lymphodepletion Regimen
- Disease burden at infusion (Blast count, MRD, CNS disease, extramedullary sites)

Post CART variables:

- CRS (Y/N, grade)
- ICANS (Y/N, grade)
- Post-CAR HCT (Y/N, date)
- Relapse (Y, N, date)
- Site of Relapse (BM, CNS, testicular, skin, other extramedullary sites)
- CAR Persistence
- Antigen Loss
- B-cell Aplasia
- Survival (Date of last f/u, Date of death)

Sample requirements:
N/A

Study design:
This is a retrospective observational registry study evaluating relapse following CAR T cell therapy for ALL in children and adults. For Aim 1, the study cohort will include patients with relapsed/refractory ALL who received any CAR T cell product and were reported to the CIBMTR. Descriptive characteristics will characterize the study population, which will be stratified based upon post- CAR relapse vs no-relapse. Chi2 and ttest will be used to evaluate categorical and continuous variables, respectively. Patients who receive HCT in remission post CAR will be censored at time of HCT. Multivariable Kaplan Meier method will be used to evaluate overall survival for patients with and without relapse following CAR. logistic regression will be performed to evaluate for baseline characteristics associated with relapse following CAR. A second analytical dataset using just patients who have relapsed post CAR will be used to for Aim 2. We will describe the frequencies of target antigen loss, B-cell aplasia at time of relapse, and timing of relapse (before or after 6 months post CAR). Univariable logistic regressions will be performed to evaluate for variables associated with each of these relapse patterns; multivariable analyses will be performed if the sample size allows.

Non-CIBMTR data source:
NA

Conflicts of interest:
None

References:
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Baseline characteristics for patients undergoing 1st CAR-T for ALL

Characteristic	N (%)
No. of patients	302
No. of centers	56
Age at infusion, by category - no. (%)	
Median (min-max)	13.58 (0.41-74.63)
< 10	96 (31.8)
10-19	140 (46.4)
20-29	53 (17.5)
30-39	3 (1)
40-49	2 (0.7)
50-59	3 (1)
60-69	3 (1)
>= 70	2 (0.7)
Gender - no. (%)	
Male	179 (59.3)
Female	123 (40.7)
Recipient race - no. (%)	
White	210 (69.5)
African-American	18 (6)
Asian	12 (4)
Other	4 (1.3)
More than one race	41 (13.6)
Not reported	17 (5.6)
Recipient ethnicity - no. (%)	
Hispanic or Latino	115 (38.1)
Non Hispanic or non-Latino	158 (52.3)
Non-resident of the U.S.	10 (3.3)
Unknown	19 (6.3)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	202 (66.9)
80	49 (16.2)
< 80	37 (12.3)
Not reported	14 (4.6)
Disease classification - no. (%)	
B-lymphoblastic leukemia, with t(5:14), IL3-IGH	1 (0.3)
B-lymphoblastic leukemia, with hyperdiploidy	17 (5.6)
B-lymphoblastic leukemia, BCR-ABL1-like	6 (2)

Characteristic	N (%)
B-lymphoblastic leukemia, with iAMP21	7 (2.3)
Early T-cell precursor lymphoblastic leukemia	5 (1.7)
B-lymphoblastic leukemia, NOS	197 (65.2)
B-lymphoblastic leukemia, with t(9:22), BCR-ABL1	26 (8.6)
B-lymphoblastic leukemia, with t(v:11q23), KMT2A rearranged	21 (7)
B-lymphoblastic leukemia, with t(1:19), TCF3-PBX1	4 (1.3)
B-lymphoblastic leukemia, with t(12:21), ETV6-RUNX1	10 (3.3)
T-cell lymphoblastic leukemia/lymphoma	1 (0.3)
Not reported	7 (2.3)
Disease status prior to CT - no. (%)	
CR1	22 (7.3)
CR2	30 (9.9)
CR3+	45 (14.9)
Relapse, 1st	76 (25.2)
Relapse, other	80 (26.5)
PIF/Untreated	41 (13.6)
Not reported	8 (2.6)
Types of prior HCTs - no. (%)	
No	187 (61.9)
Yes	112 (37.1)
Prior allo-HCT(s)	101 (33.4)
Prior auto-HCT(s)	3 (1)
Prior auto and allo-HCT(s)	1 (0.3)
Not reported	7 (2.3)
Not reported	3 (1)
Year of CT - no. (%)	
2015	3 (1)
2016	9 (3)
2017	52 (17.2)
2018	157 (52)
2019	81 (26.8)
Commercial vs. noncommercial CAR-T product - no. (%)	
Commercial	208 (68.9)
Noncommercial	94 (31.1)

Proposal: 1911-115

Title:
Resource utilization with CAR-T cells

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Research hypothesis:
- Cellular immunotherapy is associated with a high burden of resource utilization
- Inflammatory markers and/or max toxicity grade will serve as predictors of resource utilization

Specific aims:
- Describe the characteristics of patients receiving IECT in the registry
- Investigate differences in resource utilization (and variance) of CAR-T therapy across demographic groups (disease type, gender, obesity, agent, cancer type, trial vs commercial status)
- Describe and model measures of health resource utilization
- Identify surrogates for resource utilization (such as inflammatory markers or max toxicity grade)

Scientific impact:
First comprehensive registry study of resource utilization for CAR-T cells likely to impact health-economic decision making.
Identifying robust surrogate markers will allow prediction of resource utilization.

Scientific justification:
Immune effector cell therapy (IECT) a revolutionary but high-intensity treatment modality that redirects T lymphocytes towards an expressed cancer surface antigen. There are three major steps required: collection of autologous T lymphocytes by apheresis, manufacture of the IECT and then the administration of these cells to the recipient after lymphodepleting chemotherapy. There is paucity of information regarding resource utilization for IEC. This results in uncertainty regarding estimates of costs, staffing, and infrastructural requirements.
This study will
- Describe the characteristics of patients receiving IECT in the registry
- Describe the resources utilized in delivering IECT.
- Investigate differences in resource utilization (and variance) of CAR-T therapy across demographic groups (disease type, gender, obesity, agent, cancer type, trial vs commercial status)

Patient eligibility population:
- While there is considerable heterogeneity in disease indication (solid vs heme malignancy) and cell manufacture (auto vs allo), for simplicity we will focus on the commonest: autologous immune effector cell therapy for heme malignancy.
- First administration.

Data requirements:
No additional data, all data available through CTED forms

Sample requirements:
No samples required

Study design:
- To be determined based upon input by the WC.
- Consider landmarks such as d30 and d100
- Patient characteristics: age, gender, weight, BMI, performance
- Disease characteristics- type, stage/remission status, #lines of prior therapy Lymphodepletion strategy.
- Autologous cell collection: # mobilizations, # collections, method of collection, mobilizing agent.
- Engineering: manipulation, transfection, target, transfection efficiency, viability, on-site vs off-site
- Product infusion: cell dose, date, concomitant immunomodulation
- Clinical outcomes: Best response, time to ANC/platelet recovery, time to relapse/progression, CRS (time, therapy, resolution), neurotoxicity, overall survival, causes of death (primary/contributing).
- Biological correlates: inflammatory markers.
- Resource utilization measures: Duration of cytopenias, CRS duration, CRS therapy (eg. toci or steroids), neurotox duration, neurotox therapy, hypotension/pressors, severe hypoxia/ventilation, renal failure/ hemodialysis, grade 4 organ tox, immunoglobulin.

Non-CIBMTR data source:
None

Conflicts of interest:
None

References:
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Baseline characteristics for patients undergoing 1st CAR-T for hematologic malignancies

Characteristic	N (%)
No. of patients	1249
No. of centers	105
Age at infusion, by category - no. (%)	
Median (min-max)	56.87 (0.41-88.99)
< 10	96 (7.7)
10-19	144 (11.5)
20-29	74 (5.9)
30-39	50 (4)
40-49	103 (8.2)
50-59	242 (19.4)
60-69	353 (28.3)
>= 70	187 (15)
Gender - no. (%)	
Male	782 (62.6)
Female	466 (37.3)
Not reported	1 (0.1)
Recipient race - no. (%)	
White	1019 (81.6)
African-American	66 (5.3)
Asian	53 (4.2)
Other	6 (0.5)
More than one race	62 (5)
Not reported	43 (3.4)
Recipient ethnicity - no. (%)	
Hispanic or Latino	208 (16.7)
Non Hispanic or non-Latino	959 (76.8)
Non-resident of the U.S.	27 (2.2)
Unknown	54 (4.3)
Not reported	1 (0.1)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	583 (46.7)
80	320 (25.6)
< 80	200 (16)
Not reported	146 (11.7)
Disease - no. (%)	
AML	1 (0.1)

Characteristic	N (%)
ALL	302 (24.2)
NHL	886 (70.9)
HD	2 (0.2)
PCD/MM	58 (4.6)
Types of prior HCTs - no. (%)	
No	748 (59.9)
Yes	495 (39.6)
Prior allo-HCT(s)	124 (9.9)
Prior auto-HCT(s)	338 (27.1)
Prior auto and allo-HCT(s)	10 (0.8)
Not reported	23 (1.8)
Not reported	6 (0.5)
Year of CT - no. (%)	
2015	3 (0.2)
2016	19 (1.5)
2017	85 (6.8)
2018	739 (59.2)
2019	403 (32.3)
Commercial vs. noncommercial CAR-T product - no. (%)	
Commercial	1024 (82)
Noncommercial	225 (18)

Proposal: 1911-166

Title:
Real World Experience Of Costs And Healthcare Utilization In Children And Young Adults Receiving Kymriah For Acute Lymphoblastic Leukemia

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Objective:
To study the cost and healthcare utilization (HCU) in children who receive Kymriah (Tisagenlecleucel-T) cell therapy for relapsed/refractory of acute lymphoblastic leukemia.

Background:
The use of chimeric antigen receptor (CAR) T-cell therapy (CTL019) in treating children and young adults with relapsed or refractory acute lymphoblastic leukemia (ALL) is one of the great successes in modern medicine[1,2]. While conventional therapy is associated with 10 year OS of less than 30%[3,4], CTL019 therapy is associated with remission rates of 81-93% and DFS rates approaching 50-73%[1,2]. With both Kymriah and Yescarta now FDA approved, the number of patients who will received CD19 CAR T cells are expected to increase exponentially in the coming years. CAR-T cell Therapy has generated a lot of attention not only because of its clinical potential but also because of its high upfront cost. With a onetime infusion cost of 475,000 US dollars, Kymriah is one of the one of the most expensive drugs approved by the FDA for cancer treatment. In addition, complications such as cytokine release syndrome (CRS), infections, cytokine related encephalopathy syndrome (CRES) and infections can be associated with prolonged hospitalization, ICU admission and need for long term medications (e.g prophylactic medications, IVIG replacement) that can further escalate the costs of care. Therefore, depending on the severity of these complications, increases in healthcare utilization (HCU) can add significantly to the cost of care after Kymriah. While some centers infuse Kymriah as a bridge to allogeneic hematopoietic cell transplantation (alloHCT), others perform alloHCT only in patients who relapse post Kymriah therapy. Both these scenarios could result in significant additional costs and can make Kymriah therapy as a less cost-effective proposition.
The cost effectiveness data of anti-CD19 CAR-T cell therapy is limited[5-8]. Using a microsimulation model, Sarkar et al[6], found that despite high costs, CAR therapy treatment is cost effective compared to standard therapy largely due to the survival advantage offered by CAR-T therapy. They reported that CAR T therapy led to an improvement of 8QALYs (quality-adjusted life years) in pediatric B cell ALL patients. The incremental cost effectiveness ratio (ICER) ratio was 64,600 /QALY gained. Their base model assumed a 76% 1year OS and CR rates of 81% post CD19 CAR T therapy. In their analysis they found that if 1 year OS and CR rates decreased to 57.8% and 56.2% respectively CAR T therapy was no longer cost effective. This hypothetical observation is critical as in the recently published ELIANA trial the 1 year EFS was 50%[1]. Patients enrolled in CD19 CAR T trials have to meet stringent study criteria. However, patients receiving commercially approved product may not meet stringent study criteria and potentially can have inferior outcomes compared to patients enrolled on clinical trials. This "real-world" results can result in Kymriah being a cost ineffective treatment.

Scientific justification for the proposed study:
US spending on cancer rose from $27 billion in 1990 to 87.8 billion in 2014 and is projected to reach $158 billion in 2020. Increase in cancer drug prices represent a key component in the uptick of overall

cancer expenditure[9,10]. The average cancer drug price before the year 2000 was under 10,000 per year although by year 2012, the cost of 12-13 drugs approved for cancer topped 100,000 per year[11]. Therefore, with the high price tag of Kymriah therapy, it is important to ascertain the true costs and extent of health care resources utilized post treatment. A study of this nature will be not only provide data on costs associated with management of complications post Kymriah infusion but also enable hospitals and health insurance companies to allocate appropriate resources and reimbursement. It may also lay the groundwork for future robust cost effectiveness analysis studies. Therefore, we propose capturing real world costs incurred and health care utilization rates in a contemporary cohort of children and young adults post Kymriah therapy. We aim to do this by linking cost data obtained from the Pediatric Health Information System (PHIS database) and merging this data with the clinical data obtained from the CIBMTR database

Hypothesis:
We hypothesize that Kymriah infusion and its immediate clinical sequelae will incur high costs and HCU
Primary endpoint:
To determine costs and health care utilization incurred during the first year post Kymriah infusion in a contemporary cohort of children and young adults treated at pediatric centers from July 2018to June 2020.

Secondary endpoint:
To compare the cost of Kymriah treated patient with alloHCT cost among patients with ALL in CIBMTR HS 14-01 study (Investigating clinical outcomes and inpatient health care resource utilization of hematopoietic cell transplantation for children with acute leukemia).

Proposed methods:
Data source:
PHIS (Children's Hospital Association, Overland Park, KS) is a confidential database of 50 children's hospitals in the U.S. that submit de-identified data for each child treated at the hospital. The database contains baseline institution, provider and patient specific information, all of which is linked to hospital charges. These include, but are not limited to, date of service, diagnosis and visit codes, length of stay (LOS), ICU admissions, mechanical ventilation, dialysis, adjusted charges/costs, medications and daily ancillary billing data (4). These records of inpatient hospital charges provide extensive clinical care data with comprehensive HCU data.

Data:
Data will be collected on children and young adults treated at pediatric hospitals centers approved by Novartis for use of Kymriah. All included hospitals will also be part of PHIS. Patients in the PHIS database will be identified based on the ICD-10 code for ALL (C91.0x) and CD19 immunotherapy codes (XW033C3- or XW043C3, Z51.11, Z51.12) and drug codes (Q2042)..

Variables to be collected:
PHIS database:
PHIS Financial and HCU variables starting from admission through one-year post-CTL019 infusion will be pulled in from the PHIS database.

- Age
- Sex
- Ethnicity
- Diagnosis ALL

- Date of Immunotherapy
- Treatment center
- Length of hospital stay for initial therapy (date of admission and date of discharge)
- ICU care, ICU length of stay
- Need for mechanical ventilation Y/N, duration of mechanical ventilation, type (conventional ventilator, oscillator, ECMO, other)
- Dialysis Y/N Type
- Infections post CD19 CAR therapy
- Number of hospital admissions post CD19 CAR therapy
- Costs incurred in the 1st year post CD19 CAR therapy categorized as follows: Total adjusted charges, pharmacy charges, imaging charges, laboratory charges, room charges, physician fees.

Clinical variables obtained from the CIBMTR database:

- Patient-related: Age, sex, race, ethnicity, performance score, comorbidity score, prior HSCT Y/N
- Disease-related: Date of first ALL diagnosis, date of first relapse, site of relapse, indication for CTL019, disease status prior to CTL019 infusion, date of CTL019 infusion, date of admission to the hospital,
- Post CDTL019 events: CRS Y/N Severity, Neurological toxicities Y/N, Infections Y/N specify
- Last follow up
- Disease status at last follow up
- Alive/Dead at Last follow up
- If dead, cause of death.
- Did patient undergo HCT post CAR T therapy Y/N if Y when

The following variables will be used to link patient data from PHIS with that of the CIBMTR database:

- Age (Date of birth)
- Diagnosis ALL
- Sex
- Date of Immunotherapy
- Center where treatment given

Feasibility:

We the PIs have extensive experience in working with the PHIS database and have independently extracted data from PHIS database for several published studies. [12-15] Therefore, our prior experience conducting healthcare utilization studies in children and adolescents with hematologic disorders and cancers is testament to our ability to successfully complete the proposed project. At our center (CUMC), we recently conducted a study of cost-effectiveness and HCU in patients undergoing alloHCT for the treatment of sickle cell disease[16] . In projects as mentioned above we merged the robust data from our center with that from the PHIS database[15]. This enabled us to analyze the cost of unrelated donor alloHCT at our center. Additionally, it allowed us to examine the fiscal trends and treatment patterns around alloHCT at our center over an 11-year period (2005-2016). As a testament to the success of our early studies, we were granted permission to merge thousands of records from the Center of International Blood and Marrow Transplant Research (CIBMTR) with data from PHIS. With this unique linked dataset, we examined HCU in a larger cohort of patients undergoing alloHCT for treatment of sickle cell disease as well as in a separate cohort of patients undergoing alloHCT for treatment of leukemia (CIBMTR study HS13-02[16] and HS 14-01[17]). HS14-01 study will provide a comparison cohort for the patients enrolled on the proposed study, which will enable comparison of HCU in pediatric patients

who undergo alloHCT for ALL vs. in those who receive CTL019 for the treatment of relapsed/refractory ALL.

Statistical analysis:
Descriptive statistics were used to summarize all data. Median costs incurred during the first-year post immunotherapy along with interquartile ranges will be calculated. Median and Range will be calculated for the following health care utilization variables: length of hospital stay, length of ICU stay. Percentages representing frequency of usage will be calculated for the following variables, rates of ICU utilization, need for mechanical ventilation, dialysis. The impact of the following variables on costs and HCU will be analyzed by a multivariate analysis: age, disease status pre-CAR T infusion, prior HSCT, comorbidity index, performance score, number of prior therapies pre CAR T infusion, post CAR: CRS presence and severity, neurological toxicity presence and severity and infectious complications.

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Baseline characteristics for patients undergoing 1st commercial CAR-T for ALL

Characteristic	N (%)
No. of patients	208
No. of centers	46
Age at infusion, by category - no. (%)	
Median (min-max)	13.19 (0.41-63.48)
< 10	70 (33.7)
10-19	100 (48.1)
20-29	37 (17.8)
60-69	1 (0.5)
Gender - no. (%)	
Male	126 (60.6)
Female	82 (39.4)
Recipient race - no. (%)	
White	150 (72.1)
African-American	15 (7.2)
Asian	7 (3.4)
Other	4 (1.9)
More than one race	19 (9.1)
Not reported	13 (6.3)
Recipient ethnicity - no. (%)	
Hispanic or Latino	81 (38.9)
Non Hispanic or non-Latino	114 (54.8)
Non-resident of the U.S.	7 (3.4)
Unknown	6 (2.9)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	138 (66.3)
80	34 (16.3)
< 80	27 (13)
Not reported	9 (4.3)
Disease classification - no. (%)	
B-lymphoblastic leukemia, with t(5:14), IL3-IGH	1 (0.5)
B-lymphoblastic leukemia, with hyperdiploidy	13 (6.3)
B-lymphoblastic leukemia, BCR-ABL1-like	6 (2.9)
B-lymphoblastic leukemia, with iAMP21	6 (2.9)
B-lymphoblastic leukemia, NOS	145 (69.7)
B-lymphoblastic leukemia, with t(9:22), BCR-ABL1	12 (5.8)

Characteristic	N (%)
B-lymphoblastic leukemia, with t(v:11q23), KMT2A rearranged	14 (6.7)
B-lymphoblastic leukemia, with t(1:19), TCF3-PBX1	4 (1.9)
B-lymphoblastic leukemia, with t(12:21), ETV6-RUNX1	5 (2.4)
Not reported	2 (1)
Disease status prior to CT - no. (%)	
CR1	19 (9.1)
CR2	22 (10.6)
CR3+	31 (14.9)
Relapse, 1st	53 (25.5)
Relapse, other	51 (24.5)
PIF/Untreated	30 (14.4)
Not reported	2 (1)
Types of prior HCTs - no. (%)	
No	139 (66.8)
Yes	66 (31.7)
Prior allo-HCT(s)	59 (28.4)
Prior auto-HCT(s)	1 (0.5)
Prior auto and allo-HCT(s)	1 (0.5)
Not reported	5 (2.4)
Not reported	3 (1.4)
Year of CT - no. (%)	
2017	16 (7.7)
2018	127 (61.1)
2019	65 (31.3)
Commercial vs. noncommercial CAR-T product - no. (%)	
Commercial	208

Proposal: 1911-187

Title:
Comparison of resource utilization patterns in adult patients receiving inpatient vs outpatient chimeric antigen receptor therapy for relapsed lymphoma

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Research hypothesis:
Centers that offer outpatient CAR-T therapy for NHL will utilize fewer healthcare resources in comparison to centers that deliver the therapy inpatient.

Specific aims:
To evaluate differences in resource utilization between centers that perform CAR-T inpatient vs outpatient in the treatment of R/R lymphoma

Scientific impact:
Given the expense associated with cost of the currently available CAR-T products for NHL, understanding the differences in resource utilization between offering this therapy for NHL as inpatient vs outpatient is crucial in understanding the overall impact of this innovative therapy on healthcare spending, resource allocation, and treatment delivery infrastructure. The analysis we are seeking to perform can guide centers about the necessary resources and infrastructure that need to be in place to safely and cost-effectively deliver this care. In addition, it can inform and influence various medical societies' decision making regarding most cost-effective therapies in the search for a cure for NHL. Finally, the results of this analysis may influence policy makers to craft reasonable appropriate reimbursement for the use of CAR-T therapy in NHL.

Scientific justification:
Patients with relapsed or refractory (R/R) lymphoma are presented with an increasing number of treatment options with curative intent including chimeric antigen receptor therapy (CAR-T). CAR-T became commercially available in 2017 following FDA approval of tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta). CAR-T can be administered either as an outpatient treatment or during a hospitalization. Treatment practices vary by center; however CAR-T can be associated with significant toxicity such as cytokine release syndrome or neurotoxicity that necessitates hospital admission. Given the high cost associated with these therapies, understanding the differences in resource utilization between practices that perform CAR-T inpatient vs outpatient is important for healthcare organizations, insurers, and policymakers.

Patient eligibility population:
- Adults (18+)
- Patients with lymphoma who have been treated with FDA approved CAR-T in standard of care practice and with expanded access protocols for products out of specification
- Standard and high-risk disease
- Data from the centers within United States only

Data requirements:

- 2000 R4.0, 4000 R5.0, 4003 R2.0, 4100 R4.0
- Include a list of variables from the existing CIBMTR data collection forms that need to be analyzed, and desired outcome variables:

Baseline Recipient Data	**Post transplant**
Diagnosis	Survival
Demographic	Engraftment
Clinical – comorbidities, pre HCT history	Relapse
Karnofsky score	Immune reconstitution
Health insurance status and type	Infection
	Organ function
	Subsequent treatment
	Cause of death
	Duration of hospital stay (days)
	Duration of ICU stay (days)

- Our study would require the collection of data that may not be currently captured by CIBMTR data collection forms. The supplemental data are listed below.

Intent to treat all SOC for lymphoma as outpatient: (Y/N?)	Laboratory investigations
Emergency room visits (<3, >3)	Radiology studies
Number of Hospitalizations (<3, >3)	Tocilizumab doses
Hospitalization LOS	Dexamethasone doses
Number of clinic visits	

Sample requirements:

- None

Study design:

- Describe, in non-technical terms, how specific aims would be addressed using information from the CIBMTR database.
    - By analyzing patient data stratified by intent to treat as an outpatient, we will able to analyze potential difference between these two populations for metrics outlined in section VIII.
- Include the specific statistical methodology planned, with a discussion of limitations, if relevant (CIBMTR biostatisticians are available to provide assistance with this process, including relevant power calculations).
    - The analytic framework is yet to be determined, but may include odds ratio calculations, two-sample t-test, Pearson's chi-square test, or logistic regression.

Data source:

CIBMTR Research Database

Conflicts of interest:

Mustaqeem Siddiqui: Consultancy with Celgene, travel. No personal compensation
Yi Lin: research funding from Janssen, Kite/Gilead, Celgene, BlueBird Bio; consultancy with Kite/Gilead, Novartis, Janssen, Legend Biotech, BlueBird Bio, Celgene, JUNO, AlloGene, Gamida Cells. DSMB:

Sorrento. Steering Committee: Legend Biotech, Janssen, Celgene. All funds paid to Mayo, no personal compensation.
Shahrukh Hashmi: None

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Baseline characteristics for patients aged >= 18 undergoing 1st commercial CAR-T for NHL

Characteristic	N (%)
No. of patients	815
No. of centers	71
Age at infusion, by category - no. (%)	
Median (min-max)	62.27 (18.45-88.99)
10-19	3 (0.4)
20-29	18 (2.2)
30-39	40 (4.9)
40-49	84 (10.3)
50-59	202 (24.8)
60-69	307 (37.7)
>= 70	161 (19.8)
Gender - no. (%)	
Male	522 (64)
Female	293 (36)
Recipient race - no. (%)	
White	699 (85.8)
African-American	37 (4.5)
Asian	35 (4.3)
Other	1 (0.1)
More than one race	19 (2.3)
Not reported	24 (2.9)
Recipient ethnicity - no. (%)	
Hispanic or Latino	81 (9.9)
Non Hispanic or non-Latino	687 (84.3)
Non-resident of the U.S.	16 (2)
Unknown	31 (3.8)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	307 (37.7)
80	246 (30.2)
< 80	148 (18.2)
Not reported	114 (14)
Disease status prior to CT - no. (%)	
CR1	7 (0.9)
CR2	8 (1)
CR3+	11 (1.3)
Relapse, 1st	194 (23.8)
Relapse, other	259 (31.8)
PIF/Untreated	333 (40.9)

Characteristic	N (%)
Not reported	3 (0.4)
Types of prior HCTs - no. (%)	
No	535 (65.6)
Yes	277 (34)
Prior allo-HCT(s)	19 (2.3)
Prior auto-HCT(s)	242 (29.7)
Prior auto and allo-HCT(s)	3 (0.4)
Not reported	13 (1.6)
Not reported	3 (0.4)
Year of CT - no. (%)	
2017	6 (0.7)
2018	505 (62)
2019	304 (37.3)

Proposal: 1911-92

Title:
Not everyone has access to care with CAR T cells for relapsed/refractory Diffuse Large B Cell Lymphoma

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Hypothesis:
We hypothesize that there are disparities in the access to care with CAR T cells based on varied demographic, geographic and socio-economic characteristics of patients with relapsed/refractory (R/R) Diffuse large B cell Lymphoma (DLBCL). Prior evidence has shown underutilization of hematopoietic cell transplantation (autoHCT) as compared to the Surveillance, Epidemiology, and End Results (SEER) data[1–3] and we predict that there is further underutilization and disparity when it comes to CAR T cells.

Specific aims:
Assess rate of utilization of treatment with CAR T cells for patients with R/R DLBCL, according to demographic, geographic and socio-economic characteristics.
General Outcomes to be examined include:
Primary objective:

- Assess rate of utilization CAR T cells for patients with DLBCL R/R after autoHCT, according to demographic, geographic and socio-economic characteristics.

Secondary objectives:

- Assess the impact of demographic, geographic and socio-economic factors on rate of utilization of CAR T cells, by comparing them to the same factors for patients undergoing autoHCT and patients at diagnosis.
- Compare the rate of utilization of CAR T cells with the rate of utilization of allogeneic HCT (alloHCT) as salvage options for patients with DLBCL R/R after autoHCT

The analysis will be conducted based on the following assumptions (see figure 1):

- incidence of new diagnosis of DLBCL is known, based on data from the SEER database
- rate of R/R DLBCL after 1st line therapy is known[4]; assuming all patients are referred and clinically eligible for autoHCT, this represents the expected proportion of patients undergoing autoHCT
- actual access to autoHCT will be calculated based on CIBMTR data compared to the expected proportion of patients undergoing autoHCT for R/R DLBCL
- rate of R/R DLBCL after autoHCT is known[5]; this represents the expected proportion of patients undergoing CAR T cells treatment for R/R DLBCL
- actual access to CAR T cells therapy will be calculated based on CIBMTR data compared to the expected proportion of patients undergoing CAR T cells treatment
- demographic, geographic and socio-economic characteristics are available for these data

Scientific impact:
Rates of utilization of CAR T cells for R/R DLBCL after the FDA approval of axicabtagene ciloleucel and tisagenlecleucel are not currently available but are likely below what would be predicted based on the

incidence of DLBCL in the US population. A better definition of rates of utilization according to demographic, geographic and socio-economic characteristics of this population can provide important information on how to improve access to CAR T cells and allocation of resources at medical centers.

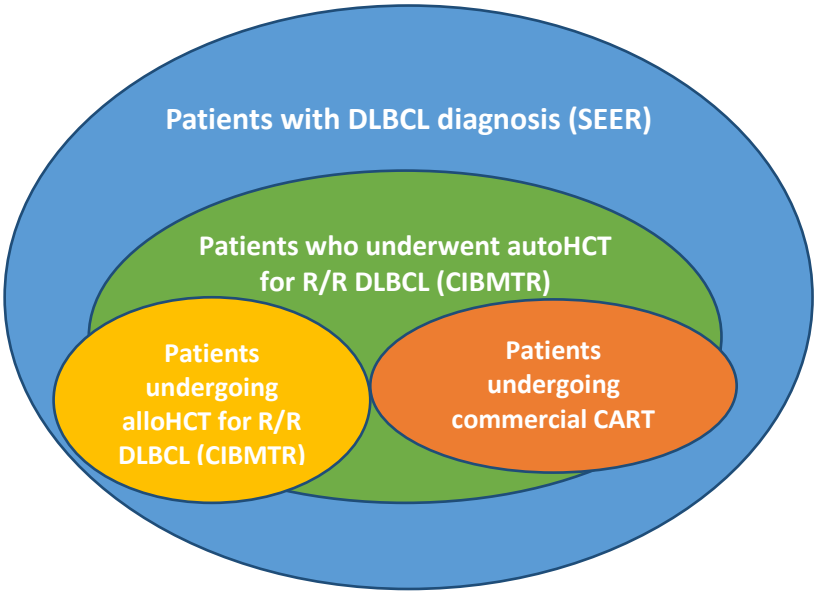

Figure 1. Study population: All groups will be stratified according to demographic, geographic and socio-economic characteristics

Scientific justification:
Patients with R/R DLBCL have dismal outcomes, with median overall survival (OS) of 6-9 months for chemo-refractory patients or patients who relapse after autoHCT [6,7]. Until recently, no curative options were available for this population, but in the last 2 years important advancements have been made thanks to the availability of CAR T cells. The JULIET and ZUMA-1 phase II trials have shown significant improvement in progression free survival (PFS) and OS, with possible curative results in 30-40% of patients with DLBCL treated with anti CD19 CAR T cells after failure of autoHCT or two lines of therapy [8–10]. These encouraging results have led to the approval by the US FDA of two CAR T cells products for commercial use in this population, axicabtagene ciloleucel and tisagenlecleucel. Recently the outcomes of 274 patients treated with commercial axicabtagene ciloleucel in the "real world experience" have been reported with rates of responses and toxicities similar to the ZUMA-1 trial [11].
Being the first approved curative treatment for patients with R/R DLBCL, CAR T cells are expected to be broadly used in this setting of patients. However, besides restrictions secondary to possible treatment-related toxicities, barriers in access to care remain present for possible candidates to CAR T cells, as this treatment is currently delivered only in highly specialized academic centers and, until recently additional financial barriers existed for patients > 65 due to Medicare coverage. Importantly, this patient population represents a consistent proportion of patients with DLBCL [12].

Potential limitations:
This study might underrepresent chemo-refractory patients or patients who did not undergo autoHCT for comorbidities or other reasons.

Patient eligibility population:

Inclusion criteria:

- Adults (age ≥ 18) with diagnosis of DLBCL
- Having undergone autoHCT for R/R DLBCL from 2017 to 2019
- Having received either axicabtagene ciloleucel or tisagenlecleucel, as commercial products for R/R DLBCL after FDA approval
- Having undergone alloHCT for R/R DLBCL from 2017 to 2019 (excluding alloHCT after CAR T cells)

Exclusion criteria:

- Having received either axicabtagene ciloleucel or tisagenlecleucel as part of a clinical trial

Data requirements:

- CIBMTR: data regarding autoHCT, alloHCT and CAR T cells infusion, including data forms #2400 #2402 #2450 #4000. The parameters to be assessed are outlined in the table below.
- SEER: Utilizing data collected by SEER regarding incidence of new diagnosis of DLBCL.

Type of data	Data point	Specific data
Patient Specific	At diagnosis	Age Gender Race/Ethnicity Region of residence (and related poverty indicator) Insurance Status (private vs public) Disease Histology
	- At autoHCT - At CAR T cells infusion - At alloHCT	Age Gender Race/Ethnicity Region of residence (and related poverty indicator) Insurance Status (private vs public) Disease Histology Prior autologous transplant Indication for treatment (autoHCT, alloHCT, CAR T cells) Significant comorbidities Karnofsky performance status
Transplant specific	After autoHCT	Relapse after autoHCT (yes vs no) (date of relapse)
CAR T cells Specific	Leuko-apheresis	Leuko-apheresis date
	Infusion date	CAR T cells infusion date
	Type of Product	Axicabtagene Ciloleucel / Tisagenlecleucel
	Area of infusion	Medical Center where the product was infused

Study design:

A retrospective study will be conducted utilizing CIBMTR data paired with data from the SEER database.

- Calculate the incidence of new DLBCL diagnosis for the time of our study, based on SEER data
- Calculate the rate of R/R DLBCL after first line treatment for the time of our study, based on literature [4] (~40%), multiplied by the incidence of DLBCL diagnosis (SEER data); assuming all patients were referred and clinically eligible for autoHCT, this would represent the expected proportion of patients undergoing autoHCT for R/R DLBCL

- Calculate actual access to autoHCT, based on CIBMTR data on number of autoHCTs performed in the US during the time of our study, compared to the expected proportion of patients undergoing autoHCT for R/R DLBCL
- Calculate the rate of R/R DLBCL after autoHCT for the time of our study, based on literature [5] (~60%), multiplied by the number of autoHCTs performed in the US (CIBMTR data); assuming all patients were referred and clinically eligible for CAR T cells, this would represent the expected proportion of patients undergoing CAR T cells therapy for R/R DLBCL
- Calculate actual access to CAR T cells therapy, based on number of CAR T cells infusions performed in the US during the time of our study (CIBMTR data), compared to the expected proportion of patients undergoing CAR T cells treatment for R/R DLBCL
- The analysis will be stratified according to demographic, geographic and socio-economic data
- Analogously, assess the rate of utilization of alloHCT and compare it to that of CAR T cells

Descriptive tables will be created to show treatment rates across different demographic/geographic and socio-economic groups.

Conflicts of interest:

- Dr. Pennisi has no conflict of interest.
- Dr. Perales reports honoraria from Abbvie, Bellicum, Celgene, Bristol-Myers Squibb (>$5,000), Incyte, Merck (>$5,000), Novartis (>$5,000), Nektar Therapeutics, Omeros, and Takeda. He serves on DSMBs for Cidara Therapeutics, Servier and Medigene, and the scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of American Society for Transplantation and Cellular Therapy (ASTCT) and Be the Match (National Marrow Donor Program, NMDP), as well as on the CIBMTR Cellular Immunotherapy Data Resource (CIDR) Committee.

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Baseline characteristics for patients aged >= 18 with prior auto-HCT undergoing 1st commercial CAR-T for DLBCL

Characteristic	N (%)
No. of patients	229
No. of centers	58
Age at infusion, by category - no. (%)	
Median (min-max)	62.29 (21.89-82.46)
20-29	4 (1.7)
30-39	10 (4.4)
40-49	20 (8.7)
50-59	65 (28.4)
60-69	90 (39.3)
>= 70	40 (17.5)
Gender - no. (%)	
Male	148 (64.6)
Female	81 (35.4)
Recipient race - no. (%)	
White	198 (86.5)
African-American	11 (4.8)
Asian	12 (5.2)
More than one race	3 (1.3)
Not reported	5 (2.2)
Recipient ethnicity - no. (%)	
Hispanic or Latino	19 (8.3)
Non Hispanic or non-Latino	198 (86.5)
Non-resident of the U.S.	5 (2.2)
Unknown	7 (3.1)
Karnofsky/Lansky performance score prior to CT - no. (%)	
90-100	95 (41.5)
80	57 (24.9)
< 80	37 (16.2)
Not reported	40 (17.5)
Disease classification - no. (%)	
Diffuse, large B-cell lymphoma - NOS	98 (42.8)
T-cell/histiocytic rich large B-cell lymphoma	2 (0.9)
Primary mediastinal (thymic) large B-cell lymphoma	5 (2.2)
Diffuse, large B-cell lymphoma - germinal center B-cell type	70 (30.6)
Diffuse, large B-cell lymphoma - activated B-cell type	40 (17.5)
High-grade B-cell lymphoma, NOS	2 (0.9)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	12 (5.2)

Characteristic	N (%)
Disease status prior to CT - no. (%)	
CR1	2 (0.9)
CR2	3 (1.3)
CR3+	7 (3.1)
Relapse, 1st	52 (22.7)
Relapse, other	140 (61.1)
PIF/Untreated	24 (10.5)
Not reported	1 (0.4)
Types of prior HCTs - no. (%)	
Yes	229
Prior auto-HCT(s)	226 (98.7)
Prior auto and allo-HCT(s)	3 (1.3)
Year of CT - no. (%)	
2017	3 (1.3)
2018	144 (62.9)
2019	82 (35.8)
Commercial vs. noncommercial CAR-T product - no. (%)	
Commercial	229
Lymphodepleting chemotherapy - no. (%)	
Bendamustine	1 (0.4)
Bendamustine + Corticosteroids	2 (0.9)
Corticosteroids + Other	1 (0.4)
Cyclophosphamide + Fludarabine	222 (96.9)
Cyclophosphamide + Fludarabine + Monoclonal antibody	1 (0.4)
Not reported	2 (0.9)