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# CD19 directed CAR T therapy for intravascular large B-cell lymphoma

**Running title:** CAR T for IVLBCL

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Intravascular large B-cell lymphoma (IVLBCL) is a rare type of extranodal aggressive B-cell non-Hodgkin lymphoma (NHL) characterized by selective proliferation of lymphoma cells within small- to medium-sized blood vessels (particularly capillaries and postcapillary venules) of various organs throughout the body. Common clinical manifestations at the time of original diagnosis of IVLBCL include fever, fatigue, neurological symptoms, and skin rashes. It frequently involves the central nervous system (CNS), and since lymphadenopathy is generally absent, diagnosis if often challenging (1). This histological type is associated with concurrent hemophagocytic lymphohistiocytosis (HLH), particularly in Asian patients. Despite the use of rituximab-based chemoimmunotherapy, prognosis remains poor, with a median overall survival under 18 months (2). There are no established therapies for relapsed/refractory IVLBCL. While CD19-directed chimeric antigen receptor T-cell (CAR-T) therapy has transformed treatment of B-cell NHL (3,4), its safety and efficacy in IVLBCL remain unknown, as does the risk of immune effector cell–associated HLH-like syndrome (IEC-HLH) in a disease often associated with HLH. The latter is an important clinical consideration due to increasing awareness of the risk of IEC-HLH following CAR-T cell therapies (5)

Using the Center for International Blood and Marrow Transplant Research (CIBMTR) registry, we identified patients with relapsed/refractory IVLBCL who received commercial CD19-directed CAR-T therapy between 2019 to 2024. Observational studies are conducted by the CIBMTR in compliance with all pertinent federal regulations regarding protection of human research participants. All patients included in this analysis have provided written consent for research. The Institutional Review Board of Medical College of Wisconsin approved this study. Overall survival was the primary outcome. Death from any cause was considered an event for overall survival analysis. Secondary outcomes included progression-free survival, non-relapse mortality, and relapse/progression, cytokine release syndrome (CRS) and immune-effector-cell-associated neurologic syndrome (ICANS). For progression-free survival, progression/relapse or death from any cause were considered events. Non-relapse mortality was defined as death without evidence of lymphoma progression/relapse, where relapse was considered a competing risk. Kaplan-Meier estimates were used for overall survival and progression-free survival. CRS and ICANS were reported according to the consensus American Society for Transplantation and Cellular Therapy criteria (6). All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.4 (Vienna, Austria).

Nine patients from participating centers met inclusion criteria**. Table 1**. shows relevant demographic, baseline disease, and treatment-related characteristics of the study population. All patients had received rituximab plus anthracycline-based first line chemoimmunotherapy. Median age at CAR-T was 66 years (range, 51–86); four (44.4%) were female, and six were white (66.6%). Median prior therapy lines were 2 (range, 1–5); three (33.3%) had undergone autologous hematopoietic cell transplant. No patients had active CNS disease at time of CAR-T infusion. Median Karnofsky performance score was 80 (range, 70-100). Median interval from diagnosis to CAR-T was 22 months (range, 6–95). One patient received bridging with a Bruton’s tyrosine kinase inhibitor. Six

patients had active disease at the time of CAR-T cell administration, while three patients (patient numbers 4, 6, and 8) were in complete remission prior to CAR-T cell infusion. All patients received fludarabine and cyclophosphamide for lymphodepletion. Seven received axicabtagene ciloleucel; two received lisocabtagene maraleucel, including one out-of-specification product (patient #8). Median follow-up was 8 months (range, 4–36).

Eight (88.8%) patients experienced any-grade CRS; one (11.1%) had grade 3 CRS. Median CRS onset was 3 days (range, 1–7). Median time to CRS resolution was 5.8 days (range, 4-8). Treatment administered for CRS management included tocilizumab alone (N=2) or tocilizumab and corticosteroids (N=1). Four patients received no CRS treatment while this information was missing in two cases. Two patients developed ICANS (one subject had grade 1 ICANS, while the other patient had grade 3 ICANS). Both ICANS cases had onset at day 10 and took two days to resolve. Grade 1 ICANS received not treatment, while treatment information on grade 3 ICANS was missing. No IEC-HLH was observed. Six patients (66.7%) achieved complete remission. There was one case each of ongoing neutropenia and thrombocytopenia at one month post CAR-T, while two patients reported prolonged cytopenias beyond three months post CAR-T cell treatment. Among the three patients (case numbers 1, 5 & 8) with durable complete remissions, CAR-T therapy was administered after 3, 2 and 2 prior lines of treatment, respectively. The median duration of complete remission was 13 months. One-year non-relapse mortality, relapse/progression, progression-free survival, and overall survival were 0%, 71.4% (95%CI, 29.3-98.3%), 28.6% (95%CI, 3.7-64.7%), and 50% (95%CI, 18.1-81.9%), respectively (**Figure 1**). The median progression-free and overall survival were 5.86 and 12.45 months respectively. One year progression-free survival and overall survival following axicabtagene ciloleucel (N=7) were 20% and 50%, respectively. While the progression-free survival and overall survival following lisocabtagene maraleucel (N=2) were 50% and 50% respectively. At last follow-up, six patients had died from recurrent/refractory disease.

With the limitations of small sample size (in an exceedingly rare disease), reporting bias (registry only capturing patients successfully infused with CAR-T), heterogeneity of CAR-T product administered, short follow up (limiting ability to assess durability of complete remission) and no central review of pathology in mind, these data collectively do not show an unusual toxicity signal in terms of CRS, ICANS and IEC-HLH with CAR-T therapy in IVLBCL. In conclusion, while treatment failure was common, CAR-T treatment appears to provide durable remissions in subset of IVLBCL patients with otherwise extremely poor prognosis.

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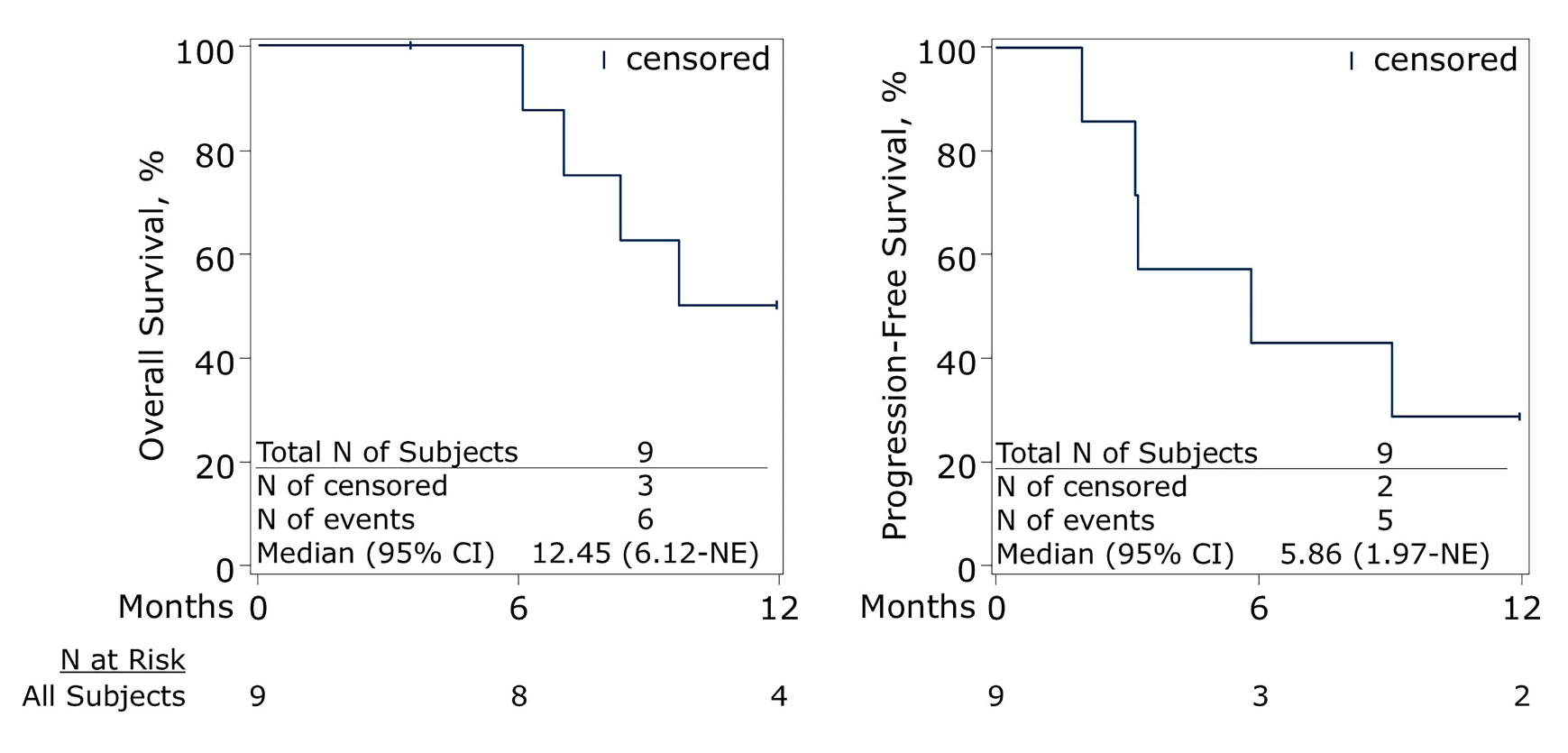
**Table 1. Intravascular large B-cell lymphoma patients undergoing CAR-T cell therapy.**

| Case# | Age/ Sex | Race | First line therapy | Primary refractory disease | Extranodal involvement (beyond blood vessels) at diagnosis | Prior auto-HCT | No of Lines of therapy prior to CAR-T | KPS prior to CAR-T | Elevated LDH prior to infusion | Type of CAR-T | Best Response to CAR-T response at Day 100 | Relapse or Disease Progression | Status at Last Follow up | Cause of death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 51/F | White | R-EPOCH + IT-MTX | Not Reported | Ocular | Yes | 3 | 80 | No | Axi-cel | CR | No | Alive (4+ mo) | NA |
| **2** | 86/M | White | R-CHOP | No | Spleen | No | 2 | 80 | Not reported | Axi-cel | CR | Yes | Dead | Primary Disease |
| **3** | 59/F | Asian | R-CHOP + HD-MTX | No | CNS | Yes | 3 | 100 | Yes | Axi-cel | Progressive disease | Yes | Dead | Primary Disease |
| **4** | 67/M | White | R-CHOP | No | Not Reported | Yes | 5 | 90 | No | Liso-cel | CR | Yes | Dead | Primary Disease |
| **5** | 57/M | White | R-CHOP | No | Spleen; Lungs | No | 2 | 80 | Not reported | Axi-cel | CR | No | Alive (36+ mo) | NA |
| **6** | 52/F | White | R-CHOP | No | Liver, cervix, vagina, sellar region | No | 1 | 80 | No | Axi-cel | CR | Yes | Dead | Primary Disease |
| **7** | 70/M | Hispanic | R-CHOP | Yes | No | No | 2 | 100 | Not reported | Axi-cel | Stable Disease | Yes | Dead | Primary Disease |
| **8** | 66/M | White | R-CHOP | No | Spleen, adrenal gland | No | 2 | Not Reported | No | Liso-cel | CR | No | Alive (13+ mo) | NA |
| **9** | 67/F | Hispanic | RCHOP | Not Reported | Not Reported | No | 1 | 70 | Yes | Axi-cel | Progressive disease | Yes | Dead | Primary Disease |

**Abbreviations:** Axi-cel= axicabtagene ciloleucel; CAR-T=chimeric antigen receptor modified T-cell; CNS=central nervous system; CR=complete remission; EPOCH=etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, F=female; HD=high dose; IT=interthecal; KPS=karnofsky performance score; LDH=lactate dehydrogenase; liso-cel= lisocabtagene maraleucel; M=male; mo=months; MTX=methotrexate; NA= not applicable; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone,

**Figure legend:**

**Figure 1. Overall and progression free survival of intravascular large B-cell lymphoma patients undergoing CAR-T cell therapy.**


Overall Survival, %
100
80
60
40
20
0
censored
Total N of Subjects 9
N of censored 3
N of events 6
Median (95% CI) 12.45 (6.12-NE)
Months 0 6 12
N at Risk
All Subjects 9 8 4
Progression-Free Survival, %
100
80
60
40
20
0
censored
Total N of Subjects 9
N of censored 2
N of events 5
Median (95% CI) 5.86 (1.97-NE)
Months 0 6 12
9 3 2