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

Intravascular large B-cell lymphoma (IVLBCL) is a rare type of extranodal aggressive B-cell non-Hodgkin lymphoma 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 the original diagnosis of IVLBCL include fever, fatigue, neurological symptoms, and skin rashes. It frequently involves the central nervous system and, since lymphadenopathy is generally absent, the 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 of less than 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 the treatment of B-cell non-Hodgkin lymphoma,[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 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 provided written consent to research. The Institutional Review Board of the 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 neurological 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, USA) and R version 4.4 (Vienna, Austria).

Nine patients from participating centers met the 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. The median age of the patients at CAR-T therapy was 66 years (range, 51-86); four (44.4%) were female, and six were white (66.6%). The median number of prior lines of therapy lines was two (range, 1–5); three patients (33.3%) had undergone autologous hematopoietic cell transplant. No patients had active central nervous system disease at the time of CAR-T infusion. The median Karnofsky performance score was 80 (range, 70-100). The median interval from diagnosis to CAR-T therapy was 22 months (range, 6-95). One patient received bridging with a Bruton tyrosine kinase inhibitor. Six patients had active disease at the time of CAR-T administration, while three patients (patients #4, #6, and #8) were in complete remission prior to CAR-T 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). The median follow-up was 8 months (range, 4-36).

Eight (88.8%) patients experienced any-grade CRS; one (11.1%) had grade 3 CRS. The median CRS onset was 3 days (range, 1-7). The median time to CRS resolution was 5.8 days (range, 4-8). Treatment administered for CRS management included tocilizumab alone (N=2) and 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). The onset of ICANS was on day 10 in both cases and the syndrome took 2 days to resolve. The patient with grade 1 ICANS did not receive any treatment, while treatment information on the patient with 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 1 month after CAR-T therapy, while two patients reported prolonged cytopenias beyond 3 months after CAR-T treatment. Among the three patients (case numbers #1, #5 and #8) with durable complete remissions, CAR-T therapy was administered after three, two and two 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 rates were 0%, 71.4% (95% confidence interval [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 progres-

**Table 1.** Intravascular large B-cell lymphoma patients undergoing chimeric antigen receptor T-cell therapy.

| Case # | Age/ Sex | Race | First-line therapy | Primary refractory disease | Extranodal involvement (beyond blood vessels) at diagnosis | Prior auto-HCT | N 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 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+ months) | 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+ months) | 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+ months) | NA |
| 9 | 67/F | Hispanic | R-CHOP | Not reported | Not reported | No | 1 | 70 | Yes | Axi-cel | Progressive disease | Yes | Dead | Primary disease |

Auto-HCT: autologous hematopoietic cell transplant; CAR-T: chimeric antigen receptor modified T cells; KPS: Karnofsky performance score; LDH: lactate dehydrogenase; F: female; R-EPOCH: rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; IT: intrathecal; MTX: methotrexate; axi-cel: axicabtagene ciloleucel; CR: complete remission; NA: not applicable; M: male; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; HD: high-dose; CNS: central nervous system; liso-cel: lisocabtagene maraleucel.

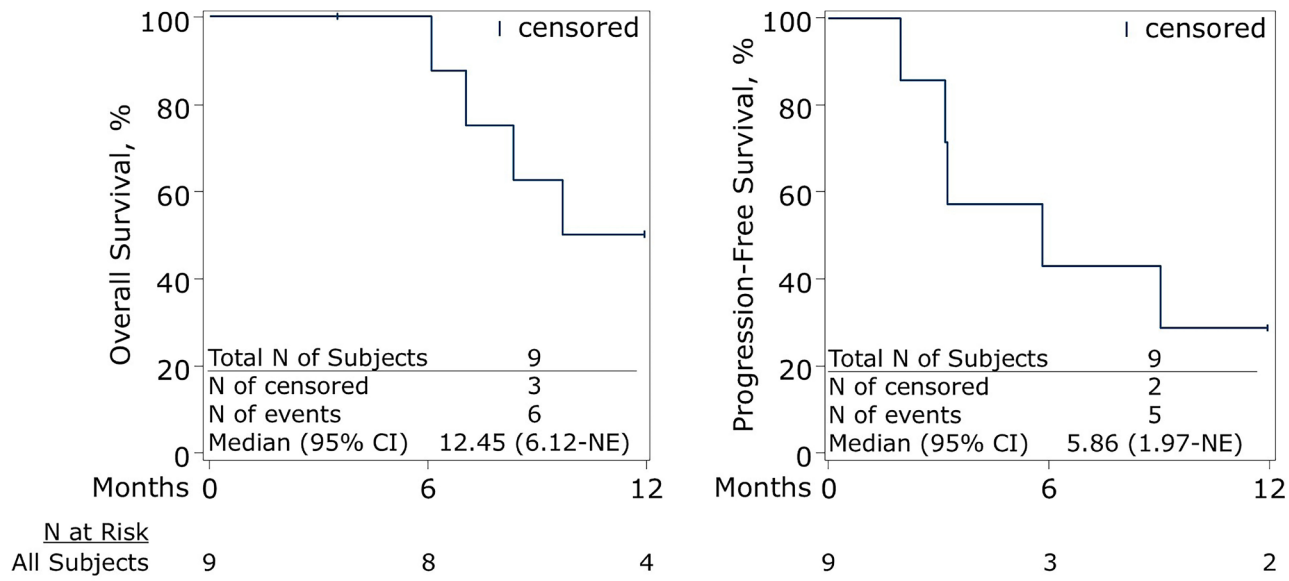



**Figure 1. Overall and progression-free survival of patients with intravascular large B-cell lymphoma undergoing chimeric antigen receptor T-cell therapy.** 95% CI: 95% confidence interval; NE: not estimated.

sion-free and overall survival were 5.86 and 12.45 months, respectively. One-year progression-free survival and overall survival rates following axicabtagene ciloleucel (N=7) were 20% and 50%, respectively, while the progression-free survival and overall survival rates 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 a subset of IVLBCL patients with otherwise extremely poor prognosis.

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https://doi.org/10.3324/haematol.2025.288838

Received: August 21, 2025.
Accepted: October 31, 2025.
Early view: November 6, 2025.

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**Disclosures**

AG has received research funding from Merck, I-Mab bio, IgM Bio, Takeda, Gilead, AstraZeneca, Agios, Janssen, BMS, SeaGen, Teva, Genmab, Beigene, Pfizer and Umoja; has provided consultancy services for and/or received honoraria from Incyte, Kite, Morphosys/Incyte, ADCT, Acrotech, Merck, Karyopharm, Servier, Beigene, Cellectar, Janssen, Compliment, SeaGen, Epizyme, I-Mab bio, Gilead, Genentech, Lilly, Caribou, Fresenius-Kabi, Scitech, Sana and Compliment; and holds stock options with Compliment Corporation and SciTech. HC has received honoraria from or participated in advisory boards for Kite and BMS. MH has received research support and/or funding from ADC Therapeutics, Spectrum Pharmaceuticals and Astellas Pharma; has provided consultancy services for ADC Therapeutics, CRISPR, BMS, Kite, AbbVie, Caribou, Genmab, Autolus, Forte Biosciences, Byondis, Allovir and Poseidon; participated in speakers bureau for ADC Therapeutics, AstraZeneca, Bei Gene, Kite and Sobi; participated in a Data Monitoring Committee for, Myeloid Therapeutics and CRISPR. The other authors have no conflicts of interest to disclosure. The Center for International Blood and Marrow Transplant Research (CIBMTR) is supported primarily by the Public Health Service U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases (NIAID); 75R60222C00011 from the Health Resources and Services Administration (HRSA); and N00014-24-1-2057 and N00014-25-1-

2146 from the Office of Naval Research. Additional federal support is provided by U01AI184132 from the National Institute of Allergy and Infectious Diseases (NIAID); and UG1HL174426 from the National Heart, Lung and Blood Institute (NHLBI). Support is also provided by the Medical College of Wisconsin, NMDP, Gateway for Cancer Research, Pediatric Transplantation and Cellular Therapy Consortium and from the following commercial entities: AbbVie; Actinium Pharmaceuticals, Inc.; Adaptimmune LLC; Adaptive Biotechnologies Corporation; ADC Therapeutics; Adienne SA; Alexion; AlloVir, Inc.; Amgen, Inc.; Astellas Pharma US; AstraZeneca; Atara Biotherapeutics; Autolus Limited; BeiGene; BioLineRX; Blue Spark Technologies; Bluebird Bio, Inc.; Blueprint Medicines; Bristol Myers Squibb Co.; CareDx Inc.; Caribou Biosciences, Inc.; CSL Behring; CytoSen Therapeutics, Inc.; DKMS; Elevance Health; Eurofins Viracor, DBA Eurofins Transplant Diagnostics; Gamida-Cell, Ltd.; Gift of Life Biologics; Gift of Life Marrow Registry; HistoGenetics; ImmunoFree; Incyte Corporation; Iovance; Janssen Research & Development, LLC; Janssen/Johnson & Johnson; Jasper Therapeutics; Jazz Pharmaceuticals, Inc.; Karius; Kashi Clinical Laboratories; Kiadis Pharma; Kite, a Gilead Company; Kyowa Kirin; Labcorp; Legend Biotech; Mallinckrodt Pharmaceuticals; Med Learning Group; Medac GmbH; Merck & Co.; Mesoblast, Inc.; Millennium, the Takeda Oncology Co.; Miller Pharmacal Group, Inc.; Miltenyi Biotec, Inc.; MorphoSys; MSA-EDITLife; Neovii Pharmaceuticals AG; Novartis Pharmaceuticals Corporation; Omeros Corporation; Orca Biosystems, Inc.; OriGen BioMedical; Ossium Health, Inc.; Pfizer, Inc.; Pharmacyclics, LLC, an AbbVie Company; Registry Partners; Rigel Pharmaceuticals; Sanofi; Sarah Cannon; Seagen Inc.; Sobi, Inc.; Sociedade Brasileira de Terapia Celular e Transplante de Medula Óssea (SBTMO); Stemcell Technologies; Stemline Technologies; STEMSOFT; Takeda Pharmaceuticals; Talaris Therapeutics; TScan Therapeutics; Vertex Pharmaceuticals; Vor Biopharma Inc.; Inc. and Xenikos BV.

**Contributions**

All authors contributed to performing the research and data analysis and supervised the study.

**Data-sharing statement**

The Center for International Blood and Marrow Transplant Research (CIBMTR) supports accessibility of research in accord with the National Institutes of Health Data Sharing Policy and the National Cancer Institute Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases deidentified datasets that comply with all relevant global regulations regarding privacy and confidentiality.

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