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Real-World Outcomes of Anti-CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy for Third-Line Relapsed or Refractory Diffuse Large B-Cell Lymphoma: A Single-Center Study

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Abstract: Background: Diffuse large B-cell lymphoma (DLBCL) is the most common diagnosed aggressive B-cell lymphoma, with poor outcomes in those who experience relapsed or refractory (R/R) disease. Landmark clinical trials have demonstrated the efficacy and safety of anti-CD19 chimeric antigen receptor (CAR) T-cell therapy for patients with R/R DLBCL, though further exploration of real-world outcomes (RWOs) and safety data is warranted. Methods: A retrospective chart review was performed to collect patient and disease characteristics from patients with R/R DLBCL receiving CAR T-cell therapy for third-line treatment or beyond at the John Theurer Cancer Center as the standard of care. Results: We report on 82 patients with R/R DLBCL that successfully completed an infusion of an anti-CD19 CAR T-cell product at our institution. Best overall and complete response rates were 74.4% (95% CI, 64.9 to 83.8) and 67.1% (95% CI, 56.9 to 77.2), respectively. From the time of CAR T-cell infusion, median PFS was 26.5 months (95% CI, 8.6 months could not be estimated) and OS was not reached. Subgroup analyses revealed no statistical differences in outcomes by use of bridging therapy, Karnofsky performance status, transformed DLBCL status, and the type of CAR T-cell product used for this study. CAR T-cell therapy was well tolerated, with 58 patients (70.7%) experiencing cytokine-release syndrome and 17 patients (20.7%) experiencing immune effector cell-associated neurotoxicity syndrome. Conclusions: These results of RWOs in third-line patients with R/R DLBCL receiving anti-CD19 CAR T-cell therapy are comparable or superior to prior clinical trials and studies of RWOs, validating the strong efficacy and manageable toxicities of CAR T-cell therapy.

Keywords: diffuse large B-cell lymphoma; DLBCL; non-Hodgkin lymphoma; NHL; cytokine release syndrome; CRS; immune effector cell-associated neurotoxicity syndrome; ICANS; CAR T-cell therapy; real-word outcomes; RWOs

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1. Introduction

Diffuse large B-cell lymphoma (DLBCL) remains the most commonly diagnosed lymphoma, accounting for approximately 30% of non-Hodgkin lymphoma (NHL) cases in

the United States [1]. For DLBCL patients without high-risk features, first-line treatment consists of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), a chemoimmunotherapy regimen introduced over two decades ago, with cure rates between 60% and 70% [2,3]. Despite these impressive outcomes, nearly 30% to 40% of patients experience disease progression or refractoriness within the first 2 years of diagnosis [1,4]. These patients with relapsed or refractory (R/R) DLBCL often have a more aggressive disease course and limited salvage therapy options, leading to higher relapse rates and poorer outcomes. This underscores the need for a better understanding of the outcomes of these patients to optimize sequencing of subsequent therapies.

Historically, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) was the standard of care for R/R DLBCL, yet over 50% of patients relapsed with this intensive approach [5,6]. The breakthrough era of anti-CD19 chimeric antigen receptor (CAR) T-cell therapy revolutionized the treatment landscape for R/R DLBCL, significantly improving patient outcomes in recent years [7,8]. Anti-CD19 CAR T-cell therapy works by targeting the CD19 receptor on malignant and non-malignant B-cells to allow for identification and destruction of lymphoma by engineered host T-cells through direct cytotoxicity and cytokine release. Anti-CD19 CAR T-cells are genetically modified to express the CAR construct, consisting of a CD19-targeting binding domain (or single-chain variable fragment), a hinge and transmembrane domain, costimulatory domain, and a signaling or activating domain of the T-cell receptor (generally consisting of the CD3ζ chain) [9]. Currently, there are three anti-CD19 CAR T-cell therapies approved for R/R DLBCL: axicabtagene ciloleucel (axi-cel), lisocabtagene maraleucel (liso-cel), and tisagenlecleucel (tisa-cel). These products are similar in that they target CD-19 on cancer cells and possess the CD3ζ signaling domain but differ in regard to the type of costimulatory domain (CD28 vs. 4-1BB) and manufacturing time (longer with tisa-cel compared to axi-cel or liso-cel), which have been thought to account for differences observed amongst these products in relation to efficacy and safety.

Anti-CD19 CAR T-cell therapy was initially approved for patients with R/R DLBCL after two or more prior lines of therapy [10,11]. In 2022, results of the ZUMA-7 trial led to the approval of anti-CD19 CAR T-cell therapy as an alternative second-line treatment, particularly for DLBCL patients who relapse within the first 12 months of treatment or have primary refractory disease [11,12]. Although a promising treatment modality, CAR T-cell therapy is associated with high-grade toxicities, such as cytokine release syndrome (CRS) and neurotoxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS) [9,13]. CRS arises from a release of proinflammatory cytokines from activated or lysed effector cells upon CAR binding, which subsequently leads to activation of bystander immune cells, including macrophages and endothelial cells, that release large amounts of interleukin-6 (IL-6), resulting in symptoms such as fever, hypotension, capillary leak (hypoxia), and end organ dysfunction [14,15]. The exact pathophysiology of ICANS is unknown but is thought to be related to a combination of increased inflammation and expression of cytokines as well as disruption of the blood–brain barrier, resulting in complications such as aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema [14,15].

Treatment of CAR T-cell-related toxicities varies between institutions and is dependent on the grade of toxicity. Grade 1 CRS is managed with antipyretics and cooling interventions [16,17]. Persistent grade 1 or 2 CRS is managed with an anti-IL-6 monoclonal antibody, tocilizumab, and sometimes supplemented with corticosteroid therapy for patients at risk of severe CRS. Once tocilizumab dosing is maximized, corticosteroid therapy is often utilized [17,18]. CRS greater than grade 3 often requires treatment in the intensive care unit as further supportive therapy, such as vasopressors or intubation, may

be required [16,17]. ICANS is primarily managed with corticosteroids and prophylactic antiepileptics [19,20].

Several clinical trials support the use of anti-CD19 CAR T-cell therapy for treatment of R/R DLBCL [7,12,21–24]. Still, additional investigation of real-world clinical outcomes and safety results, as well as evaluation of certain patient populations purposefully excluded from clinical trials, such as those who received prior CD19-targeted therapy and patients with DLBCL arising from Richter transformation, remain areas of interest [12]. To date, there are many studies of real-world outcomes (RWOs) that have explored the use of anti-CD19 CAR T-cell therapy in R/R DLBCL, with reported similar efficacy and safety as landmark clinical trials, but many of these studies focus solely on one or two types of anti-CD19 CAR T-cell products, making comparisons to the earliest trial data, with some studies having similar eligibility criteria as the foundational trials [25–30].

Considering the poorer outcomes associated with R/R DLBCL, there is a dire need to better understand the RWOs of anti-CD19 CAR T-cell therapy in certain patient subgroups and with different CAR T-cell products. Herein, we report the patient characteristics and RWOs of R/R DLBCL patients treated with anti-CD19 CAR T-cell therapy in a retrospective, single-center study. We aim to expand upon the understanding of clinical and safety outcomes of three anti-CD19 CAR T-cell products in the context of the typical community-based treatment and referral continuum observed in the real-world setting.

2. Materials and Methods

2.1. Patient Selection

This is a retrospective, single-center study of 82 consecutive patients who underwent anti-CD19 CAR T-cell therapy as third-line or later for R/R DLBCL between 13 March 2018 and 23 November 2022 at the John Theurer Cancer Center (92 Second Street, Hackensack, NJ 07601, USA) at Hackensack Meridian Health (HMH). Patient selection for this study was based on early CAR T-cell product approval by the U.S. Food and Drug Administration for R/R DLBCL patients after receiving 2 or more lines of systemic therapy [31]. Patients eligible for this study included those aged 18 years or older with a diagnosis of R/R primary DLBCL or transformed DLBCL from another indolent NHL such as chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), or follicular lymphoma (FL) and who received anti-CD19 CAR T-cell therapy. Institutional Review Board (IRB) approval for this study was obtained from Hackensack Meridian Health's IRB (Pro2021-0256). This study was conducted under the International Conference on Harmonization Good Clinical Practice Guidelines and according to the revised Declaration of Helsinki. The requirement for patient informed consent (verbal or written) was waived by the IRB as this project represented a non-interventional study using routinely collected data for secondary research purposes.

Patients in this study received 1 of 3 anti-CD19 CAR T-cell products: axi-cel, liso-cel, and tisa-cel. The choice of CAR T-cell product, the use of bridging therapy, and the timing of pretreatment imaging were per the treating physician. Bridging therapy was defined as any lymphoma-specific therapy administered after leukapheresis and before initiation of conditioning chemotherapy. All patients received lymphodepleting chemotherapy with fludarabine and cyclophosphamide or bendamustine. All patients were hospitalized following anti-CD19 CAR T-cell infusion and monitored for subsequent toxicities. At least 6 weeks of follow-up from the date of CAR T-cell infusion were allowed prior to assessment of outcomes and survival status. First response assessment and subsequent imaging were per institutional practice. Survival outcomes were assessed in all patients who received a CAR T-cell infusion.

2.2. Data Collection and Diagnostic Criteria

Data were collected from HMH's electronic health record (Epic), which is utilized throughout the network. Demographics, clinical characteristics, treatments, and outcomes were manually extracted. Data abstracted by the team were entered into a REDCap database and exported as an Excel spreadsheet for analysis, with quality control performed by physicians overseeing data collection.

The Hans algorithm was utilized for stratification into germinal center B-cell (GCB) and non-GCB DLBCL subtypes [32]. Mutation status for genes of interest was evaluated by next-generation sequencing using Genomic Testing Cooperative's Hematology Profile test, which takes a peripheral blood sample to obtain cfDNA and cfRNA in order to screen for 302 DNA and more than 1600 RNA genes associated with either diagnostic, prognostic, or therapeutic relevance [33–35]. CD19+ status was assessed prior to CAR T-cell manufacturing by flow cytometry or immunohistochemistry. Karnofsky performance status (KPS) was used to quantify the functional status of DLBCL patients [36]. CRS and ICANS were graded according to the American Society for Transplantation and Cellular Therapy criteria [14]. Response was assessed using imaging reviewed by the treating physician according to the Cheson criteria [37].

2.3. Statistical Analysis

The primary aim of this study was to investigate patient characteristics, disease outcomes, and safety profiles in patients with R/R DLBCL receiving cellular therapy. Secondary analyses focused on subgroups of interest related to high-risk R/R DLBCL patient populations and comparisons between different CAR T-cell products used in this study.

Descriptive statistics, including mean, median, and range for continuous variables and counts with percentages for categorical variables are provided. For statistical analyses, the software GraphPad Prism 9.3.1 was used for Mac (GraphPad Software, Boston, MA, USA). A two-sided test $p < 0.05$ was accepted as statistically significant. The Kaplan–Meier method was used to estimate progression-free survival (PFS) and overall survival (OS) rates. PFS was defined as the time from infusion (unless otherwise specified) for all treated patients to the first observation of progressive disease or death as a result of any cause. Progressive disease was assessed by the treating physician according to the Cheson criteria [37], and was defined as an increase in intensity of preexisting lesions or new lesions and/or new or recurrent bone marrow involvement on imaging. OS was defined as the time from infusion (unless otherwise specified) for all treated patients to death as a result of any cause. The log-rank (Mantel–Cox) test was used to evaluate the difference in the distribution of PFS or OS in sensitivity analyses. Asymmetrical confidence bands for probability of survival were used to calculate the 95% confidence interval (CI) for median PFS and OS. Fisher's exact test was used to evaluate the association between two categorical variables and the chi-squared test was used to evaluate the association between more than two categorical variables. For continuous variables, group differences were determined by one-way ANOVA.

Multivariable-adjusted analyses were conducted by linear regression modeling to assess independent predictors between risk factors and outcomes: either safety (CRS and ICANS) and efficacy (PFS and OS). Variable selection involved selection for variables based on biological, clinical, and empirical data-driven approaches. Variables included in these models were age, KPS, use of bridging, primary refractory disease, transformed disease, bulky disease, TP53 mutated status, DH/TH/DE status, and number of prior lines of therapy. These analyses were carried out using R (version 4.3.2) and RStudio (version 2023.12.0+369) statistical software with the following packages: Hmisc, moments, tidyverse, and dplyr.

3. Results

3.1. Patient and Disease Characteristics

In this single-center study, 82 patients who underwent leukapheresis and infusion of an anti-CD19 CAR T-cell product at our institution for treatment of R/R DLBCL were considered evaluable for this study. Patient demographics and lymphoma characteristics are summarized in Table 1. Patients in this sample were mostly male (57.3%), with a median age of 64.2 years (range, 22–83), where the majority had ≥2 comorbidities (56.1%) (Table S1).

Table 1. Baseline patient and disease characteristics at time of CAR T-cell treatment.

Characteristics	**N = 82** ***n* (%)**
Age, median years (range)	64.2 (22–83)
<60	28 (34.1)
≥60	54 (65.9)
Male sex	47 (57.3)
Karnofsky performance status	
>70	39 (47.6)
≤70	41 (50)
Unknown/Unavailable	2 (2.4)
Disease type	
Primary DLBCL	54 (65.9)
Transformed CLL\SLL	4 (4.9)
Transformed FL	24 (29.3)
High Ki-67 expression (≥80%)	38 (46.3)
Cell of origin	
GCB-like	31 (37.8)
Non-GCB	24 (29.3)
Unclassified/Unavailable	27 (32.9)
Double- or triple-hit lymphoma [1]	10 (12.2)
Double-expressor lymphoma [2]	20 (24.4)
Mutation status [4]	
TP53	17 (20.7)
MYD88	2 (2.4)
EZH2	6 (7.3)
Disease involvement at relapse	
Extranodal	35 (42.7)
Bulky disease	34 (41.5)
CNS	5 (6.1)
Prior stem cell transplant	
Autologous	15 (18.3)
Allogeneic	5 (6.1)
Primary refractory disease	36 (43.9)
Refractory to most recent therapy	36 (43.9)
Disease status pre-apheresis	
Partial Response	12 (14.6)
Stable Disease	4 (4.9)
Progressive Disease	66 (80.5)

Table 1. *Cont.*

Characteristics	N = 82 *n* (%)
Conditioning regimen	
Bendamustine	13 (15.9)
Fludarabine/cyclophosphamide	69 (84.1)
Anti-CD19 CAR T-cell product	
Axicabtagene ciloleucel	53 (64.6)
Lisocabtagene maraleucel	15 (18.3)
Tisagenlecleucel	14 (17.1)
Bridging therapy type	
Any therapy	26 (31.7)
Rituximab	17 (20.7)
Polatuzumab (anti-CD79b)	12 (14.6)
Ibrutinib	4 (4.9)
Time from leukapheresis to CAR T-cell infusion, median days (range)	32 (24–186)

CLL = chronic lymphocytic leukemia; CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; GCB = germinal center B-cell; SLL = small lymphocytic lymphoma. [1] Double-hit lymphoma was defined as *MYC* and either *BCL2* or *BCL6* rearrangements detected by FISH or standard cytogenetics. Triple-hit lymphoma was defined as rearrangements in *MYC*, *BCL2*, and *BCL6* as detected by FISH or standard cytogenetics. [2] Double-expressor lymphoma was defined as overexpression of *MYC* and either *BCL2 or BCL6* detected by FISH or standard cytogenetics. [4] Mutation status for genes of interest was evaluated using next-generation sequencing.

Patient subgroups of interest included those with a KPS score of ≤70 (50%) as well as those with high-grade DLBCL subtypes, including double- or triple-hit (DH/TH) DLBCL (12.2%) and double-expressor (DE) DLBCL (24.4%). High-risk genetics identified in this sample included mutated TP53 (20.7%), MYD88 (2.4%), and EZH2 (7.3%). High-risk features included elevated Ki-67 expression (≥80%) in 46.3% of patients as well as extranodal and bulky disease in 42.7% and 41.5%, respectively.

Bridging therapy was used in 31.7% of patients, with the most common types used being rituximab (20.7%), polatuzumab (14.6%), and ibrutinib (4.9%). The median time from leukapheresis to CAR T-cell infusion was 32 days (range, 24–186 days). Anti-CD19 CAR T-cell products infused included axi-cel (64.6%), liso-cel (18.3%), and tisa-cel (17.1%). At the time of infusion, the majority of patients (80.5%) in our sample had progressive disease (PD), 14.6% had a partial response (PR), and 4.9% had stable disease (SD).

3.2. Response to Anti-CD19 CAR T-Cell Therapy

In the 82 patients who underwent anti-CD19 CAR T-cell infusion, the best overall response rate (ORR) and complete response (CR) rate were 74.4% (95% CI, 64.9 to 83.8) and 67.1% (95% CI, 56.9 to 77.2), respectively (Table 2). From the time of leukapheresis, median PFS was 27.4 months (95% CI, 9.8 months to could not be estimated) and median OS was not reached. Median PFS from the time of anti-CD19 CAR T-cell infusion was 26.5 months (95% CI, 8.6 months to could not be estimated; Figure 1A) and median OS was not reached (Figure 1B). Twelve-month follow-up PFS and OS from the time of CAR T-cell infusion were 58.2% (95% CI, 44.9% to 69.3%) and 77.5% (95% CI, 64.7% to 86.2%), respectively. Twenty-four-month follow-up PFS and OS were 51.0% (95% CI, 35.8% to 64.4%) and 58.3% (95% CI, 39.8% to 72.9%), respectively (Table 2).

When stratifying by response to CAR T-cell treatment, median PFS was not reached in patients who achieved a CR, compared to a median PFS of 5.4 months (95% CI, 2.9 to 8.0 months) in patients who did not achieve a CR ($p < 0.0001$; Figure 1C). Similarly, median OS was not reached in patients who achieved a CR, compared to a median OS of

16.3 months (95% CI, 7.2 months to could not be estimated) in patients who did not achieve a CR (p = 0.01; Figure 1D).

Table 2. Rates of best response and survival at 12 and 24 months after anti-CD19 CAR T-cell infusion.

Response Rates	**N = 82** ***n*% (95% CI)**
Overall response rate	74.4 (64.9–83.8)
Complete response rate	67.1 (56.9–77.2)
Partial response rate	7.3 (1.7–13.0)
12-month progression-free survival	58.2 (44.9–69.3)
12-month overall survival	77.5 (64.7–86.2)
24-month progression-free survival	51.0 (35.8–64.4)
24-month overall survival	58.3 (39.8–72.9)

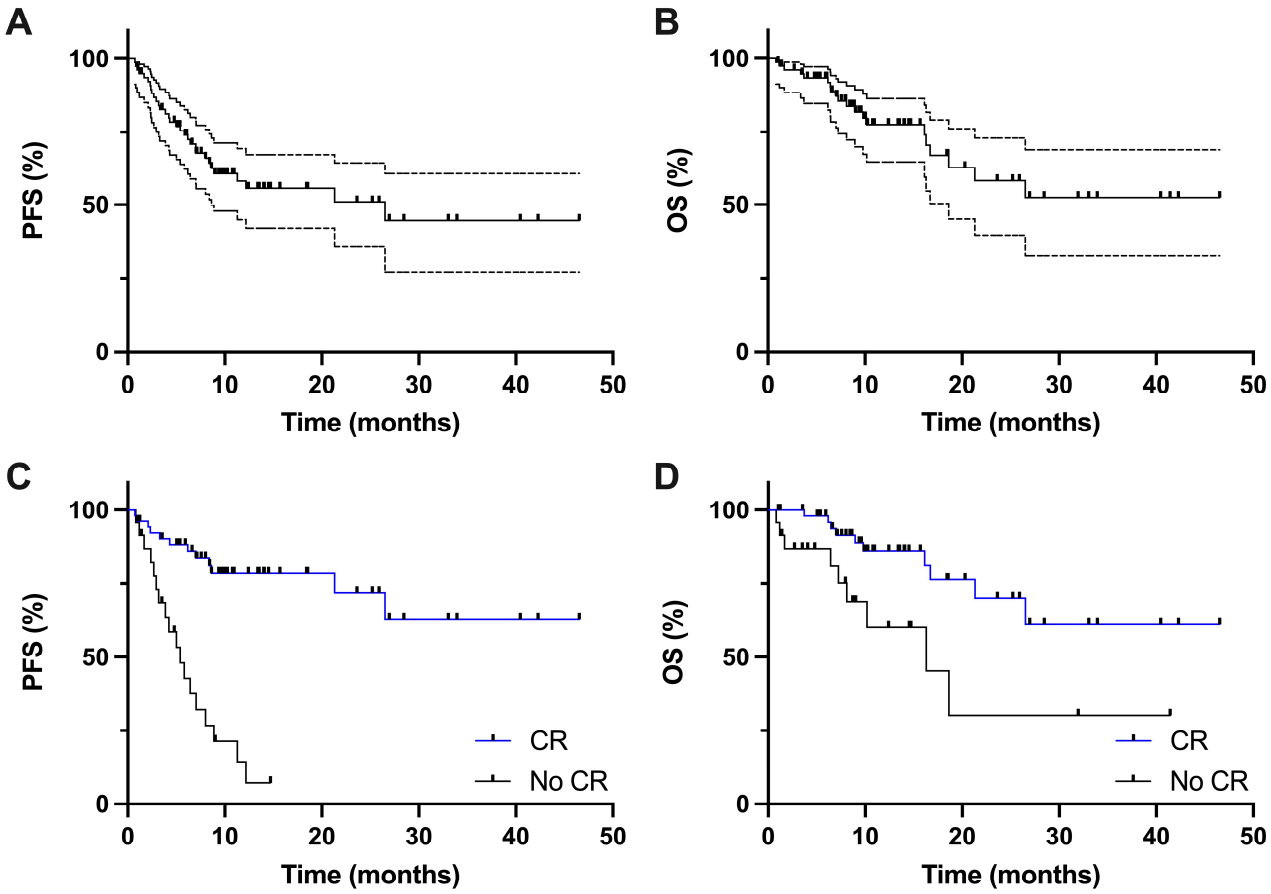

Figure 1. Progression-free survival (PFS) and overall survival (OS) estimates. (**A**) PFS and (**B**) OS from the time of CAR T-cell infusion, where dotted lines represent upper and lower 95% confidence intervals. (**C**) PFS and (**D**) OS stratified by complete response (CR).

3.2.1. Response to Anti-CD19 CAR T-Cell Therapy by Subgroups

Analyses based on the clinical and molecular DLBCL subgroups of interest were performed in this study. The frequencies of CR did not differ between patients who received bridging therapy (p = 0.49; Figure 2A). Median PFS in patients who received bridging therapy was 21.3 months (95% CI, 5.0 months to could not be estimated) compared to 26.5 months (95% CI, 8.4 months to could not be estimated) in patients who did not receive bridging therapy (Figure 2B). Median OS in patients who received bridging therapy was 21.3 months (95% CI, 16.3 months to could not be estimated) and was not yet reached in patients who did not receive bridging therapy (Figure 2C).

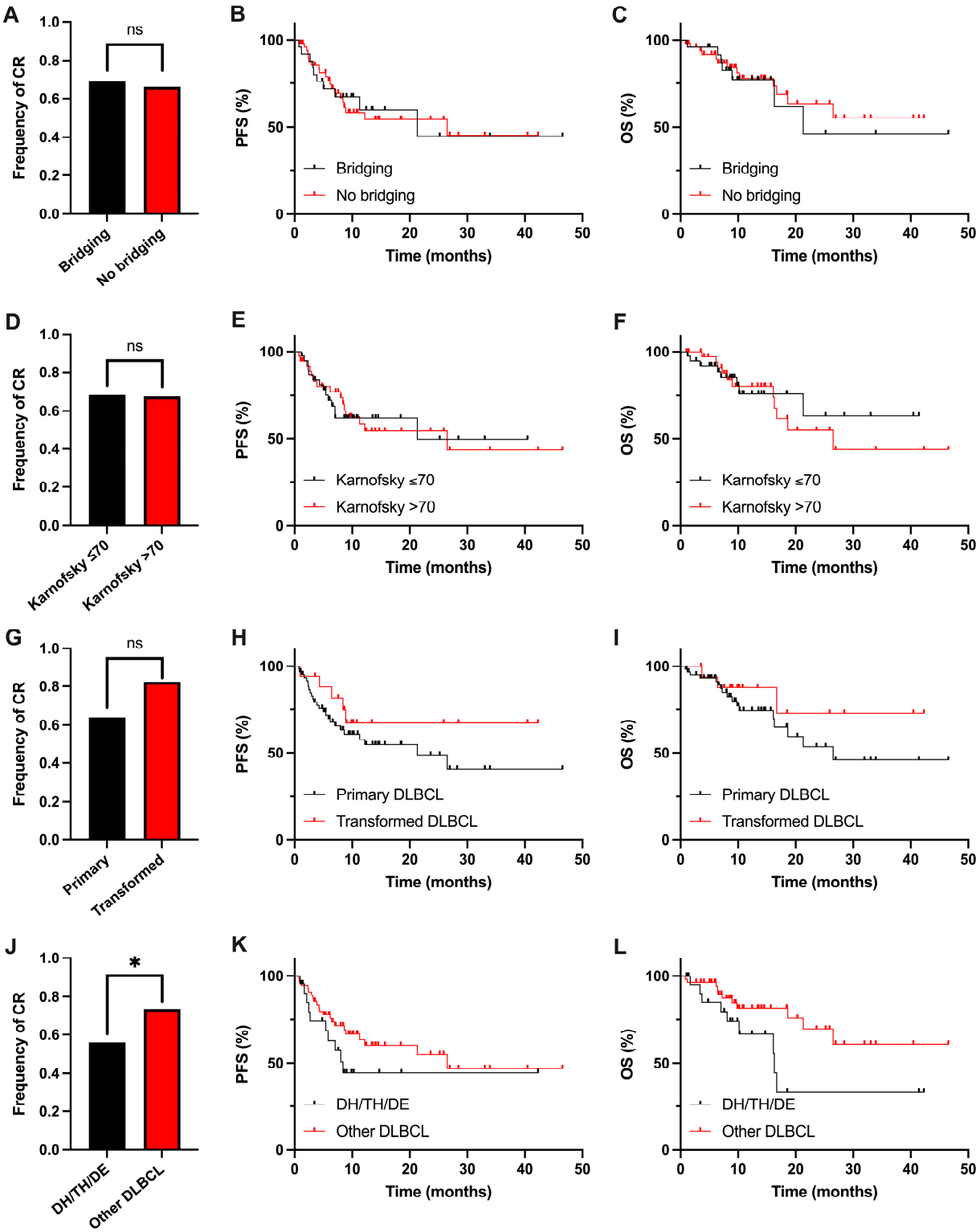

Figure 2. DLBCL subgroup analyses for patients treated with anti-CD19 CAR T-cell therapy. (**A**) Frequency of complete response (CR), (**B**) PFS from CAR T-cell infusion, and (**C**) OS from CAR T-cell infusion comparing patients who did or did not receive bridging therapy prior to CAR T-cell infusion. (**D**) Frequency of CR, (**E**) PFS from CAR T-cell infusion, and (**F**) OS from CAR T-cell infusion comparing patients by their Karnofsky performance status. (**G**) Frequency of CR, (**H**) PFS from CAR T-cell infusion, and (**I**) OS from CAR T-cell infusion comparing patients by primary DLBCL versus transformed DLBCL. (**J**) Frequency of CR, (**K**) PFS from CAR T-cell infusion, and (**L**) OS from CAR T-cell infusion comparing patients with double-hit, triple-hit, or double-expressor (DH/TH/DE) DLBCL versus other DLBCLs. Asterisks denote significance: * $p < 0.05$, ns $p > 0.05$.

When stratifying patients by functional status, no significant differences in the frequencies of CR were observed between patients with a KPS score ≤ 70 compared to those with a KPS score > 70 ($p = 0.56$; Figure 2D). Median PFS in patients with a KPS score ≤ 70 was 21.3 months (95% CI, 6.9 months to could not be estimated) compared to 26.5 months (95% CI, 8.6 months to could not be estimated) in patients with a KPS score > 70 (Figure 2E). Median OS in patients with a KPS score ≤ 70 was not yet reached compared to 26.5 months (95% CI, 16.3 months to could not be estimated) in patients with a KPS score > 70 (Figure 2F).

Twenty-eight patients (34.1%) had a diagnosis of transformed DLBCL from a previously diagnosed indolent NHL (Table 1). The frequencies of CR did not differ between primary DLBCL patients when compared to transformed DLBCL patients ($p = 0.24$; Figure 2G). Median PFS in patients with primary DLBCL was 21.3 months (95% CI, 8.0 months to could not be estimated) and was not yet reached in patients with transformed DLBCL (Figure 2H). Median OS in patients with primary DLBCL was 26.5 months (95% CI, 16.2 months to could not be estimated) and was not yet reached in patients with transformed DLBCL (Figure 2I). When stratifying patients by the high-risk DH/TH/DE DLBCL subtype, patients with DH/TH/DE DLBCL had a lower frequency of CR than patients with another DLBCL ($p = 0.048$; Figure 2J), with an odds ratio of 0.38 (95% CI, 0.15 to 1.00). Median PFS in patients with DH/TH/DE DLBCL was 8.4 months (95% CI, 2.6 months to could not be estimated) compared to 26.5 months (95% CI, 11.2 months to could not be estimated) in other DLBCL patients (Figure 2K). Median OS in patients with DH/TH/DE DLBCL was 16.3 months (95% CI, 8.0 months to could not be estimated) and was not yet reached in other DLBCL patients (Figure 2L). Of the patients included in the DH/TH/DE DLBCL subgroup, 16 patients received axi-cel, 6 patients received liso-cel, and 3 patients received tisa-cel.

Multivariable-adjusted analyses assessed potential associations between these subgroups and other clinically relevant risk factors of DLBCL (Table S2), but were unable to detect meaningful associations between most factors and outcomes of interest in this sample. Outcomes for efficacy included PFS and OS and outcomes for safety included CRS and ICANS. CNS involvement at CAR T-cell infusion ($n = 5$) was another subgroup of interest in this study, with median PFS of 3.3 months and median OS of 6.5 months (95% CIs not estimated) and only one patient achieving a CR.

3.2.2. Response to Anti-CD19 CAR T-Cell Therapy by Type of CAR T-Cell Product

Comparisons among axi-cel, liso-cel, and tisa-cel showed minimal differences in efficacy and safety among these anti-CD19 CAR T-cell products in our study population. Time from leukapheresis to infusion was shortest in patients receiving axi-cel when compared to either liso-cel or tisa-cel ($p < 0.0001$; Figure 3A). Mean time from leukapheresis to infusion was 30.0 days (95% CI, 27.9 to 31.5 days) in the axi-cel group, 49.3 days (95% CI, 34.0 to 64.6 days) in the liso-cel group, and 53.1 days (95% CI, 30.6 to 75.5 days) in the tisa-cel group. The estimated median PFS was 26.5 months (95% CI, 7.0 months to could not be estimated) for patients who received axi-cel, 21.3 months (95% CI, 4.9 months to could not be estimated) for patients who received liso-cel, and 20.3 months (95% CI, 6.4 months to could not be estimated) for patients who received tisa-cel (Figure 3B). The estimated median OS was 26.5 months (95% CI, 16.1 months to could not be estimated) for patients who received axi-cel, 21.3 months (95% CI not estimated) for patients who received liso-cel, and was not yet reached in the tisa-cel group (Figure 3C).

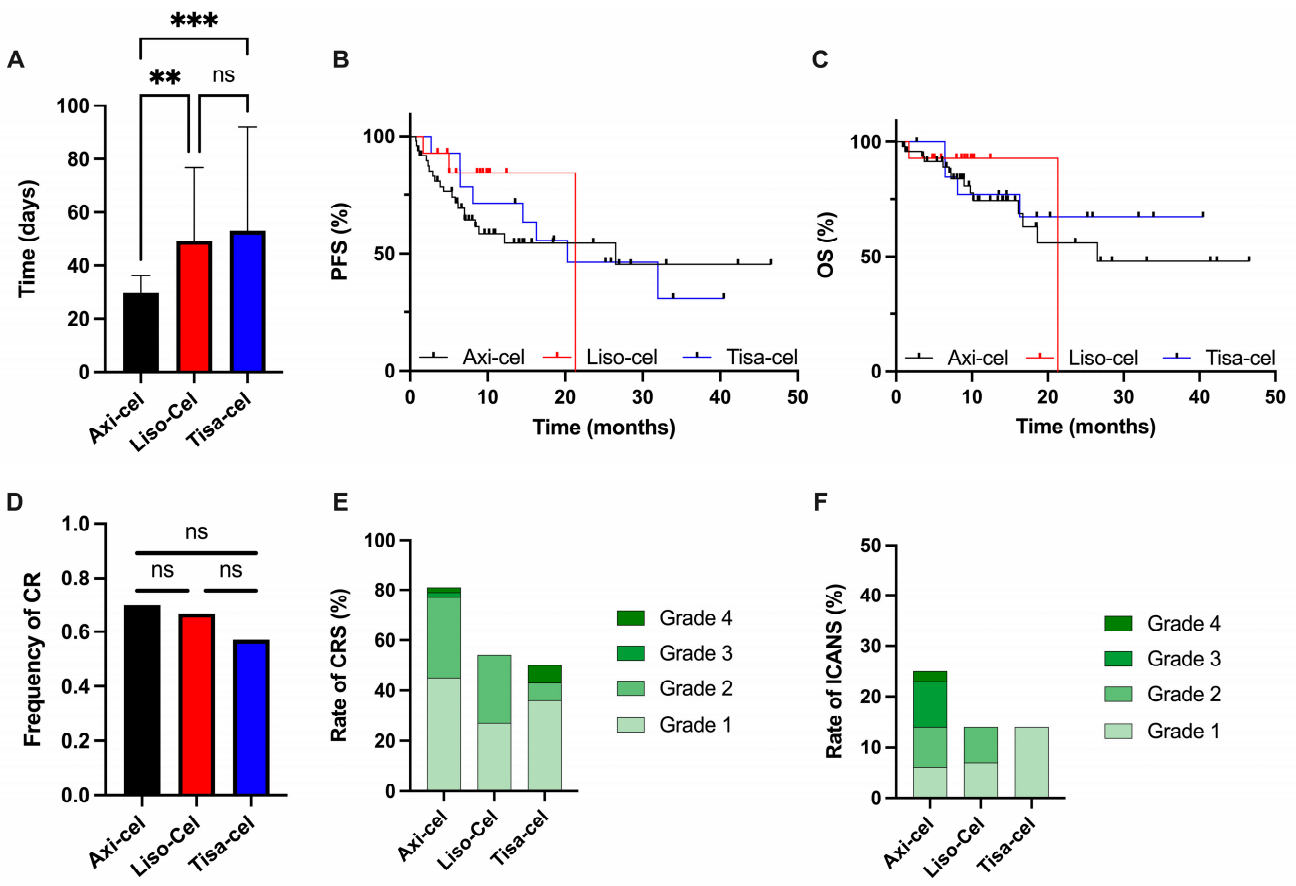

Figure 3. Comparisons among anti-CD19 CAR T-cell products. (**A**) Time from leukapheresis to CAR T-cell infusion between products. (**B**) PFS from the time of CAR T-cell infusion between products. (**C**) OS from the time of CAR T-cell infusion between products. (**D**) Frequency of CR for each product. (**E**) Rate of CRS for each CAR T-cell product. (**F**) Rate of ICANS for each CAR T-cell product. Asterisks denote significance: ** $p < 0.01$, *** $p < 0.001$, ns $p > 0.05$.

Of the three anti-CD19 CAR T-cell products included in this study, there were no significant differences in the rate of CR ($p = 0.67$) observed in this sample (Figure 3D). In patients who received axi-cel, 14 patients died (26.4%): 8 deaths were related to lymphoma relapse/progression, 4 were due to nonrelapse mortality, and 2 were unknown. In patients who received liso-cel, two patients died (13.3%): one death was due to nonrelapse mortality, and the other was unknown. In patients who received tisa-cel, four patients died (28.6%): three deaths were related to lymphoma relapse/progression and one was due to nonrelapse mortality. For all CAR T-cell products, the majority of CRS (Figure 3E) and ICANS (Figure 3F) experienced by patients were grades 1 and 2.

3.3. Toxicity

CRS occurred in 58 patients (70.7%), with 3 patients (3.7%) experiencing grade 3 or higher events (Table 3). ICANS occurred in 17 patients (20.7%), with 6 patients (7.3%) experiencing grade 3 or higher events. No patients experienced grade 5 CRS or grade 5 ICANS in this sample. The most common therapies used for CRS and ICANS prophylaxis and treatment included tocilizumab and corticosteroids. Three patients received tocilizumab, and one patient received corticosteroids for CRS/ICANS prophylaxis. For treatment of CRS/ICANS, 26 patients (31.7%) received tocilizumab, and 21 patients (25.6%) received corticosteroids. Median time to resolution of CRS was 2 days (range, 0–37 days) and median time to resolution of ICANS was 3 days (range, 0–7 days).

Table 3. Safety characteristics of CAR T-cell treatment.

Event	N = 82 *n* (%)
Cytokine release syndrome	58 (70.7)
Grade 1	33 (40.2)
Grade 2	22 (26.8)
Grade 3	1 (1.2)
Grade 4	2 (2.4)
Neurotoxicity/ICANS	17 (20.7)
Grade 1	6 (7.3)
Grade 2	5 (6.1)
Grade 3	5 (6.1)
Grade 4	1 (1.2)
Unplanned hospitalization < 30 days post-infusion	2 (2.4)
Cytokine release syndrome	1 (1.2)
Fever/Infection	1 (1.2)
Therapy given for CRS/ICANS Prevention	
Corticosteroids	3 (3.7)
Tocilizumab	1 (1.2)
Therapy given for CRS/ICANS Treatment	
Corticosteroids	21 (25.6)
Tocilizumab	26 (31.7)
Antiepileptics	17 (20.7)
ICU Admission < 30 days post-infusion	4 (4.9)

CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; ICU = intensive care unit.

Four patients (4.9%) were admitted to the ICU within 30 days after anti-CD19 CAR T-cell infusion (Table 3). The causes of ICU admission were all due to at least one type of infection: viral infection (4.9%), bacteremia (3.7%), secondary infections (2.4%), and pneumonia (1.2%). Three patients (3.7%) required vasopressors, three patients (3.7%) required intubation, and one (1.2%) patient required dialysis for treatment. Median ICU stay was 18 days (range, 4–39 days) and two patients died during ICU admission.

4. Discussion

In this study, we report a single-center, retrospective study of RWOs, in which 82 patients underwent leukapheresis and infusion of anti-CD19 CAR T-cell therapy for R/R DLBCL. Patients were analyzed for efficacy and safety outcomes as an entire cohort as well as in subgroups of interest, including those with high-risk molecular features, poor performance status, and receipt of bridging therapy prior to CAR T-cell infusion. Our cohort uniquely consists of patients who received one of three different anti-CD19 CAR T-cell therapy products, axi-cel, liso-cel, and tisa-cel, allowing us to compare these products in a real-world setting. We observed considerable efficacy across all three products for patients with R/R DLBCL, with an overall well-tolerated safety profile amongst this sample.

The majority of patients (64.6%) in this study received axi-cel, which obtained its original FDA approval after the ZUMA-1 trial demonstrated efficacy in patients with R/R large B-cell lymphoma after two or more prior lines of treatment [21]. ZUMA-1 initially reported an ORR of 82% and a CR rate of 54%, which is comparable to results in our study, with an ORR and CR of 74.4% and 67.1%, respectively. These initial results from ZUMA-1 were followed-up at 5 years, with a median PFS of 5.9 months (95% CI, 3.3 to 15.0 months) and median OS of 25.8 months (95% CI, 12.8 months to could not be estimated) [38]. In our study, we report a median PFS of 26.5 months and a median OS that was not yet reached,

notably better than those observed in the landmark trials of all three CAR T-cell products, and reflecting our higher observed CR rate compared to ZUMA-1.

Liso-cel and tisa-cel received their FDA approvals for R/R DLBCL after two or more prior lines of therapy based on the results of the TRANSCEND and JULIET trials, respectively [7,22]. The TRANSCEND trial reported that median PFS was 6.8 months (95% CI, 3.3 to 14.1 months) and median OS was 21.1 months (95% CI, 13.3 could not be estimated) [7]. The JULIET trial originally reported that median PFS and OS were not yet reached, but the estimated rate of OS at 12 months was 49% compared to 77.5%, which we report in our study despite tisa-cel being the least commonly administered CAR T-cell product in this cohort [22]. A long-term analysis of the JULIET trial later reported that median PFS was 2.9 months (95% CI, 2.3 to 5.2 months) and median OS was 11.1 months (95% CI, 6.6 to 23.9 months) [39]. While our study was not powered to detect clinically significant differences between CAR T-cell products, median PFS and median OS for each product were comparable between products and superior to those described in their respective landmark trials. However, results for liso-cel and tisa-cel should be interpreted judiciously due to low numbers, as the majority of patients (64.6%) in this study received axi-cel.

In similar studies of RWOs with more than 80 patients and a majority receiving axi-cel, estimates of median PFS were between 3.5 and 8.6 months and estimates of median OS were between 14.8 and 21.8 months or not yet reached [26,29,30,40]. Of note, Bachy et al. reported a significantly higher ORR and a longer PFS and OS with axi-cel compared to tisa-cel [29]. Although we did not observe meaningful differences in survival outcomes between axi-cel, liso-cel, and tisa-cel in our study, the improved PFS and OS associated with all three products in our cohort help validate their use in the real-world setting. One difference among anti-CD19 CAR T-cell products that we did observe in our study was a shorter time from leukapheresis to CAR T-cell infusion in patients receiving axi-cel compared to other products. This trend was similar to other studies of RWOs comparing axi-cel to another CAR T-cell product [29,30]. One limitation of this study is that patients with higher-risk DLBCL and a poorer prognosis would likely have received axi-cel faster than another product, which may have influenced the treating physician's choice of CAR T-cell product. Additionally, fludarabine/cyclophosphamide was the predominant conditioning regimen, but bendamustine was still used in 15.9% of the enrolled population. This pronounced bifurcation may be attributed to shortages of fludarabine/cyclophosphamide that occurred and subsequently not mimic the utilization share observed in clinical practice [41,42].

One possible explanation for the improved PFS and OS outcomes observed in our study is the increased awareness and publishing of guidelines for managing adverse events due to CAR T-cell therapy [14]. CRS and ICANS are high-risk acute toxicities associated with CAR T-cell therapy and were frequently described in early clinical trials of CAR T-cell therapy for R/R DLBCL [13,43]. In this study, we report an incidence of CRS and ICANS of 70.7% and 20.7% of patients, respectively. These findings were similar to or lower than previous reports when compared. The ZUMA-1 (axi-cel), TRANSCEND (liso-cel), and JULIET (tisa-cel) trials reported CRS in 93%, 42%, and 57%, respectively, and ICANS/neurotoxicity in 64%, 30%, and 20% of patients, respectively [7,12,22,38]. These differences could be explained by patient characteristics, distinct baseline inflammatory states, or evolving prophylaxis and treatment practices of CRS and ICANS. Still, only four patients reported here received steroids as CRS/ICANS prophylaxis. Importantly, we observed no grade 5 CRS or ICANS events, highlighting the increasing safety of these therapies in the real-world setting. This is particularly noteworthy given our inclusion of high-risk patients in this study, suggesting anti-CD19 CAR T-cell therapy can be safely administered even to those with multiple comorbidities or high-risk disease features.

Given the inclusion of DLBCL patients with high-risk disease features in this study, we chose to examine the clinical outcomes of some of these subgroups. Patients with transformed DLBCL are associated with a poorer prognosis compared to those with primary DLBCL, demonstrating higher rates of refractory disease and decreased OS [44–46]. In this sample, we describe 28 patients (34.1%) with a diagnosis of transformed DLBCL receiving anti-CD19 CAR T-cell therapy. Despite the adverse outcomes associated with transformed DLBCL, we observed comparable CR, PFS, and OS between these patients and those with primary DLBCL. Indeed, previous reports have highlighted the high responsiveness of transformed DLBCLs to CAR-T cell therapy, but with smaller sample sizes [47,48]. These observations support the need for further investigations to understand the role of CAR T-cell therapy in this unique DLBCL population.

Despite the noteworthy efficacy of anti-CD19 CAR T-cell treatment in R/R DLBCL, there remain patients with persistently poor outcomes. Patients with high-grade genetics, such as those with DH, TH, or DE DLBCL, are associated with more aggressive disease and have higher rates of relapse after frontline treatment [49–51]. These high-grade DLBCL patients that do relapse often experience dismal clinical outcomes compared to typical R/R DLBCL [52,53]. In this study, we observed inferior CR and median OS in patients with DH, TH, or DE DLBCL compared to other R/R DLBCL patients. These data are even more meaningful, as many prior studies of CAR T-cell therapy for R/R DLBCL have not shown these potential differences that may exist in this high-risk patient population [22,25,26,54]. Interestingly, the ZUMA-7 trial demonstrated that treatment with axi-cel was superior to standard care (high-dose chemotherapy and ASCT) in subgroup analyses for DH or TH lymphoma and DE lymphoma [12]. A recent review of high-grade B-cell lymphomas treated with anti-CD19 CAR T-cell therapy calls attention to these favorable outcomes and notes that these patients still may benefit from CAR T-cell therapy used as second-line [55]. Possible reasons for why we may have observed poorer outcomes amongst DH, TH, or DE DLBCL patients in our study may be due to other high-risk characteristics of our population, as approximately 43.9% were primary refractory and 80.5% of patients were in progression at the time of CAR T-cell therapy. Even with a possible advantage of CAR T-cell therapy in patients with high-grade genetics, our findings stress the need for increased research and the development of effective therapeutics for this population.

An advantage of our study is the inclusion of patients that would historically be excluded from landmark CAR T-cell clinical trials. The ZUMA-1 and ZUMA-7 trials elected to exclude patients receiving systemic bridging therapy prior to axi-cel infusion, which potentially introduced an enrollment bias against patients with rapidly progressing or bulky disease [56]. We describe 26 patients (31.7%) who received bridging therapy, with similar efficacy and safety compared to the rest of the sample. Indeed, these outcomes of patients who received bridging therapy were also comparable to those described in other studies of RWOs exploring anti-CD19 CAR T-cell therapy for R/R DLBCL [26,30,40]. These data are also influenced by changing practices during the time of the study. Clinical trials avoided the use of bridging therapy and early study patients who did not receive bridging therapy achieved better outcomes post-CAR T [57]. Still, recent patients are more likely to receive bridging, but practices vary greatly due to differences between institutions, provider preferences, and patient-specific considerations [58,59].

Patients with a poor performance status (defined as an ECOG score > 1) were also excluded from ZUMA-1, but we could not identify differences in CR, median PFS, and median OS in our 44 patients (49.4%) with a KPS score ≤ 70, which typically correlates to an ECOG score > 1 [60]. In patients with CNS involvement (5.6%) that were also excluded, we did observe poorer outcomes, but this represented only a small subgroup of patients. Even multivariable analyses of well-described risk factors of DLBCL were

unable to demonstrate meaningful differences in PFS, OS, CRS, and ICANS for most variables assessed, underscoring the potential durability of responses in a broader DLBCL patient population.

Assessments of the longer-term RWOs of patients receiving CAR-T cell therapy are also underreported, as is the case with any novel treatment modality. After the favorable initial results were originally described by the US lymphoma consortium [26], follow-up revealed a 5-year PFS of 29% and 5-year OS of 40% [61]. Still, additional research is required to properly assess the long-term RWOs of these patients and characterize the durability of response. While this study's retrospective nature, single-center design, predominance of axi-cel given as the CAR T-cell product, and small heterogenous subgroups hold the potential to introduce biases and limit the generalizability of the results, studies exploring RWOs are critical to support the external validity of clinical trials and to address questions that cannot be answered in foundational trials [62,63]. These studies also serve to increase the generalizability of clinical trials by studying patient populations that would have otherwise been excluded.

This study adds to the growing literature on the RWOs of CAR T-cell therapy, with important implications for the clinical management of R/R DLBCL. The observed efficacy and safety in this sample supports the broader use of CAR T-cell therapy for higher-risk patients traditionally excluded from early clinical trials. While the predominance of axi-cel should be considered, the similar efficacy and safety between CAR T-cell products in our study may contribute to clinical decision making. Still, prospective multicenter studies with larger sample sizes and balanced characteristics are needed to further compare axi-cel, liso-cel, and tisa-cel. Exploring ways to streamline the manufacturing process and reduce wait times from leukapheresis to infusion, particularly for lisa-cel and tisa-cel, may also increase feasibility for routine clinical use. Furthermore, multicenter large-scale studies would aid in validating these RWOs and refining the clinical approach to CAR T-cell selection. Ultimately, the real-world evidence provided in this study serves to inform clinical decision making and guiding research for CAR T-cell therapy in R/R DLBCL.

5. Conclusions

These real-word data we report further support use of anti-CD19 CAR T-cell therapy for the treatment of R/R DLBCL. We demonstrate comparable efficacy in terms of ORR, CR, PFS, and OS, as well as well-tolerated safety profiles compared to those seen in major clinical trials. These results are also similar to studies of RWOs assessing the use of CAR T-cells in R/R DLBCL. These findings further validate the efficacy and safety of CAR T-cell treatment outside of the clinical trial setting and in a broader, more diverse DLBCL population.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/hemato6010003/s1: Table S1: Comorbidities present in this patient sample; Table S2: Baseline characteristic assessed as independent predictors for CRS, ICANS, PFS and OS in multivariable linear regression models of patients treated with CAR T-cell therapy.

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