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Real-World Evidence of Axicabtagene Ciloleucel for the Treatment of Large B Cell Lymphoma in the United States

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A B S T R A C T

Axicabtagene ciloleucel (axi-cel) is a standard-of-care for patients with relapsed or refractory (r/r) large B cell lymphoma who have received 2 or more lines of prior therapy. Patients receiving axi-cel in the real world could have broader a demographic, disease, and treatment profile compared with that of the cohort in the pivotal ZUMA-1 trial. The present study was conducted to evaluate the outcomes of axi-cel therapy in the real-world setting. A total of 1297 patients receiving commercial axi-cel between 2017 and 2020 were selected from the Center for International Blood and Marrow Transplant Research's data registry, of whom 739 (57%) would have been ineligible for inclusion in the ZUMA-1 cohort. Efficacy and safety outcomes were described for the entire cohort and by ZUMA-1 eligibility. Their associations with age, Eastern Cooperative Oncology Group Performance Score, and comorbidities were evaluated using multivariable logistic and Cox regressions. At a median follow-up of 12.9 months, the overall response rate (ORR) was 73%, with a 56% complete response (CR) rate. Median overall survival (OS) and progression-free survival (PFS) were 21.8 months (95% confidence interval [CI], 17.4 to 28.8 months) and 8.6 months (95% CI, 6.5 to 12.1 months), respectively. Duration of response (DOR) was comparable in the ZUMA-1 ineligible patients and ZUMA-1 eligible patients (62% by 1 year [95% CI, 57% to 66%] versus 67% [95% CI, 62% to 72%]). Patients age ≥65 years had favorable ORR (odds ratio [OR], 1.39; 95% CI, 1.05 to 1.83) despite having a higher risk of cytokine release syndrome (CRS) (OR, 1.41; 95% CI, 1.02 to 1.94) and immune effector cell-associated neurotoxicity syndrome (ICANS) (OR, 1.77; 95% CI, 1.39-2.26). Eastern Cooperative Oncology Group Performance Score ≥2 was associated with inferior efficacy outcomes (OR for ORR, 0.32; 95% CI, 0.18-0.56; hazard ratio [HR] for OS, 3.27; 95% CI, 2.37 to 4.52) and higher incidence of ICANS (OR, 2.63; 95% CI, 1.40 to 4.93). The patients ineligible for ZUMA-1 still had a durable response with axi-cel. Elderly patients had favorable

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efficacy outcomes despite higher rates of CRS and ICANS. Patient selection for standard-of-care axi-cel should consider comorbidities and risk-to-benefit ratio rather than be based strictly on ZUMA-1 eligibility.

INTRODUCTION

Diffuse large B cell lymphoma (DLBCL) is an aggressive blood cancer and the most common subtype of non-Hodgkin lymphoma (NHL), accounting for approximately 30% of newly diagnosed NHL cases. Between 30% and 40% of patients with DLBCL relapse following successful treatment or present with a refractory disease [1,2]. Patients with relapsed or refractory (r/r) DLBCL have poor outcomes, with a median overall survival (OS) of 6.3 months [3].

Recent advances in immunotherapy have resulted in the development of chimeric antigen receptor (CAR)-modified T cell (CAR-T) therapy. Axicabtagene ciloleucel (axi-cel), a CD19-directed autologous CAR-T therapy, was approved by the US Food and Drug Administration (FDA) in 2017 for the treatment of adult patients with r/r DLBCL, primary mediastinal large B cell lymphoma (PMBCL), high-grade B cell lymphoma (HGBCL), and transformed follicular lymphoma, collectively referred to as large B cell lymphoma (LBCL), after receipt of 2 or more lines of systemic therapy. The approval was based on the primary analysis of the ZUMA-1 clinical trial [4]; in a subsequent 2-year follow-up analysis, 83% of patients treated with axi-cel had an overall response, 58% had a complete response (CR), and the median OS was not reached [5].

Because clinical trials often have stringent eligibility criteria, their efficacy and safety outcomes might not be observed in real-world medical practice, where treated patients could have more proliferative disease or comorbidities that would have excluded them from the trials. In a study with standard-of-care setting use of axi-cel across 17 centers, including patients with comorbidities that would have made them ineligible for the ZUMA-1 trial, efficacy and safety outcomes were comparable to those of ZUMA-1 [6]. In a small multicenter real-world study, axi-cel use was shown to retain its overall response and toxicity profile even though ZUMA-1 eligible patients had more favorable CR rates, DOR, and OS [7]. To better understand the efficacy and safety outcomes of commercial axi-cel, we conducted this long-term follow-up study using the infrastructure created by the Center for International Blood and Marrow Transplant Research (CIBMTR).

METHODS

Approval of CAR-T therapy by the FDA and other national health authorities required implementation of a mechanism to follow patients for assessment of safety and efficacy outcomes for 15 years. The approach to this for axi-cel was to develop a prospective, noninterventional cohort study. This post-authorization safety study (PASS) was reviewed and approved by the FDA and by the National Marrow Donor Program's central Institutional Review Board and was administered by the Cellular Immunotherapy Data Resource infrastructure managed by the CIBMTR. Data collection is done using a secondary database mechanism whereby recipients of axi-cel therapy provided signed informed consent for data sharing with the CIBMTR for research purposes. The accrual goal for the PASS was 1500 patients with r/r DLBCL, PMBCL, or HGBCL; accrual started in October 2017 along with the commercial approval of axi-cel and was completed in August 2020, with 79 centers participating. Patients who received noncommercial axi-cel (eg, those enrolled in expanded access programs or clinical trials) were not eligible for the PASS study. Among the 1500 enrolled patients, 7 were excluded /for the following reasons: rescinded consent (n = 1), reporting error in query (n = 1), and confirmed enrollment in a clinical trial after data query (n = 5). The eligibility for this analysis further excluded patients with a prior history of CAR-T infusion (n = 31), who were last contacted at <180 days postinfusion (n = 123), and who had an unknown comorbidity (n = 42) (Supplementary Figure S1).

A total of 1297 eligible patients from 78 centers with at least 6 months of follow-up were included in the analysis. Patients with preexisting end-organ impairments were not excluded from the study, and comorbidities were collected by categories according to the Hematopoietic Cell Transplantation Comorbidity Index elements [8], which were analyzed individually as originally described. All study data were obtained from clinical, laboratory, and diagnostic assessments conducted during routine medical practice. Participating sites were responsible for completing a data collection form at the time of axi-cel administration; at 3, 6, and 12 months postinfusion; and then annually for up to 15 years.

Endpoints and Assessments

Analyses of efficacy endpoints included overall response rate (ORR), complete response (CR) and partial response (PR) rates, duration of response (DOR), progression-free survival (PFS), nonrelapse mortality (NRM), and overall survival (OS). Disease responses were assessed according to the International Working Group's revised response criteria for malignant lymphoma [9] and the Lugano classification scheme [10]. Relapse and progression were determined by radiological and/or clinical assessment. PFS was defined as time from the first axi-cel infusion to the earliest documented relapse or progression or to death from any cause, whichever occurred first. NRM was defined as death without previous experience of relapse or progression.

Analyses of safety endpoints included cytokine release syndrome (CRS), immune-effector cell-associated neurotoxicity syndrome (ICANS), hematologic recovery, serious infections, and subsequent neoplasms. The type and severity of CRS and ICANS [11,12], as well as individual signs and symptoms, treatments, date to onset, and date of resolution were captured. Events of failed recovery of normal neutrophil and platelet counts by day 30 were recoded. The type and timing of viral, bacterial, or fungal infections were captured.

Statistical Analysis

Descriptive statistics are provided as mean and standard deviation or median and range for continuous variables and as percentage for categorical variables. Event rates for dichotomous outcomes, including ORR, CRS, and ICANS, were calculated with Fisher exact 95% confidence intervals (CIs). Event-free probabilities and 95% CIs for time-to-event efficacy outcomes, including DOR, PFS, and OS, were summarized using the Kaplan-Meier (KM) estimator. Cumulative incidences and 95% CIs for NRM and resolutions of CRS and ICANS were estimated based on the cumulative incidence function. The median duration of follow-up was estimated using the reverse KM method.

Multivariable analysis was conducted to explore potential risk factors for both efficacy and safety outcomes. The process of variable selection involved a combination of biologically, clinically, and empirically data-driven approaches. Certain key variables were forced into the model, including age at infusion (≥65 years versus <65 years), sex (male versus female), Eastern Cooperative Oncology Group (ECOG) Performance Score (PS) at infusion (<2 versus ≥2, with higher scores indicating greater disability, translated from the Karnofsky Performance Status score) [13]; bridging therapy (yes or no); and comorbidities of moderate to severe pulmonary disease; cardiac, cerebrovascular, or heart valve disease; obesity (body mass index >35 kg/m^2), moderate to severe renal disease; moderate to severe hepatic disease; and any prior malignancy other than nonmelanoma skin cancer. A stepwise regression procedure was implemented for selection of other baseline variables. The proportionality assumption for the Cox model was tested via Schoenfeld residuals [14]. Multiple comparison adjustments were not performed, and nominal *P* values were reported. A *P* value cutoff of .05 was used to report significant variables. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Baseline characteristics of the 1297 patients, including 1029 (79%) with DLBCL, 39 (3%) with PMBCL, and 210 (16%) with HGBCL, are summarized in Table 1. In the latter group, 192 (15%) had HGBCL with C-MYC and either BCL-2 and/or BCL-6 translocations. Transformed LBCL was present in 361 (28%) of cases (Supplementary Table S1). Seven hundred and thirty-nine patients (57%) were considered ZUMA-1 ineligible (Supplementary Table S2); 1 patient was diagnosed with primary central nervous system lymphoma, and 18 patients had secondary involvement of the central nervous system. Histologic transformation from CLL occurred in 22 patients. At infusion, 5% of the patients had an ECOG PS ≥2. Of the reported comorbidities, 28% of the patients had moderate to severe pulmonary disease; 13% had cardiac, cerebrovascular, or heart valve disease; 5% had inflammatory

Table 1
Baseline Demographics and Disease Characteristics by ZUMA-1 Eligibility

Characteristic	Ineligible for ZUMA-1 (N = 739)	Eligible for ZUMA-1 or Unknown (N = 558)	Overall (N = 1297)
Disease, n (%)			
DLBCL	587 (80)	442 (79)	1029 (79)
PMBCL	20 (3)	19 (3)	39 (3)
HGBCL	112 (15)	98 (18)	210 (16)
Other B cell lymphoma	19 (3)	0 (0)	19 (1)
Disease histology at diagnosis, n (%)			
DLBCL	587 (80)	442 (79)	1029 (79)
DLBCL, NOS	569 (77)	430 (77)	999 (77)
T cell/histiocytic-rich LBCL	10 (1)	6 (1)	16 (1)
Intravascular LBCL	1 (< 1)	0 (0)	1 (< 1)
Primary cutaneous DLBCL, leg type	1 (< 1)	1 (< 1)	2 (< 1)
EBV$^+$ DLBCL, NOS	4 (< 1)	4 (< 1)	8 (< 1)
DLBCL associated with chronic inflammation	1 (< 1)	0 (0)	1 (< 1)
LBCL with IRF4 rearrangement	1 (< 1)	0 (0)	1 (< 1)
ALK$^+$ LBCL	0 (0)	1 (< 1)	1 (< 1)
PMBCL	20 (3)	19 (3)	39 (3)
PMBCL, thymic	20 (3)	19 (3)	39 (3)
HGBCL	112 (15)	98 (18)	210 (16)
HGBCL, NOS	5 (< 1)	13 (2)	18 (1)
HGBCL, with MYC and BCL2 and/or BCL6 rearrangements	107 (14)	85 (15)	192 (15)
Other B cell lymphoma	19 (3)	0 (0)	19 (1)
Primary diffuse LBCL of the central nervous system	1 (< 1)	0 (0)	1 (< 1)
Nodal marginal zone B cell lymphoma	1 (< 1)	0 (0)	1 (< 1)
Other B cell lymphoma	4 (< 1)	0 (0)	4 (< 1)
B cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL	5 (< 1)	0 (0)	5 (< 1)
Follicular, predominantly large cell (grade IIIB)	6 (< 1)	0 (0)	6 (< 1)
Follicular, predominantly large cell (grade IIIA vs IIIB unspecified)	2 (< 1)	0 (0)	2 (< 1)
Age, yr, median (range)	63.1 (19.6-90.8)	60.1 (21.5-80.6)	62.1 (19.6-90.8)
Age ≥65 yr, n (%)	310 (42)	174 (31)	484 (37)
Male sex, n (%)	469 (63)	372 (67)	841 (65)
Race, n (%)			
White	609 (82)	447 (80)	1056 (81)
African American	44 (6)	23 (4)	67 (5)
Asian	35 (5)	37 (7)	72 (6)
Other	51 (7)	51 (9)	102 (8)
Hispanic or Latino ethnicity, n (%)	68 (9)	78 (14)	146 (11)
ECOG PS before infusion, n (%)	59 (8)	0 (0)	59 (5)
Comorbidities, n (%)			
Hepatic (moderate/severe)	28 (4)	0 (0)	28 (2)
Cardiac/cerebrovascular/heart valve disease	167 (23)	0 (0)	167 (13)
Renal (moderate/severe)	30 (4)	0 (0)	30 (2)
Pulmonary (moderate/severe)	367 (50)	0 (0)	367 (28)
Inflammatory bowel/ rheumatologic disease	59 (8)	0 (0)	59 (5)
Infection requiring ongoing antimicrobial treatment	54 (7)	0 (0)	54 (4)
Prior malignancy (other than nonmelanoma skin cancer)	173 (23)	0 (0)	173 (13)
Obesity	71 (10)	46 (8)	117 (9)
Chemoresistant before infusion, n (%)	500 (68)	354 (63)	854 (66)
Disease characteristics at diagnosis, n (%)			
Histologic transformation	219 (30)	142 (25)	361 (28)
HGBCL with cMYC with either BCL2 either/or BCL6 translocations	107 (14)	85 (15)	192 (15)
Ann Arbor stage III or IV	440 (60)	300 (54)	740 (57)
Elevated LDH	217 (29)	151 (27)	368 (28)
Two or more extranodal involvement sites	194 (26)	120 (22)	314 (24)
Lines of prior therapies			
Median (range)	3 (2-18)	3 (1-11)	3 (1-18)
1 to 2 lines, n (%)	177 (24)	179 (32)	356 (27)

(*continued*)

Table 1 (*Continued*)

Characteristic	Ineligible for ZUMA-1 (N = 739)	Eligible for ZUMA-1 or Unknown (N = 558)	Overall (N = 1297)
3 lines, n (%)	231 (31)	176 (32)	407 (31)
4 lines, n (%)	122 (17)	111 (20)	233 (18)
≥5 lines, n (%)	169 (23)	70 (13)	239 (18)
Prior history of HCT, n (%)	217 (29)	152 (27)	369 (28)
Bridging therapy, n (%)	167 (23)	114 (20)	281 (22)
Days since leukapheresis			
Median (range)	28 (6-223)	27 (5-145)	27 (5-223)
≥28 d since leukapheresis, n (%)	383 (52)	260 (47)	643 (50)
Months since diagnosis			
Median (range)	15.2 (1.6-282.5)	13.2 (1.2-405.8)	14.2 (1.2-405.8)
≥12 mo since diagnosis, n (%)	450 (61)	300 (54)	750 (58)

cHL indicates classic Hodgkin lymphoma; EBV, Epstein-Barr virus; NOS, not otherwise specified; LDH, lactate dehydrogenase; HCT, hematopoietic stem cell transplantation.

bowel or rheumatologic disease, 2% had moderate to severe renal disease, 2% had moderate to severe hepatic disease, 4% had infection requiring ongoing antimicrobial treatment, and 13% had prior malignancy other than nonmelanoma skin cancer. A prior history of allogeneic hematopoietic cell transplantation was reported for 18 patients, and 35 patients had received previous checkpoint inhibitor therapy.

Efficacy

At a median follow-up of 12.9 months, ORR as best response among the 1297 patients was 73% (95% CI, 71% to 75%), including a 56% (95% CI, 53% to 58%) CR rate and a 18% (95% CI, 16% to 20%) PR rate. The median DOR was not reached, whereas 64% (95% CI, 61% to 67%) and 57% (95% CI, 52% to 62%) of patients remained in relapse and progression-free by 12 months and 24 months, respectively, since the initial response. The KM estimate for DOR is shown in Figure 1A. The median OS was 21.8 months (95% CI, 17.4 to 28.8), and 62% (95% CI, 60 to 65) and 50% (95% CI, 46 to 53) of the patients were expected to survive beyond 12 months and 24 months postinfusion, respectively. The median PFS was 8.6 months (95% CI, 6.5 to 12.1 months), and 47% (95% CI, 44% to 50%) and 39% (95% CI,

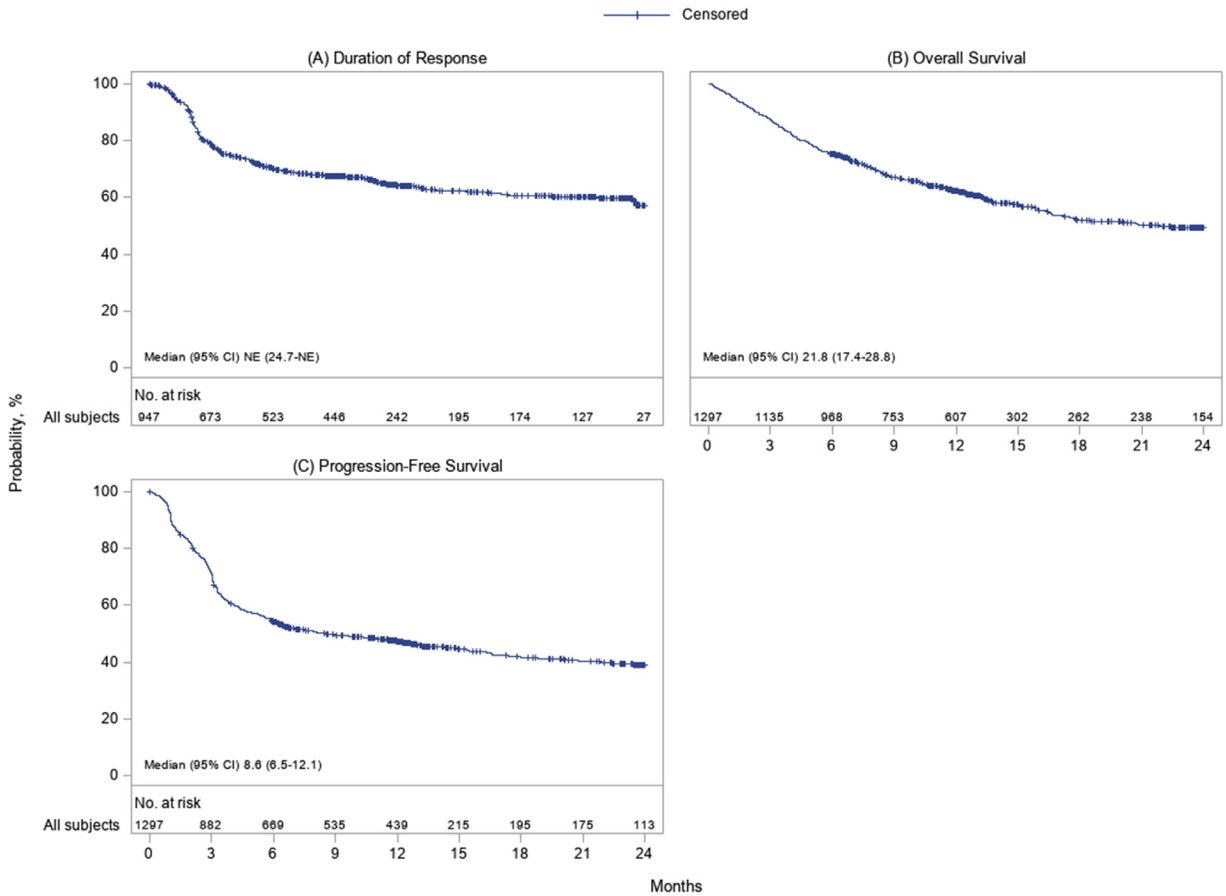

Figure 1. KM plots for DOR (A), OS (B), and PFS (C). NE indicates not estimable. PFS and DOR were both censored at subsequent transplantations or cellular therapies. DOR was estimated among patients who achieved CR/PR as best response.

36% to 43%) of the patients were expected to have no relapse, disease progression, or death at 12 months and 24 months, respectively (Table 2). The KM estimates for OS and PFS are provided in Figure 1B,C. A total of 544 deaths (42%) were reported at the data cutoff. Disease relapse or progression was the most frequently identified cause of death (74% among those who died), followed by infection (11%) and organ failure (5%) (Supplementary Table S3). NRM occurred in 1% (95% CI, <1% to 2%) of the cohort by 1 month and in 3% (95% CI, 2% to 4%) by 3 months (Table 2). Efficacy outcomes by ZUMA-1 eligibility are shown in Table 2.

Based on the multivariable analysis (Supplementary Table S4), having an elevated ECOG PS ≥2 or being chemoresistant prior to infusion were associated with inferior ORR (OR, 0.32 [95% CI, 0.18 to 0.56] and 0.54 [95% CI, 0.38 to 0.76], respectively), DOR (HR, 3.29 [95% CI, 2.00 to 5.40] and 1.39 [95% CI, 1.05 to 1.83], respectively), OS (HR, 3.27 [95% CI, 2.37 to 4.52] and 1.44 [95% CI, 1.15 to 1.81], respectively) and PFS (HR, 2.61 [95% CI, 1.90 to 3.60] and 1.48 [95% CI, 1.21 to 1.79], respectively). Moderate to severe pulmonary disease was associated with inferior ORR (OR, 0.75; 95% CI, 0.57 to 1.00) whereas moderate to severe hepatic disease was associated with worse DOR (HR, 2.63; 95% CI, 1.30 to 5.32), OS (HR, 2.69; 95% CI, 1.72 to 4.20), and PFS (HR, 2.38; 95% CI, 1.50 to 3.79). In addition, patients age ≥65 years had favorable ORR (OR, 1.39; 95% CI, 1.05 to 1.83).

Safety

As shown in Table 3, among the 1297 patients, 1073 (83%) developed CRS of any grade, and 107 (8%) developed grade 3 or higher CRS [11]. Seven hundred and fourteen patients (55%) developed ICANS of any grade, including 313 (24%) with grade 3 or higher [12]. The median time to onset from axi-cel infusion was 4 days (range, 1 to 28 days) for CRS and 7 days (range, 1 to 36 days) for ICANS. Among all 1297 patients, 219 (17%) received tocilizumab without corticosteroids, 96 (7%) received corticosteroids but not tocilizumab, and 532 (68%) were treated with both. Tocilizumab was given to 79% of the patients experiencing both CRS and ICANS and to 53% of those with only CRS. In addition, 81% of the patients with both CRS and ICANS were treated with corticosteroids. Resolution rates by week 3 since onset were 92% (95% CI, 90% to 94%) for CRS and 77% (95% CI, 73 to 80) for ICANS. As of the data cutoff, 295 patients (24% of those who survived to 30 days post-infusion) had prolonged cytopenia, of which 82 (7%) were neutropenia and 271 (22%) were thrombocytopenia. Five hundred and eighty patients (45%) experienced clinically significant infections. Fifty patients (4%) developed subsequent neoplasms, among which myelodysplasia syndrome (n = 15), squamous cell skin malignancy (n = 11), and myelodysplasia/myeloproliferative neoplasm (n = 4) were the most common. Two patients had multiple subsequent neoplasms.

Based on the multivariable analysis (Supplementary Table S5), age ≥65 years was associated with increased risk of CRS (OR, 1.41; 95% CI, 1.02 to 1.94) and ICANS (OR, 1.77; 95% CI, 1.39 to 2.26). Moderate to severe hepatic disease was associated with higher odds of grade 3 or higher CRS (OR, 3.70; 95% CI, 1.43 to 9.56), and ECOG PS ≥2 was associated with higher incidences of ICANS (OR, 2.63; 95% CI, 1.40 to 4.93) and ICANS of grade 3 or higher (OR, 3.23; 95% CI, 1.81 to 5.74).

DISCUSSION

Based on the data for 1297 patients from 78 centers, this is the largest real-world prospective study thus far to report on patients treated with CAR-T therapy. Our findings demonstrate comparable efficacy of real-world axi-cel use for r/r LBCL to response outcomes reported in clinical trials. We observed an ORR of 73% and a CR rate of 56%, which align with the findings of the pivotal portion of the ZUMA-1 trial [4]. Our data also show comparable DOR for patients who would have been ineligible for ZUMA-1 and the ZUMA-1 eligible group (62% by 1 year [95% CI, 57% to 66%] versus 67% [95% CI, 62% to 72%]). Furthermore, certain comorbidities such as prior malignancy, which would have excluded patients from being eligible for ZUMA-1, were not associated with inferior efficacy outcomes.

Table 2
Effectiveness Outcomes by ZUMA-1 Eligibility

Measure (95% CI)	Ineligible for ZUMA-1 (N = 739)	Eligible for ZUMA-1 or Unknown (N = 558)	Overall (N = 1297)
ORR*	70.9 (67.5-74.2)	75.8 (72.0-79.3)	73.0 (70.5-75.4)
CR*	52.4 (48.7-56.0)	59.7 (55.5-63.8)	55.5 (52.8-58.2)
PR*	18.5 (15.8-21.5)	16.1 (13.2-19.4)	17.5 (15.5-19.7)
DOR†			
Median, mo	25.2 (23.6-NE)	NE (24.7-NE)	NE (24.7-NE)
At 1 yr	61.7 (56.8-66.2)	67.0 (61.7-71.6)	64.1 (60.6-67.4)
At 2 years	53.7 (45.7-61.1)	60.4 (52.3-67.6)	57.0 (51.5-62.1)
OS			
Median, mo	16.5 (15.1-21.8)	28.0 (22.4-NE)	21.8 (17.4-28.8)
At 1 yr	58.1 (54.3-61.7)	67.8 (63.6-71.7)	62.3 (59.5-64.9)
At 2 yr	45.2 (40.6-49.8)	55.1 (49.7-60.2)	49.5 (46.0-52.9)
PFS			
Median, mo	6.4 (5.5-9.0)	13.0 (8.3-21.8)	8.6 (6.5-12.1)
At 1 yr	43.7 (39.9-47.4)	52.0 (47.6-56.1)	47.3 (44.4-50.1)
At 2 yr	35.8 (31.5-40.1)	43.6 (38.4-48.5)	39.2 (35.9-42.5)
NRM			
At 1 mo	1.4 (0.7-2.5)	0.9 (0.4-2.0)	1.2 (0.7-1.9)
At 3 mo	3.8 (2.6-5.4)	1.8 (0.9-3.3)	3.0 (2.1-4.0)
Median follow-up, mo	12.9 (12.6-13.2)	13.1 (12.7-13.5)	12.9 (12.8-13.2)

NE indicates not estimable.
* As best response.
† Among patients who achieved CR/PR as best response (n = 947).

Table 3
Safety Outcomes by ZUMA-1 Eligibility

Measure (%)	Ineligible for ZUMA-1 (N = 739)	Eligible for ZUMA-1 or Unknown (N = 558)	Overall (N = 1297)
CRS			
Any grade, n (%)	612 (83)	461 (83)	1073 (83)
Grade ≥3, n (%)*	73 (10)	34 (6)	107 (8)
Grade 4, n (%)*	38 (5)	15 (3)	53 (4)
Grade 5, n (%)*	14 (2)	8 (1)	22 (2)
Time to onset, d, median (range)†	4 (1-25)	4 (1-28)	4 (1-28)
Duration, d, median (range)†	7 (1-121)	6 (1-81)	6 (1-121)
Resolution rate by day 21 since onset, % (95% CI)†	91.1 (88.5-93.1)	93.7 (91.0-95.6)	92.2 (90.4-93.6)
ICANS			
Any grade, n (%)	425 (58)	289 (52)	714 (55)
Grade ≥3, n (%)*	193 (26)	120 (22)	313 (24)
Grade 4, n (%)*	73 (10)	41 (7)	114 (9)
Grade 5, n (%)*	8 (1)	5 (<1)	13 (1)
Time to onset, d, median (range)‡	7 (1-36)	7 (1-25)	7 (1-36)
Duration, d, median (range)‡	7 (1-115)	7 (1-112)	7 (1-115)
Resolution rate by day 21 since onset, % (95% CI)‡	75.4 (70.9-79.3)	78.6 (73.5-82.9)	76.7 (73.4-79.7)
Treatment for CRS or ICANS, n (%)			
Tocilizumab without corticosteroids	122 (17)	97 (17)	219 (17)
Corticosteroids without tocilizumab	56 (8)	40 (7)	96 (7)
Both tocilizumab and corticosteroids	297 (40)	235 (42)	532 (41)
Prolonged cytopenia, n (%)§	195 (28)	100 (18)	295 (24)
Neutropenia	45 (6)	37 (7)	82 (7)
Thrombocytopenia	182 (26)	89 (16)	271 (22)
Clinically significant infection, n (%)	374 (51)	206 (37)	580 (45)
Subsequent neoplasms, n (%)	36 (5)	14 (3)	50 (4)

* Lee criteria for CRS grade; American Society of Transplant and Cellular Therapy consensus criteria for ICANS grade.
† Among patients with CRS (n = 1073).
‡ Among patients with ICANS (n = 714).
§ Among patients alive at day 30 postinfusion (n = 1238).

Similar observations have been reported in a much smaller series of patients [6]. Notably, the odds of achieving an overall response were 39% higher in patients age ≥65 years compared with younger patients even after multivariable adjustment. NRM after axi-cel infusion also remained at a very low level.

The CRS rate in this study was similar to that reported in ZUMA-1, but CRS of grade 3 or higher trended lower at 8% versus 11% in ZUMA-1 [4,5]. The median time to onset of CRS was 4 days (range, 1 to 28 days) and the median time until resolution was 6 days, compared with 2 days (range, 1 to 12) and 8 days, respectively, in ZUMA-1. In the same vein, ICANS of grade 3 or higher in this study was 24% compared with 28% in ZUMA-1. The median time to onset of ICANS was 7 days (range, 1 to 36 days) versus 5 days (range, 1 to 17 days) in ZUMA-1. Other than the association between moderate to severe hepatic disease and grade 3 or higher CRS, none of the comorbidities assessed was associated with CRS or ICANS. Low prevalences of thrombocytopenia, neutropenia, and infections were observed relative to the pivotal clinical trial of axi-cel and reported by single centers [15,16]. The improved safety profile for grade 3 or higher CRS and ICANS in the real-world setting versus early clinical trials was mostly likely accounted for by increased use of tocilizumab, corticosteroids, siltuximab, and other drugs as part of the emerging pattern of toxicity management of CAR-T therapy [17], whereas lower pretreatment levels of inflammation and disease burden because of improved bridging options may account for the longer median time to onset of CRS and ICANS [18].

This is the first study of its size to include long-term follow-up of patients treated with axi-cel in the real world with a high incidence of medical comorbidities. It is also the first PASS for a CAR-T cell product to have completed its targeted accrual to meet health authority requirements for approval of these agents. These observations highlight the feasibility of using an existing secondary outcomes database to fulfill postmarket requirements and evaluate the important outcomes of novel cellular therapies in large cohorts in the real-world setting.

There are some limitations to this study. As it was an observational study, there was no way to prespecify an intervention for the patients, selection of patients, or the type and timing of evaluations of outcome responses. All response assessments were according to the primary oncologists, and a central review of response assessments was lacking. Certain key disease features known to be associated with response to axi-cel, including tumor burden, systemic and tumor inflammation, and CAR T cell expansion in the blood, also could not be evaluated [18,19]. Cell dose from axi-cel manufacturing results also was not available for assessing its impact with outcomes. Importantly, owing to the nature of the data registry, characteristics of patients who never had a chance to receive axi-cel therapy were not reported, and the classification of ZUMA-1 eligibility was not based on intention to treat. The greater efficacy of axi-cel in patients age >65 years raises the question of whether this is related to selection bias based on disease aggressiveness or comorbidities, or whether there are biological differences in immunity in older patients impacting outcomes of CAR-T therapy. Further studies may be needed to uncover the biology behind the observed association.

In conclusion, our findings suggest that patients not meeting the eligibility criteria for the pivotal ZUMA-1 trial still had

durable response with axi-cel. Elderly patients had favorable efficacy outcomes with axi-cel despite higher rates of CRS and ICANS. Patient selection for standard-of-care axi-cel should consider comorbidities and the risk-to-benefit ratio rather than be based strictly on ZUMA-1 eligibility. These results add significantly to the growing body of evidence on axi-cel use in the real-world setting and expand the potential patient population that may benefit from this treatment.

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Data access and responsibility: M.C.P. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2022.05.026.

REFERENCES

1. Raut LS, Chakrabarti PP. Management of relapsed-refractory diffuse large B cell lymphoma. *South Asian J Cancer*. 2014;3:66–70.
2. Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. *Blood*. 2015;125:22–32.
3. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130:1800–1808.
4. 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;377:2531–2544.
5. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol*. 2019;20:31–42.
6. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. *J Clin Oncol*. 2020;38:3119–3128.
7. Jacobson CA, Hunter BD, Redd R, et al. Axicabtagene ciloleucel in the non-trial setting: outcomes and correlates of response, resistance, and toxicity. *J Clin Oncol*. 2020;38:3095–3106.
8. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106:2912–2919.
9. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25:579–586.
10. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32:3059–3068.
11. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124:188–195.
12. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25:625–638.
13. The Medical College of Wisconsin, Inc., National Marrow Donor Program. CIBMTR Forms instruction manual. Appendix L: Karnofsky/Lansky performance status. Available at: https://www.cibmtr.org/manuals/fim/1/en/topic/appendix-l-karnofsky-lansky-performance-status. Accesssed July 30, 2021.

14. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika*. 1982;69:239–241.
15. Lin RJ, Lobaugh SM, Pennisi M, et al. Impact and safety of chimeric antigen receptor T-cell therapy in older, vulnerable patients with relapsed/refractory large B-cell lymphoma. *Haematologica*. 2021;106:255–258.
16. Logue JM, Zucchetti E, Bachmeier CA, et al. Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma. *Haematologica*. 2021;106:978–986.
17. Iacoboni G, Villacampa G, Martinez-Cibrian N, et al. Real-world evidence of tisagenlecleucel for the treatment of relapsed or refractory large B-cell lymphoma. *Cancer Med*. 2021;10::3214–3223.
18. Locke FL, Rossi JM, Neelapu SS, et al. Tumor burden, inflammation, and product attributes determine outcomes of axicabtagene ciloleucel in large B-cell lymphoma. *Blood Adv*. 2020;4:4898–4911.
19. Jain MD, Zhao H, Wang X, et al. Tumor interferon signaling and suppressive myeloid cells are associated with CAR T-cell failure in large B-cell lymphoma. *Blood*. 2021;137:2621–2633.