original reports

Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium

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abstract

PURPOSE Axicabtagene ciloleucel (axi-cel) is an autologous CD19-directed chimeric antigen receptor (CAR) T-cell therapy approved for relapsed/refractory large B-cell lymphoma (LBCL) on the basis of the single-arm phase II ZUMA-1 trial, which showed best overall and complete response rates in infused patients of 83% and 58%, respectively. We report clinical outcomes with axi-cel in the standard-of-care (SOC) setting for the approved indication.

PATIENTS AND METHODS Data were collected retrospectively from all patients with relapsed/refractory LBCL who underwent leukapheresis as of September 30, 2018, at 17 US institutions with the intent to receive SOC axi-cel. Toxicities were graded and managed according to each institution's guidelines. Responses were assessed as per Lugano 2014 classification.

RESULTS Of 298 patients who underwent leukapheresis, 275 (92%) received axi-cel therapy. Compared with the registrational ZUMA-1 trial, 129 patients (43%) in this SOC study would not have met ZUMA-1 eligibility criteria because of comorbidities at the time of leukapheresis. Among the axi-cel–treated patients, grade ≥ 3 cytokine release syndrome and neurotoxicity occurred in 7% and 31%, respectively. Nonrelapse mortality was 4.4%. Best overall and complete response rates in infused patients were 82% (95% CI, 77% to 86%) and 64% (95% CI, 58% to 69%), respectively. At a median follow-up of 12.9 months from the time of CAR T-cell infusion, median progression-free survival was 8.3 months (95% CI, 6.0 to15.1 months), and median overall survival was not reached. Patients with poor Eastern Cooperative Oncology Group performance status of 2-4 and elevated lactate dehydrogenase had shorter progression-free and overall survival on univariable and multivariable analysis.

CONCLUSION The safety and efficacy of axi-cel in the SOC setting in patients with relapsed/refractory LBCL was comparable to the registrational ZUMA-1 trial.

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ASSOCIATED CONTENT

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma in the United States.[1] Patients with chemorefractory DLBCL face dismal outcomes, with most succumbing to their disease. In the SCHOLAR-1 international multicohort retrospective analysis, median overall survival (OS) was 6.3 months among patients with refractory DLBCL, and only 20% of patients were alive at 2 years.[2] Although frontline anthracycline-based chemoimmunotherapy is curative for many patients,[3,4] only a small fraction with relapsed disease achieve prolonged disease-free survival with salvage chemotherapy and autologous stem-cell transplantation (ASCT).[2,4,5]

Chimeric antigen receptor (CAR) T-cell therapy, a gene-modified cellular therapy, has demonstrated substantial efficacy in patients with chemorefractory aggressive B-cell lymphomas.[6-8] Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 CAR T-cell therapy approved for the treatment of relapsed or refractory (R/R) large B-cell lymphomas (LBCLs), including DLBCL, primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma, and transformed follicular lymphoma, after at least 2 prior lines of systemic therapy.[9] In the multicenter ZUMA-1 registrational trial that tested axi-cel in patients with R/R LBCL, the objective response rate (ORR) and complete response (CR) rate were 83% and 58%, respectively.[6,7] Grade ≥ 3 cytokine release syndrome (CRS) and neurologic

CONTEXT

Key Objective

Seventeen US centers set out to delineate the characteristics and outcomes of 298 patients apheresed with intention to be treated with commercially available axicabtagene ciloleucel, an autologous anti-CD19 CAR T-cell.

Knowledge Generated

Practice patterns varied from the registrational ZUMA-1 trial. 43% of patients had comorbidities or characteristics that would have deemed them ineligible. Despite this, safety and efficacy outcomes were comparable to ZUMA-1. We identified patient and disease characteristics associated with outcomes.

Relevance

Our findings suggest favorable outcomes reported in prospective trials with axicabtagene ciloleucel can be achieved across multiple centers in the United States using commercial product as a standard of care.

events were observed in 11% and 32% of the patients, respectively.[7] With a median follow-up of 27.1 months, the median duration of response was 11.1 months (95% CI, 4.1 months to not estimable), 39% of patients remained in ongoing response, and the median OS was not reached.[7] These 2-year follow-up data suggested that axi-cel can induce durable remissions and meaningful OS benefit in patients with R/R aggressive B-cell lymphoma.

Clinical trials often have stringent eligibility criteria, and the outcomes observed in clinical trials may or may not be observed in real-life clinical practice because the study population in the clinical trials may not be representative of those treated in clinical practice. Therefore, we set out to delineate the characteristics of patients treated with commercially available axi-cel and to evaluate its safety and effectiveness outside the confines of a clinical trial.

PATIENTS AND METHODS

Study Design and Participants

Seventeen US centers obtained independent institutional review board approval for this retrospective study conducted in accordance with the International Conference on Harmonization guidelines. All patients, at all centers, who underwent leukapheresis as of September 30, 2018, with the intent to manufacture commercial axi-cel for the treatment of R/R LBCL were included (Fig 1; Appendix Fig A1, online only). If the CAR T-cell product did not meet commercial release criteria, patients were offered treatment with the manufactured product in the ZUMA-9 expanded access study (ClinicalTrials.gov identifier: NCT03153462), and their results were included.

Treatment and Clinical Assessment

Disease status at leukapheresis was defined as primary refractory, never achieving end-of-treatment CR; refractory, not primary refractory and no response to the most recent therapy; or relapsed, responded to the most recent therapy and either relapsed or progressed. Bridging therapy was defined as any lymphoma-specific therapy administered after leukapheresis and before conditioning chemotherapy. Cyclophosphamide and fludarabine conditioning followed by axi-cel infusion were performed as in ZUMA-1.[6] Pathologic diagnoses and molecular classification of patients with DLBCL by Hans algorithm were determined locally.[10] Toxicity grading and management were according to each institution's guidelines. CRS was graded according to the Lee et al[11] or CAR T-Cell Therapy–Associated Toxicity (CARTOX) criteria. Neurotoxicity was graded by CARTOX CAR-T-cell–related encephalopathy syndrome criteria in 7 centers[12] and Common Terminology Criteria for Adverse Events (version 4.03; CTCAE) in 10 centers. Severe CRS and neurotoxicity were defined as grade ≥ 3. Tumor response assessments were performed locally per Lugano 2014 classification.[13]

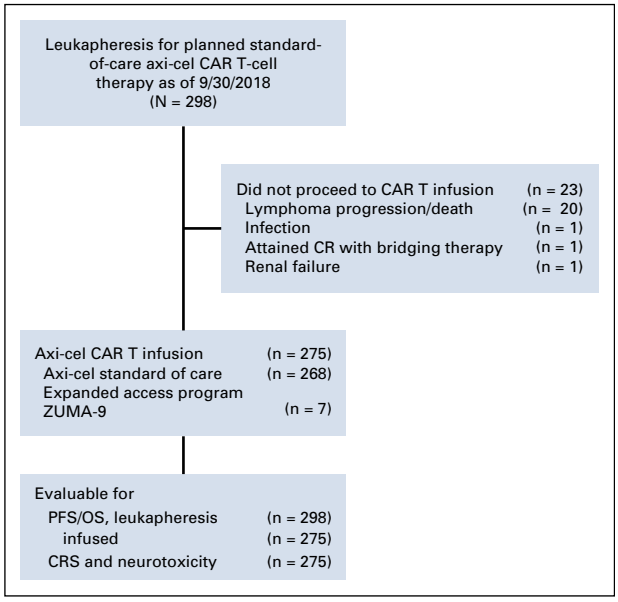

FIG 1. Patient flow diagram. Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; OS, overall survival; PFS, progression-free survival.

TABLE 1. Baseline Patient Characteristics

Characteristic	No. (%)
No. of patients	298
Age, years	
< 60	144 (48.3)
≥ 60	154 (51.7)
Median (range)	60 (21-83)
Sex (male)	192 (64.0)
ECOG PS	
0	76 (25.5)
1	164 (55.0)
2	46 (15.4)
3	11 (3.7)
4	1 (< 1.0)
Disease stage	
I or II	52 (17.6)
III or IV	244 (82.4)
International Prognostic Index score[a]	
0-2	136 (45.6)
3-5	162 (54.4)
Disease type	
DLBCL	203 (68.1)
PMBCL	19 (6.4)
TFL	76 (25.5)
GCB-like[b]	158 (59.8)
Non-GCB[b]	106 (40.1)
Double/triple-hit[c]	64 (22.8)
Double expressor[c]	98 (37.4)
CD19 status[d]	
Positive by flow cytometry	137 (92.6)
Positive by IHC	57 (87.7)
LDH > ULN at leukapheresis[e]	157 (60.6)
LDH > ULN at conditioning[e] chemotherapy	155 (59.4)
Bulky disease (≥ 10 cm)	68 (22.7)
Prior therapies	
≥ 3 prior lines of therapy	222 (74.5)
Median No. of prior lines (range)	3 (2-11)
History of primary refractory disease	101 (33.9)
Refractory to most recent therapy	125 (42.0)
Relapsed	72 (24.0)
Prior ASCT	98 (32.9)
Prior allogeneic SCT	7 (2.4)
Prior CD-19–directed therapy[f]	5 (1.7)
ZUMA-1 comorbidity exclusion criteria at the time of leukapheresis	
No. of patients with exclusion criteria	129 (43.0)
1 criterion	76 (58.9)
≥ 2 criteria	53 (41.1)
ECOG PS > 1	58 (19.0)
Platelets < 75,000/μL	34 (11.4)
DVT/PE within 6 months	31 (10.4)
History of CNS disease	21 (7.0)
Renal insufficiency (GFR < 60 mL/min/1.73 m^2)	21 (7.0)
Prior checkpoint inhibitor therapy	17 (5.7)
LVEF < 50%	10 (3.4)
Symptomatic pleural effusion	10 (3.4)
Bilirubin > 1.5 g/dL	7 (2.4)
Prior CD19-directed therapy	5 (1.7)

(continued in next column)

Abbreviations: ASCT, autologous stem-cell transplantation; DLBCL, diffuse large B-cell lymphoma; DVT, deep vein thrombosis; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B cell; GFR, glomerular filtration rate; IHC, immunohistochemistry; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; PE, pulmonary embolism; PMBCL, primary mediastinal B-cell lymphoma; SCT, stem-cell transplantation; TFL, transformed follicular lymphoma; ULN, upper limit of normal.

[a]At the time of relapse.

[b]Percentages do not include 34 patients in whom cell of origin was unavailable.

[c]Percentages do not include 18 patients in whom fluorescence in situ hybridization results were unavailable and 36 patients in whom IHC to determine double expression was unavailable.

[d]Percentages do not include 150 patients in whom CD19 status by flow cytometry or 233 patients by IHC was unknown.

[e]Percentages do not include 39 patients in whom LDH at leukapheresis or 37 patients before conditioning was unknown.

[f]Prior CD19 chimeric antigen receptor T cells (n = 3), CD19 bispecific antibody (n = 1), or CD19 antibody (n = 1).

Statistical Methods

Descriptive statistics, including mean, standard deviation, median, and range for continuous variables, and percentages for categorical variables, are provided. Fisher's exact test or χ^2 test was used to evaluate the association between two categorical variables. Multivariable logistic regression model was fitted to assess the effect of important covariates on response. Wilcoxon rank sum test or Kruskal-Wallis test was used to evaluate the difference in a continuous variable between/among patient groups. Kaplan-Meier method was used to estimate PFS and OS rates, and log-rank test was used to evaluate the difference in PFS or OS between/among patient groups. For all patients who underwent leukapheresis, and alternatively for all that underwent axi-cel infusion, PFS and OS were computed since the procedure. The median follow-up time, in months, was calculated among patients still alive. Rates of toxicity and safety data were calculated in patients who received axi-cel.

Cox proportional hazards regression models were used for multivariable analysis to include significant covariates. The Schoenfeld residual was used to check the proportional hazards assumption. Variables with at least marginal association with PFS/OS from the univariable analysis ($P < 0.2$) were included in the initial multivariable model. A stepwise selection method was used and a significance level of .2 was the criterion for a variable to stay in the model. Collinearity diagnostics were performed for the final models and indicated no collinearity problem. SAS 9.4 (SAS Institute, Cary, NC) and Spotfire S+ 8.2 (TIBCO Software, Palo Alto, CA) statistical software were used for all the analyses.

Corticosteroids or tocilizumab use was not considered a baseline variable when assessing the association with PFS or OS. Corticosteroids or tocilizumab were initiated within 30 days of axi-cel in all patients, so landmark analysis that started at 30 days after axi-cel for PFS or OS by corticosteroid or tocilizumab use was performed. Patients with follow-up < 30 days were excluded from this landmark analysis.

RESULTS

Patient Characteristics and Disposition

As of September 30, 2018, 298 patients completed leukapheresis with intent to manufacture and receive commercial axi-cel at 17 centers. Median follow-up from leukapheresis was 13.8 months (range, 3.9-21.6 months). At leukapheresis, 129 patients (43%) had comorbidities that would have made them ineligible for ZUMA-1 (ClinicalTrials.gov identifier: NCT02348216). Patient characteristics are listed in Table 1. The median time from leukapheresis to initiation of conditioning chemotherapy was 21 days (range, 11-71 days; interquartile range, 20-24 days). Bridging therapy, which was not permitted in ZUMA-1,[6] was used in 158 patients (53%). Bridging therapies were chemotherapy with or without other therapy in 54%, corticosteroids in 23%, radiation with or without corticosteroids in 12%, and targeted therapies such as lenalidomide or ibrutinib alone in 10%. Characteristics of patients who received bridging therapy are listed in Appendix Table A1 (online only).

After conditioning chemotherapy with cyclophosphamide and fludarabine, 275 patients (92%) received axi-cel infusion (Fig 1), with 12.9 months median follow-up from infusion (range, 3.2-20.7 months). Of these, 268 (97%) received commercial axi-cel, and 7 (3%) were treated under the ZUMA-9 study; 255 (93%) received axi-cel as an inpatient. Of 20 outpatient infusions, all required admission at median day 1 (range, days 0-8).

Safety

Median hospital stay was 14 days (range, 3-66 days). Any grade and grade ≥ 3 CRS occurred in 91% and 7% of patients, respectively (Table 2). One patient died as a result of hemophagocytic lymphohistiocytosis (HLH).[14] Any grade and grade ≥ 3 neurotoxicity occurred in 69% and 31%, respectively (Table 2). All neurotoxicity events resolved except for 1 event of grade 5 cerebral edema. Sixty-two percent received tocilizumab (median number of doses, 1; 1 dose, n = 83; 2 doses, n = 46; ≥ 3 doses, n = 40); 55% received glucocorticoids for CRS, neurologic events, or both; and 33% were transferred to the intensive care unit. Of all patients infused, 7% required vasopressors, 7% intubation/mechanical ventilation, and 3% dialysis.

Among patients who received axi-cel infusion, 97 died: 84 deaths were lymphoma related, and 12 were a result of nonrelapse mortality (4.4%). Causes of nonrelapse mortality included infection (n = 8), axi-cel–related toxicity (n = 2; 1 HLH and 1 cerebral edema), and unknown causes not attributable to lymphoma (n = 2). One additional patient died as a result of graft-versus-host disease, unrelated to axi-cel, after an allogeneic transplantation following axi-cel relapse (Appendix Table A2, online only).

Univariable (Appendix Table A3, online only) and multivariable (Appendix Table A4, online only) analyses were performed to determine the association between baseline characteristics and risk of severe CRS and/or neurotoxicity. Multivariable analysis found that severe CRS was significantly associated with a poor Eastern Cooperative Oncology Group performance status (ECOG PS) of 2-4 (odds ratio [OR] 5.3; 95% CI, 2.0 to 14.3; $P = .001$) and elevated bilirubin (OR, 7.6; 95% CI, 2.0 to 14.3; $P = .001$). Severe neurotoxicity was significantly associated with bulky disease > 10 cm (OR, 2.2; 95% CI, 1.2 to 4.1; $P = .01$) and left ventricular ejection fraction < 50% (OR, 4.5; 95% CI, 1.05 to 19.3; $P = .04$) on multivariable analysis.

Response to Therapy

The best ORR and CR rate among the 275 patients who received axi-cel were 82% (95% CI, 77% to 86%) and 64% (95% CI, 58% to 69%), respectively. Median time to response was 30 days, and no patients achieved a first response beyond day 90. The majority of patients who achieved a CR (n = 121) at day 30 remained in CR at day 90 (78%). Among the 93 patients with a partial response (PR) at day 30, 32% improved to a CR at day 90, but only 1 (7%) of 14 patients with stable disease at day 30 improved to a CR at day 90. The median duration of response has not been reached (95% CI, 6.2 months to not reached; Fig 2A). Among the 24 patients who had no evidence of CRS, 75% had an objective response (CR, n = 8; PR, n = 10).

Univariable (Appendix Table A3) and multivariable (Appendix Table A4) analyses were performed to determine baseline characteristics associated with a best response of CR by 12 months. Multivariable analysis found associations with age > 60 years (OR, 2.3; 95% CI, 1.3 to 3.9; $P = .004$)

TABLE 2. Summary of Safety With Standard-of-Care Axicabtagene Ciloleucel

Event and Grade	No. (%)
Cytokine release syndrome	
Any	251 (91.2)
1	94 (34.2)
2	138 (50.2)
3	12 (4.4)
4	6 (2.2)
5	1 (0.4)
Median time to maximum severity, days	3
Range	0-37
Interquartile range	1-5
Neurotoxicity	
Any	189 (68.7)
1	49 (17.8)
2	55 (20)
3	66 (24)
4	18 (6.6)
5	1 (0.4)
Median time to maximum severity, days	6
Range	0-27
Interquartile range	5-8
Hospitalization	
Median hospital stay, days (range)	14 (3-66)
Intensive care unit stay	91 (33)
Tocilizumab use	170 (62)
Corticosteroid use	149 (54)

and normal lactate dehydrogenase (LDH) at the time of conditioning (OR, 2.2; 95% CI, 1.2 to 4.0; $P = .007$).

PFS and OS

Of the 298 patients who underwent leukapheresis, the median PFS was 7.2 months from leukapheresis (95% CI, 5.7 to 12.4 months), with median OS not reached (Figs 2A and 2B). The 12-month PFS and OS estimates were 45% (95% CI, 39% to 51%) and 64% (95% CI, 59% to 70%), respectively.

For the 275 patients who received axi-cel, the median PFS was 8.3 months from infusion (95% CI, 6.0 to 15.1 months), with median OS not reached (Figs 2C and 2D). The 12-month PFS and OS estimates were 47% (95% CI, 41% to 53%) and 68% (95% CI, 63% to 74%), respectively. Baseline characteristics associated with worse PFS and OS in those receiving axi-cel were identified by univariable (Appendix Table A3) and multivariable (Table 3) analyses. Kaplan-Meier curves for ECOG PS ≥ 2 and elevated LDH are shown as common covariates that affect PFS and OS (Figs 3A-3D). Infused patients who were ineligible for ZUMA-1 because of comorbidities at the time of leukapheresis had lower PFS and OS (Appendix Fig A2, online only). Efficacy outcomes compared with ZUMA-1 are listed in Appendix Table A5 (online only).

Day 30 landmark analysis revealed a significant univariable association between OS and corticosteroid use ($P = .04$) but not tocilizumab use ($P = .07$). However, in multivariable analysis using the day 30 landmark, neither tocilizumab (hazard ratio [HR], 1.7; 95% CI, 0.9 to 2.4; $P = .17$) nor corticosteroids (HR, 1.3; 95% CI, 0.8 to 2.2; $P = .2$) significantly affected OS.

DISCUSSION

We report clinical outcomes in a large observational cohort of 298 patients with R/R LBCL who underwent leukapheresis with the intent to administer SOC axi-cel at 17 US centers. Forty-three percent of patients would have been ineligible, on the basis of comorbidities, for the pivotal ZUMA-1 trial that resulted in approval of axi-cel.[6] Despite this, axi-cel could be administered to 92% of the patients who underwent leukapheresis, comparable to the 91% administered in ZUMA-1.[6] Of patients infused with axi-cel, most (97%) received commercial axi-cel, while 3% were treated in the ZUMA-9 expanded access study because of product specifications not meeting commercial release criteria. This demonstrated feasibility of axi-cel outside of clinical trials, with a high manufacturing success rate. Importantly, assessment of clinical outcomes after CAR T infusion showed that the safety and efficacy were comparable to ZUMA-1, which is noteworthy and suggests that this therapy is tolerable and effective in patients with comorbidities and a certain degree of organ dysfunction (Table 1).

The overall incidence of CRS was comparable to ZUMA-1, but grade ≥ 3 CRS was slightly lower at 7% *v* 11% in ZUMA-1.[7] This observation might be accounted for by greater use of tocilizumab and corticosteroids (62% and 55%, respectively) in our study compared with ZUMA-1 (43% and 27%, respectively) in line with evolving practice patterns for toxicity management. In the ZUMA-1 trial, the use of tocilizumab and corticosteroids primarily for grade ≥ 3 CRS and neurotoxicity did not seem to affect ORR, CR rate, or durability of response.[6,7] Similarly, we did not note significant differences in PFS or CR rates in patients treated with these agents. Corticosteroid use was associated with lower OS in a univariable landmark analysis that considered only patients alive at day 30 onward but was not significant upon multivariable analysis. Nonrelapse mortality in our study was 4.4% and comparable to ZUMA-1 (3.7%).[7] A definition of the optimal infectious prophylaxis in these patients may further improve outcomes because 8 of the 12 deaths occurred as a result of infection (Appendix Table A2).

The rate of grade ≥ 3 neurotoxicity in our study was similar to ZUMA-1 (31% *v.* 32%).[7] However, it should be noted that the scoring system for neurotoxicity has changed since

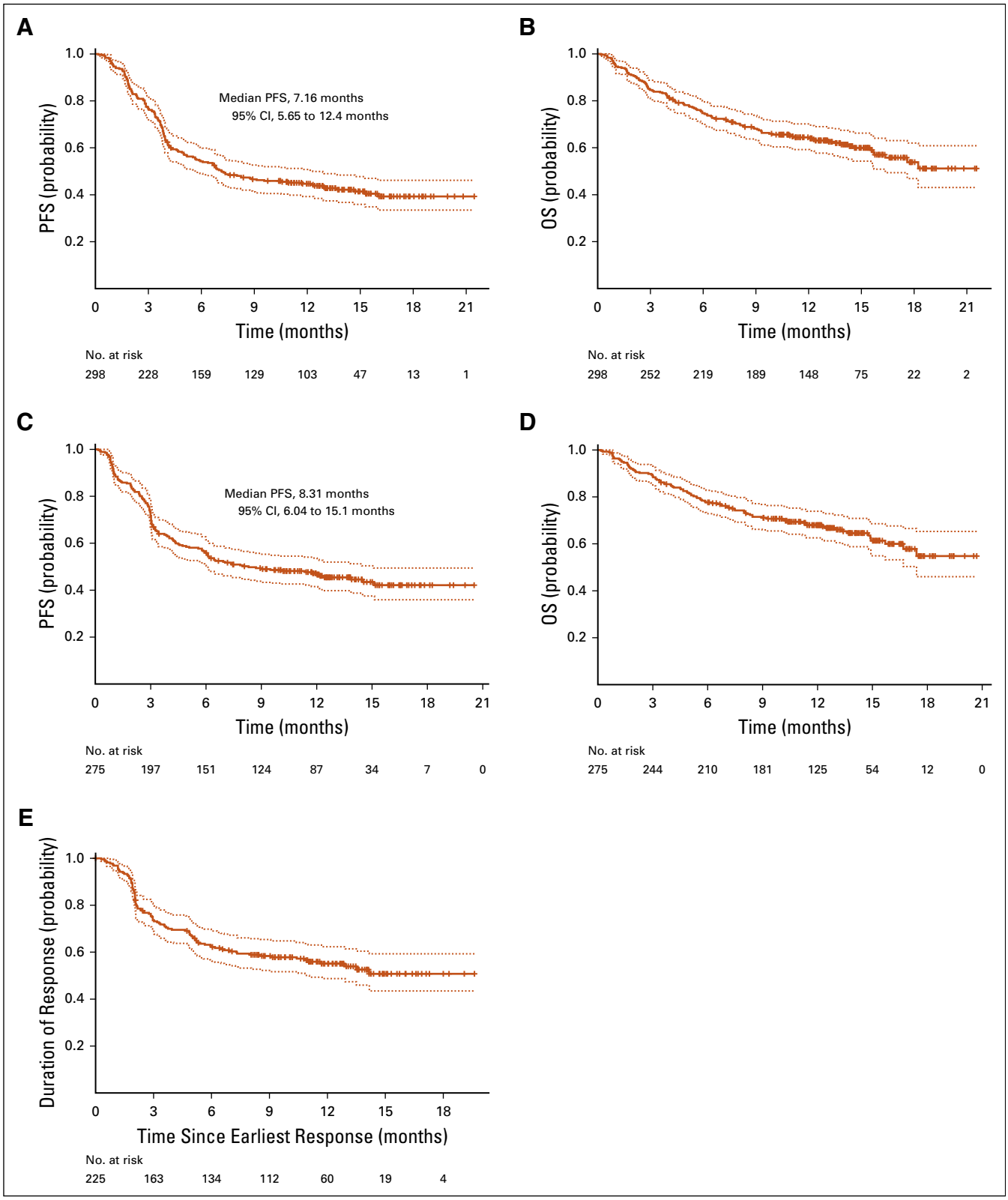

FIG 2. Duration of response, progression-free survival (PFS), and overall survival (OS) estimates. (A) PFS from leukapheresis. (B) OS from leukapheresis. (C) PFS from axi-cel infusion. (D) OS from axi-cel infusion. (E) Duration of response in axicabtagene ciloleucel (axicel) responders.

TABLE 3. Baseline Characteristics Significantly Associated With PFS and OS in Multivariable Models of Axicabtagene Ciloleucel–Treated Patients

	PFS		OS	
Characteristic	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**
Total bilirubin > 1.5 g/dL				
Yes *v* no	.009	3.9 (1.4 to 11.1)	.0020	5.1 (1.80 to 14.50)
LDH before conditioning				
> ULN *v* normal	.001	1.9 (1.3 to 2.9)	.0001	3.0 (1.70 to 5.40)
Sex				
Male *v* female	.005	1.8 (1.2 to 2.7)	.0400	1.7 (1.02 to 2.70)
ECOG PS				
2-4 *v* 0-1	.010	1.7 (1.1 to 2.7)	.0200	1.8 (1.10 to 3.00)
Age, years				
< 60 *v* ≥ 60	.010	1.6 (1.1 to 2.3)	NA	NA
Cell of origin by Hans algorithm				
ABC-like *v* GCB-like	.100	1.4 (0.9 to 2.0)	NA	NA
No. of prior lines of therapy				
≥ 3 *v* < 3	.140	1.4 (0.9 to 2.1)	NA	NA
Prior checkpoint inhibitor therapy				
No *v* yes	.120	2.1 (0.8 to 5.1)	NA	NA
Disease status at leukapheresis				
Primary refractory *v* relapsed	NA	NA	.0400	1.9 (1.02 to 3.60)
Refractory *v* relapsed	NA	NA	.0800	1.8 (0.90 to 3.30)
Bridging therapy				
Yes *v* no	NA	NA	.0300	1.7 (1.04 to 2.70)

Abbreviations: ABC, activated B-cell-like; ECOG PS, Eastern Cooperative Group performance status; GCB, germinal center B-cell-like; HR, hazard ratio; LDH, lactate dehydrogenase; NA, not applicable (characteristic not a part of the multivariable-adjusted model for the listed outcome); OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal.

the inception of ZUMA-1, with the majority of patients in our study graded using a more sensitive CARTOX grading system,[12] which was recently modified into the American Society for Transplantation and Cellular Therapy consensus grading system for neurotoxicity now referred to as immune effector cell–associated neurotoxicity syndrome.[15] The effect of grading systems on neurotoxicity outcomes was studied in a patient-level analysis of the JULIET trial.[16] When CTCAE and CARTOX assessments of neurotoxicity were compared, more patients were observed to have grade 1-2 toxicity by CARTOX than by CTCAE, although the number of patients scored as having grade ≥ 3 was similar. Therefore, it is likely that patients who experience severe neurotoxicity are captured by both grading systems and that the overall rate of severe neurotoxicity is similar between our cohort and ZUMA-1.

Multivariable analysis of baseline characteristics showed that high tumor burden was associated with severe neurotoxicity. Equally important are factors not significantly associated with the risk of severe neurotoxicity, including age, history of CNS lymphoma, or lymphoma-specific features such as subtype or double-hit histology. It is likely that higher tumor burden may increase the risk of neurotoxicity by promoting greater expansion of CAR T cells.[6,17]

The large sample size of this study also allowed analysis of covariates associated with efficacy. Consideration of some of these results in context is warranted. Among the covariates tested, baseline ECOG PS 2-4 and an elevated LDH at the time of conditioning chemotherapy seem to associate with poorer PFS and OS and were relatively common in our cohort. It is conceivable that these baseline characteristics may be a surrogate marker for patients with a different biology of disease that is less responsive to axi-cel therapy. Conversely, we found that younger patients (< 60 years old) had worse PFS and CR rates, which suggests that simple reliance on existing prognostic scoring systems validated with traditional therapies, such as the revised International Prognostic Index that assigns both elevated LDH and older age as poor prognostic factors,[17a] may be inadequate. Additional investigation is needed to understand the mechanistic basis of these risk factors and build a better model to predict CAR T efficacy a priori. Interestingly,

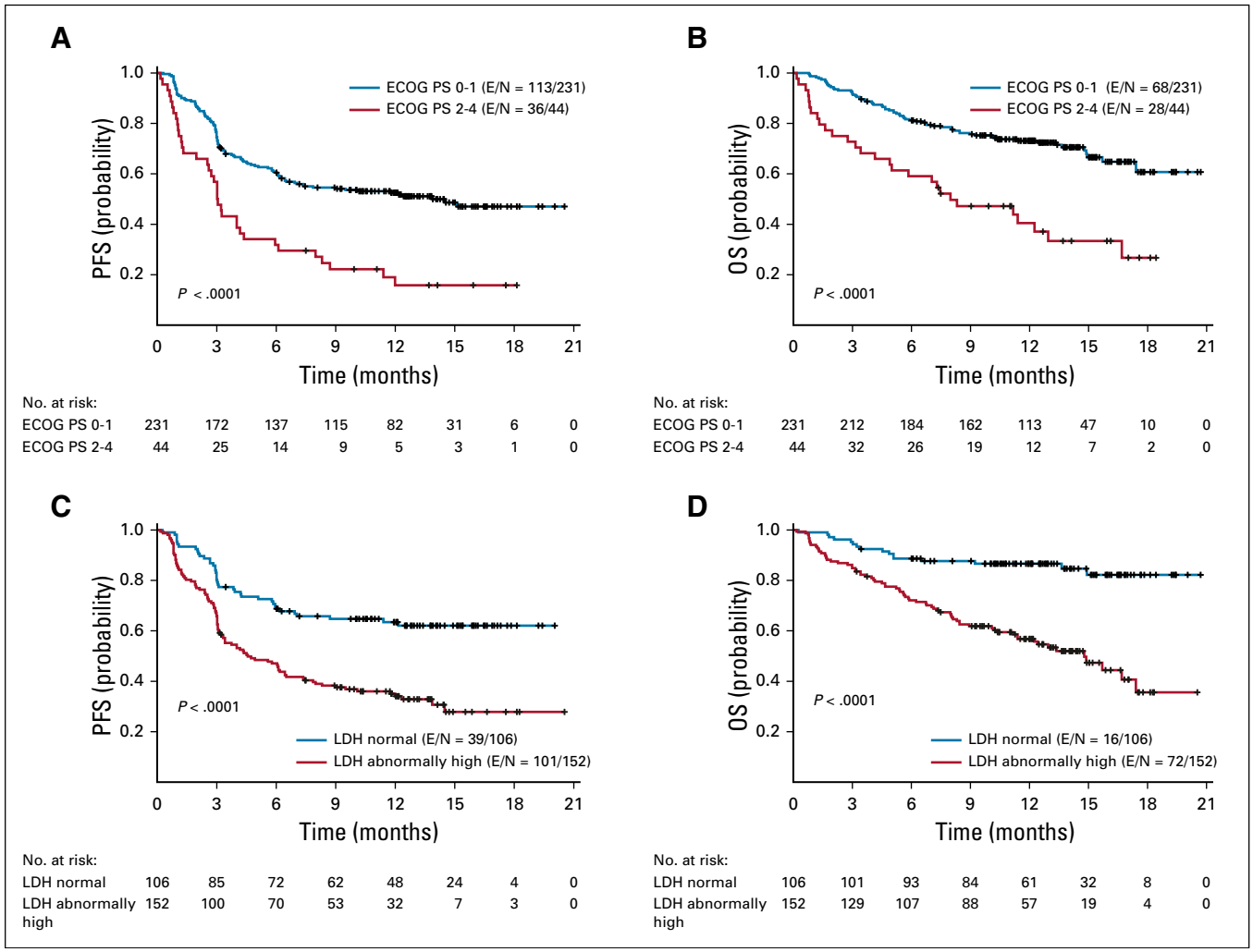

FIG 3. Progression-free survival (PFS) and overall survival (OS) estimates from axicabtagene ciloleucel (axi-cel) infusion, stratified by Eastern Cooperative Oncology Group performance status (ECOG PS) or baseline lactate dehydrogenase (LDH). (A) PFS by ECOG PS at baseline. (B) OS by ECOG PS at baseline. (C) PFS by LDH at conditioning. (D) OS by LDH at conditioning. E, events in a group; N, number of patients in a group.

females had significantly better outcomes than males after axi-cel, which has also been observed in patients with DLBCL treated with chemotherapy.[18] Finally, we found that patients who required bridging therapy had worse OS. To fully understand these findings, a more focused and in-depth analysis of the contributions and interactions among baseline risk factors, specific bridging interventions, and disease biology is needed.

Our results suggest that patients need not meet ZUMA-1 eligibility criteria to benefit from axi-cel, nor should there be an upper age limit. We found that PFS and OS for patients who did not have comorbidities was particularly favorable compared with the ZUMA-1 study. It is possible that this may be a result of differences in certain baseline characteristics in this study versus ZUMA-1. In the current study, there was a higher proportion of patients with transformed follicular lymphoma and prior ASCT and a lower proportion of patients with disease refractory to most recent therapy. These subgroups were associated with improved outcomes in the ZUMA-1 study.[7,18a] Moreover, it is likely that in the SOC setting, because of increased availability of manufacturing slots, patients are being treated earlier after referral when they may have lower tumor burden, another factor associated with improved outcome.[19] Although patients who would have been ineligible for ZUMA-1 because of comorbidities at the time of leukapheresis had worse PFS and OS (Appendix Fig A2), the 12-month PFS rate of 34% fell within the 95% CI of the 12-month PFS rate from ZUMA-1 (Appendix Table A5, online only). Some specific baseline features, in particular ECOG PS 2-4, a ZUMA-1 exclusion criterion, were associated with higher risk for severe toxicity and worse efficacy: Careful consideration before selecting these patients for axi-cel is warranted. Nevertheless, given our findings, broadening the eligibility criteria of prospective studies would improve access to more patients and help us to better characterize the risk factors for safety and efficacy.

There are several limitations of this study beyond its retrospective nature. First, there was heterogeneity in the grading of CRS and neurotoxicity across the centers. Future investigation should prospectively evaluate the concordance of various toxicity scales to allow comparability across trials. Second, a proinflammatory state before axi-cel was seen in some patients who experienced severe toxicity in ZUMA-1.[7,20] However, we were unable to examine the association of inflammatory markers with acute toxicity because C-reactive protein and ferritin were not consistently captured across the 17 centers. Third, longer follow-up is required to determine whether axi-cel induces durable remissions at the same rate described in ZUMA-1.[7] Finally, most baseline characteristics were captured at the time of leukapheresis, as in ZUMA-1, when earliest commitment to axi-cel was made. Patients with R/R LBCL can have rapid changes in ECOG PS and other features during manufacture. For example, we found that elevated LDH before conditioning chemotherapy was more significantly associated with outcomes compared with LDH at leukapheresis. Future studies should evaluate covariates immediately before axi-cel infusion.

In conclusion, our study shows that delivery of axi-cel therapy is feasible outside clinical trials. Overall, our study demonstrates that the overall safety and efficacy of axi-cel in the SOC setting is comparable to what was observed on the pivotal ZUMA-1 trial, despite the observation that many patients would not have met eligibility criteria for the pivotal trial because of comorbidities.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium

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APPENDIX

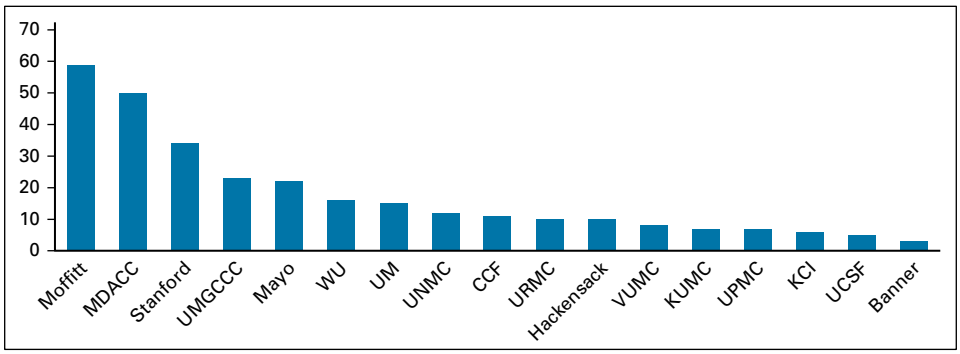

FIG A1. Contribution of patients by center. Banner, MD Anderson Cancer Center; CCF, Cleveland Clinic; KCI, Karmanos Cancer Institute; KUMC, University of Kansas Medical Center; Mayo, Mayo Clinic; MDACC, MD Anderson Cancer Center; Moffitt, H. Lee Moffitt Cancer Center & Research Institute; Stanford, Stanford University Medical Center; UCSF, University of California, San Francisco; UM, University of Miami; UMGCCC, University of Maryland Greenebaum Comprehensive Cancer Center; UNMC, University of Nebraska Medical Center; UPMC, University of Pittsburgh Medical Center; URMC, University of Rochester Medical Center; VUMC, Vanderbilt University Medical Center; WU, Washington University.

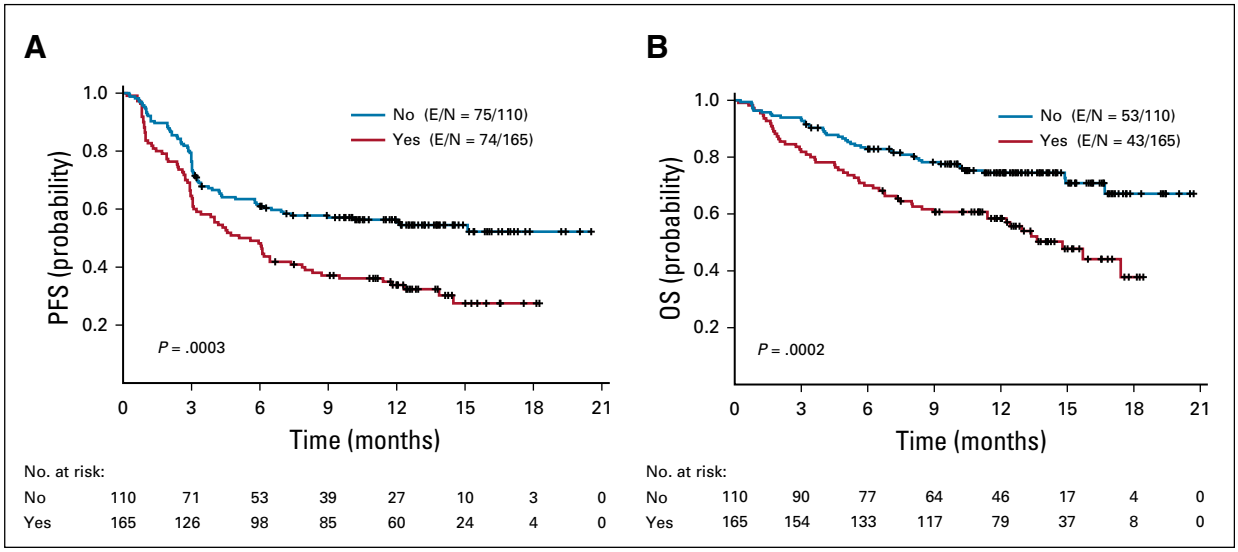

FIG A2. (A) Progression-free survival (PFS) and (B) overall survival (OS) in patients who received axicabtagene ciloleucel infusions, stratified by the presence (yes) or absence (no) of any comorbidity at the time of leukapheresis that was a ZUMA-1 exclusion criterion. E, events in a group; N, number of patients in a group.

TABLE A1. Characteristics of Patients Who Received Bridging Therapy

Characteristic	No Bridging, No. (%)	Received Bridging, No. (%)	*P*
Age, years			
< 60	66 (48)	78 (49)	.7500
> 60	73 (53)	80 (51)	
Sex			
Male	88 (63)	103 (65)	.7400
ECOG PS			
0-1	128 (92)	111 (70)	< .0001
2-4	11 (8)	47 (30)	
Disease type			
DLBCL	96 (69)	106 (67)	.0700
PMBCL	13 (9)	6 (4)	
TFL	30 (22)	46 (29)	
Stage			
I/II	35 (25)	17 (11)	.0010
III/IV	104 (75)	139 (89)	
IPI			
0-2	87 (63)	49 (31)	< .0001
3-5	52 (37)	109 (69)	
Prior lines of therapy			
< 3	39 (29)	37 (23)	.2500
≥ 3	97 (71)	125 (77)	
Disease status			
Primary refractory	39 (28)	62 (39)	.1300
Refractory	63 (45)	61 (39)	
Relapsed	37 (27)	35 (22)	
Bulky disease			
> 10 cm	19 (14)	49 (31)	.0004
LDH > ULN			
At leukapheresis	43 (36)	113 (81)	< .0001
At conditioning	55 (45)	100 (73)	< .0001

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Group performance status; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PMBCL, primary mediastinal B-cell lymphoma; TFL, transformed follicular lymphoma; ULN, upper limit of normal.

TABLE A2. Cause of Death in Patients Who Received Axicabtagene Ciloleucel

Cause of Death	No. (%)
Toxicity (NRM)	12 (4.4)
Infection	8
Bacterial	5
Fungal	3
Cerebral edema	1
HLH	1
Unknown	2
Lymphoma	84 (31)
Other[a]	1 (< 0.1)

Abbreviations: HLH, hemophagocytic lymphohistiocytosis; NRM, nonrelapse mortality.

[a]Graft-*v*-host disease after allogeneic stem-cell transplantation given post–axicabtagene ciloleucel relapse.

TABLE A3. Characteristics Associated With Grade ≥ 3 CRS, Grade ≥ 3 Neurotoxicity, Best Response of CR Up to 12 months, 12-Month PFS, and 12-Month OS in Patients Infused With Axicabtagene Ciloleucel, by Univariable Analysis

Characteristic	CRS Grade ≥ 3, No. (%)	P*	Neurotoxicity Grade ≥ 3, No. (%)	P*	Best CR at 12 Months, No. (%)	P*	PFS Rate at 12 Months (%)	P*	OS Rate at 12 Months (%)	P*
Age, years										
< 60 *v* ≥ 60	8 (6) *v* 11 (8)	.5500	40 (30) *v* 45 (32)	.710	**73 (55) *v* 102 (72)**	**.0020**	42 *v* 51	.0550	66 *v* 70	.5200
Sex										
Female *v* male	8 (8) *v* 11 (6)	.4700	36 (38) *v* 49 (27)	.070	65 (68) *v* 110 (61)	.2300	**60 *v* 40**	**.0300**	75 *v* 64	.0900
ECOG PS										
0/1 *v* 2-4	**10 (4) *v* 9 (21)**	**.0001**	**65 (28) *v* 20 (46)**	**.020**	**155 (67) *v* 20 (46)**	**.0060**	**53 *v* 16**	**< .0001**	**73 *v* 40**	**< .0001**
Lymphoma type										
DLBCL *v* PMBCL *v* TFL	15 (8) *v* 1 (5) *v* 3 (4)	.7300	59 (31) *v* 7 (37) *v* 19 (28)	.740	122 (65) *v* 11 (58) *v* 42 (62)	.7800	44 *v* 58 *v* 51	.5100	65 *v* 84 *v* 70	.3800
Double hit										
Yes *v* no	3 (5) *v* 14 (7)	.9900	19 (34) *v* 63 (31)	.680	36 (64) *v* 127 (63)	.8100	39 *v* 48	.4300	69 *v* 68	.9900
Double expressor										
Yes *v* no	4 (4) *v* 13 (9)	.3000	25 (27) *v* 51 (34)	.240	59 (63) *v* 94 (63)	.9000	39 *v* 51	.1000	64 *v* 70	.2400
Cell of origin										
GCB-like *v* ABC-like	12 (8) *v* 5 (5)	.4500	46 (31) *v* 28 (29)	.710	95 (64) *v* 63 (65)	.4400	52 *v* 41	.1000	68 *v* 67	.6900
Stage										
I/II *v* III/IV	2 (4) *v* 17 (8)	.5400	11 (22) *v* 74 (33)	.100	32 (63) *v* 142 (64)	.8300	54 *v* 45	.1300	**82 *v* 64**	**.0100**
IPI										
0-2 *v* 3-5	5 (4) *v* 14 (10)	.0600	36 (27) *v* 49 (35)	.180	92 (69) *v* 83 (59)	.0600	**58 *v* 37**	**.0002**	**80 *v* 57**	**< .0001**
Bulky disease (≥ 10 cm)										
Yes *v* no	6 (10) *v* 13 (6)	.2500	**27 (47) *v* 58 (27)**	**.004**	**28 (48) *v* 147 (68)**	**.0060**	**36 *v* 49**	**.0400**	**53 *v* 72**	**.0050**
No. of prior therapies										
2 *v* ≥ 3	3 (4) *v* 16 (8)	.4200	19 (26) *v* 66 (33)	.250	54 (73) *v* 121 (60)	.0510	**56 *v* 43**	**.0200**	**81 *v* 63**	**.0100**
Disease status										
Primary refractory *v* refractory *v* relapsed	8 (9) *v* 6 (5) *v* 5 (7)	.5400	34 (38) *v* 35 (30) *v* 16 (23)	.120	52 (58) *v* 72 (61) *v* 51 (74)	.1100	**47 *v* 39 *v* 60**	**.0300**	62 *v* 66 *v* 79	.0700
Prior HDT/ASCT										
Yes *v* no	5 (6) *v* 14 (8)	.6200	22 (25) *v* 63 (34)	.120	**65 (73) *v* 110 (59)**	**.0300**	50 *v* 45	.2000	74 *v* 65	.0600
Prior allogeneic SCT										
Yes *v* NO	0 *v* 19 (7)	.9900	1 (17) *v* 84(31)	.670	4 (67) *v* 171 (64)	.9900	0 *v*47	.0900	67 *v* 68	.4900

(continued on following page)

TABLE A3. Characteristics Associated With Grade ≥ 3 CRS, Grade ≥ 3 Neurotoxicity, Best Response of CR Up to 12 months, 12-Month PFS, and 12-Month OS in Patients Infused With Axicabtagene Ciloleucel, by Univariable Analysis (continued)

Characteristic	CRS Grade ≥ 3, No. (%)	*P**	Neurotoxicity Grade ≥ 3, No. (%)	*P**	Best CR at 12 Months, No. (%)	*P**	PFS Rate at 12 Months (%)	*P**	OS Rate at 12 Months (%)	*P**
ZUMA-1 ineligible by comorbidity[a]										
No *v* yes	8 (5) *v* 11 (10)	.1000	46 (28) *v* 39 (36)	.180	**114 (69) *v* 61 (56)**	**.0200**	**55 *v* 34**	**.0003**	**74 *v* 58**	**.0002**
Bridging therapy										
Yes *v* no	12 (9) vs. 7 (5)	.2800	48 (34) *v* 37 (28)	.250	**81 (57) *v* 94 (70)**	**.0300**	**39 *v* 55**	**.0090**	**56 *v* 81**	**< .0001**
Platelets < 75,000/μL										
Yes *v* no	4 (17) *v* 15 (6)	.0700	11 (46) *v* 74 (30)	.100	13 (54) *v* 162 (65)	.3100	36 *v* 48	.2400	**48 *v* 70**	**.0010**
LDH > ULN at leukapheresis										
Yes *v* no	14 (10) *v* 5 (5)	.2300	48 (34) *v* 25 (25)	.120	**78 (56) *v* 75 (75)**	**.0020**	**36 *v* 56**	**.0010**	**55 *v* 83**	**< .0001**
LDH > ULN at conditioning chemotherapy										
Yes *v* no	14 (9) *v* 4 (4)	.1300	54 (36) *v* 27 (25)	.080	**83 (55) *v* 82 (77)**	**.0002**	**34 *v* 63**	**< .0001**	**57 *v* 87**	**< .0001**
History of CNS disease										
Yes *v* no	3 (17) *v* 16 (6)	.1200	7 (43) *v* 78 (30)	.450	9 (50) *v* 166 (65)	.2100	44 *v* 47	.2300	56 *v* 69	.2100
Prior CD19 therapy										
Yes *v* no	0 *v* 19 (7)	.9900	0 *v* 85 (32)	.330	3 (60) *v* 172 (64)	.9900	**0 *v* 49**	**.0070**	40 *v* 69	.0700
GFR < 60 mL/min/1.73 m^2										
Yes *v* no	0 *v* 19 (7)	.6100	7 (44) *v* 78 (30)	.250	9 (56) *v* 166 (64)	.5300	38 *v* 47	.3600	50 *v* 69	.1700
Prior checkpoint inhibitor										
Yes *v* no	2 (13) *v* 17 (7)	.3000	7 (44) *v* 78 (30)	.250	12 (75) *v* 163 (63)	.4300	69 *v* 45	.1100	75 *v* 68	.4700
LVEF < 50%										
Yes *v* no	2 (22) *v* 17 (7)	.1200	**6 (67) *v* 79 (30)**	**.030**	6 (64) *v* 168 (64)	.9900	22 *v* 48	.1200	67 *v* 68	.5000
Total bilirubin > 1.5 g/dL										
Yes *v* no	**2 (40) *v* 17 (6)**	**.0400**	2(40) *v* 83 (31)	.650	2 (40) *v* 173 (64)	.3600	20 *v* 47	.1000	**20 *v* 69**	**.0030**

NOTE. Boldface indicates significance at $P < .05$.

Abbreviations: ABC, activated B cell; ASCT, autologous stem-cell transplantation; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B cell; GFR, glomerular filtration rate; HDT, high-dose therapy; IPI, International Prognostic Index; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; SCT, stem-cell transplantation; TFL, transformed follicular lymphoma; ULN, upper limit of normal.

[a]Yes indicates that patient had at least 1 comorbidity that would have made them ineligible for ZUMA-1.

**P* values not corrected for multiple comparisons.

TABLE A4. Multivariable Models for Grade ≥ 3 CRS, Grade ≥ 3 Neurotoxicity, and Best Response of CR up to 12 Months

Effect	*P*	OR Estimate	Wald 95% CI
Grade ≥ 3 CRS			
ECOG PS 2-4	.001	5.3	2.0 to 14.3
Total bilirubin > 1.5 g/dL	.047	7.6	1.03 to 56.8
Grade ≥ 3 neurotoxicity			
Male	.09	1.6	0.9 to 2.8
Bulky disease ≥ 10 cm	.01	2.2	1.2 to 4.1
LVEF < 50%	.04	4.5	1.05 to 19.3
Platelets < 75,000/μL	.07	2.2	0.9 to 5.4
Best response of CR by 12 months			
Age > 60	.004	2.3	1.3 to 3.9
ECOG PS 0-1 *v* 2-4	.07	2.0	0.9 to 4.1
< 3 lines of therapy	.13	1.7	0.9 to 3.2
Prior ASCT	.07	1.8	0.96 to 3.3
LDH < ULN before conditioning	.007	2.2	1.2 to 4.0

Abbreviations: ASCT, autologous stem-cell transplantation; CR, complete response; CRS, cytokine release syndrome; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; OR, odds ratio; ULN, upper limit of normal.

TABLE A5. Large B-Cell Lymphoma Efficacy Outcomes After Infusion of SOC Axicabtagene Ciloleucel or in ZUMA-1

Study	No. of Patients	ORR (%)	CR Rate (%)	Median PFS, Months (95% CI)	PFS Rate, % (95% CI)		OS Rate, % (95% CI)	
					6 Month	12 Month	6 Month	12 Month
ZUMA-1[6]								
Phase I and II (cohorts 1 and 2)	108	82	58	5.8 (3.3 to NE)	49 (39 to 58)	44 (34 to 53)	78 (69 to 85)	59 (49 to 68)
SOC cohort								
Total infused	275	82	64	8.3 (6.0 to 15.1)	56 (50 to 62)	47 (41 to 53)	78 (73 to 83)	68 (63 to 74)
Infused with comorbidities that were ZUMA-1 exclusion criteria[a]	110	74	56	5.3 (3.4 to 8.0)	48 (40 to 58)	34 (26 to 44)	70 (62 to 79)	58 (50 to 69)
Infused without comorbidities that were ZUMA-1 exclusion criteria[a]	165	87	69	NE (9.0 to NE)	61 (54 to 69)	55 (48 to 64)	83 (77 to 87)	74 (68 to 82)

NOTE. For both published ZUMA-1 analysis and this SOC data set analysis, outcomes are calculated with infusion of axicabtagene ciloleucel as day 0.

Abbreviations: CR, complete response; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care.

[a]Patients were considered ineligible for ZUMA-1 if they had ≥ 1 comorbid conditions that would have precluded eligibility for ZUMA-1 at the time of leukapheresis.