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ORIGINAL ARTICLE

Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma

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ABSTRACT

BACKGROUND

The prognosis of patients with early relapsed or refractory large B-cell lymphoma after the receipt of first-line chemoimmunotherapy is poor.

METHODS

In this international, phase 3 trial, we randomly assigned, in a 1:1 ratio, patients with large B-cell lymphoma that was refractory to or had relapsed no more than 12 months after first-line chemoimmunotherapy to receive axicabtagene ciloleucel (axi-cel, an autologous anti-CD19 chimeric antigen receptor T-cell therapy) or standard care (two or three cycles of investigator-selected, protocol-defined chemoimmunotherapy, followed by high-dose chemotherapy with autologous stem-cell transplantation in patients with a response to the chemoimmunotherapy). The primary end point was event-free survival according to blinded central review. Key secondary end points were response and overall survival. Safety was also assessed.

RESULTS

A total of 180 patients were randomly assigned to receive axi-cel and 179 to receive standard care. The primary end-point analysis of event-free survival showed that axi-cel therapy was superior to standard care. At a median follow-up of 24.9 months, the median event-free survival was 8.3 months in the axi-cel group and 2.0 months in the standard-care group, and the 24-month event-free survival was 41% and 16%, respectively (hazard ratio for event or death, 0.40; 95% confidence interval, 0.31 to 0.51; P<0.001). A response occurred in 83% of the patients in the axi-cel group and in 50% of those in the standard-care group (with a complete response in 65% and 32%, respectively). In an interim analysis, the estimated overall survival at 2 years was 61% in the axi-cel group and 52% in the standard-care group. Adverse events of grade 3 or higher occurred in 91% of the patients who received axi-cel and in 83% of those who received standard care. Among patients who received axi-cel, grade 3 or higher cytokine release syndrome occurred in 6% and grade 3 or higher neurologic events in 21%. No deaths related to cytokine release syndrome or neurologic events occurred.

CONCLUSIONS

Axi-cel therapy led to significant improvements, as compared with standard care, in event-free survival and response, with the expected level of high-grade toxic effects. (Funded by Kite; ZUMA-7 ClinicalTrials.gov number, NCT03391466.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Locke can be contacted at frederick.locke@moffitt.org or at the H. Lee Moffitt Cancer Center, Dept. of Blood and Marrow Transplant and Cellular Immunotherapy, 12902 USF Magnolia Dr., Suite 3057, Tampa, FL 33612.

*A list of all the ZUMA-7 investigators and contributing Kite members is provided in the Supplementary Appendix, available at NEJM.org.

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Standard-care second-line treatment in the curative setting for patients with relapsed or refractory large B-cell lymphoma is high-dose chemotherapy with autologous stem-cell transplantation if the disease is responsive to salvage chemoimmunotherapy.[1-3] Certain disease characteristics, such as primary refractoriness, a high second-line age-adjusted International Prognostic Index (IPI), and double- or triple-hit genetic lesions in the tumor (rearrangement of *MYC* with *BCL2* or *BCL6* [or both]), limit the likelihood of response.[4,5] Patients whose disease does not respond to salvage chemotherapy and those who are not considered to be candidates for high-dose chemotherapy with autologous stem-cell transplantation have poor outcomes.[4,6,7] These patients may benefit from second-line therapies that have different mechanisms of action.

The autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy axicabtagene ciloleucel (axi-cel) is approved for the treatment of patients with relapsed or refractory large B-cell lymphoma who have received at least two previous systemic therapies.[8,9] In the ZUMA-1 trial, which involved patients with refractory large B-cell lymphoma treated with axi-cel, 83% of the patients had a response and 58% had a complete response[10]; the median overall survival was 25.8 months, and the 5-year overall survival was 43%.[11] Thus, we conducted ZUMA-7, an international, randomized, phase 3 trial comparing axi-cel with standard care as second-line treatment in patients with early relapsed or refractory large B-cell lymphoma. We report here the results of the primary and key secondary analyses.

Methods

Trial Design and Oversight

We conducted this trial at 77 sites worldwide (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Eligible patients were at least 18 years of age and had histologically confirmed large B-cell lymphoma, according to the World Health Organization 2016 classification criteria,[12] that was refractory to first-line treatment or that had relapsed from complete remission no more than 12 months after the completion of first-line chemoimmunotherapy including an anti-CD20 monoclonal antibody and anthracycline-containing regimen; patients intended to proceed to high-dose chemotherapy with autologous stem-cell transplantation. Refractory disease was defined as a lack of complete response to first-line therapy, and relapsed disease as biopsy-proven disease relapse occurring no more than 12 months after the completion of first-line therapy.

All the patients provided written informed consent. After institutional review board approval of the trial protocol (available at NEJM.org), the trial was conducted in compliance with the principles of the Declaration of Helsinki. Kite, a Gilead company (the trial sponsor), and the authors collaborated on the trial design and the data collection, analysis, and interpretation. The first draft was written by the first and last authors, with medical writing assistance funded by the sponsor. All the authors contributed to the writing of the manuscript and vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. The authors were under a confidentiality agreement and had data access after trial unblinding.

After screening, patients underwent randomization in a 1:1 ratio to receive axi-cel or investigator-selected standard-care chemoimmunotherapy. Randomization was stratified according to response to first-line therapy (refractory vs. relapsed disease) and the second-line age-adjusted IPI (0 or 1 risk factor [indicating low or intermediate risk] vs. 2 or 3 risk factors [indicating high risk]). Patients in the axi-cel group underwent leukapheresis, followed by conditioning chemotherapy with cyclophosphamide (at a dose of 500 mg per square meter of body-surface area per day) and fludarabine (30 mg per square meter per day) at −5, −4, and −3 days before receiving a single infusion of axi-cel (target dose, 2×10^6 CAR T cells per kilogram of body weight). Optional bridging therapy was limited to glucocorticoids only. Patients in the standard-care group received two or three cycles of protocol-defined, investigator-selected, platinum-based chemoimmunotherapy. Patients who had a complete or partial response proceeded to high-dose chemotherapy with autologous stem-cell transplantation. Although crossover between the treatment groups was not planned, patients who did not have a response to standard care could receive cellular immunotherapy outside the protocol (treatment switching). Management guidelines for CAR T-cell–related adverse events followed

that used in cohorts 1 and 2 of ZUMA-1.[13] The severity of the cytokine release syndrome was graded according to the modified criteria of Lee et al.[14] Adverse events, including symptoms related to the cytokine release syndrome and neurologic events, were graded according to the Common Terminology Criteria for Adverse Events, version 4.03, of the National Cancer Institute.

END POINTS AND ASSESSMENTS

The primary end point was event-free survival (defined as the time from randomization to the earliest date of disease progression according to the Lugano classification,[15] the commencement of new therapy for lymphoma, death from any cause, or a best response of stable disease up to and including the response on the day 150 assessment after randomization) according to blinded central review. Key secondary end points were response and overall survival. Secondary end points included event-free survival as assessed by the investigator, progression-free survival (defined as the time from randomization to disease progression or death from any cause), and the incidence of adverse events. Exploratory end points included blood CAR T-cell levels (in the axi-cel group). Disease assessments occurred on days 50, 100, and 150 after randomization, followed by every 3 months until 2 years of follow-up, and then every 6 months until 5 years of follow-up. Patient-reported outcomes were assessed but are not reported here.

STATISTICAL ANALYSIS

The protocol-specified primary efficacy analysis was to be conducted when 250 events, as assessed by blinded central review, had occurred. We calculated that this number of events would provide the trial with approximately 90% power at a one-sided 2.5% significance level to detect event-free survival that was 50% longer in the axi-cel group than in the standard-care group. Patients who did not meet the event criteria had their data censored; disease progression events and censoring times were determined on the basis of blinded central review. A subgroup analysis of event-free survival was conducted for prespecified covariates.

Statistical testing of the primary and key secondary end points was conducted hierarchically. Event-free survival was tested first; conditional on significantly longer event-free survival being observed in the axi-cel group than in the standard-care group, response was tested at the 2.5% level at the time of the primary analysis of event-free survival. Conditional on significantly longer event-free survival and a significantly higher percentage of patients with a response being observed in the axi-cel group than in the standard-care group, overall survival was to be tested up to three times, according to the rho-family spending function, at an overall alpha level of 2.5%. An interim analysis of overall survival, reported here, occurred at the time of the primary analysis. A prespecified sensitivity analysis of overall survival was conducted to adjust for the confounding effect of treatment switching from standard care to cellular immunotherapy.

Efficacy analyses were conducted according to the intention-to-treat principle and included all the patients who underwent randomization. Safety analyses included all the patients who underwent randomization and received at least one dose of axi-cel or standard-care therapy according to the protocol; patients were analyzed according to the protocol therapy they received. The safety population for autologous stem-cell transplantation comprised the patients who underwent autologous stem-cell transplantation according to the protocol.

Kaplan–Meier estimates were provided for time-to-event end points. Estimated hazard ratios with two-sided 95% confidence intervals were calculated from a Cox proportional-hazards model with stratification according to the randomization stratification factors. Stratified log-rank P values (two-sided) were calculated for time-to-event end points. A stratified Cochran–Mantel–Haenszel test was performed for analysis of response. Details of the statistical analysis are provided in the Supplementary Appendix.

RESULTS

PATIENTS

Of the 437 patients screened, 359 underwent randomization between January 25, 2018, and October 4, 2019; a total of 180 patients were assigned to the axi-cel group and 179 to the standard-care group (Fig. 1). As of March 18, 2021, the median follow-up from randomization to the data-cutoff date was 24.9 months. The median age of the patients was 59 years; 30% of the patients were 65 years of age or older. A total

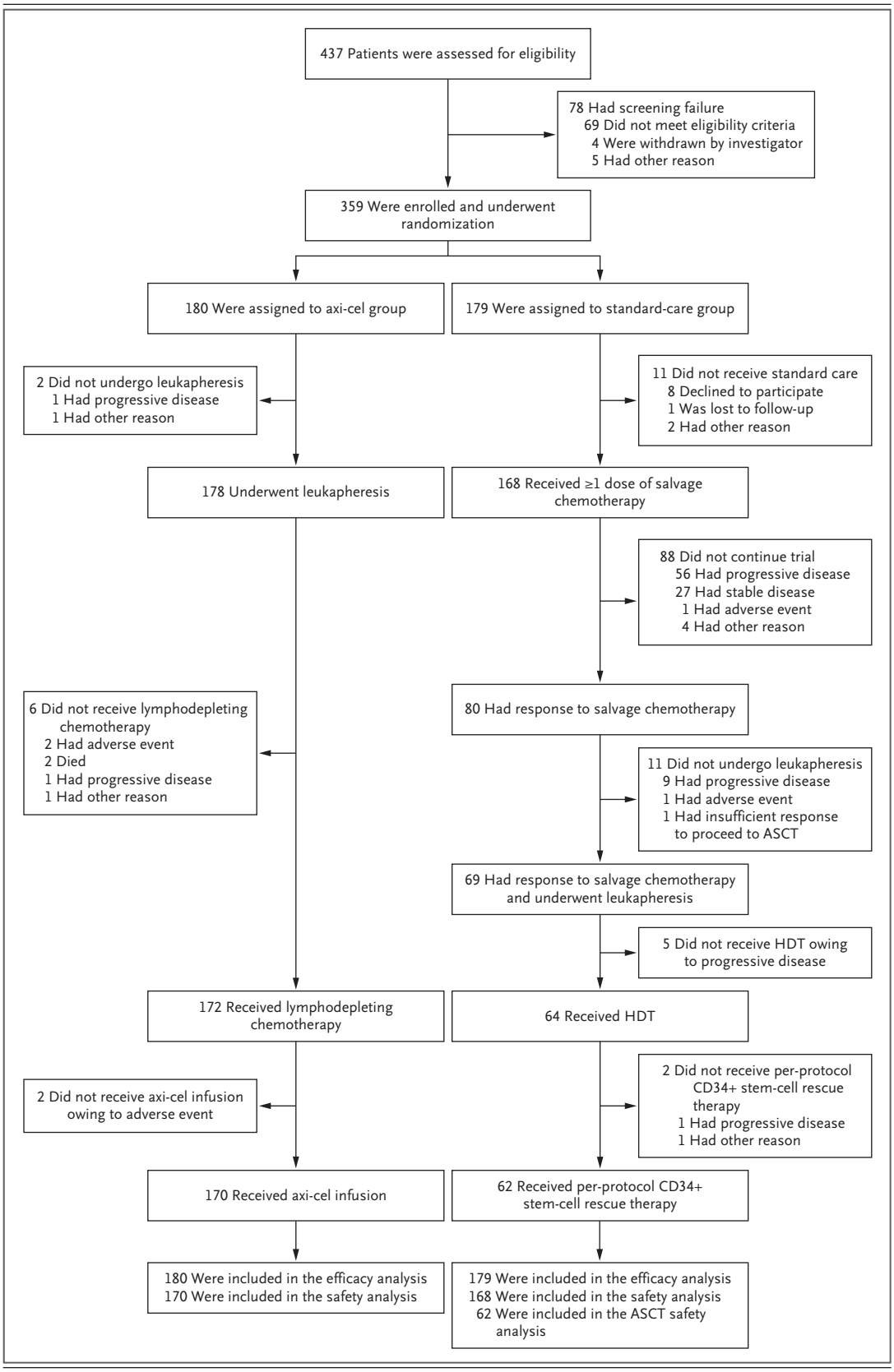


Figure 1 (facing page). Randomization, Treatment, and Follow-up of the Patients.

Five patients did not pass screening owing to insurance issues (in 3), rapid disease progression (in 1), and decision to opt out (in 1). The efficacy analysis population included all the patients who underwent randomization; the safety analysis population included all the patients who underwent randomization and received at least one dose of axicabtagene ciloleucel (axi-cel) or standard-care chemotherapy as protocol therapy. The safety analysis population for autologous stem-cell transplantation (ASCT) included all the patients in the standard-care group who underwent ASCT as part of protocol therapy.

In the axi-cel group, 1 patient did not undergo leukapheresis owing to ineligibility. Adverse events that precluded lymphodepleting chemotherapy included an increase in the alanine aminotransferase level and hyperbilirubinemia (in 1 patient each); in addition, 1 patient had false progression at baseline, and reassessment showed no progression. Adverse events that precluded receipt of an axi-cel infusion included cerebrovascular accident and small intestinal perforation (in 1 patient each).

Standard-care chemotherapy regimens included R-ICE (rituximab, ifosfamide, carboplatin, and etoposide), R-GDP (rituximab, gemcitabine, dexamethasone, and cisplatin [or carboplatin]), R-DHAP or R-DHAX (rituximab, dexamethasone, high-dose cytarabine, and cisplatin or oxaliplatin), and R-ESHAP (rituximab, etoposide, methylprednisolone, high-dose cytarabine, and cisplatin) (Table S3). One patient did not receive therapy owing to a negative disease biopsy, and 1 had a false positive result on positron-emission tomography–computed tomography and did not have refractory double-hit lymphoma after five cycles of R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin). Response to salvage chemotherapy was determined by the investigator, with progressive disease being defined here as a best response of progressive disease or disease progression after an initial response to salvage chemotherapy. Four patients with a best response of progressive disease and 1 with stable disease underwent leukapheresis but did not proceed further in the trial, and 1 had an adverse event of acute kidney injury. Four patients did not proceed further owing to lack of response to salvage chemoimmunotherapy with R-ICE, an inability to receive R-GDP owing to adverse events and a subsequent switch to R-ICE, a change of treatment after one cycle of R-DHAP owing to renal impairment, and insufficient overall response to proceed to ASCT (in 1 patient each). One patient had an adverse event of blood stem-cell harvest failure and did not undergo leukapheresis. One patient was inadvertently enrolled on an alternate protocol and did not receive CD34+ stem-cell rescue therapy per protocol. HDT denotes high-dose chemotherapy.

of 74% of the patients had primary refractory disease, 45% had a high second-line age-adjusted IPI (2 or 3 risk factors), 54% had an elevated lactate dehydrogenase level, 79% had stage III or IV disease, and 19% had high-grade B-cell lymphoma (including double- or triple-hit lymphomas) according to the investigator's assessment (Table 1). The characteristics of the patients at baseline were generally balanced between the two treatment groups and were consistent with those expected in persons with relapsed or refractory diffuse large B-cell lymphoma (Table S1 in the Supplementary Appendix).

Among the patients in the axi-cel group, 178 (99%) underwent leukapheresis and 170 (94%) received axi-cel; 65 patients (36%) received bridging therapy with glucocorticoids. Axi-cel was successfully manufactured for all the patients who underwent leukapheresis (see the Supplementary Results section). Among the 170 patients who received axi-cel, the median time from leukapheresis to product release (i.e., when the product passed quality testing and was made available to the investigator) was 13 days. Among the patients in the standard-care group, 168 (94%) received platinum-based salvage chemotherapy, and 64 (36%) received high-dose chemotherapy and underwent autologous stem-cell transplantation (including 2 patients who underwent autologous stem-cell transplantation outside the protocol) (Fig. 1 and Tables S2 and S3).

EFFICACY

The median event-free survival according to blinded central review was significantly longer in the axi-cel group (8.3 months; 95% confidence interval [CI], 4.5 to 15.8) than in the standard-care group (2.0 months; 95% CI, 1.6 to 2.8) (Fig. 2A). The estimated event-free survival at 24 months was 41% (95% CI, 33 to 48) in the axi-cel group, as compared with 16% (95% CI, 11 to 22) in the standard-care group (Table S4). The event-free survival curves show that treatment with axi-cel was superior to standard care (hazard ratio for event or death, 0.40; 95% CI, 0.31 to 0.51; $P<0.001$). The improvements in event-free survival with axi-cel as compared with standard care were consistent in all prespecified key subgroups (Fig. 2B).

The percentage of patients with a response in the axi-cel group was 1.66 times as high as that in the standard-care group (83% vs. 50%; difference, 33 percentage points; $P<0.001$) (Figs. S1 and S2). A complete response was observed in 65% of the patients in the axi-cel group and in 32% of those in the standard-care group.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Axi-cel (N=180)	Standard Care (N=179)	Total (N=359)
Age			
Median (range) — yr	58 (21–80)	60 (26–81)	59 (21–81)
≥65 yr — no. (%)	51 (28)	58 (32)	109 (30)
Male sex — no. (%)	110 (61)	127 (71)	237 (66)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	0	1 (1)	1 (<1)
Asian	12 (7)	10 (6)	22 (6)
Black	11 (6)	7 (4)	18 (5)
Native Hawaiian or other Pacific Islander	2 (1)	1 (1)	3 (1)
White	145 (81)	152 (85)	297 (83)
Other	10 (6)	8 (4)	18 (5)
Hispanic or Latino ethnic group — no. (%)†			
Yes	10 (6)	8 (4)	18 (5)
No	167 (93)	169 (94)	336 (94)
Not reported	3 (2)	2 (1)	5 (1)
ECOG performance-status score of 1 — no. (%)‡	85 (47)	79 (44)	164 (46)
Disease stage — no. (%)			
I or II	41 (23)	33 (18)	74 (21)
III or IV	139 (77)	146 (82)	285 (79)
Second-line age-adjusted IPI of 2 or 3 — no. (%)§	82 (46)	79 (44)	161 (45)
Molecular subgroup according to central laboratory — no. (%)¶			
Germinal center B-cell–like	109 (61)	99 (55)	208 (58)
Activated B-cell–like	16 (9)	9 (5)	25 (7)
Unclassified	17 (9)	14 (8)	31 (9)
Not applicable	10 (6)	16 (9)	26 (7)
Missing data	28 (16)	41 (23)	69 (19)
Response to first-line therapy at randomization — no. (%)			
Primary refractory disease	133 (74)	131 (73)	264 (74)
Relapse at ≤12 mo after the initiation or completion of first-line therapy	47 (26)	48 (27)	95 (26)
Disease type according to central laboratory — no. (%)			
Diffuse large B-cell lymphoma‖	126 (70)	120 (67)	246 (69)
High-grade B-cell lymphoma, not otherwise specified	0	1(1)	1 (<1)
High-grade B-cell lymphoma, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	31 (17)	25 (14)	56 (16)
Not confirmed or missing data	18 (10)	28 (16)	46 (13)
Other	5 (3)	5 (3)	10 (3)
Disease type according to the investigator — no. (%)			
Large B-cell lymphoma, not otherwise specified	110 (61)	116 (65)	226 (63)
T-cell– or histiocyte–rich large B-cell lymphoma	5 (3)	6 (3)	11 (3)
Epstein–Barr virus–positive diffuse large B-cell lymphoma	2 (1)	0	2 (1)
Large-cell transformation from follicular lymphoma	19 (11)	27 (15)	46 (13)

Table 1. (Continued.)

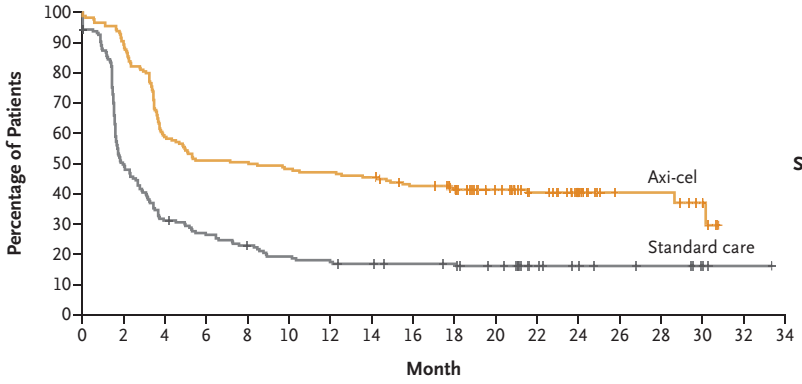
Characteristic	Axi-cel (N=180)	Standard Care (N=179)	Total (N=359)
High-grade B-cell lymphoma, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	43 (24)	27 (15)	70 (19)
Primary cutaneous diffuse large B-cell lymphoma, leg type	1 (1)	0	1 (<1)
Other	0	3 (2)	3 (1)
Prognostic marker according to central laboratory — no. (%)			
High-grade B-cell lymphoma, double- or triple-hit	31 (17)	25 (14)	56 (16)
Double-expressor lymphoma	57 (32)	62 (35)	119 (33)
MYC rearrangement	15 (8)	7 (4)	22 (6)
Not applicable	74 (41)	70 (39)	144 (40)
Missing data	3 (2)	15 (8)	18 (5)
CD19+ status on immunohistochemical testing — no. (%)**	144 (80)	134 (75)	278 (77)
Bone marrow involvement — no. (%)††	17 (9)	15 (8)	32 (9)
Elevated lactate dehydrogenase level — no. (%)‡‡	101 (56)	94 (53)	195 (54)
Median tumor burden (range) — mm^2§§	2123 (181–22,538)	2069 (252–20,117)	2118 (181–22,538)

* Patients were randomly assigned to receive axicabtagene ciloleucel (axi-cel) or standard care. Percentages may not total 100 because of rounding.
† Race and ethnic group were determined by the investigator.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with a score of 0 indicating no symptoms and higher scores indicating greater disability. A score of 1 indicates that the patient is ambulatory but restricted from strenuous activity.
§ Values are the second-line age-adjusted International Prognostic Index (IPI) at randomization, which were similar to the second-line age-adjusted IPI according to the investigator as entered into the clinical database. The second-line age-adjusted IPI is used to assess prognostic risk on the basis of various factors after adjustment for patient age and extranodal status at the time of diagnosis of refractory disease; risk categories are assessed as low (0 factors), intermediate (1 factor), or high (2 or 3 factors).
¶ The molecular subgroup as assessed by the investigator was as follows: germinal center B-cell–like in 96 patients (53%) in the axi-cel group, 84 (47%) in the standard-care group, and 180 (50%) overall; non–germinal center B-cell–like in 47 (26%), 54 (30%), and 101 (28%), respectively. The molecular subgroup was not assessed in 37 patients (21%) in the axi-cel group, 41 (23%) in the standard-care group, and 78 (22%) overall.
‖ The definition of diffuse large B-cell lymphoma according to the central laboratory included cases of incomplete evaluation that were due to inadequate sample amount or sample type, for which further classification of the subtype was not possible. Diffuse large B-cell lymphoma, not otherwise specified, according to the World Health Organization 2016 definition,[12] is also included.
** CD19 staining was not required for participation in the trial. Testing was conducted by the central laboratory.
†† The data shown were as collected on the diagnosis history case-report form.
‡‡ An elevated lactate dehydrogenase level was defined as a level that was above the upper limit of the normal range according to the local laboratory.
§§ Tumor burden was determined on the basis of the sum of product diameters of the target lesions, according to the Cheson criteria,[16] and was assessed by the central laboratory.

The median overall survival, evaluated as an interim analysis, was not reached in the axi-cel group and was 35.1 months in the standard-care group (hazard ratio for death, 0.73; 95% CI, 0.53 to 1.01; P=0.054 [two-sided], statistical significance not reached) (Fig. 3A). In the interim analysis, the estimated overall survival at 2 years was 61% in the axi-cel group and 52% in the standard-care group. Overall, 72 patients (40%) in the axi-cel group and 81 (45%) in the standard-care group died from any cause; 52 patients (29%) in the axi-cel group and 65 (36%) in the standard-care group died from progressive disease.

A total of 56% of the patients in the standard-care group received subsequent cellular immunotherapy. Results of a prespecified sensitivity analysis of overall survival, which was conducted to address the confounding effects of this treatment-switching in the standard-care group, showed a difference in overall survival in favor

A Event-free Survival



	No. of Patients	Median Event-free Survival (95% CI)
		mo
Axi-cel	180	8.3 (4.5–15.8)
Standard Care	179	2.0 (1.6–2.8)

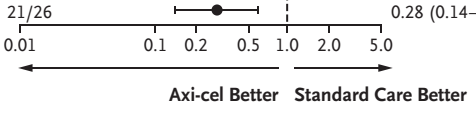
Stratified hazard ratio for event or death, 0.40 (95% CI, 0.31–0.51)
P<0.001

No. at Risk

Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6
Standard care	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

B Subgroup Analysis

Subgroup	Axi-cel	Standard Care	Hazard Ratio for Event or Death (95% CI)
	no. of patients with event/total no.		
Overall	108/180	144/179	0.40 (0.31–0.51)
Age			
<65 yr	81/129	96/121	0.49 (0.36–0.67)
≥65 yr	27/51	48/58	0.28 (0.16–0.46)
Response to first-line therapy at randomization			
Primary refractory disease	85/133	106/131	0.43 (0.32–0.57)
Relapse ≤12 mo after initiation or completion of first-line therapy	23/47	38/48	0.34 (0.20–0.58)
Second-line age-adjusted IPI			
0 or 1	54/98	73/100	0.41 (0.28–0.58)
2 or 3	54/82	71/79	0.39 (0.27–0.56)
Prognostic marker according to central laboratory			
HGBL, double- or triple-hit	15/31	21/25	0.28 (0.14–0.59)
Double-expressor lymphoma	35/57	50/62	0.42 (0.27–0.67)
Molecular subgroup according to central laboratory			
Germinal center B-cell–like	64/109	80/99	0.41 (0.29–0.57)
Activated B-cell–like	11/16	9/9	0.18 (0.05–0.72)
Unclassified	8/17	12/14	—
Disease type according to investigator			
DLBCL, not otherwise specified	68/110	97/116	0.37 (0.27–0.52)
Large-cell transformation from follicular lymphoma	10/19	24/27	0.35 (0.16–0.77)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	23/43	18/27	0.47 (0.24–0.90)
Disease type according to central laboratory			
DLBCL	79/126	95/120	0.44 (0.32–0.60)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	15/31	21/26	0.28 (0.14–0.59)



of axi-cel (stratified hazard ratio, 0.58; 95% CI, 0.42 to 0.81) with the rank-preserving structural failure time method. An additional analysis, which was conducted with the use of the inverse probability of censoring weights model, showed a stratified hazard ratio of 0.70 (95% CI, 0.46 to 1.05) (Fig. S3).

The median progression-free survival was 14.7 months (95% CI, 5.4 to could not be estimated) in the axi-cel group and 3.7 months

Figure 2 (facing page). Event-free Survival.

Panel A shows the Kaplan–Meier estimate of event-free survival (defined as the time from randomization to the earliest date of disease progression according to the Lugano classification,[15] the commencement of new therapy for lymphoma, or death from any cause), as assessed by blinded central review, among 180 patients in the axi-cel group and 179 in the standard-care group. Patients who did not meet the criteria for an event had their data censored (tick marks) (see the Supplementary Methods section). In the axi-cel group, 108 patients had an event; 82 (76%) had progression, 11 (10%) had a change in therapy, 11 (10%) died, and 4 (4%) had a best response of stable disease up to and including the day 150 assessment after randomization. In the standard-care group, 144 patients had an event; 75 (52%) had progression, 63 (44%) had a change in therapy, and 6 (4%) died. Panel B shows the subgroup analysis of event-free survival for key baseline and clinical covariates, including response to first-line therapy and the second-line age-adjusted International Prognostic Index (IPI) at randomization. The second-line age-adjusted IPI is used to assess prognostic risk on the basis of various factors after adjustment for patient age and extranodal status at the time of diagnosis of refractory disease; risk categories are assessed as low (0 factors), intermediate (1 factor), or high (2 or 3 factors). Hazard ratios were formed from baseline covariates (see the Supplementary Methods section). The 95% confidence intervals were calculated with the use of the Clopper–Pearson method and are not adjusted for multiplicity and thus should not be used for inference. The hazard ratio for the unclassified molecular subgroup could not be estimated owing to the small sample size. DLBCL denotes diffuse large B-cell lymphoma, and HGBL high-grade B-cell lymphoma.

(95% CI, 2.9 to 5.3) in the standard-care group (hazard ratio for progression or death, 0.49; 95% CI, 0.37 to 0.65) (Fig. 3B). The estimated progression-free survival at 24 months was 46% (95% CI, 38 to 53) in the axi-cel group and 27% (95% CI, 20 to 35) in the standard-care group.

SAFETY

All the patients had at least one adverse event of any grade. Adverse events of grade 3 or higher occurred in 155 of 170 patients (91%) who received axi-cel and in 140 of 168 patients (83%) who received standard care. The most commonly reported adverse event of grade 3 or higher was neutropenia, which occurred in 69% of the patients who received axi-cel and in 41% of those who received standard care (Table 2). Serious adverse events of any grade occurred in 50% of the patients who received axi-cel and in 46% of those who received standard care (Table S5). Various infections of any grade occurred in 41% of the patients who received axi-cel and in 30% of those who received standard care, with infections of grade 3 or higher occurring in 14% and 11%, respectively.

The frequency of cytopenias is summarized in Table 2. Prolonged cytopenias of grade 3 or higher that were present at or after 30 days after the initiation of definitive therapy (i.e., from receipt of the axi-cel infusion or first dose of high-dose chemotherapy) occurred in 49 patients (29%) who received axi-cel and in 12 of 62 patients (19%) in the standard-care group who underwent per-protocol autologous stem-cell transplantation (Table S6). No cases of replication-competent retrovirus infection or axi-cel treatment–related secondary cancer were reported. Hypogammaglobulinemia during treatment occurred in 11% of the patients who received axi-cel and in 1% of those who received standard care; all the events were grade 1 or 2 (Table S7). Among 160 patients who received axi-cel and were tested for B-cell aplasia, 47% had B-cell aplasia up to 6 months after the infusion and 36% did so up to 12 months after the infusion (Table S8). Utilization of the intensive care unit is summarized in the Supplementary Results section.

Fatal adverse events occurred in 7 patients (4%) in the axi-cel cohort (of which only one event [hepatitis B virus reactivation] was considered by the investigators to be related to axi-cel) and in 2 patients (1%) in the standard-care cohort (both events [cardiac arrest and acute respiratory distress syndrome] were considered by the investigators to be related to high-dose chemotherapy) (Table S9).

Cytokine release syndrome occurred in 157 patients (92%) who received axi-cel (Table 2), with an event of grade 3 or higher occurring in 11 patients (6%). No deaths related to cytokine release syndrome occurred. In the safety population, tocilizumab was administered to 65% of the patients, glucocorticoids to 24%, and vasopressors to 6%. The median cumulative use of tocilizumab, regardless of indication, was 1396 mg (range, 430 to 7200). The median time to the onset of cytokine release syndrome was 3 days (range, 1 to 10) after the infusion, and the median duration was 7 days (range, 2 to 43). All the events resolved.

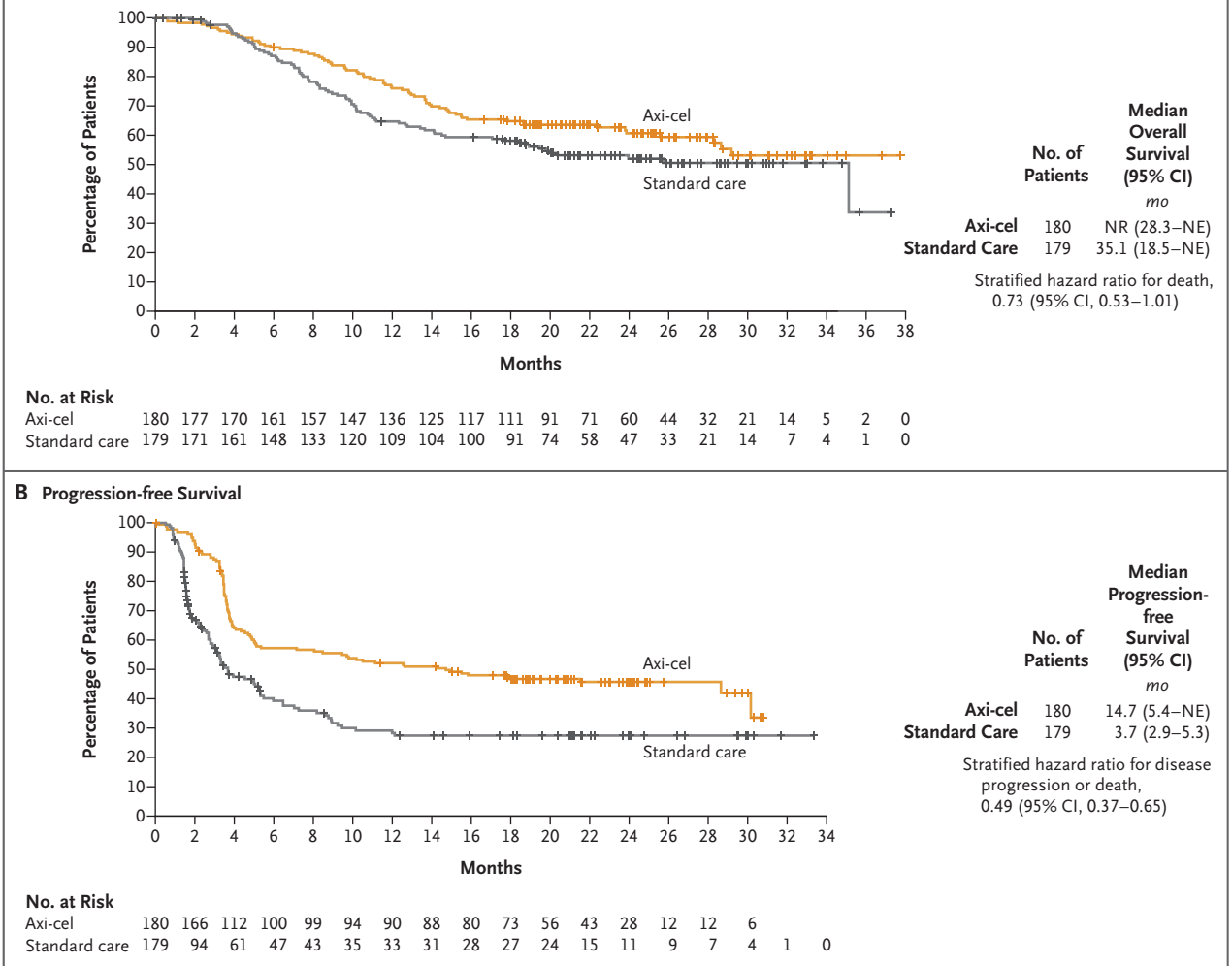


Figure 3. Overall Survival and Progression-free Survival.

Panel A shows the Kaplan–Meier estimate of overall survival, and Panel B the Kaplan–Meier estimate of progression-free survival as assessed by the investigator. The 95% confidence intervals were not adjusted for multiplicity and should not be used for inference. NE denotes could not be estimated, and NR not reached.

Neurologic events occurred in 102 patients (60%) who received axi-cel and in 33 (20%) who received standard care; neurologic events of grade 3 or higher occurred in 36 patients (21%) and 1 patient (1%), respectively. No deaths related to neurologic events occurred. In the axi-cel group, glucocorticoids were used in 32% of the patients for the management of neurologic events. The median time to the onset of neurologic events was 7 days in the axi-cel group and 23 days in the standard-care group, and the median duration was 9 days and 23 days, respectively. At the time of data cutoff, 2 patients had ongoing neurologic events; 1 patient who received axi-cel had grade 2 paresthesia and grade 1 memory impairment, and 1 who received standard care had grade 1 paresthesia.

CAR T-CELL LEVELS

The median time to peak CAR T-cell levels was 7 days (range, 2 to 233) after the axi-cel infusion (Table S10 and Fig. S5). The median peak CAR T-cell level was 25.84 cells per cubic millimeter, with CAR T cells remaining detectable in 12 of

30 patients (40%) who could be evaluated by 24 months. The CAR T-cell peak and area under the curve within the first 28 days after treatment correlated with response (data not shown), findings that were consistent with those observed in the ZUMA-1 study.[18] No occurrences of anti–axi-cel antibodies were confirmed.

DISCUSSION

The prognosis for patients with relapsed or refractory large B-cell lymphoma after the receipt of first-line therapy remains poor, with most patients unable to receive definitive therapy with high-dose chemotherapy and autologous stem-cell transplantation.[4,6,7] In this international, randomized, phase 3 trial of axi-cel as compared with second-line standard care in patients with early relapsed or refractory large B-cell lymphoma, we observed a clear improvement with axi-cel, as compared with standard care, in event-free survival and the percentage of patients with a response. Event-free survival is a widely accepted, robust early efficacy end point in clinical trials involving patients with large B-cell lymphoma, on the basis of retrospective analyses of randomized trials that have shown a correlation between improvements in event-free survival and overall survival.[19-21] Patients with relapsed or refractory large B-cell lymphoma who do not have a response to salvage chemotherapy (i.e., who have progressive or stable disease) will not benefit from high-dose chemotherapy with autologous stem-cell transplantation.[22] In this scenario, a change to third-line therapy is indicated, sometimes in the absence of progressive disease.[6] These reasons underscore why event-free survival is an important end point for this trial.

Axi-cel therapy was superior to standard care with a median event-free survival that was longer by a factor of more than 4, a 2-year event-free survival that was higher by a factor of 2.5, a significantly higher percentage of patients with a response, and double the percentage of patients with a complete response. Event-free survival outcomes with standard care in this trial were consistent with those that have been observed in patients with refractory or early relapsed disease who were receiving second-line therapy in the post-rituximab era.[4,6,7] Treatment with axi-cel also led to longer event-free survival than standard care across key subgroups, including patients with high-risk features, such as high-grade B-cell lymphoma (including double- or triple-hit lymphomas) and an age of 65 years or more, although further improvements in these subgroups are needed.[23] Although 30% of the patients in our trial were 65 years of age or older, elderly patients may not qualify for transplantation in certain regions of the world.[24,25] This trial showed that axi-cel can be an effective second-line therapeutic option in elderly patients who do not have clinically significant coexisting conditions.

The difference in overall survival between the two groups did not reach statistical significance. Patients who had disease progression or lack of response in the standard-care group could receive CAR T-cell therapy outside the protocol (which occurred in 56% of the patients), which may have confounded the analysis of overall survival, as suggested by the results of the prespecified sensitivity analyses (Fig. S3). The median overall survival in the standard-care group was longer than has been observed in historical studies[7,26]; this finding is potentially due to the availability of newer agents, such as CAR T-cell therapy, that can be used in patients whose disease is refractory to or relapses after second-line therapy.

Although nearly all the patients who had been randomly assigned to the axi-cel group received an infusion of axi-cel, only a minority of patients (36%) in the standard-care group received high-dose chemotherapy with autologous stem-cell transplantation; this percentage is consistent with findings in historical studies, especially those with high proportions of patients with primary refractory disease and early relapse and of patients who had received rituximab previously (Table S11).[4,7,26] Given that it is not known a priori which patients will have a response to salvage therapy, and because the majority of patients do not receive definitive therapy with high-dose chemotherapy and autologous stem-cell transplantation, outcomes with the current standard-care therapy are poor. By design, the ZUMA-7 trial randomly assigned patients to groups before the receipt of salvage chemoimmunotherapy and showed that avoidance of salvage chemoimmunotherapy and earlier use of CAR T-cell therapy could result in improvements in event-free survival and response.

Table 2. Most Common Adverse Events, Cytokine Release Syndrome, and Neurologic Events.*

Event	Axi-cel (N=170)		Standard Care (N=168)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any adverse event — no. (%)	170 (100)	155 (91)	168 (100)	140 (83)
Pyrexia	158 (93)	15 (9)	43 (26)	1 (1)
Neutropenia†	121 (71)	118 (69)	70 (42)	69 (41)
Hypotension	75 (44)	19 (11)	25 (15)	5 (3)
Fatigue	71 (42)	11 (6)	87 (52)	4 (2)
Anemia	71 (42)	51 (30)	91 (54)	65 (39)
Diarrhea	71 (42)	4 (2)	66 (39)	7 (4)
Headache	70 (41)	5 (3)	43 (26)	2 (1)
Nausea	69 (41)	3 (2)	116 (69)	9 (5)
Sinus tachycardia	58 (34)	3 (2)	17 (10)	1 (1)
Leukopenia‡	55 (32)	50 (29)	43 (26)	37 (22)
Thrombocytopenia§	50 (29)	25 (15)	101 (60)	95 (57)
Chills	47 (28)	1 (1)	14 (8)	0
Hypokalemia	44 (26)	10 (6)	49 (29)	11 (7)
Hypophosphatemia	45 (26)	31 (18)	29 (17)	21 (12)
Cough	42 (25)	1 (1)	18 (11)	0
Decreased appetite	42 (25)	7 (4)	42 (25)	6 (4)
Hypoxia	37 (22)	16 (9)	13 (8)	7 (4)
Dizziness	36 (21)	2 (1)	21 (12)	1 (1)
Constipation	34 (20)	0	58 (35)	0
Vomiting	33 (19)	0	55 (33)	1 (1)
Febrile neutropenia	4 (2)	4 (2)	46 (27)	46 (27)
Cytokine release syndrome — no. (%)	157 (92)	11 (6)	—	—
Pyrexia — no./total no. (%)	155/157 (99)	14/157 (9)	—	—
Hypotension — no./total no. (%)	68/157 (43)	18/157 (11)	—	—
Sinus tachycardia — no./total no. (%)	49/157 (31)	3/157 (2)	—	—
Chills — no./total no. (%)	38/157 (24)	0/157	—	—
Hypoxia — no./total no. (%)	31/157 (20)	13/157 (8)	—	—
Headache — no./total no. (%)	32/157 (20)	2/157 (1)	—	—
Neurologic event — no. (%)	102 (60)	36 (21)	33 (20)¶	1 (1)
Tremor	44 (26)	2 (1)	1(1)	0
Confusional state	40 (24)	9 (5)	4 (2)	0
Aphasia	36 (21)	12 (7)	0	0
Encephalopathy	29 (17)	20 (12)	2 (1)	0
Paresthesia	8 (5)	1 (1)	14 (8)	0
Delirium	3 (2)	3 (2)	5 (3)	1 (1)

* Shown are any adverse events of any grade that occurred in at least 20% of the patients in either the axi-cel group or the standard care-group, as well as events of the cytokine release syndrome that occurred in at least 15% of the patients in the axi-cel group and neurologic events of any grade that occurred in at least 15% of the patients in the axi-cel group or at least 3% of those in the standard-care group. The severity of the cytokine release syndrome was graded according to Lee et al.[14] Neurologic events were identified with the use of prespecified search list of preferred terms in the *Medical*

Table 2. (Continued.)

Dictionary for Regulatory Activities, version 23.1, on the basis of known neurotoxic effects associated with anti-CD19 immunotherapy, and were specifically identified with the use of methods that were based on the phase 2 study of blinatumomab.[17] The severity of all adverse events, including neurologic events and symptoms of the cytokine release syndrome, was graded with the use of the Common Terminology Criteria for Adverse Events, version 4.03, of the National Cancer Institute.

† Neutropenia refers to the combined preferred terms of neutropenia and neutrophil count decreased.

‡ Leukopenia refers to the combined preferred terms of leukopenia and white-cell count decreased.

§ Thrombocytopenia refers to the combined preferred terms of thrombocytopenia and platelet count decreased.

¶ Other preferred terms that were reported in one or two patients in the standard-care group included somnolence, agitation, hypoesthesia, lethargy, depressed level of consciousness, cognitive disorder, memory impairment, bradyphrenia, taste disorder, hallucination, visual hallucination, nystagmus, head discomfort, and neuralgia.

The adverse-event profile of axi-cel in this trial included high-grade events, a finding consistent with other studies of intensive treatment for refractory large B-cell lymphoma.[13,27] The frequency of adverse events, including those of grade 3 or higher and of serious adverse events, was high in the two treatment groups, although the adverse-event profile differed between the two groups, with the incidence of cytokine release syndrome and neurologic events being higher in the axi-cel group.

In this trial, bridging therapy was restricted to glucocorticoids to avoid the progression of lymphoma during the axi-cel manufacturing process and to isolate the effects of CAR T-cell therapy as second-line therapy. Although this approach potentially limited the enrollment of patients for whom urgent therapy was indicated, enrolled patients had aggressive disease, with 74% of the patients having primary refractory disease. Prohibition of the use of chemotherapy bridging, which could alone result in 40 to 50% of patients having a response,[4,7,26] ensured that the results in the axi-cel group were not confounded. In the real world, however, bridging chemotherapy may sometimes need to be started urgently.

In patients who received and had a response to salvage chemoimmunotherapy and thus were able to proceed to high-dose chemotherapy with autologous stem-cell transplantation, outcomes were not as poor. Although the duration of response was numerically favorable for axi-cel, the 95% confidence interval was broad and consistent with the possibility of no effect (Fig. S4). Nevertheless, because chemosensitivity is unknown before the initiation of treatment, the use of axi-cel as second-line therapy may avoid additional chemotherapy in patients who would ultimately not receive a transplant, may shorten the time to definitive therapy, and may avoid both the risk of clinical deterioration and the potential effect on CAR T-cell fitness with more numerous previous lines of therapy.[28]

Not all patients benefited from axi-cel as second-line therapy. The ZUMA-7 trial has some limitations, including the lack of examination of CD19 expression on progressive tumors, determination of whether CAR T cells reexpand in blood at progression, ex vivo evaluation of CAR T-cell function at progression, or elucidation of resistance mechanisms associated with tumor size or inflammation.[29-31] Additional correlative analyses are necessary to determine markers of response durability and mechanisms of resistance. Given that it remains unclear which therapies may be useful in patients who have a relapse after the receipt of axi-cel, these additional data, together with real-world outcomes and clinical trials, may help inform treatment decisions in the future.[32]

Whereas the majority of patients with large B-cell lymphoma have a relapse less than 12 months after the receipt of induction therapy in the post-rituximab era,[33,34] this trial did not enroll patients with large B-cell lymphoma relapse that occurred more than 12 months after the receipt of induction therapy. Relapses occurring later after induction therapy are generally associated with a greater probability of response to second-line therapy. However, the 2-year event-free survival of 41% among patients with refractory or early relapsed disease in the axi-cel group compares favorably with that in previous phase 3 trials[4,7] involving patients receiving standard care who had received rituximab previously and had later disease relapse (>12 months after the diagnosis).

The ZUMA-7 trial showed a significant improvement in efficacy with axi-cel therapy, as

compared with second-line standard care, in patients with relapsed or refractory large B-cell lymphoma. Treatment with axi-cel induced high-grade adverse events in the vast majority of patients, but few patients had fatal effects from treatment and the magnitude of the toxicity was consistent with previous reports in third-line therapy, although unique problems attend CAR T-cell therapy.[13] Axi-cel appears to be a viable alternative to a regimen of chemoimmunotherapy, high-dose chemotherapy, and autologous stem-cell transplantation for the second-line treatment of relapsed or refractory large B-cell lymphoma.

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APPENDIX

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