ORIGINAL ARTICLE

Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma

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ABSTRACT

BACKGROUND

In an analysis of the primary outcome of this phase 3 trial, patients with early relapsed or refractory large B-cell lymphoma who received axicabtagene ciloleucel (axi-cel), an autologous anti-CD19 chimeric antigen receptor T-cell therapy, as second-line treatment had significantly longer event-free survival than those who received standard care. Data were needed on longer-term outcomes.

METHODS

In this trial, we randomly assigned patients with early relapsed or refractory large B-cell lymphoma in a 1:1 ratio to receive either axi-cel or standard care (two to three cycles of chemoimmunotherapy followed by high-dose chemotherapy with autologous stem-cell transplantation in patients who had a response). The primary outcome was event-free survival, and key secondary outcomes were response and overall survival. Here, we report the results of the prespecified overall survival analysis at 5 years after the first patient underwent randomization.

RESULTS

A total of 359 patients underwent randomization to receive axi-cel (180 patients) or standard care (179 patients). At a median follow-up of 47.2 months, death had been reported in 82 patients in the axi-cel group and in 95 patients in the standard-care group. The median overall survival was not reached in the axi-cel group and was 31.1 months in the standard-care group; the estimated 4-year overall survival was 54.6% and 46.0%, respectively (hazard ratio for death, 0.73; 95% confidence interval [CI], 0.54 to 0.98; P=0.03 by stratified two-sided log-rank test). This increased survival with axi-cel was observed in the intention-to-treat population, which included 74% of patients with primary refractory disease and other high-risk features. The median investigator-assessed progression-free survival was 14.7 months in the axi-cel group and 3.7 months in the standard-care group, with estimated 4-year percentages of 41.8% and 24.4%, respectively (hazard ratio, 0.51; 95% CI, 0.38 to 0.67). No new treatment-related deaths had occurred since the primary analysis of event-free survival.

CONCLUSIONS

At a median follow-up of 47.2 months, axi-cel as second-line treatment for patients with early relapsed or refractory large B-cell lymphoma resulted in significantly longer overall survival than standard care. (Funded by Kite; ZUMA-7 ClinicalTrials.gov number, NCT03391466.)

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FOR NEARLY 30 YEARS, THE STANDARD second-line treatment of large B-cell lymphoma with curative intent has been a multistep regimen that begins with platinum-based chemotherapy, followed in patients who have a response by high-dose chemotherapy and autologous stem-cell transplantation (HDT-ASCT).[1] However, only half the patients in this population are likely to be eligible for this approach,[2,3] and of these patients, approximately 20% are ultimately cured.[4] Outcomes for patients who cannot proceed to HDT-ASCT are poor, with a median overall survival of 4.4 months.[5]

Axicabtagene ciloleucel (axi-cel), an anti-CD19 autologous chimeric antigen receptor (CAR) T-cell therapy given as a one-time dose, was previously approved as a third-line or later treatment.[6,7] The phase 3 ZUMA-7 trial was designed to compare axi-cel with second-line standard-care therapy in patients with early relapsed or primary refractory large B-cell lymphoma.[8] The results for the primary outcome of event-free survival (according to blinded central review) showed that axi-cel was superior to standard care (hazard ratio, 0.40; P<0.001 by stratified log-rank test). With 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; at 24 months, event-free survival was 41% and 16%, respectively. A response (according to blinded central review) occurred in 83% of patients in the axi-cel group and in 50% in the standard-care group, with a complete response in 65% and 32%, respectively. Here, we report the primary overall survival analysis of ZUMA-7 after a protocol-defined interval of 5 years after the first patient underwent randomization.

METHODS

TRIAL DESIGN AND OVERSIGHT

The trial design and protocol have been reported previously.[8] Eligible adult patients (≥18 years of age) had histologically confirmed large B-cell lymphoma[9] that was refractory to first-line treatment or that had relapsed within 12 months after first-line chemoimmunotherapy.

Patients were randomly assigned in a 1:1 ratio to receive axi-cel or standard care (two or three cycles of investigator-selected, protocol-specified chemoimmunotherapy followed by HDT-ASCT in patients who had a complete or partial response). Randomization was stratified according to the response to first-line therapy and to the second-line age-adjusted International Prognostic Index (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). In the axi-cel group, optional bridging therapy with glucocorticoids was allowed if necessary according to the investigator. Additional treatment details are provided in the Supplementary Appendix. Although crossover between treatment groups was not planned according to the protocol (also available at NEJM.org), patients could receive subsequent off-protocol therapy, including cellular immunotherapy.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and was funded by Kite. The protocol was approved by the institutional review board at each participating institution. All the patients provided written informed consent. The authors collaborated on trial design and data collection, analysis, and interpretation of the results. The first draft of the manuscript was written by the first and last authors with sponsor-funded medical writing support. All the authors contributed to the writing of the manuscript and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The authors were under a confidentiality agreement with the sponsor and had data access. The sponsor participated in the assessment of the data.

OUTCOMES AND ASSESSMENTS

The primary outcome of ZUMA-7 was event-free survival (defined as the time from randomization to disease progression according to the Lugano classification,[10] the initiation of new therapy for lymphoma, or death from any cause), according to blinded central review. Protocol-specified key secondary outcomes were the objective response (according to blinded central review) and overall survival. Other secondary outcomes were progression-free survival (defined as the time from randomization to disease progression according to the Lugano classification or death from any cause) and event-free survival, according to investigator assessment because of the per-protocol discontinuation of blinded central review after the primary analysis of event-free survival had been performed. Details regarding disease assessments, safety outcomes, management of CAR T-cell–related adverse events, and exploratory analysis methods are provided in the Supplementary Appendix.

A Quick Take is available at NEJM.org

STATISTICAL ANALYSIS

The prespecified primary overall survival analysis was to be conducted in the intention-to-treat population after the occurrence of approximately 210 deaths or no later than 5 years after the first patient had undergone randomization; the latter criterion triggered the analysis in this article. A group sequential testing procedure for overall survival was performed to control the overall one-sided alpha level of 2.5% (see the Supplementary Methods).[8] We used a log-rank test stratified according to randomization factors for the primary comparison of overall survival with an efficacy boundary (two-sided significance level) of 0.0498. In addition to the intention-to-treat analysis, we also performed two prespecified sensitivity analyses of overall survival to adjust for the confounding effect of subsequent off-protocol cellular immunotherapy in the standard-care group (defined as treatment switching).

Efficacy analyses that were based on the intention-to-treat principle included all the patients who had undergone randomization. Safety analyses included all the patients who had received at least one dose of axi-cel or standard-care treatment according to the protocol. All adverse events were reported from randomization through the trial visit at 150 days after randomization or until a change in lymphoma therapy, whichever came first. After day 150, targeted serious adverse events were reported through the data-cutoff date, until disease progression, or until the initiation of new lymphoma therapy, whichever occurred first. Serious adverse events that the investigator assessed as being related to axi-cel were reported regardless of time of occurrence. Stratified Cox regression models were used to provide estimated hazard ratios and two-sided 95% confidence intervals for axi-cel as compared with standard care. Stratified log-rank P values (two-sided) were calculated for overall survival. Additional statistical methods are described in the Supplementary Appendix.

RESULTS

PATIENTS

From January 25, 2018, to October 4, 2019, a total of 359 patients were enrolled and randomly assigned to receive either axi-cel (180 patients) or standard care (179 patients).[8] The demographi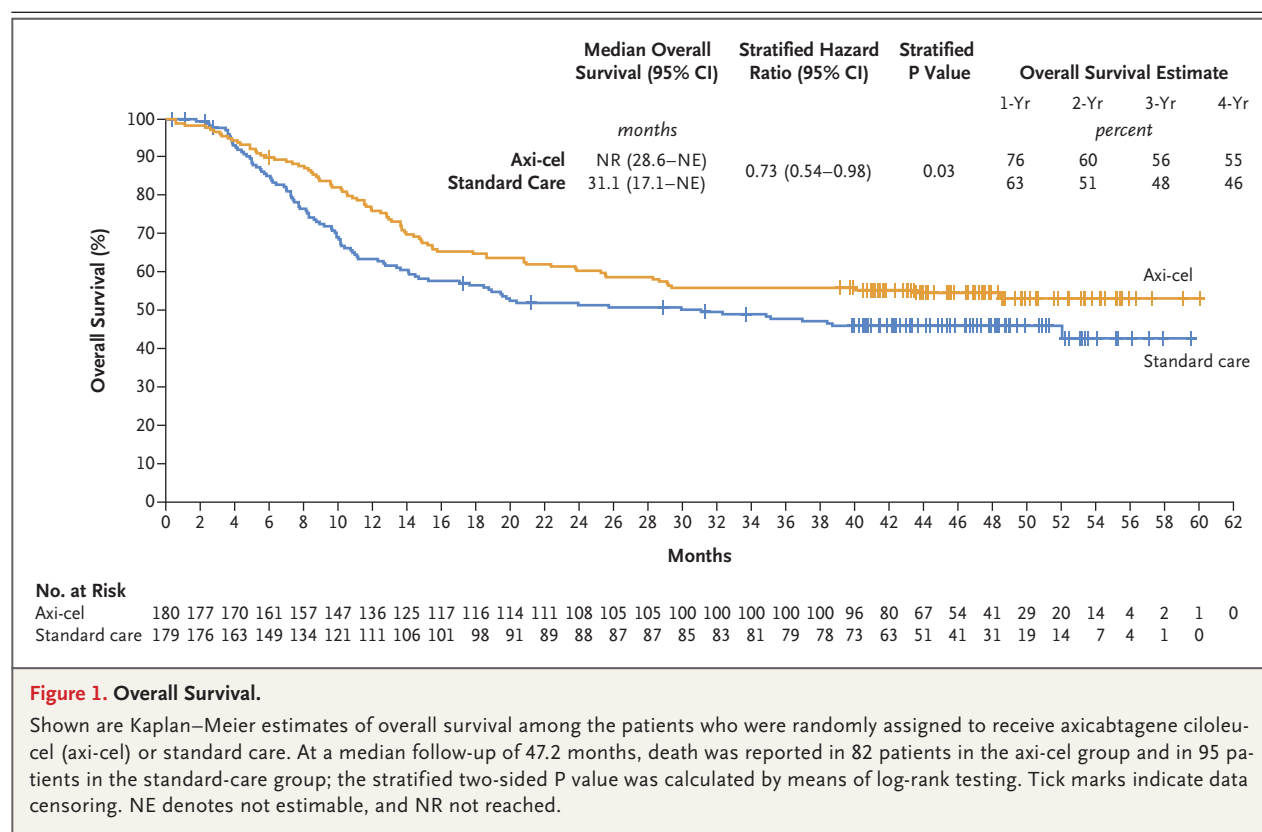c and disease characteristics of the patients at baseline were similar in the two groups. The proportion of patients who were non-Hispanic White was larger than the proportions of other races or ethnic groups in the two trial groups (Table S2). High-risk features were common, including 73.5% of the patients with disease refractory to first-line therapy, 30.4% with an age of 65 years or older, and 19.5% with high-grade B-cell lymphomas that included double-hit lymphomas (i.e., containing rearrangement of *MYC* with either *BCL2* or *BCL6*, according to the World Health Organization 2016 classification[9]) according to local pathological review.

EFFICACY

At a median follow-up of 47.2 months (range, 39.8 to 60.0), death had been reported in 82 patients in the axi-cel group and in 95 patients in the standard-care group. The primary analysis of overall survival showed a significant improvement in overall survival with axi-cel over standard care (hazard ratio for death, 0.73; 95% confidence interval [CI], 0.54 to 0.98; P=0.03 by stratified two-sided log-rank test). The estimated overall survival at 4 years was 54.6% (95% CI, 47.0 to 61.6) with axi-cel and 46.0% (95% CI, 38.4 to 53.2) with standard care (Table S3). The median overall survival was not reached (95% CI, 28.6 months to not estimable) with axi-cel and was 31.1 months (95% CI, 17.1 to not estimable) with standard care (Fig. 1). Overall survival with axi-cel as compared with standard care is shown across key prespecified patient subgroups in Figure S1.

In the standard-care group, 102 patients (57.0%) received subsequent off-protocol cellular immunotherapy owing to disease progression or lack of response (Table S4). Of these patients, 79 (77.5%) received axi-cel (Table S5). Prespecified sensitivity analyses that were designed to assess the confounding effect of treatment switching on overall survival in the standard-care group showed an even greater overall survival benefit with axi-cel than with standard care (Fig. S2 and Supplementary Results).

Investigator-assessed progression-free survival confirmed the benefit of axi-cel over standard care, with a median progression-free survival of 14.7 months (95% CI, 5.4 to 43.5) with axi-cel and 3.7 months (95% CI, 2.9 to 5.3) with standard care (hazard ratio, 0.51; 95% CI, 0.38 to 0.67) (Fig. 2A). Estimated progression-free survival at 4 years was 41.8% (95% CI, 34.1 to 49.2) with

Figure 1. Overall Survival.

Shown are Kaplan–Meier estimates of overall survival among the patients who were randomly assigned to receive axicabtagene ciloleu-cel (axi-cel) or standard care. At a median follow-up of 47.2 months, death was reported in 82 patients in the axi-cel group and in 95 pa-tients in the standard-care group; the stratified two-sided P value was calculated by means of log-rank testing. Tick marks indicate data censoring. NE denotes not estimable, and NR not reached.

axi-cel and 24.4% (95% CI, 17.2 to 32.2) with stan-dard care. Median investigator-assessed event-free survival (distinct from the primary outcome of event-free survival according to central review[8]) was 10.8 months (95% CI, 5.0 to 25.5) with axi-cel and 2.3 months (95% CI, 1.7 to 3.1) with standard care, with an estimated 4-year event-free survival of 38.9% and 17.3%, respectively (hazard ratio, 0.42; 95% CI, 0.33 to 0.55) (Fig. 2B).
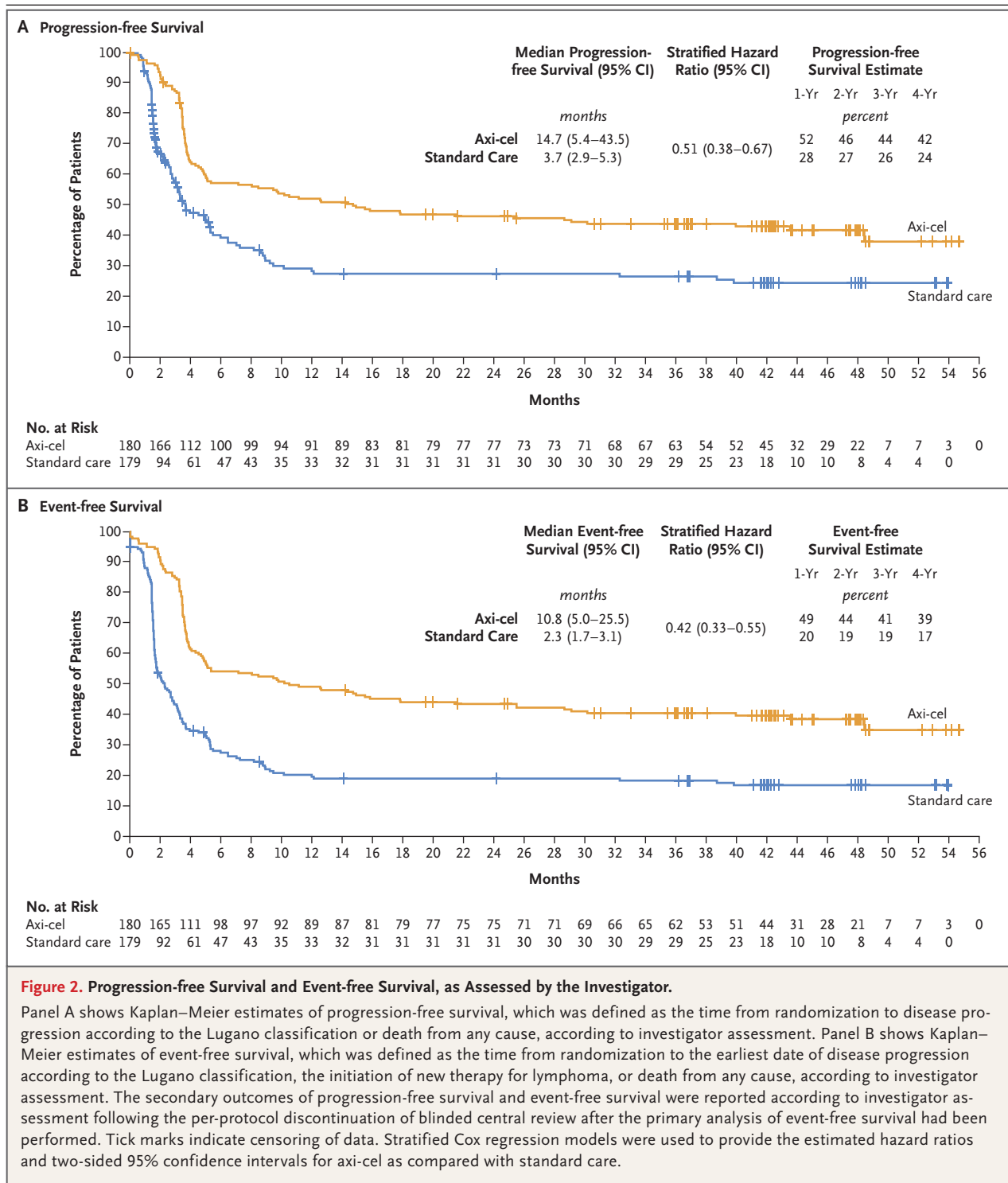
SAFETY

The safety analysis set included 170 patients who had received axi-cel and 168 who had received standard care. All the patients reported at least one adverse event; cumulative adverse events of any grade and of grade 3 or higher and serious adverse events are shown in Table S6 and Table S7, respectively. In the safety analysis set, 74 pa-tients in the axi-cel group and 91 patients in the standard-care group died since trial initiation (Table 1). Disease progression was the most com-mon cause of death in both the axi-cel group (51 patients) and the standard-care group (71 patients). A summary of all deaths that occurred since the

publication of the results of the primary analysis of event-free survival[8] is provided in Table S8.

Since the previous publication, no changes in cumulative treatment-related serious adverse events or treatment-related fatal adverse events occurred. Since the trial initiation, new or secondary can-cers were reported in 11 patients (8 in the axi-cel group and 3 in the standard-care group, includ-ing 1 patient with 2 new cancers) (Table S9). No cases of replication-competent retrovirus infec-tion were reported.

Infections of any grade were reported in 76 patients (44.7%) in the axi-cel group and in 53 (31.5%) in the standard-care group; infections of grade 3 or higher were reported in 28 patients (16.5%) and in 20 (11.9%), respectively (Table S10).

B-cell aplasia (undetectable B cells) occurred in 62.3% of the patients at 3 months and in 22.6% at 24 months after infusion in the patients in the axi-cel group who were evaluated for B-cell levels at these time points (Fig. 3 and Table S11). B-cell recovery was observed over time with wide interpatient variability. Median B-cell levels were at or below the lower limit of quantitation (0.017%)

A Progression-free Survival

	Median Progression-free Survival (95% CI)	Stratified Hazard Ratio (95% CI)	Progression-free Survival Estimate			
			1-Yr	2-Yr	3-Yr	4-Yr
	months		*percent*			
Axi-cel	14.7 (5.4–43.5)	0.51 (0.38–0.67)	52	46	44	42
Standard Care	3.7 (2.9–5.3)		28	27	26	24

No. at Risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56
Axi-cel	180	166	112	100	99	94	91	89	83	81	79	77	77	73	73	71	68	67	63	54	52	45	32	29	22	7	7	3	0
Standard care	179	94	61	47	43	35	33	32	31	31	31	31	31	30	30	30	30	29	29	25	23	18	10	10	8	4	4	0	

B Event-free Survival

	Median Event-free Survival (95% CI)	Stratified Hazard Ratio (95% CI)	Event-free Survival Estimate			
			1-Yr	2-Yr	3-Yr	4-Yr
	months		*percent*			
Axi-cel	10.8 (5.0–25.5)	0.42 (0.33–0.55)	49	44	41	39
Standard Care	2.3 (1.7–3.1)		20	19	19	17

No. at Risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56
Axi-cel	180	165	111	98	97	92	89	87	81	79	77	75	75	71	71	69	66	65	62	53	51	44	31	28	21	7	7	3	0
Standard care	179	92	61	47	43	35	33	32	31	31	31	31	31	30	30	30	30	29	29	25	23	18	10	10	8	4	4	0	

Figure 2. Progression-free Survival and Event-free Survival, as Assessed by the Investigator.

Panel A shows Kaplan–Meier estimates of progression-free survival, which was defined as the time from randomization to disease progression according to the Lugano classification or death from any cause, according to investigator assessment. Panel B shows Kaplan–Meier estimates of event-free survival, which was defined as the time from randomization to the earliest date of disease progression according to the Lugano classification, the initiation of new therapy for lymphoma, or death from any cause, according to investigator assessment. The secondary outcomes of progression-free survival and event-free survival were reported according to investigator assessment following the per-protocol discontinuation of blinded central review after the primary analysis of event-free survival had been performed. Tick marks indicate censoring of data. Stratified Cox regression models were used to provide the estimated hazard ratios and two-sided 95% confidence intervals for axi-cel as compared with standard care.

until 6 months after infusion and started to increase at 9 months, which coincided with the disappearance of or very low levels of CAR T cells in blood (median, approximately 0.1 cells per cubic millimeter at 9 months). Hypogammaglobulinemia was reported in 11.2% of the patients in the axi-

cel group and in 0.6% of those in the standard-care group (Table S12). Hypogammaglobulinemia that was prolonged (i.e., ≥6 months after the axi-cel infusion) was reported in 10 patients (5.9%). Intravenous immune globulin therapy was administered according to investigator discretion in 28 patients (16.5%) in the axi-cel group. Prolonged cytopenia (i.e., ≥6 months after the initiation of definitive therapy) of grade 3 or higher was reported in 8 patients (4.7%) in the axi-cel group, including 6 patients (3.5%) with prolonged neutropenia and 2 (1.2%) with prolonged anemia. Among the 62 patients who had undergone HDT-ASCT according to the protocol in the standard-care group, 1 (1.6%) had thrombocytopenia of grade 3 or higher at least 6 months after the initiation of definitive therapy (Table S13). No new cases of cytokine release syndrome or neurologic events were reported in either trial group since the primary event-free survival analysis (Table S6 and Supplementary Results).

EXPLORATORY TRANSLATIONAL ANALYSES

Peak CAR T-cell levels and area under the curve within the first 28 days after infusion were not significantly associated with overall survival (Fig. S3). In the axi-cel group, the overall survival benefit was independent of axi-cel product characteristics with two notable exceptions (Table S14): improved overall survival was associated with a greater proportion of juvenile or stem memory T-cell phenotype cells (CCR7+CD45RA+ T cells) in the axi-cel product (hazard ratio, 0.57; 95% CI, 0.36 to 0.92) (Fig. S4A) and with a lower proportion of differentiated T cells — specifically, effector memory cells (CCR7−CD45RA− T cells) (hazard ratio with increased median number, 1.8; 95% CI, 1.1 to 2.8) (Fig. S4B).

DISCUSSION

In this trial comparing two second-line curative treatment strategies for patients with early relapsed or refractory large B-cell lymphoma, axi-cel resulted in a 27.4% reduction in the risk of death and an absolute improvement in survival of 8.6 percentage points at 4 years. These findings showed the superiority of axi-cel over second-line platinum-based chemotherapy and autologous stem-cell transplantation, the longtime standard second-line treatment. Thus, axi-cel is

Table 1. Deaths among Treated Patients (Safety Analysis Population).*

Death	Axi-cel (N=170)	Standard Care (N=168)
	number of patients	
Total deaths	74	91
Progressive disease	51	71
Fatal adverse event	8	2
Covid-19	2	0
Sepsis	2†	0
Acute respiratory distress syndrome	0	1‡
Cardiac arrest	0	1‡
Hepatitis B reactivation	1§	0
Myocardial infarction	1	0
Pneumonia	1	0
Progressive multifocal leukoencephalopathy	1	0
New or secondary cancer	2¶	0
Other reason‖	13	18
Covid-19	4	4
Other infection or inflammation	3	7**
Neurologic organ failure	2	0
Respiratory organ failure	1	1
Cardiac organ failure	1	0
Cardiopulmonary and neurologic organ failure	0	1
Progressive disease	1††	0
Unknown	1	5

* The safety analysis population included all the patients who had received at least one dose of axicabtagene ciloleucel (axi-cel) or standard care according to the protocol. Covid-19 denotes coronavirus disease 2019.

† One patient who died of sepsis also had ongoing grade 3 myelodysplastic syndrome at the time of death.

‡ In this patient who received high-dose chemotherapy and underwent autologous stem-cell transplantation, the cause of death was considered by the investigator to be related to high-dose chemotherapy.

§ This patient had a history of hepatitis B virus (HBV) infection with positive hepatitis B core antibody and surface antigen, but HBV was undetectable on polymerase-chain-reaction assay at enrollment, so the patient met the trial eligibility criteria. The patient was treated with antiviral therapy for hepatitis B viremia and prophylaxis, which had been started during the patient's initial treatment with first-line rituximab-containing chemotherapy. After the discontinuation of entecavir, grade 5 fulminant hepatic failure occurred because of reactivation of HBV approximately 1 year after the administration of axi-cel.

¶ One patient died of acute myeloid leukemia, and one died of lung adenocarcinoma.

‖ This category includes fatal events that occurred outside the reporting period for adverse events.

** One patient died from infection with progressive disease.

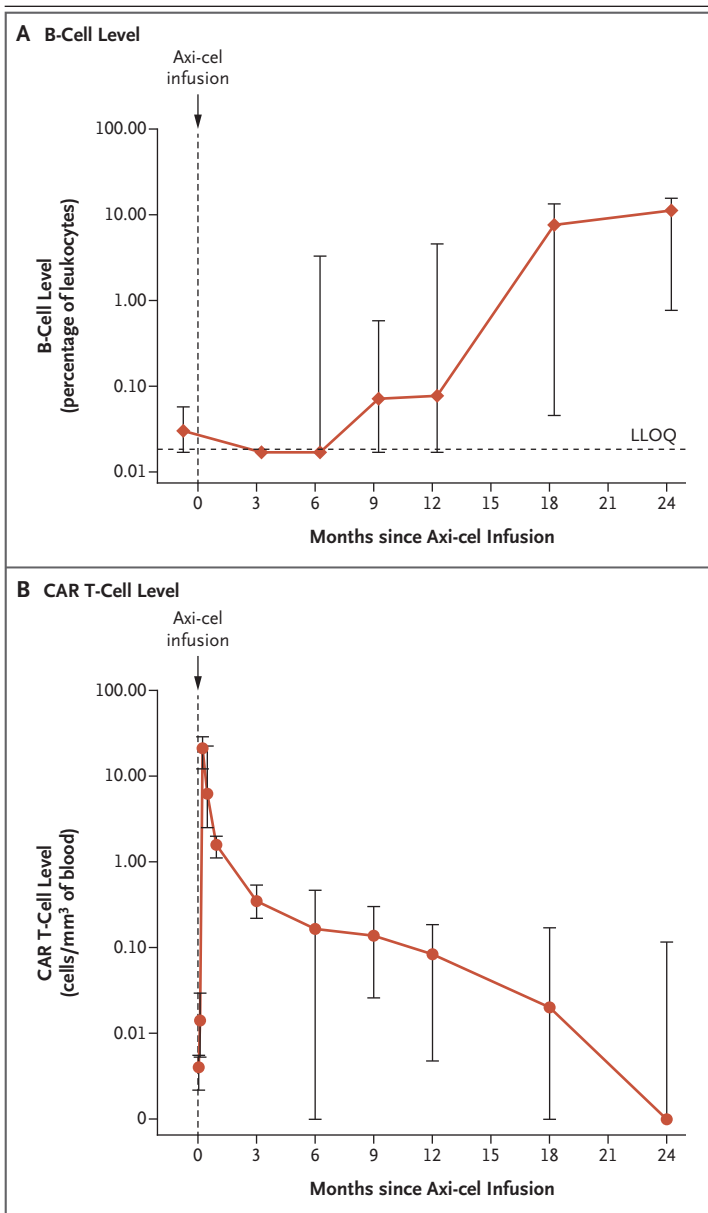†† This patient died from euthanasia that was performed because of progressive disease.

A B-Cell Level

Axi-cel infusion

B CAR T-Cell Level

Axi-cel infusion

Figure 3. CAR T-Cell and B-Cell Levels.

Shown are median $\log_{10}$ values for the percentage of B cells of total leukocytes (Panel A) and the number of chimeric antigen receptor (CAR) T cells targeting CD19 in blood (Panel B) from baseline to 24 months after axi-cel infusion among evaluable patients. The I bars indicate 95% confidence intervals. A value of 0.017% was the lower limit of quantitation (LLOQ).

Before the advent of CAR T-cell therapy, patients who were receiving second-line therapy for large B-cell lymphoma and who were unable to proceed to definitive therapy with HDT-ASCT had poor outcomes, with a median overall survival of 4.4 months.[5] Numerous attempts to improve survival for patients with second-line curative treatment had been unsuccessful. The most recent trial that showed a survival improvement was the 1995 Parma study, which was conducted before the approval of rituximab.[1] Thus, a new nonchemotherapy-based second-line approach was needed for patients with early relapsed or refractory large B-cell lymphoma, which prompted the design of the ZUMA-7 trial.

Historically, the estimated 3-year overall survival for patients receiving standard care was 39% for those with early relapse and 40% for those who had received previous rituximab treatment.[11] Among the patients in both categories, which included the population in ZUMA-7, 3-year survival was under 40%.[11,12] In contrast, among the patients in the standard-care group in ZUMA-7, the estimated 3-year overall survival was 48% at 3 years and 46% at 4 years, a difference from the findings in historical studies that may be due in part to the availability of subsequent cellular immunotherapy. Despite the increased survival in the standard-care group relative to historical studies, axi-cel increased survival over standard care. The frequency of subsequent cellular immunotherapy in our trial was similar to that in other contemporary randomized trials of anti-CD19 CAR T-cell therapies that included a protocol-specified crossover design.[13,14]

The improvement in overall survival with axi-cel over standard care was observed in the intention-to-treat population, which included patients with high-risk features known to confer a poor prognosis, such as disease refractory to first-line therapy, an age of 65 years or older, and high-grade B-cell lymphoma. The benefit of axi-cel in older patients is of particular interest, because patients who would otherwise be considered ineligible for definitive therapy with HDT-ASCT owing to their age may still qualify for CAR T-cell therapy and thus benefit from curative-intent therapy.[2,3,15] These findings confirm that age alone should not be a barrier for consideration of CAR T-cell therapy.[7,15-17] Other published analyses of data from ZUMA-7 showed that axi-cel was associated with improved quality-of-life measures

a second-line treatment option in this population on the basis of a significant improvement in survival, as opposed to a strategy of delaying cellular immunotherapy until after progression or an inadequate response to platinum-based chemotherapy.

as compared with standard care, including among patients who were 65 years of age or older.[15,18,19] Among all the patients in our trial, those who received axi-cel had a significantly longer time without symptoms or toxic effects, with a clinically important gain in quality-adjusted survival,[19] clinically meaningful improvements in quality of life, and faster recovery to baseline as compared with standard care.[18]

The long-term safety profile of axi-cel was consistent with data in previous studies.[7] The protocol-defined reporting period for adverse events ended with disease progression or the initiation of new lymphoma therapy, both of which were disproportionately more common in the standard-care group. Fewer patients in the standard-care group remained in the adverse-event reporting period in the trial, so cross-group comparisons of adverse events warrant cautious interpretation. With CD19-targeted CAR T-cell therapy, prolonged cytopenia and immune deficiency, including the induction of B-cell aplasia and infection, are anticipated and represent a class effect of these therapies owing to target antigen expression on nontumor cells.[6,20-22] The incidence of prolonged cytopenia of grade 3 or higher decreased over time, beginning at 6 months after axi-cel infusion, and B-cell recovery was observed over time in the majority of patients who received axi-cel. The observation of B-cell recovery implies that durable clinical benefit with axi-cel may not depend on the indefinite persistence of functional CAR T cells, a finding that is consistent with previous results in third-line or later treatment.[6]

Even though these toxic effects may be expected to decrease over time, the potential for long-term persistence and corresponding risk of complications require awareness. Clinical monitoring of patients treated with CAR T-cell therapy and potential use of intravenous immune globulin therapy may be important to mitigate the long-term risk of infection in light of the incidence of infections of grade 3 or higher, prolonged hypogammaglobulinemia, and B-cell aplasia with axi-cel. Furthermore, the death of a patient in the axi-cel group from reactivation of hepatitis B after late discontinuation of antiviral therapy (Table 1) highlights the importance of appropriate screening, monitoring for evidence of reactivation, and the use of prophylactic and suppressive antiviral medications in patients receiving B-cell–depleting agents, including anti-CD19 CAR T-cell therapy. Finally, although bone marrow toxic effects and secondary cancers are known potential complications of first- or second-line standard chemotherapy (including transplantation), the immunosuppressive nature of lymphodepleting chemotherapy within the axi-cel treatment regimen could also contribute to the risk of infection or secondary cancers, so additional investigation is warranted. In our trial, new cancers were observed in eight patients treated with axi-cel and in three patients treated with standard care (Table S9).

Our trial has several limitations. The proportion of patients who were non-Hispanic White was greater than the proportion of other racial or ethnic groups, which may reflect access to care and the general underrepresentation of diverse racial and ethnic groups in clinical trials (Table S2). Although favorable outcomes have been observed with axi-cel treatment regardless of race or ethnicity,[23,24] interventions that are aimed at increasing the enrollment of diverse racial and ethnic groups in trials should be encouraged, a strategy that is supported by recent guidance for industry from the Food and Drug Administration and the National Cancer Plan.[25] In addition, our trial had specific eligibility criteria, similar to most clinical studies. However, previous analyses of real-world use of axi-cel as third-line or later treatment have shown that patients who would have been ineligible for the registrational phase 1–2 ZUMA-1 trial were able to benefit from axi-cel.[26] Real-world data for axi-cel as second-line treatment are currently lacking but will be important to corroborate our findings.

The superiority of axi-cel over second-line platinum-based chemotherapy and HDT-ASCT is definitively shown by the primary analysis of overall survival, an objective outcome that is not subject to observer bias. Also encouraging was the stability of overall and progression-free survival at 4 years. However, although the use of axi-cel resulted in long-term survival in more than half of treated patients, it is important to continue to strive to improve patient outcomes. Axi-cel in an earlier line of treatment may benefit patients by providing a product with higher fitness — namely, with a greater proportion of T cells with more juvenile or stem memory phenotypes and an improved therapeutic index, as observed in patients with newly diagnosed high-grade large

B-cell lymphoma and other cancers.[16,27-32] These findings, coupled with the improvement in overall survival with axi-cel, highlight the importance of early referral for second-line axi-cel before the initiation of platinum-based chemotherapy.

We found that axi-cel as a second-line treatment for patients with early relapsed or refractory large B-cell lymphoma was superior to platinum-based chemotherapy and autologous stem-cell transplantation as a curative therapy.

APPENDIX

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REFERENCES

1. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995;333:1540-5.
2. Sehn LH, Salles G. Diffuse large B-cell lymphoma. N Engl J Med 2021;384:842-58.
3. Westin J, Sehn LH. CAR T cells as a second-line therapy for large B-cell lymphoma: a paradigm shift? Blood 2022; 139:2737-46.
4. Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. Hematology Am Soc Hematol Educ Program 2011; 2011:498-505.
5. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the international CORAL study. Bone Marrow Transplant 2016;51:51-7.
6. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axi-

cabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. Lancet Oncol 2019;20:31-42.
7. Neelapu SS, Jacobson CA, Ghobadi A, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood 2023;141:2307-15.
8. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med 2022;386:640-54.
9. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-90.
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;32:3059-68.
11. Gisselbrecht C, Glass B, Mounier N,

et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184-90.
12. van Imhoff GW, McMillan A, Matasar MJ, et al. Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: the ORCHARRD study. J Clin Oncol 2017;35:544-51.
13. Bishop MR, Dickinson M, Purtill D, et al. Second-line tisagenlecleucel or standard care in aggressive B-cell lymphoma. N Engl J Med 2022;386:629-39.
14. Kamdar M, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. Lancet 2022; 399:2294-308.

15. Westin JR, Locke FL, Dickinson M, et al. Safety and efficacy of axicabtagene ciloleucel versus standard of care in patients 65 years of age or older with relapsed/refractory large B-cell lymphoma. Clin Cancer Res 2023;29:1894-905.

16. Neelapu SS, Dickinson M, Munoz J, et al. Axicabtagene ciloleucel as first-line therapy in high-risk large B-cell lymphoma: the phase 2 ZUMA-12 trial. Nat Med 2022;28:735-42.

17. Lunning MA, Wang H-L, Hu Z-H, et al. Outcomes of axicabtagene ciloleucel in comparison with chemoimmunotherapy (CIT) in an elderly population for treatment of relapsed or refractory (r/r) large B-cell lymphoma (LBCL) after two or more lines of prior therapy. Blood 2022; 140:Suppl 1:1852-5.

18. Elsawy M, Chavez JC, Avivi I, et al. Patient-reported outcomes in ZUMA-7, a phase 3 study of axicabtagene ciloleucel in second-line large B-cell lymphoma. Blood 2022;140:2248-60.

19. Kersten MJ, Qiao Y, Shah R, et al. Quality-adjusted time without symptoms or toxicity: analysis of axicabtagene ciloleucel versus standard of care in patients with relapsed/refractory large B cell lymphoma. Transplant Cell Ther 2023;29(5): 335.e1-335.e8.

20. Strati P, Varma A, Adkins S, et al. Hematopoietic recovery and immune reconstitution after axicabtagene ciloleucel in patients with large B-cell lymphoma. Haematologica 2021;106:2667-72.

21. Stewart AG, Henden AS. Infectious complications of CAR T-cell therapy: a clinical update. Ther Adv Infect Dis 2021; 8:20499361211036773.

22. 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; 106:978-86.

23. Kato K, Makita S, Goto H, et al. Phase 2 study of axicabtagene ciloleucel in Japanese patients with relapsed or refractory large B-cell lymphoma. Int J Clin Oncol 2022;27:213-23.

24. Locke FL, Siddiqi T, Jacobson CA, et al. Real-world outcomes of axicabtagene ciloleucel (axi-cel) for the treatment of large B-cell lymphoma (LBCL) by race and ethnicity. J Clin Oncol 2022;40:Suppl 16: 7571. abstract.

25. Food and Drug Administration. Diversity plans to improve enrollment of participants from underrepresented racial and ethnic populations in clinical trials: draft guidance for industry, availability. April 2022 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations).

26. Jacobson CA, Locke FL, Ma L, et al. Real-world evidence of axicabtagene ciloleucel for the treatment of large B cell lymphoma in the United States. Transplant Cell Ther 2022;28(9):581.e1-581.e8.

27. Arcangeli S, Bove C, Mezzanotte C, et al. CAR T cell manufacturing from naive/stem memory T lymphocytes enhances antitumor responses while curtailing cytokine release syndrome. J Clin Invest 2022; 132(12):e150807.

28. Larson SM, Walthers CM, Ji B, et al. CD19/CD20 bispecific chimeric antigen receptor (CAR) in naive/memory T cells for the treatment of relapsed or refractory non-Hodgkin lymphoma. Cancer Discov 2023;13:580-97.

29. Ren H, Cao K, Wang M. A correlation between differentiation phenotypes of infused T cells and anti-cancer immunotherapy. Front Immunol 2021;12:745109.

30. Locke F, Rossi J, Neelapu S, et al. Tumor burden, inflammation, and product attributes determine outcomes of axi-cel in large B-cell lymphoma. Blood Adv 2020;4:4898-911.

31. Fraietta JA, Lacey SF, Orlando EJ, et al. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. Nat Med 2018;24:563-71.

32. Tantalo DG, Oliver AJ, von Scheidt B, et al. Understanding T cell phenotype for the design of effective chimeric antigen receptor T cell therapies. J Immunother Cancer 2021;9(5):e002555.

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