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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

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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

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ABSTRACT

Purpose: Older patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) may be considered ineligible for curative-intent therapy including high-dose chemotherapy with autologous stem-cell transplantation (HDT-ASCT). Here, we report outcomes of a preplanned subgroup analysis of patients ≥65 years in ZUMA-7.

Patients and Methods: Patients with LBCL refractory to or relapsed ≤12 months after first-line chemoimmunotherapy were randomized 1:1 to axicabtagene ciloleucel [axi-cel; autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy] or standard of care (SOC; 2–3 cycles of chemoimmunotherapy followed by HDT-ASCT). The primary endpoint was event-free survival (EFS). Secondary endpoints included safety and patient-reported outcomes (PROs).

Results: Fifty-one and 58 patients aged ≥65 years were randomized to axi-cel and SOC, respectively. Median EFS was greater with axi-cel versus SOC (21.5 vs. 2.5 months; median follow-up: 24.3 months; HR, 0.276; descriptive $P < 0.0001$). Objective response rate was higher with axi-cel versus SOC (88% vs. 52%; OR, 8.81; descriptive $P < 0.0001$; complete response rate: 75% vs. 33%). Grade ≥3 adverse events occurred in 94% of axi-cel and 82% of SOC patients. No grade 5 cytokine release syndrome or neurologic events occurred. In the quality-of-life analysis, the mean change in PRO scores from baseline at days 100 and 150 favored axi-cel for EORTC QLQ-C30 Global Health, Physical Functioning, and EQ-5D-5L visual analog scale (descriptive $P < 0.05$). CAR T-cell expansion and baseline serum inflammatory profile were comparable in patients ≥65 and <65 years.

Conclusions: Axi-cel is an effective second-line curative-intent therapy with a manageable safety profile and improved PROs for patients ≥65 years with R/R LBCL.

Introduction

Age can be a determining factor when using curative-intent therapy, in part due to increased toxicity (1–3). Historically, patients were frequently deemed transplant-ineligible based upon age due to an inability to tolerate the toxicities of high-dose chemotherapy, and recommended therapies for older patients were described as palliative with a very poor chance of long-term disease control (4). Older patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) are at risk of worse outcomes and an inability to tolerate second-line standard-of-care (SOC) chemotherapy-based treatment (1–3). Given the increased risk for toxicities with SOC treatment, including nausea, fatigue, and infections, quality of life (QoL) is significantly decreased after SOC-based regimens (5). Considering the median age at LBCL diagnosis is 66 years (2), there remains a large unmet need for effective and tolerable curative-intent therapies in older patients with R/R LBCL.

Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for the treatment of R/R LBCL in adult patients after ≥2 lines of systemic therapy. In addition, in the United States and the European Union, axi-cel is approved for LBCL that is refractory to or relapsed ≤12 months after

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Translational Relevance

Older patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) may be considered ineligible for curative-intent treatments such as high-dose chemotherapy with autologous stem-cell transplantation due to age and/or the presence of comorbidities that increase the risk of intolerable adverse events. In this preplanned subgroup analysis of patients aged ≥65 years enrolled in the ZUMA-7 trial of axicabtagene ciloleucel [axi-cel; an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy] versus standard of care (SOC) in second-line R/R LBCL, CAR T-cell expansion was comparable, with patients aged ≥65 years and axi-cel having significantly improved event-free survival and health-related quality of life over SOC. Although the pharmacodynamic (serum proinflammatory and immune-modulatory analytes, including cytokines and chemokines) profile of axi-cel was elevated post axi-cel infusion in patients ≥65 years versus patients <65 years, adverse events were manageable. Together, these results support axi-cel as a viable and effective curative-intent second-line treatment option for older patients with R/R LBCL.

first-line chemoimmunotherapy, based on the phase III ZUMA-7 (NCT03391466) study comparing axi-cel to SOC as second-line treatment in patients with R/R LBCL (6, 7). In the primary analysis of ZUMA-7, axi-cel significantly improved event-free survival (EFS) versus SOC (HR, 0.398, $P < 0.0001$), with a longer median EFS (8.3 vs. 2.0 months) and higher estimated 24-month EFS rate (40.5% vs. 16.3%; ref. 8). The adverse event (AE) profile of axi-cel was consistent with a prior axi-cel study in refractory LBCL (9).

Quality of life (QoL) is an important consideration for patients when selecting a therapeutic approach, and may be a determining factor for older patients. Second-line SOC is often associated with poor health-related QoL (10), and QoL further declines following chemotherapy (11, 12). Patient-reported outcome (PRO) instruments, including the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and EuroQoL 5-dimension questionnaire using a 5-level scale (EQ-5D-5L), are used in oncology clinical trials to assess cancer and/or cancer therapies' impact on health-related QoL. PRO data from clinical trials are considered by regulatory agencies during evaluation of new drug applications and development of product labeling (13–15). However, despite the potential usefulness of PRO data to inform treatment decisions, there is a lack of published literature on health-related QoL in R/R LBCL, especially in older patients. In ZUMA-7, axi-cel patients demonstrated clinically meaningful QoL improvement versus SOC patients (8).

Here, we report the results from a preplanned subgroup analysis of patients ≥65 years with R/R LBCL assessing clinical outcomes and PROs of second-line axi-cel versus SOC in the ZUMA-7 trial. In addition, we report levels of CAR T cells and serum markers of inflammation in patients ≥65 years compared with patients <65 years.

Patients and Methods

Patients

Full ZUMA-7 details were previously reported (8). Briefly, eligible patients were ≥18 years (no upper age limit), had LBCL confirmed by histology according to World Health Organization 2016 classification criteria (16), and were refractory to first-line treatment or had relapsed ≤12 months after completing first-line chemoimmunotherapy. Patients were intended to proceed to high-dose chemotherapy with autologous stem-cell transplantation (HDT-ASCT).

Trial design

All patients provided written informed consent. The trial was conducted after institutional review board approval of the protocol and in compliance with the Declaration of Helsinki. Patients were randomized 1:1 to receive axi-cel or investigator-selected SOC chemoimmunotherapy, stratified by response to first-line therapy and second-line age-adjusted International Prognostic Index (sAAIPI; ref. 8). Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) 5, 4, and 3 days before receiving an axi-cel infusion (target dose, 2×10^6 CAR T cells/kg). Optional bridging therapy was limited to glucocorticoids to isolate the effects of CAR T-cell therapy as second-line therapy (8). SOC patients received 2 to 3 cycles of protocol-defined, investigator-selected platinum-based chemoimmunotherapy. Patients who had a complete or partial response following chemoimmunotherapy proceeded to HDT-ASCT. Disease assessments per Lugano classification (17) occurred at time points specified from randomization. Although trial crossover between treatment groups was not planned, patients who did not respond to SOC could receive off-protocol treatment, including cellular immunotherapy.

Endpoints and assessments

The primary endpoint was EFS [time from randomization to the earliest date of disease progression according to the Lugano classification (17), new lymphoma therapy, death from any cause, or a best response of stable disease up to and including the response on day 150 assessment after randomization, per blinded central review]. Key secondary endpoints were objective response rate (ORR) and overall survival (OS). Other secondary endpoints were progression-free survival (PFS) and incidence of AEs, including cytokine release syndrome (CRS; ref. 18), neurologic events (19), and QoL.

Peak CAR T-cell levels and change over time were exploratory endpoints (8). Pharmacokinetic (PK) analysis of CAR T cells was performed by qPCR, as previously described (8, 20). Peak of anti-CD19 CAR T cells (cells/μL blood) was calculated as previously described (20). Serum cytokines, chemokines, and other inflammatory markers were analyzed with validated Meso Scale Discovery methods at MedPace. Peak of cytokine levels post baseline was defined as the maximum level of cytokines in serum attained after baseline up to week 4 postinfusion. AUC of cytokine levels from baseline to week 4 postinfusion was defined as the AUC in a plot of levels of cytokines against scheduled visits (from baseline to week 4 postinfusion). This AUC measured the total levels of cytokines over time. The trapezoidal rule was used to estimate AUC (21).

PRO instruments (EORTC QLQ-C30 and EQ-5D-5L; Supplementary Table S1) were administered at baseline, day 50, day 100, day 150, month 9, and every 3 months thereafter from randomization up to 24 months but were not required after an EFS event. PRO instrument analyses were conducted as previously reported for the full study population.

Statistical analysis

The primary efficacy analysis was previously reported (8), and analyses conducted for this preplanned subset analysis were similar. Multivariate analyses of EFS, ORR, OS, and PFS (per investigator assessment) were conducted to adjust for multiple covariates [gender,

disease type per investigator, molecular subgroup per investigator, lactate dehydrogenase, tumor burden (sum of product diameters per investigator, mm^2; ref. 22), and age (year)]. Reported here is an OS interim analysis that occurred at primary analysis of EFS; a prespecified sensitivity analysis of OS (rank preserving structure failure time model; ref. 23) was conducted to adjust for the confounding effect of treatment switching from SOC to cellular immunotherapy.

Prespecified hypotheses for PRO domains [EORTC QLQ-C30 Physical Functioning, EORTC QLQ-C30 Global Health Status/QoL, and EQ-5D-5L visual analog scale (VAS)] were tested as previously reported (24, 25). A mixed-effects model with repeated measures at day 100 and at subsequent time points conditional on statistical significance at the previous time point was used. A clinically meaningful change was defined as 10 points for each EORTC QLQ-C30 score, 7 points for each EQ-5D-5L VAS score, and 0.06 point for EQ-5D-5L index (26, 27). Sensitivity analyses were conducted to control for patterns of missingness (Model 2) and patterns of missingness with additional covariates (Model 3) to account for attrition over time.

Efficacy analyses were conducted according to the intention-to-treat principle and included randomized ZUMA-7 patients ≥65 years, with additional analyses conducted in patients ≥70 years. Safety analyses included randomized patients ≥65 years who received axi-cel or ≥1 dose of SOC therapy per protocol, analyzed by protocol therapy received. The QoL subgroup included patients ≥65 years who had a baseline PRO and ≥1 post-baseline measure completed (24, 25). CAR T-cell level analyses included axi-cel infused patients with ≥1 evaluable blood sample collected ≤1 month postinfusion.

Kaplan–Meier estimates for time-to-event endpoints were provided. Estimated HRs with two-sided 95% confidence intervals (CI) were calculated from a stratified Cox proportional-hazards model. Stratified log-rank *P* values (one-sided) were calculated for time-to-event endpoints. Response was evaluated with stratified Cochran–Mantel–Haenszel test. All reported *P* values are descriptive.

Data availability statement

Kite is committed to sharing clinical trial data with external medical experts and scientific researchers in the interest of advancing public health, and access can be requested by contacting medinfo@kitepharma.com.

Results

Patients

Of 359 patients randomized in the ZUMA-7 primary analysis, 109 patients were ≥65 years (axi-cel: 51 and SOC: 58; **Fig. 1**). Of those patients, 53 were ≥70 years (axi-cel: 26 and SOC: 27). As of March 18, 2021, the median follow-up from randomization was 24.3 months. The median age of all patients ≥65 years was 69 years (range, 65–81). Overall, 70% of patients had primary refractory disease. Baseline characteristics were generally balanced between the axi-cel and SOC arms, although more axi-cel versus SOC patients had high-risk features, including high sAAIPI 2–3 (53% vs. 31%), elevated lactate dehydrogenase (61% vs. 41%), and high-grade B-cell lymphoma (per investigator; 33% vs. 14%; **Table 1**).

The manufacturing success rate of axi-cel for patients ≥65 years was 100%. Of 51 patients randomized to axi-cel, 49 (96%) received axi-cel. Among 58 patients randomized to SOC, 55 (95%) initiated second-line chemoimmunotherapy and 20 (34%) reached HDT-ASCT (**Fig. 1**). For patients who received axi-cel, median time from leukapheresis to product release (when the product passed quality testing and was made available to the investigator) was 12 days (range, 10–19) and median time from leukapheresis to delivery of axi-cel at study site was 18 days (range, 13–49; Supplementary Table S2). In patients ≥70 years, 24 (92%) axi-cel patients received axi-cel, and 6 (22%) SOC patients reached HDT-ASCT.

Efficacy

The primary endpoint of EFS in patients ≥65 years was significantly longer in the axi-cel versus the SOC arm (HR, 0.276; descriptive $P < 0.0001$; **Fig. 2A**) with a median EFS of 21.5 months [95% CI, 5.0–not estimable (NE)] vs. 2.5 months (95% CI, 1.6–3.2), respectively. The Kaplan–Meier estimate of the EFS rate at 24 months was 47.8% (95% CI, 33.2–61.0) in the axi-cel and 15.1% (95% CI, 7.1–25.8) in the SOC arm. The Kaplan–Meier estimate of the EFS rate at 12 months in patients ≥70 years was 42.3% (95% CI, 23.5–60.0) in the axi-cel and 3.7% (95% CI, 0.3–15.9) in the SOC arm (Supplementary Fig. S1A). Multivariate analyses showed similar EFS results when adjusted for baseline characteristics differences (HR, 0.23; 95% CI, 0.12–0.45; descriptive $P < 0.0001$). ORR was significantly higher in the axi-cel versus the SOC arm [88% vs. 52%; OR, 8.81 (95% CI, 2.71–32.14; descriptive $P < 0.0001$) in patients ≥65 years; **Fig. 2B**] and in patients ≥70 years (88% vs. 41%; descriptive $P < 0.001$; Supplementary Fig. S1B). After adjusting for differences in baseline characteristics among patients ≥65 years, odds of achieving objective response continued to favor axi-cel (OR, 9.61; 95% CI, 2.54–36.32; descriptive $P < 0.001$). Complete response (CR) rate was higher with axi-cel versus SOC [CR: 75% vs. 33%; OR, 8.95; 95% CI, 2.78–25.02; descriptive $P < 0.0001$) in patients ≥65 years; similar results were seen in patients ≥70 years (69% vs. 22%; descriptive $P < 0.01$).

In patients ≥65 years, OS, evaluated as a preplanned interim analysis, was prolonged in the axi-cel versus the SOC arm (HR, 0.517; 95% CI, 0.277–0.964; **Fig. 3A**). Similar results were seen in multivariate analysis after adjusting for differences in baseline characteristics (HR, 0.40; 95% CI, 0.18–0.90), and among patients ≥70 years (HR, 0.260; 95% CI, 0.097–0.698; Supplementary Fig. S2A). In patients ≥65 years, the Kaplan–Meier estimate of OS at 2 years was 64% and 51% in the axi-cel and SOC arm, respectively. Thirty-three (57%) SOC patients received commercially available or investigational CAR T-cell therapy off protocol as subsequent treatment. A sensitivity analysis adjusting for subsequent CAR T-cell therapy in the SOC arm also suggested an OS benefit for axi-cel versus SOC (HR, 0.364; 95% CI, 0.183–0.723; Supplementary Fig. S3).

The median PFS was 21.5 months (95% CI, 5.1–NE) for the axi-cel and 5.0 months (95% CI, 2.8–7.3) for the SOC arm (HR, 0.384; 95% CI, 0.214–0.691; descriptive $P = 0.0005$; **Fig 3B**) for patients ≥65 years. Multivariate analyses showed similar PFS results when adjusted for baseline characteristics differences (HR, 0.31; 95% CI, 0.15–0.64; descriptive $P < 0.002$). The estimated PFS at 2 years was 50% in the axi-cel and 30% in the SOC arm. In patients ≥70 years, median PFS was 11.4 months (95% CI, 4.1–NE) for the axi-cel and 2.7 months (95% CI, 1.7–5.0) for the SOC arm (HR, 0.206; 95% CI, 0.078–0.547; descriptive $P < 0.001$; Supplementary Fig. S2B).

Axi-cel significantly improved efficacy outcomes versus SOC in patients ≥65 years, which was comparable with the overall ZUMA-7 primary analysis population (Supplementary Table S3).

Safety

In the safety analysis population, all patients ≥65 years had ≥1 any grade AE. Grade ≥3 treatment-emergent AEs occurred in 46/49 (94%) axi-cel and 45/55 (82%) SOC patients. The most commonly reported grade ≥3 AE was neutropenia, which occurred in 39 of 49 (80%) axi-cel and 24 of 55 (44%) SOC patients (**Table 2**). Serious AEs occurred in

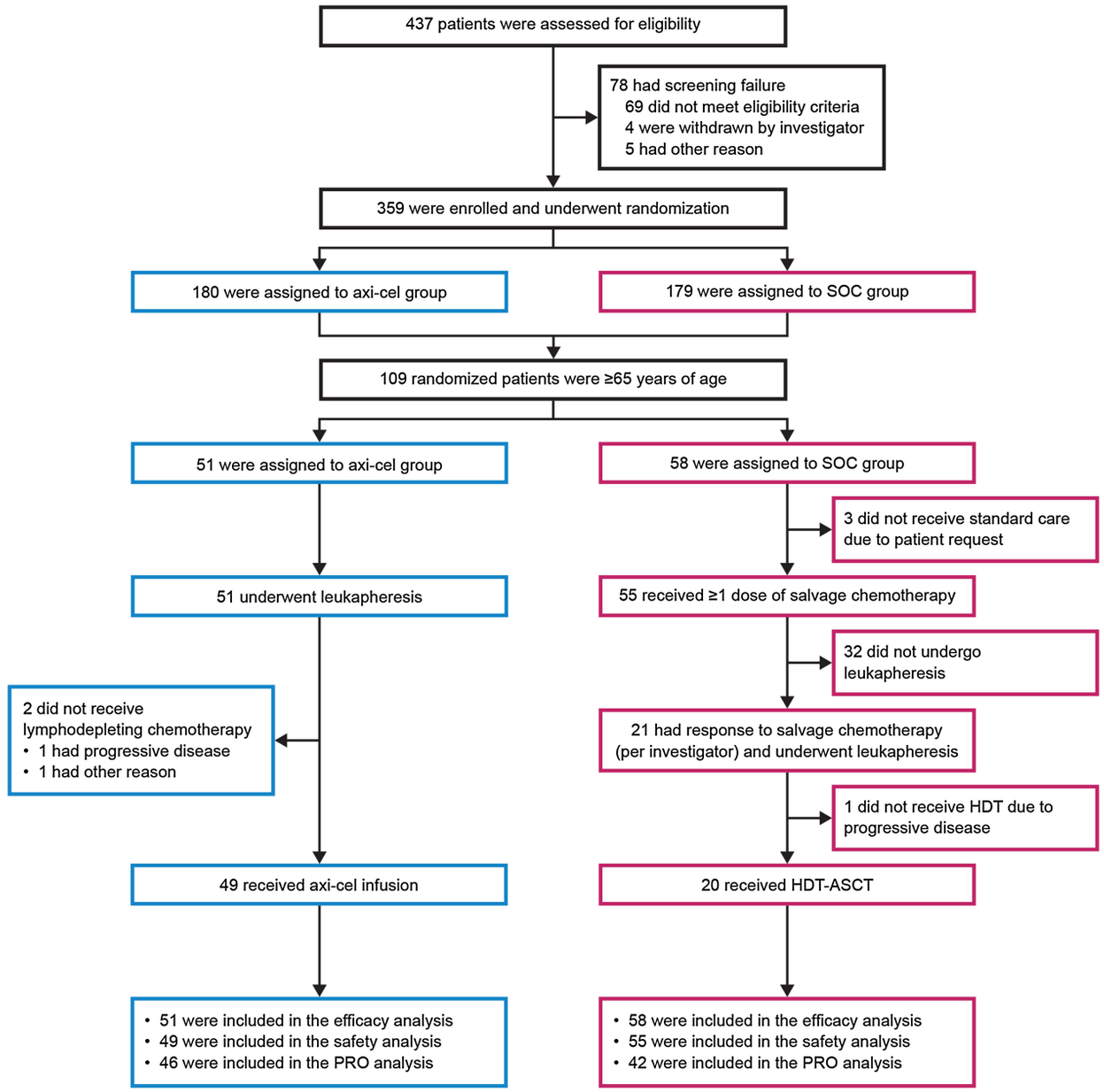

Figure 1.
Randomization, treatment, and follow-up of patients ≥65 years. Figure shows the disposition of patients ≥65 years randomized to axi-cel and SOC arms.

29 of 49 (59%) axi-cel and 26 of 55 (47%) SOC patients (Supplementary Table S4). Grade ≥3 prolonged cytopenias present ≥90 days after definitive therapy initiation occurred in 6 of 49 (12%) axi-cel and 2 of 20 (10%) SOC patients (Supplementary Table S5). Fatal events occurred in 21 axi-cel and 26 SOC patients (Supplementary Table S6). Grade 5 treatment-related AEs occurred in 0 axi-cel and in 1 (cardiac arrest) SOC patient.

In patients ≥65 years, CRS occurred in 48 of 49 (98%) axi-cel patients, with grade ≥3 CRS occurring in 4 of 49 (8%) patients (**Table 2**). Tocilizumab was administered to 67%, glucocorticoids to 29%, and vasopressors to 6% of axi-cel patients for CRS management. The median time to onset of CRS was 3 days (range, 1–10), and the median duration was 8 days (range, 3–22). No deaths related to CRS occurred.

Neurologic events occurred in 32 of 49 (65%) axi-cel and 14 of 55 (25%) SOC patients (**Table 2**). Grade ≥3 neurologic events occurred in 13 of 49 (27%) axi-cel and 1 of 55 (2%) SOC patients. In the axi-cel arm, glucocorticoids were used in 45% of patients for the management of neurologic events. The median time to onset of neurologic events was 7 days (range, 2–12) in the axi-cel arm and 26 days (range, 2–108) in the SOC arm; the median duration was 9 days (range, 2–817) and 39 days (range, 1–253), respectively. Unresolved neurologic events at 30 days occurred in 6 patients in the axi-cel arm (confusional state, tremor, lethargy, mental status changes, tremor, and cognitive

Table 1. Baseline characteristics in patients ≥65 years.[a]

Characteristic	Axi-Cel, *N* = 51	SOC, *N* = 58	Overall, *N* = 109
Median age (range), years	70 (65–80)	69 (65–81)	69 (65–81)
Male sex, *n* (%)	28 (55)	39 (67)	67 (61)
Race or ethnic group, *n* (%)[b]			
American Indian or Alaska Native	0	1 (2)	1 (1)
Asian	2 (4)	2 (3)	4 (4)
White	47 (92)	54 (93)	101 (93)
Other	2 (4)	1 (2)	3 (3)
Hispanic or Latino ethnic group, *n* (%)[b]			
Yes	3 (6)	4 (7)	7 (6)
No	47 (92)	53 (91)	100 (92)
Not reported	1 (2)	1 (2)	2 (2)
ECOG performance status score of 1, *n* (%)[c]	26 (51)	22 (38)	48 (44)
Disease stage, *n* (%)			
I-II	9 (18)	14 (24)	23 (21)
III-IV	42 (82)	44 (76)	86 (79)
sAAIPI of 2–3, *n* (%)[d,e]	27 (53)	18 (31)	45 (41)
Molecular subgroup according to central laboratory, *n* (%)[f]			
Germinal center B-cell–like	32 (63)	34 (59)	66 (61)
Activated B-cell–like	3 (6)	3 (5)	6 (6)
Unclassified	4 (8)	3 (5)	7 (6)
Not applicable	7 (14)	7 (12)	14 (13)
Missing data	5 (10)	11 (19)	16 (15)
Disease type according to central laboratory, *n* (%)			
DLBCL not otherwise specified/without further classification possible[g]	33 (65)	42 (72)	75 (69)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	12 (24)	7 (12)	19 (17)
Not confirmed or missing data	5 (10)	7 (12)	12 (11)
Other	1 (2)	2 (3)	3 (3)
Disease type according to the investigator, *n* (%)			
DLBCL not otherwise specified	27 (53)	40 (69)	67 (61)
T-cell/histiocyte-rich LBCL	0	1 (2)	1 (1)
Large cell transformation from follicular lymphoma[h]	7 (14)	9 (16)	16 (15)
HGBL with/without *MYC* and *BCL2* and/or *BCL6* rearrangement	17 (33)	8 (14)	25 (23)
Prognostic marker according to central laboratory, *n* (%)			
HGBL, double or triple hit	12 (24)	7 (12)	19 (17)
Double-expressor lymphoma	20 (39)	23 (40)	43 (39)
MYC rearrangement	4 (8)	2 (3)	6 (6)
Not applicable	15 (29)	21 (36)	36 (33)
Missing data	0	5 (9)	5 (5)
Response to 1L therapy, *n* (%)[e]			
Primary refractory	37 (73)	39 (67)	76 (70)
Relapse ≤12 months after initiation or completion of 1L therapy	14 (27)	19 (33)	33 (30)
Bone marrow involvement, *n* (%)[i]	1 (2)	4 (7)	5 (5)
Elevated LDH level, *n* (%)[j]	31 (61)	24 (41)	55 (50)
Median tumor burden (range), mm^{2}[k]	1826 (181–22538)	1722 (252–16649)	1775 (181–22538)

Abbreviations: 1L, first-line; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HGBL, high-grade B-cell lymphoma; LDH, lactate dehydrogenase; sAAIPI, second-line age-adjusted International Prognostic Index.

[a]Patients were randomly assigned to receive axi-cel or SOC. Percentages may not total 100 because of rounding.

[b]Race and ethnic group were determined by the investigator.

[c]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. Only patients with an ECOG performance status score of 0–1 were included in the study.

[d]Values are the sAAIPI at randomization, which were like the sAAIPI according to the investigator as entered into the clinical database. The sAAIPI is used to assess prognostic risk based on 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).

[e]As reported by investigator at time of randomization via Interactive Voice/Web Response System.

[f]The molecular subgroup as assessed by the investigator was as follows: germinal center B-cell–like in 28 patients (55%) in the axi-cel arm, 24 (41%) in the SOC arm, and 52 (48%) overall; non–germinal center B-cell–like in 15 (29%), 21 (36%), and 36 (33%), respectively. The molecular subgroup was not assessed in 8 patients (16%) in the axi-cel arm, 13 (22%) in the SOC arm, and 21 (19%) overall.

[g]The definition of DLBCL 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. DLBCL, not otherwise specified, according to the World Health Organization 2016 definition (16), is also included.

[h]Transformation was defined as the presence of large cells noted anywhere in the biopsy sample.

[i]The data shown were as collected on the diagnosis history case-report form.

[j]An elevated lactate dehydrogenase level was defined as a level that was above the upper limit of the normal range per local laboratory reference range.

[k]Tumor burden was determined on the basis of the sum of product diameters of the target lesions, according to the Cheson criteria (54) and was assessed by the central laboratory.

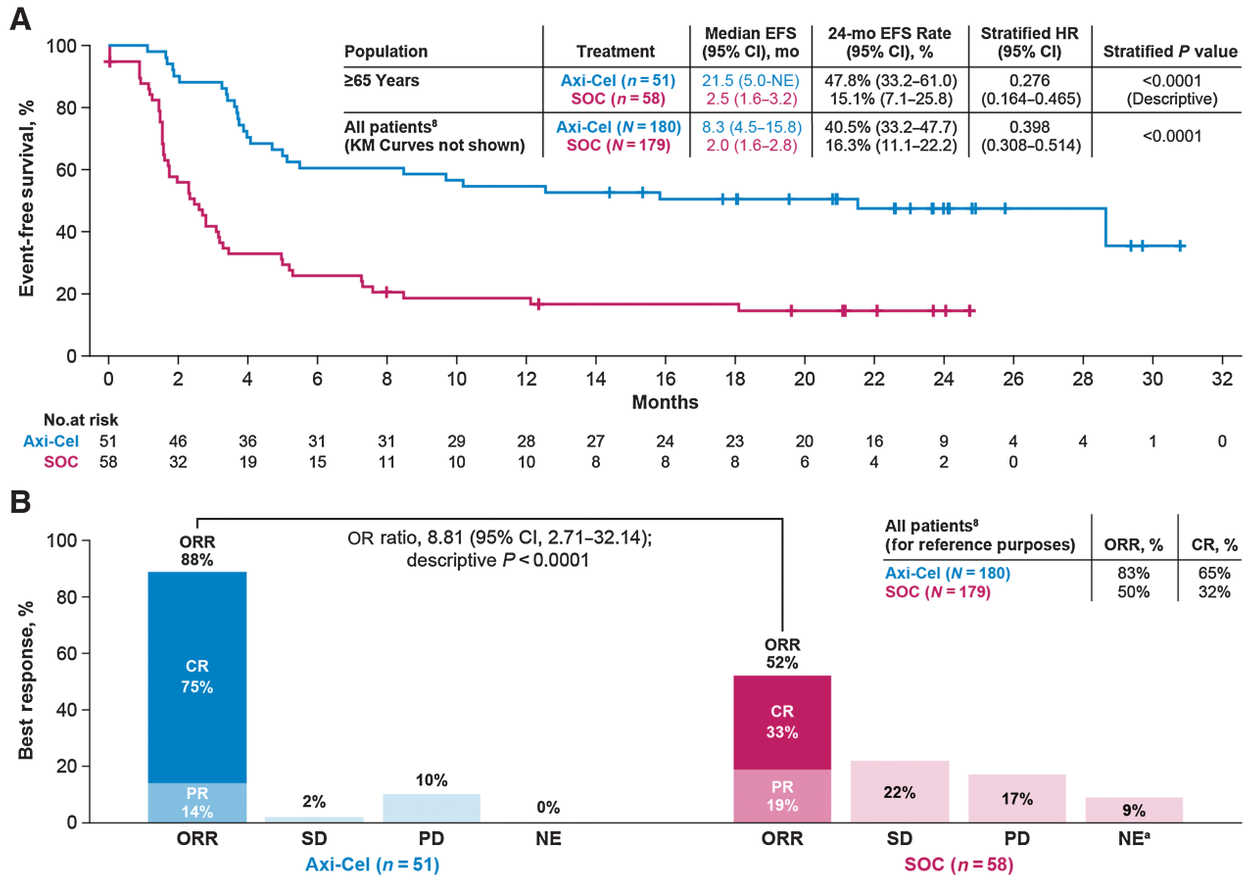

Figure 2.

Event-free survival per central review and ORR in patients ≥65 years**. A,** The Kaplan–Meier estimate of EFS by blinded central review in patients ≥65 years. EFS was defined as the time from randomization to the earliest date of disease progression according to the Lugano classification (17), new lymphoma therapy, death from any cause, or a best response of stable disease up to and including the response on day 150 assessment after randomization, per blinded central review. Tick marks indicate patients who did not meet the criteria for an event and were censored. **B,** Summary of best response by blinded central review in patients ≥65 years. [a] In the SOC arm, 1 patient had undefined disease, and 4 did not have response assessments completed. EFS, event-free survival; PD, progressive disease; PR, partial response; SD, stable disease.

disorder) and 5 patients in the SOC arm (paresthesia and somnolence). Unresolved neurologic events at 90 days occurred in 4 patients in the axi-cel arm (tremor, taste disorder, hypoesthesia, and cognitive disorder) and 4 patients in the SOC arm (visual hallucination, somnolence, delirium, and paresthesia). Unresolved neurologic events at the time of death or data cutoff occurred in 3 patients in the axi-cel arm (tremor, taste disorder, and hypoesthesia) and 1 patient in the SOC arm (paresthesia). No deaths related to neurologic events occurred.

The rates of grade ≥3 CRS and grade ≥3 neurologic events were numerically higher in patients aged ≥65 years compared with the overall ZUMA-7 population (Supplementary Table S3; ref. 8), although a formal statistical analysis was not prespecified or conducted. These results are consistent with the elevated serum inflammatory profile in patients aged ≥65 years compared with patients <65 years (Supplementary Table S7). CRS occurred in 98% and 8% for any grade and grade ≥3, respectively, in patients ≥65 years compared with 92% and 6% in the overall ZUMA-7 population. In the axi-cel arm, neurologic events occurred in 65% and 27% for any grade and grade ≥3, respectively, in patients ≥65 years compared with 60% and 21% in the overall ZUMA-7 population.

Among patients ≥70 years in the safety analysis set, all had AEs, with grade ≥3 AEs occurring in 22 of 24 (92%) axi-cel and 20 of 26 (77%) SOC patients (Supplementary Table S8). Fatal events occurred in 13 axi-cel and 15 SOC patients (Supplementary Table S9). CRS occurred in 24 of 24 (100%) patients who received axi-cel, with grade ≥3 CRS occurring in 2 of 24 (8%) patients (Supplementary Table S8). Neurologic events occurred in 18 of 24 (75%) axi-cel patients and in 5 of 26 (19%) SOC patients, with grade ≥3 neurologic events occurring in 8 of 24 (33%) and 0 patients, respectively (Supplementary Table S8).

Patient-reported outcomes

Eighty-eight patients ≥65 years met the criteria for the QoL analysis set (axi-cel, 46 patients; SOC, 42 patients). Baseline characteristics for the QoL analysis set were comparable among all patients ≥65 years (Supplementary Table S10). There was a clinically meaningful difference for patients ≥65 years in mean change of scores from baseline at day 100 in favor of axi-cel for the prespecified PRO domains EORTC QLQ-C30 Global Health (descriptive $P < 0.0001$), Physical Functioning (descriptive $P = 0.0019$), and EQ-5D-5L VAS (descriptive $P < 0.0001$; **Fig. 4A–C**) versus SOC. Similar results were observed with

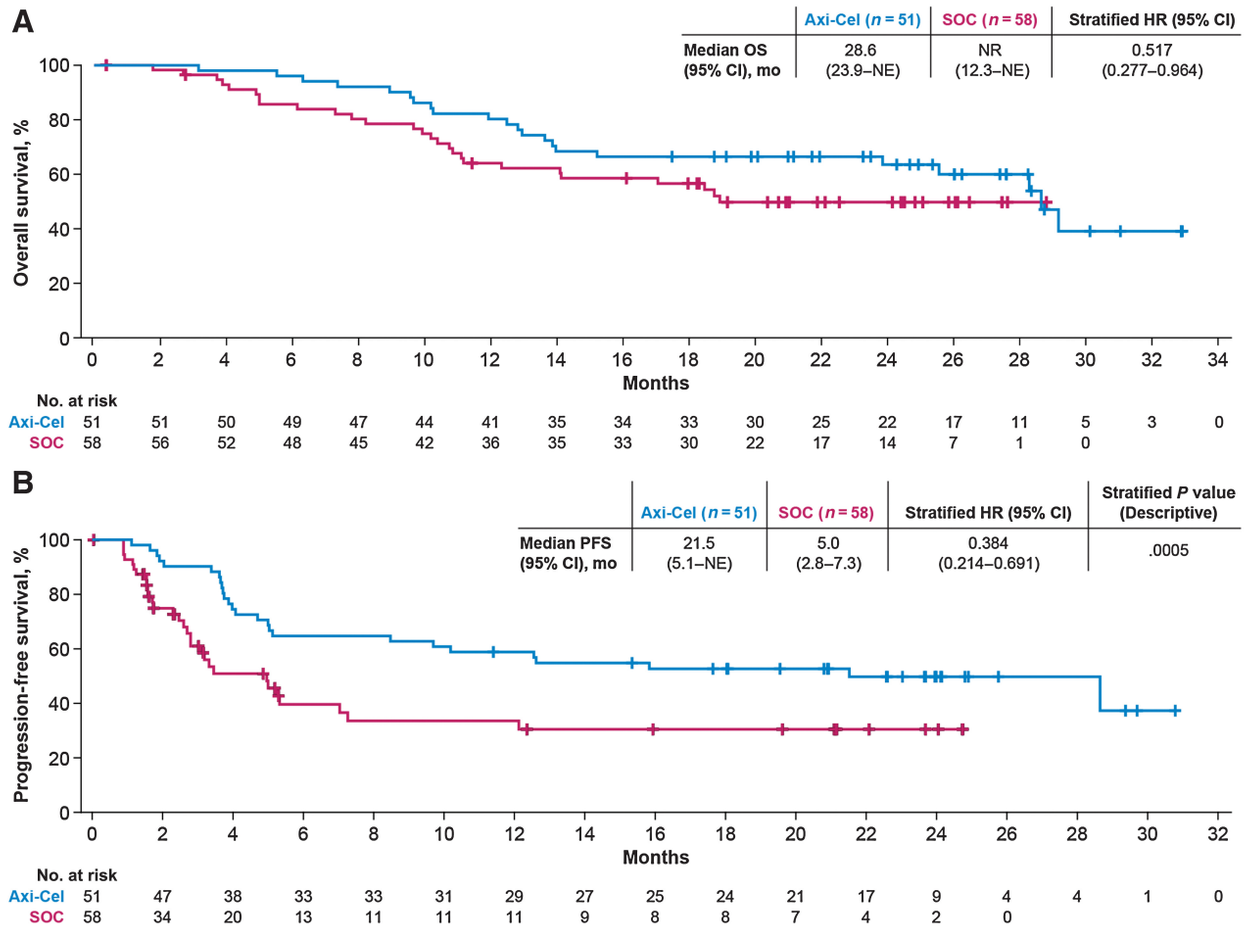

Figure 3.

OS (interim) and PFS in patients ≥65 years. **A,** Kaplan–Meier estimate of OS in patients ≥65 years. **B,** Kaplan–Meier estimate for PFS as assessed by investigator in patients ≥65 years. NR, not reached.

sensitivity analyses controlling for patterns of missingness and covariates (Supplementary Table S11). Scores also favored ($P < 0.05$) axi-cel over SOC at day 150 for all 3 domains and for Physical Functioning at month 9. By day 150, the mean estimated scores numerically returned to or exceeded baseline scores in the axi-cel arm. The QoL analysis set included 27 patients in the axi-cel arm and 19 patients in the SOC arm completing the questionnaires at day 150. Conversely, by month 15, the mean estimated scores never equaled or exceeded baseline scores in the SOC arm. In exploratory analyses of additional PRO domains, EORTC QLQ-C30 emotional functioning, appetite loss, and diarrhea, and EQ-5D Index at day 100; EORTC QLQ-C30 Role Functioning at day 100 and 150; and EORTC QLQ-C30 Social Functioning, Fatigue, and Dyspnea at day 100, 150, and month 9 (Supplementary Fig. S4) showed descriptive $P < 0.05$ for mean changes in scores in favor of axi-cel.

CAR T-cell levels and serum inflammatory profile

In patients ≥65 years, the median peak CAR T-cell level was 34.80 cells/μL, and median AUC from days 0–28 (AUC_{0-28}) following axi-cel infusion was 445.11 cells/μL× days (Supplementary Fig. S5). The expansion of CAR T cells in patients ≥65 years was comparable to patients <65 years (Supplementary Fig. S5).

The serum inflammatory profiles of patients ≥65 years versus patients <65 years were comparable at baseline. However, vascular cell adhesion protein 1 (VCAM-1) and IL7 were elevated at baseline in patients ≥65 years versus patients <65 years (VCAM-1: 706.9 ng/mL vs. 589.5 ng/mL, descriptive $P = 0.0005$ and IL7: 21.0 pg/mL vs. 18.5 pg/mL, descriptive $P = 0.049$; Supplementary Table S7). Post-infusion, C-X-C motif chemokine ligand 10, ferritin, IFNγ, IL2 receptor alpha, IL15, VCAM-1, GM-CSF, and VEGF, presented significantly ($P < 0.05$) higher peaks and/or AUC in patients ≥65 years versus <65 years (Supplementary Table S7). Association results were exploratory in nature. Nominal *P* values are descriptive, and results should be interpreted with caution.

Discussion

CAR T-cell therapy has dramatically changed the treatment landscape for patients with R/R LBCL, providing a curative-intent alternative to HDT-ASCT. However, after first-line therapy, older patients with R/R LBCL face barriers that may limit curative-intent therapies. For example, patients ≥65 years may be ineligible for stem cell transplantation due to an increased risk for toxicity or mortality, or due to regional and/or institutional guidelines that limit stem cell

Table 2. Most common AEs, CRS, and neurologic events in patients ≥65 years.

	Axi-Cel, $N = 49$		SOC, $N = 55$	
***n* (%)**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any AE	49 (100)	46 (94)	55 (100)	45 (82)
Pyrexia	47 (96)	4 (8)	14 (25)	0
Neutropenia[a]	39 (80)	39 (80)	24 (44)	24 (44)
Nausea	23 (47)	1 (2)	37 (67)	3 (5)
Anemia	22 (45)	19 (39)	32 (58)	25 (45)
Thrombocytopenia[b]	21 (43)	14 (29)	37 (67)	35 (64)
Leukopenia[c]	19 (39)	18 (37)	10 (18)	10 (18)
Fatigue	17 (35)	2 (4)	31 (56)	1 (2)
Diarrhea	17 (35)	1 (2)	24 (44)	0
Decreased appetite	18 (37)	2 (4)	19 (35)	2 (4)
Hypokalemia	16 (33)	7 (14)	17 (31)	5 (9)
Hypotension	23 (47)	6 (12)	8 (15)	1 (2)
Constipation	9 (18)	0	21 (38)	0
Headache	14 (29)	0	14 (25)	1 (2)
Hypophosphatemia	20 (41)	15 (31)	8 (15)	7 (13)
Cough	18 (37)	0	9 (16)	0
Edema peripheral	9 (18)	0	15 (27)	1 (2)
Vomiting	5 (10)	0	18 (33)	1 (2)
Chills	18 (37)	0	4 (7)	0
Hypocalcemia	16 (33)	0	6 (11)	0
Sinus tachycardia	18 (37)	1 (2)	4 (7)	0
Confusional state	19 (39)	6 (12)	2 (4)	0
Hypoxia	15 (31)	8 (16)	6 (11)	4 (7)
Hypomagnesemia	7 (14)	1 (2)	13 (24)	1 (2)
Acute kidney injury	7 (14)	1 (2)	12 (22)	3 (5)
Lymphocyte count decreased	10 (20)	10 (20)	7 (13)	7 (13)
Alanine aminotransferase increased	10 (20)	1 (2)	4 (7)	1 (2)
Hypoalbuminemia	10 (20)	1 (2)	4 (7)	0
Encephalopathy	12 (24)	7 (14)	1 (2)	0
Tremor	12 (24)	0	1 (2)	0
Febrile neutropenia	0	0	12 (22)	12 (22)
Hypogammaglobulinemia	10 (20)	0	1 (2)	0
Aphasia	10 (20)	3 (6)	0	0
CRS	48 (98)	4 (8)	—	—
Pyrexia	47 (98)	3 (6)	—	—
Hypotension	21 (44)	5 (10)	—	—
Sinus tachycardia	16 (33)	1 (2)	—	—
Chills	13 (27)	0	—	—
Hypoxia	12 (25)	6 (13)	—	—
Headache	8 (17)	0	—	—
Neurologic events	32 (65)	13 (27)	14 (25)	1 (2)
Confusional state	19 (39)	6 (12)	2 (4)	0
Encephalopathy	12 (24)	7 (14)	1 (2)	0
Tremor	12 (24)	0	1 (2)	0
Aphasia	10 (20)	3 (6)	0	0
Somnolence	5 (10)	3 (6)	2 (4)	0
Delirium	1 (2)	1 (2)	4 (7)	1 (2)
Paresthesia	0	0	5 (9)	0

Note: Shown are any adverse events of any grade that occurred in at least 20% of the patients in either the axi-cel arm or the SOC arm, as well as events of the CRS that occurred in at least 15% of the patients in the axi-cel arm and neurologic events of any grade that occurred in at least 15% of the patients in the axi-cel arm or at least 3% of those in the SOC arm. The severity of the CRS was graded according to Lee and colleagues (18). Neurologic events were identified with the use of a prespecified search list of preferred terms in the Medical 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 II study of blinatumomab (19). The severity of all adverse events, including neurologic events and symptoms of the CRS, was graded with the use of the Common Terminology Criteria for Adverse Events, version 4.03, of the NCI.

[a]Neutropenia refers to the combined preferred terms of neutropenia and neutrophil count decreased.

[b]Thrombocytopenia refers to the combined preferred terms of thrombocytopenia and platelet count decreased.

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

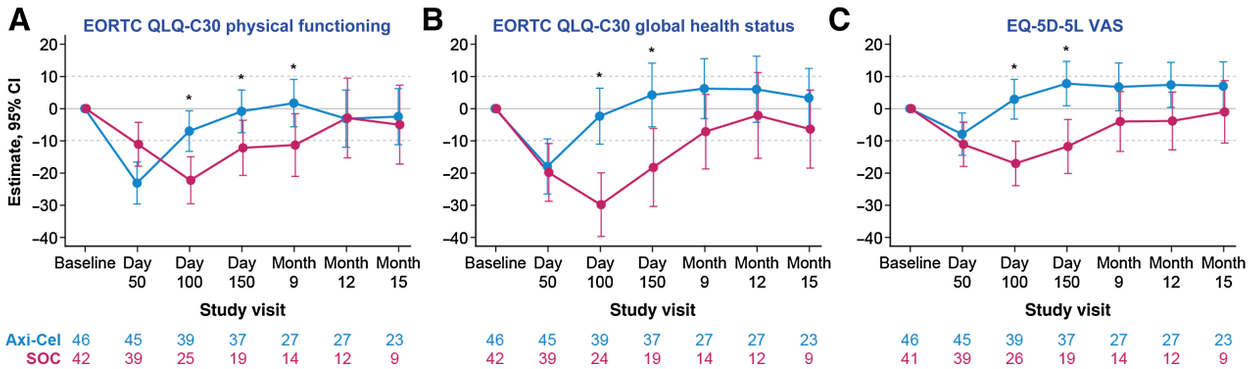

Figure 4.

Mixed model with repeated measures for change from baseline for prespecified patient-reported outcome endpoints in patients ≥65 years. Results were populated through month 15 due to lack of model convergence when using time points. Figures are based on Model 1. Horizontal lines, provided for clarity of interpretation, indicate the minimally important difference thresholds for clinically meaningful change. Mixed model includes variables for treatment, time, and treatment by time interaction (primary analysis) and is controlled for response to first-line therapy and age-adjusted IPI at screening. *, $P < 0.05$. **A,** The change from baseline of EORTC QLQ-C30 Physical Functioning in patients ≥65 years. **B,** The change from baseline of EORTC QLQ-C30 Global Health Status in patients ≥65 years. **C,** The change from baseline of EQ-5D-5L VAS in patients ≥65 years.

transplantation based upon age (5, 28–31). Historically, outcomes for patients considered "transplant-ineligible" were poor and therapy was described as palliative. Patients who are transplant-ineligible have almost no chance of survival or prolonged disease control (4). Even for those who are transplant-eligible, QoL is often negatively affected by adverse events associated with treatments, which often dissuades not only physicians, but also older patients themselves, from pursuing current SOC therapy options. In this analysis, axi-cel demonstrated superior efficacy over SOC in patients ≥65 years despite greater frequency of high-risk features in the axi-cel arm versus the SOC arm. Thus, we demonstrate that axi-cel is both feasible and effective in patients ≥65 years with R/R LBCL after first-line therapy, establishing a new SOC therapeutic option (32).

In ZUMA-7, the manufacturing success rate for patients ≥65 years was 100%, which was comparable to the overall population (8). In addition, in the axi-cel arm, 96% of patients ≥65 years received axi-cel, compared with 94% in the overall population (8). Peak CAR T cells and AUC_{0-28} for patients ≥65 years were comparable to that of patients <65 years, demonstrating that there are no technological limitations associated with axi-cel treatment for older patients. The serum inflammatory profiles for patients ≥65 years versus patients <65 years were comparable overall at baseline. However, VCAM-1 was elevated in patients ≥65 years, which is consistent with previous reports and may be due to an increased rate of vasculatory injury in older patients (33, 34).

Axi-cel had a manageable safety profile in patients ≥65 years that was consistent with previous clinical trials and real-world experience in adult patients of any age. This contrasts with the increased toxicity risk with chemotherapy in advanced age (9, 35), which in this study may be underreported due to outpatient monitoring during salvage chemotherapy (with few patients receiving HDT-ASCT, likely accounting for the lower rate of AEs, in general, in the SOC versus axi-cel arm) versus inpatient monitoring after axi-cel infusion. While incidence of CRS and neurologic events was numerically higher for patients ≥65 years compared with the overall population (8), incidence of CRS events of grade ≥3 was still relatively low (8%), even among a further subgroup of patients ≥70 years. Furthermore, neurologic events of grade ≥3 occurred in 27% of patients ≥65 years and 33% of patients ≥70 years. Importantly, there were no deaths due to neurologic events or CRS in axi-cel–treated patients ≥65 years. While the incidence of neurologic events appears to increase with age, only one-third of patients ≥70 years experienced grade ≥3 neurologic events. Nevertheless, future studies should focus on implementing strategies for better toxicity management, which may improve the axi-cel therapeutic index (36, 37).

Overall, toxicity in patients ≥65 years was manageable, despite elevation in some proinflammatory and immune-modulatory cytokines and chemokines, which are known to be associated with grade ≥3 toxicities (9, 38). Therefore, although a recent meta-analysis demonstrated that older patients are at a higher risk of immune effector cell–associated neurotoxicity syndrome compared with younger patients (39), the safety profile of axi-cel in this prospective randomized trial demonstrates that toxicities associated with neurologic events are manageable and that interventions that aim to minimize higher-grade toxicity for this patient population are effective.

The risk/benefit profile of therapies for elderly patients with R/R LBCL remains favorable, given limited therapeutic options with curative intent for this patient population and the potential for long-term survival with CAR T-cell therapies (32). With two products currently approved in second-line LBCL (7, 40) and additional CAR T-cell therapies possibly approved in the future, multiple options may become available in the near future. Therapy selection may therefore be dependent on clinical risk factors and predictive biomarkers of response and toxicity (20), which have yet to be fully elucidated. In the meantime, efforts to optimize management of adverse events, especially high-grade toxicities, are ongoing (36, 37, 41–44).

Axi-cel showed meaningful improvement in QoL over SOC; axi-cel patients showed faster recovery to pretreatment QoL, indicating satisfactory symptom resolution from the patient's perspective. These data suggest that axi-cel benefit over SOC is multifaceted and that efficacy and QoL together affect patients' overall sense of well-being. Although PRO measurements are becoming more common in oncology, including in third-line LBCL (45–48), there is a paucity of literature on health-related QoL in second-line LBCL, especially in older patients (10). In one study, patients with hematologic malignancies treated with CAR T-cell therapy reported superior short-term QoL compared with autologous or allogeneic stem cell transplantation (49). More PRO data comparing CAR

T-cell therapy with SOC are expected as second-line studies are completed (50, 51).

In this preplanned subgroup analysis, axi-cel demonstrated clinical benefit over SOC in a patient population with high unmet need. Nonetheless, there are limitations to our study. As previously published in a supplementary table describing the representativeness of our study's patient population (8), there was limited racial and ethnic diversity of patients in this trial, as with many clinical trials. Generally, however, the demographics of the participants in the ZUMA-7 study, including the median patient age, the ratio of males to females, and the proportion of non-Hispanic White patients, were consistent with that observed in clinical trials in this setting; though, ZUMA-7 enrolled a greater proportion of patients ≥65 years versus most of the studies analyzed (8). Notably, real-world studies in the third-line setting showed that axi-cel provides favorable outcomes in patients with LBCL regardless of race and ethnicity (52). Furthermore, axi-cel has demonstrated real-world effectiveness among patients ≥65 years (53), suggesting that axi-cel utility may extend beyond those patients fit enough for or those included within clinical studies. In addition, although PRO data are meaningful to assess patient experience, limitations are based on the implicit nature of self-reported measurements that are often not completed following an EFS event. Therefore, cautious interpretation of results is warranted, especially at later time points, as attrition due to disease progression, new lymphoma therapy, or death was disproportionately higher on the SOC arm and could contribute to a selection bias of patients with the best outcomes, which has the potential to overestimate the QoL of the SOC patient population.

In conclusion, the results presented herein demonstrated the clinical benefit of axi-cel over SOC for second-line treatment of R/R LBCL in patients ≥65 years. In ZUMA-7, older patients had clinical outcomes similar to the overall population, and axi-cel was associated with superior clinical efficacy and QoL versus SOC, with similar, manageable toxicity. In addition, patients ≥65 years and patients <65 years had comparable CAR T-cell expansion and serum inflammatory profiles at baseline. Although a number of serum inflammatory and immunemodulatory analytes were elevated post axi-cel infusion in patients ≥65 years compared with patients <65 years, toxicity was manageable. In patients ≥65 years, nearly triple the proportion of patients randomized to axi-cel received definitive therapy compared with those randomized to SOC. Taken together, these data suggest that age should not prohibit the consideration of cellular therapy for patients with LBCL. Historically, older patients were often deemed ineligible for curative-intent therapy with transplantation due to age and/or comorbidities; therefore, they have no other curative treatment options (5, 28–31). Our results clearly demonstrate that older patients can safely receive second-line therapy with axi-cel, and together with the superior efficacy and improvements in QoL that were observed (compared with SOC), these data suggest that axi-cel should be considered as second-line therapy for patients ≥65 with R/R LBCL.

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Note

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