Poster
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Improved Overall Survival With Axicabtagene Ciloleucel vs Standard of Care in Second-Line Large B-Cell Lymphoma Among the Elderly: A Subgroup Analysis of ZUMA-7

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BACKGROUND

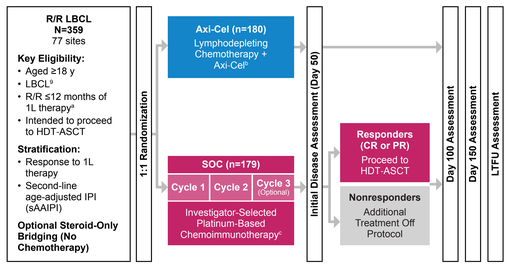
- The median age at large B-cell lymphoma (LBCL) diagnosis is 66 years, and outcomes worsen with increasing age[1]
- Older patients with relapsed or refractory (R/R) LBCL are often deemed ineligible for curative-intent autologous stem cell transplantation (ASCT) due to age and concern for increased toxicity related to comorbidities[2,3]
- For these reasons, new treatment options are needed
- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved in many countries for the treatment of LBCL that was refractory to first-line treatment or that had relapsed within 12 months after first-line chemoimmunotherapy and for R/R LBCL after ≥2 lines of systemic therapy[4,5]
- In ZUMA-7 (NCT03391466), the first randomized, global, multicenter, Phase 3 study of axi-cel versus standard of care (SOC; **Figure 1**) as second-line treatment in patients with early R/R LBCL, axi-cel showed significantly improved event-free survival (EFS) compared with second-line SOC (hazard ratio [HR], 0.398, *P*<.0001; median 8.3 versus 2.0 months, respectively; 24-month EFS rate: 41% versus 16%, respectively; 24.9-month median follow-up)[6]
  - Similar findings were observed among patients aged ≥65 years, whereby axi-cel was safely administered and resulted in improved EFS, response rates, and quality of life compared with SOC[7]
- At a median follow-up of 47.2 months, results from the ZUMA-7 primary overall survival (OS) analysis demonstrated superior OS in the intention-to-treat population (HR, 0.726; 95% CI, 0.540-0.977; one-sided *P*=.0168)[8]

OBJECTIVE

- To present updated efficacy and safety results from the primary OS analysis among ZUMA-7 patients aged ≥65 years and ≥70 years

METHODS

Figure 1. ZUMA-7 Study Schema and Endpoints[6]



[a] Refractory disease was defined as no CR to 1L therapy; relapsed disease was defined as CR followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy. [b] Axi-cel patients underwent leukapheresis followed by lymphodepleting chemotherapy with cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10⁶ CAR T cells/kg). [c] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [d] EFS was defined as time from randomization to the earliest date of disease progression per Lugano Classification,[10] commencement of new lymphoma therapy, or death from any cause.
1L, first line; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; EFS, event-free survival; HDT-ASCT, high-dose chemotherapy with autologous stem cell transplantation; IPI, International Prognostic Index; LTFU, long-term follow-up; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; R-ESHAP, rituximab, etoposide, methylprednisolone, cytarabine, and cisplatin; R-GDP, rituximab, gemcitabine, dexamethasone, and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; R/R LBCL, relapsed/refractory large B-cell lymphoma; SOC, standard of care.

- In ZUMA-7, eligible patients were randomized 1:1 to axi-cel or SOC, and the primary OS analysis occurred 5 years after the first patient was randomized (01/25/2018) per protocol (**Figure 1**)
- A planned subgroup analysis of patients aged ≥65 years was conducted in addition to further analysis for those aged ≥70 years
- Multivariate analyses were performed to examine treatment efficacy with axi-cel compared with SOC after adjusting for multiple covariates, including sex, disease type, molecular subgroup, lactate dehydrogenase (LDH), tumor burden, and age
  - Strata for these analyses included second-line age-adjusted International Prognostic Index (sAAIPI), and relapsed versus refractory disease
- Exploratory analyses were conducted to determine the association between OS and axi-cel product characteristics for patients aged ≥65 years
  - The percentage of T cells was divided into subgroups based on median value
  - Stratified Cox regression models were used to provide the estimated HR and 2-sided 95% CI for high percentage (>median) relative to low percentage (≤median) of naive T cells (juvenile/stem memory phenotype; CCR7+CD45RA+)

RESULTS

Table 1. Baseline Patient and Disease Characteristics Among Elderly Patients

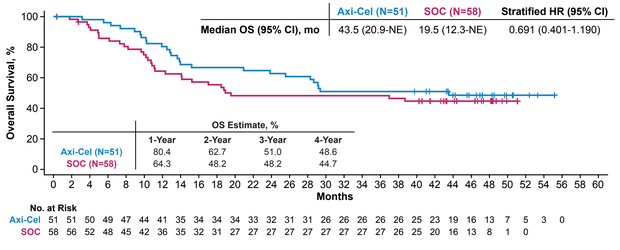
Characteristic	Axi-Cel, ≥65 Years N=51	SOC, ≥65 Years N=58	Overall, ≥65 Years N=109
Median age, years (range)	70 (65-80)	69 (65-81)	69 (65-81)
Sex, male, n (%)	28 (55)	39 (67)	67 (61)
Disease stage III-IV, n (%)	42 (82)	44 (76)	86 (79)
Derived sAAIPI total score of 2, n (%)	27 (53)	18 (31)	45 (41)
Response to 1L therapy,[a] n (%)			
Primary refractory	37 (73)	39 (67)	76 (70)
Relapse ≤12 months of 1L therapy	14 (27)	19 (33)	33 (30)
Disease type per investigator, n (%)			
DLBCL not specified	27 (53)	40 (69)	67 (61)
T-cell/histiocyte-rich LBCL	0 (0)	1 (2)	1 (1)
Large cell transformation from follicular lymphoma	7 (14)	9 (16)	16 (15)
HGBL with or without *MYC* and *BCL2* and/or *BCL6* rearrangement	17 (33)	8 (14)	25 (23)
Elevated LDH[b] level	31 (61)	24 (41)	55 (50)

[a] As reported by investigator at the time of randomization via Interactive Voice/Web Response System. [b] LDH level greater than upper limit of normal per local laboratory reference range.
1L, first line; axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma; HGBL, high-grade B-cell lymphoma; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; sAAIPI, second-line age-adjusted International Prognostic Index; SOC, standard of care.

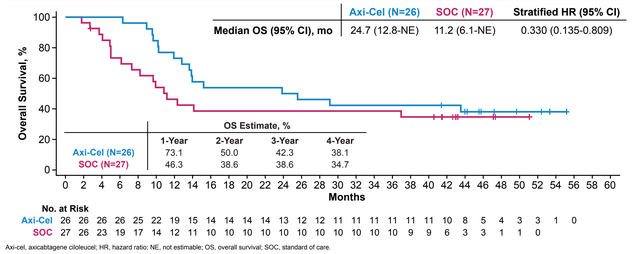
- A total of 109 patients aged ≥65 years were included in the ZUMA-7 elderly subgroup analysis (**Table 1**)
  - In the axi-cel arm, 51 patients were aged ≥65 years, 26 of whom were aged ≥70 years, and the maximum age was 80 years
  - In the SOC arm, 58 patients were aged ≥65 years, 27 of whom were aged ≥70 years, and the maximum age was 81 years
  - Compared with SOC patients at baseline, more axi-cel patients had high-risk features, including sAAIPI 2-3, elevated LDH, and high-grade B-cell lymphoma

Figure 2. OS of Axi-Cel Versus SOC in Patients Aged ≥65 Years and ≥70 Years

Patients Aged ≥65 Years



Patients Aged ≥70 Years

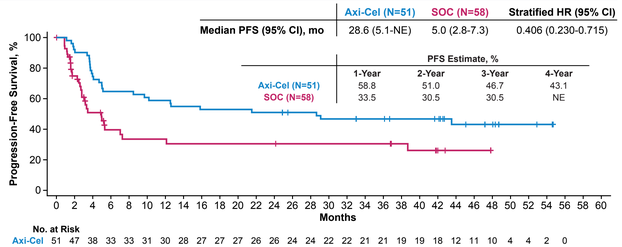


Axi-cel, axicabtagene ciloleucel; HR, hazard ratio; NE, not estimable; OS, overall survival; SOC, standard of care.

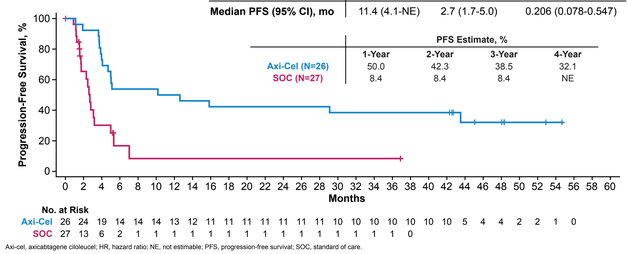
- At a median follow-up of 46.6 months, OS was prolonged in the axi-cel versus SOC arm in patients aged ≥65 years (HR, 0.691; 95% CI, 0.401-1.190) and for those ≥70 years (HR, 0.330; 95% CI, 0.135-0.809; **Figure 2**)
  - Similar results were observed using the piecewise Cox regression model (not shown)
- For patients aged ≥65 years, the median OS in the axi-cel arm was 43.5 months (95% CI, 20.9-not estimable [NE]) and 19.5 months (95% CI, 12.3-NE) in the SOC arm
- For patients aged ≥70 years, the median OS for axi-cel was 24.7 months (95% CI, 12.8-NE) and 11.2 months (95% CI, 6.1-NE) for SOC
- In the SOC arm, 57% and 52% of patients received subsequent cellular immunotherapy off protocol in patients aged ≥65 years and ≥70 years, respectively
- Sensitivity analysis adjusting for treatment switching in the SOC arm confirmed the OS benefit with axi-cel versus SOC for patients ≥65 years (HR, 0.449; 95% CI, 0.255-0.792)
- Multivariate analyses demonstrated an even greater OS benefit with axi-cel over SOC when adjusting for differences in baseline characteristics in patients aged ≥65 years (HR, 0.526; 95% CI, 0.266-1.041) and in patients aged ≥70 years (HR, 0.184; 95% CI, 0.045-0.755)

Figure 3. PFS of Axi-Cel Versus SOC in Patients Aged ≥65 Years and ≥70 Years

Patients Aged ≥65 Years



Patients Aged ≥70 Years



Axi-cel, axicabtagene ciloleucel; HR, hazard ratio; NE, not estimable; PFS, progression-free survival; SOC, standard of care.

- PFS assessed by investigator confirmed benefit of axi-cel over SOC in patients aged ≥65 years (HR, 0.406; 95% CI, 0.230-0.715) and in patients aged ≥70 years (HR, 0.206; 95% CI, 0.078-0.547; **Figure 3**)
- For patients aged ≥65 years, the median PFS was 28.6 months (95% CI, 5.1-NE) for the axi-cel arm and was 5.0 months (95% CI, 2.8-7.3) for the SOC arm
- For patients aged ≥70 years, the median PFS for axi-cel was 11.4 months (95% CI, 4.1-NE) and 2.7 months (95% CI, 1.7-5.0) for SOC

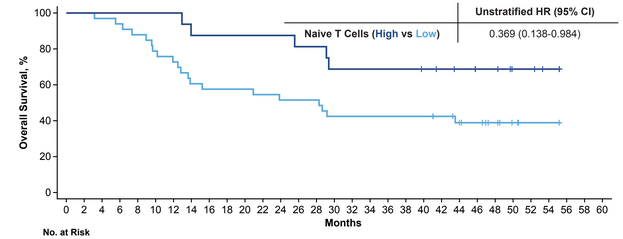
Table 2. Key Safety Data Among Elderly Patients Since Start of Treatment

	Axi-Cel, ≥65 Years N=49		SOC, ≥65 Years N=55	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
AEs of Interest, n (%)				
CRS	48 (98)	4 (8)	–	–
Neurologic event	33 (67)	13 (27)	14 (25)	1 (2)
Hypogammaglobulinemia	10 (20)	0 (0)	1 (2)	0 (0)
Cytopenia	41 (84)	41 (84)	45 (82)	42 (76)
Infections	30 (61)	14 (29)	21 (38)	9 (16)
Reason for Death, n (%)	25 (51)		29 (53)	
Progressive disease	20 (41)		20 (36)	
Grade 5 AE during protocol-specific reporting period	2 (4)[a]		1 (2)[b]	
New or secondary malignancy	1 (2)[c]		0 (0)	
Other reason for death	2 (4)[d]		8 (15)[e]	
Definitive therapy–related mortality	0 (0)		1 (2)[f]	

Data here are presented for the safety analysis set (ie, randomized patients who received axi-cel or ≥1 dose of SOC therapy per protocol). Any grade and Grade ≥3 AEs of interest, respectively, among patients ≥70 years in the axi-cel arm (N=24): 24 (100) and 2 (8) patients with CRS; 18 (75) and 8 (33) patients with neurologic events; and 13 (54) and 5 (21) patients with infections. Any grade and Grade ≥3 AEs of interest, respectively, among patients ≥70 years in the SOC arm (N=26): 5 (19) and 0 patients with neurologic events; and 10 (38) and 3 (12) patients with infections.
[a] Due to pneumonia (n=1) and COVID-19 (n=1). [b] Due to cardiac arrest. [c] Due to acute myeloid leukemia. [d] Due to COVID-19 (n=1) and natural progression from prior subdural hematoma, unrelated per investigator assessment to lymphodepleting chemotherapy and axi-cel (n=1). [e] Due to COVID-19 (n=4), cardiopulmonary arrest, subarachnoid hemorrhage and subdural hematoma (n=1), sepsis (n=1), urosepsis (n=1), and unknown cause of death (n=1). [f] Due to cardiac arrest.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; SOC, standard of care.

- The key safety data for this mature analysis of patients ≥65 years are shown in **Table 2** for the safety analysis set since start of treatment
- No new treatment-related deaths occurred among all patients, irrespective of age, since the primary EFS analysis[6]
- Fewer SOC patients remained in the adverse event (AE) reporting period post-progression or start of new lymphoma therapy; thus, cross-arm comparisons of AE rates warrant cautious interpretation
- There were no manufacturing failures for any patient who underwent leukapheresis

Figure 4. Association of OS With the Percentage of Naive T Cells in the Axi-Cel Product for Patients Aged ≥65 Years



Naive T cells refer to T cells with CCR7+CD45RA+ phenotype, indicative of more juvenile/stem memory T-cell phenotype.
Axi-cel, axicabtagene ciloleucel; HR, hazard ratio; OS, overall survival.

- Similar associations between product characteristics and outcomes were observed among the elderly and overall populations[9]
  - Improved OS was associated with a greater (>median) proportion of naive T cells (juvenile/stem memory phenotype; CCR7+CD45RA+) in the axi-cel product among patients aged ≥65 years (HR, 0.369; 95% CI, 0.138-0.984; **Figure 4**)

CONCLUSIONS

- Axi-cel as second-line therapy showed prolonged survival over SOC in patients aged ≥65 years, including in patients aged ≥70 years
  - In patients aged ≥65 years, improved OS was associated with a greater proportion of naive T cells in the axi-cel product
- Axi-cel had a manageable safety profile that was consistent with previous studies, regardless of age[8]
- These findings confirm that age alone should not be a barrier for consideration of CAR T-cell therapy, supporting the use of axi-cel as a curative-intent second-line therapeutic option for elderly patients with R/R LBCL

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DISCLOSURES

Full author disclosures are available through the virtual meeting platform