Abstract 54

Superiority of Axicabtagene Ciloleucel in Second-Line Large B-Cell Lymphoma in the Elderly

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BACKGROUND

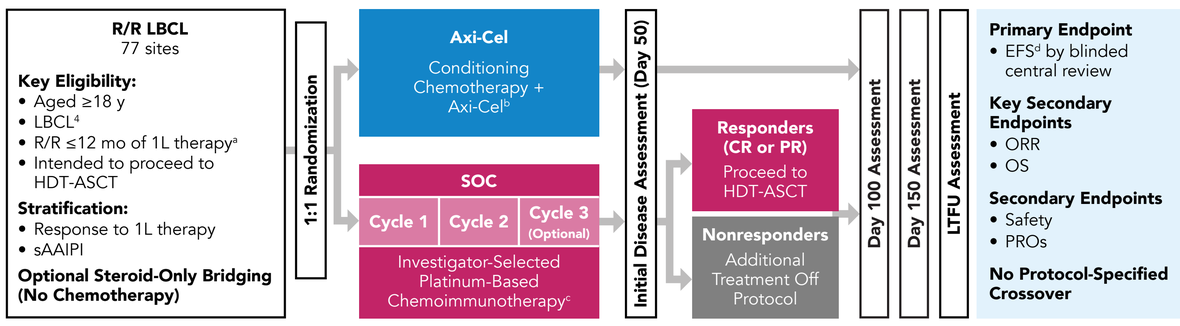
- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor T-cell therapy approved for the treatment of adult patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) after ≥2 lines of systemic therapy
- A minority of patients with R/R LBCL ultimately receive definitive therapy with high-dose chemoimmunotherapy and autologous stem cell transplantation (HDT-ASCT) due to low fitness or intolerability/lack of response to platinum-based salvage chemotherapy[1]
- The median age at LBCL diagnosis is 66 years[2]
- Age can be a determining factor in the decision to use curative therapy[2]
- For these reasons, new treatment options are needed, particularly among elderly patients
- ZUMA-7 (NCT03391466) is the first randomized, global, multicenter Phase 3 study of axi-cel versus standard of care (SOC) as second-line treatment in patients with R/R LBCL
- In ZUMA-7, axi-cel significantly improved event-free survival (EFS) compared with second-line SOC in R/R LBCL (hazard ratio [HR], 0.398, *P*<0.0001; median 8.3 vs 2 months, respectively; 24-month EFS rate: 41% vs 16%, respectively; 24.9-month median follow-up)[3]

OBJECTIVE

- To present the safety and efficacy outcomes in a planned subgroup analysis of ZUMA-7 patients aged ≥65 years

METHODS

Figure 1. ZUMA-7 Study Schema and Endpoints

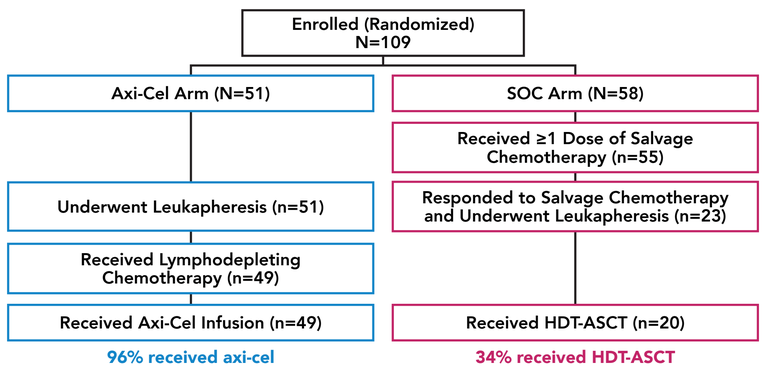


[a] Refractory disease was defined as no CR to 1L therapy; relapsed disease was defined as CR followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy. [b] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m²/day) and 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,[5] 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 chemoimmunotherapy and autologous stem cell transplantation; LBCL, large B-cell lymphoma; LTFU, long-term follow-up; ORR, objective response rate; OS, overall 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, cisplatin, and dexamethasone; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide phosphate; R/R, relapsed/refractory; sAAIPI, second-line age-adjusted International Prognostic Index; SOC, standard of care.

- Disease assessments by positron emission tomography and computed tomography scan per Lugano Classification[5] occurred at specified time points from randomization (**Figure 1**)
- Primary endpoint was EFS, defined as time from randomization to the earliest date of disease progression per Lugano Classification, commencement of new lymphoma therapy, or death from any cause
- Key secondary endpoints included objective response rate (ORR) and overall survival (OS)
- Safety and patient-reported outcomes were secondary endpoints
- Statistical testing of primary and key secondary endpoints was conducted hierarchically
  - Given statistically significant improvement in EFS, ORR was tested and given statistically significant improvement, OS was tested (interim analysis)
- Multivariate analyses were conducted to examine efficacy in treatment with axi-cel compared with SOC after adjusting for multiple covariates (treatment, gender, disease type, molecular subgroup, lactate dehydrogenase, tumor burden, and age)

RESULTS

Figure 2. ZUMA-7 Elderly Patient Disposition



Axi-cel, axicabtagene ciloleucel; HDT-ASCT, high-dose chemoimmunotherapy and autologous stem cell transplantation; SOC, standard of care.

- A total of 359 patients were enrolled in ZUMA-7 (N=180 and N=179 for axi-cel and SOC arms, respectively)
  - The subgroup analysis of patients aged ≥65 years included 109 patients (N=51 and N=58 for axi-cel and SOC arms, respectively; **Figure 2**)
- While 49/51 (96%) patients received axi-cel, only 20/58 (34%) received HDT-ASCT
- Axi-cel was successfully manufactured for all patients who underwent leukapheresis

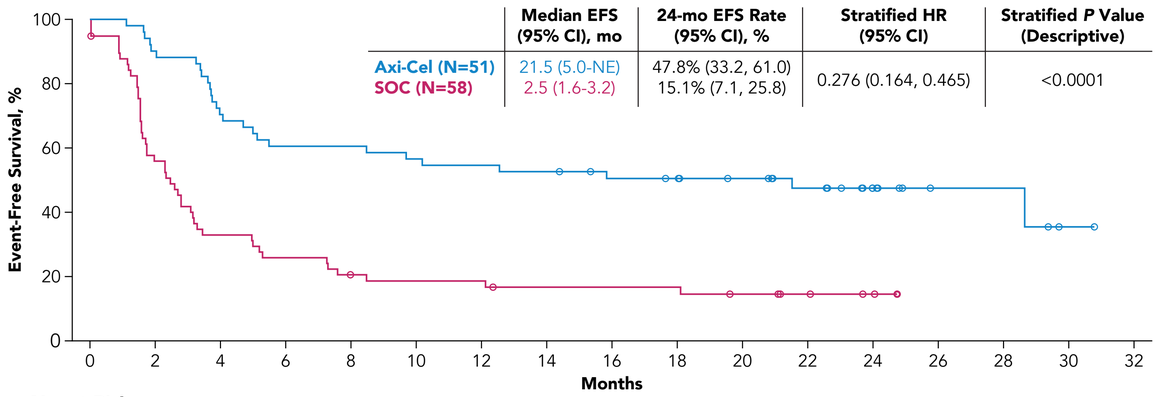
Table 1. Baseline Characteristics for Elderly Patients

Characteristic	Axi-Cel N=51	SOC N=58	Overall N=109
Median age (range), years	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)
sAAIPI of 2-3[a], 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/without *MYC* and *BCL2* and/or *BCL6* rearrangement	17 (33)	8 (14)	25 (23)
Elevated LDH level[b]	31 (61)	24 (41)	55 (50)

[a] As reported by 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.

- Compared with SOC patients at baseline, more axi-cel patients had high-risk features, including second-line age-adjusted International Prognostic Index 2-3 (53% vs 31%), elevated lactate dehydrogenase (61% vs 41%), and high-grade B-cell lymphoma (including double-/triple-hit lymphoma; 33% vs 14%; **Table 1**)

Figure 3. Primary Endpoint: Event-Free Survival per Blinded Central Review in Elderly Patients

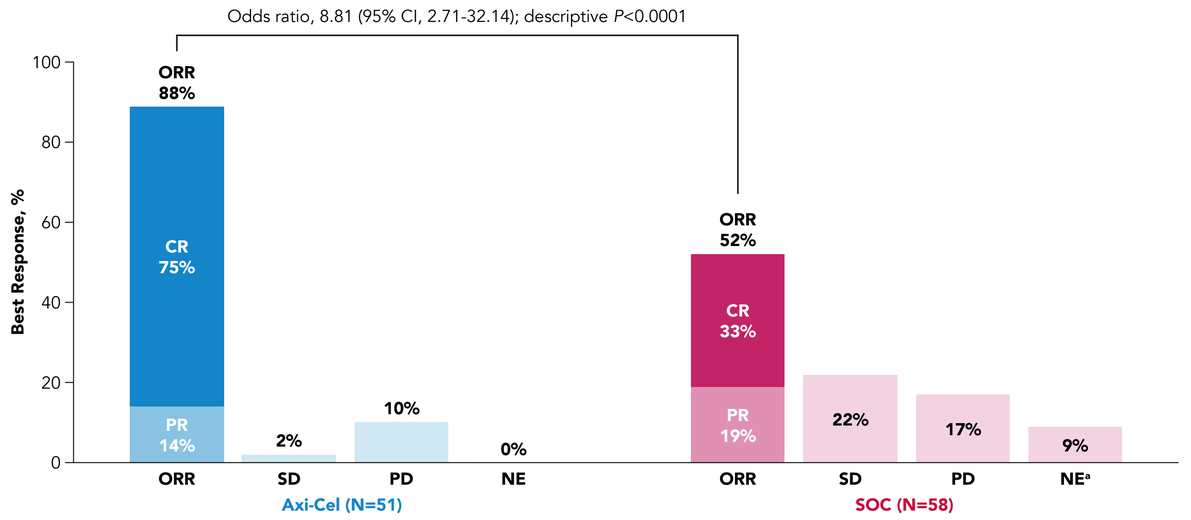


Axi-cel, axicabtagene ciloleucel; EFS, event-free survival; NE, not evaluable; SOC, standard of care.

- The primary endpoint of EFS showed that treatment with axi-cel was superior to SOC (HR, 0.276, *P*<0.0001; **Figure 3**)
- In elderly patients, with 24.3-months median follow-up, median EFS was longer with axi-cel versus SOC (21.5 months [95% CI, 5.0-not evaluable] vs 2.5 months [95% CI, 1.6-3.2], respectively)
- Kaplan-Meier estimates of the 24-month EFS rates were significantly higher for axi-cel than for SOC (47.8% vs 15.1%, respectively)
- Multivariate analyses showed similar EFS results when adjusting for differences in baseline characteristics (HR, 0.23, *P*<0.0001)

RESULTS *(Continued)*

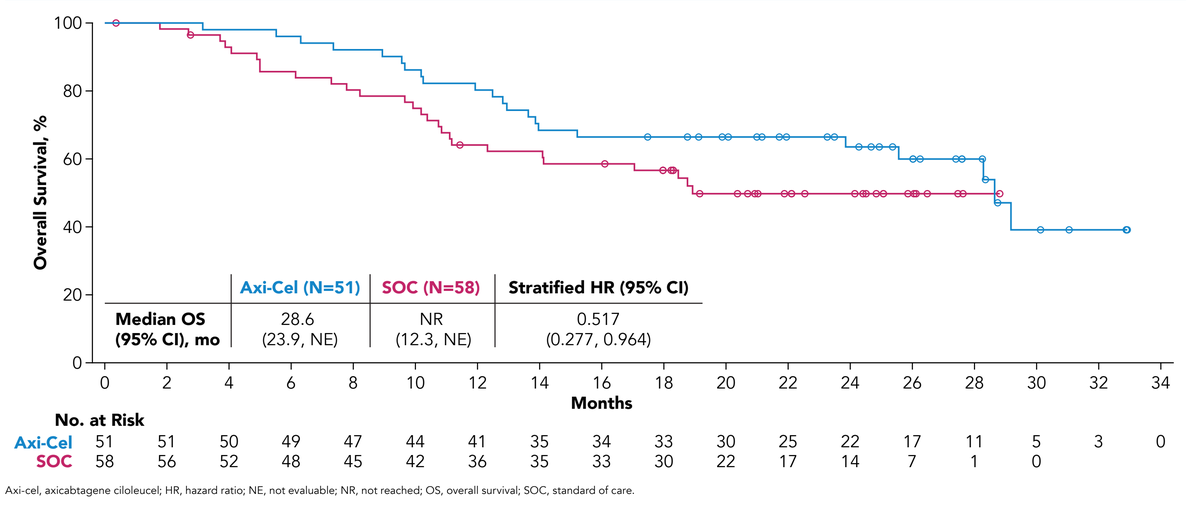
Figure 4. Objective Response Rate in Elderly Patients



[a] NE: In the SOC arm, there was 1 patient with undefined disease and 4 who did not have response assessments done.
Axi-cel, axicabtagene ciloleucel; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SOC, standard of care.

- ORR was higher with axi-cel versus SOC (descriptive *P*<0.0001) and complete response (CR) rate of the axi-cel arm was over double that of the SOC arm (75% vs 33%, respectively; **Figure 4**).

Figure 5. Overall Survival in Elderly Patients, Evaluated as an Interim Analysis



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

- Median OS was 28.7 months in the axi-cel arm and not reached in the SOC arm (HR, 0.517; 95% CI, 0.277, 0.964; *P*=0.0175; **Figure 5**)
- In the SOC arm, 33 (57%) patients received subsequent cellular immunotherapy (off protocol)

Table 2. Safety Overview in Elderly Patients

	Axi-Cel n=49		SOC n=55	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE, n (%)[a]	**49 (100)**	**46 (94)**	**55 (100)**	**45 (82)**
Pyrexia	47 (96)	4 (8)	14 (25)	0 (0)
Neutropenia[b]	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[c]	21 (43)	14 (29)	37 (67)	35 (64)
Leukopenia[d]	19 (39)	18 (37)	10 (18)	10 (18)
Fatigue	17 (35)	2 (4)	31 (56)	1 (2)
Any serious AE, n (%)	**29 (59)**	**25 (51)**	**26 (47)**	**23 (42)**
CRS, n (%)[e]	48 (98)	4 (8)	-	-
CRS management,[f] n (%)				
Tocilizumab	33 (67)		-	
Corticosteroids	14 (29)		-	
Vasopressors	3 (6)		-	
Median time to onset, days	3		-	
Median duration of events, days	8		-	
Neurologic event, n (%)[f]	32 (65)	13 (27)	14 (25)	1 (2)
Management with corticosteroids,[g] n (%)	22 (45)		0 (0)	
Median time to onset, days	7		26	
Median duration of events, days	9		39	
Reason for deaths, n (%)				
Progressive disease	19 (39)		20 (36)	
Grade 5 AEs during protocol-specified reporting period	1 (2)[h]		1 (2)[i]	
Definitive therapy-related mortality	0 (0)		1 (2)[i]	
Other[j]	1 (2)		5 (9)	

[a] Included are AEs of any grade occurring in ≥40% of patients in the overall population. [b] Neutropenia refers to the combined preferred terms of neutropenia and neutrophil count decreased. [c] Thrombocytopenia refers to the combined preferred terms of thrombocytopenia and platelet count decreased. [d] Leukopenia refers to the combined preferred terms of leukopenia and white-cell count decreased. [e] CRS was graded according to Lee et al.[6] [f] Neurologic events were identified per prespecified search list based on methods used in the blinatumomab registrational study.[7] [g] Toxicity management followed ZUMA-1 pivotal cohorts. [h] Due to COVID-19. [i] Due to cardiac arrest. [j] Other reasons for death included natural progression from prior subdural hematoma (n=1) in the axi-cel arm and COVID-19 (n=2), cardiopulmonary arrest (n=1), urosepsis (n=1), and sepsis (n=1) in the SOC arm.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; SOC, standard of care.

- Grade ≥3 adverse events (AEs) occurred in 46/49 (94%) axi-cel patients and 45/55 (82%) SOC patients (**Table 2**)
- Serious AEs occurred in 29/49 (59%) and 26/55 (47%) patients in the axi-cel and SOC arms, respectively
- Grade 5 treatment-related AEs occurred in 0 and 1 (cardiac arrest) patient in the axi-cel and SOC arms, respectively
- Grade ≥3 cytokine release syndrome (CRS) occurred in 4/49 (8%) axi-cel patients and grade ≥3 neurologic events occurred in 13/49 (27%) and 1/55 (2%) patients in the axi-cel and SOC arms, respectively (**Table 2**)
- There were slightly higher rates of CRS and neurologic events, including grade ≥3, in the elderly compared with the overall ZUMA-7 population[3]

CONCLUSIONS

- Axi-cel demonstrated superiority over second-line SOC in patients ≥65 years, despite the greater frequency of high-risk features in the axi-cel arm, with
  - >8-fold improvement in median EFS (21.5 months vs 2.5 months, respectively; *P*<0.0001)
  - >3-fold improvement in estimated 24-month EFS rate
  - Over double the CR rate
  - Almost triple the proportion of patients receiving definitive therapy
- OS, evaluated as a preplanned interim analysis, was prolonged in the axi-cel arm compared with the SOC arm
- Axi-cel had a manageable safety profile that was consistent with previous studies and real-world experience, regardless of age[8,9]
- Axi-cel is an effective and manageable second-line therapy for elderly patients with R/R LBCL

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