Yescarta® (axicabtagene ciloleucel) Outcomes in Elderly Patients in the ZUMA-7 Study

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Relevant Prescribing Information[1]

According to the YESCARTA US Prescribing Information (USPI), in the overall ZUMA-7 study population, the median age was 59 years (range: 21 to 81 years) and the median age of the YESCARTA-treated safety population was 59 years (range: 21 to 80 years). Additionally, in section 8.5 Geriatric Use: of the 422 patients with NHL who received YESCARTA in clinical trials, 127 patients (30%) were 65 years of age and older. No clinically important differences in safety or effectiveness were observed between patients aged 65 years and older and younger patients.

Outcomes in Elderly Patients in ZUMA-7

ZUMA-7 Study Description

The ZUMA-7 study is an international, multicenter, randomized, phase 3 trial comparing Yescarta with standard care as second-line treatment in patients with early relapsed (≤12 months) or refractory large B-cell lymphoma (LBCL).[1,2] Patients were randomized to receive either Yescarta or standard care. The standard care regimen consisted of 2-3 cycles of an investigator-selected, protocol-defined chemoimmunotherapy regimen followed by high-dose chemotherapy, and patients that were responsive to chemoimmunotherapy proceeded to autologous stem cell transplant. As such, ZUMA-7 was designed to evaluate patients that were intended to proceed to high-dose therapy with autologous stem cell transplant (HDT-ASCT).

The primary endpoint for ZUMA-7 was event-free survival (EFS) by blinded central review. EFS was defined as the time from randomization to the earliest date of disease progression (Lugano Classification), commencement of new lymphoma therapy, death from any cause, or a best response of stable disease up to and including the response on the Day 150 assessment after randomization.[2] Key secondary endpoints included objective response rates (ORR), overall survival (OS), progression-free survival (PFS), incidence of AEs

(including cytokine release syndrome [CRS] and neurologic events), and patient-reported outcomes.

Subgroup Analysis in Patients Aged ≥65 Years

A pre-planned subgroup analysis of ZUMA-7 (a randomized, open-label, multicenter, phase 3 study [NCT03391466][2]) assessed the safety and efficacy of Yescarta as second-line therapy in patients with relapsed/refractory LBCL who were ≥65 years.[3,4,5]

Patient Characteristics

The median age for the 359 patients enrolled and randomized in ZUMA-7 was 59 years (range, 21–81), with 109 patients (30%) ≥65 years.[2,4] The median age for the 180 patients in the Yescarta arm was 58 years (range, 21-80), with 51 patients (28%) ≥65 years. Of the 179 patients randomized to the standard-care arm, the median age was 60 years (range 26–81), with 58 patients (32%) ≥65 years.[2] In the Yescarta and standard of care arms, 26 and 27 patients were ≥70 years of age, respectively.[3]

The subgroup analysis included 109 patients aged ≥65 years. The median age was 69 years (range, 65–81), with 51 and 58 patients in the Yescarta and standard care arms, respectively. Baseline characteristics are shown in Table 1.[3,4,5]

Table 1. Baseline Characteristics for Patients Aged ≥65 Years in ZUMA-7 (N=109)[3,4,5]

	Yescarta (n=51)	SOC (n=58)	Overall (N=109)
Median age (range), years	70 (65–80)	69 (65–81)	69 (65–81)
Male, n (%)	28 (55)	39 (67)	67 (61)
Disease stage III or 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/history-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)

Abbreviations: 1L=first-line; 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]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.

Efficacy

The primary endpoint of EFS showed a stratified HR of 0.276 (95% CI, 0.164–0.465) and a stratified *P*-value (descriptive) of <0.0001. In elderly patients, with 24.3 months median follow-up, median EFS was longer with Yescarta versus standard care (21.5 months

[95% CI, 5.0–not evaluable] vs 2.5 months [95% CI, 1.6–3.2], respectively).[3] Kaplan-Meier estimates of the 24-month EFS rates for the Yescarta arm and standard care arm were 47.8% (95% CI, 33.2–61.0) and 15.1% (95% CI, 7.1–25.8), respectively.[3] Multivariate analyses also showed similar EFS results when adjusted for differences in baseline characteristics (HR, 0.23; 95% CI, 0.12-0.45; descriptive *P*<0.0001).[3,4,5]

Among the elderly patients, ORR for the Yescarta arm and standard care arm were 88% (75% CR) and 52% (33% CR), respectively, with an odds ratio of 8.81 (95% CI, 2.71–32.14) and descriptive *P*-value of <0.0001.[3,4,5]

Table 2. Efficacy in Patients Aged ≥65 Years in ZUMA-7[2,3,5,6]

Event-free Survival				
	≥ 65 years		**All Patients**	
	Yescarta (N=51)	**Standard Care (N=58)**	**Yescarta (N=180)**	**Standard Care (N=179)**
Median EFS (95% CI), mo	21.5 (5.0–NE)	2.5 (1.6–3.2)	8.3 (4.5–15.8)	2.0 (1.6–2.8)
24-mo EFS Rate (95% CI), %	47.8% (33.2–61.0)	15.1% (7.1–25.8)	40.5% (33.2–47.7)	16.3% (11.1–22.2)
Stratified HR (95% CI)	0.276 (0.164–0.465)		0.398 (0.308–0.514)	
Stratified P-Value (descriptive)	<0.0001		<0.0001	
Objective Response Rate				
	≥ 65 years		**All Patients**	
	Yescarta (N=51)	**Standard Care (N=58)**	**Yescarta (N=180)**	**Standard Care (N=179)**
ORR, %	88%	52%	83%	50%
Odds ratio (95% CI)	8.81 (2.71–32.14)		5.31 (3.08–8.90)	
P-value	<0.0001 (descriptive)		<0.001	
CR, %	75%	33%	65%	32%

Abbreviations: CR=complete response; EFS=event-free survival; HR=hazard ratio; NE=not evaluable; ORR=objective response rate.

Figure 1. EFS in Patients ≥65 Years in ZUMA-7[3,4,5]

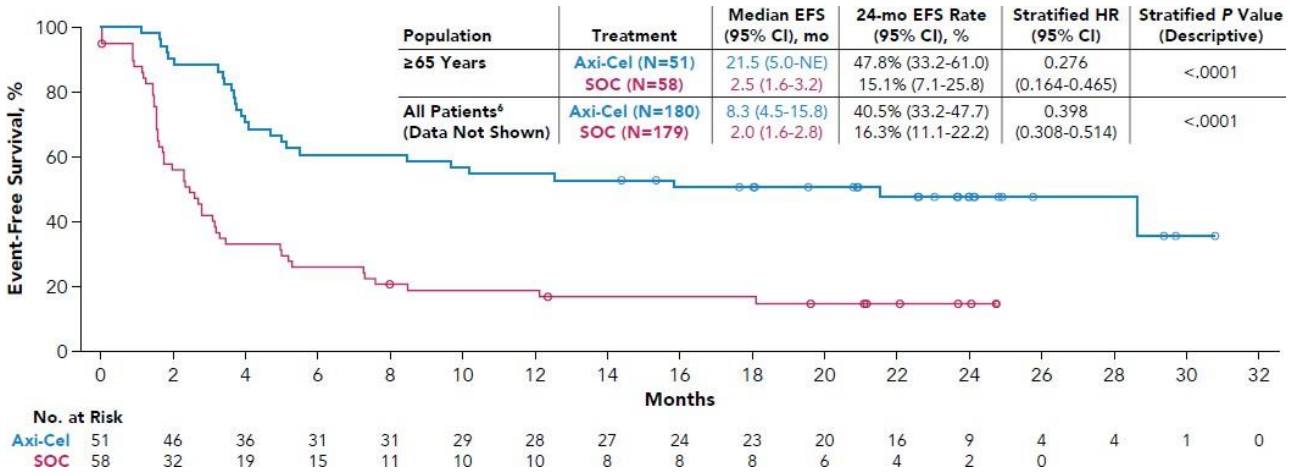

Figure adapted with permission.
Abbreviations: Axi-cel=axicabtagene ciloleucel; EFS=event-free survival; HR=hazard ratio; mo=month; NE=not evaluable; SOC=standard of care.

Results from the primary OS analysis of patients aged ≥65 and ≥70 years from the ZUMA-7 study showed that at a median follow-up of 46.6 months, Yescarta was associated with prolonged OS (Figure 2) and PFS (Figure 3) compared to SOC treatment. In patients aged ≥65 years, median OS was 43.5 months (95% CI, 20.9–NE) in the Yescarta arm and 19.5 months in the standard care arm (95% CI, 12.3–NE), with a stratified HR of 0.691 (95% CI, 0.401–1.190); median PFS was 28.6 months (95% CI, 5.1–NE) for the Yescarta arm and 5.0 months (95% CI, 2.8–7.3) for the standard care arm (HR, 0.406; 95% CI, 0.230–0.715). In patients aged ≥70 years, median OS was 24.7 months (95% CI, 12.8–NE) in the Yescarta arm and 11.2 months in the standard care arm (95% CI, 6.1–NE), with a stratified HR of 0.330 (95% CI, 0.135-0.809); median PFS was 11.4 months (95% CI, 4.1–NE) for the Yescarta arm and 2.7 months (95% CI, 1.7–5.0) for the standard care arm (HR, 0.206; 95% CI, 0.078–0.547).[7]

Figure 1. OS of Yescarta Versus SOC in Patients Aged ≥65 and ≥70 Years in ZUMA-7[7]

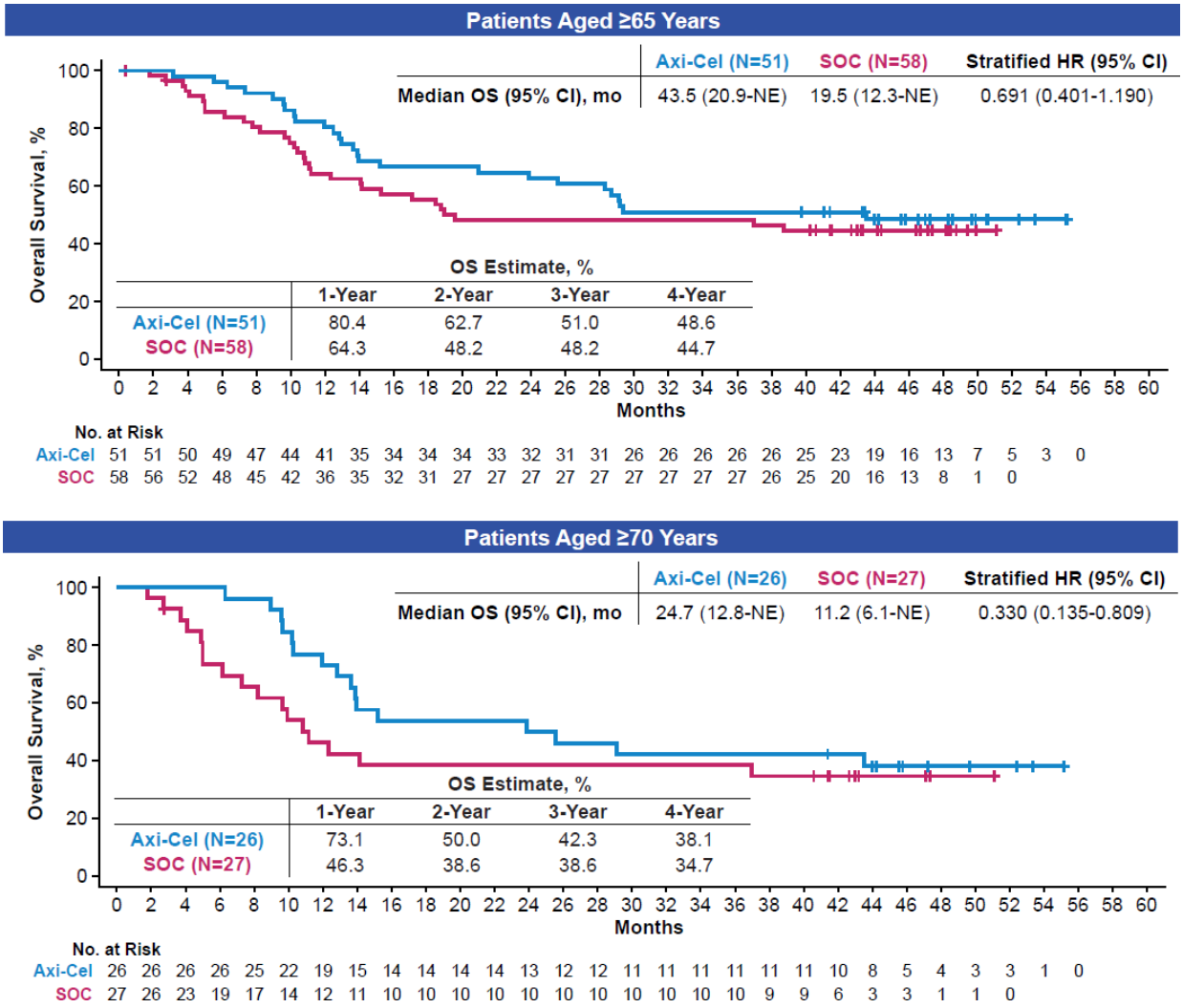

Figure adapted with permission.
Abbreviations: Axi-cel=axicabtagene ciloleucel; HR=hazard ratio; NE=not estimable; OS=overall survival; SOC=standard of care.

Figure 2. PFS of Yescarta Versus SOC in Patients Aged ≥65 and ≥70 Years in ZUMA-7[7]

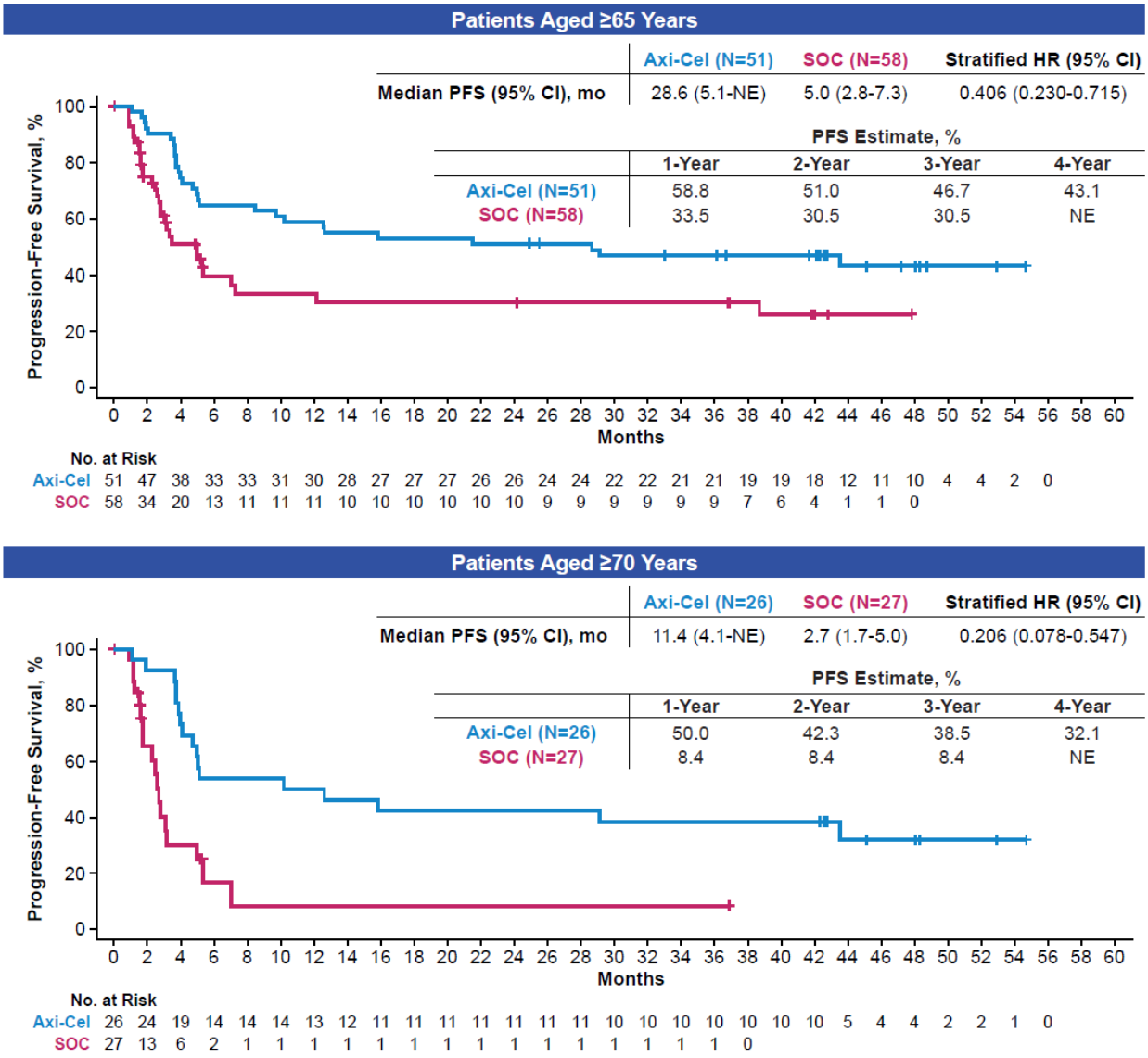

Figure adapted with permission.
Abbreviations: Axi-cel=axicabtagene ciloleucel; HR=hazard ratio; NE=not estimable; PFS=progression-free survival; SOC=standard of care.

Safety

Adverse events (AEs) of any grade occurred in 100% of elderly patients. AEs of Grade ≥3 occurred in 46/49 (94%) patients in the Yescarta arm and 45/55 (82%) patients in the standard-care arm (Table 3). Cytokine release syndrome was recorded only for patients treated with Yescarta. Any grade CRS occurred in 48 (98%) patients, and Grade ≥3 CRS occurred in 4 (8%) patients. The median time to CRS onset was 3 days, with a median duration of 8 days. In the Yescarta arm, neurologic events of any grade occurred in 32 (65%) patients, and 13 (27%) patients had Grade ≥3 neurologic events. The median time to neurologic event onset in the Yescarta arm was 7 days, with a median duration of 9 days. In the standard care arm, neurologic events of any grade occurred in 14 (25%)

patients, and 1 (2%) patient had Grade ≥3 neurologic events. The median time to neurologic event onset in the standard care arm was 26 days, with a median duration of 39 days.[3,4,5]

Rates of cytokine release syndrome (CRS) and neurologic events, including Grade ≥3 events, were slightly higher in patients aged ≥65 years compared with the overall ZUMA-7 population. CRS occurred in 98% and 8% for any grade and Grade ≥3, respectively, in patients ≥65 years of age. In the overall ZUMA-7 population, CRS occurred in 92% and 6% for any grade and Grade ≥3, respectively.[3,5]

In the Yescarta arm, neurologic events occurred in 65% and 27% for any grade and Grade ≥3, respectively, in patients ≥65 years of age. In the overall Yescarta population, neurologic events occurred in 60% and 21% for any grade and Grade ≥3, respectively.[3,5]

In the standard care arm, neurologic events occurred in 25% and 2% for any grade and Grade ≥3, respectively, in patients ≥65 years of age.[5] In the overall standard care population, neurologic events occurred in 20% and 1% for any grade and Grade ≥3, respectively.[2]

Table 3. Summary of Grade ≥3 AEs in Patients ≥65 Years in ZUMA-7[4,5,7]

n (%)	Yescarta (n=49)	SOC (n=55)
Any Grade ≥3 AE[a,b]	46 (94)	45 (82)
Pyrexia	4 (8)	0 (0)
Neutropenia[c]	39 (80)	24 (44)
Nausea	1 (2)	3 (5)
Any Grade ≥3 serious AE, n (%)[d]	25 (51)	23 (42)
Grade ≥3 CRS[e,f]	4 (8)	–
Grade ≥3 neurologic events[g,h]	13 (27)	1 (2)
Reason for Death, n (%)	25 (51)	29 (53)
Progressive disease	20 (41)	20 (36)
Grade 5 AEs during protocol-specified reporting period	2 (4)[i]	1 (2)[j]
New or secondary malignancy	1 (2)[k]	0 (0)
Other reason for death	2 (4)[l]	8 (15)[m]
Definitive therapy-related mortality	0 (0)	1 (2)[n]

Abbreviations: AE, adverse event; CRS, cytokine release syndrome; SOC, standard of care.
[a]Included are the 3 most common AEs of any grade occurring in the Yescarta arm.
[b]In patients aged <65 years, Grade ≥3 AEs occurred in 109 (90%) Yescarta patients and 95 (84%) SOC patients.
[c]Neutropenia refers to the combined preferred terms of neutropenia and neutrophil count decreased.
[d]In patients aged <65 years, Grade ≥3 serious AEs occurred in 47 (39%) Yescarta patients and 44 (39%) SOC patients.
[e]CRS was graded according to Lee et al.[8]
[f]In patients aged <65 years, Grade ≥3 CRS occurred in 7 (6%) Yescarta patients.
[g]Neurologic events were identified per prespecified search list based on methods used in the blinatumomab registrational study.
[h]In patients <65 years, Grade ≥3 neurologic events occurred in 23 (19%) Yescarta patients and 0 (0%) SOC patients.
[i]Due to pneumonia (n=1) and COVID-19 (n=1).
[j]Due to cardiac arrest.
[k]Due to acute myeloid leukemia.

[l]Due to COVID-19 (n=1) and natural progression from prior subdural hematoma, unrelated per investigator assessment to lymphodepleting chemotherapy and Yescarta (n=1).
[m]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).
[n]Due to cardiac arrest.

Patient-Reported Outcomes

Patient-reported outcomes were evaluated in a pre-planned subgroup analysis of ZUMA-7 patients aged ≥65 years, and the quality of life (QoL) analysis set comprised 46 Yescarta and 42 SOC patients aged ≥65 years. There was a clinically meaningful difference in mean change of scores from baseline at Day 100 in favor of Yescarta for European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire- Core 30 (QLQ-C30) Global Health (P<0.0001), Physical Functioning (P=0.0019), and EuroQoL 5-dimension questionnaire using a 5-level scale (EQ-5D-5L) visual analog scale (VAS; P<0.0001).[3,5]

For all 3 domains (EORTC QLQ-C30 Global Health Status, EORTC QLQ-C30 physical functioning, EQ-5D-5L VAS), scores favored (P<0.05) Yescarta over SOC at Day 150. The mean estimated scores numerically returned to or exceeded baseline scores earlier in the Yescarta arm (by Day 150) but never equaled or exceeded baseline scores by Month 15 in the SOC arm.[3,5]

Additional PRO domains with mean change of scores from baseline to Day 100 in favor of Yescarta were EQ-5D-5L Index and EORTC QLQ-C30 Role Functioning, Emotional Functioning, Social Functioning, Fatigue, Dyspnea, Appetite Loss, and Diarrhea.[3,5]

References

1. YESCARTA® (axicabtagene ciloleucel) [US Prescribing Information]. Santa Monica, CA: Kite Pharma, Inc.; 2023.
2. 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(7):640-654. doi:10.1056/NEJMoa2116133
3. 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(10):1894-1905.
4. van Meerten T, Westin JR, Locke FL, et al. Superiority of axicabtagene ciloleucel in second-line large B-cell lymphoma in the elderly. Poster presented at the European CAR T-cell Meeting; February 10-12, 2022. Abstract #54.
5. Westin JR, Locke FL, Dickinson M, et al. Clinical and patient-reported outcomes in a phase 3, randomized, open-label study evaluating axicabtagene ciloleucel versus standard-of-care therapy in elderly patients with relapsed/refractory large B-cell lymphoma (ZUMA-7). Poster presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022. Poster 7548.
6. Supplement to: 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(7):640-654. doi:10.1056/NEJMoa2116133
7. Kersten MJ, Farooq U, Rapoport S, et al. 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. Poster presented at the American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA. Poster 1761.
8. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome [published correction appears in Blood. 2015 Aug 20;126(8):1048. Dosage error in article text] [published correction appears in Blood. 2016 Sep 15;128(11):1533]. *Blood*. 2014;124(2):188-195. doi:10.1182/blood-2014-05-552729

Abbreviations

AE=adverse event
CR=complete response
CRS=cytokine release syndrome
DLBCL=diffuse large B-cell lymphoma
EFS=event-free survival
EORTC=European Organization for Research and Treatment of Cancer
EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D-5L=EuroQoL five-dimension questionnaire using a five-level scale
HDT-ASCT=high-dose therapy with autologous stem cell transplant
ICANS=immune effector cell-associated neurotoxicity
LBCL=large B-cell lymphoma
OR=objective response
ORR=objective response rate
OS=overall survival
PFS=progression-free survival
SOC=standard of care

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