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

Tom van Meerten, MD, PhD[1]; Jason R. Westin, MD, MS, FACP[2]; Frederick L. Locke, MD[3]; Olalekan O. Oluwole, MBBS, MPH[4]; Michael Dickinson MBBS, DMEdSc[5]; Armin Ghobadi, MD[6]; Mahmoud Elsawy, MD, MSc[7]; David B. Miklos, MD, PhD[8]; Matthew Ulrickson, MD[9]; Miguel-Angel Perales, MD[10]; Umar Farooq, MD[11]; Luciano Wannesson, MD[12]; Lori A. Leslie, MD[13]; Marie José Kersten, MD, PhD[14]; Caron A. Jacobson, MD, MMSc[15]; John M. Pagel, MD, PhD, DSc[16]; Gerald Wulf, MD, PhD[17]; Patrick Johnston, MD, PhD[18]; Aaron P. Rapoport, MD[19]; Leo I. Gordon, MD[20]; Yin Yang, MD, MS[21]; Andrew Peng, MS[21]; Linqiu Du[21]; Jina Shah, MD, MPH[21]; Marco Schupp, MD[21]; Paul Cheng, MD, PhD[21]; Christina To, MD[21]; and Anna Sureda, MD, PhD[22]

[1]University Medical Center Groningen, Groningen, The Netherlands, on behalf of HOVON / LLPC; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Moffitt Cancer Center, Tampa, FL, USA; [4]Vanderbilt University Cancer Center, Nashville, TN, USA; [5]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and the University of Melbourne, Melbourne, Victoria, Australia; [6]Washington University School of Medicine, St Louis, MO, USA; [7]Division of Hematology, Department of Medicine, Dalhousie University, Halifax, Nova Scotia; [8]Stanford University School of Medicine, Stanford, CA, USA; [9]Banner MD Anderson Cancer Center, Gilbert, Arizona, USA; [10]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [11]University of Iowa, Iowa City, IA, USA; [12]Istituto Oncologico della Svizzera Italiana, Bellinzona, Switzerland; [13]John Theurer Cancer Center, Hackensack, NJ, USA; [14]Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands, on behalf of HOVON / LLPC; [15]Dana-Farber Cancer Institute, Boston, MA, USA; [16]Swedish Cancer Institute, Seattle, WA, USA; [17]University Medicine Göttingen, Göttingen, Germany; [18]Mayo Clinic, Rochester, Minnesota, USA; [19]University of Maryland School of Medicine and Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA; [20]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [21]Kite, a Gilead Company, Santa Monica, CA, USA; and [22]Institut Català d'Oncologia-Hospitalet, Barcelona, Spain

Disclosures

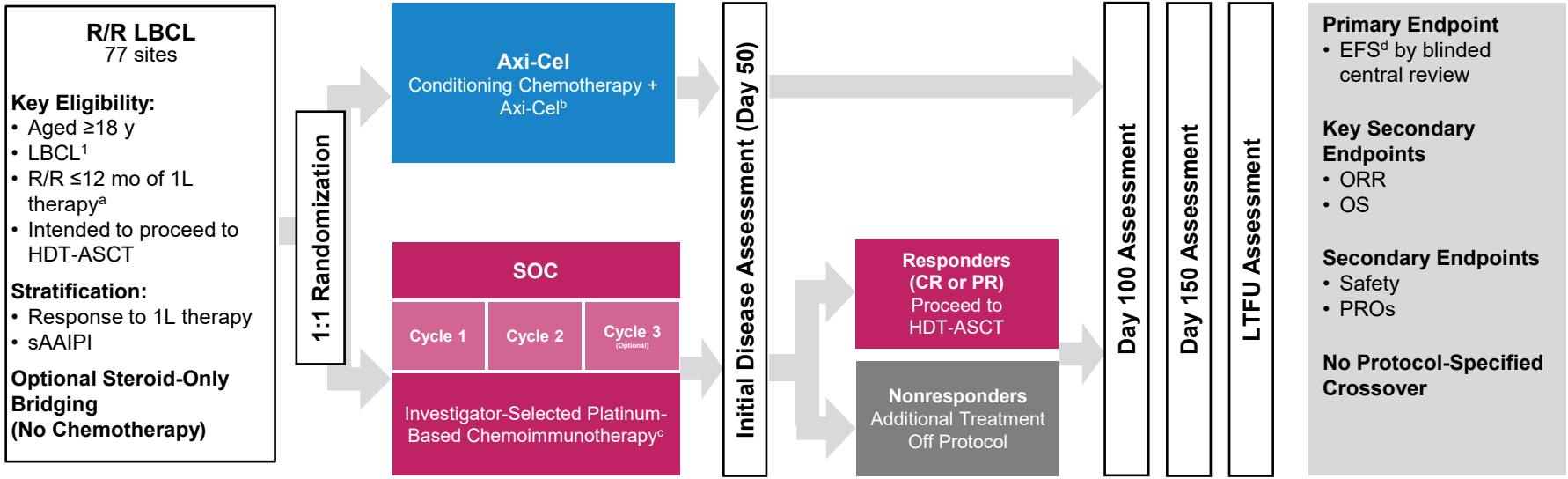
Tom van Meerten: honoraria from Kite, and consultancy or advisory role for Janssen.

Background

- Axi-cel is an autologous anti-CD19 chimeric antigen receptor T-cell therapy approved for the treatment of adult patients with R/R LBCL after ≥2 lines of systemic therapy
- A minority of patients with R/R LBCL ultimately receive definitive therapy with 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, and 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 SOC as second-line treatment in patients with R/R LBCL
- In ZUMA-7, axi-cel significantly improved EFS compared with second-line SOC in R/R LBCL (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]
- Here, we present the safety and efficacy outcomes for ZUMA-7 patients aged ≥65 years

1. Sehn LH, et al. *N Engl J Med.* 2021;384:842-858. 2. Di M, et al. *Oncologist.* 2021;26:120-132. 3. Locke FL, et al. *N Engl J Med.* 2021;386(7):640-654.
Axi-cel, axicabtagene ciloleucel; EFS, event-free survival; HDT-ASCT, high-dose chemotherapy and autologous stem cell transplantation; HR, hazard ratio; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; SOC, standard of care.

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/m^2/day) and fludarabine (30 mg/m^2/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10^6 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,[2] commencement of new lymphoma therapy, or death from any cause.

1. Swerdlow SH, et al. *Blood*. 2016;127:2375-2390. 2. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

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/R, relapsed/refractory; sAAIPI, second-line age-adjusted International Prognostic Index; SOC, standard of care.

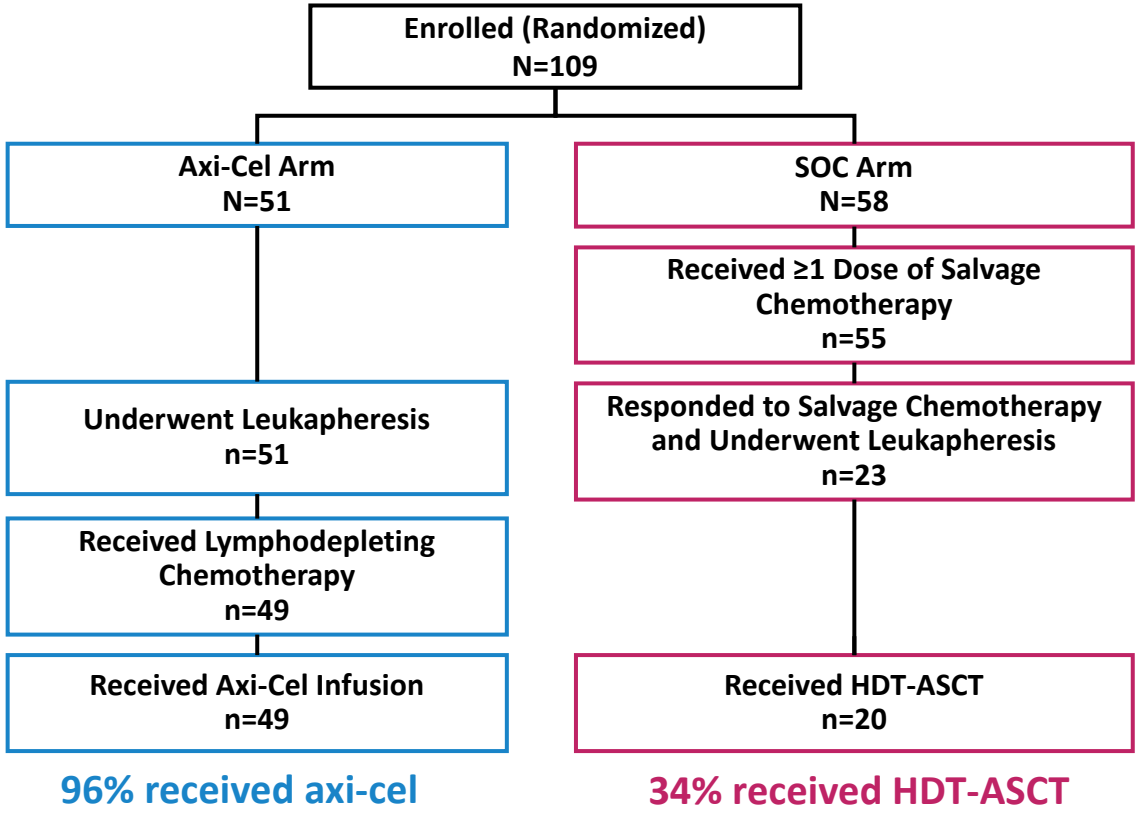
Methods

- The primary endpoint was EFS, defined as time from randomization to the earliest date of disease progression per Lugano Classification,[1] commencement of new lymphoma therapy, or death from any cause
- 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)
- The present analysis of outcomes in patients aged ≥65 years was a prespecified subgroup analysis

1. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068.

Axi-cel, axicabtagene ciloleucel; EFS, event-free survival; ORR, objective response rate; OS, overall survival; SOC, standard of care.

ZUMA-7 Disposition for Patients ≥65 Years of Age



- The subgroup analysis of patients aged ≥65 years included 109 patients (N=51 and N=58 patients in the axi-cel and SOC arms, respectively)
- Axi-cel was successfully manufactured for all patients who underwent leukapheresis

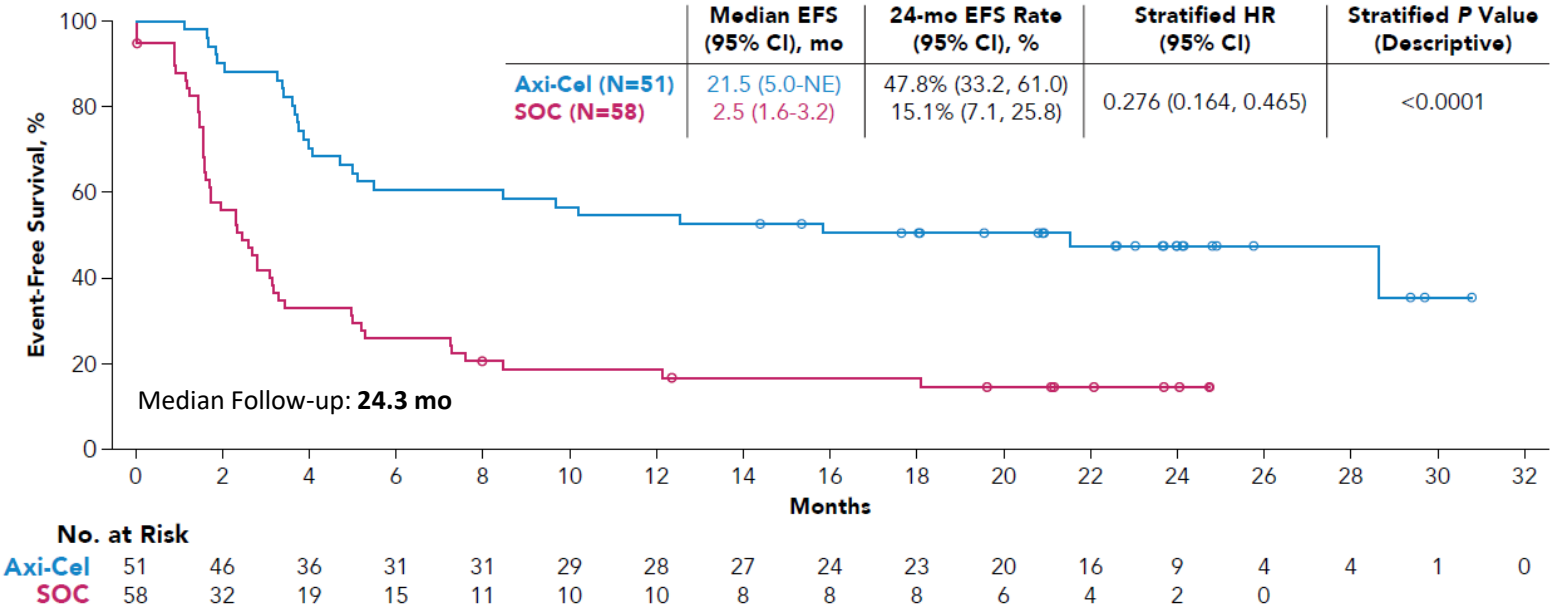
Axi-cel, axicabtagene ciloleucel; HDT-ASCT; high-dose chemoimmunotherapy and autologous stem cell transplantation; SOC, standard of care.

Baseline Characteristics of Patients ≥65 Years of Age

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 investigator 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.

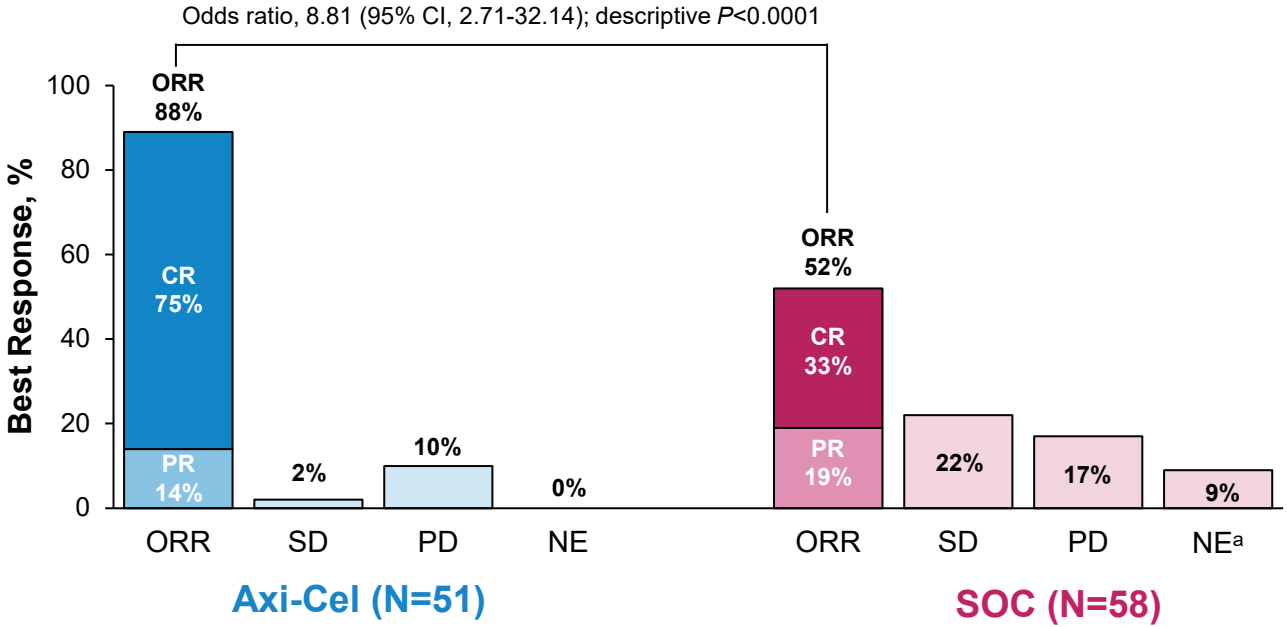
Primary Endpoint in Patients ≥65 Years of Age



- Multivariate analyses showed similar EFS results when adjusting for differences in baseline characteristics (HR, 0.23, *P*<0.0001)

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

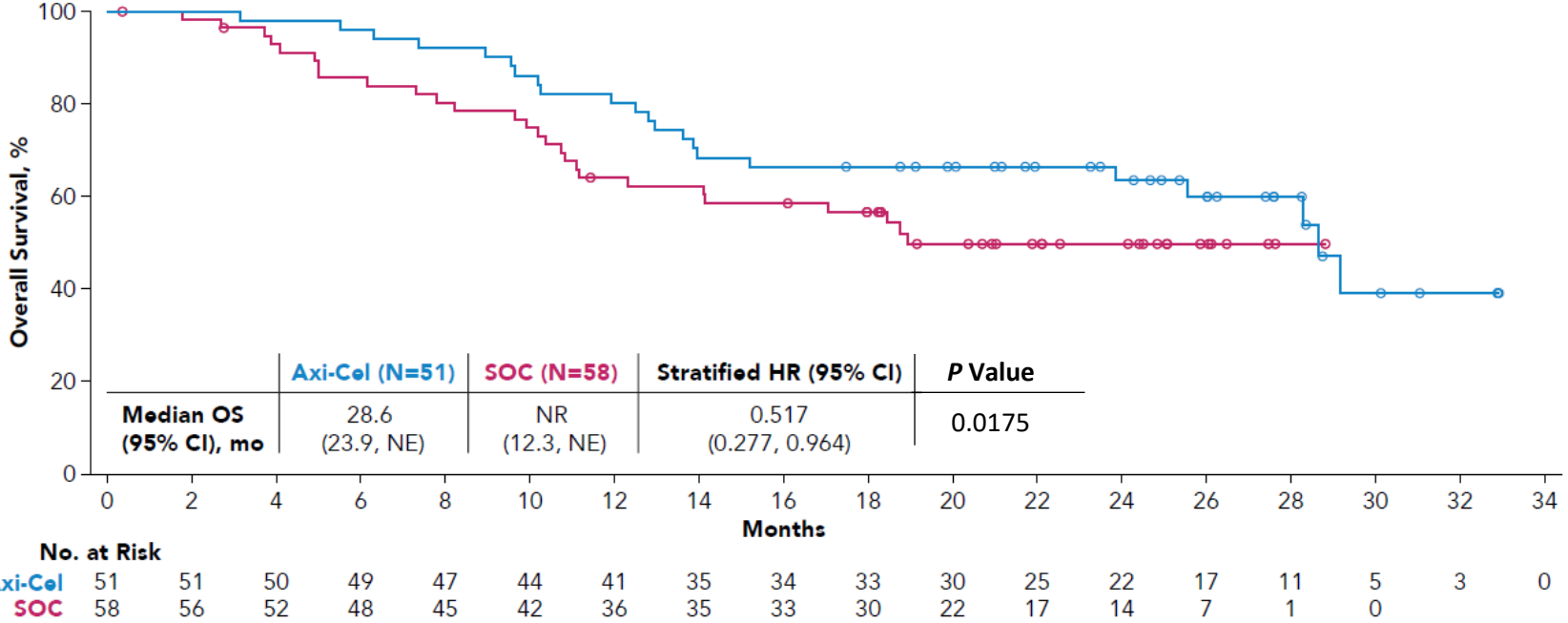
Objective Response Rate in Patients ≥65 Years of Age



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

[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.

Overall Survival in Patients ≥65 Years of Age (Evaluated as an Interim Analysis)



	Axi-Cel (N=51)	SOC (N=58)	Stratified HR (95% CI)	*P* Value
Median OS (95% CI), mo	28.6 (23.9, NE)	NR (12.3, NE)	0.517 (0.277, 0.964)	0.0175

- In the SOC arm, 33 (57%) patients received subsequent cellular immunotherapy (off protocol)

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

Overall Safety Profile in Patients ≥65 Years of Age

Adverse Events, n (%)	Axi-Cel n=49		SOC n=55	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE[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)	25 (64)
Leukopenia[d]	19 (39)	18 (37)	10 (18)	10 (18)
Fatigue	17 (35)	2 (4)	31 (56)	1 (2)
Any serious AE	**29 (59)**	**25 (51)**	**26 (47)**	**23 (42)**

Reason for Death	Axi-Cel n=49	SOC n=55
Progressive disease	19 (39)	20 (36)
Grade 5 AEs during protocol-specified reporting period	1 (2)[e]	1 (2)[f]
Definitive therapy-related mortality	0 (0)	1 (2)[f]
Other[g]	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] Due to COVID-19. [f] Due to cardiac arrest. [g] 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; SOC, standard of care.

Rates of CRS and Neurologic Events in Patients ≥65 Years of Age

Parameter	Axi-Cel n=49		SOC n=55	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
CRS, n (%)[a]	48 (98)	4 (8)	-	-
CRS management,[b] 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 (%)[c]	32 (65)	13 (27)	14 (25)	1 (2)
Management with corticosteroids,[b] n (%)	22 (45)		0 (0)	
Median time to onset, days	7		26	
Median duration of events, days	9		39	

[a] CRS was graded according to Lee et al.[1,b] Toxicity management followed ZUMA-1 pivotal cohorts. [c] Neurologic events were identified per prespecified search list based on methods used in the blinatumomab registrational study.[2]

1. Lee DW, et al. *Blood*. 2014;124:188-195. 2. Topp MS, et al. *Lancet Oncol.* 2015;16:57-66.

Axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; SOC, standard of care.

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[1,2]
- Axi-cel is an effective second-line therapy for elderly patients with R/R LBCL

1. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531-2544. 2. Locke FL, et al. *Lancet Oncol*. 2019;20:31-42.
Axi-cel, axicabtagene ciloleucel; EFS, event-free survival; LBCL, large B-cell lymphoma; OS, overall survival; R/R, relapsed/refractory; SOC, standard of care.

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- All employees of Kite involved over the course of the study for their contributions
- These data were previously presented at the 2022 European CAR T-cell Meeting[1]

ZUMA-7 Global Phase 3 Clinical Trial Sites

1. van Meerten T, et al. EU CAR T 2022. Poster #54.