Primary Analysis of ZUMA-7: A Phase 3 Randomized Trial of Axicabtagene Ciloleucel (Axi-Cel) Versus Standard-of-Care (SOC) Therapy in Patients With Relapsed/Refractory Large B-Cell Lymphoma

Frederick L. Locke, MD[1]; David B. Miklos, MD, PhD[2]; Caron A. Jacobson, MD, MMSc[3]; Miguel-Angel Perales, MD[4]; Marie José Kersten MD, PhD[5]; Olalekan O. Oluwole, MBBS, MPH[6]; Armin Ghobadi, MD[7]; Aaron P. Rapoport, MD[8]; Joseph P. McGuirk, DO[9]; John M. Pagel, MD, PhD[10]; Javier Muñoz, MD, MS, MBA, FACP[11]; Umar Farooq, MD[12]; Tom van Meerten, MD, PhD[13]; Patrick M. Reagan, MD[14]; Anna Sureda, MD, PhD[15]; Ian W. Flinn, MD, PhD[16]; Peter Vandenberghe, MD, PhD[17]; Kevin W. Song, MD, FRCPC[18]; Michael Dickinson, MBBS, D Med Sci, FRACP, FRCPA[19]; Monique C. Minnema, MD, PhD[20]; Peter A. Riedell, MD[21]; Lori A. Leslie, MD[22]; Sridhar Chaganti, MD[23]; Yin Yang, MS, MD[24]; Simone Filosto, PhD[24]; Marco Schupp, MD[24]; Christina To, MD[24]; Paul Cheng, MD, PhD[24]; Leo I. Gordon, MD[25]; and Jason R. Westin, MD, MS, FACP[26]

[1]Moffitt Cancer Center, Tampa, FL, USA; [2]Stanford University School of Medicine, Stanford, CA, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [6]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [7]Washington University School of Medicine, St. Louis, MO, USA; [8]The Marlene and Stewart Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD, USA; [9]University of Kansas Cancer Center, Kansas City, KS, USA; [10]Swedish Cancer Institute, Seattle, WA, USA; [11]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [12]University of Iowa, Iowa City, IA, USA; [13]University Medical Center Groningen, Groningen, Netherlands; [14]University of Rochester School of Medicine, Rochester, NY, USA; [15]IDIBELL, Universitat de Barcelona, Hematology Department, Institut Català d'Oncologia-Hospitalet, Barcelona, Spain; [16]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; [17]University Hospitals Leuven, Leuven, Belgium; [18]Division of Hematology, University of British Columbia and Leukemia/BMT Program of BC, Vancouver General Hospital, BC Cancer, Vancouver, BC, Canada; [19]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and the University of Melbourne, Melbourne, Victoria, Australia; [20]University Medical Center Utrecht, Utrecht, The Netherlands; [21]The University of Chicago Medical Center, Chicago, IL, USA; [22]John Theurer Cancer Center, Hackensack, NJ, USA; [23]Centre for Clinical Haematology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [24]Kite, a Gilead Company, Santa Monica, CA, USA; [25]Northwestern University Feinberg School of Medicine and the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; and [26]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Disclosures

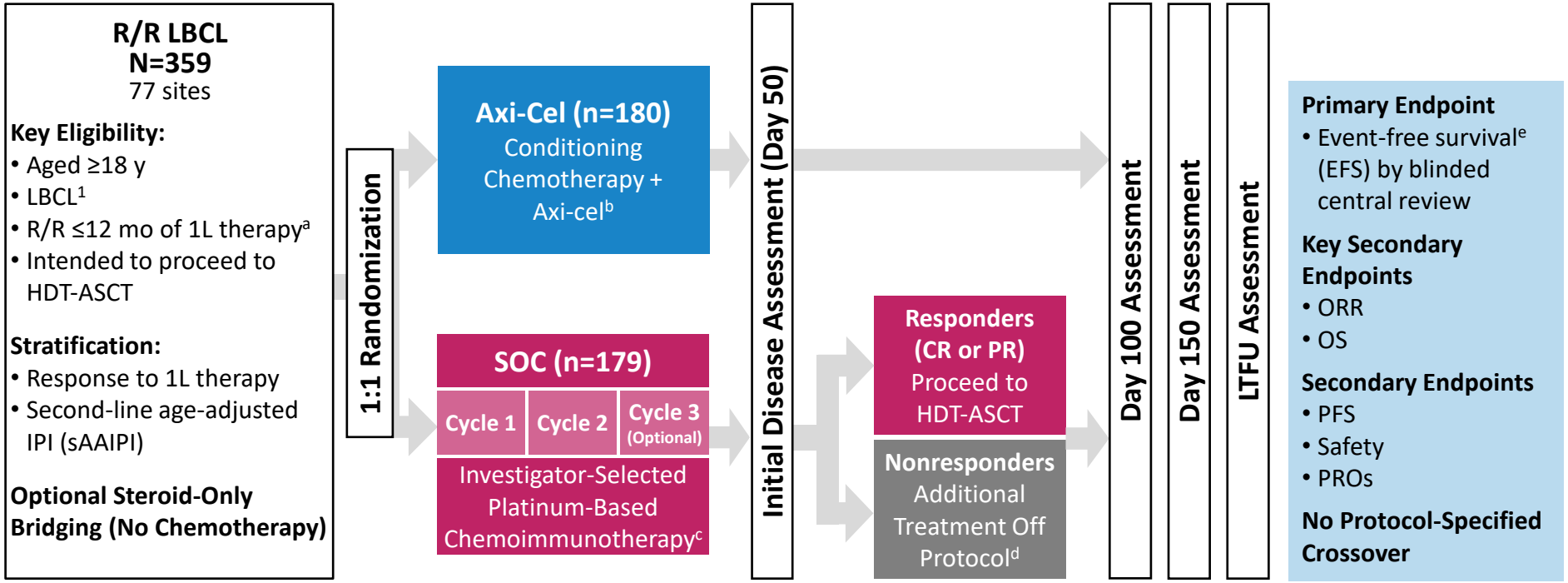
Tom van Meerten: honoraria from Kite, a Gilead Company; and consultancy or advisory role for Janssen.

Background

- Axi-cel is an autologous anti-CD19 CAR T-cell therapy approved for the treatment of adult patients with R/R LBCL after ≥2 lines of systemic therapy
- Current SOC second-line treatment in the curative setting for patients with R/R LBCL is salvage chemotherapy followed by consolidative HDT-ASCT[1]
- Many patients cannot receive HDT-ASCT, and their prognosis is poor[2-4]
- 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

1. Zahid U, et al. *Curr Hematol Malig Rep.* 2017;12:217-226. 2. Gisselbrecht C, et al. *J Clin Oncol.* 2010;28:4184-4190. 3. Van Den Neste E, et al. *Bone Marrow Transplant.* 2016;51:51-57. 4. van Imhoff GW, et al. *J Clin Oncol.* 2017;35:544-551.

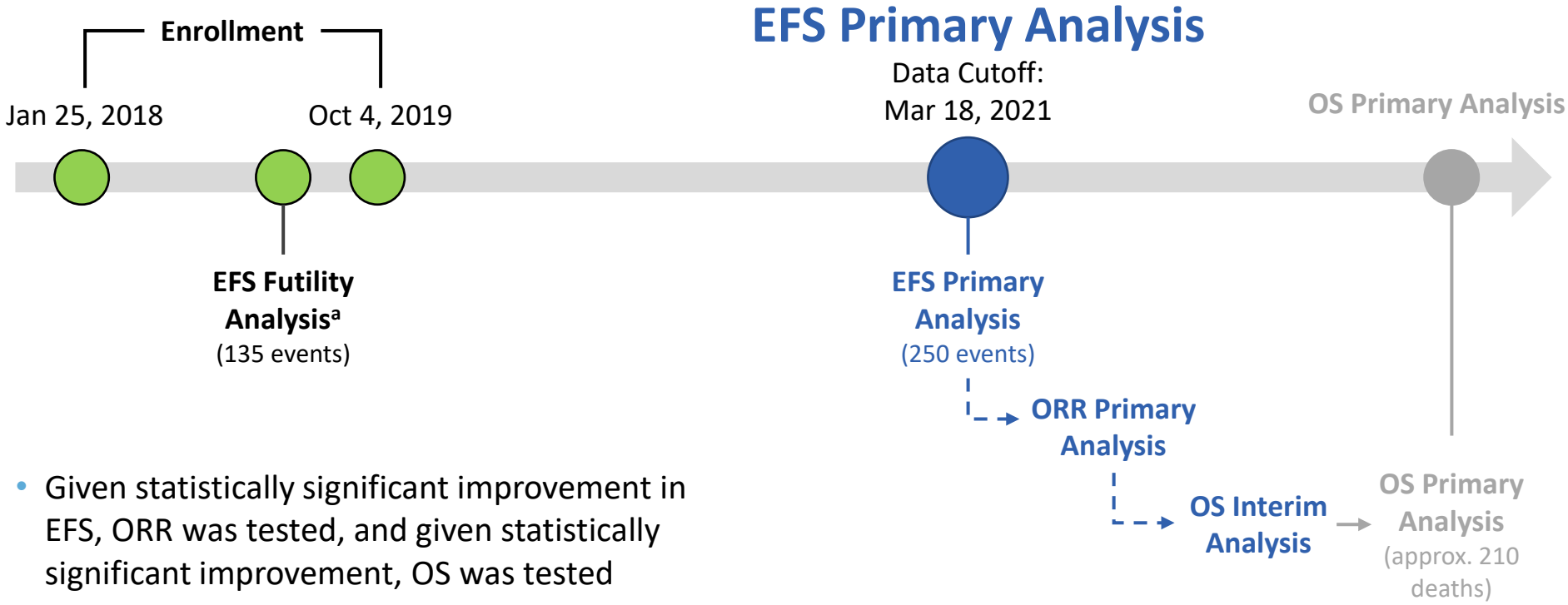
ZUMA-7 Study Schema and Endpoints: Axi-Cel Versus SOC as Second-Line Therapy in Patients With R/R LBCL



[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] 56% of patients received subsequent cellular immunotherapy. [e] 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.

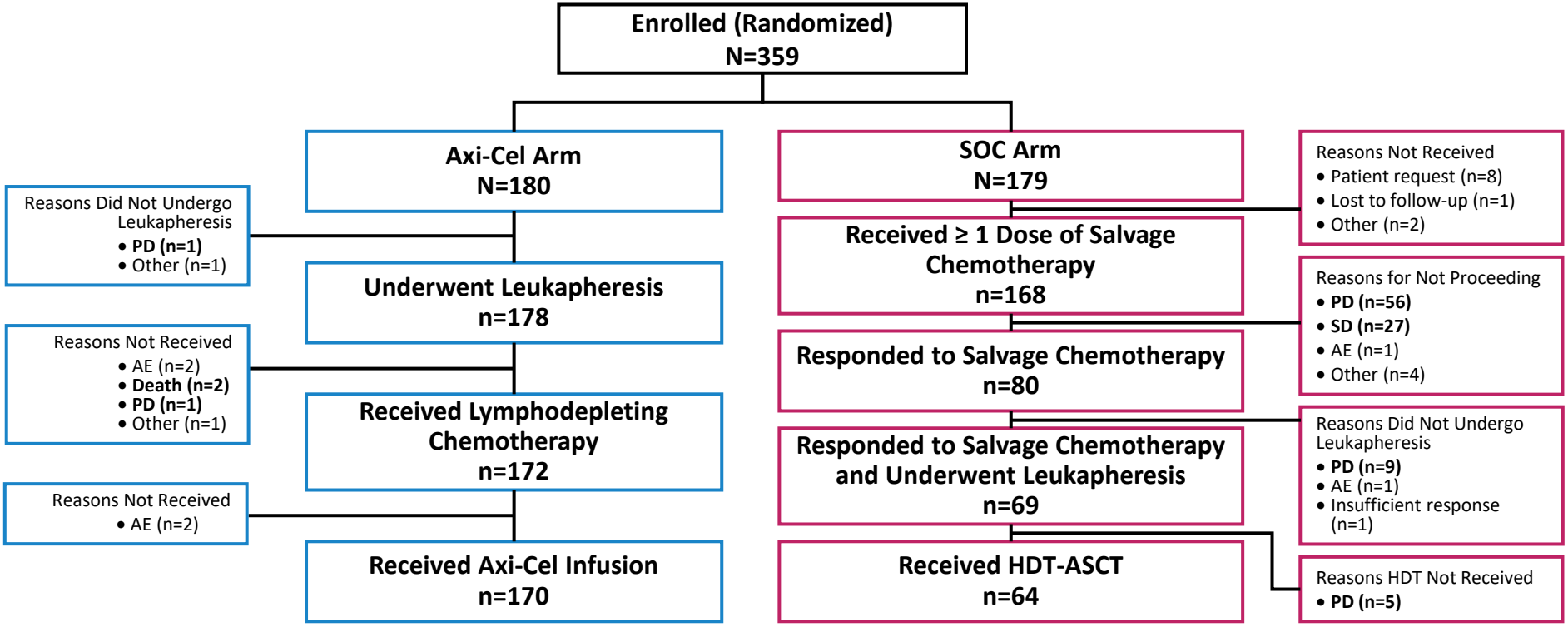
Hierarchical Statistical Testing of Endpoints in ZUMA-7: EFS → ORR → OS



- Given statistically significant improvement in EFS, ORR was tested, and given statistically significant improvement, OS was tested

[a] Conducted for the DSMB only. Although a futility analysis was preplanned, the positive efficacy results were not announced, and the study was not stopped early to ensure that the primary analysis results were mature and not biased. All testing was performed at the 1-sided 2.5% level. Analyses were event-driven and occurred when the required number of events were observed regardless of anticipated timing.

Patient Disposition: Nearly 3× as Many Axi-Cel Patients Received Definitive Therapy Versus SOC Patients

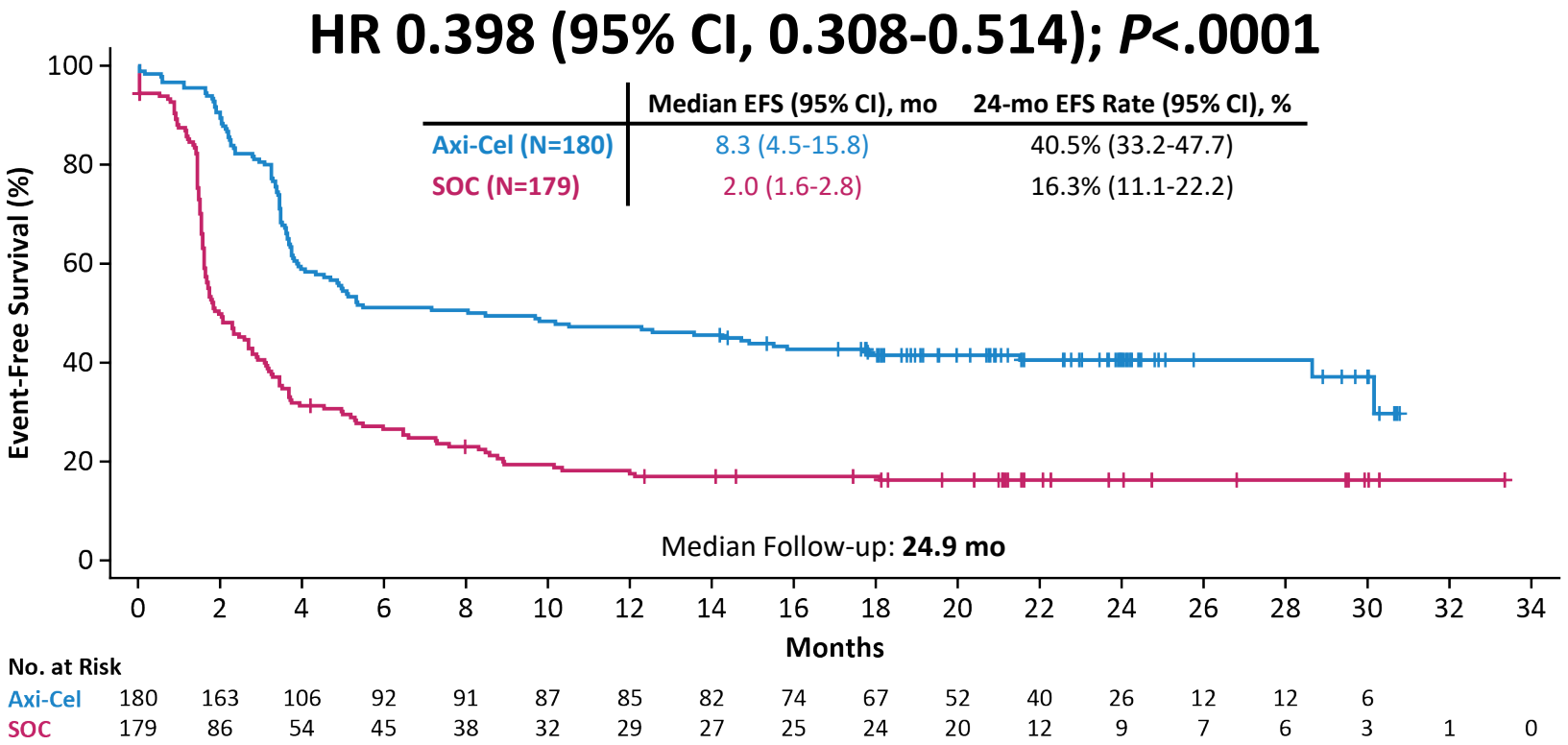


Baseline Characteristics Were Generally Balanced Between the Axi-Cel and SOC Arm

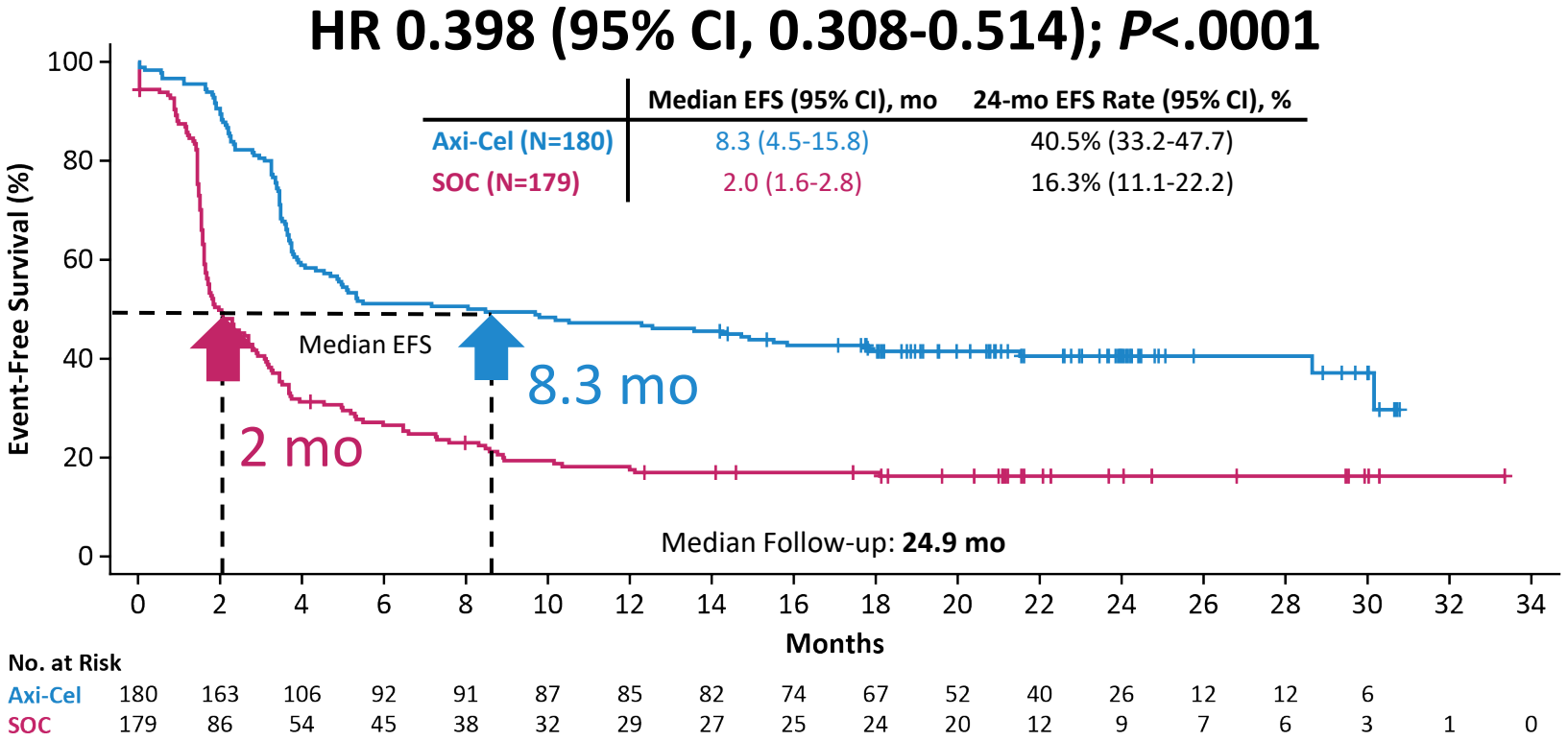
Characteristic	Axi-Cel N=180	SOC N=179	Overall N=359
Median age (range), years	58 (21-80)	60 (26-81)	59 (21-81)
≥65 years, n (%)	51 (28)	58 (32)	109 (30)
Disease stage III-IV, n (%)	139 (77)	146 (82)	285 (79)
sAAIPI of 2-3[a], n (%)	82 (46)	79 (44)	161 (45)
Response to 1L therapy[a], n (%)			
Primary refractory	133 (74)	131 (73)	264 (74)
Relapse ≤12 mo of 1L therapy	47 (26)	48 (27)	95 (26)
Prognostic marker per central laboratory, n (%)			
HGBL (including double-/triple-hit)	31 (17)	25 (14)	56 (16)
Double expressor lymphoma	57 (32)	62 (35)	119 (33)
MYC rearrangement	15 (8)	7 (4)	22 (6)
Elevated LDH level[b]	101 (56)	94 (53)	195 (54)

[a] As reported by investigator at the time of randomization. [b] Lactate dehydrogenase level greater than upper limit of normal per local laboratory reference range.

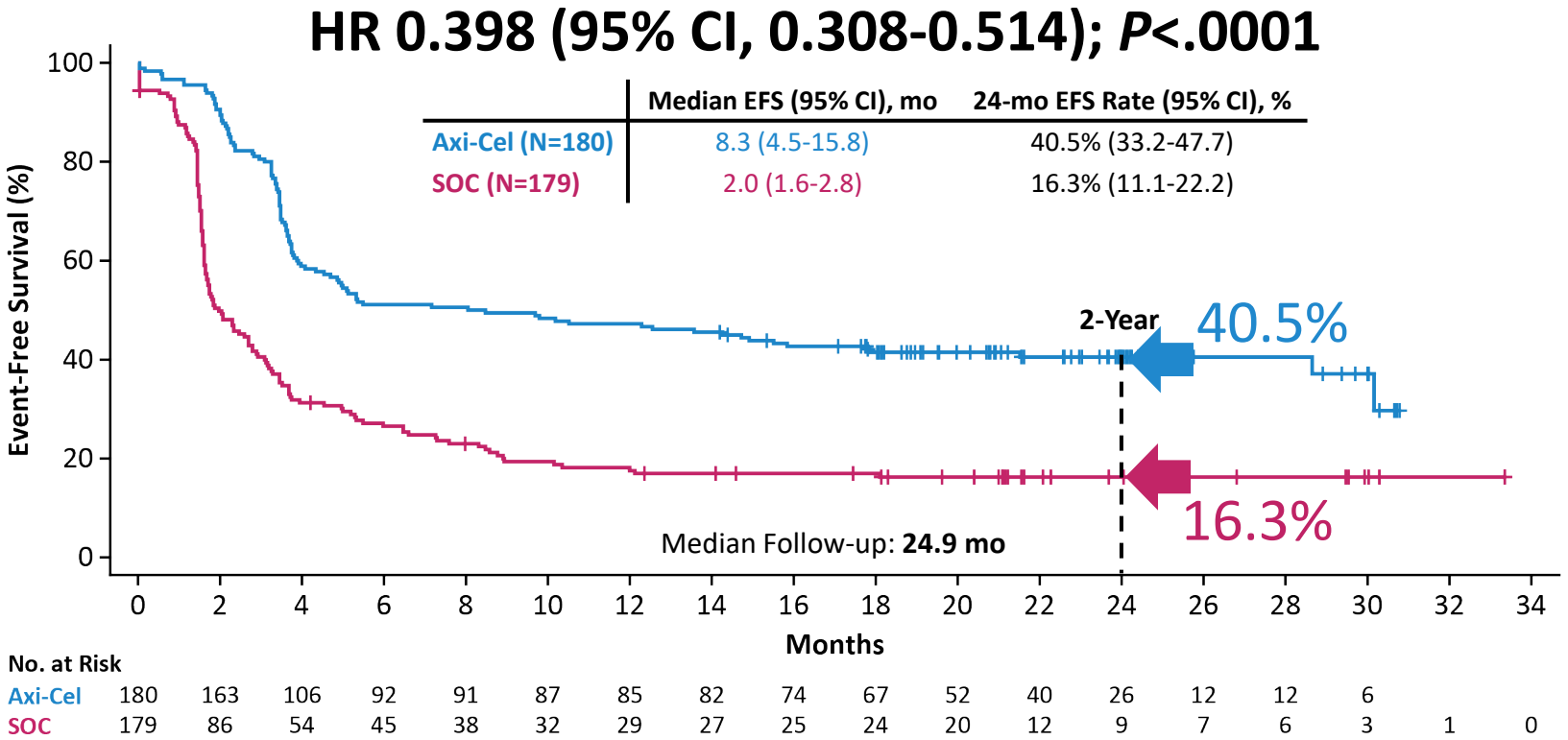
Primary EFS Endpoint: Axi-Cel Is Superior to SOC



Primary EFS Endpoint: Axi-Cel Is Superior to SOC

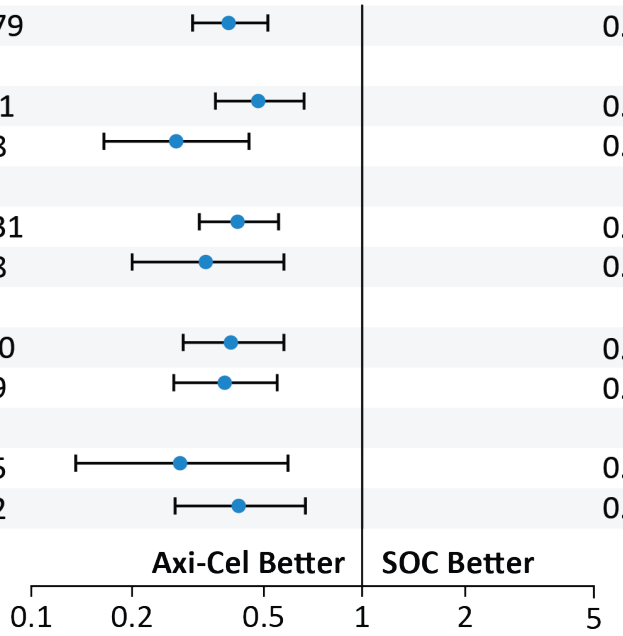


Primary EFS Endpoint: Axi-Cel Is Superior to SOC

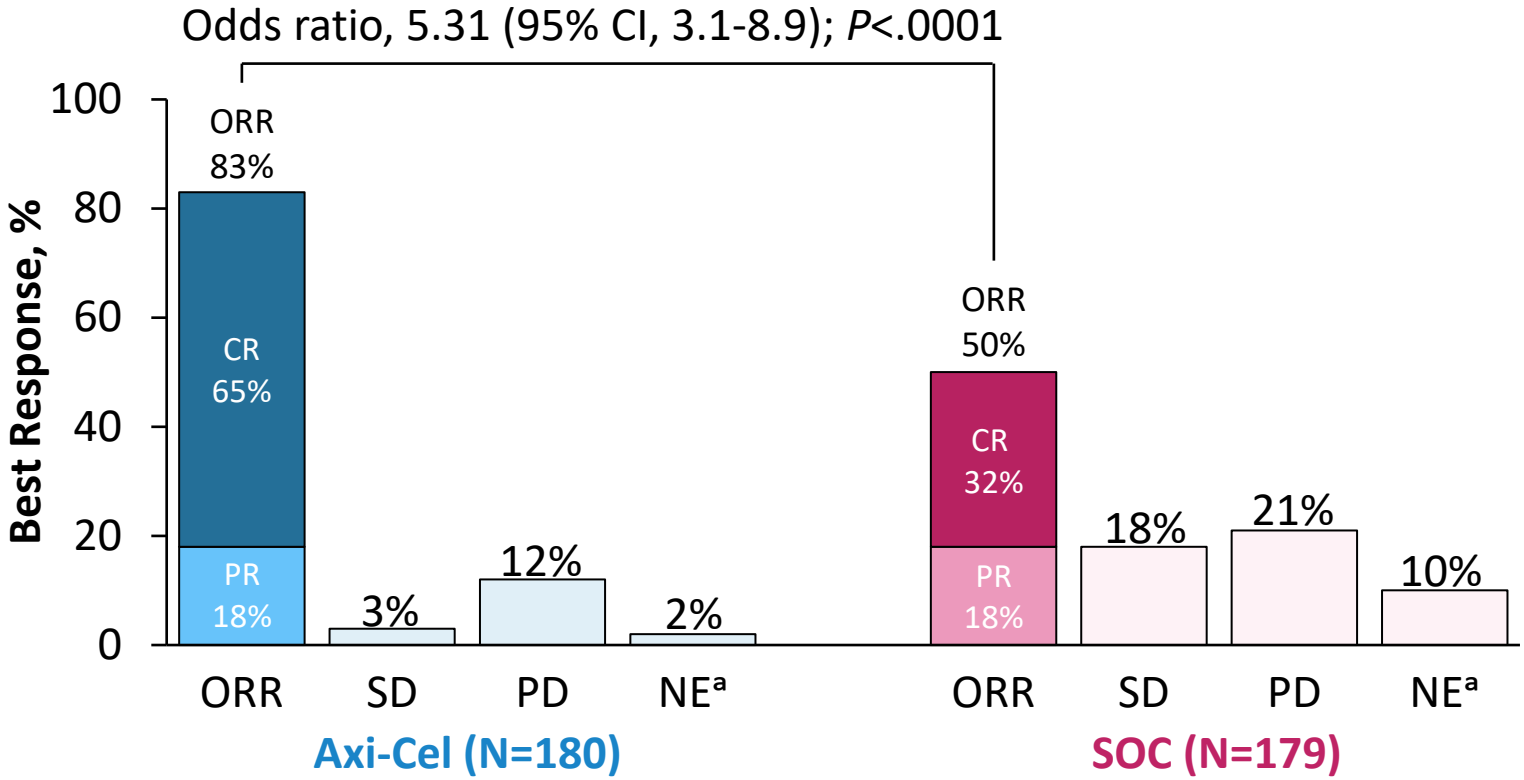


EFS Improvements With Axi-Cel Versus SOC Were Consistent Among Key Patient Subgroups

	Axi-Cel EFS Event/N	SOC EFS Event/N	HR (95% CI)
Overall	108/180	144/179	0.398 (0.308-0.514)
Age, years			
<65	81/129	96/121	0.490 (0.361-0.666)
≥65	27/51	48/58	0.276 (0.164-0.465)
Response to 1L therapy at randomization			
Primary refractory	85/133	106/131	0.426 (0.319-0.570)
Relapse ≤12 months of 1L therapy	23/47	38/48	0.342 (0.202-0.579)
sAAIPI			
0-1	54/98	73/100	0.407 (0.285-0.582)
2-3	54/82	71/79	0.388 (0.269-0.561)
Prognostic marker per central laboratory			
HGBL-double/triple hit	15/31	21/25	0.285 (0.137-0.593)
Double expressor lymphoma	35/57	50/62	0.424 (0.268-0.671)

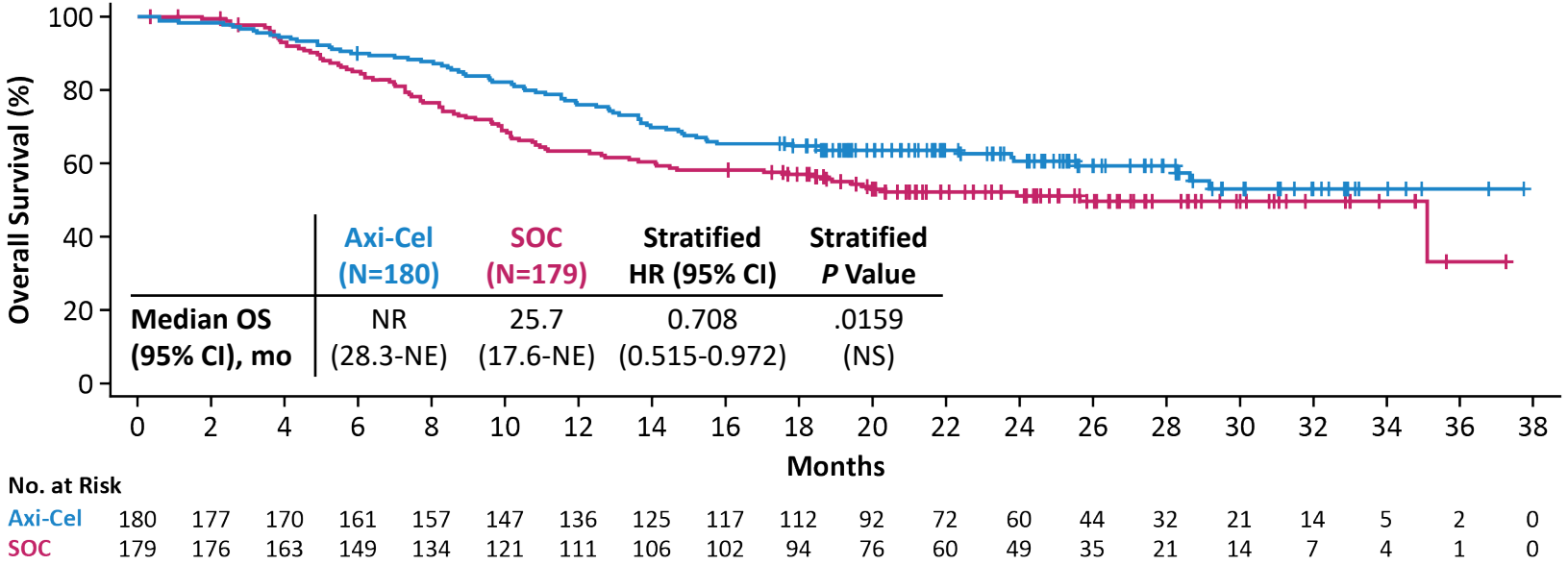


ORR Was Significantly Higher in Axi-Cel Versus SOC Patients



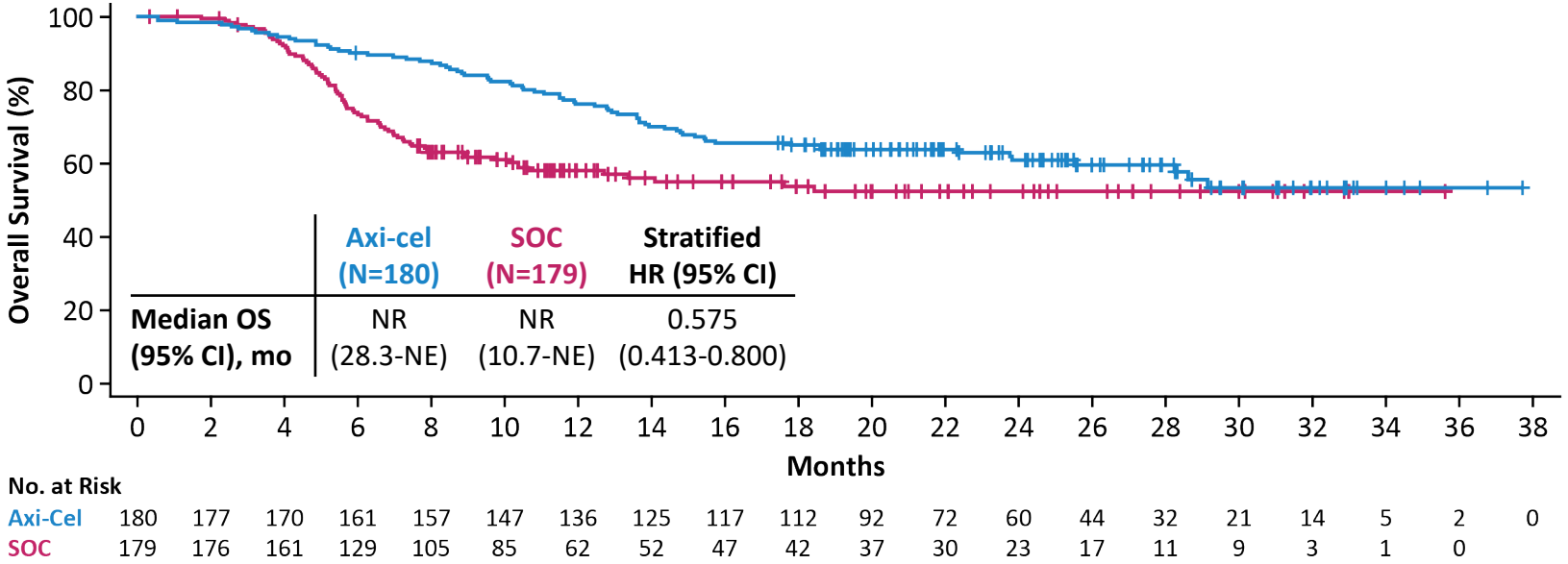
[a] Not evaluable (NE): In the axi-cel arm, response assessments were not done for 4 patients. In the SOC arm, there were 4 patients with undefined disease and 14 who did not have response assessments done.

Median OS, Evaluated as an Interim Analysis, Was Not Reached for Axi-Cel Versus 25.7 Months for SOC



- 56% of SOC patients received subsequent cellular immunotherapy (off protocol)
- ZUMA-7 interim OS analysis was updated following an FDA-requested survival sweep and includes information from public records prior to data cutoff of March 18, 2021

Sensitivity Analysis of Median OS Suggested an OS Benefit of Axi-Cel



- Preplanned sensitivity analysis suggested an OS benefit in favor of axi-cel with the Rank Preserving Structural Failure Time model[1] (stratified HR, 0.575 [95% CI, 0.413-0.800])
  - An additional analysis using the Inverse Probability of Censoring Weights model showed a stratified HR of 0.618 (95% CI, 0.417-0.916)

1. Robins JM and Tsiatis AA. *Commun Stat Theory Methods*. 1991;2609-2631.

Safety Profile of Axi-Cel Was Manageable and Consistent With Previous Studies in Refractory LBCL[1,2]

Adverse Events, n (%)[a]	Axi-Cel n=170		SOC n=168	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	**170 (100)**	**155 (91)**	**168 (100)**	**140 (83)**
Pyrexia	158 (93)	15 (9)	43 (26)	1 (1)
Neutropenia[b]	121 (71)	118 (69)	70 (42)	69 (41)
Hypotension	75 (44)	19 (11)	25 (15)	5 (3)
Fatigue	71 (42)	11 (6)	87 (52)	4 (2)
Anemia	71 (42)	51 (30)	91 (54)	65 (39)
Diarrhea	71 (42)	4 (2)	66 (39)	7 (4)
Headache	70 (41)	5 (3)	43 (26)	2 (1)
Nausea	69 (41)	3 (2)	116 (69)	9 (5)
Sinus tachycardia	58 (34)	3 (2)	17 (10)	1 (1)
Leukopenia[c]	55 (32)	50 (29)	43 (26)	37 (22)
Any serious AE	**85 (50)**	**72 (42)**	**77 (46)**	**67 (40)**

Reason for Death	Axi-Cel n=170	SOC n=168
Progressive disease, n (%)	**47 (28)**	**64 (38)**
Grade 5 AE during protocol-specified reporting period, n (%)	**7 (4)[d]**	**2 (1)[e]**
Definitive therapy-related mortality, n/N (%)	**1/170 (1)[f]**	**2/64 (3)[e]**

1. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531-2544. 2. Locke FL, et al. *Blood.* 2017;130:2826.

[a] Included are any adverse events of any grade occurring in ≥20% of patients in either the axi-cel or SOC arm. [b] Combined preferred terms of neutropenia and neutrophil count decreased. [c] Combined preferred terms of leukopenia and white blood cell count decreased. [d] COVID-19 (n=2) and lung adenocarcinoma, myocardial infarction, progressive multifocal leukoencephalopathy, sepsis, and hepatitis B reactivation (n=1 each). [e] Cardiac arrest and acute respiratory distress syndrome (n=1 each). [f] Hepatitis B reactivation.

Grade ≥3 CRS and Neurologic Events Were Generally Consistent With Third-Line Treatment of Patients[1]

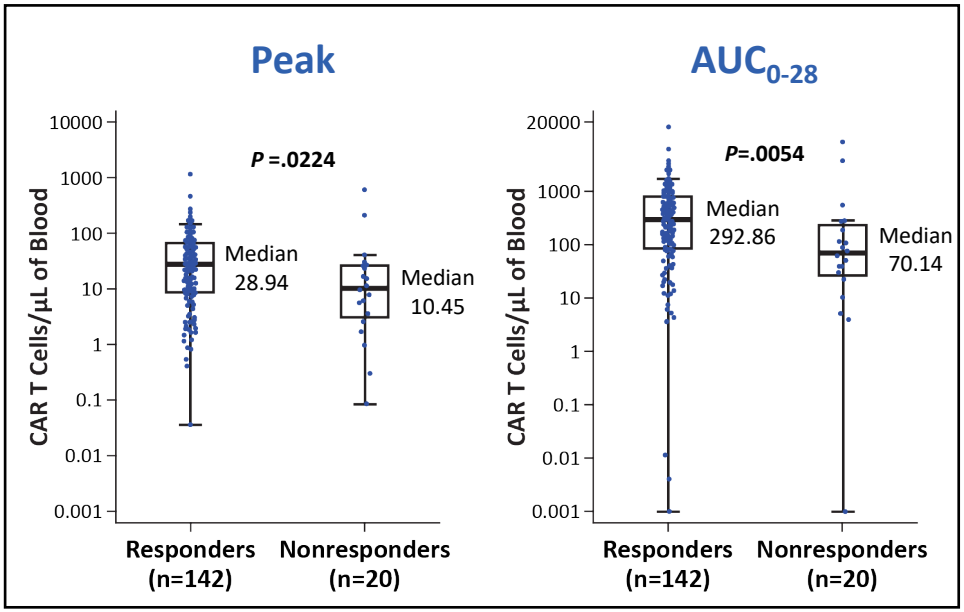
CRS Parameter	Axi-Cel n=170
CRS, n (%)[a]	
Any grade	157 (92)
Grade ≥3	11 (6)
Grade 5	0
Most common any-grade symptoms, n/n (%)	
Pyrexia	155/157 (99)
Hypotension	68/157 (43)
Sinus tachycardia	49/157 (31)
AE management[d], n (%)	
Tocilizumab	111 (65)
Corticosteroids	40 (24)
Vasopressors	11 (6)
Median time to onset, days	3
Median duration of events, days	7

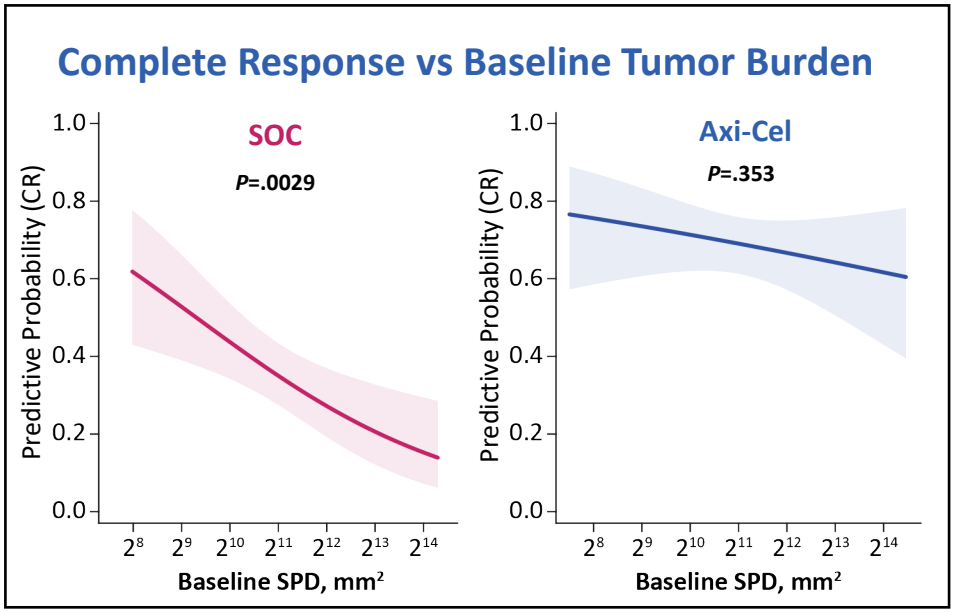
Neurologic Event Parameter	Axi-Cel n=170	SOC n=168
Neurologic events, n (%)[b]		
Any grade	102 (60)	33 (20)[c]
Grade ≥3	36 (21)	1 (1)
Grade 5	0	0
Most common any-grade symptoms, n (%)		
Tremor	44 (26)	1 (1)
Confusional state	40 (24)	4 (2)
Aphasia	36 (21)	0
AE management[d], n (%)		
Corticosteroids	54 (32)	-
Median time to onset, days	7	23
Median duration of events, days	9	23

1. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531-2544. 2. Lee DW, et al. *Blood.* 2014;124:188-195. 3. Topp MS, et al. *Lancet Oncol.* 2015;16:57-66.

[a] CRS was graded according to Lee et al.[2] [b] Neurologic events were identified per prespecified search list based on methods used in the blinatumomab registrational study.[3] Neurologic events were graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. [c] Other preferred terms reported in the SOC arm (in ≤2 patients) included somnolence, agitation, hypoesthesia, lethargy, depressed level of consciousness, cognitive disorder, memory impairment, bradyphrenia, taste disorder, hallucination, hallucination visual, nystagmus, head discomfort, and neuralgia. [d] Toxicity management followed ZUMA-1 pivotal cohorts.

ZUMA-7 CAR T-Cell Levels Associated With Objective Response and Tumor Burden Impacted CR Rate in the SOC Arm





SPD: sum of product of diameters of 6 target lesions.

Conclusions

- ZUMA-7 is the first randomized CAR T-cell trial and has 24.9 months median follow-up
- ZUMA-7 met its primary EFS endpoint, demonstrating statistically significant and clinically meaningful improvement in efficacy with axi-cel versus second-line SOC in R/R LBCL
- Axi-cel showed superiority over SOC

>4-fold greater median EFS	2.5-fold greater 2-year EFS	33% higher ORR	Double the CR rate	EFS improvements across key subgroups

- Nearly 3× the number of patients in the axi-cel arm received definitive therapy versus the SOC arm
- Axi-cel had a manageable safety profile that was consistent with previous studies[1,2]
- Paradigm shift: Axi-cel should be the new standard for patients with second-line R/R LBCL

1. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531-2544. 2. Locke FL, et al. *Blood*. 2017;130:2826.

Acknowledgments

- The patients, families, friends, and caregivers
- The entire ZUMA-7 study team of investigators, coordinators, and health care staff at each study site
- Medical writing support was provided by Jennifer Yang, PhD, and Ashley Skorusa, PhD, of Nexus Global Group Science LLC, funded by Kite
- All employees of Kite involved over the course of the study for their contributions
- These data were in part previously presented at the 2021 Annual Meeting of the American Society of Hematology and published in *The New England Journal of Medicine*[1,2]

ZUMA-7 Global Phase 3 Clinical Trial Sites

1. Locke FL, et al. ASH 2021. Plenary Abstract 2. Locke FL, et al. *N Engl J Med* 2021; DOI: 10.1056/NEJMoa2116133.