

Primary Analysis of ZUMA-7: a Phase 3 Randomized Trial of Axicabtagene Ciloleucel versus Standard-of-Care Therapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma

Frederick L. Locke, MD¹; David B. Miklos, MD, PhD²; Caron A. Jacobson, MD, MMSc³; Miguel-Angel Perales, MD⁴; Marie José Kersten MD, PhD⁵; Olalekan O. Oluwole, MBBS, MPH⁶; Armin Ghobadi, MD⁷; Aaron P. Rapoport, MD⁸; Joseph P. McGuirk, DO⁹; John M. Pagel, MD, PhD¹⁰; Javier Muñoz, MD, MS, MBA, FACP¹¹; Umar Farooq, MD¹²; Tom van Meerten, MD, PhD¹³; Patrick M. Reagan, MD¹⁴; Anna Sureda, MD, PhD¹⁵; Ian W. Flinn, MD, PhD¹⁶; Peter Vandenberghe, MD, PhD¹⁷; Kevin W. Song, MD, FRCPC¹⁸; Michael Dickinson, MBBS, D Med Sci, FRACP, FRCPA¹⁹; Monique C. Minnema, MD, PhD²⁰; Peter A. Riedell, MD²¹; Lori A. Leslie, MD²²; Sridhar Chaganti, MD²³; Yin Yang, MS, MD²⁴; Simone Filosto, PhD²⁴; Marco Schupp, MD²⁴; Christina To, MD²⁴; Paul Cheng, MD, PhD²⁴; Leo I. Gordon, MD²⁵; and Jason R. Westin, MD, MS, FACP²⁶, on behalf of all ZUMA-7 investigators and contributing Kite members

¹Moffitt Cancer Center, Tampa, FL, USA; ²Stanford University School of Medicine, Stanford, CA, USA; ³Dana-Farber Cancer Institute, Boston, MA, USA; ⁴Memorial Sloan-Kettering Cancer Center, New York, NY, USA;

⁵Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands, on behalf of HOVON/LLPC; ⁶Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; ⁷Washington University School of Medicine, St Louis, MO, USA; ⁸The Marlene and Stewart Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD, USA; ⁹University of Kansas Cancer Center, Kansas City, KS, USA; ¹⁰Swedish Cancer

Institute, Seattle, WA, USA; ¹¹Banner MD Anderson Cancer Center, Gilbert, AZ, USA; ¹²University of Iowa, Iowa City, IA, USA; ¹³University Medical Center Groningen, Groningen, Netherlands, on behalf of HOVON/LLPC;

¹⁴University of Rochester School of Medicine, Rochester, NY, USA; ¹⁵Hematology Department, Institut Català d'Oncologia-Hospitalet, IDIBELL, Universitat de Barcelona, Barcelona, Spain; ¹⁶Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; ¹⁷University Hospitals Leuven, Leuven, Belgium; ¹⁸Division of Hematology, University of British Columbia and Leukemia/BMT Program of BC, Vancouver General Hospital, Vancouver, BC, Canada; ¹⁹Peter MacCallum Cancer Centre, Royal Melbourne Hospital and the University of Melbourne, Melbourne, Victoria, Australia; ²⁰UMC, University of Utrecht, The Netherlands, on

behalf of HOVON/LLPC; ²¹The University of Chicago Medical Center, Chicago, IL, USA; ²²John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; ²³Centre for Clinical Haematology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; ²⁴Kite, a Gilead Company, Santa Monica, CA, USA; ²⁵Northwestern University Feinberg School of Medicine and the Robert H. Lurie

Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; and ²⁶The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Disclosures

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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-ASCT¹
- Many patients cannot receive HDT-ASCT, and their prognosis is poor²⁻⁴
- 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

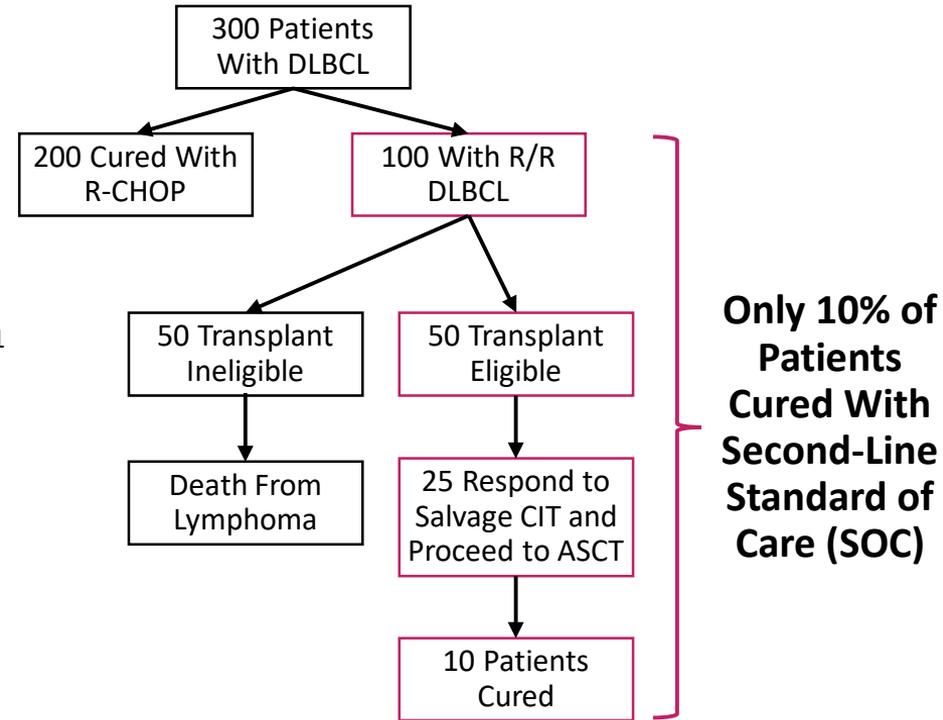
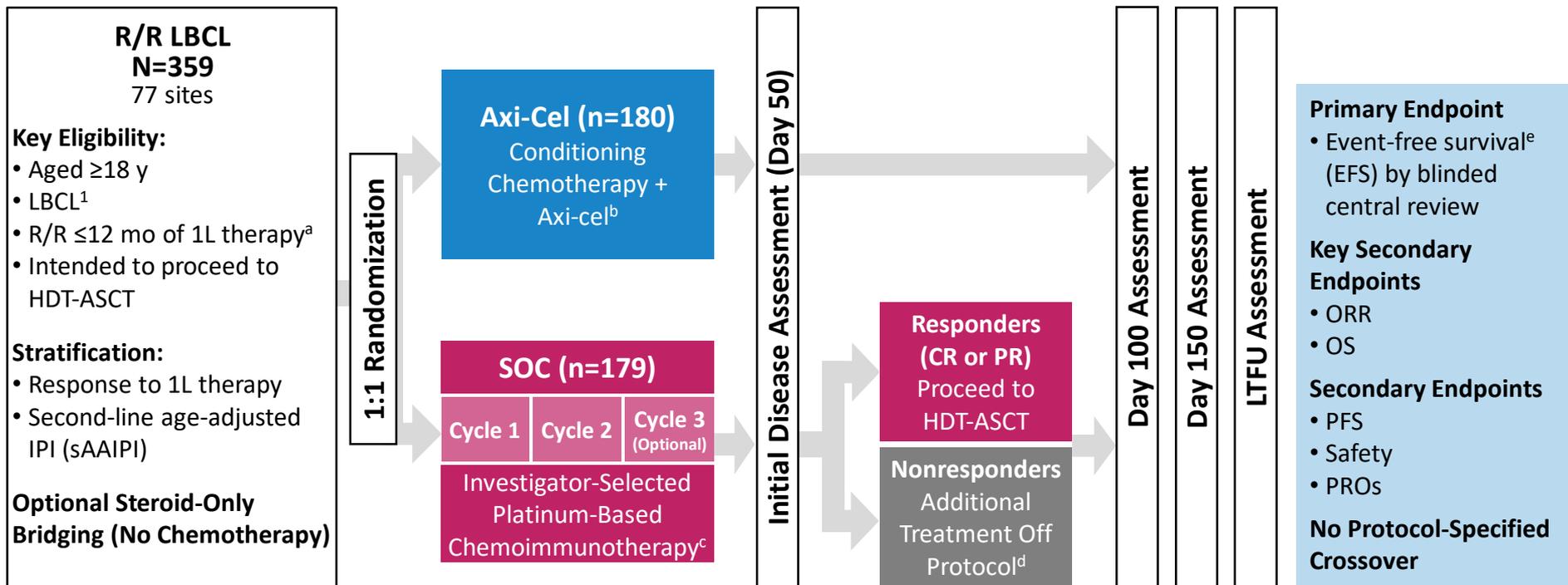


Figure adapted with permission from Friedberg. *Hematology Am Soc Hematol Educ Program*. 2011;2011:498-505.

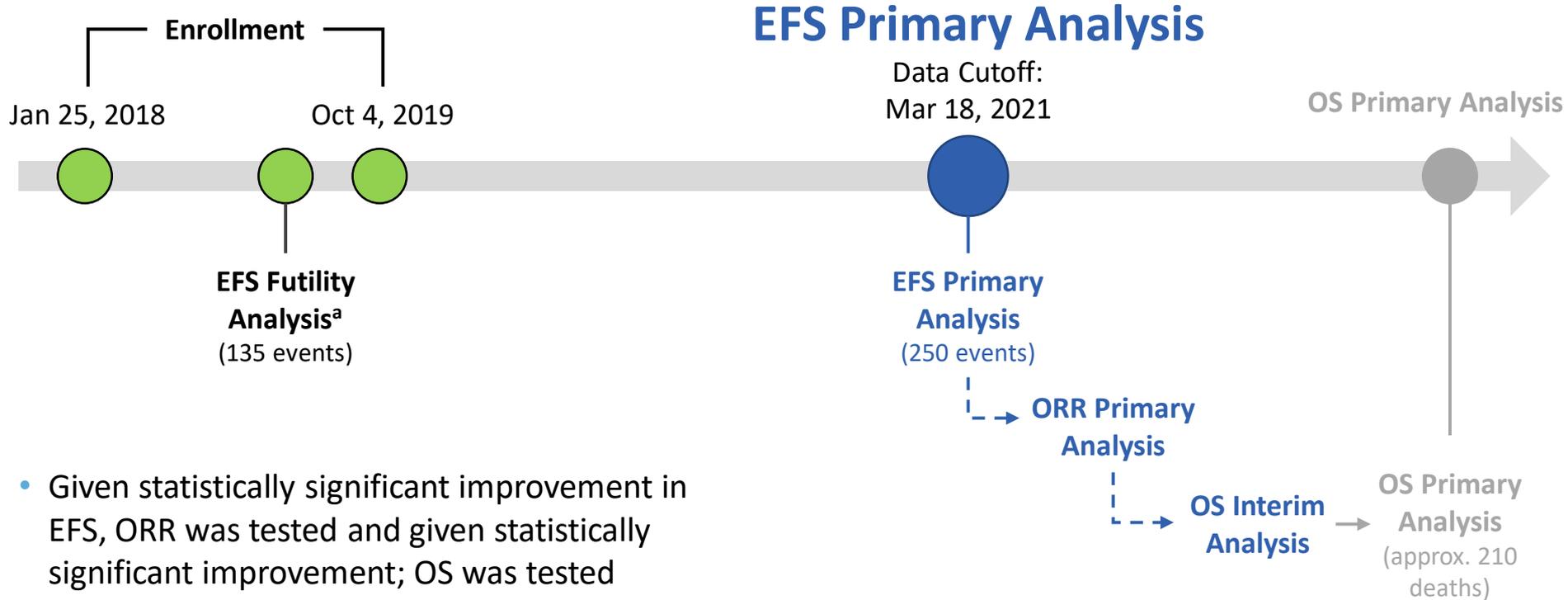
1. Zahid U, et al. *Curr Hematol Malig Rep*. 2017;12:217-226. 2. Gisselbrecht C, et al. *J Clin Oncol*. 2010;28:4184-4190. 3. Van Den Neste E, et al. *Bone Marrow Transplant*. 2016;51:51-57. 4. van Imhoff GW, et al. *J Clin Oncol*. 2017;35:544-551.

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



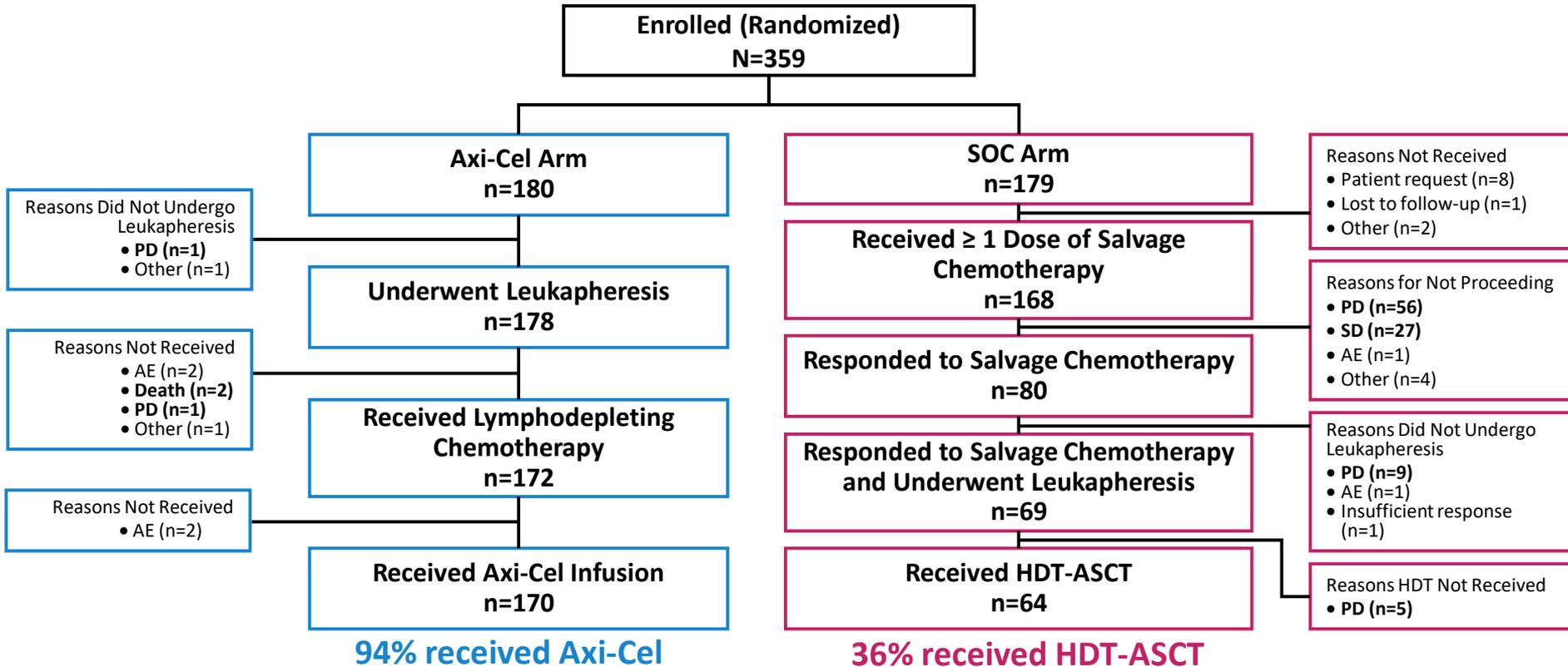
^a Refractory disease was defined as no CR to 1L therapy; relapsed disease was defined as CR followed by biopsy-proven disease relapse ≤ 12 months from completion of 1L therapy. ^b Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/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



^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



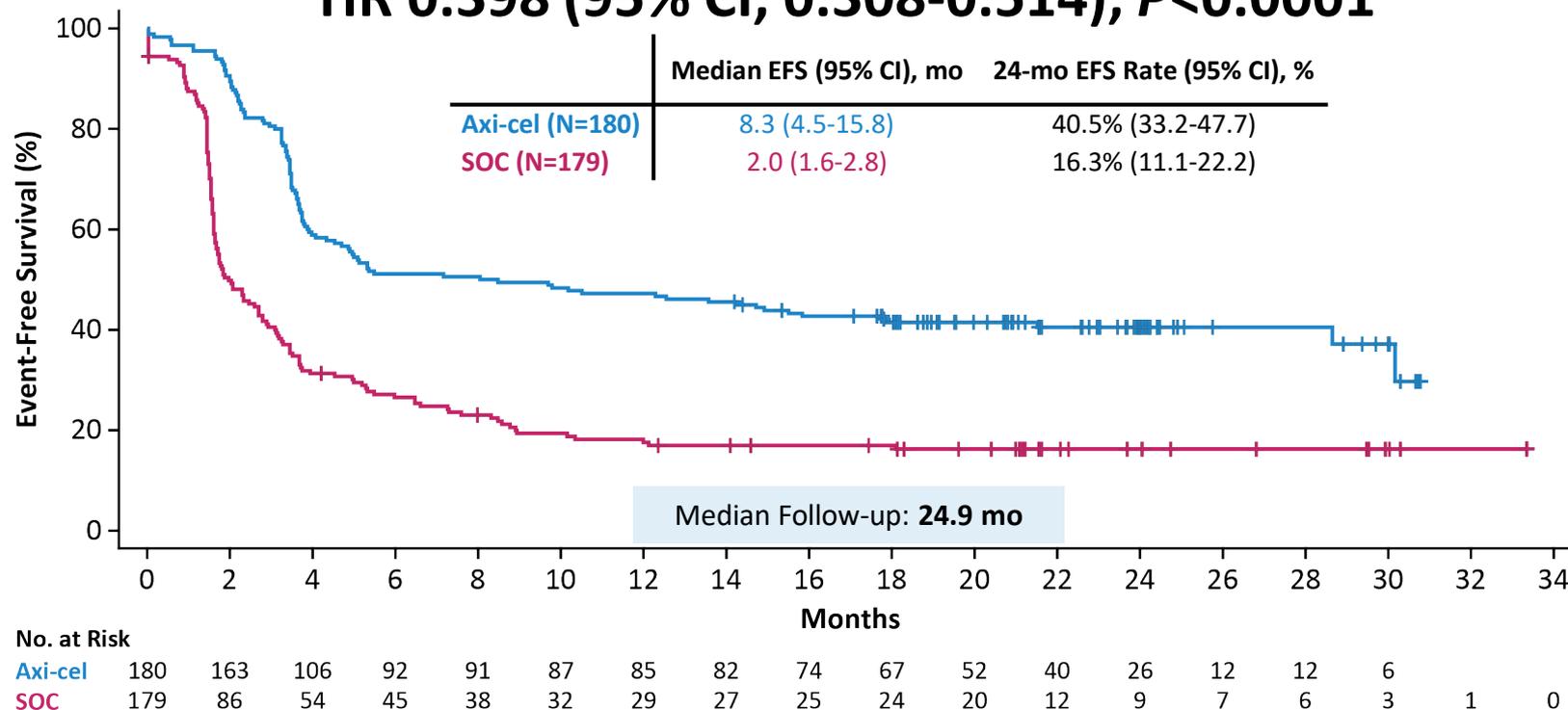
Baseline Characteristics Were Generally Balanced Between the Axi-Cel and SOC Arm

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)
<i>MYC</i> 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

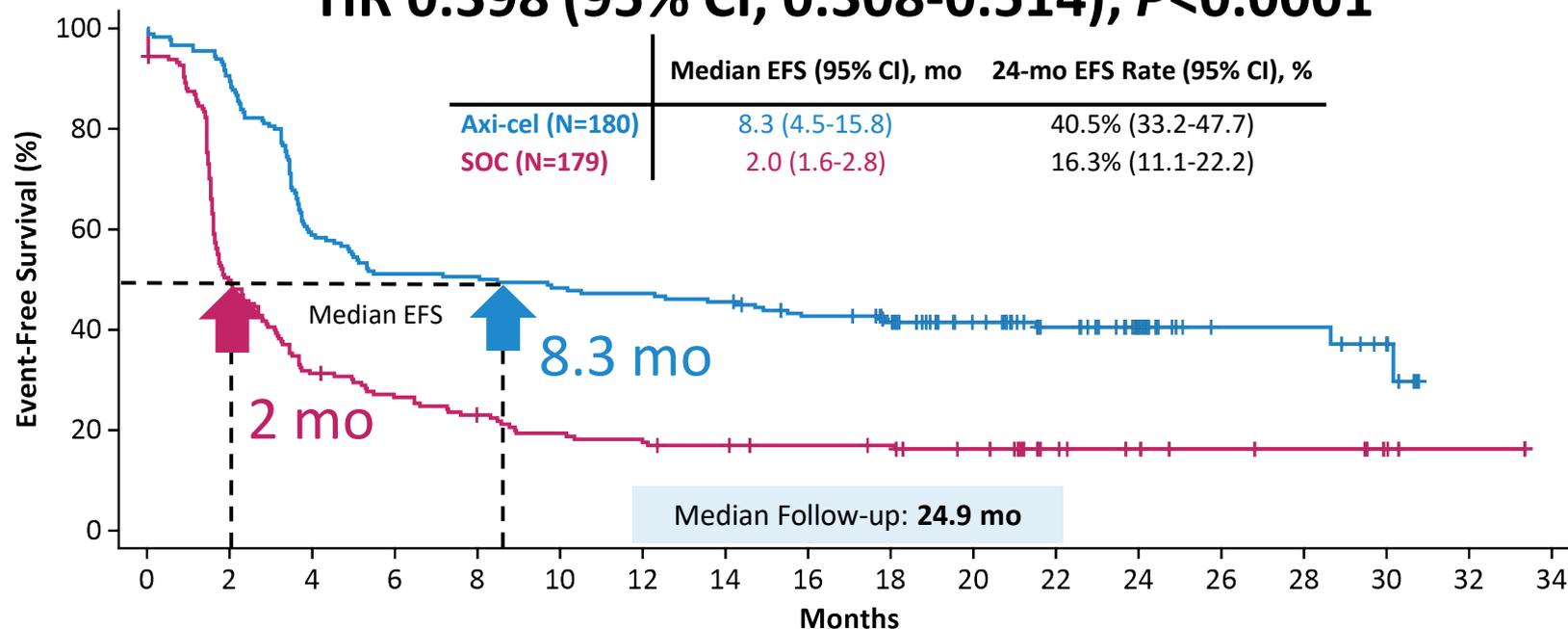
HR 0.398 (95% CI, 0.308-0.514); $P < 0.0001$



Median Follow-up: 24.9 mo

Primary EFS Endpoint: Axi-Cel Is Superior to SOC

HR 0.398 (95% CI, 0.308-0.514); $P < 0.0001$

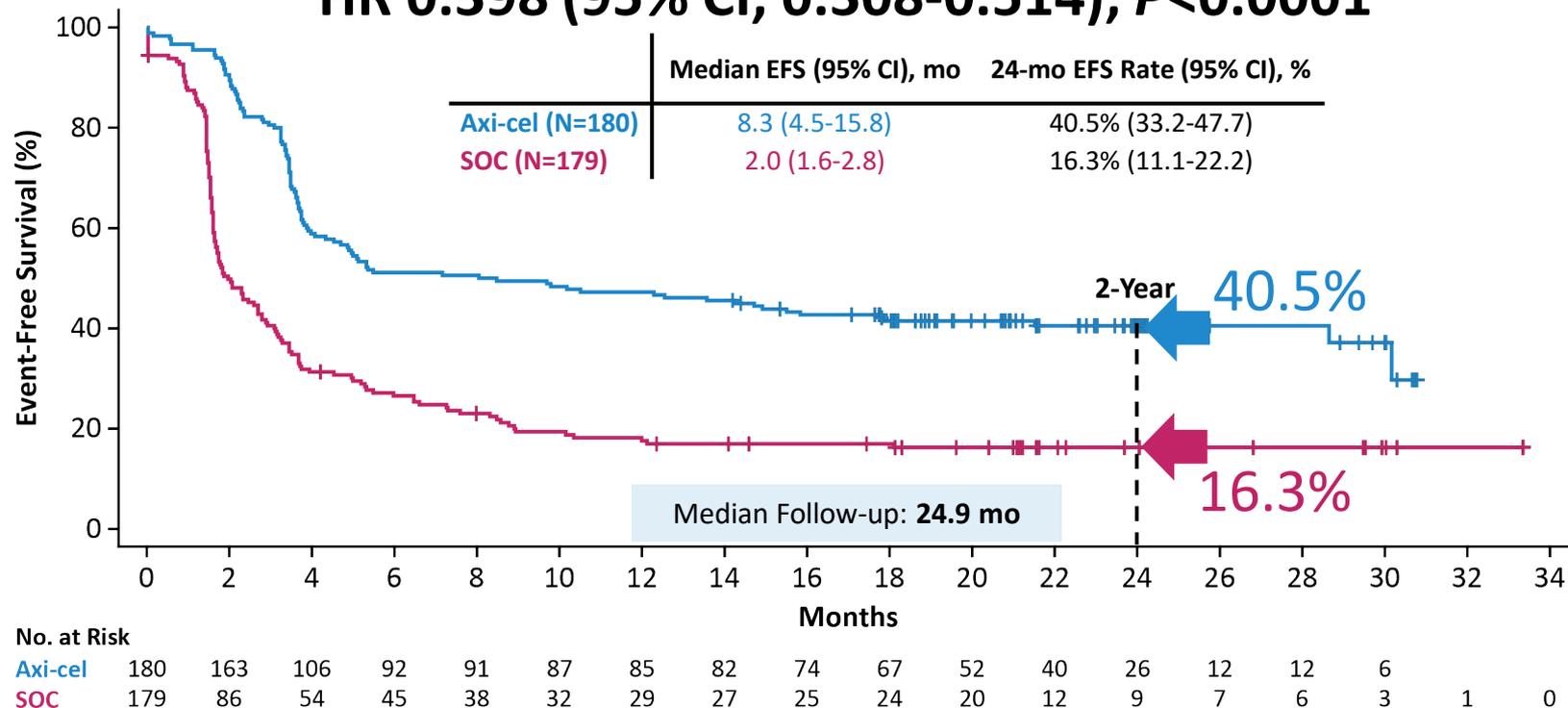


No. at Risk

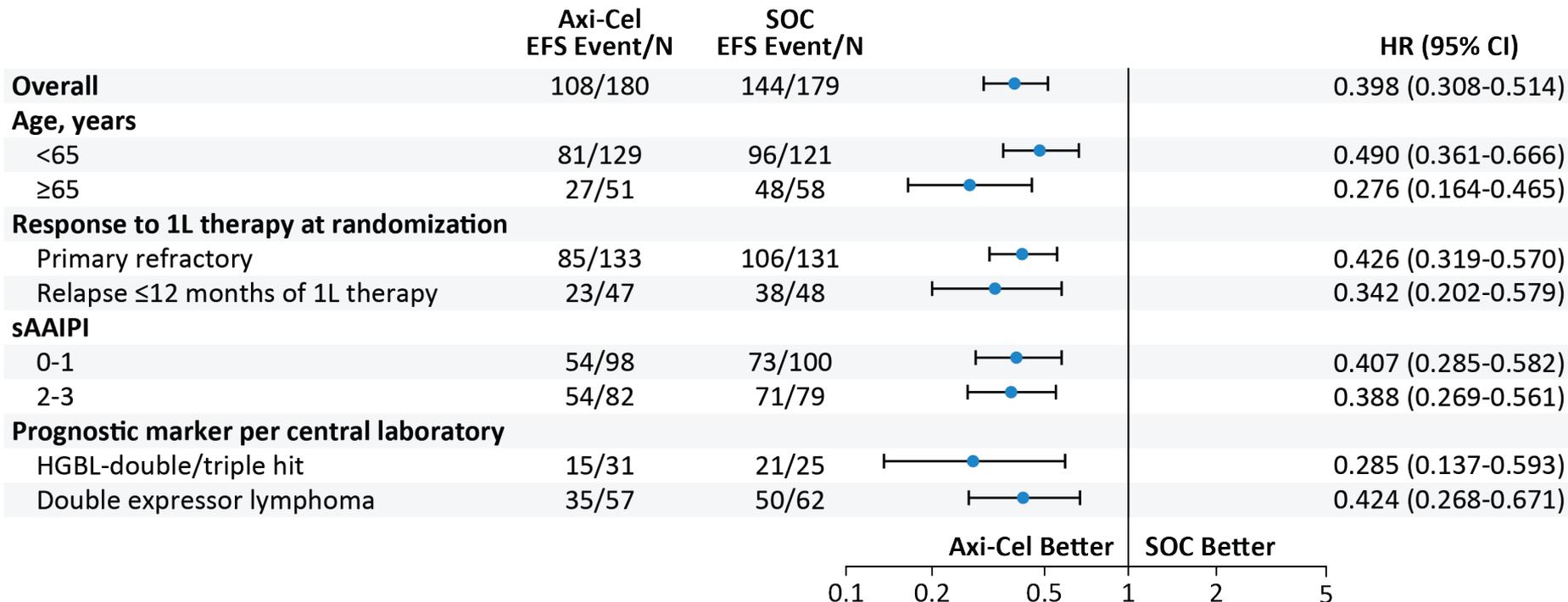
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6	1	0
SOC	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

Primary EFS Endpoint: Axi-Cel Is Superior to SOC

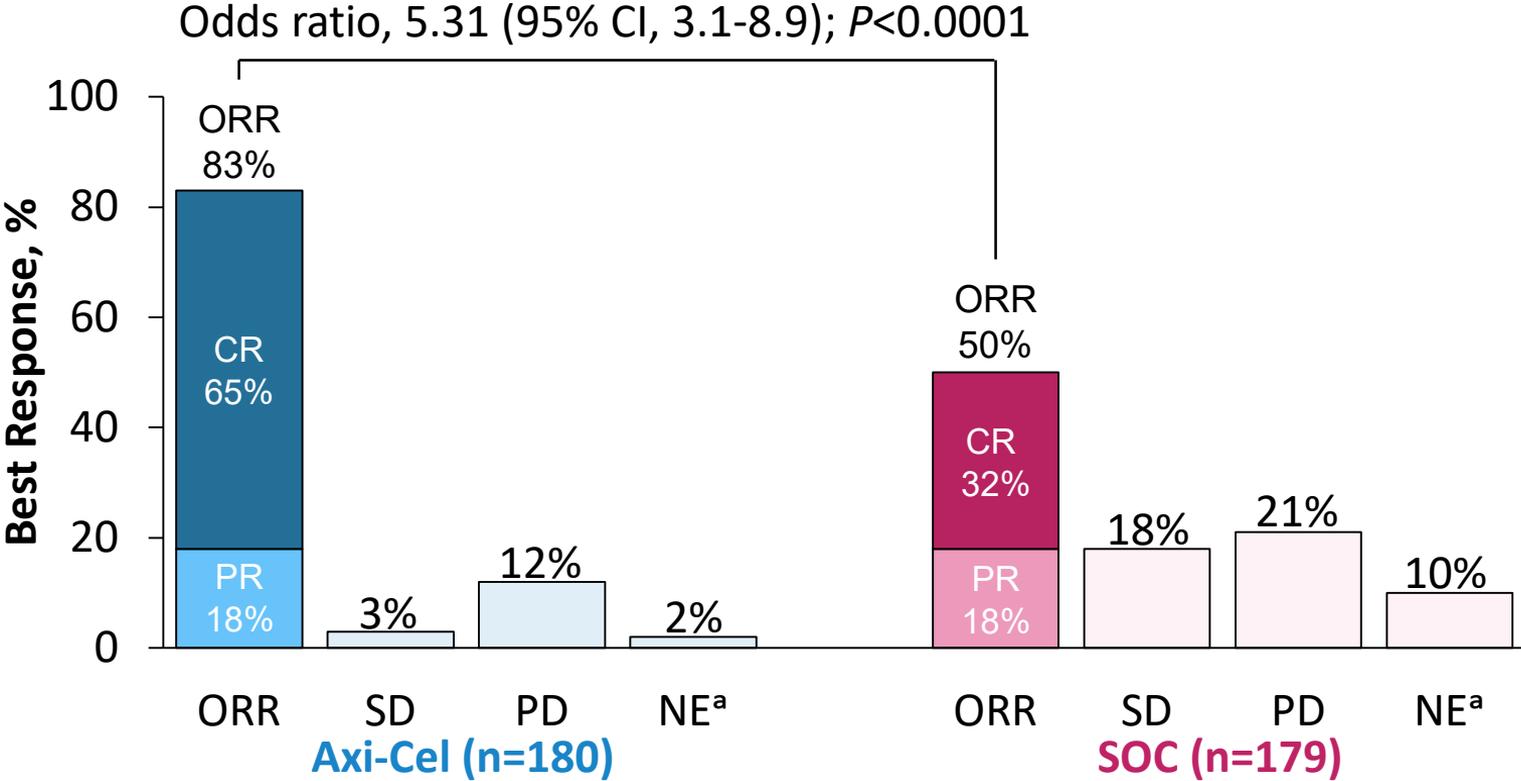
HR 0.398 (95% CI, 0.308-0.514); $P < 0.0001$



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

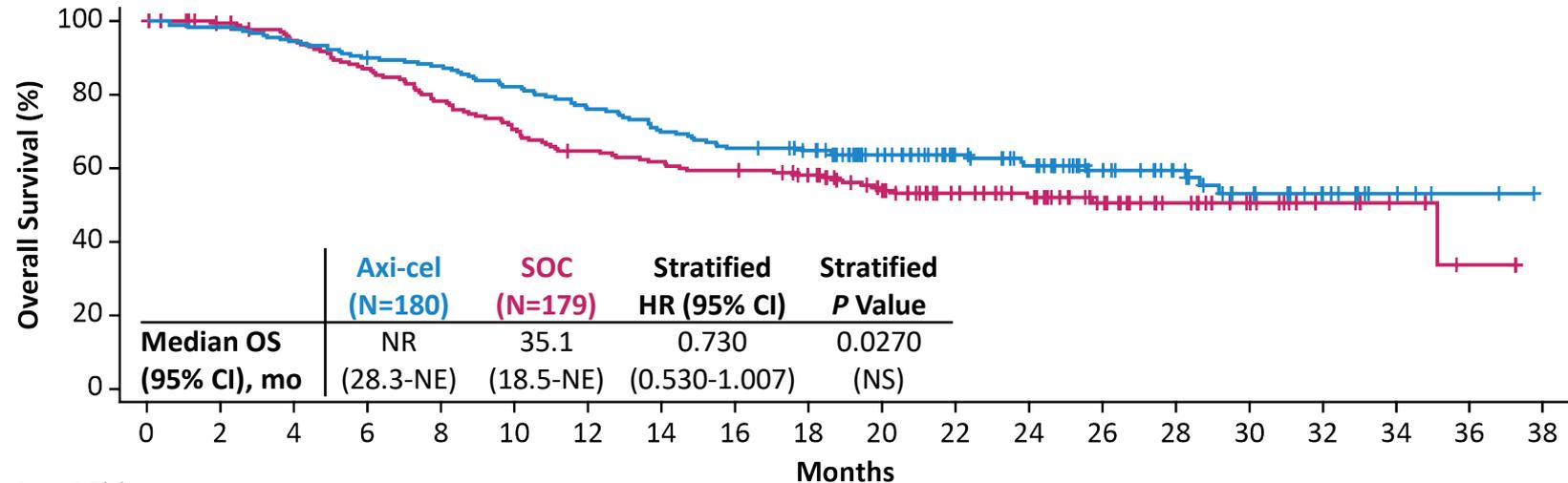


ORR Was Significantly Higher in Axi-Cel Versus SOC Patients



^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 35.1 Months for SOC



No. at Risk

Axi-cel	180	177	170	161	157	147	136	125	117	111	91	71	60	44	32	21	14	5	2	0
SOC	179	171	161	148	133	120	109	104	100	91	74	58	47	33	21	14	7	4	1	0

- 56% of SOC patients received subsequent cellular immunotherapy (off protocol)
- Preplanned sensitivity analysis^a suggests an OS benefit, likely confounded by SOC treatment switching

^a Analysis utilized the validated and commonly used Rank Preserving Structural Failure Time model, which preserves randomization as described by Robins and Tsiatis (*Commun Stat Theory Methods*. 1991;2609-2631) and revealed the difference in treatment effect if SOC patients did not receive subsequent cellular immunotherapy. Stratified hazard ratio was 0.580 (95% CI, 0.416-0.809).

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.

^aIncluded are any adverse events of any grade occurring in ≥20% of patients in either the axi-cel or SOC arm. ^bCombined preferred terms of neutropenia and neutrophil count decreased. ^cCombined preferred terms of leukopenia and white blood cell count decreased. ^dCOVID-19 (n=2) and lung adenocarcinoma, myocardial infarction, progressive multifocal leukoencephalopathy, sepsis, and hepatitis B reactivation (n=1 each). ^eCardiac arrest and acute respiratory distress syndrome (n=1 each). ^fHepatitis B reactivation.

Grade ≥ 3 CRS and Neurologic Events Were Generally Consistent With Third-Line Treatment of Patients¹

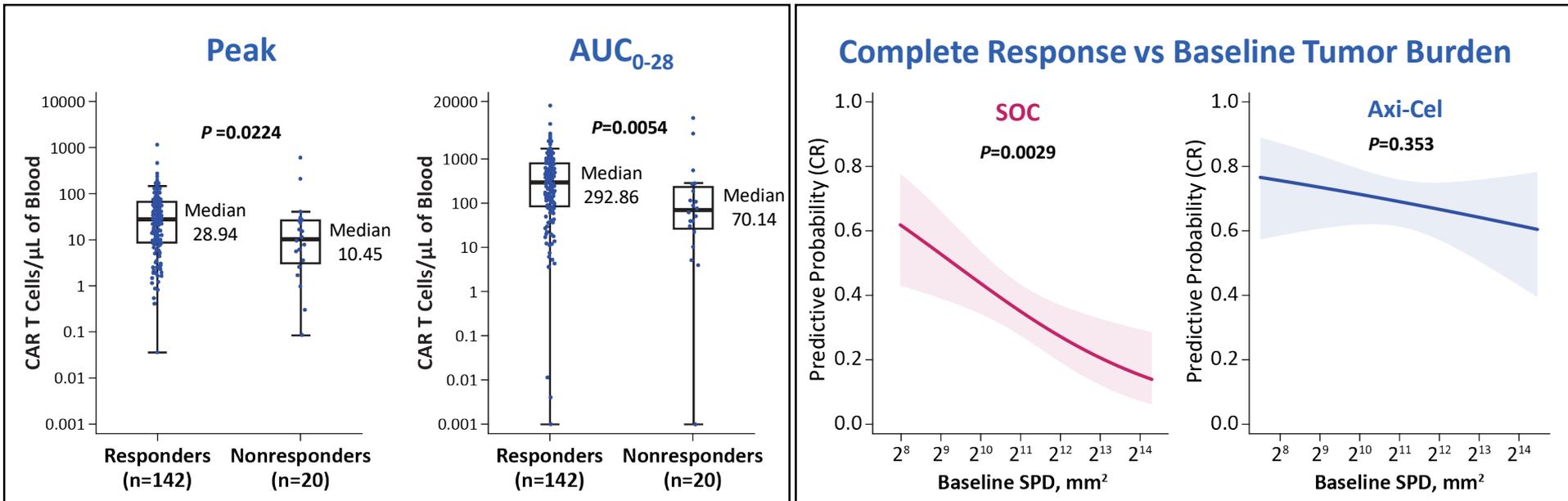
CRS Parameter	Axi-Cel n=170
CRS, n (%)^a	
Any grade	157 (92)
Grade ≥ 3	11 (6)
Grade 5	0
Most common any-grade symptoms, n/n (%)	
Pyrexia	155/157 (99)
Hypotension	68/157 (43)
Sinus tachycardia	49/157 (31)
AE management^d, n (%)	
Tocilizumab	111 (65)
Corticosteroids	40 (24)
Vasopressors	11 (6)
Median time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

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.

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ZUMA-7 Global Phase 3 Clinical Trial Sites



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