Primary Overall Survival Analysis of the Phase 3 Randomized ZUMA-7 Study of Axicabtagene Ciloleucel Versus Standard-of-Care Therapy in Relapsed/Refractory Large B-Cell Lymphoma

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Prior Paradigm: Chemotherapy Followed by HDT-ASCT

- For nearly 30 years, treatment for patients with refractory or relapsed Diffuse Large B-cell Lymphoma in the second-line curative setting was chemotherapy followed by HDT-ASCT
- Most patients could not receive HDT-ASCT, and their prognosis was poor

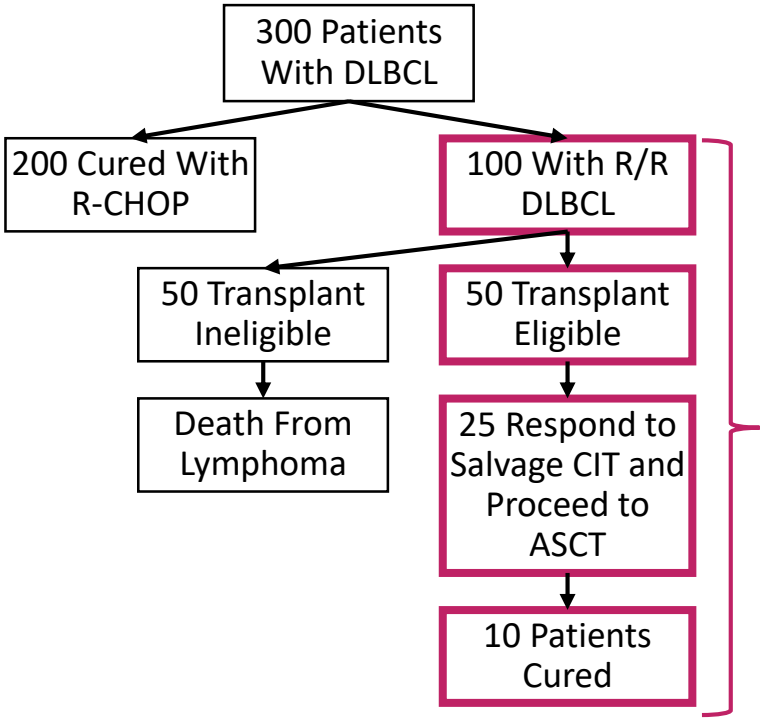

Figure adapted with permission from Friedberg JW. *Hematology Am Soc Hematol Educ Program*. 2011;2011:498-505.
Zahid U, et al. *Curr Hematol Malig Rep*. 2017;12:217-226; Philip T, et al. *N Eng J Med.* 1995;333:1540-1555; Gisselbrecht C, et al. *J Clin Oncol*. 2010;28:4184-4190; Van Den Neste E, et al. *Bone Marrow Transplant*. 2016;51:51-57; van Imhoff GW, et al. *J Clin Oncol*. 2017;35:544-551.
ASCT, autologous stem cell transplantation; CIT, chemoimmunotherapy; DLBCL, diffuse large B-cell lymphoma; HDT-ASCT, high-dose therapy with autologous stem cell transplantation; LBCL, large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R, relapsed/refractory.

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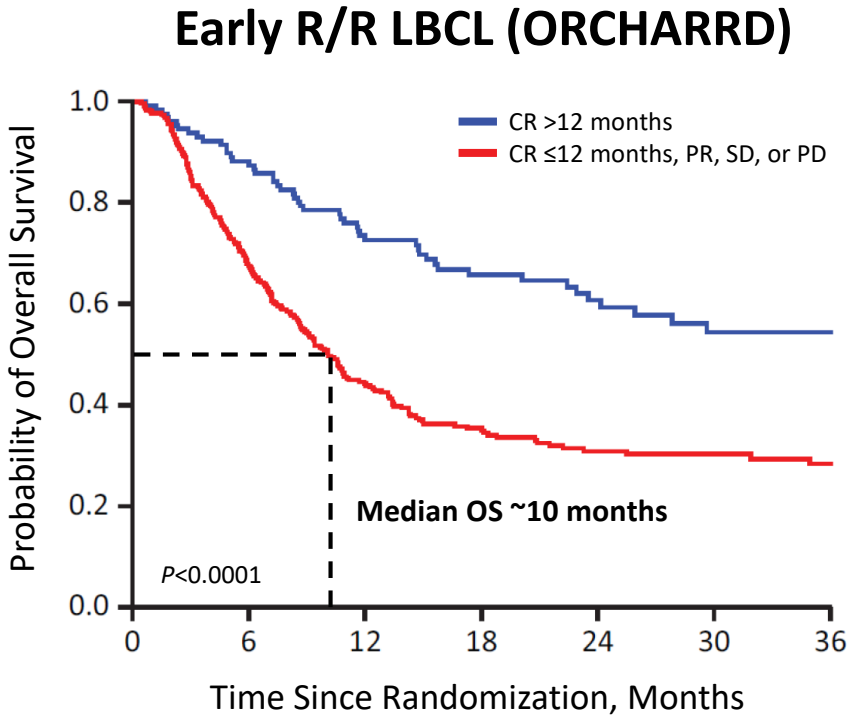

Figure adapted with permission from van Imhoff GW, et al. J Clin Oncol. 2017;35:544-551. The median OS estimate was extrapolated from the red Kaplan-Meier curve using the WebPlotDigitizer 4.6 image digitalization tool.
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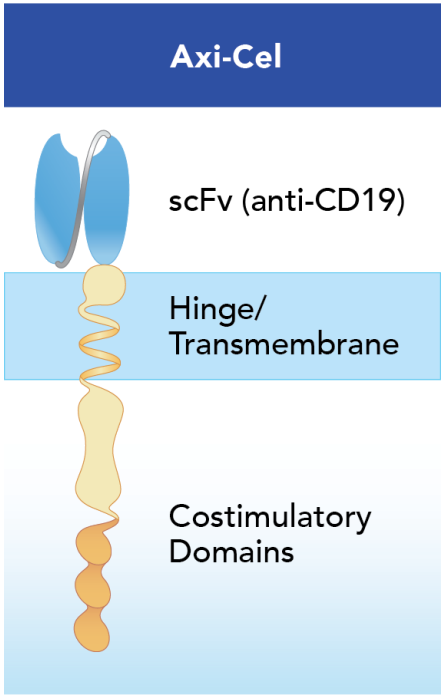
CR, complete response; HDT-ASCT, high-dose therapy with autologous stem cell transplantation; LBCL, large B-cell lymphoma; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease.

New Paradigm: Axi-Cel in Second-Line R/R LBCL

- In the ZUMA-7 trial, axi-cel (autologous CAR T-cell) was superior to chemotherapy/HDT-ASCT in second-line LBCL for the primary endpoint of EFS (HR, 0.398; *P*<0.0001)

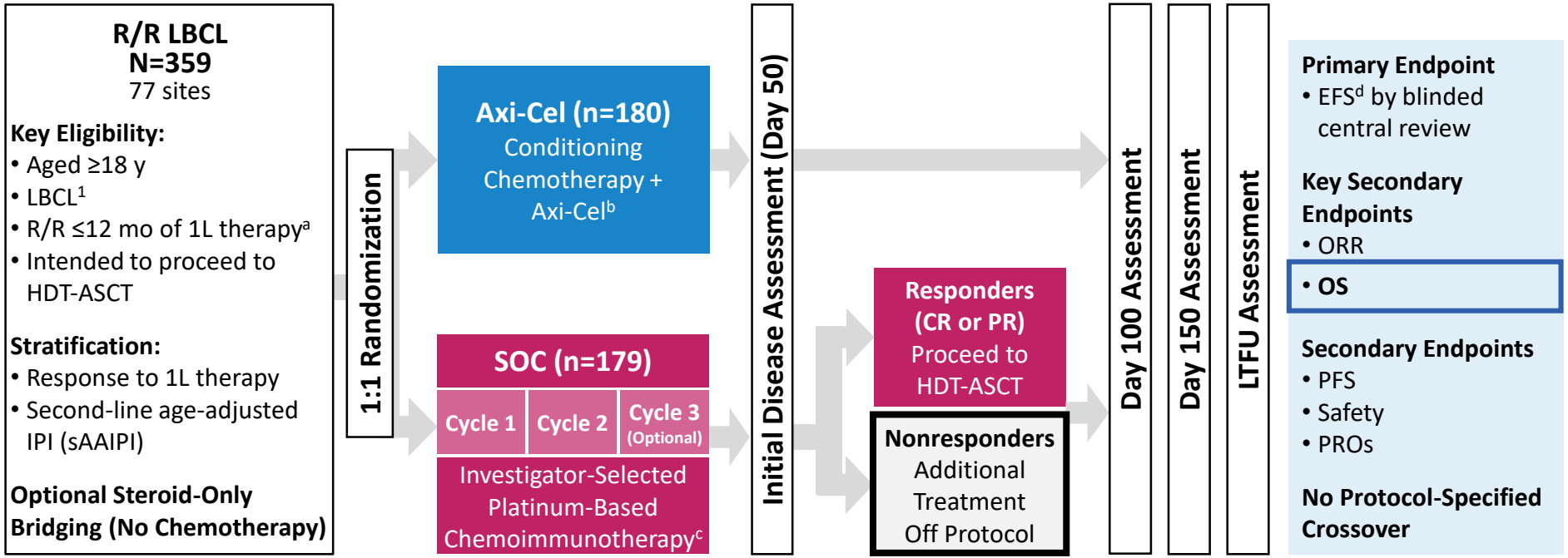
- Based on superior EFS, axi-cel was approved in many countries for adults with R/R LBCL ≤12 months after first-line therapy, in addition to after ≥2 lines of therapy

Here, we present the primary overall survival analysis of ZUMA-7



ZUMA-7 is NCT03391466. Axi-cel is approved in second or third or greater lines of therapy in the United States, European Union, Australia, Canada, Great Britain, Israel, Japan, and Switzerland.
Locke FL, et al. *N Engl J Med*. 2022;386:640-654; Locke FL, et al. *Blood* 2021;138(Suppl 1):2; YESCARTA® (axicabtagene ciloleucel) Prescribing information. Kite Pharma, Inc; 2022; YESCARTA® (axicabtagene ciloleucel) [summary of product characteristics]. Amsterdam, The Netherlands: Kite Pharma EU. 2022.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; EFS, event-free survival; HDT-ASCT, high-dose therapy with autologous stem cell transplantation; HR, hazard ratio; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; scFv, single-chain variable fragment.

ZUMA-7 Study Schema and Endpoints



[a] Refractory disease was defined as no complete response to 1L therapy; relapsed disease was defined as complete response 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 therapy with autologous stem cell transplantation; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; LTFU, long-term follow-up; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; R/R, relapsed/refractory; SOC, standard of care.

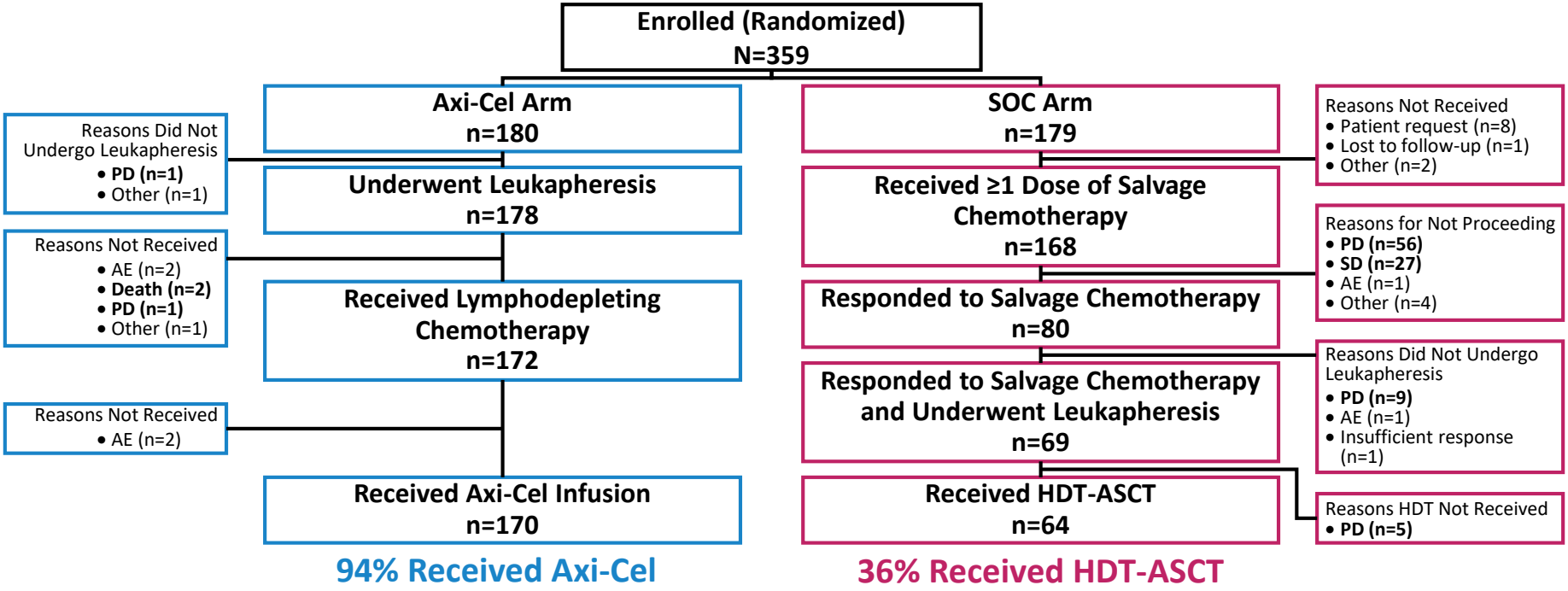
Baseline Characteristics Were Generally Balanced Between Axi-Cel and Standard of Care

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-hit lymphomas)	32 (18)[b]	25 (14)	57 (16)[b]
Double expressor lymphoma	57 (32)	62 (35)	119 (33)
MYC rearrangement	15 (8)	7 (4)	22 (6)
Elevated LDH level[c]	101 (56)	94 (53)	195 (54)

[a] As reported by investigator at the time of randomization. [b] Increase of n=1 from primary EFS analysis (Locke FL, et al. *N Engl J Med.* 2022;386:640-654) due to updated central laboratory results. [c] LDH level greater than upper limit of normal per local laboratory reference range.

1L, first line; axi-cel, axicabtagene ciloleucel; EFS, event-free survival; HGBL, high-grade B-cell lymphoma; LDH, lactate dehydrogenase; sAAIPI, second-line age-adjusted International Prognostic Index; SOC, standard of care.

Nearly 3X Patients Received Axi-Cel Versus HDT-ASCT



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AE, adverse event; axi-cel, axicabtagene ciloleucel; HDT, high-dose therapy; HDT-ASCT, high-dose therapy with autologous stem cell transplantation; PD, progressive disease; SD, stable disease; SOC, standard of care.

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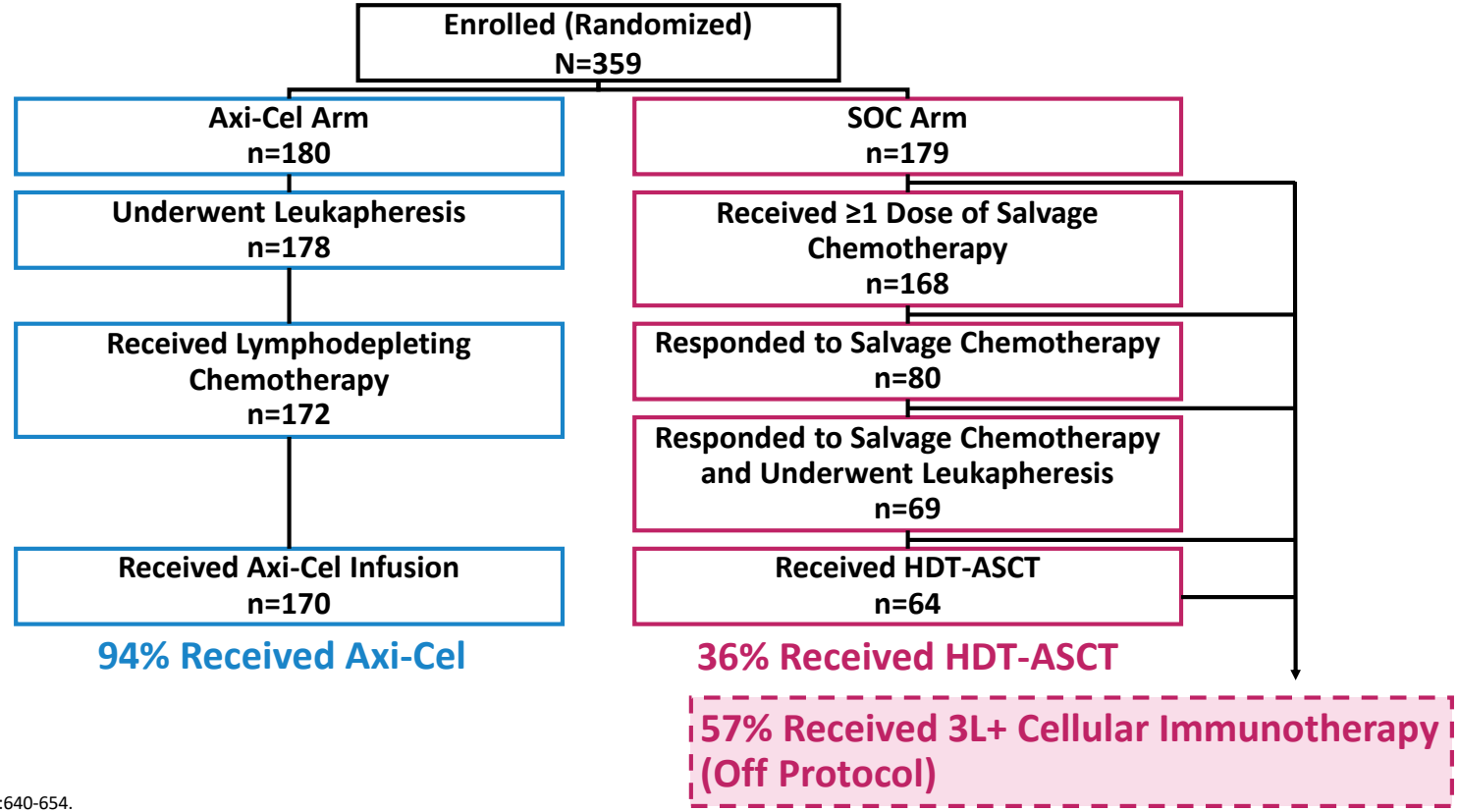

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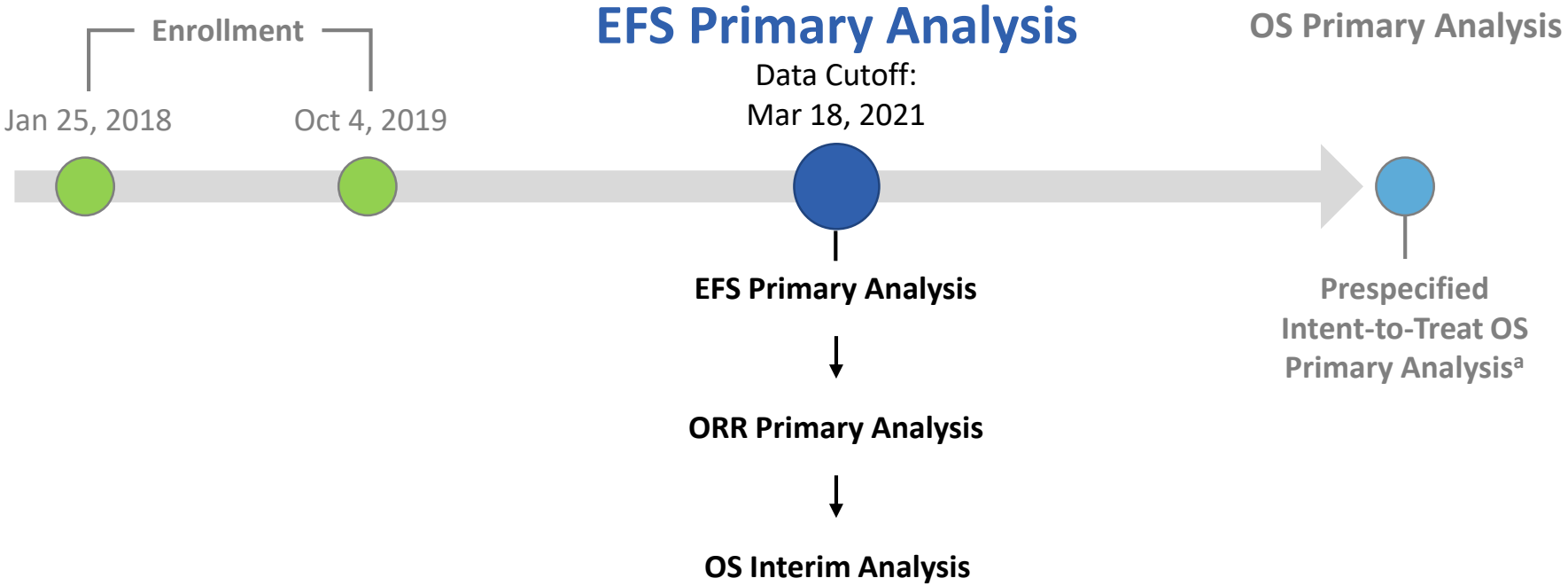
Hierarchical Statistical Testing of Endpoints in ZUMA-7: EFS → ORR → OS



Although a futility analysis was conducted, 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.

[a] Prespecified OS primary (final) analysis was to be conducted 5 years after first patient was randomized or after approximately 210 deaths, whichever occurred first.

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EFS, event-free survival; ORR, objective response rate; OS, overall survival.

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

Enrollment

Jan 25, 2018

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EFS Primary Analysis

OS Primary Analysis

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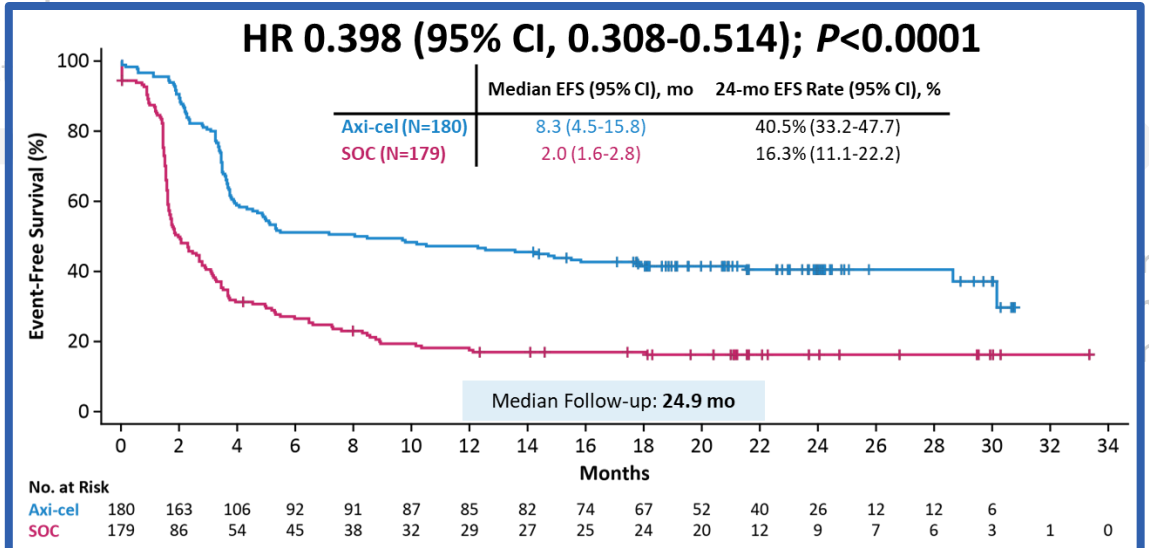

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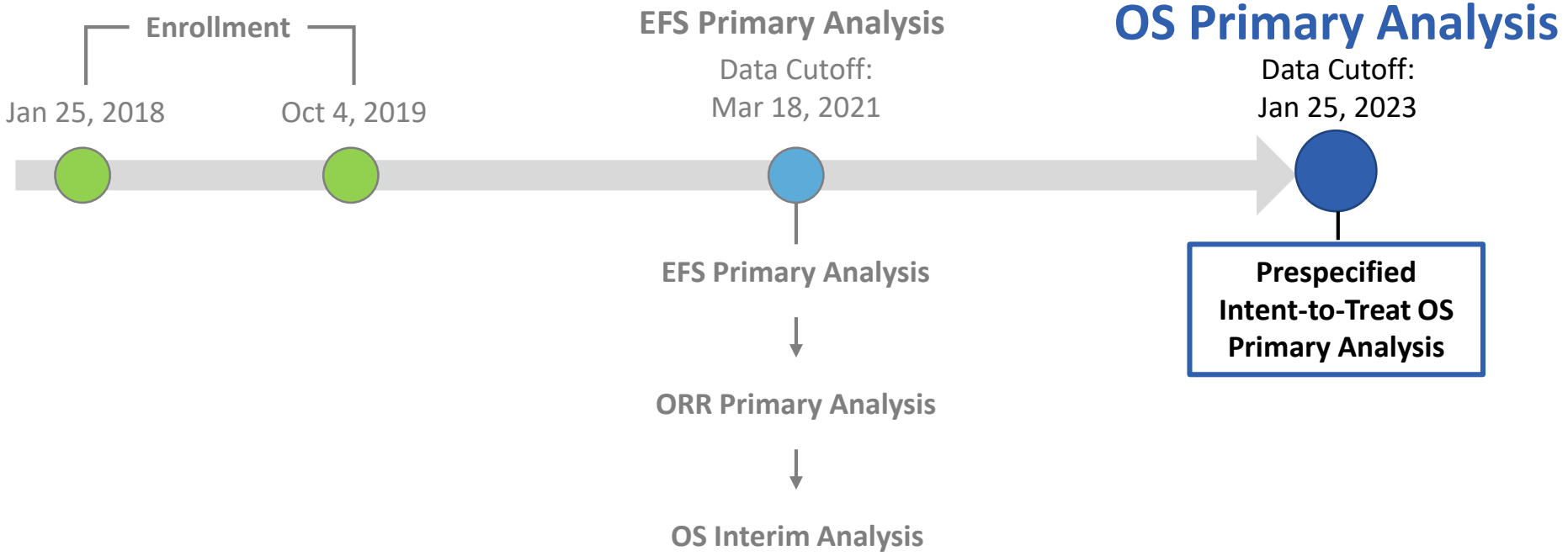

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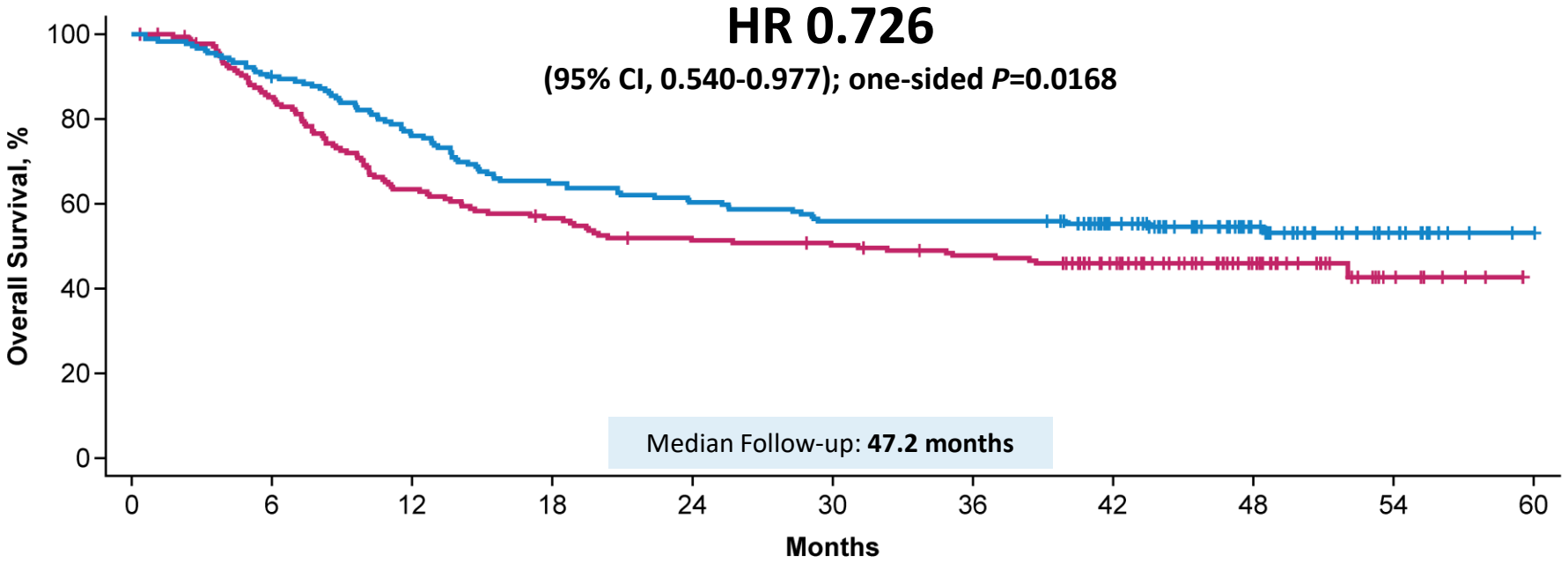
Axi-Cel Improved Overall Survival Versus Standard of Care



No. at Risk											
Axi-Cel	180	161	136	116	108	100	100	80	41	14	1
SOC	179	149	111	98	88	85	79	63	31	7	0

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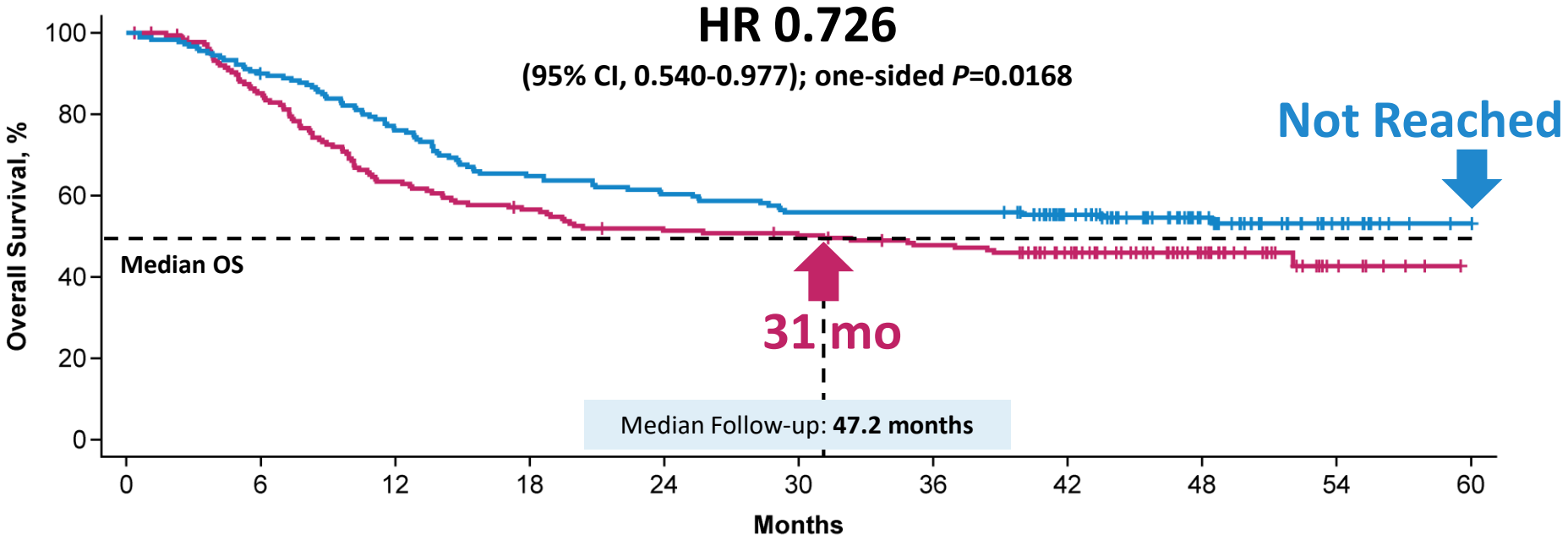
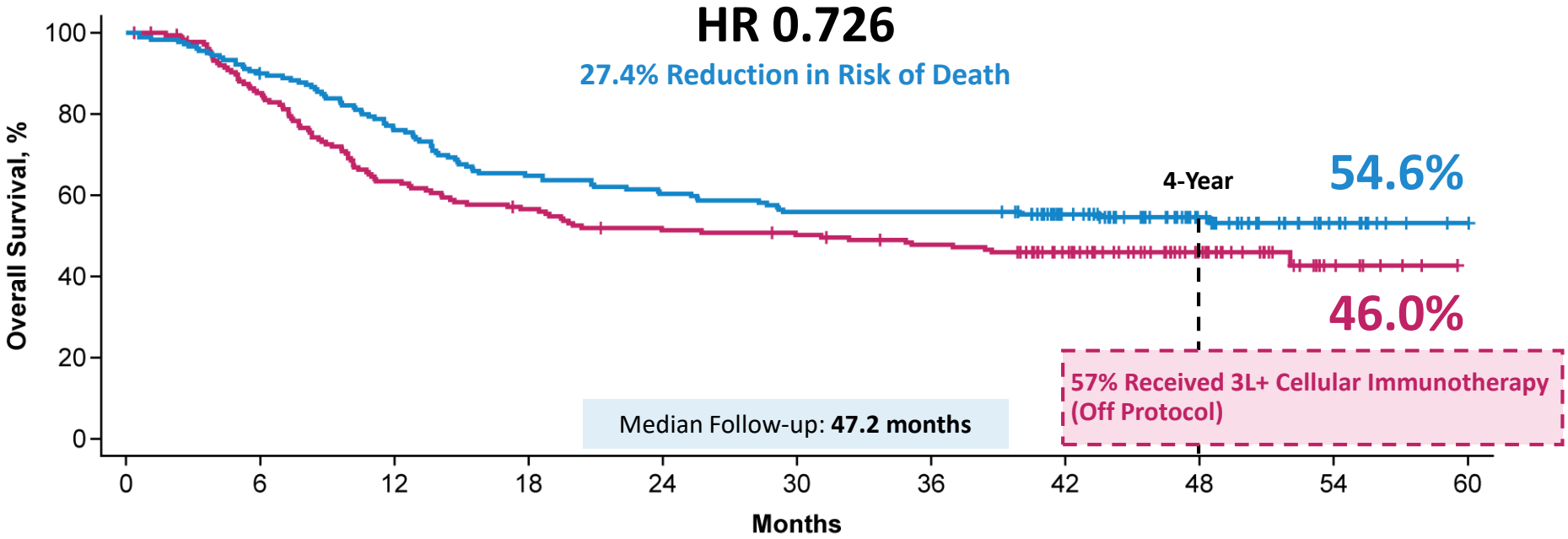


- 57% (n=102/179) of SOC patients received subsequent cellular immunotherapy (off protocol)
- Historical SOC trials had lower OS rates in early R/R LBCL, including median OS of ~10 months in ORCHARRD[a]

[a] van Imhoff GW, et al. *J Clin Oncol*. 2017;35:544-551.
Axi-cel, axicabtagene ciloleucel; HR, hazard ratio; LBCL, large B-cell lymphoma; OS, overall survival; R/R, relapsed/refractory; SOC, standard of care.

Axi-Cel Improved Overall Survival Versus Standard of Care

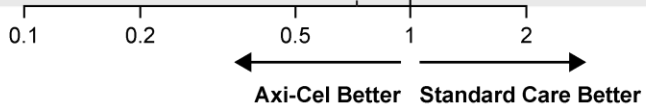


- 57% (n=102/179) of SOC patients received subsequent cellular immunotherapy (off protocol)
- Despite the increased survival in the SOC arm versus historical studies, axi-cel increased survival over SOC[a,b]

[a] Approximately 30% for early R/R LBCL in ORCHARRD (van Imhoff GW, et al. *J Clin Oncol*. 2017;35:544-551). [b] <40% for those with prior rituximab and early R/R LBCL in CORAL (Gisselbrecht C, et al. *J Clin Oncol*. 2010;28:4184-4190).
3L, third line; axi-cel, axicabtagene ciloleucel; HR, hazard ratio; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; SOC, standard of care.

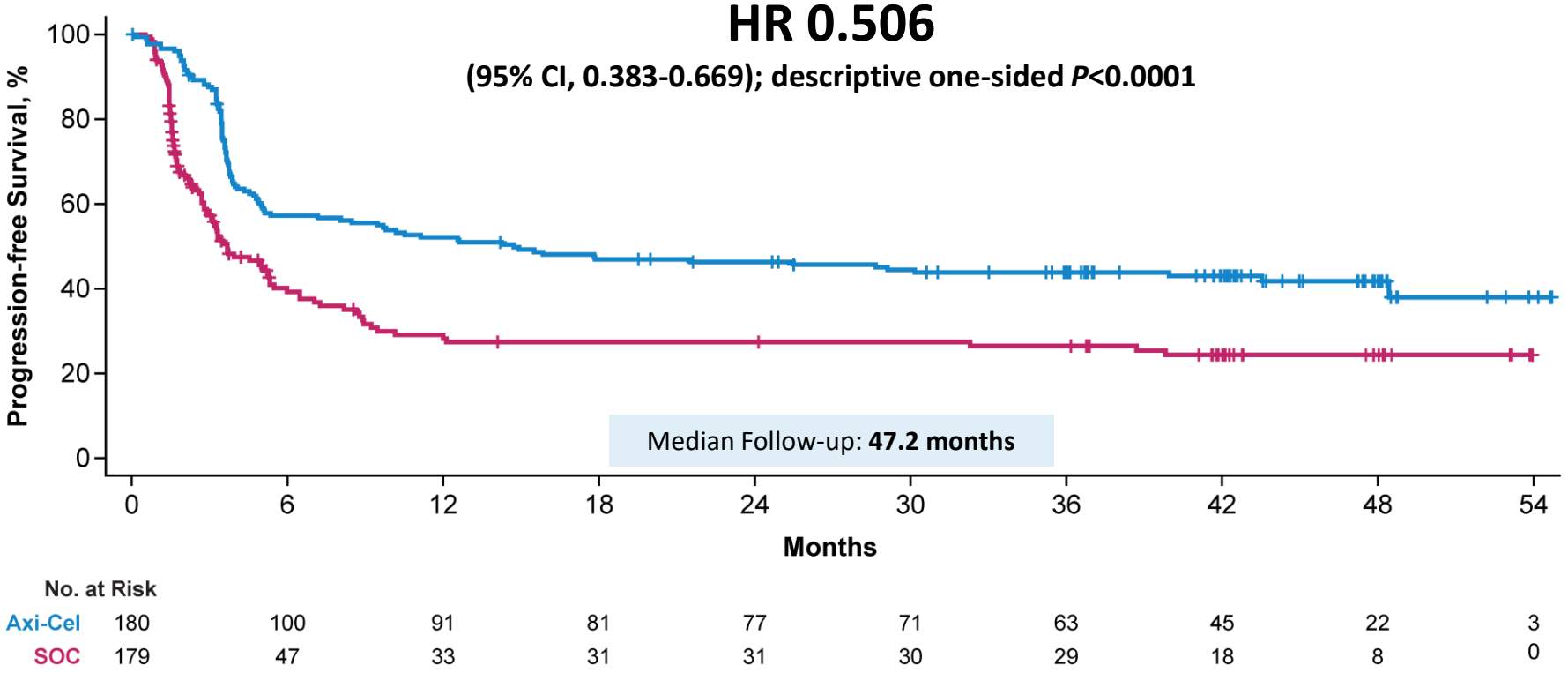
Survival Benefit Favoring Axi-Cel Was Similar Across Key Prespecified Subgroups

	Axi-Cel	SOC		(95% CI)	
	No. of Patients With Events/Total No.		Hazard Ratio	LCI	UCI
Overall[a]	82/180	95/179	0.726	0.540	0.977
Age					
<65 y	56/129	64/121	0.779	0.541	1.120
≥65 y	26/51	31/58	0.691	0.401	1.190
Response to first-line therapy at randomization					
Primary refractory disease	66/133	72/131	0.773	0.553	1.080
Relapse ≤12 mo after initiation or completion of first-line therapy	16/47	23/48	0.586	0.308	1.116
Second-line age-adjusted IPI					
0 or 1	37/98	40/100	0.842	0.538	1.317
2 or 3	45/82	55/79	0.647	0.436	0.962
Prognostic marker according to central laboratory					
HGBL, double-hit	14/32	14/25	0.716	0.330	1.553
Double-expressor lymphoma	26/57	33/62	0.729	0.435	1.221



[a] Dashed vertical line is shown at 0.726, which is the overall survival hazard ratio for death among all patients in the axi-cel arm versus the SOC arm.
Axi-cel, axicabtagene ciloleucel; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; LCI, lower confidence interval; SOC, standard of care; UCI, upper confidence interval.

PFS By Investigator Confirmed Benefit of Axi-Cel Over SOC



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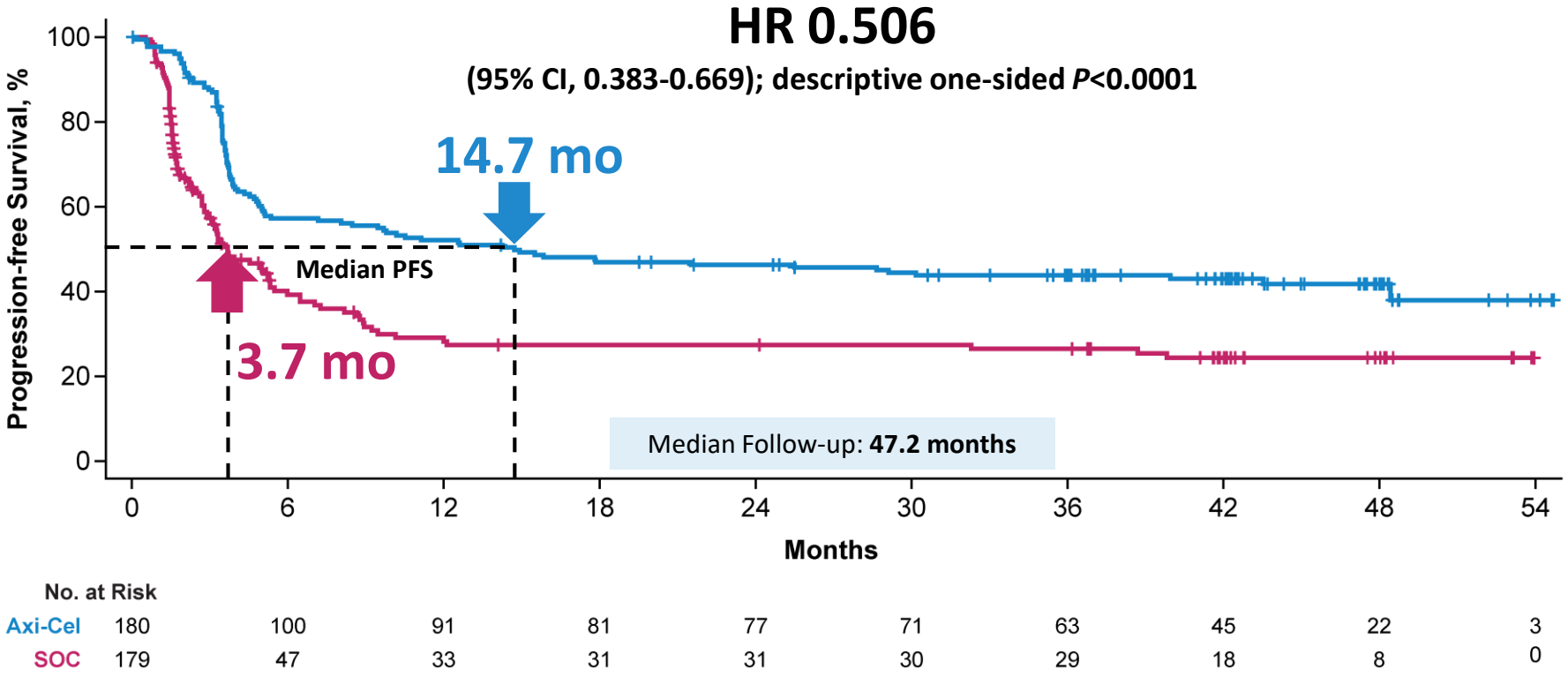

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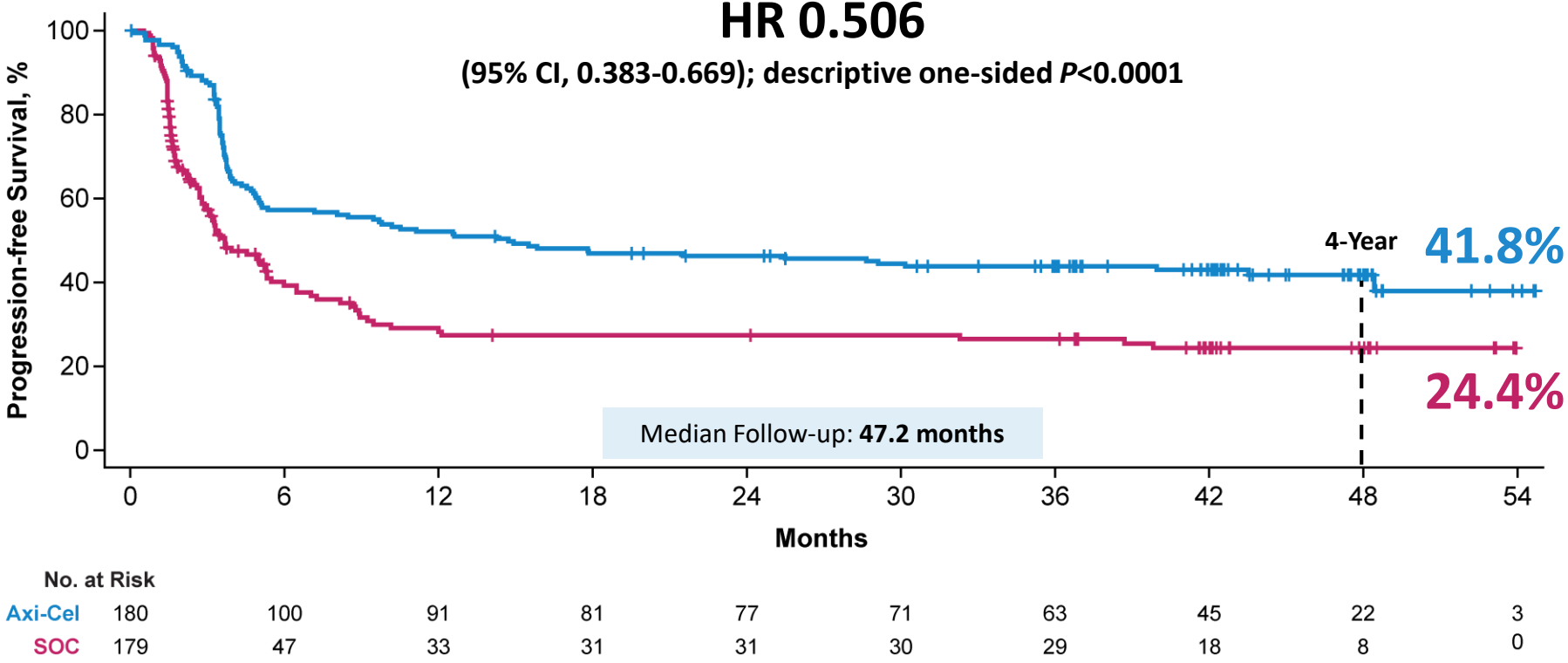

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Key Safety Data At Primary Overall Survival Analysis

AEs of Interest, %	Axi-Cel n=170		SOC n=168	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
CRS	92%	6%	–	–
Neurologic event	61%	21%	20%	1%
Hypogammaglobulinemia	11%	0%	1%	0%
Cytopenia	80%	75%	80%	75%
Infections	45%	16%	32%	12%

- No changes in cumulative treatment-related serious or fatal AEs occurred since the primary EFS analysis

Reason for Death	Axi-Cel n=170	SOC n=168
Progressive disease, n (%)	51 (30)	71 (42)
Grade 5 AE during protocol-specific reporting period, n (%)	8 (5)[a]	2 (1)[b]
New or secondary malignancy, n (%)	2 (1)[c]	0
Other reason for death,[d] n (%)	13 (8)	18 (11)
Definitive therapy-related mortality,[e] n/N (%)	1/170 (1)[f]	2/64 (3)[g]

Data here are presented for the safety analysis set. Fewer SOC patients remained in the AE reporting period post-progression or start of new lymphoma therapy; thus, cross-arm comparisons of AE rates warrant cautious interpretation. [a] COVID-19 (n=2), sepsis (n=2), hepatitis B reactivation, myocardial infarction, pneumonia, and progressive multifocal leukoencephalopathy (n=1 each). [b] Acute respiratory distress syndrome and cardiac arrest (n=1 each). [c] One patient died of acute myeloid leukemia and one died of lung adenocarcinoma, both deemed unrelated to study treatment per investigator assessment. [d] Includes fatal AEs that occurred outside of the protocol-specified AE reporting window. COVID-19 (n=4), other infection/inflammation (n=3), neurologic organ failure (n=2), respiratory organ failure, cardiac organ failure, progressive disease, and unknown (n=1 each) in the axi-cel arm. Other infection/inflammation (n=7), unknown (n=5), COVID-19 (n=4), respiratory organ failure, and cardiopulmonary/neurologic organ failure (n=1 each) in the SOC arm. [e] Related to axi-cel or high-dose therapy with autologous stem cell transplantation. [f] Hepatitis B reactivation. [g] Cardiac arrest and acute respiratory distress syndrome (n=1 each).
AE, adverse event; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; EFS, event-free survival; SOC, standard of care.

Paradigm Shift: Axi-Cel Improves Overall Survival in 2L LBCL

- Axi-cel improves overall survival in 2L for early R/R LBCL vs previous paradigm
  - Risk of death reduced by 27.4% with axi-cel vs chemotherapy and HDT-ASCT, despite 57% subsequent cellular immunotherapy after standard of care
  - Overall survival benefit was similar across key patient subgroups
- With median follow-up of 47.2 months, data are consistent with curative therapy
- First trial in nearly 30 years in 2L to significantly improve overall survival

ZUMA-7 confirms axi-cel is a second-line standard of care for patients with refractory or early relapsed large B-cell lymphoma based on superior survival

The previous paradigm consisted of chemotherapy followed by HDT-ASCT in responding patients (Philip T, et al. *N Engl J Med.* 1995;333:1540-1545).
2L, second line; axi-cel, axicabtagene ciloleucel; HDT-ASCT, high-dose therapy with autologous stem cell transplantation; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; SOC, standard of care.

Paradigm Shift: Axi-Cel As Second-Line Standard of Care
The New LBCL Algorithm

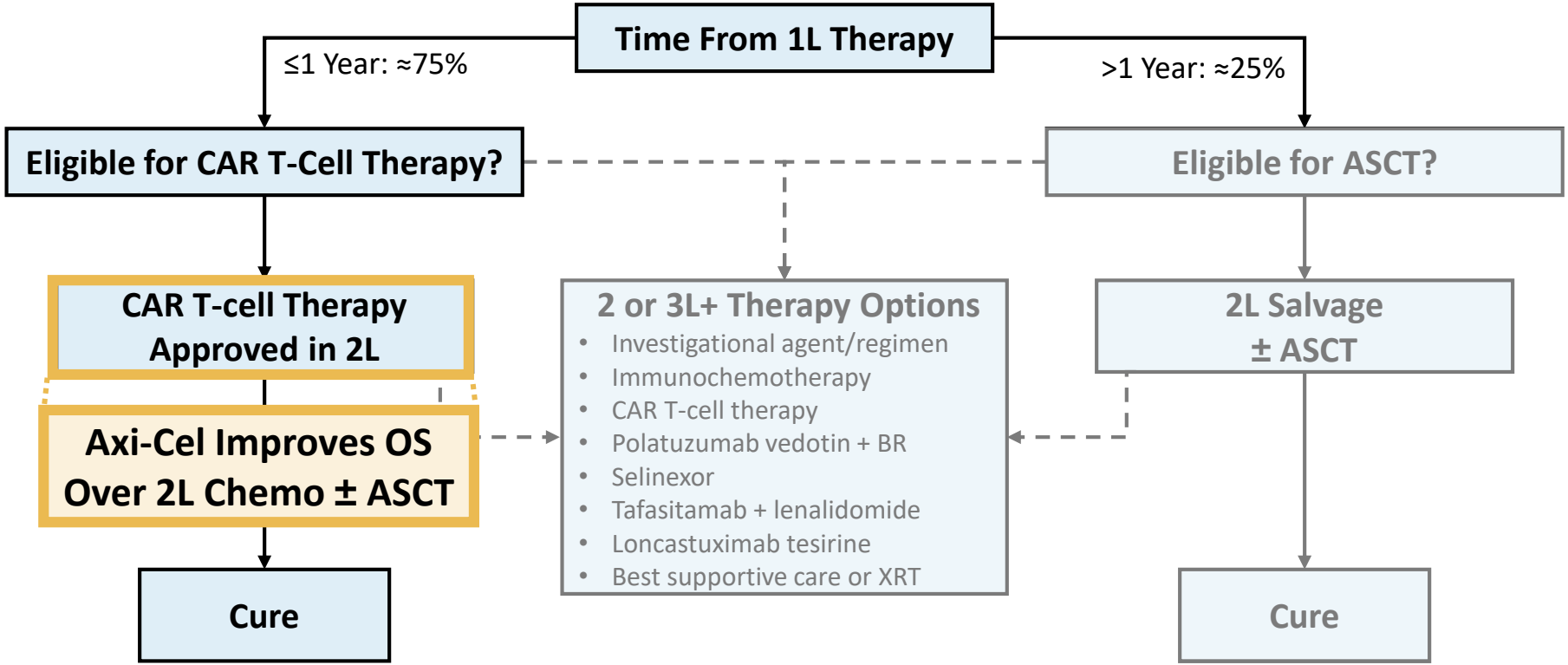

Figure adapted with permission from Westin and Sehn, *Blood*. 2022;139:2737-2746.

1L, first line; 2L, second line; 3L, third line; ASCT, autologous stem cell transplantation; axi-cel, axicabtagene ciloleucel; BR, bendamustine rituximab; CAR, chimeric antigen receptor; chemo, chemotherapy; LBCL, large B-cell lymphoma; OS, overall survival; XRT, radiation therapy.

Plain Language Summary

Partnering with Patients: The Cornerstone of Cancer Care and Research

- Axi-cel, a CAR T-cell therapy made from the patient's own immune cells, is a one time treatment for B-cell cancers
- Patients with diffuse large B-cell lymphoma that did not respond or relapsed after initial treatment had poor outcomes with previous chemotherapy-based approaches
- The ZUMA-7 trial showed more patients live longer when treated with axi-cel in second line compared with chemotherapy and stem cell transplant

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma

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Acknowledgments

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ZUMA-7 Global Phase 3 Clinical Trial Sites