

CAR-T cell therapy for diffuse large B-cell lymphoma

Jakrawadee Julamanee MD, PhD

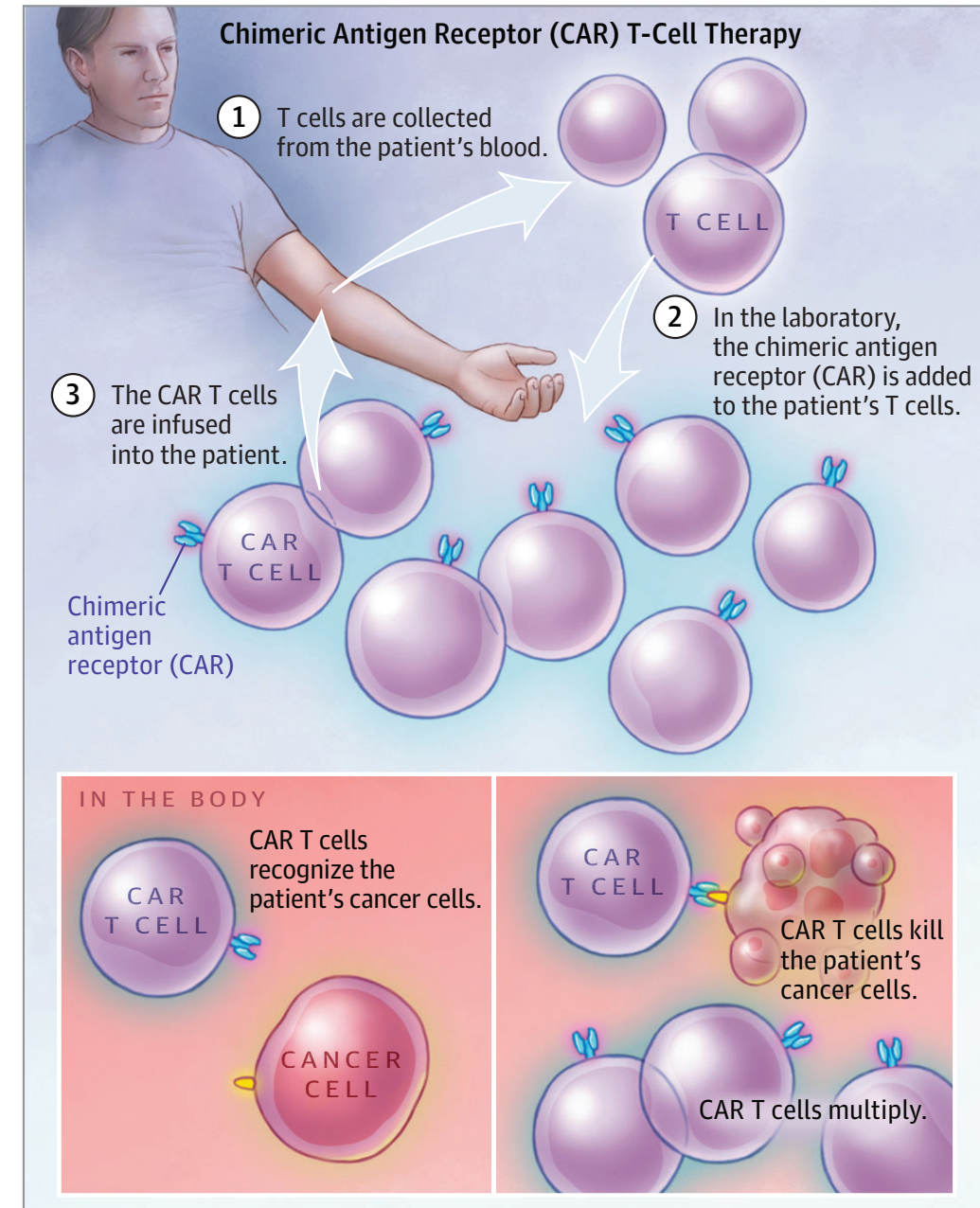
Hematology Unit, Division of Internal Medicine

Stem Cell Transplantation and Cellular Therapy Excellence Center

Faculty of Medicine, Prince of Songkla University

Outline

- Case study
- CAR-T cell function and adverse events
- CD19AR-T cell in r/r settings and earlier lines
- Future of CAR-T cell in DLBCL
- Q&A



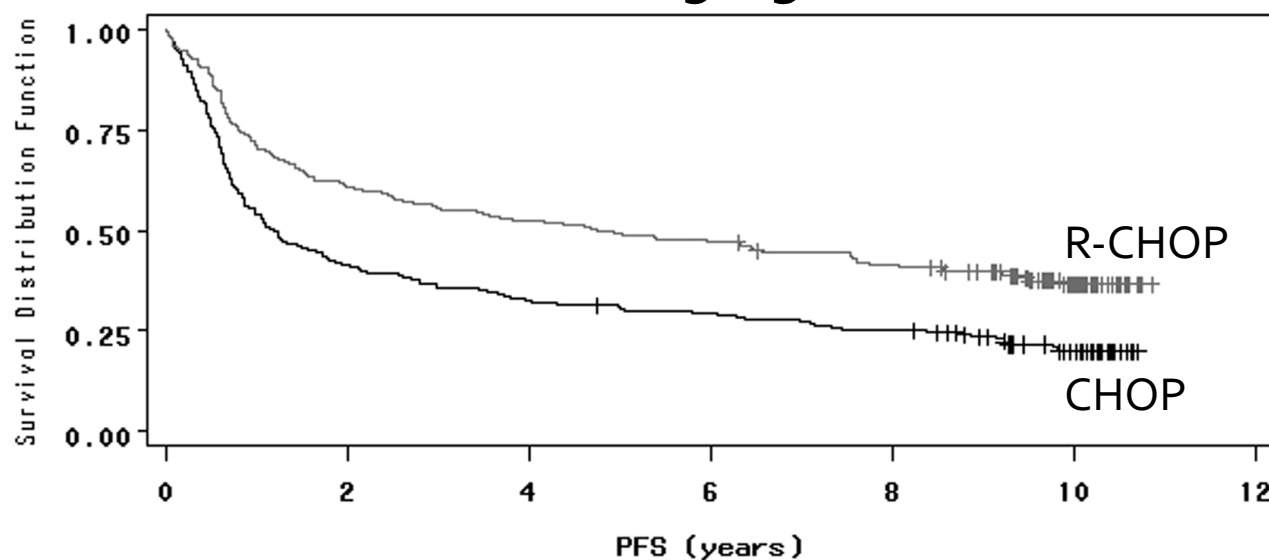
The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

<i>Large B-cell lymphomas</i>	<i>4th edition</i>
Diffuse large B-cell lymphoma, NOS	(Same)
T-cell/histiocyte-rich large B-cell lymphoma	(Same)
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with <i>MYC</i> and <i>BCL2</i> rearrangements	High-grade B-cell lymphoma with <i>MYC</i> and <i>BCL2</i> and/or <i>BCL6</i> rearrangements
ALK-positive large B-cell lymphoma	(Same)
Large B-cell lymphoma with <i>IRF4</i> rearrangement	(Same)
High-grade B-cell lymphoma with 11q aberrations	Burkitt-like lymphoma with 11q aberration
Lymphomatoid granulomatosis	(Same)
EBV-positive diffuse large B-cell lymphoma	EBV-positive diffuse large B-cell lymphoma, NOS
Diffuse large B-cell lymphoma associated with chronic inflammation	(Same)
Fibrin-associated large B-cell lymphoma	<i>Not previously included</i> (Previously considered a subtype of diffuse large B-cell lymphoma associated with chronic inflammation)
Fluid overload-associated large B-cell lymphoma	<i>Not previously included</i>
Plasmablastic lymphoma	(Same)
Primary large B-cell lymphoma of immune-privileged sites	<i>Not previously included</i> , encompassing primary diffuse large B-cell lymphoma of the CNS in revised 4 th edition (<i>plus primary large B-cell lymphoma of the vitreoretina and primary large B-cell lymphoma of the testis</i>)
Primary cutaneous diffuse large B-cell lymphoma, leg type	(Same)
Intravascular large B-cell lymphoma	(Same)
Primary mediastinal large B-cell lymphoma	(Same)
Mediastinal grey zone lymphoma	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma
High-grade B-cell lymphoma, NOS	(Same)

DLBCL: mainstay treatment

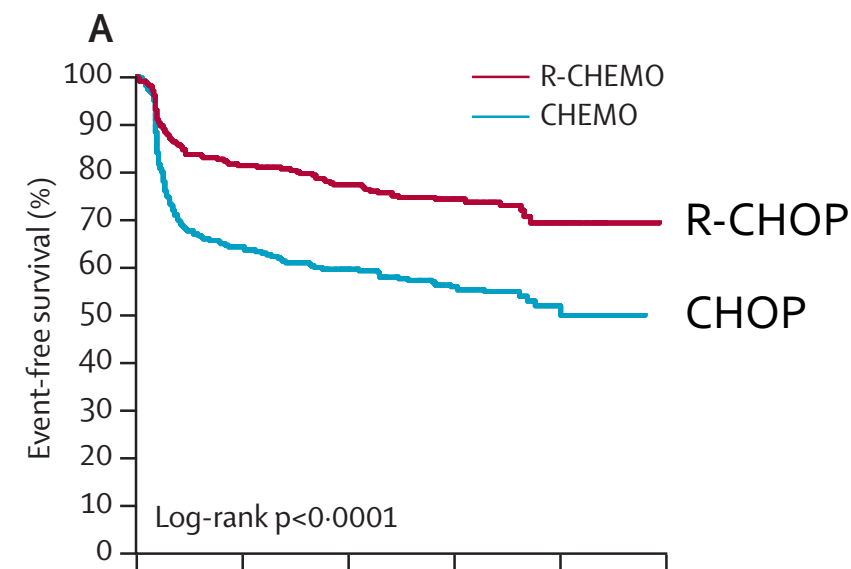
- **R-CHOP** is the current standard-of-care for DLBCL-NOS
70-80% cure rate in GCB and 40% in ABC subtype

LNH-98.5¹



STRATA: — BRAS_RANDOM=Arm A : CHOP
 + + + Censored BRAS_RANDOM=Arm A : CHOP
 — BRAS_RANDOM=Arm B : CHOP + Rituximab
 + + + Censored BRAS_RANDOM=Arm B : CHOP + Rituximab

MInT²



Number at risk

CHEMO	410	233	163	117	25	0
R-CHEMO	413	305	214	150	30	0

1.Coieffier B, et al. Blood. 2010;116(12):2040-5.

2.Pfreundschuh M, et al. 2011;12:1013-22.

Relapse/refractory DLBCL

- Nearly **40% will be refractory to or relapse** after initial treatment
- Although patient can be cured with 2L, most patients die from their disease
- Patients experience **treatment failure within first 2 years** with outcomes correlated with timing of progression or relapse
- **10-15% exhibit primary refractory disease**, typically defined as incomplete response or relapse within 3-6 mo, have poor outcomes

Salvage therapies options for young/fit patients

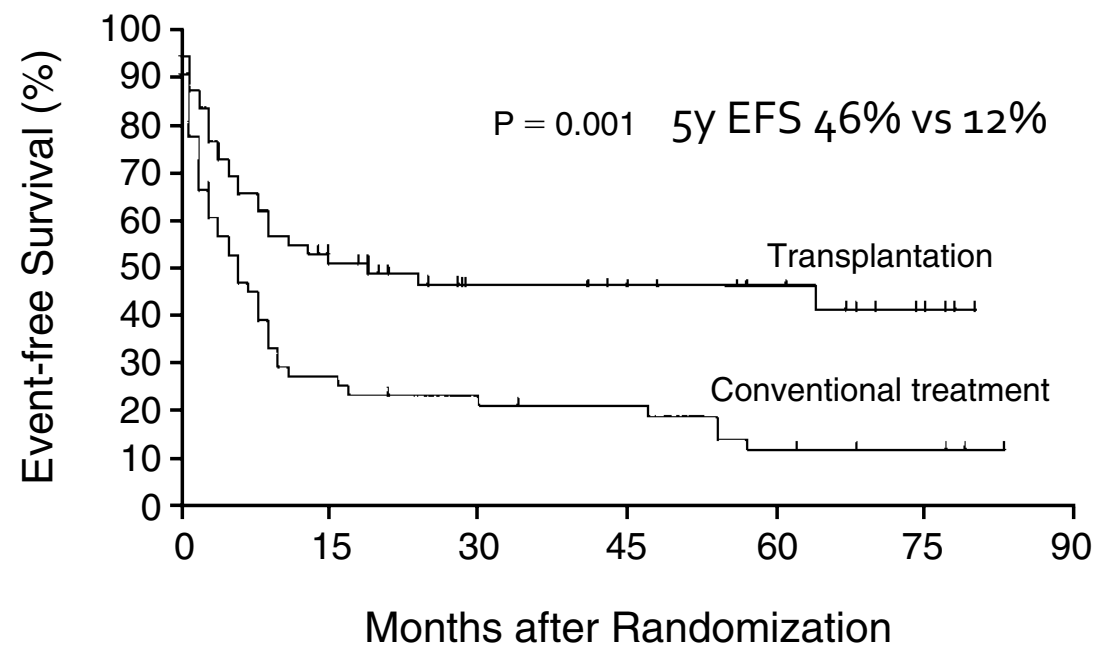
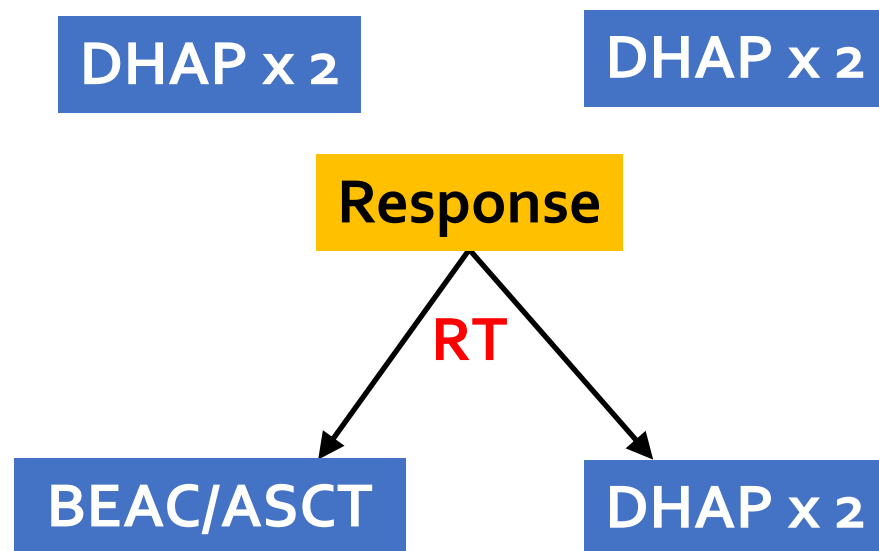
- When achievable, **HD therapy followed by ASCT** remains the **standard of care** for r/r DLBCL under the age of 65–70 y without major comorbidities
- A non-cross resistant salvage regimen is used to assess chemotherapy sensitivity before proceeding to ASCT

AUTOLOGOUS BONE MARROW TRANSPLANTATION AS COMPARED WITH SALVAGE CHEMOTHERAPY IN RELAPSES OF CHEMOTHERAPY-SENSITIVE NON-HODGKIN'S LYMPHOMA

THIERRY PHILIP, M.D., CESARE GUGLIELMI, M.D., ANTON HAGENBEEK, M.D., RENIER SOMERS, M.D.,
HANS VAN DER LELIE, M.D., DOMINIQUE BRON, M.D., PIETER SONNEVELD, M.D.,
CHRISTIAN GISSELBRECHT, M.D., JEAN-YVES CAHN, M.D., JEAN-LUC HAROUSSEAU, M.D.,
BERTRAND COIFFIER, M.D., PIERRE BIRON, M.D., FRANCO MANDELLI, M.D., AND FRANCK CHAUVIN, M.D.

PARMA

Phase III, intermediate – high risk NHL, 215 patients, 18-60 y, 51 centers



Prospective studies in transplant-eligible r/r DLBCL

ASCT eligible	Regimen, N	ORR	ASCT rate	PFS/OS
Sieniawski et al ¹	R-DHAP, 19	63%	68%	2y PFS 57%, OS 77%
Kewalramani et al ²	R-ICE, 36	53%	69%	2y PFS 54%, OS 67% (ASCT)
Vellenga et al ³ (80% DLBCL)	DHAP-VIM-DHAP, 112 R-DHAP-VIM-DHAP, 113	54% 75% (all)	46% 63%	2y PFS 31%, OS 52% 2y PFS 52%, OS 59%
Gisselbrecht et al ⁴ CORAL	R-ICE, 202 R-DHAP, 194	63.5% 62.8%	50% 54%	2y PFS 31%, OS 47% 2y PFS 42%, OS 51%
Crump et al ⁵ NCIC CTG LY.12	GDP ± R, 310 DHAP ± R, 309	44% 45%	52.1% 49.3%	HR 0.99 PFS HR 1.03 OS
Van Imhoff et al ⁶ ORCHAARD	R-DHAP, 225 Ofa-DHAP, 222	42% 38%	33% 37%	2y PFS 26%, OS 38% 2y PFS 24%, OS 41%

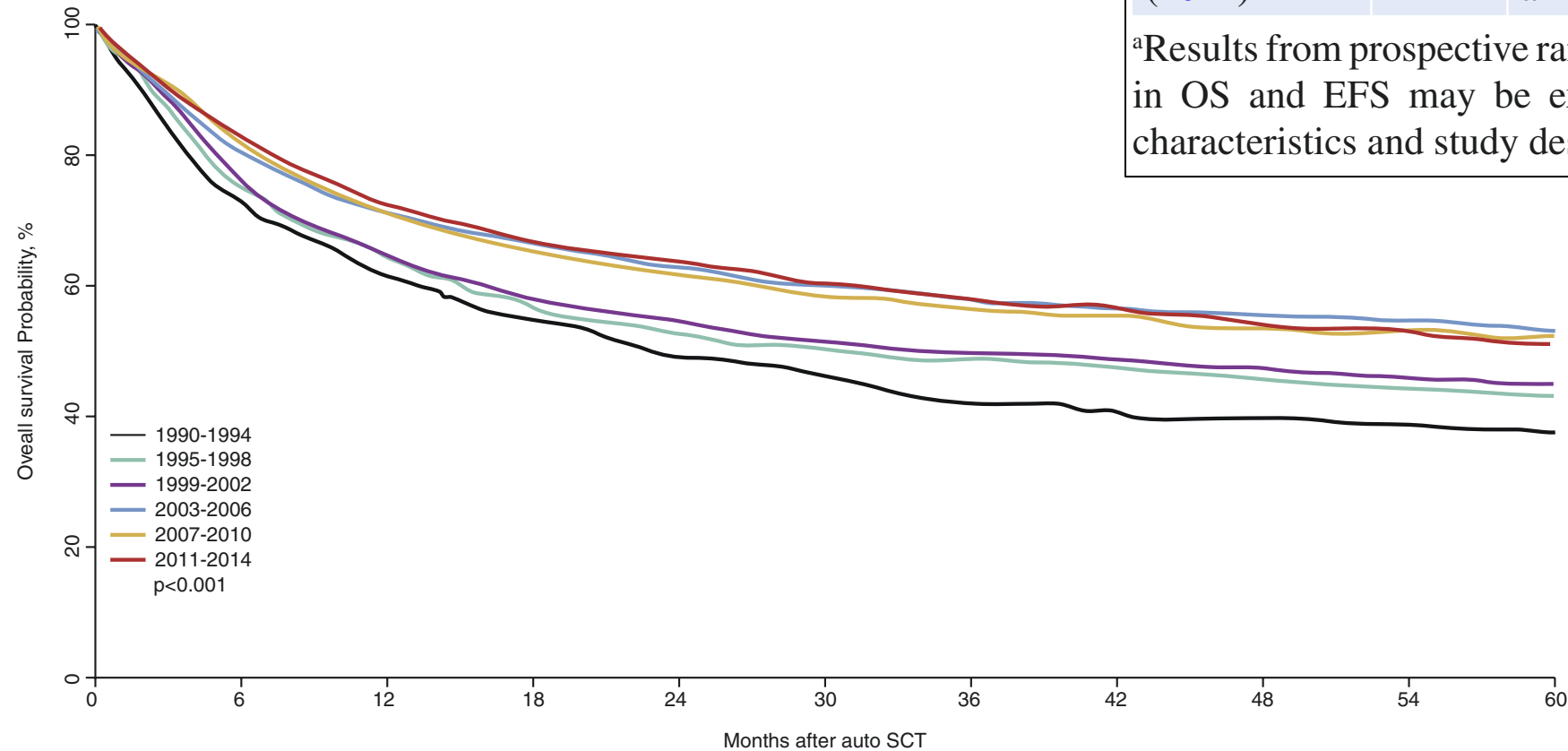
¹Sieniawski M, et al. Ann Hematol 2007;86(2):107–15. ²Kewalramani T, et al. Blood 2004;103(10):3684–8. ³Vellenga E, et al. Blood 2008;111(2):537–43.

⁴Gisselbrecht C, et al. J Clin Oncol 2010;28(27):4184–90. ⁵Crump M, et al. J Clin Oncol 2014;32(31):3490–6. ⁶van Imhoff GW, et al. J Clin Oncol 2017;35(5):544–51.

Outcomes of ASCT

	NRM	OS at 3 years	EFS at 3 years
Gisselbrecht et al. (2012)	1.4%	51% (DHAP)	35% (DHAP)
Crump et al. (2014)	NR	39% (both arms)	26% (both arms)

^aResults from prospective randomized studies. Differences in OS and EFS may be explained by differing patient characteristics and study design



CORAL study: phase III

Median 55 y, 60% prev R

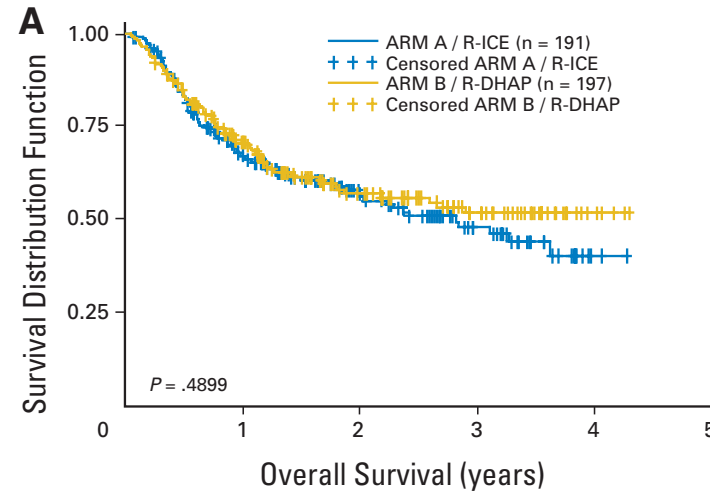
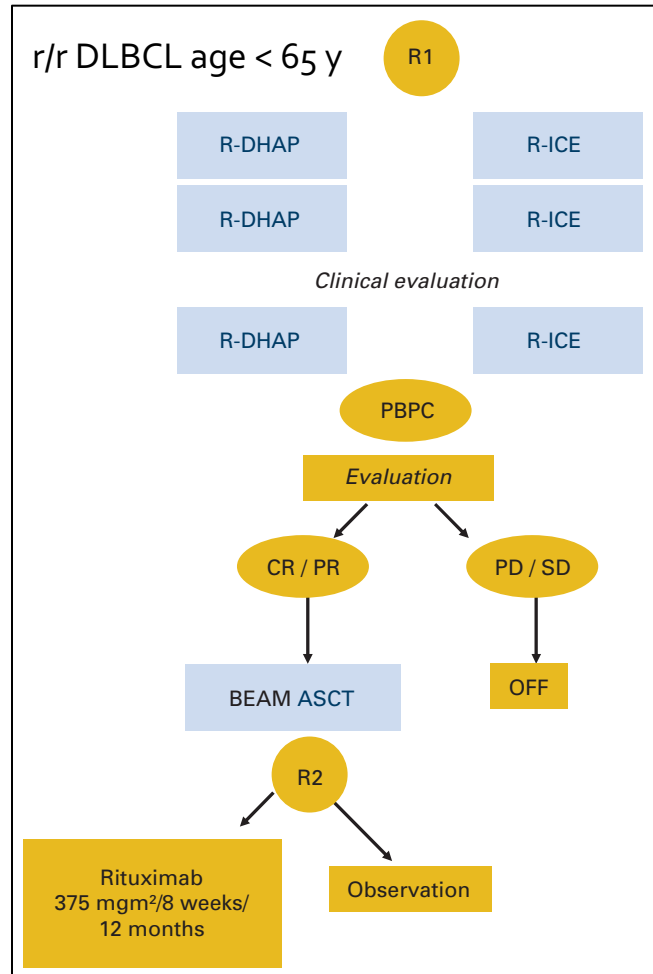


Table 2. Response After Induction Treatment (including death) for All Patients

Response	R-ICE (n = 197)		R-DHAP (n = 191)	
	No. of Patients	%	No. of Patients	%
Complete response	48	24	53	28
Unconfirmed complete response	24	12	22	12
Partial response	53	27	45	24
Stable disease	23	12	22	12
Progressive disease	38	19	35	18
Death	6	3	10	5
Premature withdrawal, not evaluated	4	2	4	2
Autologous transplantation				
Median CD34 ⁺ cells collected, million/kg	4.5		4.9	
Collection failure < 2,000,000 CD34 ⁺ cells	20	10	15	8
Mobilization-adjusted response	103	52.3	104	54.5
Consolidation with BEAM performed per protocol	101	51	105	55

Abbreviations: R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; BEAM, carmustine, etoposide, cytarabine, and melphalan.

Table 3. Response Rate and Survival According to Prognostic Factors

Factor	Total No. of Patients	Response CR/CRu/PR			3-Year Event-Free Survival		3-Year Overall Survival	
		No. of Patients	%	P	%	P	%	P
All patients	398	246	63		31		50	
CR/CRu		148	38		51		70	
Prior rituximab								
No	147	122	83	< .001	47	< .001	66	< .01
Yes	244	124	51		21		40	
Relapse, > 12 months	160	140	88	< .001	45	< .001	64	
Refractory, < 12 months	228	106	46		20		39	< .001
saalPI								
< 2	224	160	71	< .001	40		62	
> 1	146	76	52		18	< .001	32	< .001

Abbreviations: CR, complete response; CRu, unconfirmed complete response; PR, partial response; saalPI, secondary age-adjusted International Prognostic Index.

R-DHAP; rituximab, dexamethasone, high-dose cytarabine, cisplatin
R-ICE; rituximab, ifosfamide, carboplatin, etoposide

ORCHAARD study: Phase III

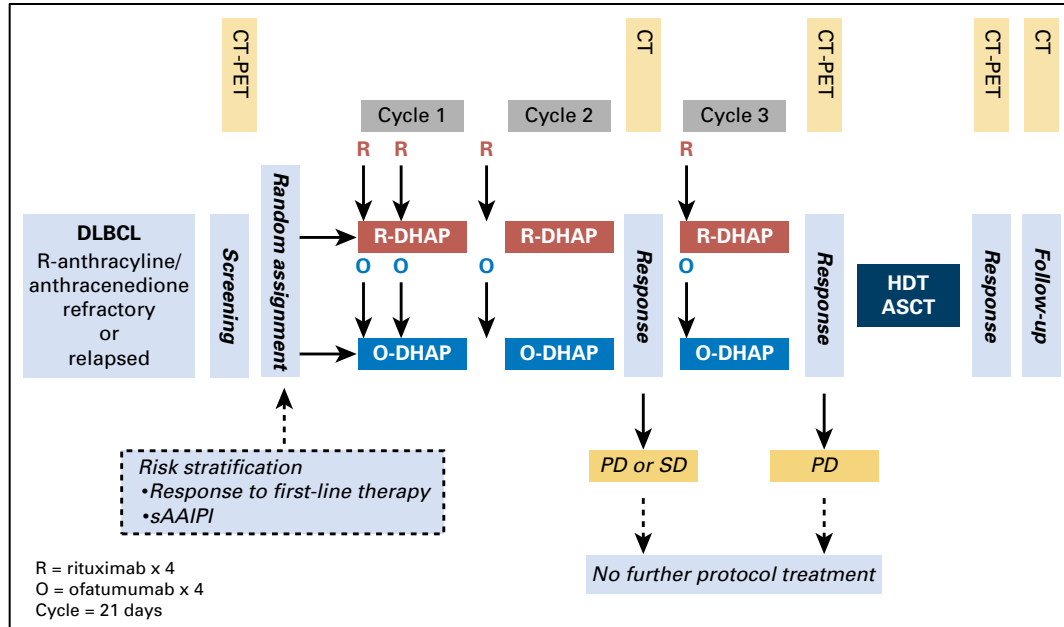
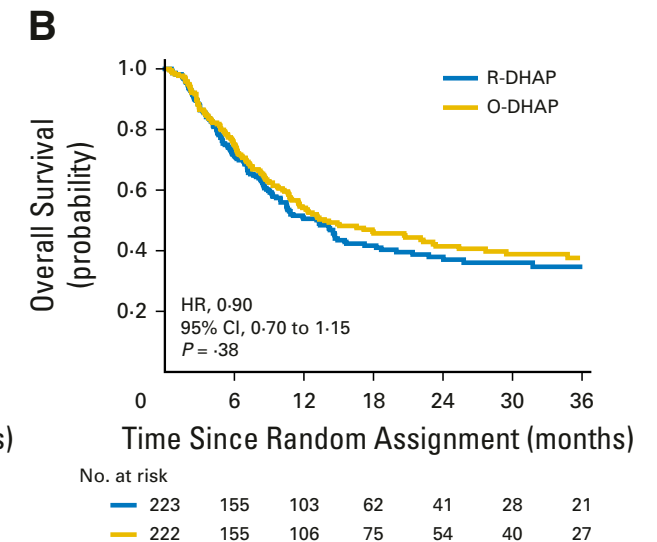
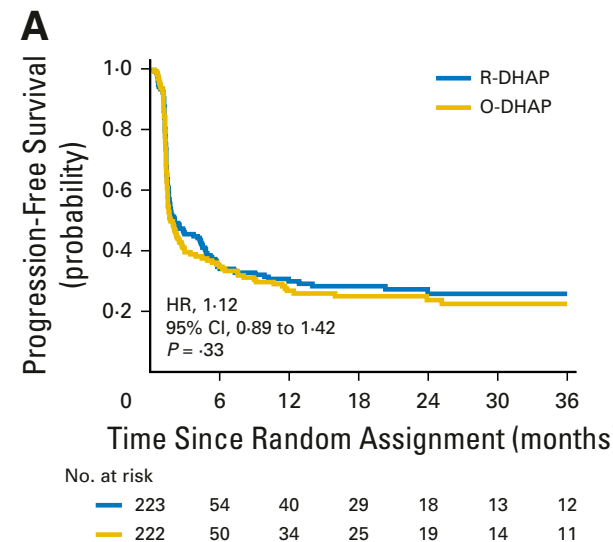


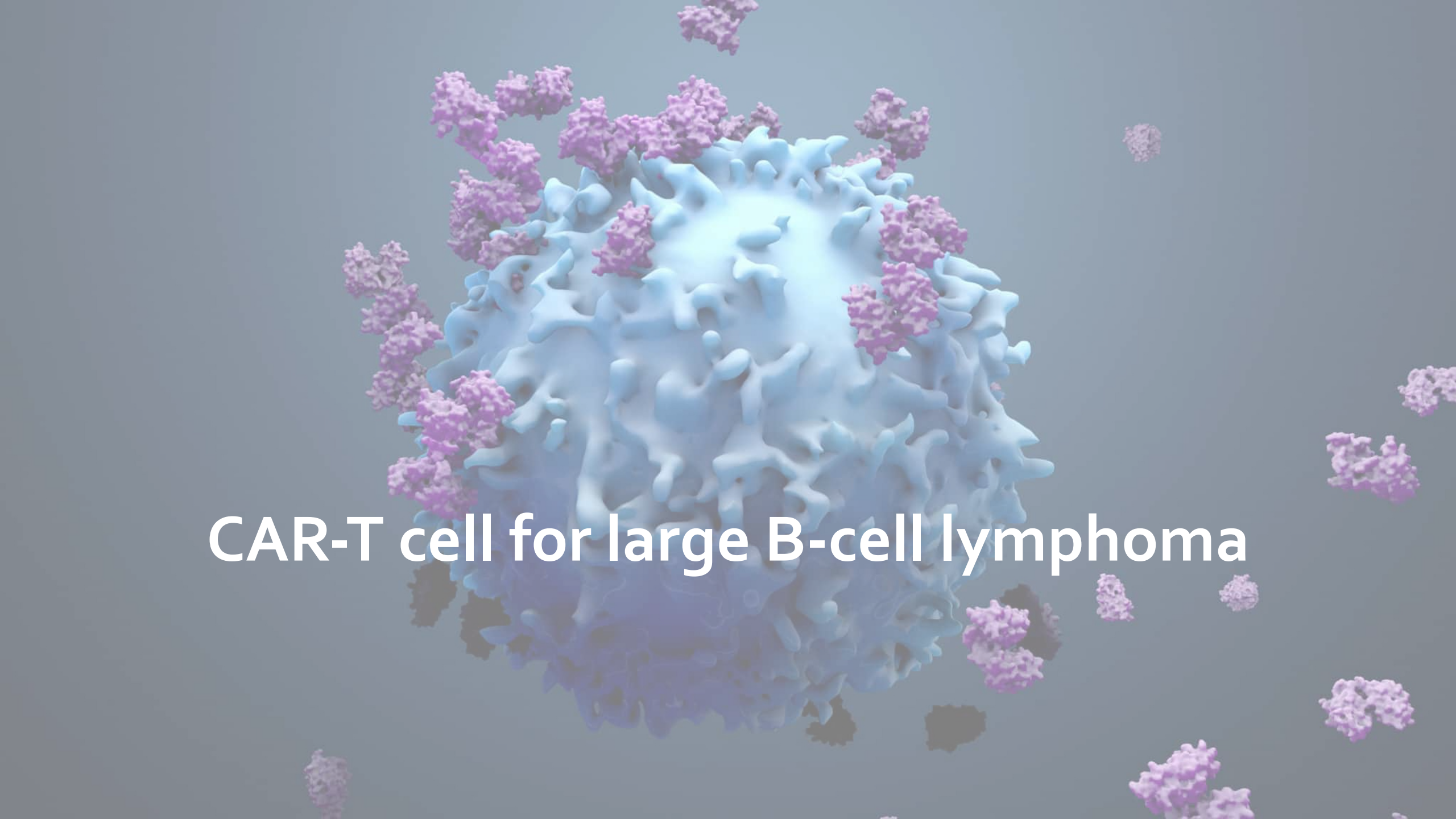
Table 2. Summary of Overall Response Rate and Complete Response Rate After Completion of Salvage Therapy and 3 Months After HDT/ASCT

Variable	Response After Completion of Salvage Therapy		Response 3 Months After HDT/ASCT	
	R-DHAP (n = 223)	O-DHAP (n = 222)	R-DHAP (n = 83)	O-DHAP (n = 74)
Response, No. (%)				
CR	48 (22)	34 (15)	44 (53)	43 (58)
PR	46 (21)	50 (23)	13 (16)	10 (14)
SD	66 (30)	64 (29)	3 (4)	4 (5)
PD	34 (15)	39 (18)	12 (14)	10 (14)
Not evaluable	4 (2)	8 (4)	3 (4)	0
Missing*	25 (11)	27 (12)	8 (10)	7 (9)
Overall response rate, No. (%)				
CR + PR	94 (42)	84 (38)	57 (69)	53 (72)
95% CI	(35.6 to 48.9)	(31.4 to 44.6)	(57.6 to 78.4)	(59.9 to 81.5)
Odds ratio (95% CI); P	0.84 (0.56 to 1.24); .41			
Complete response rate, No. (%)				
CR	48 (22)	34 (15)	44 (53)	43 (58)
95% CI	(16.3 to 27.5)	(10.8 to 20.7)	(41.7 to 64.1)	(46.1 to 69.5)
Odds ratio (95% CI); P	0.66 (0.39 to 1.10); .12			

Table 3. PFS and OS According to Prognostic Factors

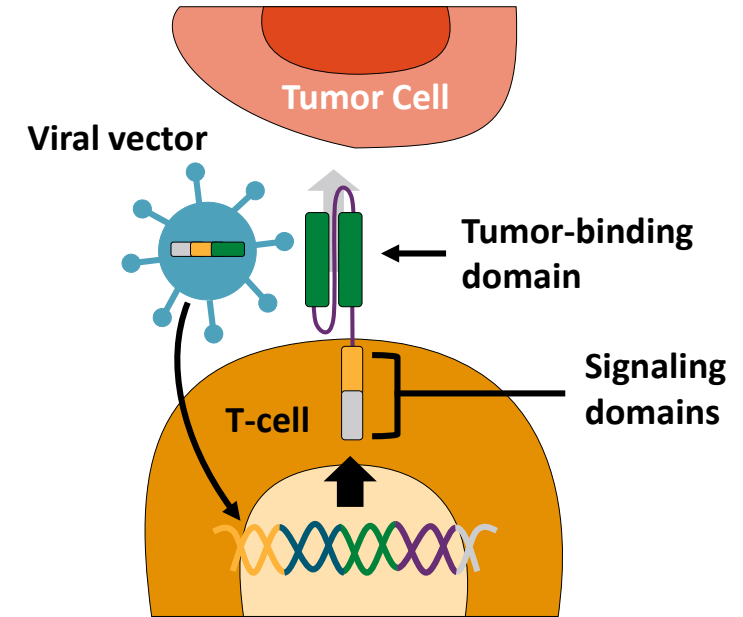
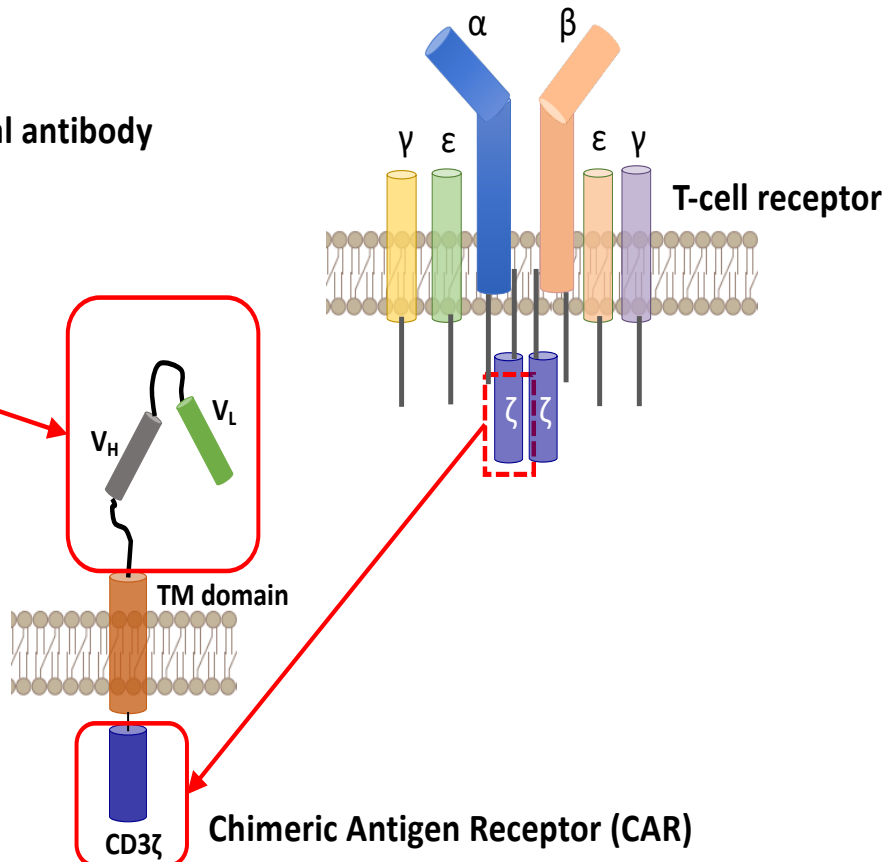
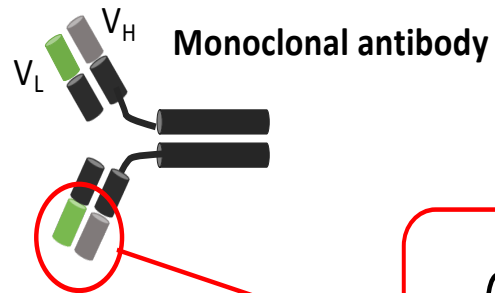
Prognostic Factor	PFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
Response to first-line therapy CR > 12 months v CR ≤ 12 months, PR, SD, or PD	0.32 (0.24 to 0.44)	< .0001	0.40 (0.29 to 0.55)	< .0001
sAAIPI score 0-1 v 2-3	0.66 (0.52 to 0.84)	.0006	0.39 (0.31 to 0.50)	< .0001
Age < 60 years v ≥ 60 years	0.92 (0.72 to 1.17)	.49	0.70 (0.54 to 0.89)	.0043



A 3D scientific illustration showing a large, light blue, irregularly shaped cell (likely a B-cell lymphoma cell) with numerous purple, branched structures (CARs) attached to its surface. The background is a dark blue gradient with several smaller purple structures floating around the main cell. The text "CAR-T cell for large B-cell lymphoma" is overlaid in white.

CAR-T cell for large B-cell lymphoma

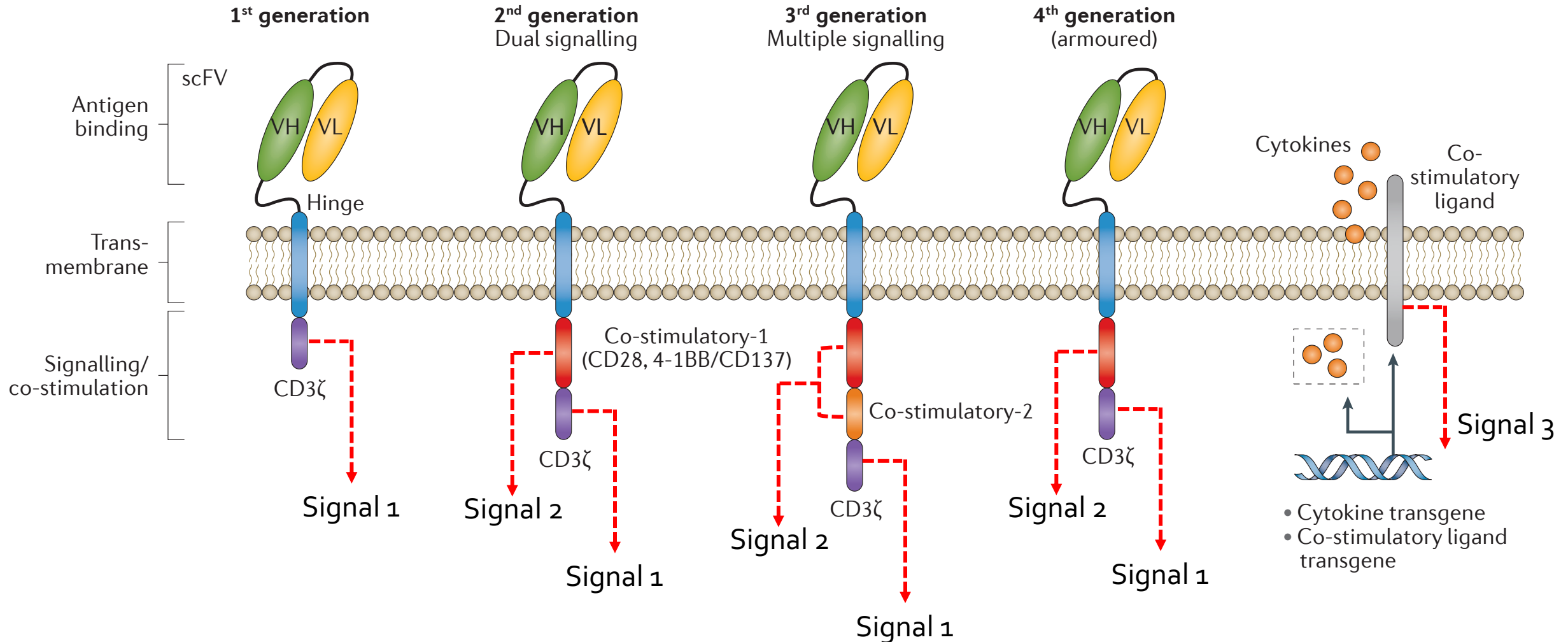
Structure of CAR-T cells



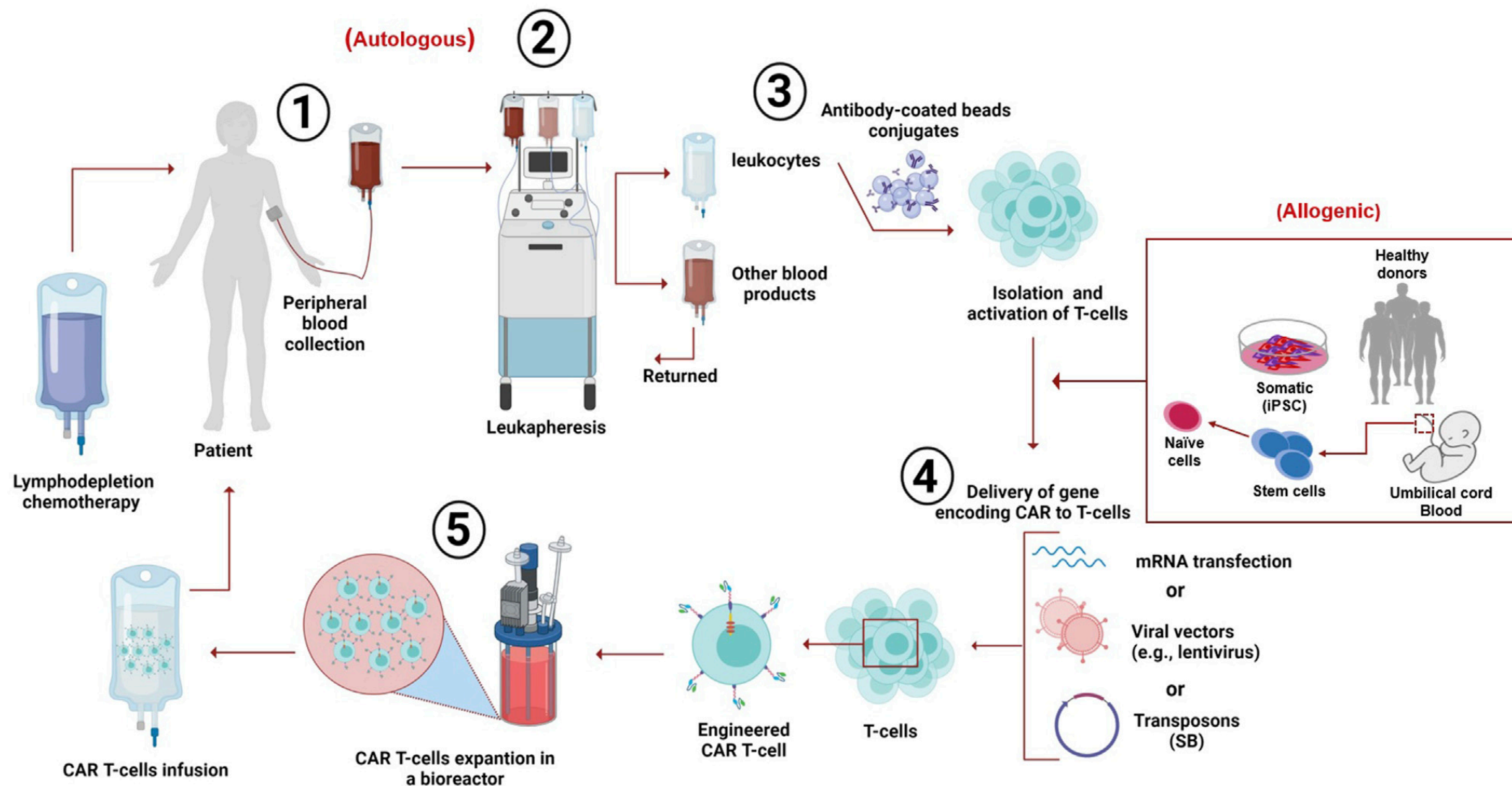
CAR Design



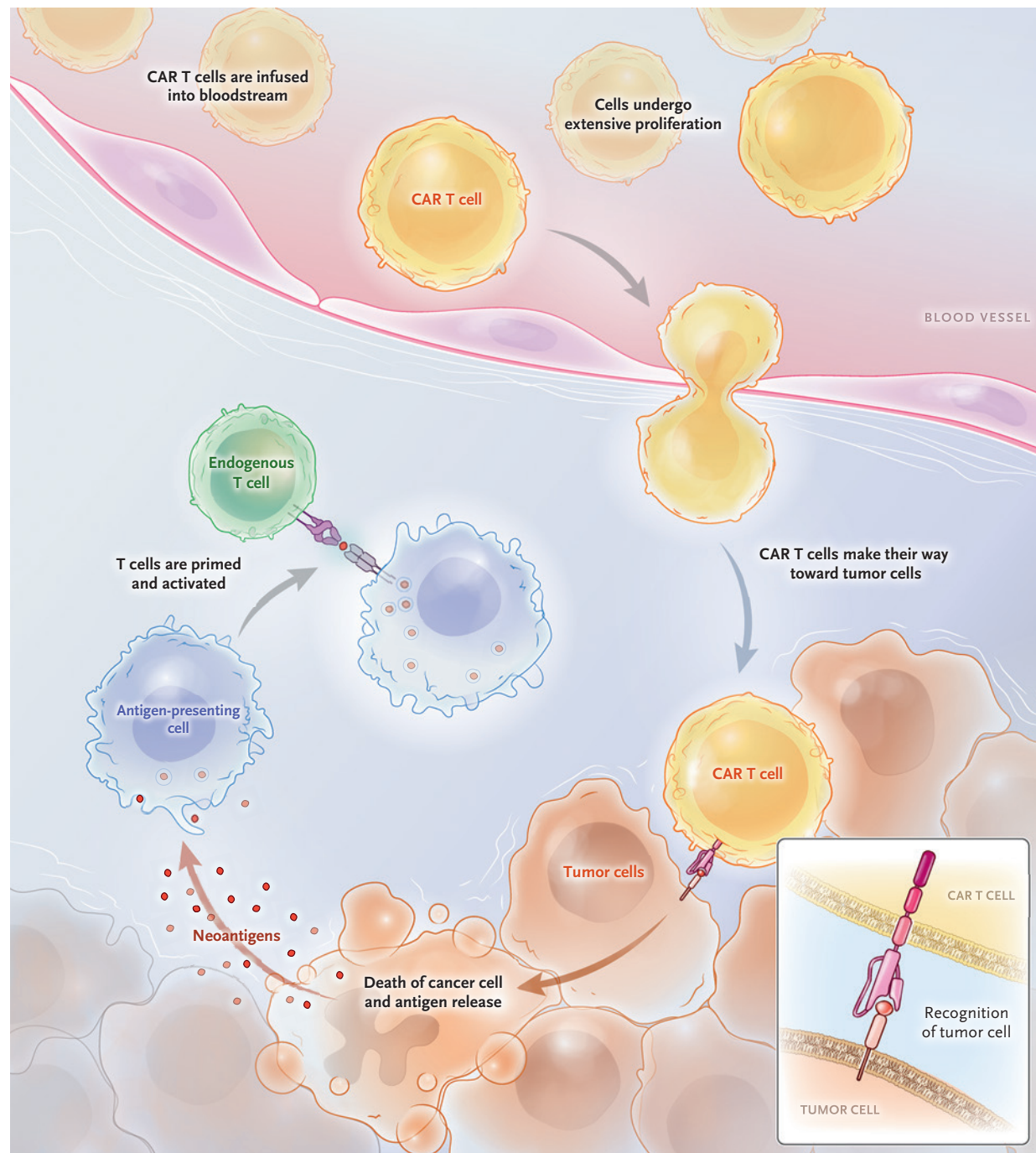
General structure of CARs



Clinical production of CAR-T cells

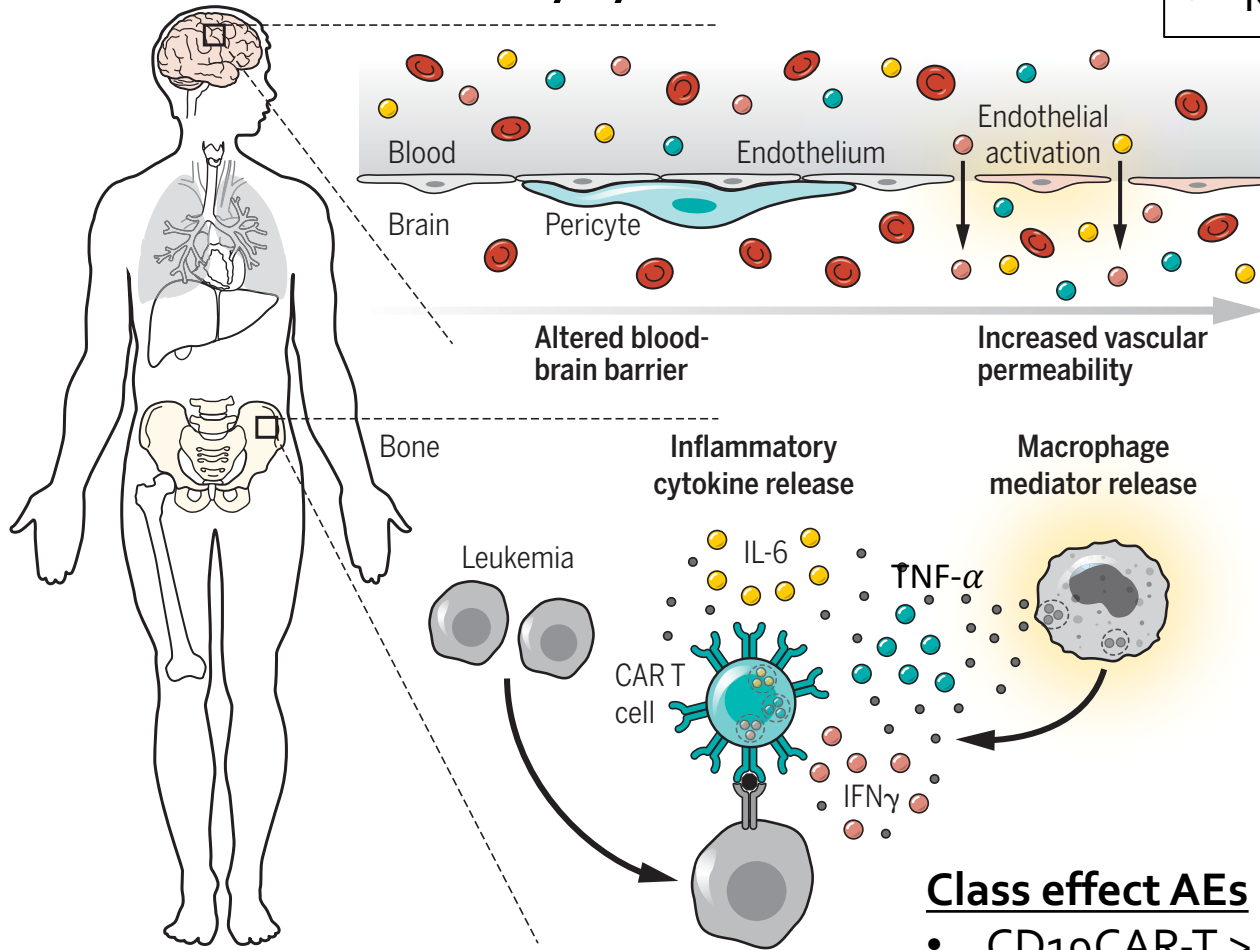


Mechanisms of action



CAR-T cell toxicity

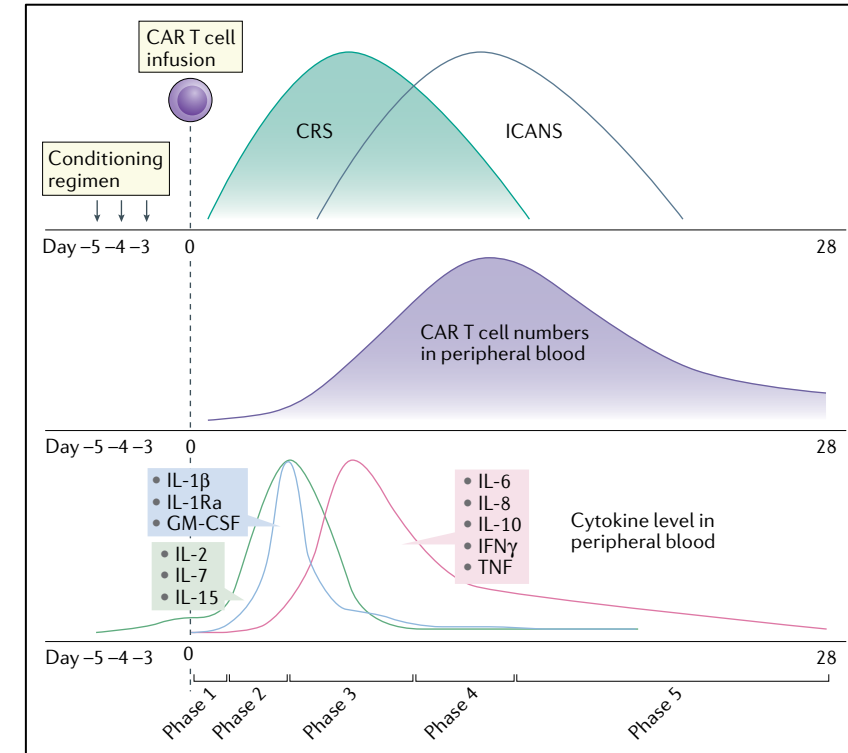
“Immune effector cell-associated neurotoxicity syndrome (ICANS)”



“Cytokine release syndrome (CRS)”

*Others

- Immune effector cell-associated hematotoxicity (ICAHT)
- Immune effector cell-associated HLH-like syndrome (IEC-HS)
- Infections
- Risk of second primary malignancies (myeloid/TCL)

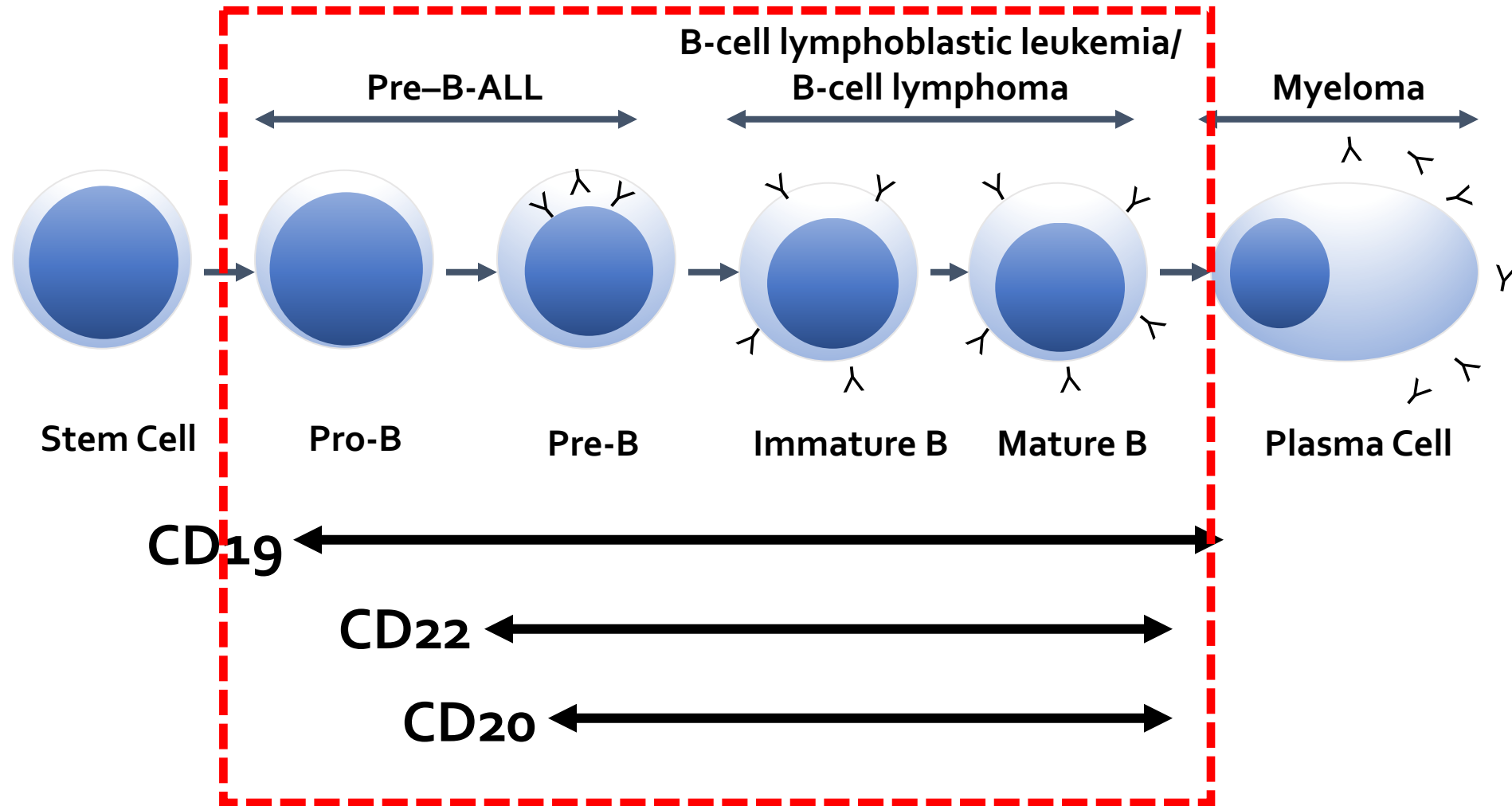


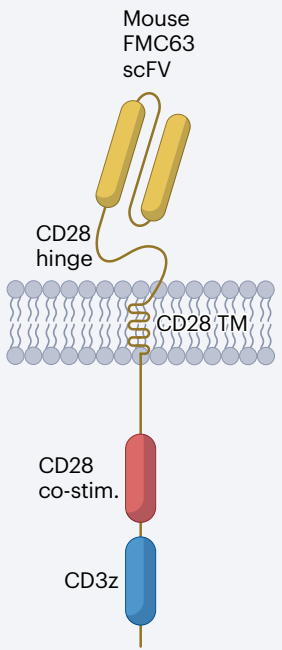
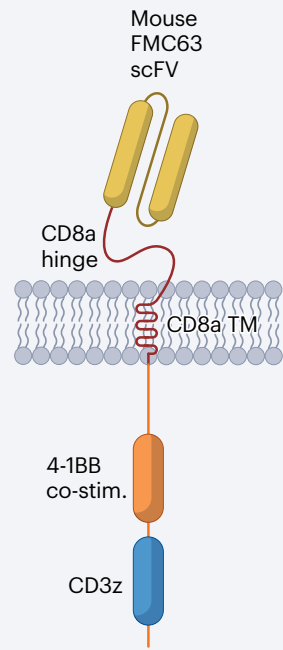
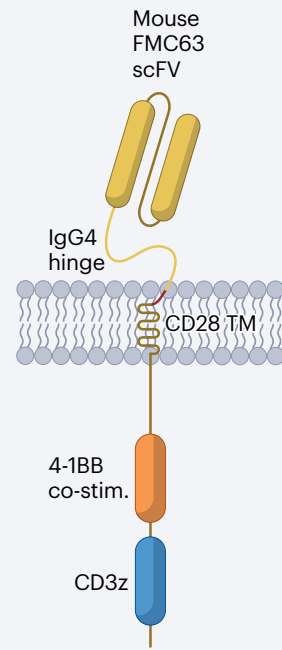
June CH, et al. Science. 2018;359:1361-1365.

Morris EC, et al. Nat Rev Immunol. 2022 Feb;22(2):85-96.

*Brudno J, et al. Nat Rev Clin Oncol. 2024 Jul;21(7):501-521.

Expression of B-cell lineage markers



	Axi-cel	Tisa-cel	Liso-cel
CAR structure FDA-approved CD19CAR-T cell For DLBCL			
FDA-approved indications	Adult patients with LBCL that is refractory to first-line chemoimmunotherapy or that has relapsed within 12 months of first-line chemoimmunotherapy Adult patients with R/R LBCL after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal LBCL, high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma	Adult patients with R/R LBCL after two or more lines of systemic therapy, including DLBCL not otherwise specified, high-grade B cell lymphoma and DLBCL arising from follicular lymphoma	Indicated for the treatment of adult patients with LBCL, including DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B cell lymphoma, primary mediastinal large B cell lymphoma, and follicular lymphoma grade 3B, who have: disease refractory to first-line chemoimmunotherapy or disease relapse within 12 months of first-line chemoimmunotherapy; or disease refractory to first-line chemoimmunotherapy or that relapsed after first-line chemoimmunotherapy and who are not eligible for HSCT owing to comorbidities and/or age; or R/R disease after two or more lines of systemic therapy
Manufacturing time	Median time from leukapheresis to infusion: 17–18 days ^{1,8} Median time from leukapheresis to release in ZUMA-7: 13 days ⁴	Median time from enrolment to infusion in JULIET: 54 days ² Median time from leukapheresis to infusion in BELINDA: 52 days ⁶	Median time from leukapheresis to infusion: 35.5–37 days ^{3,5,7}
Successful manufacturing rates in pivotal studies	99–100% ^{1,4}	93–99% ^{2,6}	99% ^{3,7}

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobson, I. Braunschweig, O.O. Oluwole, T. Siddiqi, Y. Lin, J.M. Timmerman, P.J. Stiff, J.W. Friedberg, I.W. Flinn, A. Goy, B.T. Hill, M.R. Smith, A. Deol, U. Farooq, P. McSweeney, J. Munoz, I. Avivi, J.E. Castro, J.R. Westin, J.C. Chavez, A. Ghobadi, K.V. Komanduri, R. Levy, E.D. Jacobsen, T.E. Witzig, P. Reagan, A. Bot, J. Rossi, L. Navale, Y. Jiang, J. Aycock, M. Elias, D. Chang, J. Wiecek, and W.Y. Go

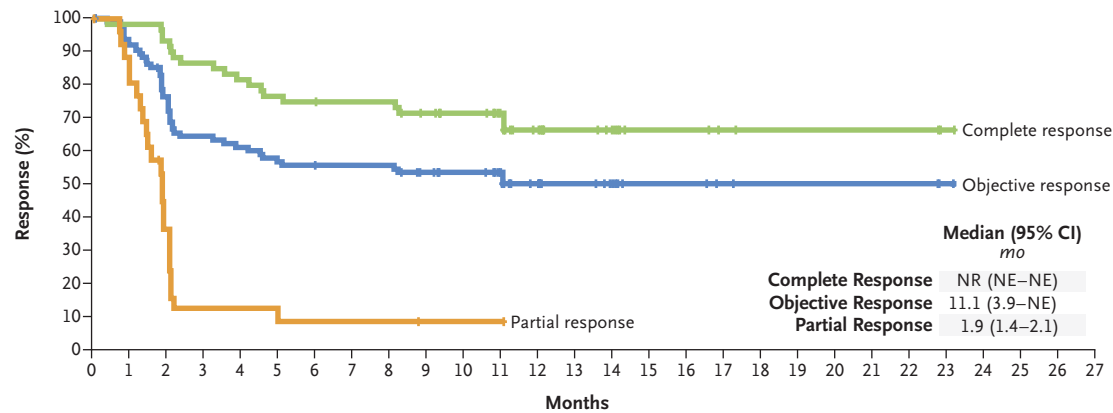
Phase II, multicenter, 101/111 pts with r/r DLBCL, PMBCL, or tFL
Received 2×10^6 cells/kg IV after LD FC regimen

ORR 82%, CR 54%, mDOR = 11.1 mo

mF/U 15.4 mo, 40% continuing CR

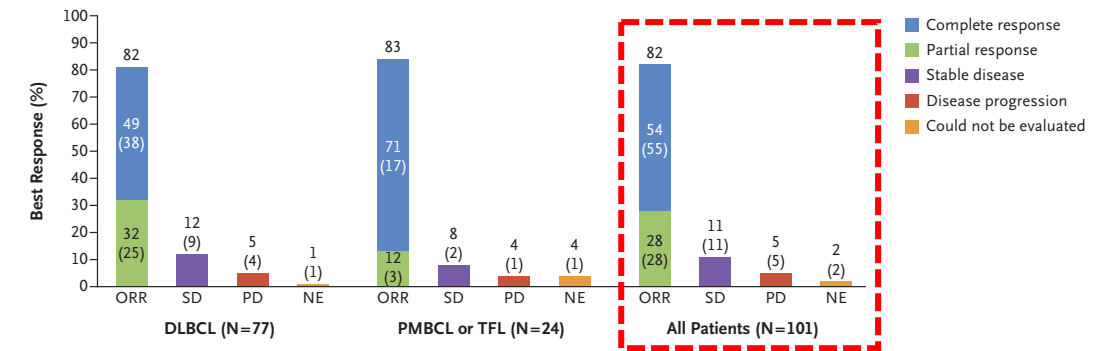
AEs: CRS and ICANs grade ≥ 3 were 13% and 28%, respectively

A Duration of Response

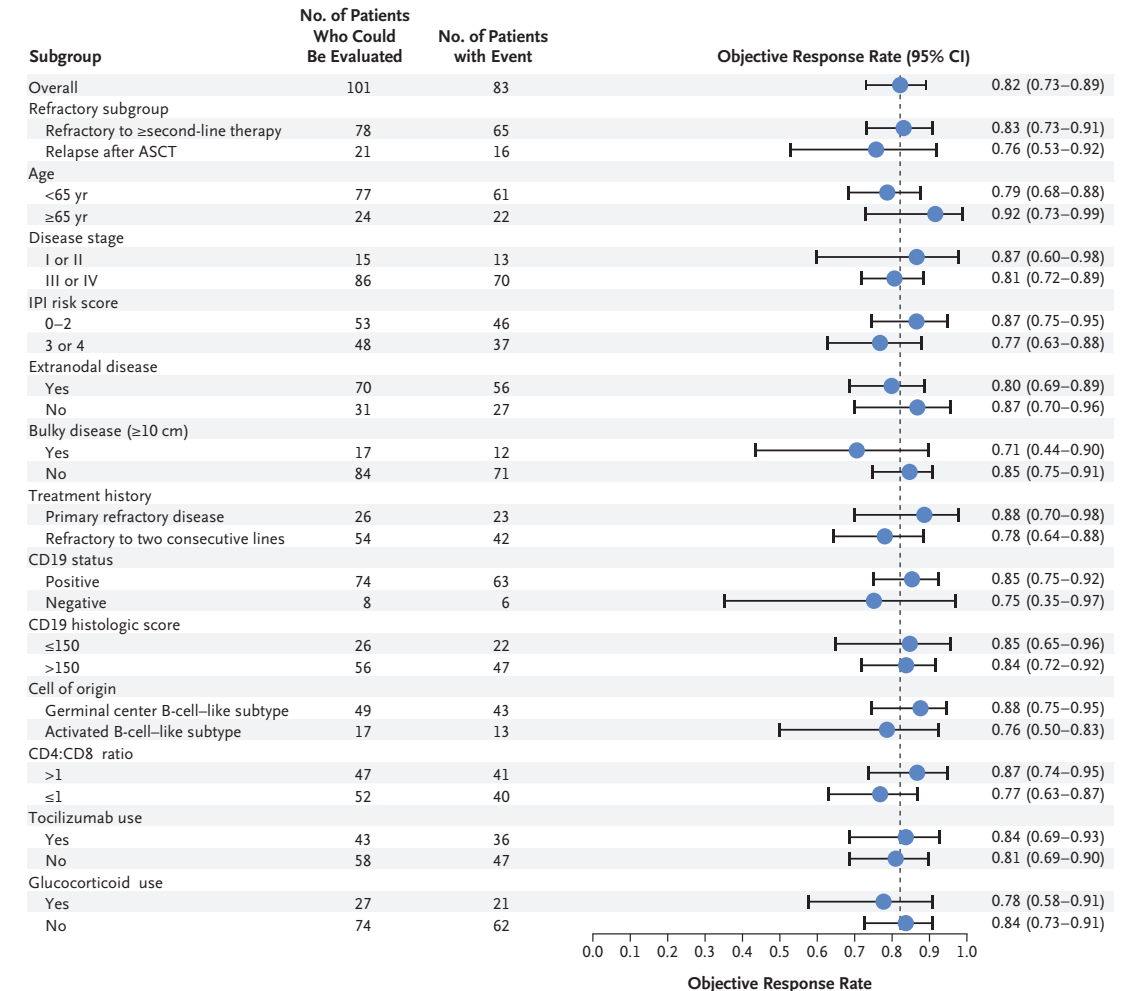


No. at Risk																								
Complete response	63	61	58	53	50	47	46	45	45	41	37	30	19	16	12	6	6	4	3	3	3	3	1	0
Objective response	89	82	67	56	53	49	48	47	47	42	38	31	19	16	12	6	6	4	3	3	3	3	1	0
Partial response	26	21	9	3	3	2	2	2	2	1	1	1	0											

A Objective Response Rate

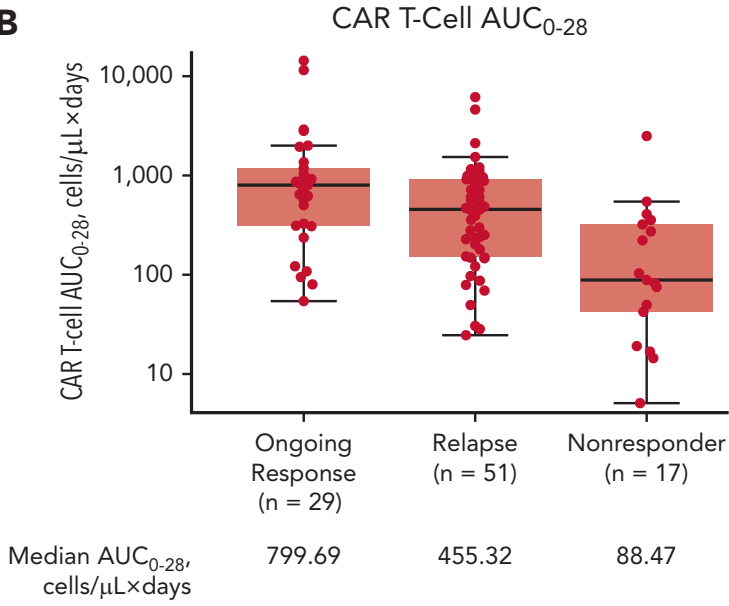
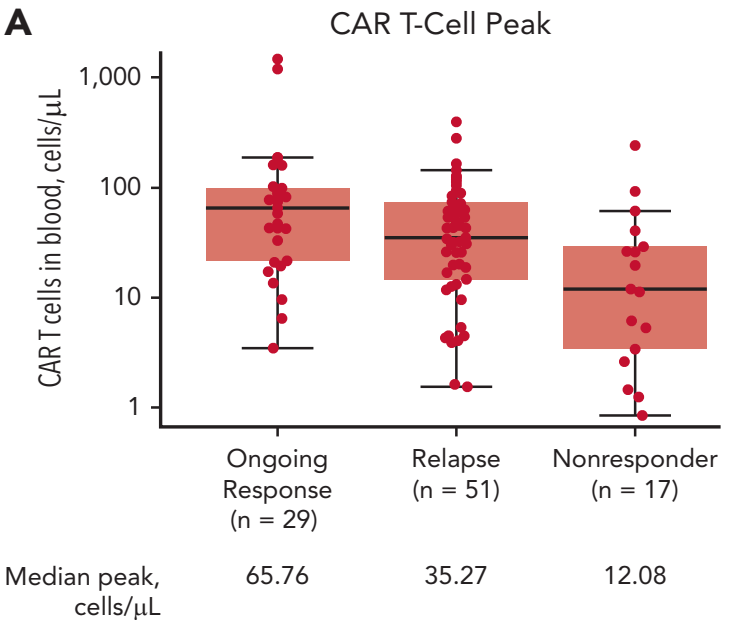
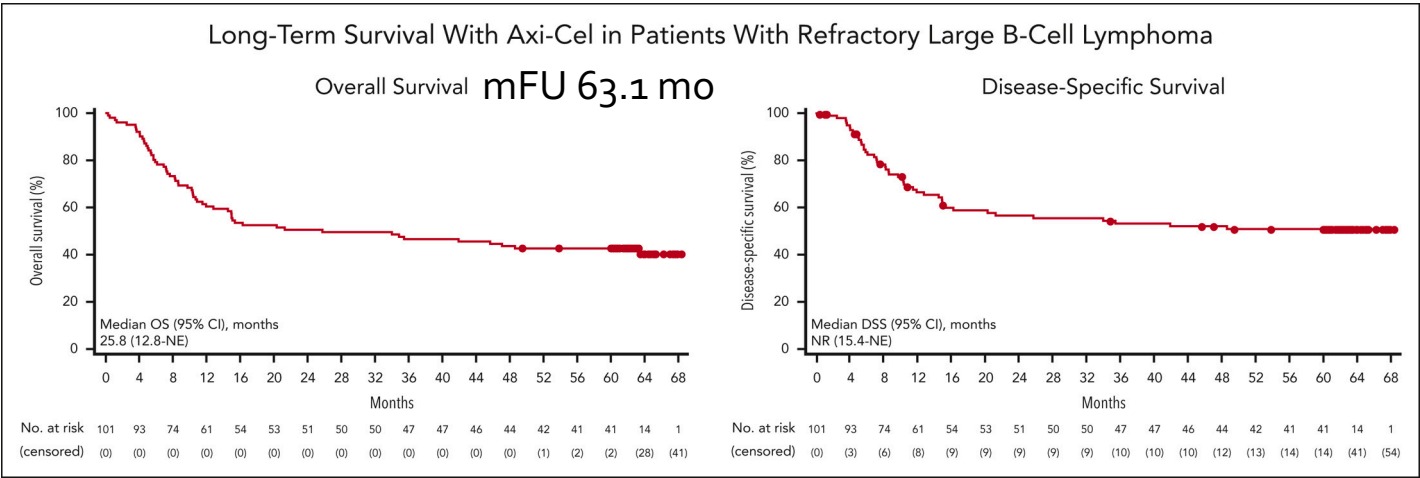
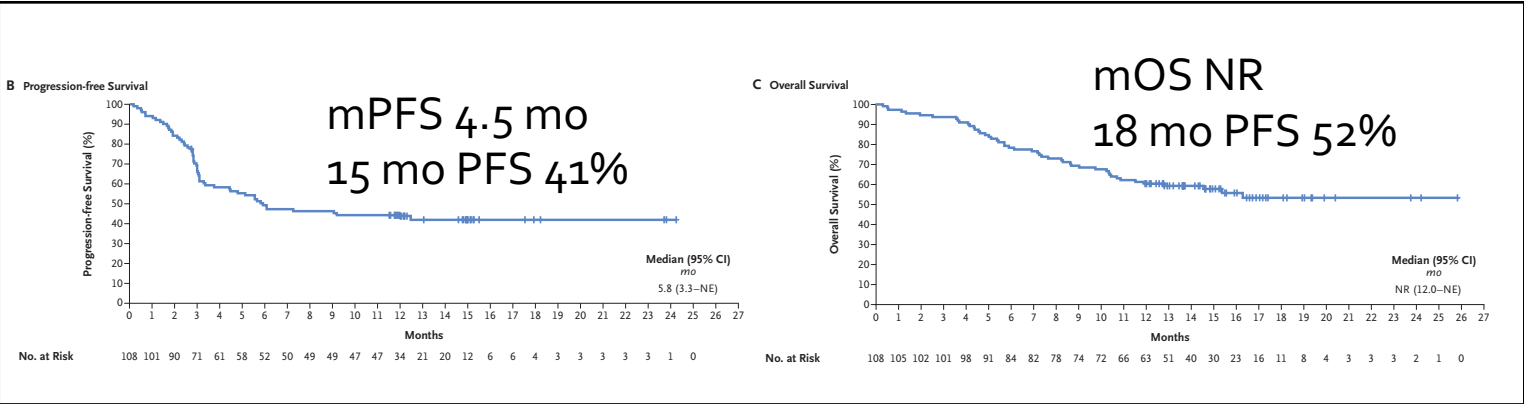


B Subgroup Analysis

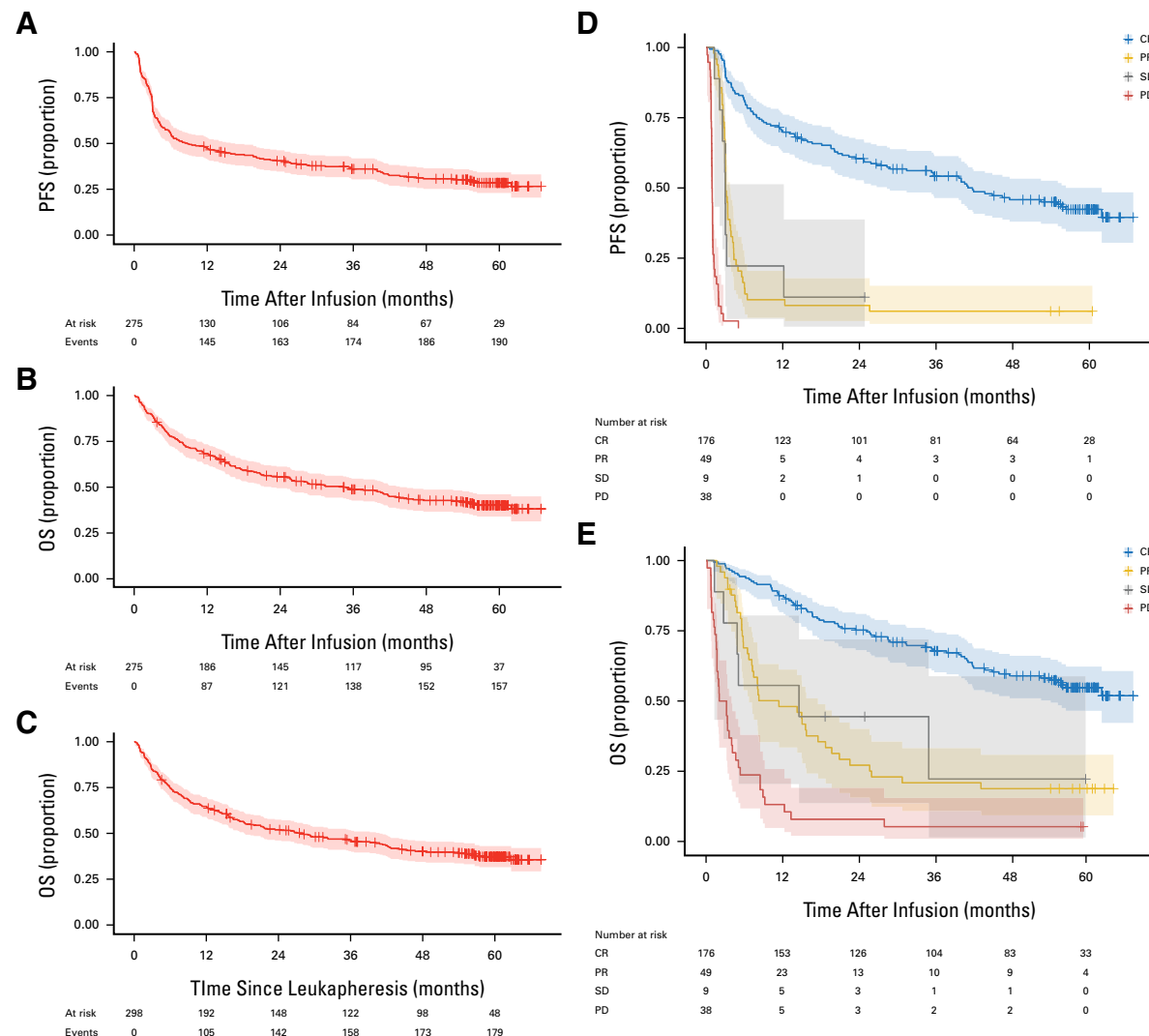


Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma

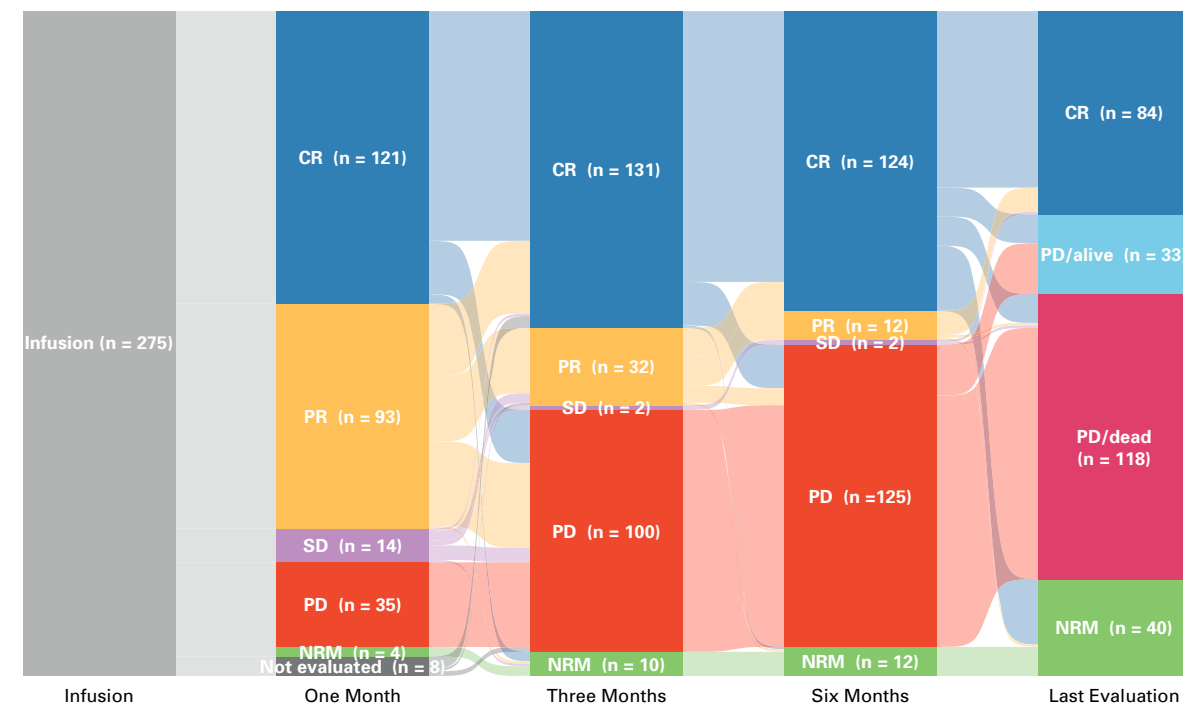
Sattva S. Neelapu,^{1,*} Caron A. Jacobson,² Armin Ghobadi,³ David B. Miklos,⁴ Lazaros J. Lekakis,⁵ Olalekan O. Oluwole,⁶ Yi Lin,⁷ Ira Braunschweig,⁸ Brian T. Hill,⁹ John M. Timmerman,¹⁰ Abhinav Deol,¹¹ Patrick M. Reagan,¹² Patrick Stiff,¹³ Ian W. Flinn,¹⁴ Umar Farooq,¹⁵ Andre H. Goy,¹⁶ Peter A. McSweeney,¹⁷ Javier Munoz,¹⁸ Tanya Siddiqi,¹⁹ Julio C. Chavez,²⁰ Alex F. Herrera,¹⁹ Nancy L. Bartlett,²¹ Adrian A. Bot,²² Rhine R. Shen,²² Jinghui Dong,²² Kanwarjit Singh,²² Harry Miao,²² Jenny J. Kim,²² Yan Zheng,²² and Frederick L. Locke^{20,*}



Five-Year Follow-Up of Standard-of-Care Axicabtagene Ciloleucel for Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium



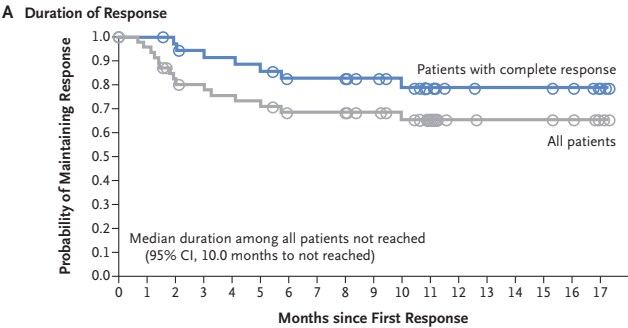
275 pts received SOC axi-cel after ≥ 2 L therapies
mF/U 58 mo: 5-y PFS 29%, 5-y OS 40%
 5-y NRM 16.2%, over half NRM occurred > 2 y
 Late NRM > infections and subsequent malignant neoplasms 9%; tMN, solid tumors, unrelated lymphoid malignancies



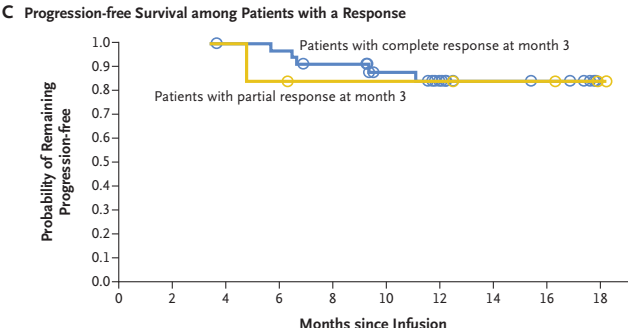
Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Stephen J. Schuster, M.D., Michael R. Bishop, M.D., Constantine S. Tam, M.D., Edmund K. Waller, M.D., Ph.D., Peter Borchmann, M.D., Joseph P. McGuirk, D.O., Ulrich Jäger, M.D., Samantha Jaglowski, M.D., Charalambos Andreadis, M.D., Jason R. Westin, M.D., Isabelle Fleury, M.D., Veronika Bachanova, M.D., Ph.D., S. Ronan Foley, M.D., P. Joy Ho, M.B., B.S., D.Phil., Stephan Mielke, M.D., John M. Magenau, M.D., Harald Holte, M.D., Ph.D., Serafino Pantano, Ph.D., Lida B. Pacaud, M.D., Rakesh Awasthi, Ph.D., Jufen Chu, Ph.D., Özlem Anak, M.D., Gilles Salles, M.D., Ph.D., and Richard T. Maziarz, M.D., for the JULIET Investigators*

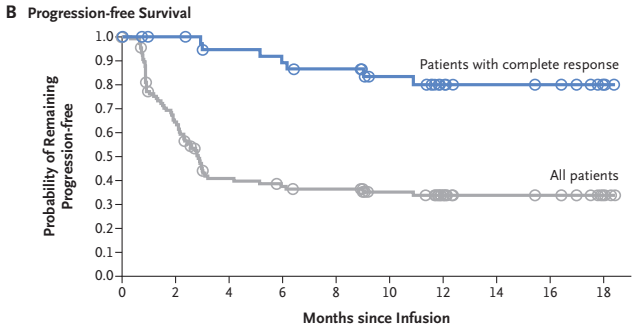
Phase II, multicenter, 93/115 pts with r/r DLBCL, tFL
ORR 52%, CR 40%, mDOR = NR
mPFS 2.9 mo, mOS 11.1 mo (12 mo ~40%)
AEs: CRS and ICANs grade ≥3 were 22% and 12%, respectively



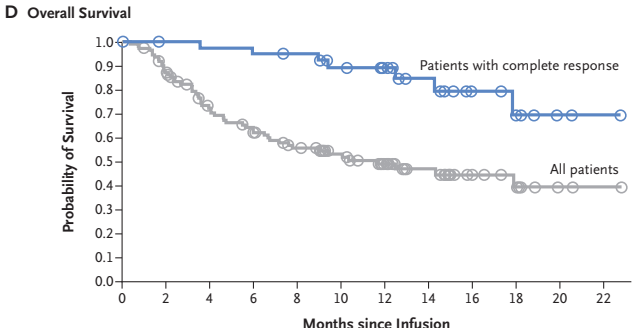
No. at Risk	37	36	35	31	30	26	26	23	21	15	9	8	8	7	4
Patients with complete response	37	36	35	31	30	26	26	23	21	15	9	8	8	7	4
All patients	48	37	32	27	27	22	10	9	8						



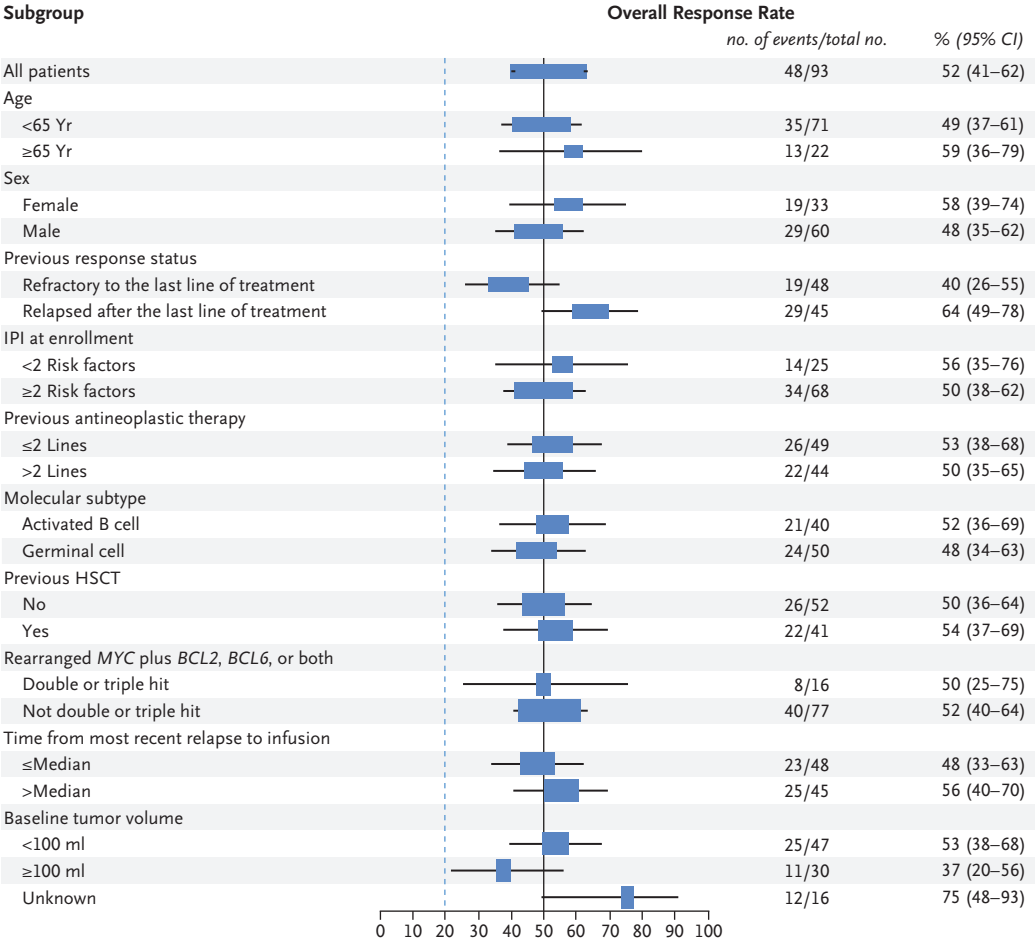
No. at Risk	32	30	28	21	12	7	6	1
Patients with complete response	32	30	28	21	12	7	6	1
Patients with partial response	6	4	4	4	4	3	3	2



No. at Risk	40	39	36	35	33	31	29	24	23	15	9	9	8	7	2
Patients with complete response	40	39	36	35	33	31	29	24	23	15	9	9	8	7	2
All patients	111	65	38	34	32	25	16	10	9	9	8	7	6	5	3



No. at Risk	40	40	40	39	38	38	37	36	30	29	23	16	16	12	9	9	7	3	2	1	1
Patients with complete response	40	40	40	39	38	38	37	36	30	29	23	16	16	12	9	9	7	3	2	1	1
All patients	111	94	71	60	50	40	28	19	11	8	2	1	1	1	1	1	1	1	1	1	1



Tisagenlecleucel Chimeric Antigen Receptor (CAR) T-Cell Therapy for Adults with Diffuse Large B-Cell Lymphoma (DLBCL): Real World Experience from the Center for International Blood & Marrow Transplant Research (CIBMTR) Cellular Therapy (CT) Registry

- 26 centers; 70 patients r/r DLBCL through **CIBMTR CT registry**
- Outcomes available from 47 patients
- Tisa-cel $0.6\text{--}6 \times 10^6$ cells/kg
- mF/U 5.8 mo: **ORR 59.6% (CR 38.3%)**
- Grade ≥ 3 CRS and ICANS 4.3%
- 29.8% died after treatment due to PD
- 1 patient developed basal cell carcinoma (prior CAR-T infusion)

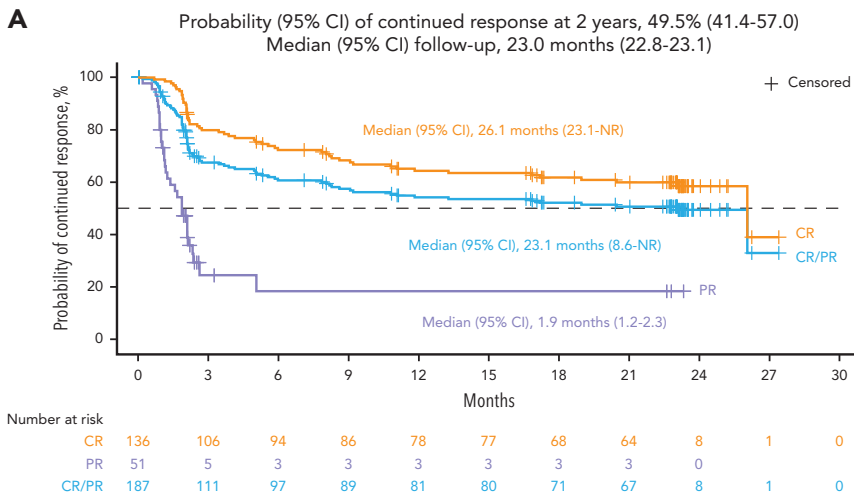
Real-World Evidence of Tisagenlecleucel for the Treatment of Relapsed or Refractory Large B-Cell Lymphoma

- 10 **Spanish institutions**; 69/91 patients r/r DLBCL
- 76% received CAR-T infusion, 56% received bridging before CAR-T
- Tisa-cel 2.2×10^8 cells
- Median time v-to-v 53 days (range; 29–225)
- **ORR 64% (CR 28%)**
- **mF/U 14.1 mo: mFPS 3 mo, mOS 10.7 mo**
- Grade ≥ 3 CRS and ICANS 4% and 0%, respectively

Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study

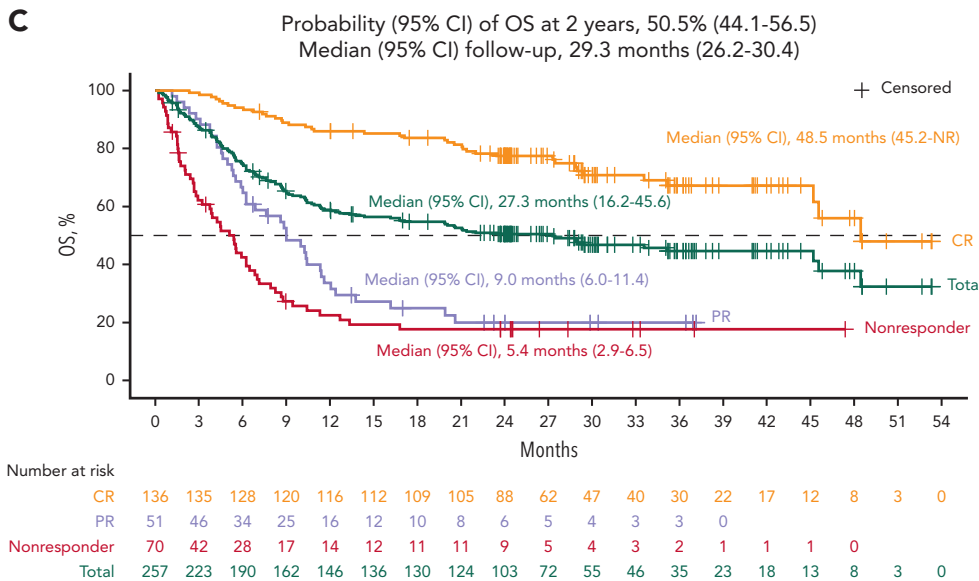
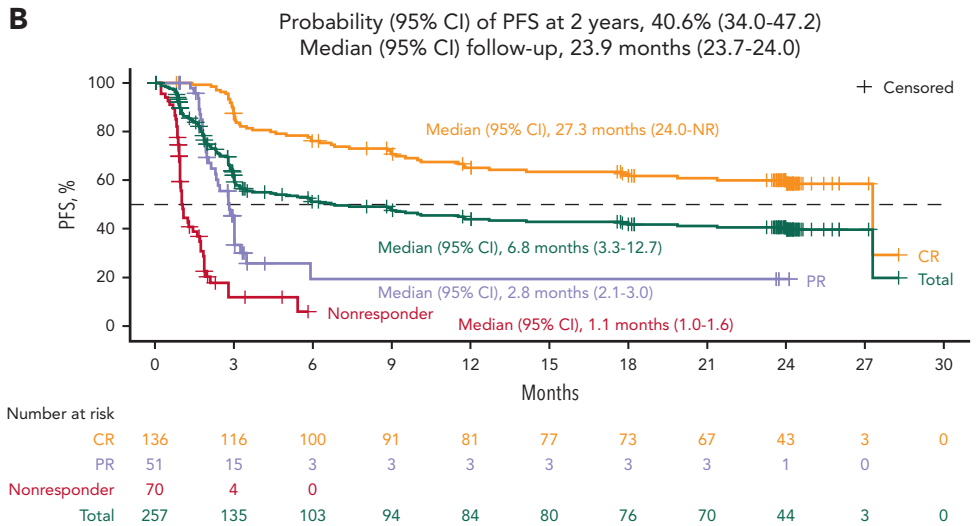
Jeremy S Abramson, M Lia Palomba, Leo I Gordon, Matthew A Lunning, Michael Wang, Jon Arnason, Amitkumar Mehta, Enkhtsetseg Purev, David G Maloney, Charalambos Andreadis, Alison Sehgal, Scott R Solomon, Nilanjan Ghosh, Tina M Albertson, Jacob Garcia, Ana Kostic, Mary Mallaney, Ken Ogasawara, Kathryn Newhall, Yeonhee Kim, Daniel Li, Tanya Siddiqi

- Phase II, multicenter, 269/344 pts with r/r DLBCL, HGBL, tDLBCL, PMBCL, or FL G3B > received liso-cel CD8:CD4 = 1:1 dose, recommended dose 10⁸ cells
- 256 pts evaluable: **ORR 73%, CR 53%**, mDOR = 11.1 mo
- mF/U 19.9 mo: **2-y DOR 49.5%, PFS 40.6%, OS 50.5%**
- AEs: CRS and ICANs grade ≥3 were 2% and 10%, respectively



Abramson JS, et al. Lancet. 2020;396:839–52.
Abramson JS, et al. Blood. 2024; 143:404–16.

Two-year follow-up of lisocabtagene maraleucel in relapsed or refractory large B-cell lymphoma in TRANSCEND NHL 001



Multicenter, Real-World Study in Patients with R/R Large B-Cell Lymphoma (LBCL) Who Received Lisocabtagene Maraleucel (liso-cel) in the United States (US)

Jennifer L. Crombie¹, Loretta J. Nastoupil, MD², Charalambos Andreadis³, Iris Isufi⁴, Bradley Hunter⁵, Allison Winter, MD⁶, Brian Hess, MD⁷, Stefan K. Barta, MD⁸, Michael J. Frigault⁹, Maria Lia Palomba, MD¹⁰, Natalie S. Grover, MD¹¹, Michael D. Jain, MD PhD¹², Tamara K. Moyo, MD¹³, Sagar S. Patel, MD¹⁴, Priyanka A Pophali, MD¹⁵, David Bernasconi¹⁶, Charimar Santiago Parrilla¹⁷, Amani Kitali, MBA, MPH, PMP¹⁶, Fei Fei Liu¹⁶, Mecide Gharibo¹⁶, Marcelo Pasquini, MDMS¹⁷

- Real-world multicenter study (> 50 sites) of US CIBMTR registry (Feb 2021– Nov 2022)
- Cutoff May 4, 2023 ; **323 pts**
- Median v-to-v time 36 days (IQR, 34–42)
- mF/U 7.4 mo: **ORR 79%, CR 65%**
- Median time to response 1.2 mo
- mDOR NR; 6-mo DOR 73%
- **mPFS and mOS NR; 6-mo PFS 64% and OS 82%**
- Grade ≥ 3 CRS and ICANs were 3% and 11%, respectively

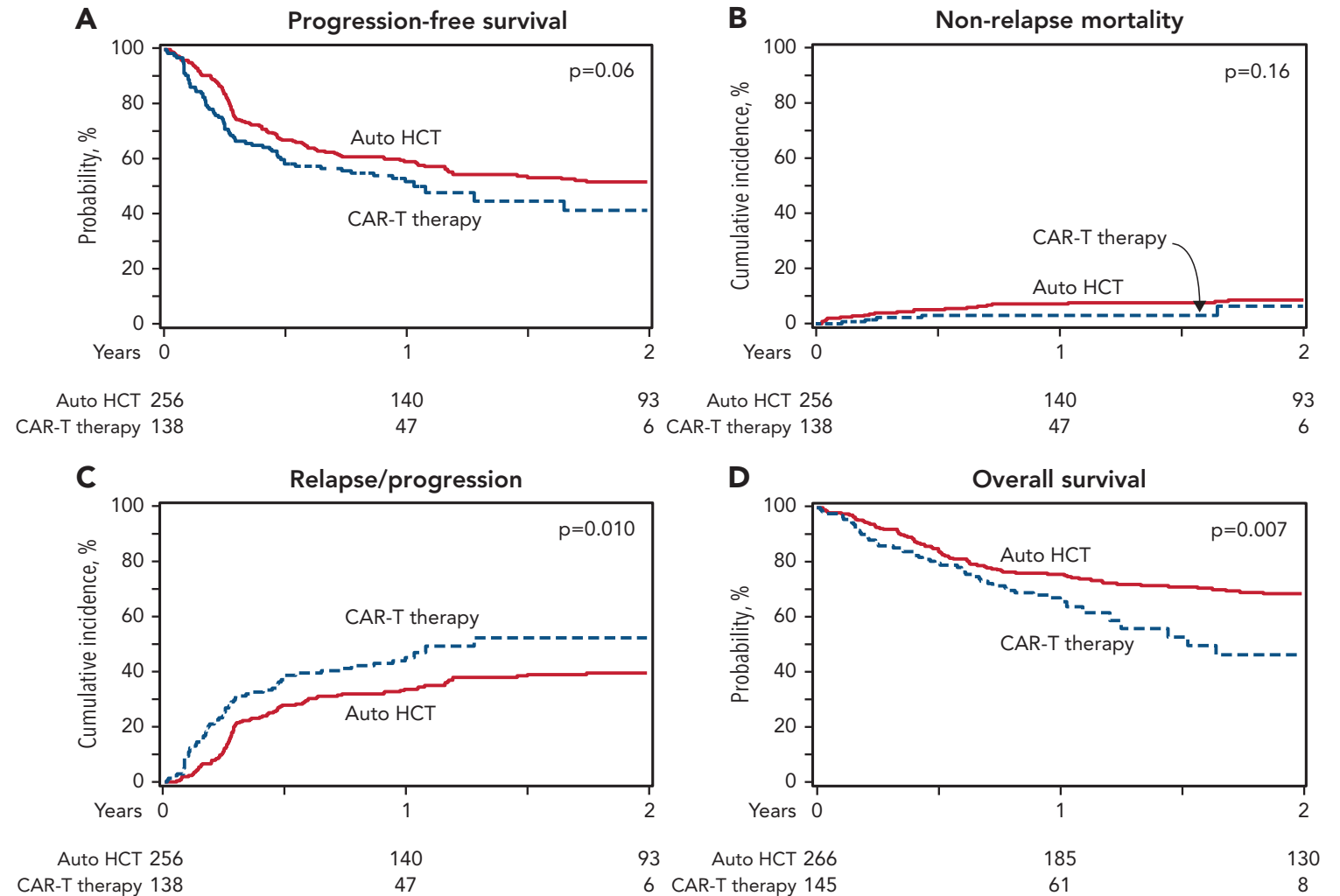
Crombie JL, et al. Blood. 2023;142: 104–6.

Characteristic	All patients (N = 323)
Male, n (%)	204 (63)
Age, median (range), years	70 (24–91)
< 65, n (%)	107 (33)
≥ 65 , n (%)	216 (67)
≥ 75 , n (%)	89 (28)
Histology, n (%)	
DLBCL	270 (84)
DLBCL NOS	263 (81)
Transformed from CLL (Richter's)	22 (7)
Transformed from other lymphoma histology	66 (20)
PMBCL	2 (1)
FL3B	4 (1)
HGBCL	38 (12)
HGBCL with <i>c-MYC</i> and either <i>BCL2</i> and/or <i>BCL6</i> translocation at infusion	32 (10)
Other	9 (3)
ECOG PS, n (%)	
0–1 / ≥ 2	274 (85) / 18 (6)
Comorbidities, n (%)	
Pulmonary (moderate/severe)	82 (25)
Cardiac	80 (25)
Obesity	30 (9)
Renal (moderate/severe)	8 (2)
Hepatic (moderate/severe)	6 (2)
Other	32 (10)
Active CNS involvement, n (%)	18 (6)
IPI score, n (%)	
0–1 / 2	84 (26) / 121 (37.5)
3 / 4–5	92 (28.5) / 26 (8)
Number of prior lines of systemic therapy, median (range)	3 (0–11)
Received standard LDC (FLU/CY), n (%)	294 (91)

CY, cyclophosphamide; FL3B, follicular lymphoma grade 3B; FLU, fludarabine; LDC, lymphodepleting chemotherapy; PMBCL, primary mediastinal B-cell lymphoma.

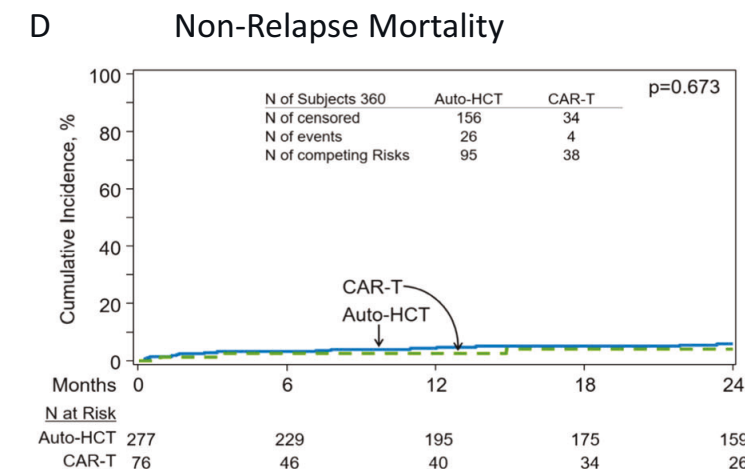
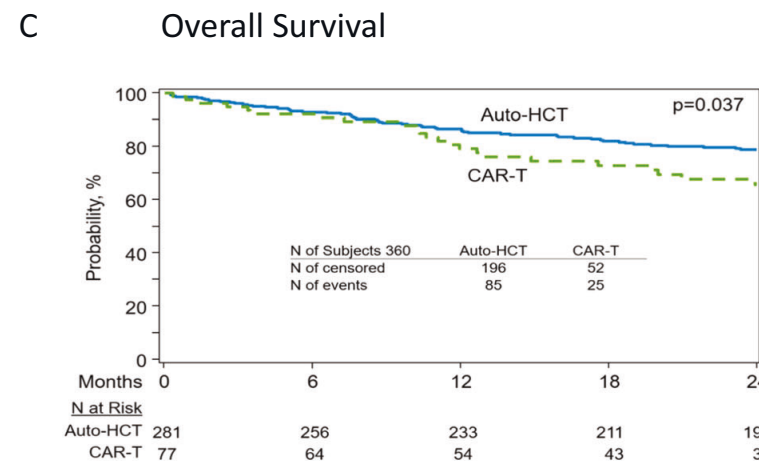
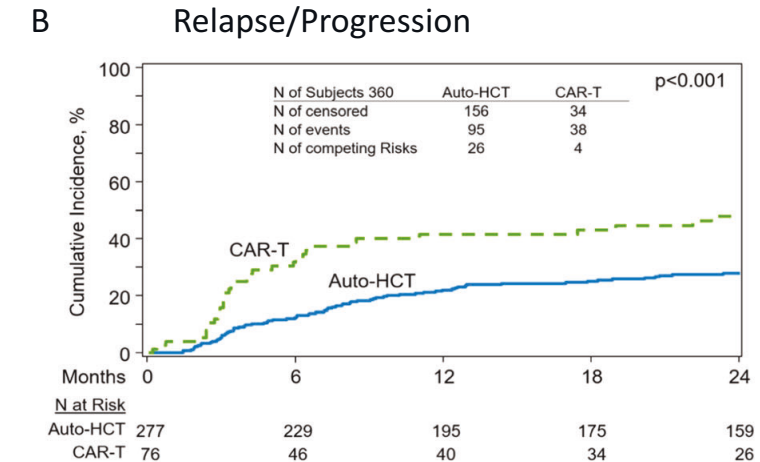
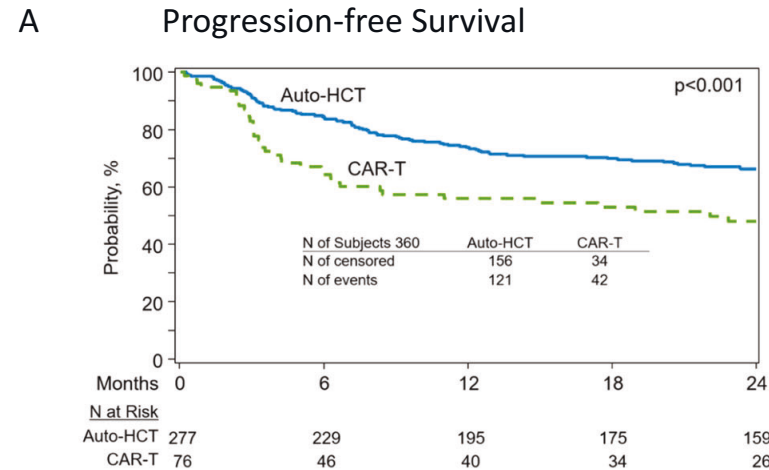
Outcomes for DLBCL treated with ASCT vs CAR-T after PR: CIBMTR

- 266 ASCT (2013-2019) vs 145 CAR-T axi-cel (2018-2019) patients receiving treatment while in PR
- Early relapse 12 mo: HCT 39% vs CAR-T 44%
- Similar PFS, NRM
- **Lower risk of CI relapse and higher OS with ASCT**
- * Not sig in subgr. ≤ 2 prior lines therapy



Outcomes for DLBCL treated with ASCT vs CAR-T after CR: CIBMTR

- 281 ASCT (2015-2021) vs 79 commercial CAR-T* (2018-2021) patients receiving treatment while in CR
- mF/U 49.7 and 24.7 mo for HCT and CAR-T
- Early relapse 12 mo: HCT 58% vs CAR-T 72.2% (sig.)
- **Higher 2-y PFS, OS and lower CI relapse in HCT vs CAR-T**
- MVA: HCT asso. superior PFS and lower relapse vs CAR-T
- * Tisa-cel 53.2%, axi-cel 45.6%, liso-cel 1.3%



CD19CAR-T in large cell lymphoma

US FDA-approved CAR-T cell

	Axi-cel	Tisa-cel	Liso-cel
CD19 scFv	FMC63	FMC63	FMC63
Signal 2	CD28	41BB	41BB
Signal 1	CD3 ξ	CD3 ξ	CD3 ξ
Source	Fresh unsorted PBMCs	Cryopreserved unsorted PBMCs	Fresh sorted PBMCs
Viral vector	Gamma retrovirus	Lentivirus	Lentivirus
Pivotal trial	ZUMA-1	Juliet	Transform
Most mature follow up (m)	63.1	40.3	24
Median duration of response (m)	11.1	NE	23.1
ORR/CR (%)	83/58	52/39	73/53
Median PFS (m)	5.9	2.9	6.8
PFS, 24 m (%)	36	33*	40.6
Median OS (m)	25.8	11.1	27.3
OS, 24 m (%)	50.5	40*	50.5
CRS: Any/Gr3+ (%)	93/13	57/23	42/2
Neuro tox: Any/Gr3+ (%)	64/28	20/11	30/10

N = 101 115 256

Trial design features: CAR-T 2L

	ZUMA-7	Belinda	Transform
Histologies included	DLBCL NOS,* including transformed from FL, HGBCL with or without MYC and BCL2/6, T/H-RLBCL, Primary cutaneous DLBCL - leg type	DLBCL NOS, including transformed from indolent NHL, HGBCL with or without MYC and BCL2/6, T/H-RLBCL, Primary cutaneous DLBCL - leg type FL grade 3B, PMBCL, Intravascular LBCL, ALK + LBCL, HHV8 + LBCL	DLBCL NOS, including transformed from indolent NHL, HGBCL with MYC and BCL2/6, T/H-RLBCL, FL grade 3B, PMBCL
Product	Axi-cel, CD28/CD3zeta 2×10^6 cells/kg	Tisa-cel, 4 - 1BB/CD3zeta $0.6-6 \times 10^8$ cells	Liso-cel, 4 - 1BB/CD3zeta 1×10^8 cells
1L refractory definition	• PD as best response • SD after at least 4 cycles • PR with + biopsy or PD <12 mo from 1L start	• PD/SD as best response	• PD/SD/PR as best response • CR with progression <3 mo
1L relapsed definition	• CR followed by + biopsy <12 mo from 1L end	• Positive biopsy $\leq$12 mo from 1L end	• CR followed by + biopsy 3-12 mo from 1L end
Age	18+	18+	18-75
Leukapheresis time point	• At randomization • Only CAR T-cell arm	• Before randomization • All patients	• Before randomization • All patients
Stratification factors	1. Refractory vs Relapse $\leq$ 6 mo vs Relapse >6-12 mo 2. 2L AAIP 0-1 vs 2-3	1. Refractory or relapsed $\leq$ 6 mo vs relapsed 6-12 mo 2. IPI <2 vs $\geq$ 2	1. Refractory vs relapse 2. 2L AAIP 0-1 vs 2-3
Bridging therapy	• Dexamethasone $\leq$40 mg for $\leq$4 d	• R-ICE • R-GDP • R-DHAP • R-GemOx	• R-ICE • R-GDP • R-DHAP
LD chemotherapy	• Fludarabine $30 \text{ mg/m}^2 \times 3 \text{ d}$ • Cyclophosphamide $500 \text{ mg/m}^2 \times 3 \text{ d}$	• Fludarabine $25 \text{ mg/m}^2 \times 3 \text{ d}$ and • Cyclophosphamide $250 \text{ mg/m}^2 \times 3 \text{ d}$ - OR • Bendamustine $90 \text{ mg/m}^2 \times 2 \text{ d}$	• Fludarabine $30 \text{ mg/m}^2 \times 3 \text{ d}$ • Cyclophosphamide $300 \text{ mg/m}^2 \times 3 \text{ d}$
SOC chemotherapy	• R-ICE • R-GDP • R-DHAP • R-ESHAP	• R-ICE • R-GDP • R-DHAP • R-GemOx	• R-ICE • R-GDP • R-DHAP
Crossover to CAR T-cell therapy	No	Yes, if • <PR/CR by 12 wk (after 2 SOC regimens) • PD at any time	Yes, if • <PR/CR by 9 wk • PD at any time • Need for new therapy after 18 wk
EFS definition	Time from randomization to: • PD • Death • $\leq$PR at day 150 assessment • Start of new lymphoma therapy	Time from randomization to: • PD • Death • <PR at/after week 12	Time from randomization to: • PD • Death • $\leq$PR by week 9 • Start of new lymphoma therapy

	ZUMA-7		Belinda		Transform	
	Axi-cel	SOC	Tisa-cel	SOC	Liso-cel	SOC
N	180	179	162	160	92	92
Median age, y (range)	58 (21-80)	60 (26-81)	60 (19-79)	58 (19-77)	60 (20-74)	58 (26-75)
Age ≥ 65 y, n (%)	51 (28)	58 (32)	54 (33)	46 (29)	36 (39)	25 (27)
Female sex (%)	70 (39)	52 (29)	59 (36)	62 (39)	48 (52)	31 (34)
AAIPI* 2-3IPI ≥ 2 (%)	82 (46)*	79 (44)*	106 (65)	92 (58)	36 (39)*	37 (40)*
GCB subgroup (%)	109 (61)	99 (55)	46 (28)	63 (39)	NR	NR
ABC subgroup (%)	16 (9)	9 (5)	52 (32)	42 (26)	NR	NR
HGBCL (%)	31 (17)	25 (14)	32 (20)	19 (12)	22 (24)	21 (23)
Refractory to 1L (%)	133 (74)	131 (73)	107 (66)	107 (67)	67 (73)	68 (74)

	ZUMA-7		Belinda		Transform	
	Axi-Cel	SOC	Tisa-Cel	SOC	Liso-Cel	SOC
Received bridging corticosteroids (%)	36	—	—	—	—	—
Received bridging chemotherapy (%)	0	—	83	—	63	—
Received >1 SOC chemotherapy regimen (%)	—	0	—	54	—	0
Received intended CAR T cell (%)	94	—	96	—	97.8	—
Median time to CAR T-cell infusion in days, (interquartile range* or range†)	29 (27-34)*	—	52 (31-135)†	—	NR	—
Received intended ASCT (%)	—	36	—	32.5	—	45.6
Crossover pn protocol (%)	—	—	—	51	—	51
Received cellular therapy off protocol (%)	—	56	—	—		—
Follow up, median in months	24.9		10		6.2	
ORR/CR rate (%)	83/65	50/32	46/28	43 /28	86/66	48/39
EFS, median in months	8.3	2	3	3	10.1	2.3
EFS, % (timepoint in months)	41 (24 mo)	16 (24 mo)	NR	NR	63 (6 mo)	33 (6 mo)
EFS HR (95% CI)	0.4 (0.31-0.51)		1.07 (0.82-1.4)		0.35 (0.23-0.53)	
PFS, median in months	14.7	3.7	NR	NR	14.8	5.7
PFS HR (95% CI)	0.49 (0.37-0.65)		NR		0.406 (0.21-0.66)	
OS, median in months	NE	25.7	16.9	15.3	NE	16.4
OS HR (95% CI)	0.708 (0.515-0.972)‡		NR		0.51 (0.26-1.004)	

CRS gr ≥3 6;5;1%
ICANS ≥3 21; 2;4%
(more in ZUMA-7)

Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: Primary analysis of phase 3 TRANSFORM study (Abramson et al)

Patients with R/R LBCL | N = 184

- ▶ **Primary endpoint:** EFS (per IRC)
- Key secondary endpoints:** CR rate (per IRC), PFS (per IRC), OS
- ▶ **Eligibility:** Adult patients with R/R LBCL ≤ 12 months after first-line therapy intended for ASCT

Open-label, Phase 3 Trial Randomized 1:1

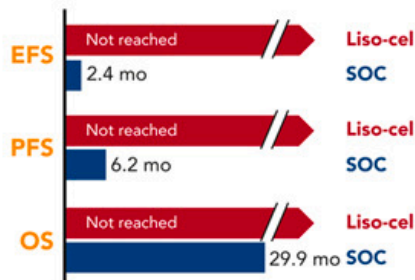
Liso-cel
n = 92
100 × 10⁶ CAR⁺ T cells

58 (63%) received bridging therapy
89 (97%) received liso-cel

SOC
n = 92
3 cycles of platinum-based immunochemotherapy + HDCT/ASCT

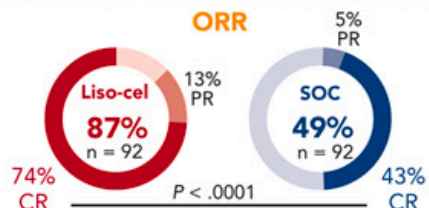
43 (47%) completed full SOC treatment
61 (66%) approved for crossover to receive liso-cel as 3rd line therapy after SOC failure

Median EFS, PFS, and OS



Stratified HR	18-month rate diff.
EFS: HR, 0.356; not retested	+31.8%
PFS: HR, 0.400; P < .0001	+29.4%
OS: HR, 0.724; P = .0987	+12.5%

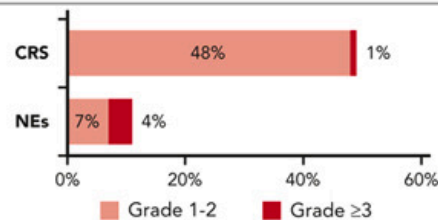
Median follow-up: 17.5 months



Grade ≥3 TEAEs



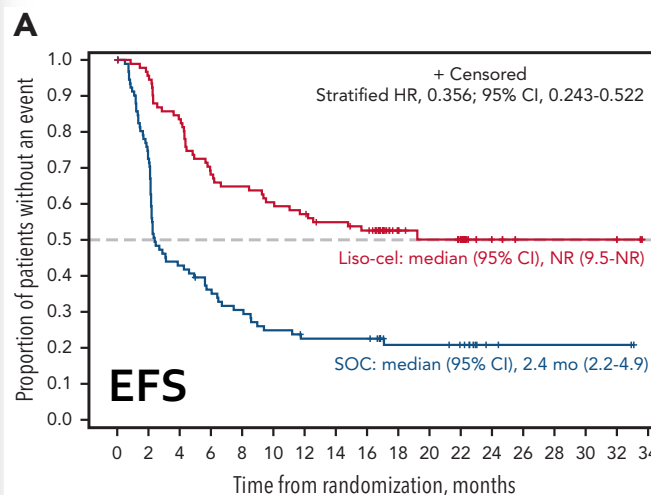
	Liso-cel	SOC
Serious AEs	48%	49%
Deaths due to TEAEs	2%	2%



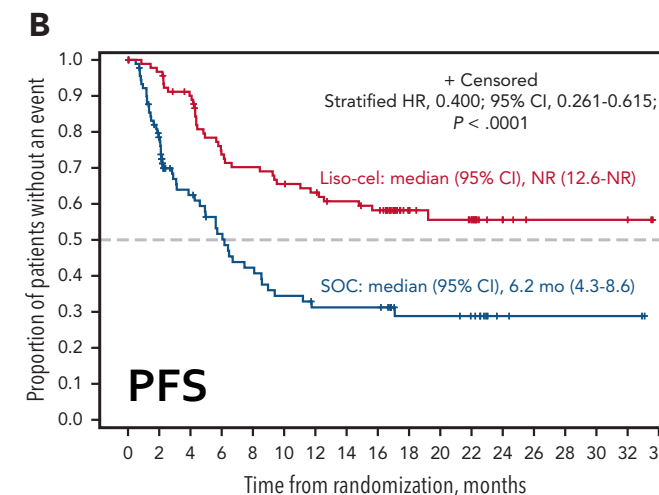
No Grade 4 or 5 CRS or NEs

No prophylactic corticosteroids or vasopressors used

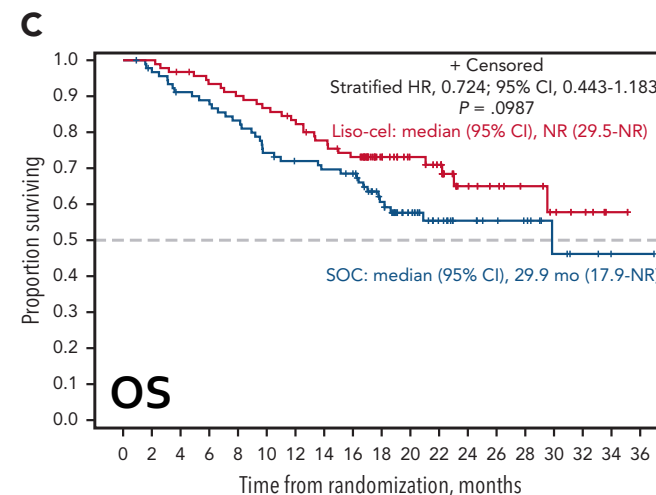
ASCT, autologous hematopoietic stem cell transplantation; CR, complete response; CRS, cytokine release syndrome; EFS, event-free survival; HDCT, high dose chemotherapy; IRC, independent review committee; NE, neurological event; ORR, objective response rate; PFS, progression-free survival; R/R, primary refractory or early relapsed; OS, overall survival; SOC, standard of care; TEAE, treatment-emergent adverse event.



No. at risk	SOC	92	66	39	32	27	22	19	19	12	12	10	3	2	2	2	2	0
Liso-cel	92	87	76	62	59	55	52	48	45	24	20	17	5	3	3	3	3	0



No. at risk	SOC	92	66	42	33	27	22	19	19	12	12	10	3	2	2	2	2	0
Liso-cel	92	88	79	63	60	56	53	49	46	25	21	18	6	3	3	3	3	0



No. at risk	SOC	92	88	81	79	74	66	62	60	58	41	30	21	15	12	10	5	3	1	1
Liso-cel		92	92	88	84	81	78	74	68	63	43	34	30	16	13	10	7	5	1	0

RESEARCH SUMMARY

Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma

Westin JR et al. DOI: 10.1056/NEJMoa2301665

CLINICAL PROBLEM

In patients with early relapsed or primary refractory large B-cell lymphoma, axicabtagene ciloleucel (axi-cel) — an anti-CD19 autologous chimeric antigen receptor (CAR) T-cell therapy — was shown to be superior to standard second-line therapy with respect to event-free survival. Data on overall survival are needed.

CLINICAL TRIAL

Design: A phase 3, multicenter, open-label, randomized trial examined survival outcomes with axi-cel, as compared with standard second-line therapy, in patients with large B-cell lymphoma.

Intervention: 359 adults with large B-cell lymphoma that was refractory to first-line treatment or had relapsed within 12 months after first-line chemioimmunotherapy were assigned to receive either axi-cel or standard care (2 or 3 cycles of chemioimmunotherapy, followed by high-dose chemotherapy and autologous stem-cell transplantation in patients with a complete or partial response). Results for the primary outcome, event-free survival, had been reported previously. Results regarding overall survival at the 5-year follow-up are reported here.

RESULTS

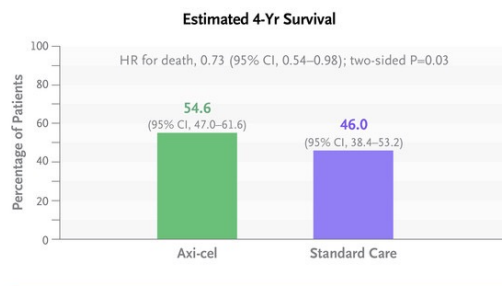
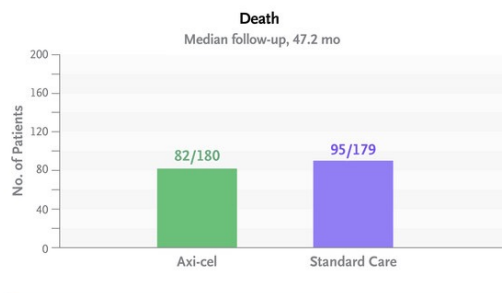
Efficacy: At a median follow-up of 47.2 months, overall survival was significantly better with axi-cel than with standard care. A secondary outcome, progression-free survival, also favored axi-cel.

Safety: All the patients reported at least one adverse event. No new treatment-related deaths occurred since the primary analysis of event-free survival.

LIMITATIONS AND REMAINING QUESTIONS

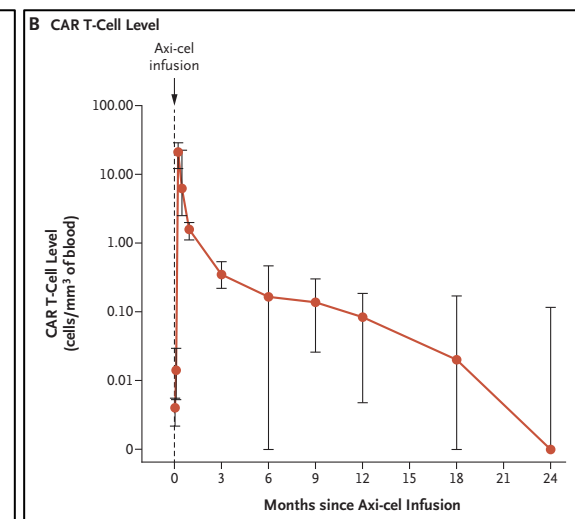
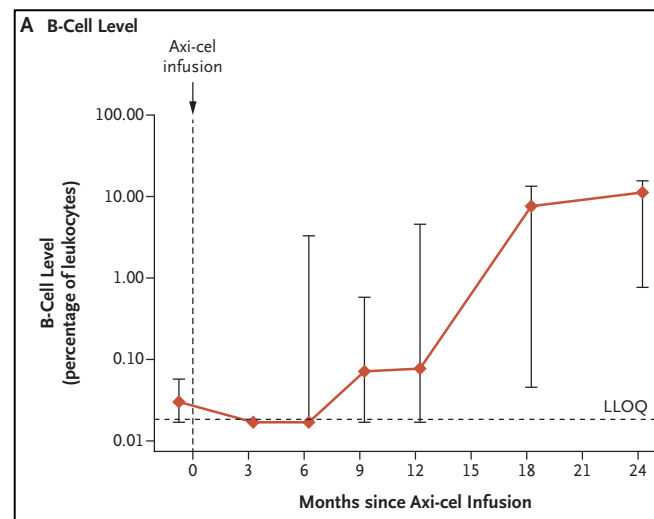
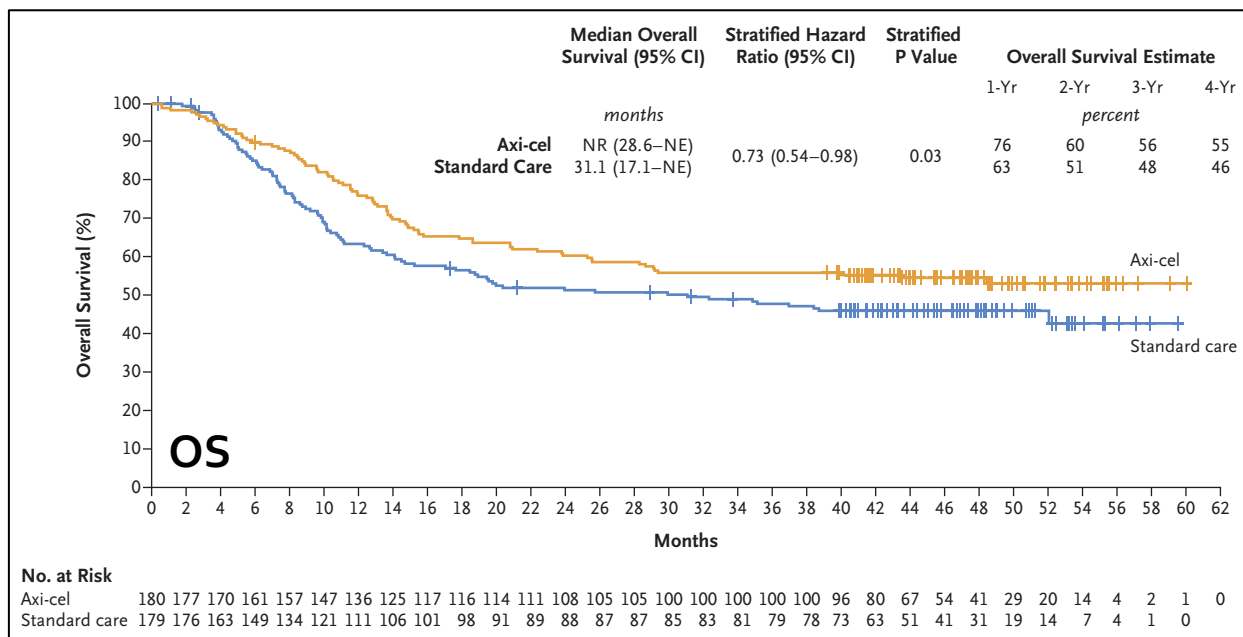
- The proportion of patients who were non-Hispanic White was greater than the proportion of other racial or ethnic groups, which may reflect access to care and the general underrepresentation of diverse racial and ethnic groups in clinical trials.
- How axi-cel performs as second-line treatment in real-world settings is unknown.

Links: Full Article | NEJM Quick Take



CONCLUSIONS

In patients with early relapsed or refractory large B-cell lymphoma, second-line treatment with axi-cel resulted in better overall survival than standard care.



Should CAR-T cell be used instead of ASCT

	Bridging allowed	% Bridging	% CAR	% ASCT	Cross-over planned	% cross-over	EFS	OS
ZUMA-7	No	0	94	36	No	56	HR 0.398; P < 0.0001	HR 0.73 P = 0.03
TRANSFORM	Yes	63	97	46	Yes	51	HR 0.349 P < 0.0001	HR 0.724 P = 0.0987
BELINDA	Yes	83	96	33	Yes	51	HR 1.07 P = 0.69	NS

Patient population: **r/r DLBCL within 12 months**

Definition of EFS (primary end point) differed between trials

Early relapsing LBCL = CAR-T cell therapy

2L CAR vs 3L CAR

- Superior OS (esp. axi-cel and trend in liso-cel)
- Also suitable for “transplant ineligible”
- Improved T-cell fitness
- All have a chance to cure

Locke FL, N Engl J Med. 2022;386:640–54.

Kamdar M, et al. Lancet. 2022;399:2294–308.

Bishop MR, et al. N Engl J Med. 2022;386:629–39.

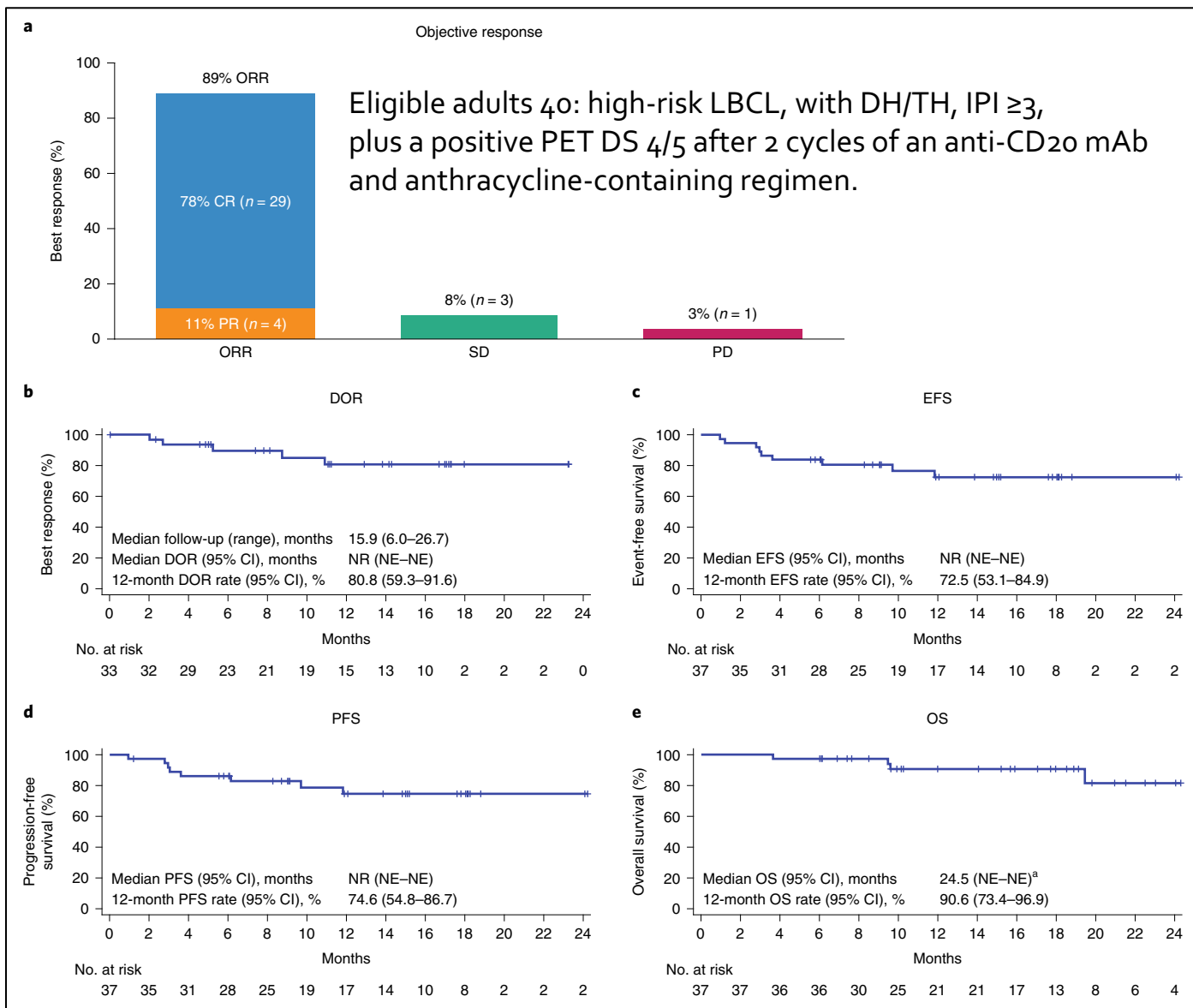
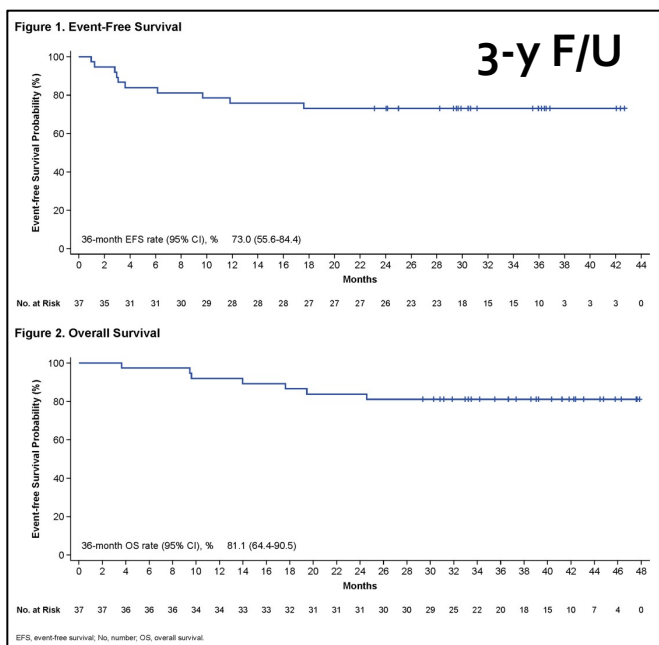


OPEN

Axicabtagene ciloleucel as first-line therapy in high-risk large B-cell lymphoma: the phase 2 ZUMA-12 trial

Sattva S. Neelapu¹✉, Michael Dickinson², Javier Munoz³, Matthew L. Ulrickson³, Catherine Thieblemont^{4,5}, Olalekan O. Oluwole⁶, Alex F. Herrera⁷, Chaitra S. Ujjani⁸, Yi Lin⁹, Peter A. Riedell¹⁰, Natasha Kekre¹¹, Sven de Vos¹², Christine Lui¹³, Francesca Milletti¹³, Jinghui Dong¹³, Hairong Xu¹³ and Julio C. Chavez¹⁴

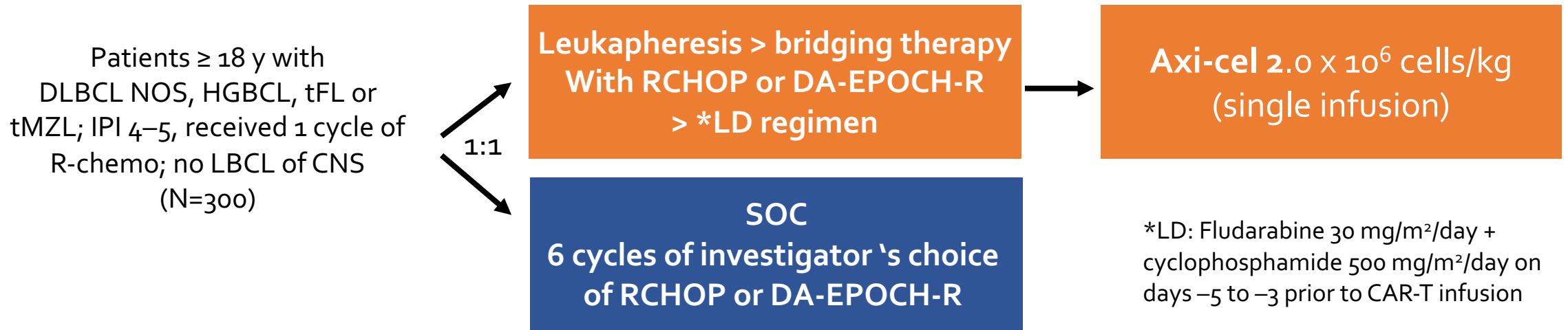
High-risk large B-cell lymphoma (LBCL) has poor outcomes with standard first-line chemoimmunotherapy. In the phase 2, multicenter, single-arm ZUMA-12 study (ClinicalTrials.gov NCT03761056) we evaluated axicabtagene ciloleucel (axi-cel), an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, as part of first-line treatment in 40 patients with high-risk LBCL. This trial has completed accrual. The primary outcome was complete response rate (CRR). Secondary outcomes were objective response rate (ORR), duration of response (DOR), event-free survival (EFS), progression-free survival (PFS), overall survival (OS), assessment of safety, central nervous system (CNS) relapse and blood levels of CAR T cells and cytokines. The primary endpoint in efficacy-evaluable patients ($n = 37$) was met, with 78% CRR (95% confidence interval (CI), 62–90) and 89% ORR (95% CI, 75–97). As of 17 May 2021 (median follow-up, 15.9 months), 73% of patients remained in objective response; median DOR, EFS and PFS were not reached. Grade ≥ 3 cytokine release syndrome (CRS) and neurologic events occurred in three patients (8%) and nine patients (23%), respectively. There were no treatment-related grade 5 events. Robust CAR T-cell expansion occurred in all patients with a median time to peak of 8 days. We conclude that axi-cel is highly effective as part of first-line therapy for high-risk LBCL, with a manageable safety profile.



Gr ≥ 3 ; CRS 8%, ICANS 23%

ZUMA-23: Axi-cel vs SOC as 1L therapy in HR-LBCL

- Global, open-label RCT, phase III



Primary endpoint: EFS

Secondary endpoints: OS, PFS

Ongoing trials evaluating CAR-T in LBCL

Study	Drugs	Phase	No of Patients	Population	Primary Endpoint
NCT05794958	Axi-cel	Ib	20	Reinfusion in R/R second-line high-risk LBCL after SOC axi-cel	DLTs
NCT04257578	Axi-cel + acalabrutinib	I/II	50	LBCL	AEs
NCT05459571 (ZUMA-24)	Axi-cel + steroids	II	30	R/R LBCL	TE-CRS, TENE
NCT05605899 (ZUMA-23)	Axi-cel vs. SOC	III	300	First-line treatment high-risk LBCL	EFS
NCT06213311	Axi-cel + glofitamab	II	40	Second-line R/R LBCL	AEs
NCT05757219	Itacitinib pre axi-cel	II	27	DLBCL	PFS
NCT05583149	Acalabrutinib + liso-cel	II	27	R/R aggressive B-cell lymphoma after 2 lines	CR rate
NCT05873712	Zanubrutinib + liso-cel	II	24	R/R richter's syndrome	ORR
NCT05672173	Liso-cel + nivolumab + ibrutinib	II	20	R/R richter's syndrome	CR UT
NCT05359211	Liso-cel + NKTR-255	I	24	R/R LBCL	AEs DLT CR rate
NCT05664217	NKTR-255 vs. placebo after liso-cel	II/III	400	R/R LBCL	EFS CR rate

Role of CD19CAR-T in PCNSL/SCNSL

Author	n	Study design	Target	Product	P/S- CNSL	Histology	Clinical presentation	LD	Bridging	CRS	ICANS	Response	Efficacy	Follow-up (median)
Nayak et al. [46]	18	Phase I	CD19	Axi-cel	PCNSL = 13 SCNSL = 4	DLBCL	NR	Flu-Cy	Corticosteroids	Any G = 89.0% G ≥ 3 = 0	Any G = 44.0% G ≥ 3 = 28.0%	ORR = 94.0% CR = 67.0% Median time to best response = 3 m	mDOR = 13.4 m mPFS = 14.3 m mOS = 26.4 m	24.2 m
2024 ASCO: pilot study axi-cel for r/r PCNSL/SCNSL														
Wu et al. [60]	13	Phase I	ASCT + CD19 + CD22 (first line)	Academic, costimulatory domain: CD28 and 4-1BB	PCNSL = 4 SCNSL = 9	DLBCL	Parenchymal = 12 Leptomeningeal = 1	BEAM or TioBuCy	CR = 1 Active disease = 12	Any G = 84.6% G ≥ 3 = 0	Any grade = 27.3% G ≥ 3 = 1/13	At 3 m, ORR = 81.8% CR = 54.6%	At 1 y, PFS = 74.6% OS = 82.5% mDOR = 14.3 m	14.2 m
Frigault et al. [37]	12	Phase I/II	CD19	Tisa-cel	PCNSL	DLBCL = 5 HGBCL = 2 PMBCL = 1	Parenchymal = 11 Leptomeningeal = 2	Flu-Cy	All, but NR	Any G = 58.3% G ≥ 3 = 0	Any = 41.6% G ≥ 3 = 8.3%	ORR = 58.3% CR = 50% PR = 16.7%		12.2 m
Tisa-cel for r/r PCNSL														
Abramson et al. [35]	7	Phase I	CD19	Liso-cel	SCNSL	DLBCL, HGBCL, PMBCL, and tFI ^a	NR	Flu-Cy	NR	G1-2 = 2/7 G ≥ 3 = 0	G3 = 33.0%	CR = 50.0%	NR	18.8 m ^a
TRANSCEND HL 001: Liso-cel for r/r SCNSL														
Liu et al. [59] ^b	7	Phase I	CD19 = 4 CD20 = 3	No costimulatory domain provided	PCNSL = 1 SCNSL = 6	DLBCL	Parenchymal = 6 Leptomeningeal = 1	Flu-Cy = 5 ASCT (BuCy-E & BEAC cladribine) = 2	ASCT = 2	NR	NR	ORR = 100% CR = 4/7 PR = 3/7	Median duration of CR = 22.4 m	10.4 m
Siddiqi et al. [62] ^b	5	Phase I (CNS cohort)	CD19	Academic	PCNSL	DLBCL	Parenchymal	Flu-Cy	HD-MTX, pomalidomide, WBRD, steroids	G1 = 60.0% G2 = 40.0%	G1-2 = 80.0% G3 = 20.0%	At 28 d: CR = 60% SD = 40%	mDOR = 43 d (13-520)	NR
Li et al. [47]	5	Phase I	ASCT + CD19 + CD22	Academic, costimulatory domain: CD28 and 4-1BB	PCNSL = 1 SCNSL = 4	DLBCL	Parenchymal	Flu-Cy	HD-MTX, lenalidomide, temozolamide, Ibrutinib, WBRT	G1 = 80.0% G2 = 20.0%	G1 = 20.0% G4 = 20.0%	At 2 m: ORR = 100.0% CR = 20.0% PR = 80.0%	3 pts relapsed at 3 m. 1 pt relapsed at 8 m. At last FU, 1 pt still in CR	14.0 m

Active clinical trials:

NCT05625594 NCI Phase I CD19CAR-T cells i.c.v. PCNSL n=20

NCT 04134117 Novartis Phase I Tisa-cel IV PCNSL HR elderly, r/r PCNSL n=6

NCT 04608487 Kite Phase I Axi-cel IV r/r PCNSL, r/r SCNSL n=18

Also CD19-CD22 CAR-T, CD19-CD20 CAR-T, CD20CAR-T cell trials are ongoing!!

Risk factors associated with survival outcomes for lymphoma with relapse after CD19 CAR T-cell infusion

Risk factor	Hazard ratio HR (95% CI)
• Response to axi-cel	OS: HR 0.45 (95% CI: 0.29–0.71; $p = 0.0005$) ⁴⁰
• Progression <30 day	OS: HR 2.93 (95% CI: 1.56–5.50; $p = 0.0009$) ³⁷
• CAR T-cell refractoriness	OS: HR 2.33 (95% CI: 1.02–5.29) ³⁸
• Grade 3–4 CRS	OS: HR 5.39 (95% CI: 2.48–11.7; $p = 2.2 \times 10^{-5}$) ⁴⁰
• Bridging chemotherapy	OS: HR 2.11 (95% CI: 1.32–3.39; $p = 0.002$) ⁴⁰
• >2 lines of therapy before CAR T-cell infusion	PFS: HR 1.89 (95% CI: 1.1–3.5; $p = 0.03$) ³⁶
• No double hit or double expressor lymphoma subtype	PFS: HR 0.42 (95% CI: 0.18–0.89; $p = 0.03$) ³⁶
• Polatuzumab-bendamustine-rituximab after CAR T-cell failure as salvage treatment	PFS: HR 0.097 (95% CI: 0.013–0.57; $p = 0.01$) ³⁶
• Lenalidomide-based after CAR T-cell failure as salvage treatment	PFS: HR 0.15, (95% CI: 0.026–0.76; $p = 0.03$) ³⁶ OS: HR 0.42 (95% CI: 0.21–0.82; $p = 0.01$) ³⁷
• High LDH at infusion	PFS: HR 3.42 (95% CI: 1.93–6.05; $p < 0.0001$) OS: HR 2.10 (95% CI: 1.16–3.78; $p = 0.01$) ³⁷ OS: HR 2.95 (95% CI: 1.61–5.38) ³⁸
• High ferritin at infusion	PFS: HR 1.02 (95% CI: 1.00–1.03; $p = 0.01$) ³⁷
• High CRP at infusion	OS: HR 1.11 (95% CI: 1.04–1.19; $p = 0.003$) ³⁷
• Bulky disease at apheresis	OS: HR 2.27 (95% CI: 1.10–4.72) ³⁸
• Older age	OS: HR 2.65 (95% CI 1.49–4.73) ³⁸

CRP, C-reactive protein; CRS, cytokine release syndrome; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

Axicabtagene ciloleucel: FDA approval and indication in DLBCL

- FDA-approved CD19CAR-T cell for **adults** with LBCL including DLBCL, PMBCL, HGBCL, and DLBCL arising from FL (**not indicate for PCNSL);
 - **Relapse and refractory** ≥ 2 lines in 2017
 - **Refractory** to 1st line CIT or **relapses within 12 months** of 1st CIT in 2022

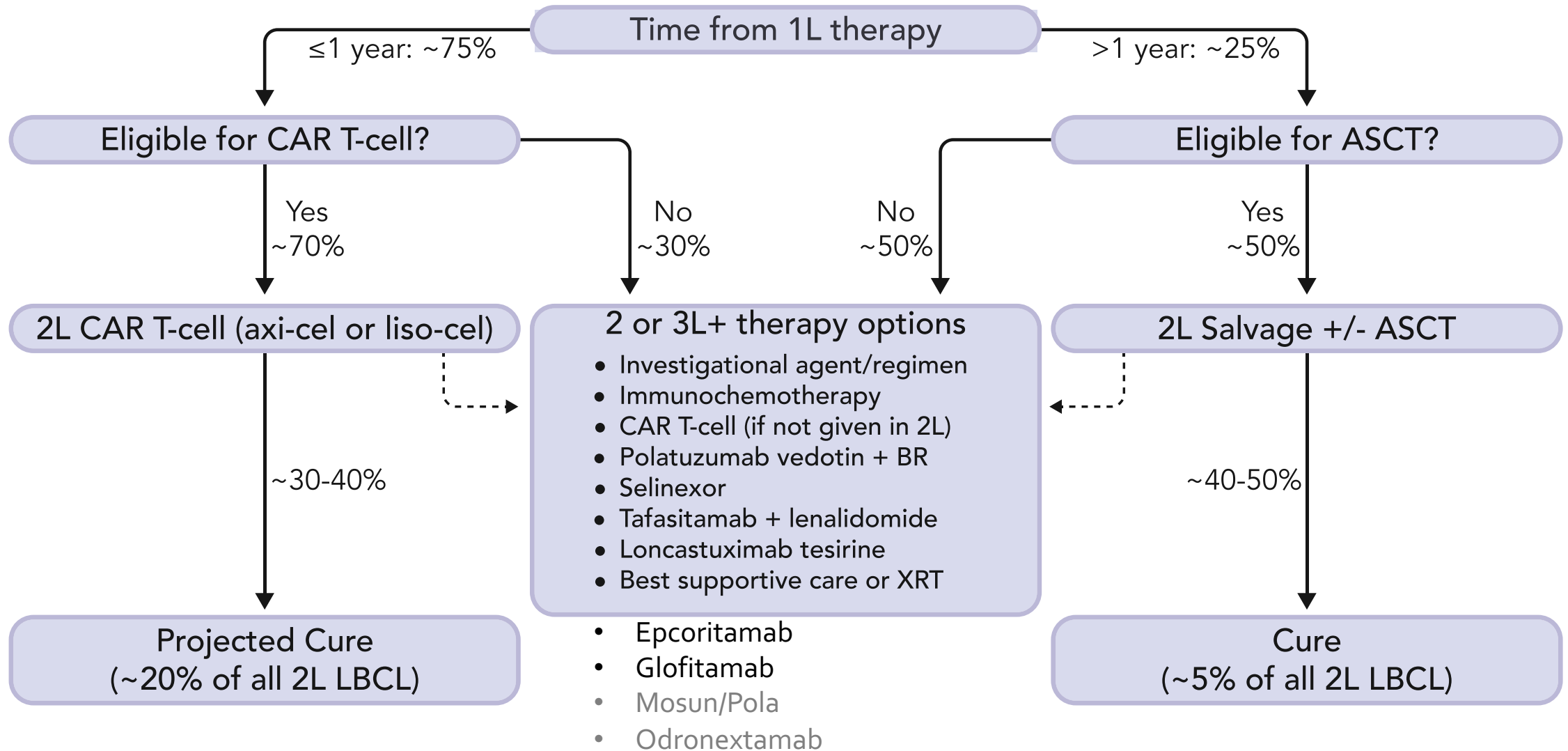
Lisocabtagene maraleucel: FDA approval and indication in DLBCL

- FDA-approved CD19CAR-T cell for **adults with LBCL**, including DLBCL NOS, DLBCL arising from indolent lymphoma, HGBCL, PMBCL, and FL grade 3 B (**not indicate for PCNSL);
 - **Relapse and refractory ≥ 2 lines** in 2021
 - **Refractory** to 1st line CIT or **relapses within 12 months** of 1st CIT or ineligible for HSCT in 2022

Tisagenlecleucel: FDA approval and indication in DLBCL

- FDA-approved CD19CAR-T cell for **adults with LBCL**, including DLBCL NOS, HGBCL, DLNCL arising from FL (**not indicate for PCNSL);
 - **Relapse and refractory ≥ 2 lines** in 2018

Algorithm for Second-line Therapy of LBCL





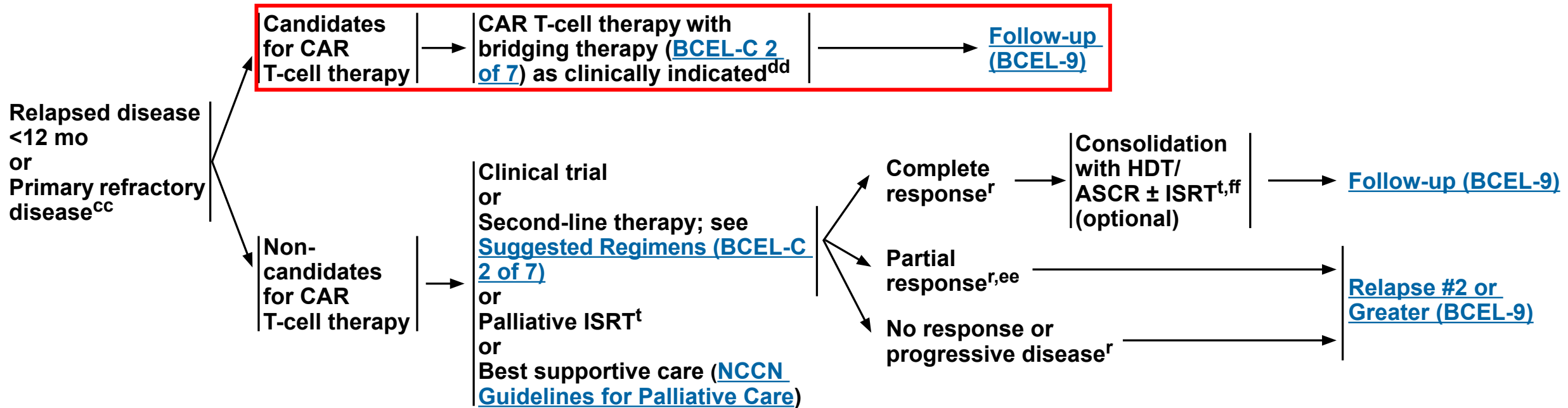
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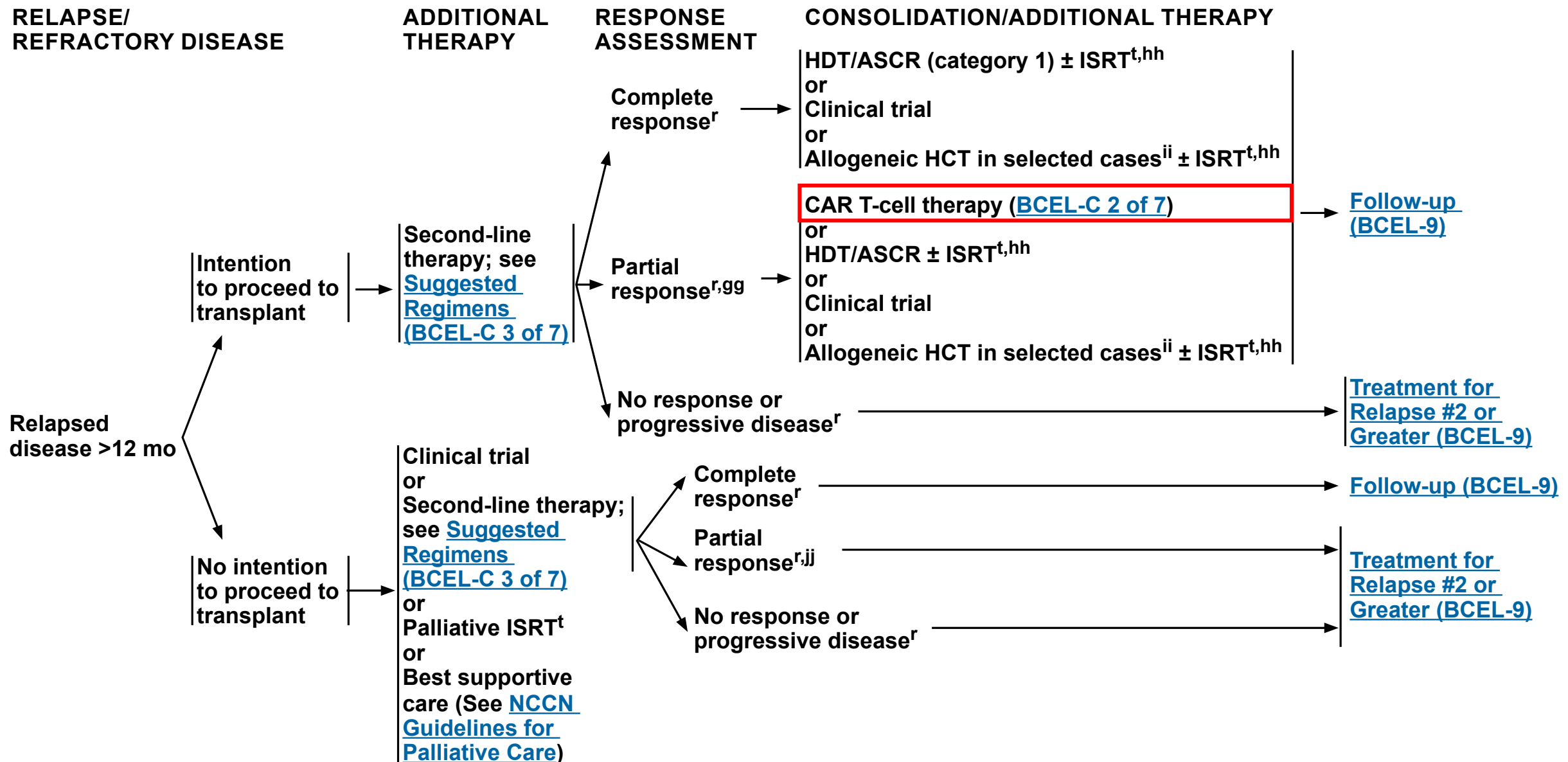
Diffuse Large B-Cell Lymphoma

RELAPSE/
REFRACTORY DISEASE

ADDITIONAL
THERAPY

RESPONSE
ASSESSMENT







SUGGESTED TREATMENT REGIMENS^{a,b}

SECOND-LINE THERAPY ^{e,j,k} (relapsed disease <12 mo or primary refractory disease)	
Candidates for CAR T-Cell Therapy	Non-Candidates for CAR T-Cell Therapy
• CAR T-cell therapy^l ▶ Axicabtagene ciloleucel (CD19-directed) (category 1) ▶ Lisocabtagene maraleucel (CD19-directed) (category 1) Bridging Therapy Options (≥1 cycles as needed until CAR T-cell product is available) • DHA + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab • GDP (gemcitabine, dexamethasone, carboplatin or cisplatin) ± rituximab • GemOx ± rituximab • ICE ± rituximab • Polatuzumab vedotin-piiq ± rituximab ± bendamustine^m • ISRT (can be used as monotherapy or sequentially with systemic therapy) (NHODG-D 3 of 4)	Preferred regimens (in alphabetical order) • Epcoritamab-bysp + GemOx^{n,o} • Glofitamab-gxbm + GemOx^{n,o} • Polatuzumab vedotin-piiq ± bendamustine^m ± rituximab • Polatuzumab vedotin-piiq + mosunetuzumab-axgb^{n,o} • Tafasitamab-cxix^p + lenalidomide (excluding primary refractory disease) Other recommended regimens (in alphabetical order) • CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab • DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab • ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab • GDP (gemcitabine, dexamethasone, carboplatin or cisplatin) ± rituximab • GemOx (gemcitabine, oxaliplatin) ± rituximab (if unable to receive epcoritamab-bysp or glofitamab-gxbm) • ICE (ifosfamide, carboplatin, etoposide) ± rituximab • MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab Useful in certain circumstances • Brentuximab vedotin for CD30+ disease^q • Ibrutinibⁿ (non-GCB DLBCL) • Lenalidomide ± rituximab (non-GCB DLBCL)

SUGGESTED TREATMENT REGIMENS^{a,b}

SECOND-LINE THERAPY ^{e,j,k} (relapsed disease >12 mo)	
Intention to Proceed to Transplant	No Intention to Proceed to Transplant
Preferred regimens (in alphabetical order) • DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab • GDP (gemcitabine, dexamethasone, carboplatin or cisplatin) ± rituximab • ICE (ifosfamide, carboplatin, etoposide) ± rituximab Other recommended regimens (in alphabetical order) • ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab • GemOx (gemcitabine, oxaliplatin) ± rituximab • MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab	Preferred regimens (in alphabetical order) • CAR T-cell therapy (CD19-directed)^l (with bridging therapy as needed; BCEL-C 2 of 7) (if eligible) ▶ Lisocabtagene maraleucel • Epcoritamab-bysp + GemOx^{n,o} • Glofitamab-gxbm + GemOx^{n,o} (category 1) • Polatuzumab vedotin-piiq ± bendamustine^m ± rituximab • Polatuzumab vedotin-piiq + mosunetuzumab-axgb^{n,o} • Tafasitamab-cxix^p + lenalidomide Other recommended regimens (in alphabetical order) • CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab • GDP (gemcitabine, dexamethasone, carboplatin or cisplatin) ± rituximab • GemOx ± rituximab (if unable to receive epcoritamab-bysp or glofitamab-gxbm) • Rituximab Useful in certain circumstances • Brentuximab vedotin for CD30+ disease^q • Ibrutinibⁿ (non-GCB DLBCL) • Lenalidomide ± rituximab (non-GCB DLBCL)



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Diffuse Large B-Cell Lymphoma

SUGGESTED TREATMENT REGIMENS^{a,b}

THIRD-LINE AND SUBSEQUENT THERAPY

Subsequent systemic therapy options include second-line therapy regimens ([BCEL-C 2 of 7](#) and [BCEL-C 3 of 7](#)) that were not previously used.

Preferred regimens

- T-cell engager therapy
 - ▶ CAR T-cell therapy^l (preferred if not previously given) (in alphabetical order)
 - ◊ Axicabtagene ciloleucel (CD19-directed)
 - ◊ Lisocabtagene maraleucel (CD19-directed)
 - ◊ Tisagenlecleucel (CD19-directed)
 - ▶ Bispecific antibody therapy (only after at least two lines of systemic therapy; including patients with disease progression after transplant or CAR T-cell therapy) (in alphabetical order)
 - ◊ Epcoritamab-bysp^{n,o}
 - ◊ Glofitamab-gxbm^{n,o}

Other recommended regimens

- Brentuximab vedotin + lenalidomide + rituximab (for CD30+ disease)^q
- Loncastuximab tesirine-lpyl^p
- Selinexor (including patients with disease progression after transplant or CAR T-cell therapy)



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Guideline

ASTCT Clinical Practice Recommendations for Transplantation and Cellular Therapies in Diffuse Large B Cell Lymphoma



Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR-T Therapy in Primary Refractory and Early Relapse (Relapse Within 12 Months of First-Line Chemoimmunotherapy) DLBCL

Consensus Statement	Grading of Recommendations*	Percentage of Panelists in Agreement
1. The panel recommends CAR-T therapy as a standard of care option in patients with DLBCL who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy.	A	96%
2. In DLBCL patients with early relapse who achieve a complete remission with salvage therapy, the panel considers autologous HCT an acceptable consolidation therapy in eligible patients.	B	88%
3. In DLBCL patients with early relapse who achieve a partial remission with salvage therapy, the panel considers autologous HCT an acceptable consolidation therapy in eligible patients.	B	96%
4. In DLBCL patients with early relapse who achieve a complete remission or partial remission to salvage therapy, the panel considers CAR-T therapy an acceptable therapeutic option.	B	84%

Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR-T Cell Therapy for Late Relapsed (Relapse Beyond 12 Months of First-Line Chemoimmunotherapy) DLBCL

Consensus Statement	Grading of Recommendations*	Percentage of Panelists in Agreement
1. In DLBCL patients with late relapse, the panel recommends autologous HCT consolidation therapy in eligible patients who have achieved a complete or partial remission after second-line therapies.	A	96%
2. In DLBCL patients with late relapse, the panel recommends CAR-T therapy in patients who have not achieved remission (complete or partial) after second-line therapies.	A	96%
3. In patients with DLBCL, the panel recommends CAR-T therapy in patients who are not eligible for autologous HCT (due to comorbidities or age) regardless of the timing of relapse.	B	96%
4. In patients with DLBCL, the panel recommends CAR-T therapy in those who have relapsed or refractory disease after 2 or more lines of systemic therapy.	A	96%
5. The panel does not consider secondary CNS involvement a contraindication for administering CAR-T therapy.	B	88%
6. In relapsed DLBCL patients with available access to CAR-T therapy, the panel recommends offering CAR-T therapy before proceeding with allogeneic HCT.	C	96%
7. The panel recommends allogeneic HCT in eligible DLBCL patients relapsing/progressing after CAR-T therapy if they achieve a complete or partial remission with subsequent antilymphoma therapies.	C	96%
8. The panel recommends allogeneic HCT in eligible relapsed or refractory DLBCL patients after autologous HCT failure in regions without access to CAR-T therapy, and in those with CAR T cell manufacturing failure, ideally after achieving a complete or partial remission with subsequent antilymphoma therapies.	C	96%
9. The panel recommends reduced-intensity conditioning or nonmyeloablative conditioning regimens for eligible patients undergoing allogeneic HCT.	B	92%



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FACULTY OF MEDICINE PRINCE OF SONGKLA UNIVERSITY

