MAYO CLINIC

CAR-T Cell Therapy in Lymphomas: 7-Years Later

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New Orleans, LA
July 21, 2024

Outline

- Approvals of chimeric antigen receptor T-cell therapy in diffuse large B-cell lymphoma, mantle cell lymphoma and follicular lymphoma
- Reproducibility in the “real world” setting
- Long-term toxicities resulting from CAR T-cell therapy
- T-cell malignancies related to CAR T-cell
- Take home messages

B-cell lymphoma indications based on commercially available products: 2024

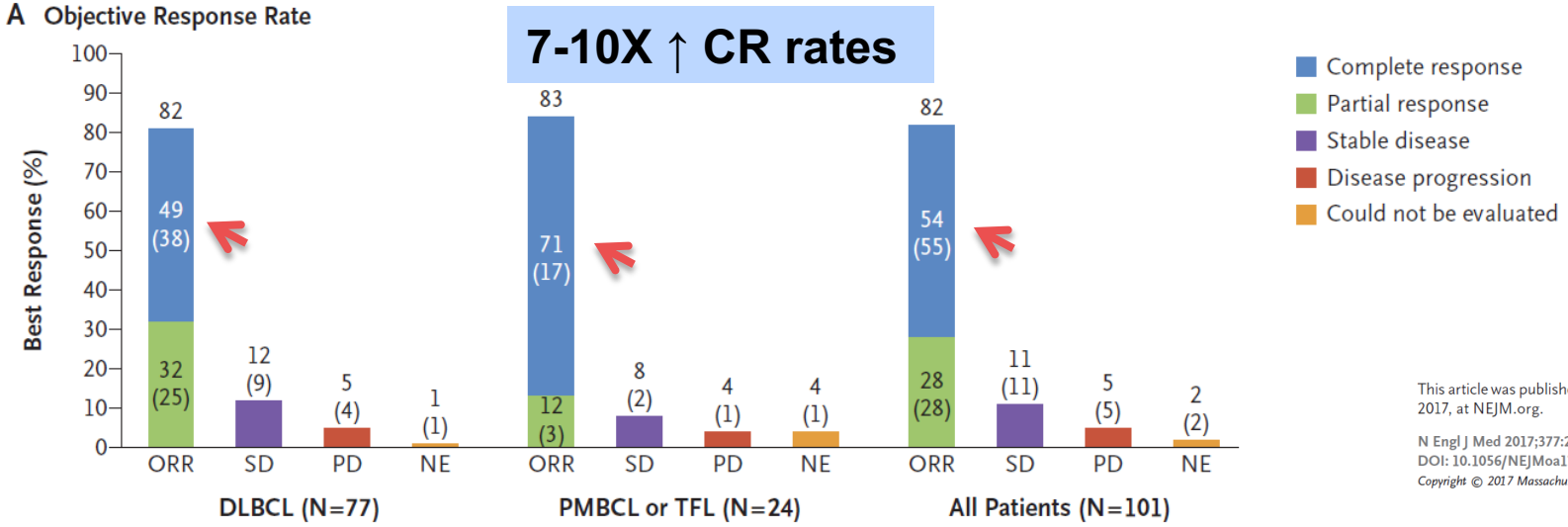
	Brexucabtagene autoleucel	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
3rd line DLBCL	No	Yes	Yes	Yes
Transformed FL	No	Yes	Yes	Yes
PMBCL	No	Yes	No	Yes
2nd line DLBCL	No	Yes	No	Yes
R/R MCL	Yes	No	No	Yes
R/R FL (non-transformed)	No	Yes	Yes	Yes
R/R CLL	No	No	No	Yes

DLBCL: FDA approved agents

	Axicabtagene Ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
FDA Approval indication for 3rd line and beyond	**Yes, ZUMA-1**	**Yes, JULIET**	**Yes, TRANSCEND NHL001**
FDA Approval indication for 2nd line and beyond	**Yes, ZUMA-7**	**No**	**Yes, TRANSFORM**
FDA approval for refractory disease to 1st line chemoimmunotherapy or relapse after 1st line chemoimmunotherapy and are **not** eligible for HCT due to comorbidities or age	-	-	**Yes, PILOT**

ZUMA 1: Axicabtagene ciloleucel

Variables	DLBCL	PMBCL or TFL	All pts
N pts enrolled	81	30	111
N pts treated with axi-cel	77 (95%)	24 (80%)	101 (91%)
Median (range) age, years	58 (25-76)	57 (23-76)	58 (23-76)
Stage III-IV disease	67 (87%)	19 (79%)	86 (85%)
≥ 3 prior lines of therapy	49 (64%)	21 (88%)	70 (69%)
Relapsed after auto-HCT	16 (21%)	5 (21%)	21 (21%)



This article was published on December 10, 2017, at NEJM.org.

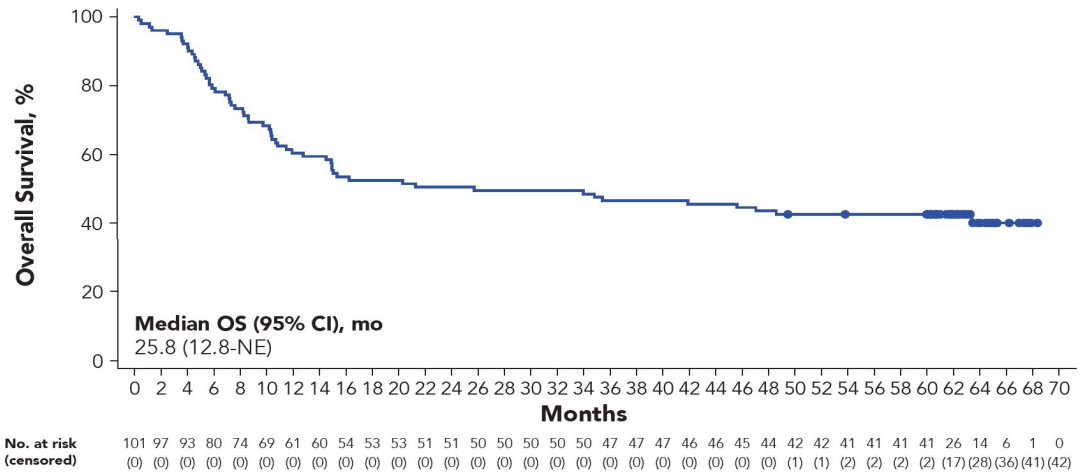
N Engl J Med 2017;377:2531-44.
DOI: 10.1056/NEJMoa1707447

Neelapu SS, et al. N Engl J Med. 2017; 377:2531-44

1764 Long-Term (4- and 5-Year) Overall Survival in ZUMA-1, the Pivotal Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Refractory Large B-Cell Lymphoma (LBCL)

Program: Oral and Poster Abstracts
Session: 704. Cellular Immunotherapies: Clinical: Poster I
Hematology Disease Topics & Pathways:
Biological, Adults, Lymphomas, Non-Hodgkin Lymphoma, B Cell Lymphoma, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Immune Mechanism, Diseases, Therapies, Lymphoid Malignancies, Biological Processes, Study Population

5-Year OS



With ≥5 years of F/U:

- **5-year OS rate** was **42.6%** (95% CI, 32.8-51.9) among pts treated with axi-cel

The 5-year OS rate:

- In CR=**64.4%** (95% CI, 50.8-75.1); the median survival time among complete responders was not reached (95% CI, 63.4-NE)
- 37 of 59 CR patients (63%) are still alive at the 5-year data cutoff

- One patient's event time was updated from Month 42 to 39 after data cutoff and is not reflected in this figure
- Axi-cel, axicabtagene ciloleucel; CR, complete response; NE, not estimable; OS, overall survival; PD, progressive disease; PR, partial response

Jacobson C, et al. ASH 2021, Abs 1764
Neelapu SS, et al. Blood. 2023. Online ahead of print

4864 Curative Potential of Axicabtagene Ciloleucel (Axi-Cel): An Exploratory Long-Term Survival Assessment in Patients with Refractory Large B-Cell Lymphoma from ZUMA-1

Program: Oral and Poster Abstracts
Session: 705. Cellular Immunotherapies: Late Phase and Commercially Available Therapies: Poster III
Hematology Disease Topics & Pathways:
Biological therapies, adult, Lymphomas, non-Hodgkin lymphoma, B Cell lymphoma, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Diseases, Therapies, aggressive lymphoma, Lymphoid Malignancies, Study Population, Human

Monday, December 11, 2023, 6:00 PM-8:00 PM

Sattva S. Neelapu, MD[1], *Caron A Jacobson, MD, MMSc*[2], *Armin Ghobadi, MD*[3], *David B. Miklos, MD, PhD*[4], *Lazaros J. Lekakis*[5*], *Clare Spooner, BSc, MBBS*[6*], *Jenny J. Kim, MD, MS*[7], *Harry Miao, MD, PhD*[6], *Allen Xiaodong Xue, PhD*[6*], *Yan Zheng, MD, PhD, MS*[6*] *and Frederick L. Locke, MD*[8]

- Exploratory analyses from ZUMA-1 using endpoints to measure cure along with survival analyses with up to 6 yrs F/U
  - **DSS:** Disease-specific survival
  - **LREFS:** lymphoma-related event-free survival

	CR at 12 months	CR at 24 months
72-month DSS	94.4%	**100%**

CR at 12 and 24 months may be predictive of extended OS (cure?)

Table 1. KM Estimates of LREFS and DOCR in Patients with a CR

	Patients with a CR				
KM Estimates	**Week 4 (n=37)**	**Month 3 (n=42)**	**Month 6 (n=39)**	**Month 12 (n=39)**	**Month 24 (n=36)**
Median LREFS, mo (95% CI)	35.6 (5.7-NE)	NR (35.7-NE)	NR (NE-NE)	NR (NE-NE)	NR (NE-NE)
60-mo LREFS rate, % (95% CI)	46.9 (30.1-62.1)	64.1 (47.7-76.6)	76.8 (60.1-87.2)	84.5 (68.6-92.7)	91.5 (75.9-97.2)
Median DOCR, mo (95% CI)	34.7 (4.6-NE)	NR (34.8-NE)	NR (NE-NE)	NR (NE-NE)	NR (NE-NE)
60-mo CR rate, % (95% CI)	46.9 (30.1-62.1)	64.1 (47.7-76.6)	76.6 (59.8-87.1)	84.3 (68.3-92.6)	91.3 (75.5-97.1)

The table reports KM estimates as of the data cutoff of the 5-year analysis among those with a disease assessment of a CR at each timepoint.
CR, complete response; DOCR, duration of complete response; KM, Kaplan-Meier; LREFS, lymphoma-related event-free survival; mo, month; NE, not estimable; NR, not reached.

Table 2. Cumulative Incidence of Death in Patients with a CR

	Patients with a CR				
Cumulative Incidences	**Week 4 (n=37)**	**Month 3 (n=42)**	**Month 6 (n=39)**	**Month 12 (n=39)**	**Month 24 (n=36)**
Cumulative incidence of death, % (95% CI)	46.2 (29.4-61.5)	31.3 (17.8-45.7)	23.6 (11.5-38.0)	18.4 (8.0-32.2)	14.2 (5.1-27.9)
Due to PD	35.1 (20.2-50.5)	19.0 (8.8-32.2)	10.4 (3.2-22.5)	5.3 (0.9-15.8)	0
Due to axi-cel–related AEs	2.7 (0.2-12.3)	2.4 (0.2-11.0)	0	0	0
Due to other reasons	8.4 (2.1-20.5)	9.9 (3.1-21.4)	13.2 (4.7-26.0)	13.1 (4.7-26.0)	14.2 (5.1-27.9)

The table reports cumulative incidence of death based on competing risk assessment as of the data cutoff of the 6-year analysis among those with a disease assessment of a CR at each timepoint.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CR, complete response; PD, progressive disease.

3rd line setting and beyond

	ZUMA-1	JULIET	TRANSCEND NHL001
Pts enrolled	111	165	344
Pts received CAR T	101	111	294 (25 nonconforming)
Median (range) age, years	58 (23-76)	56 (22-76)	63 (54-70)
Histology	DLBCL=77 tFL or PMBCL=24	DLBCL-NOS=88 tFL=21 Other =2	DLBCL=137 tFL=60 Transformed (other)=18 PMBCL=15 HGBCL (MYC/BCL2/BCL6)=36
ORR	82% DLBCL=82%	52%	73%
CR	54% DLBCL=49%	40%	53%
CRS	Any grade=93% ≥ grade 3=13%	Any grade=58% ≥ grade 3=22%	Any grade=42% ≥ grade 3=2%
Neurologic event	Any grade=64% ≥ grade 3=28%	Any grade=21% ≥ grade 3=12%	Any grade=30% ≥ grade 3=10%

Neelapu SS, et al. N Engl J Med. 2017; 377:2531-44
Schuster SJ, et al. N Engl J Med. 2019; 380:45-56
Abramson JS, et al. Lancet. 2020; 396;839-52

1032 Five Year Outcomes of Patients with Large B-Cell Lymphoma Treated with Standard-of-Care Axicabtagene Ciloleucel: Results from the US Lymphoma CAR-T Cell Consortium

Program: Oral and Poster Abstracts
Type: Oral
Session: 705. Cellular Immunotherapies: Late Phase and Commercially Available Therapies: Cellular Therapy for Multiple Myeloma, B-cell Acute Lymphoblastic Leukemia and B Cell Lymphomas: Clinical Trial and Real World Evidence
Hematology Disease Topics & Pathways:
Biological therapies, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Therapies

Monday, December 11, 2023: 5:45 PM

Jay Y. Spiegel, MD, FRCPC[1], Michael D. Jain, MD, PhD[2], Loretta J. Nastoupil, MD[3], John Tamaresis, PhD[4], Armin Ghobadi, MD[5], Yi Lin, MD, PhD[6], Lazaros J. Lekakis[7*], Patrick M. Reagan, MD[8], Olalekan O. Oluwole, MBBS[9], Joseph P McGuirk, DO[10], Abhinav Deol, MD[11*], Kathleen Dorritie, MD[12], Alison R Sehgal, MD[12], Andre Goy, MD[13], Brian T. Hill, MD[14], Charalambos Andreadis, MD[15], Javier L. Munoz[16], Matthew L. Ulrickson, MD[17], Jason Westin, MD[18], Julio C. Chavez, MD[19], Dilan A Patel[20*], Miriam T. Jacobs, MD[21*], Radhika Bansal, MBBS[6*], N. Nora Bennani, MD[22], Vivek Patel, MD[9], Aaron P. Rapoport, MD[23], Julie M. Vose, MD, MBA[24], David B. Miklos, MD, PhD[25], Sattva S. Neelapu, MD[26], Frederick L. Locke, MD[2], Matthew A. Lunning, DO, FACP[27*] and Saurabh Dahiya[25*]*

Real world data

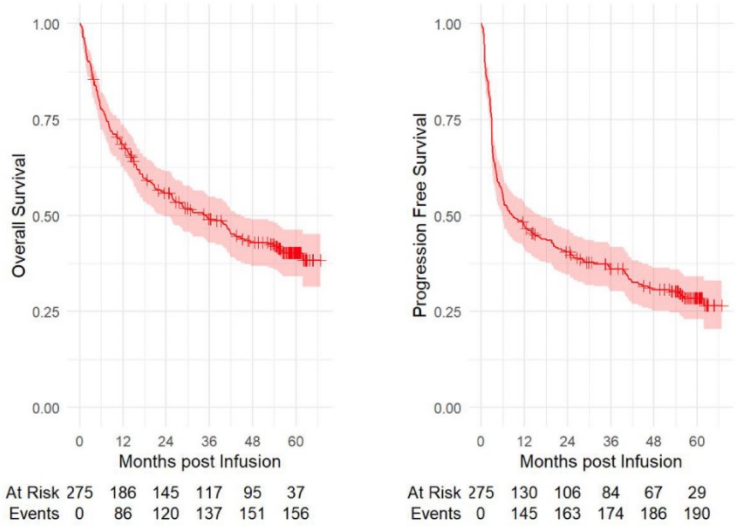


Figure 1: (A) OS and (B) PFS for the infused cohort of 275 patients

42% would not have met eligibility criteria for ZUMA-1

- 17 US academic centers
- 297 pts underwent leukapheresis with intent to manufacture axi-cel
- 275 infused, OS and PFS calculated from infusion date
- Median F/U of 58 months, median OS was 34.9 months and median PFS was 8.7 months
- 5-year OS **40.3%** (95% CI 34.2 - 46.4%)
- 5-year PFS and **28.5%** (95% CI 23 - 34.2%)

- MVA for ↓ OS: Male, LDH > ULN, ECOG of 2-4, elevated bilirubin > 1.5 mg/dL

- MVA for ↓ PFS: Male, LDH > ULN, ECOG of 2-4, elevated bilirubin > 1.5 mg/dL, ≥3 prior Rxs

- 5-year cum relapse risk= 55.2%
- 5-year risk NRM=16.2%

MAYO CLINIC

Spiegel JY, et al. Am Soc Hematol. 2023 (Abs 1032)

Moving CAR T-cell therapy to 2nd line

- **3 randomized studies:**
  - **ZUMA-7:** Axi-cel vs. SOC (Axi-cel better)
  - **TRANSFORM:** Liso-cel vs. SOC (Liso-cel better)
  - ~~**BELINDA:**~~ Tisagenlecleucel vs. SOC (no difference)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma

J.R. Westin, O.O. Oluwole, M.J. Kersten, D.B. Miklos, M.-A. Perales, A. Ghobadi, A.P. Rapoport, A. Sureda, C.A. Jacobson, U. Farooq, T. van Meerten, M. Ulrickson, M. Elsawy, L.A. Leslie, S. Chaganti, M. Dickinson, K. Dorritie, P.M. Reagan, J. McGuirk, K.W. Song, P.A. Riedell, M.C. Minnema, Y. Yang, S. Vardhanabhuti, S. Filosto, P. Cheng, S.A. Shahani, M. Schupp, C. To, and F.L. Locke, for the ZUMA-7 Investigators and Kite Members*

ZUMA 7: shows OS advantage (vs. SOC)

The NEW ENGLAND JOURNAL of MEDICINE

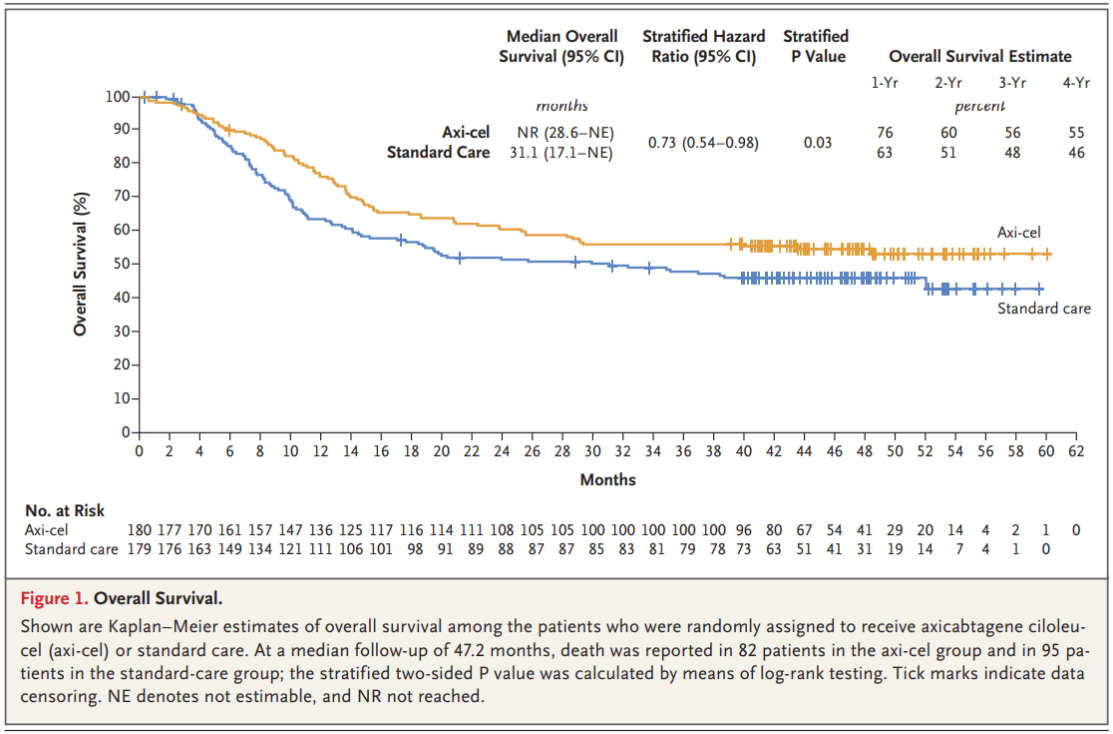


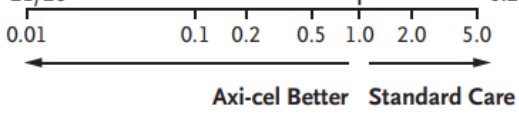
Figure 1. Overall Survival.

Shown are Kaplan–Meier estimates of overall survival among the patients who were randomly assigned to receive axicabtagene ciloleucel (axi-cel) or standard care. At a median follow-up of 47.2 months, death was reported in 82 patients in the axi-cel group and in 95 patients in the standard-care group; the stratified two-sided P value was calculated by means of log-rank testing. Tick marks indicate data censoring. NE denotes not estimable, and NR not reached.

ZUMA-7 subgroup analysis

B Subgroup Analysis

Subgroup	Axi-cel	Standard Care	Hazard Ratio for Event or Death (95% CI)
	no. of patients with event/total no.		
Overall	108/180	144/179	0.40 (0.31–0.51)
Age			
<65 yr	81/129	96/121	0.49 (0.36–0.67)
≥65 yr	27/51	48/58	0.28 (0.16–0.46)
Response to first-line therapy at randomization			
Primary refractory disease	85/133	106/131	0.43 (0.32–0.57)
Relapse ≤12 mo after initiation or completion of first-line therapy	23/47	38/48	0.34 (0.20–0.58)
Second-line age-adjusted IPI			
0 or 1	54/98	73/100	0.41 (0.28–0.58)
2 or 3	54/82	71/79	0.39 (0.27–0.56)
Prognostic marker according to central laboratory			
HGBL, double- or triple-hit	15/31	21/25	0.28 (0.14–0.59)
Double-expressor lymphoma	35/57	50/62	0.42 (0.27–0.67)
Molecular subgroup according to central laboratory			
Germinal center B-cell–like	64/109	80/99	0.41 (0.29–0.57)
Activated B-cell–like	11/16	9/9	0.18 (0.05–0.72)
Unclassified	8/17	12/14	—
Disease type according to investigator			
DLBCL, not otherwise specified	68/110	97/116	0.37 (0.27–0.52)
Large-cell transformation from follicular lymphoma	10/19	24/27	0.35 (0.16–0.77)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	23/43	18/27	0.47 (0.24–0.90)
Disease type according to central laboratory			
DLBCL	79/126	95/120	0.44 (0.32–0.60)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	15/31	21/26	0.28 (0.14–0.59)



Locke FL, et al. N Engl J Med. 2022;386(7):640-654

1761 Improved Overall Survival with Axicabtagene Ciloleucel Vs Standard of Care in Second-Line Large B-Cell Lymphoma Among the Elderly: A Subgroup Analysis of ZUMA-7

Program: Oral and Poster Abstracts
Session: 627. Aggressive Lymphomas: Clinical and Epidemiological: Poster I
Hematology Disease Topics & Pathways:
Research, Biological therapies, clinical trials, non-Hodgkin lymphoma, Lymphomas, elderly, Clinical Research, B Cell lymphoma, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Diseases, aggressive lymphoma, Therapies, Lymphoid Malignancies, Study Population, Human

Saturday, December 9, 2023, 5:30 PM-7:30 PM

Marie José Kersten, MD, PhD[1], *Umar Farooq*[2], *Aaron P. Rapoport, MD*[3], *Frederick L. Locke, MD*[4], *Lori A. Leslie, MD*[5], *Armin Ghobadi, MD*[6], *David B. Miklos, MD, PhD*[7], *Caron A Jacobson, MD, MMSc*[8], *Javier L. Munoz*[9], *Patrick B Johnston, MD, PhD*[10*], *Samantha M. Jaglowski, MD, MPH*[11], *Ian W. Flinn, MD, PhD*[12], *Tom van Meerten, MD, PhD*[13*], *Miguel-Angel Perales, MD*[14], *Peter Vandenberghe, MD, PhD*[15], *Peter A. Riedell, MD*[16], *Kathleen Dorritie, MD*[17], *David Szwajcer, MD*[18*], *Dimitrios Tzachanis, MD, PhD*[19], *Saran Vardhanabhuti*[20*], *Linqiu Du*[20*], *Simone Filosto*[20*], *Shilpa A. Shahani, MD*[20*], *Christina To, MD*[21] *and Jason Westin, MD*[22]

- 109 pts were included in analysis
- **Axi-cel= 51; pts ≥65 yrs (≥70 y=26, max age=80 yrs)**
- SOC= 58; pts ≥65 yrs (≥70 y=27, max age=81 yrs)

Figure 1: Overall Survival of Axi-cel vs Standard of Care Patients Aged ≥65 Years

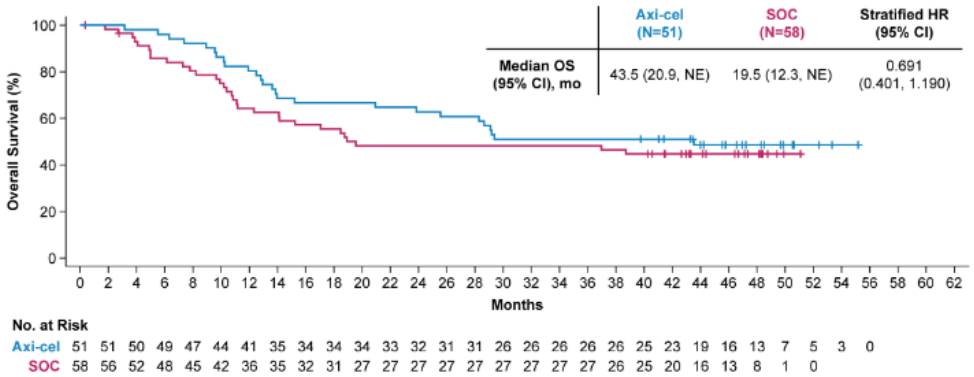
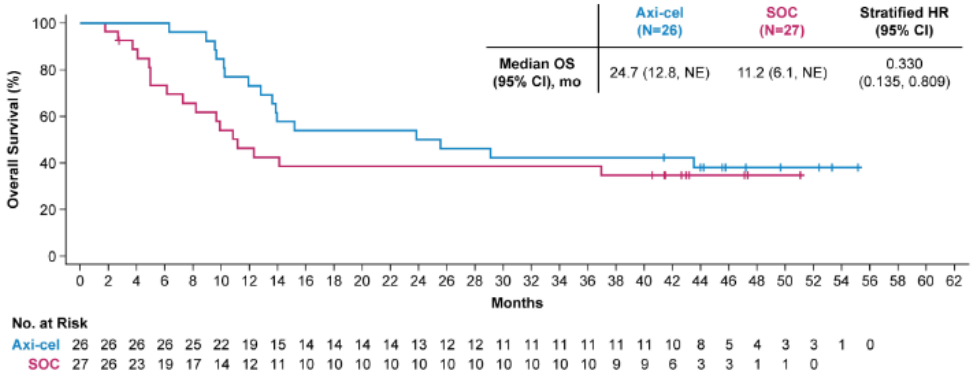


Figure 2: Overall Survival of Axi-cel vs Standard of Care Patients Aged ≥70 Years



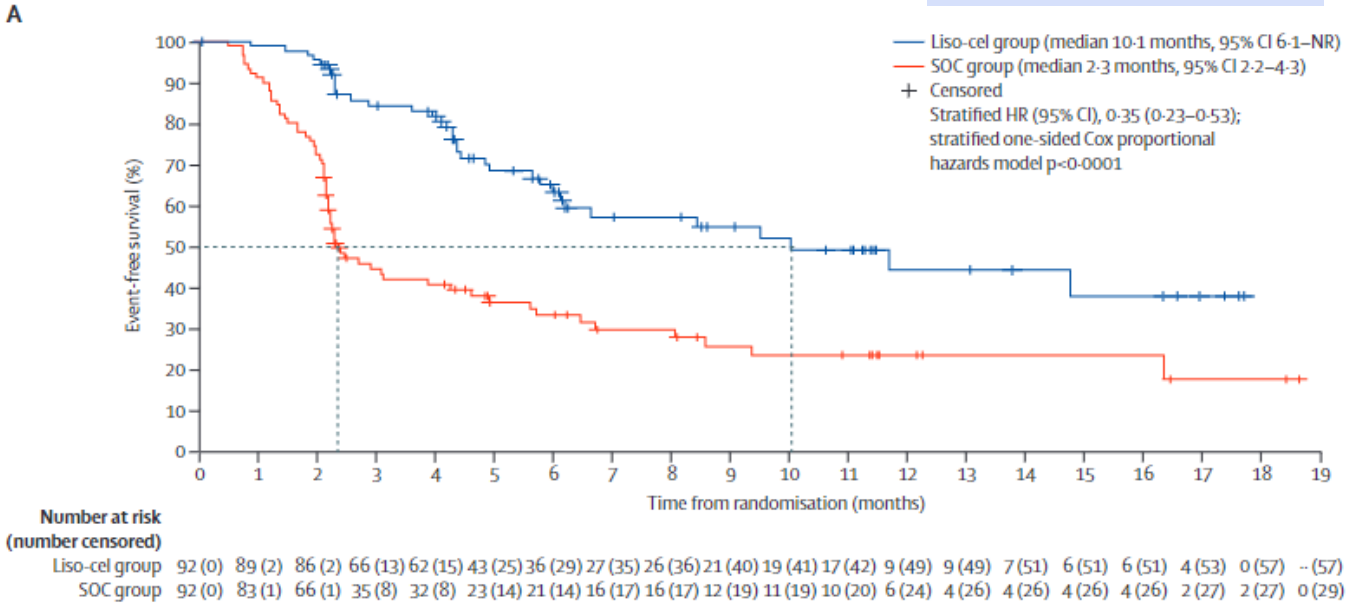
Kersten MJ, et al. Am Soc Hematol 2023 (Abs 1761)

Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial

Manali Kamdar, Scott R Solomon, Jon Arnason, Patrick B Johnston, Bertram Glass, Veronika Bachanova, Sami Ibrahimi, Stephan Mielke, Pim Mutsaers, Francisco Hernandez-Ilizaliturri, Koji Izutsu, Franck Morschhauser, Matthew Lunning, David G Maloney, Alessandro Crotta, Sandrine Montheard, Alessandro Previtali, Lara Stepan, Ken Ogasawara, Timothy Mack, Jeremy S Abramson, for the TRANSFORM Investigators†*

EFS

No updates on OS (yet)



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

CAR T-cell therapy vs. Bispecifics (DLBCL)

	CAR T-cell	Bispecifics	Winner
Indications	**2nd line, 3+ line**	3+ line	CAR T
Pre-treatment requirements	Complex (leukapheresis, LD)	Simpler (off-the-shelf)	Bispecifics
Rx. frequency	**Single infusion**	Multiple (months)	CAR T
Administration	Specialized centers	Community setting possible	Bispecifics
CNS efficacy	**Present, but limited**	?	CAR T
IP vs. OP	Mostly IP (but doable OP)	OP	Bispecifics
Toxicities	+++	+	Bispecifics
Cost	+++	++ (for up to 9 months)	Bispecifics
Follow-up	**Longer (5+ yrs)**	Short	CAR T

ZUMA-2: Baseline characteristics

Brexucabtagene autoleucel

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan

Table 1. Baseline Characteristics of All 68 Treated Patients.*

Characteristic	Patients
Median age (range) — yr	65 (38–79)
Intermediate or high risk according to Simplified MIPI — no. (%)†‡	38 (56)
Blastoid or pleomorphic morphologic characteristics of MCL — no. (%)	21 (31)
Ki-67 proliferation index ≥30% — no./total no. (%)‡	40/49 (82)
TP53 mutation — no. (%)	6/36 (17)
Positive CD19 status — no./total no. (%)	47/51 (92)
Median no. of previous therapies (range)§	3 (1–5)
≥3 Previous lines of therapy — no. (%)	55 (81)
Previous autologous stem-cell transplantation — no. (%)	29 (43)
Previous BTK inhibitor therapy — no. (%)§	68 (100)
Ibrutinib	58 (85)
Acalabrutinib	16 (24)
Both	6 (9)
Relapsed or refractory disease — no. (%)	
Relapse after autologous stem-cell transplantation	29 (43)
Refractory to most recent previous therapy	27 (40)
Relapse after most recent previous therapy	12 (18)
Disease that relapsed or was refractory to BTK inhibitor therapy — no. (%)	68 (100)
Refractory to BTK inhibitor therapy	42 (62)
Relapse during BTK inhibitor therapy	18 (26)
Relapse after BTK inhibitor therapy	5 (7)
Could not take BTK inhibitor therapy because of adverse events¶	3 (4)

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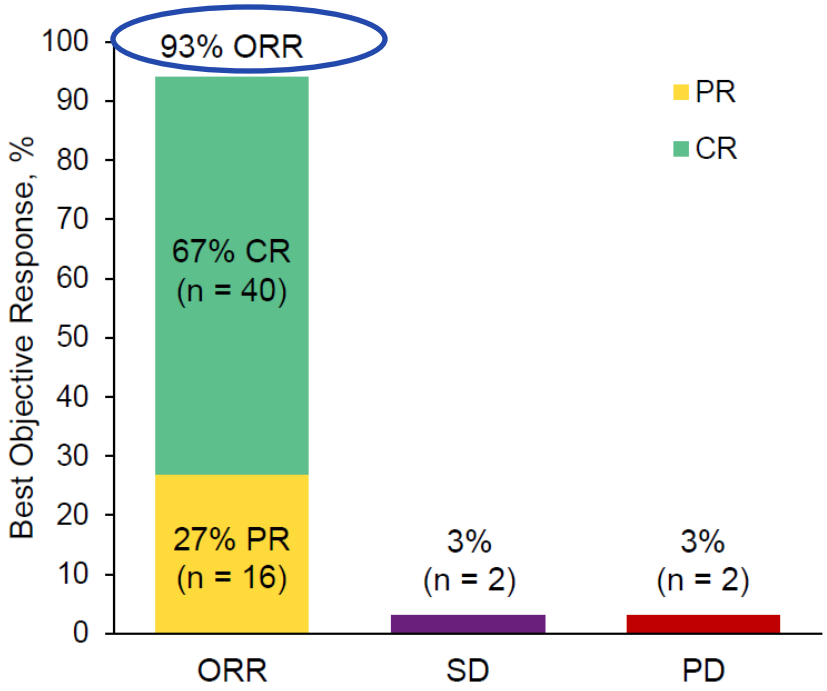
Wang M, et al. ASH 2019. Abs 754
Wang M, et al. NEJM. 2020. 382:1331

ZUMA-2: ORR

ASH 2019. Abs 754

ORR by IRRC Assessment Was 93% (95% CI, 84 – 98) and CR Rate Was 67% (95% CI, 53 – 78)



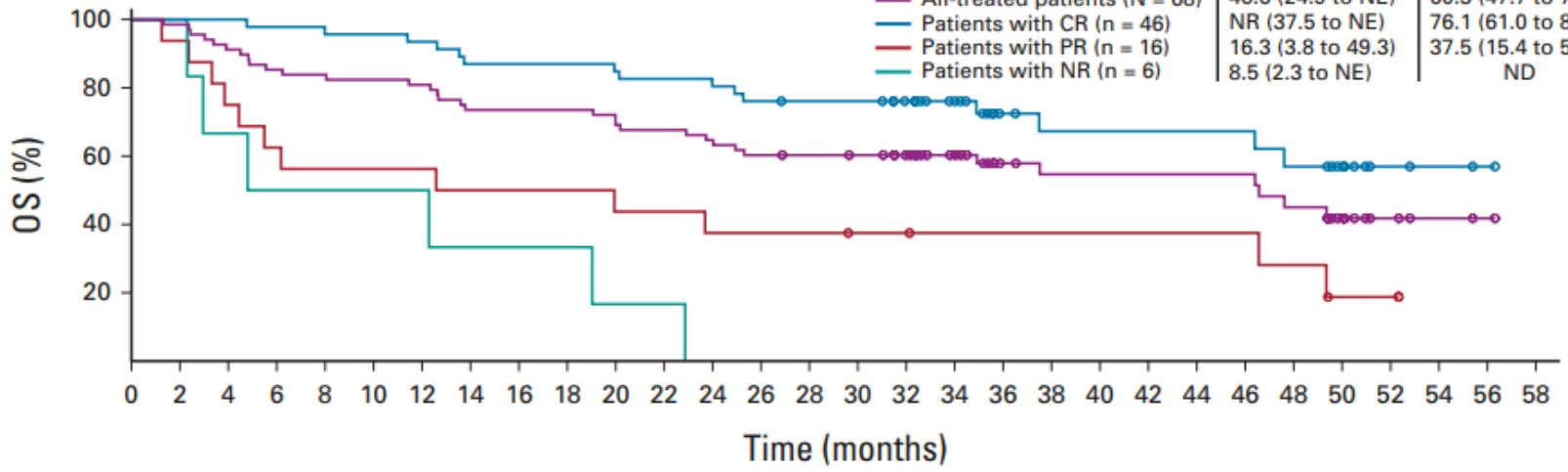
	Efficacy-Evaluable N = 60
Median follow-up (range), mo	12.3 (7.0 – 32.3)
Patients with ≥ 24 mo follow-up, n (%)	28 (47)
Median time to response (range), mo	
Initial response	1.0 (0.8 – 3.1)
CR	3.0 (0.9 – 9.3)
Patients converted from PR/SD to CR, n (%)	24 (40)
PR to CR	21 (35)
SD to CR	3 (5)

Investigator-assessed ORR in N = 60 was 88% (CR rate 70%), with 95% and 90% concordance between IRRC- and investigator-assessed ORR and CR rate, respectively. IRRC-assessed ORR in ITT (N = 74) was 85% (CR Rate 59%).
CR, complete response; IRRC, Independent Radiology Review Committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Wang M, et al. ASH 2019. Abs 754
Wang M, et al. NEJM. 2020. 382:1331

Mantle cell lymphoma: ZUMA-2 study 3-year update (OS)

C



	Median OS, Months (95% CI)	30-Month OS Rate, % (95% CI)
All-treated patients (N = 68)	46.6 (24.9 to NE)	60.3 (47.7 to 70.8)
Patients with CR (n = 46)	NR (37.5 to NE)	76.1 (61.0 to 86.0)
Patients with PR (n = 16)	16.3 (3.8 to 49.3)	37.5 (15.4 to 59.8)
Patients with NR (n = 6)	8.5 (2.3 to NE)	ND

No. at risk:

All-treated patients	68	67	62	58	56	56	55	50	50	50	47	46	43	41	40	39	35	28	19	17	17	17	17	17	14	9	4	2	1	0
Patients with CR	46	46	46	45	44	44	43	40	40	40	39	38	37	35	34	34	30	24	15	13	13	13	13	13	11	8	3	2	1	0
Patients with PR	16	15	12	10	9	9	9	8	8	8	7	7	6	6	6	5	5	4	4	4	4	4	4	4	3	1	1	0	0	0
Patients with NR	6	6	4	3	3	3	3	2	2	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Wang M, et al. J Clin Oncol. 2023;41(3):555-567

Original Reports | Hematologic Malignancy

Check for updates

Lisocabtagene Maraleucel in Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis of the Mantle Cell Lymphoma Cohort From TRANSCEND NHL 001, a Phase I Multicenter Seamless Design Study

Michael Wang, MD[1]; Tanya Siddiqi, MD, MBBS[2]; Leo I. Gordon, MD[3]; Manali Kamdar, MD, MBBS[4]; Matthew Lunning, DO[5]; Alexandre V. Hirayama, MD[6]; Jeremy S. Abramson, MD, MMSc[7]; Jon Arnason, MD[8]; Nilanjan Ghosh, MD, PhD[9]; Amitkumar Mehta, MD[10]; Charalambos Andreadis, MD, MS[11]; Scott R. Solomon, MD[12]; Ana Kostic, MD[13]; Christine Dehner, BSc[13]; Ricardo Espinola, MD[14]; Lily Peng, MS[13]; Ken Ogasawara, PhD, MPH[15]; Amy Chattin, PhD[15]; Laurie Eliason, MPH[15]; and M. Lia Palomba, MD[16]

Liso-cel treated set (N=88)	
Median (range) age, years	68.5 (36-86)
White race, n (%)	77 (87.5%)
***TP53* mutation, n (%)**	20 (23%)
Blastoid morphology, n (%)	27 (31%)
Complex karyotype, n (%)	26 (30%)
Median (range) prior Rx	3 (1-11)
Previous BTKi, n (%)	83 (94%)
Previous venetoclax, n (%)	23 (26%)
Previous HCT, n (%)	Auto=26 (30%) Allo=6 (7%)
Disease status	Relapsed=27 (31%) Refractory=61 (69%)

Median F/U= 16.1 (0.4-60.5) months

ORR= 83.1%
CR= **72.3%**

Median DOR= 15.7 months

CRS (any grade)= 61%; **Grade 3-4=1%**

Neuro events (any grade)= 31%
Grade 3-4= 9%

Follicular lymphoma: ZUMA-5

4868 Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma: 4-Year Follow-up from the Phase 2 ZUMA-5 Trial

Program: Oral and Poster Abstracts

Session: 705. Cellular Immunotherapies: Late Phase and Commercially Available Therapies: Poster III

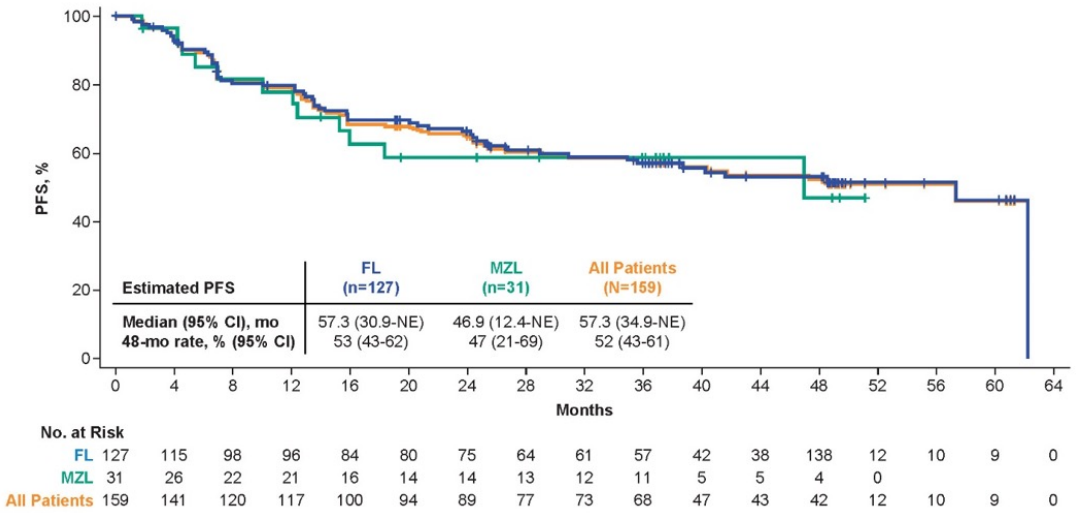
Hematology Disease Topics & Pathways:

Research, clinical trials, Biological therapies, adult, Lymphomas, non-Hodgkin lymphoma, Clinical Research, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Diseases, indolent lymphoma, Therapies, Lymphoid Malignancies, Study Population, Human

Monday, December 11, 2023, 6:00 PM-8:00 PM

Sattva S. Neelapu, MD[1], *Julio C. Chavez, MD*[2], *Alison R Sehgal, MD*[3], *Narendranath Epperla, MD, MS*[4], *Matthew L. Ulrickson, MD*[5], *Emmanuel Bachy, MD, PhD*[6], *Pashna N. Munshi, MD*[7], *Carla Casulo, MD*[8], *David G Maloney, MD, PhD*[9], *Sven de Vos, MD, PhD*[10], *Ran Reshef, MD, MSc*[11], *Lori A. Leslie, MD*[12], *Olalekan O. Oluwole, MBBS*[13], *Ibrahim Yakoub-Agha, MD, PhD*[14], *Rashmi Khanal, MD, MBBS*[15], *Joseph D. Rosenblatt, MD*[16], *Weixin Peng, MS*[17], *Christine Lui, MS*[17], *Jacob Wulff, DrPH*[17], *Rhine R. Shen, PhD*[17], *Soumya Poddar, PhD*[17], *Andrew Lee, MD*[17], *Harry Miao, MD, PhD*[17], *Olga Nikolajeva, MD*[17] *and Caron A Jacobson, MD, MMSc*[18]

Figure 1. Progression-Free Survival



- Updated outcomes from ZUMA-5 after ≥4 years median follow-up
- 159 pts enrolled (127 FL; 31 MZL) and 152 treated with axi-cel (124 FL; 28 MZL)
- **Median F/U 52.5 months** (range, 20.3-69.4; FL: 53.7, MZL: 43.8)
- Median progression-free survival= 57.3 months (95%CI=34.9-NE)
  - 4-year PFS=52%
- **Median overall survival (OS)= Not reached**
  - **4-year OS=72%**

Neelapu SS, et al. Am Soc Hematol. 2023 (Abs 4868)

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01622-0

Check for updates

Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial

Nathan Hale Fowler[1,2]✉, Michael Dickinson[3], Martin Dreyling[4], Joaquin Martinez-Lopez[5], Arne Kolstad[6], Jason Butler[7], Monalisa Ghosh[8], Leslie Popplewell[9], Julio C. Chavez[10], Emmanuel Bachy[11], Koji Kato[12], Hideo Harigae[13], Marie José Kersten[14], Charalambos Andreadis[15], Peter A. Riedell[16], P. Joy Ho[17], José Antonio Pérez-Simón[18], Andy I. Chen[19], Loretta J. Nastoupil[1], Bastian von Tresckow[20,21], Andrés José María Ferreri[22], Takanori Teshima[23], Piers E. M. Patten[24,25], Joseph P. McGuirk[26], Andreas L. Petzer[27], Fritz Offner[28], Andreas Viardot[29], Pier Luigi Zinzani[30,31], Ram Malladi[32], Aiesha Zia[33], Rakesh Awasthi[34], Aisha Masood[35], Oezlem Anak[33], Stephen J. Schuster[36,38] and Catherine Thieblemont[37,38]

N=97
Median prior therapies of 4 (2-13)
FLIPI high >3=59.8%
Median F/U 9.9 months

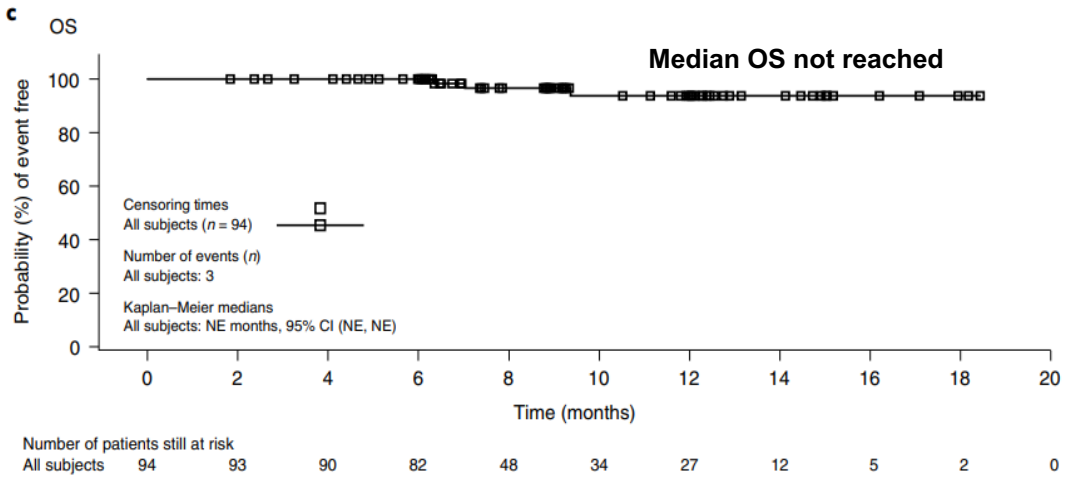


Table 2 | Best overall response in the EAS and per-protocol population[a]

Parameter	Per-protocol set, n = 85		EAS, n = 94	
	Local assessment	IRC assessment	Local assessment	IRC assessment
Best overall response, n (%)				
CR	64 (75.3); 95% CI, 64.7-84.0	62 (72.9); 95% CI, 62.2-82.0	68 (72.3); 95% CI, 62.2-81.1	65 (69.1); 95% CI, 58.5-78.3
PR	14 (16.5)	12 (14.1)	17 (18.1)	16 (17.0)
SD	2 (2.4)	3 (3.5)	3 (3.2)	3 (3.2)
PD	5 (5.9)	8 (9.4)	6 (6.4)	9 (9.6)
UNK				1 (1.1)
Overall response rate (CR + PR), n (%)	78 (91.8); 95% CI, 83.8-96.6	74 (87.1); 95% CI, 78.0-93.4	85 (90.4); 95% CI, 82.6-95.5	81 (86.2); 95% CI, 77.5-92.4

[a]The per-protocol set is a subset of patients in the primary analysis efficacy set with no major protocol deviations. UNK, unknown.

Events, n (%)	Infused patients N=97
CRS	47 (48.5)
Grade 1 or 2	47 (48.5)
Grade ≥3	0
In patients with CRS (n=47)	
Tocilizumab use during CRS	16 (34.0)
1 dose	8 (17.0)
2 doses	5 (10.6)
3 doses	3 (6.4)
Corticosteroids	3 (6.4)
Median time to onset, days (IQR)	4.0 (2–7)
Admitted to ICU, n (%)	4 (8.5)
Median total duration of ICU stay during CRS, days (range)	4.0 (2.5–5)
Patients with resolved events, n (%)	47 (100)

Extended Data Fig. 1 | Cytokine release syndrome within 8 weeks of tisagenlecleucel infusion. CRS=cytokine release syndrome; ICU=intensive care unit; IQR=interquartile range. Column titles are bolded for clarity.

Events, n (%)	Treated patients N=97 All Grades	Grade ≥3
Number of patients with at least one event	36 (37.1)	3 (3.1)
Headache	23 (23.7)	1 (1.0)
Dizziness	6 (6.2)	0
Encephalopathy	2 (2.1)	0
Immune effector cell-associated neurotoxicity syndrome	4 (4.1)	1 (1.0)
Paraesthesia	2 (2.1)	0
Tremor	2 (2.1)	0
Dyskinesia	1 (1.0)	0
Dysgeusia	1 (1.0)	0
Migraine	1 (1.0)	0
Peripheral sensory neuropathy	1 (1.0)	0
Syncope	1 (1.0)	1 (1.0)

Extended Data Fig. 3 | Neurological events within 8 weeks of tisagenlecleucel infusion. [a]G4 ICANS: Onset D10, recovered - Related to tisagenlecleucel. Patient presenting with tremors, then seizures, with concomitant HHV6 positivity on CSF. The event fully recovered after high-dose MPD and GCV. CSF=cerebrospinal fluid; GCV=ganciclovir; ICANS=immune effector cell-associated neurotoxicity syndrome; HHV6, Human Herpesvirus 6; MPD=methylprednisolone. Column titles are bolded for clarity.

601 Clinical Outcomes of Patients with Relapsed/Refractory Follicular Lymphoma Treated with Tisagenlecleucel: Phase 2 Elara 3-Year Follow-up

Program: Oral and Poster Abstracts
Type: Oral
Session: 623. Mantle Cell, Follicular, and Other Indolent B Cell Lymphomas: Clinical and Epidemiological: Immunotherapy
Hematology Disease Topics & Pathways:
Research, clinical trials, Biological therapies, adult, Lymphomas, Clinical Research, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Diseases, indolent lymphoma, Therapies, Lymphoid Malignancies, Study Population, Human

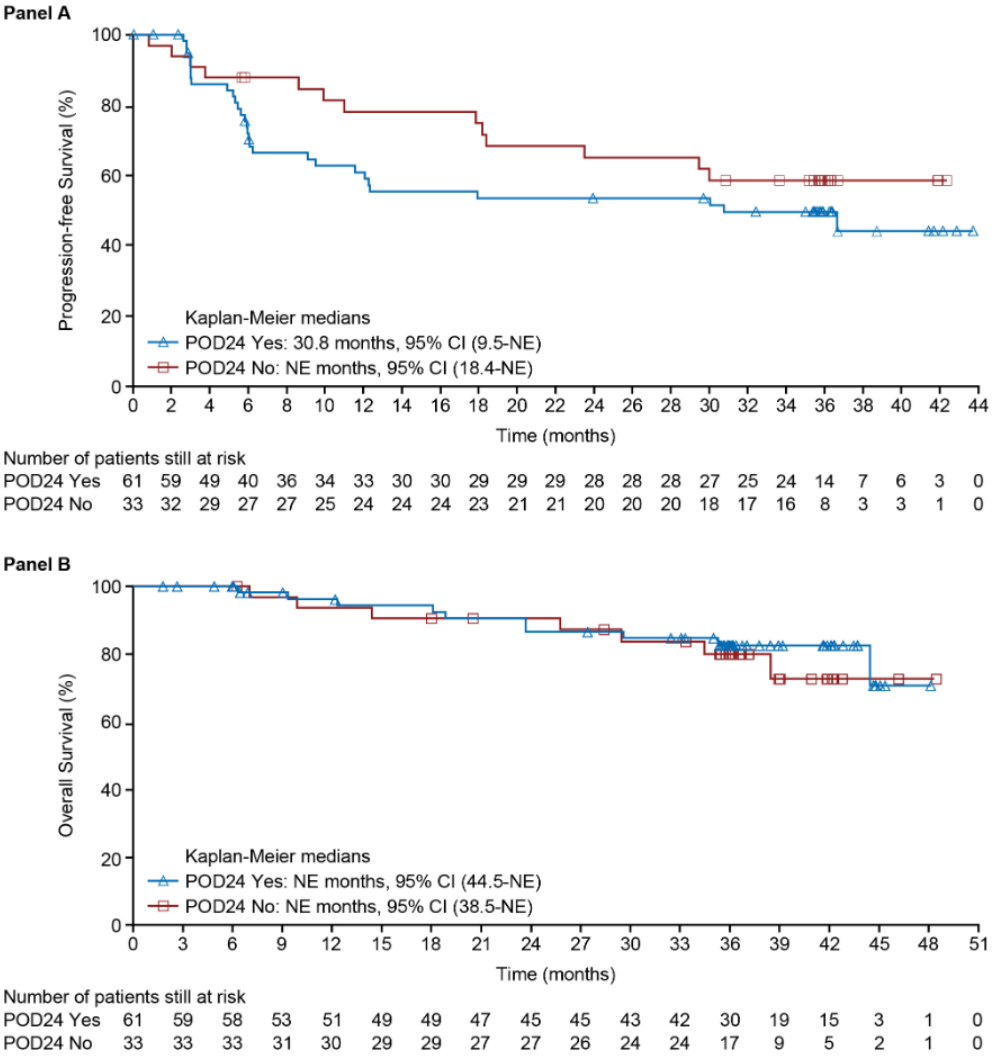
Sunday, December 10, 2023: 4:30 PM

Stephen J Schuster, MD[1], *Nathan Fowler, MD*[2,3], *Michael Dickinson, MBBS, D. Med Sci, FRACP, FRCPA*[4], *Joaquin Martinez-Lopez, MD, PhD*[5*], *Arne Kolstad, MD, PhD*[6*], *Jason Butler, MBBS*[7*], *Monalisa Ghosh, MD*[8], *Leslie L. Popplewell, MD, FACP, MPH*[9], *Julio C Chavez, MD*[10], *Emmanuel Bachy, MD, PhD*[11*], *Koji Kato, M.D., Ph.D.*[12*], *Hideo Harigae*[13], *Marie José Kersten, MD, PhD*[14], *Charalambos Andreadis*[15*], *Peter A Riedell*[16*], *Phoebe Joy Ho, MBBS, FRACP, FRCPA*[17], *Jose A. Perez-Simon, MD, PhD*[18*], *Andy Chen, MD, PhD*[19], *Loretta J. Nastoupil, MD*[2], *Bastian von Tresckow, MD*[20,21], *Andrés José María Ferreri, MD*[22], *Takanori Teshima*[23*], *Piers Patten, FRCP, FRCPath, PhD*[24], *Joseph P McGuirk, DO*[25], *Andreas L Petzer, MD*[26*], *Fritz Offner, MD*[27], *Andreas Viardot, MD PhD*[28], *Pier Luigi Zinzani, MD, PhD*[29,30], *Ram Malladi, PhD*[31*], *Aiesha Zia*[32*], *Rakesh Awasthi, PhD*[33*], *Ines Paule*[32*], *Davide Germano*[32*], *Roberto Javier Ramos, MD*[34*], *Pei Hsu*[35*], *Catherine Thieblemont, MD*[36*] *and Martin Dreyling, MD*[37]

	POD24	No POD24
36 mos-PFS	50%	59%
In vivo CAR T Expansion		Higher
CAR T persistence		Longer
36 mos-OS	83%	81%

High baseline levels of circulating CD8+ naive T cells (>2.14% of total T cells) resulted in prolonged PFS and DOR

Figure. (A) Progression-free survival by POD24, (B) Overall survival by POD24.
NE, not evaluable; POD24, progression of disease within 2 years of frontline systemic therapy.



Hematological ONCOLOGY

SUPPLEMENT ABSTRACTS | Free Access

TRANSCEND FL: PHASE 2 STUDY RESULTS OF LISOCABTAGENE MARALEUCEL (LISO-CEL) IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL)

F. Morschhauser, S. Dahiya, M. L. Palomba, A. M. Garcia-Sancho, J. L. Reguera Ortega, J. Kuruvilla, U. Jager, G. Cartron, K. Izutsu, M. Dreyling, B. Kahl, H. Ghesquieres, K. Ardeshna, H. Goto, A. M. Barbui, J. S. Abramson, P. Borchmann, I. Fleury, S. Mielke, T. Farazi, O. Fasan, J. Lymp, M. Vedal, R. Nishii, A. Avilion, J. Papuga, L. J. Nastoupil ... See fewer authors

First published: 09 June 2023 | https://doi.org/10.1002/hon.3196_LBA4 | Citations: 1

Volume 41, Issue S2
Supplement: 17th International Conference on Malignant Lymphoma, Palazzo dei Congressi, Lugano, Switzerland, 13 - 17 June, 2023
June 2023
Pages 877-880


FDA grants accelerated approval to lisocabtagene maraleucel for follicular lymphoma

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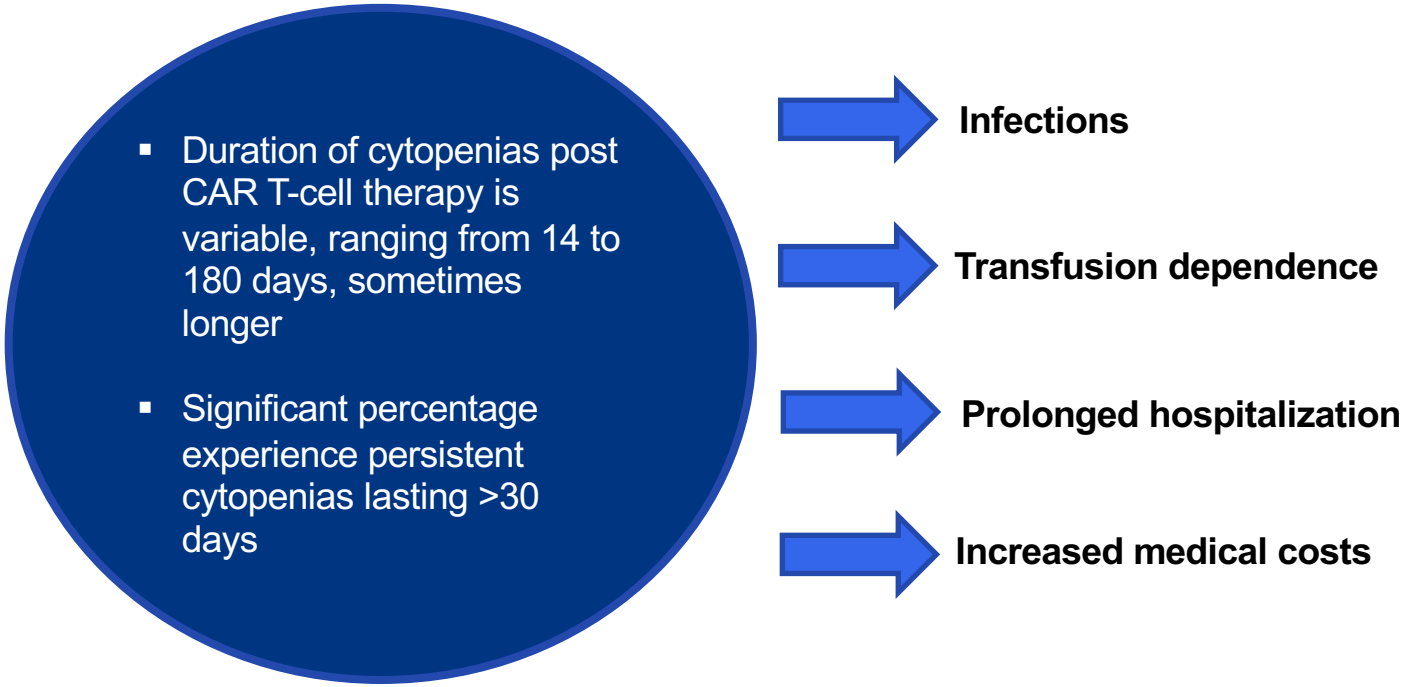
On May 15, 2024, the Food and Drug Administration granted accelerated approval to lisocabtagene maraleucel ( ) for adults with relapsed or refractory follicular lymphoma (FL) who have received two or more prior lines of systemic therapy.

- R/R FL: 3L^{+} and 2L pts with progression within 24 monts (POD24) of Dx and/or modified Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria
- Liso-cel (100 x10^{6} CAR+ T cells) after LD chemotherapy
- 1^{ry} endpoint ORR per IRC by PET/CT
- N of patients who underwent leukapheresis=139
  - N infused= 130
  - N evaluable for efficacy=124
  - Median age= 62 (23-80) years
  - High-risk FLIPI=57%
  - Median (range) prior lines of therapy= 3 (2–10)

- Median F/U=18.9 (0.3-28.2) mos
- Evaluable 3L^{+} pts=101
- **ORR= 97%**
- **CR=94.1%**

Long-term toxicities

Cytopenia (CAR-to-penia)



Zhu F et al. Cell Transplant. 2020 Jan-Dec;29:963689720919434
Yassine F et al. Hematol Oncol Stem Cell Ther. 2022; 15(3):122-130

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Research Letter

February 22, 2024

Features and Factors Associated With Myeloid Neoplasms After Chimeric Antigen Receptor T-Cell Therapy

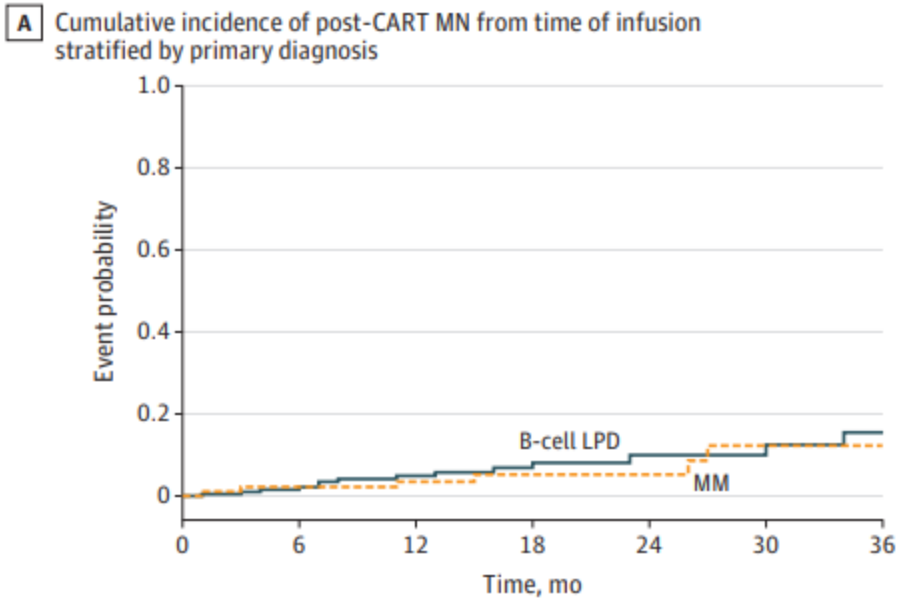
Mark Gurney, MB, BCh, BAO[1]; Anmol Baranwal, MD[1,2]; Allison Rosenthal, DO[3]; Mohamed A. Kharfan-Dabaja, MD, MBA[4]; Saad S. Kenderian, MB, ChB[1]; Yi Lin, MD, PhD[1]; Mithun Vinod Shah, MD, PhD[1]

Author Affiliations | Article Information

JAMA Oncol. 2024;10(4):532-535. doi:10.1001/jamaoncol.2023.7182

Incidence of myeloid neoplasm is comparable between LPD and MM

- **At 1-year=4%**
- **At 2-year=6%**
- **At 3-year=9%**



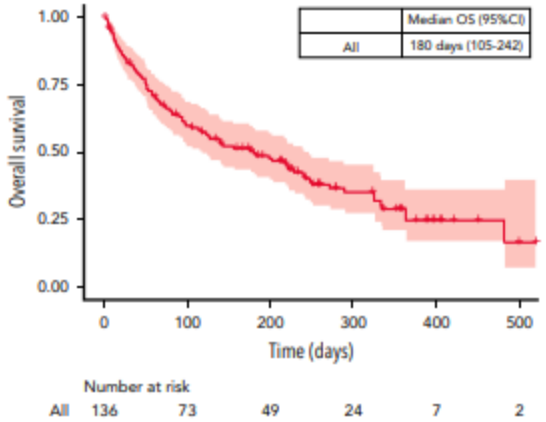
CAR T-cell therapy failure

- Dismal prognosis in general
  - Median overall survival after failing axicabtagene ciloleucel approx. 6 months

TO THE EDITOR:

Outcomes of patients with large B-cell lymphoma progressing after axicabtagene ciloleucel therapy

Jay Y. Spiegel,[1,*] Saurabh Dahiya,[2,*] Michael D. Jain,[3] John Tamaresis,[1] Loretta J. Nastoupil,[4] Miriam T. Jacobs,[5] Armin Ghobadi,[5] Yi Lin,[6] Matthew Lunning,[7] Lazaros Lekakis,[8] Patrick Reagan,[9] Olalekan Oluwole,[10] Joseph McGuirk,[11] Abhinav Deol,[12] Andre Goy,[13] Khoan Vu,[14] Charalambos Andreadis,[14] Javier Munoz,[15] N. Nora Bennani,[6] Julie M. Vose,[7] Kathleen A. Dorritie,[16] Sattva S. Neelapu,[4] Frederick L. Locke,[3] Aaron P. Rapoport,[2,†] Brian T. Hill,[17,†] and David B. Miklos[1,†]



Spiegel JY, et al. Blood. 2021; 137 (13): 1832-35

Allogeneic transplant following CAR T-cell therapy for large B-cell lymphoma

Joanna Zurko,[1] Jeremy Ramdial,[2] Mazyar Shadman,[3] Sairah Ahmed,[2] Aniko Szabo,[1] Lorenzo Iovino,[3] Ana Alarcon Tomas,[4] Craig Sauter,[4] Miguel-Angel Perales,[4] Nirav. N. Shah,[1] Utkarsh H. Acharya,[5] Caron Jacobson,[5] Robert J. Soiffer,[5] Trent Wang,[6] Krishna V. Komanduri,[6] Samantha Jaglowski,[7] Adam S. Kittai,[7] Nathan Denlinger,[7] Madiha Iqbal,[8] Mohamed A. Kharfan-Dabaja,[8] Ernesto Ayala,[8] Julio Chavez,[9] Michael Jain,[9] Frederick L. Locke,[9] Yazeed Samara,[10] Lihua E. Budde,[10] Matthew G. Mei,[10] Alexandra Della Pia,[11,12] Tatyana Feldman,[11] Nausheen Ahmed,[13] Ryan Jacobs,[14] Nilanjan Ghosh,[14] Bhagirathbhai Dholaria,[15] Olalekan O. Oluwole,[15] Brian Hess,[16] Ayesha Hassan,[1] Vaishalee P. Kenkre,[1] Patrick Reagan,[17] Farrukh Awan,[18] Yago Nieto,[2] Mehdi Hamadani[19] and Alex F. Herrera[10]

- N=88
- 18 US centers

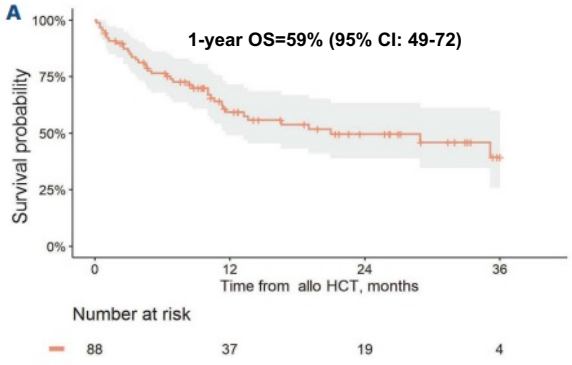


Table 3. Multivariate analysis outcomes after allogeneic hematopoietic cell transplantation.[1]

	HR	95% CI	P
Overall survival			
Race/ethnicity			0.01
White	-	-	
Hispanic	3.58	1.51–8.52	
Other	0.78	0.22–2.80	
Lines of therapy between CAR T and alloHCT			0.02
0	-	-	
1	1.12	0.39–3.23	
≥2	3.63	1.00–13.1	
Disease status prior to alloHCT			0.01
CR	-	-	
PR	4.32	1.61–11.6	
SD/PD	1.85	0.73–4.70	
Progression-free survival			
	HR	**95% CI**	**P**
Lines of therapy between CAR T and alloHCT			0.02
0	-	-	
1	1.34	0.53–3.42	
≥2	3.12	1.14–8.53	
Disease status prior to alloHCT			0.03
CR	-	-	
PR	2.61	1.27–5.37	
SD/PD	2.05	0.99–4.26	
Non-relapse mortality			
	HR	**95% CI**	**P**
Race/ethnicity			0.04
White	-	-	
Hispanic	2.51	1.04–6.08	
Other	0.32	0.04–2.76	
Lines of therapy between CAR T and alloHCT			<0.001
0	-	-	
1	4.78	0.59–38.3	
≥2	17.0	2.23-129	
Disease status prior to alloHCT			0.008
CR	-	-	
PR	4.02	1.63–9.89	
SD/PD	0.87	0.22–3.45	
Conditioning regimen			0.004
MAC	-	-	
RIC/NMA	0.25	0.10– 0.63	

[1]Variables only included in the table above if *P* value was significant at the <0.05 level on the multivariate analysis. No variables were significant for progression/relapse or graft-*versus*-host disease-free relapse free survival (GRFS). AlloHCT: allogeneic hematopoietic cell transplantation; CR: complete response; MAC: myeloablative conditioning; MRD: matched related donor; MTX: methotrexate; MUD: matched unrelated donor; NMA/RIC: non-myeloablative/reduced intensity conditioning; PD: progressive disease; PR: partial response; SD: stable disease.

CHARACTERISTIC	N (%)
Median follow-up, months (range)	15 (1-72)
Age in years (range)	54 (19-72)
Male sex	63 (72)
Race	
White	58 (66)
Hispanic	18 (20)
Black	6 (6.8)
Asian	5 (5.7)
American Indian or Alaska Native	1 (1.1)
Histologic type	
De novo DLBCL	52 (59)
Transformed indolent lymphoma[1]	23 (26)
PMBL	8 (9.1)
High grade B-cell lymphoma, NOS	5 (5.7)
Cell of origin[2]	
Non-GCB	32 (42)
Double/triple hit[3]	9 (12)
N lines of therapy prior to CAR T (range)	3 (1-7)
Best response to CAR T	
CR	31 (35)
PR	32 (36)
SD/PD	25 (29)
Time to relapse post-CAR T, days N (range)[4]	92 (7-527)
N lines of therapy between CAR T and alloHCT (range)	1 (0-7)
Disease status prior to alloHCT	
CR	45 (51)
PR	22 (25)
SD/PD	21 (24)
Ann Arbor stage at time of CAR T progression/relapse[5]	
1	26 (31)
2	9 (11)
3/4	48 (58)
Extranodal disease at time of CAR-T progression/relapse	49 (58)
Days N between CAR T infusion and day 0 of alloHCT (range)	255 (63-753)
Conditioning regimen intensity	
MAC	20 (23)
Graft source	
Peripheral blood	76 (86)
Bone marrow	10 (11)
Cord	2 (2)
Donor type	
MUD	34 (39)
Haploidentical	26 (30)
MRD	23 (26)
MMUD	3 (3)
Cord	2 (2)
GvHD prophylaxis	
CNI+MTX	22 (25)
TAC/MMF/PTCY	43 (49)
Other	23 (26)

What about bispecifics (CD3*CD20) in the setting of post CAR T-cell failure

	Epcoritamab[1]	Glofitamab[2]
n CAR T failed/**N** total	61/157 (38.9%)	51/155 (31%)
ORR	54.1%	Not reported
CR	34.4%	35%
Median DOR	9.7 months	Not reported

1. *Thieblemont C, et al. J Clin Oncol. 2023;41:2238–47*
2. *Dickinson MJ, et al. N Engl J Med. 2022; 387: 2220-31*

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Secondary Cancers after Chimeric Antigen Receptor T-Cell Therapy

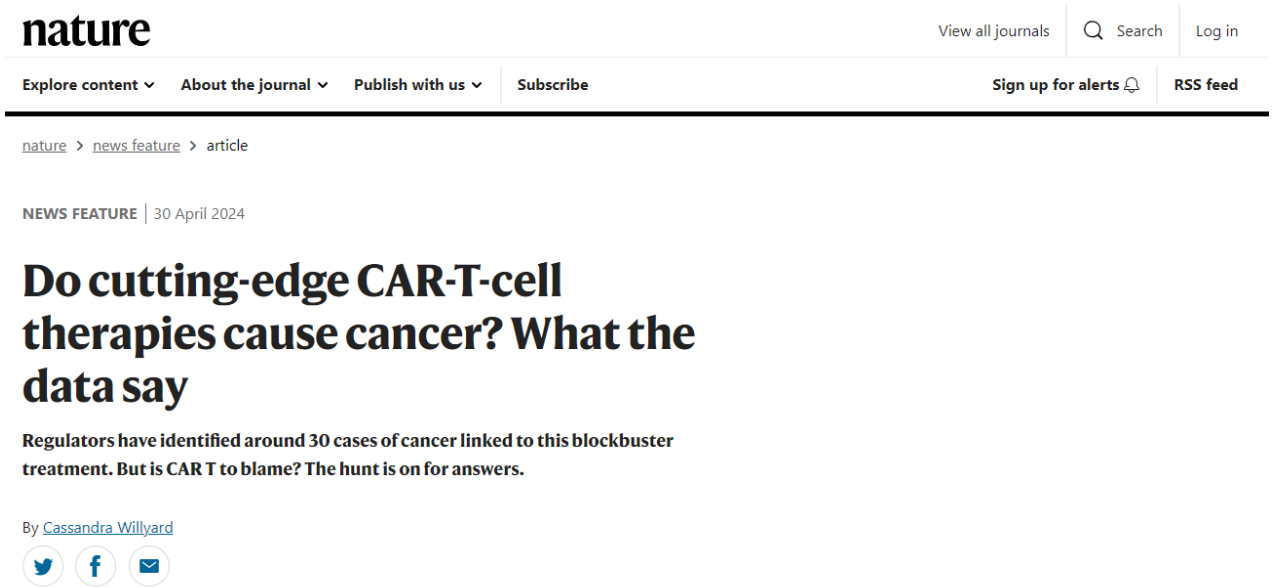
Nicole Verdun, M.D., and Peter Marks, M.D., Ph.D.

As of 12-31-2023, the FDA had become aware of 22 cases of T-cell cancers that occurred after CAR-T product treatment. Such cancers include: **T-cell lymphoma, T-cell LGL, PTCL, and CTCL**

Among 14 cases with data, cancers manifested within 2 years after CAR T cells (range, 1 to 19 months), with roughly half occurring within the 1st year

Some are still under investigation. In 3 cases for which genetic sequencing was performed, the CAR transgene was detected in the malignant clone

With > 27,000 doses of the 6 approved products having been administered in the USA, the overall rate of T-cell cancers is low (22/27,000= 0.081%)



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NEWS FEATURE | 30 April 2024

Do cutting-edge CAR-T-cell therapies cause cancer? What the data say

Regulators have identified around 30 cases of cancer linked to this blockbuster treatment. But is CAR T to blame? The hunt is on for answers.

By Cassandra Willyard

- The FDA has since documented more cases
- As of March 25th, 2024, the agency had received 33 reports of such lymphomas among some 30,000 people who had been treated **(33/30,000= 0.11%)**
- It now requires all CAR-T therapies to carry a boxed warning on the drug's packaging, which mentions that such cancers have occurred
- The European Medicines Agency has launched its own investigation

Take home messages

Realities

- CAR-T revolutionized Rx of DLBCL, MCL, and FL. Here to stay!
- In relapsed/refractory DLBCL
  - CR at 12 and 24 months→ suggest durable response **(?cure)**
- In 1ry refractory DLBCL or early relapse (<12 months)
  - Axi-cel better than SOC (↑EFS, ↑OS)
  - Liso-cel better than SOC (↑EFS)
- Brexu-cel and liso-cel approved in R/R mantle cell lymphoma
- Axi-cel, tisagenlecleucel and liso-cel in R/R follicular lymphoma
- Efficacy reproducible in the "real world" setting

Challenges

- Long-term toxicities are challenging
  - CAR-to-penia
  - Hypogammaglobulinemia
  - Therapy-related myeloid neoplasms (9% at 3 year)
    - CHIPs prior to CAR T-cell vs. after CAR T-cell?
- T-cell lymphoma(s) derived from CAR T product (CAR transgene)
  - Real phenomenon
  - Incidence very low= **0.081-0.11%**

