MAYO CLINIC

Recent advances in CAR T-cell treatments

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FLASCO, 13th Annual Puerto Rico Oncology Symposium
San Juan, Puerto Rico
February 2, 2024

Conflicts of interest

Research/Grant:

Mayo Clinic Florida site PI for clinical trial

- Novartis
- Bristol Myers Squibb
- Pharmacyclics

Invention/patent:

- Co-owner of patent for BAFF-R directed CAR T-cell (MC10029)

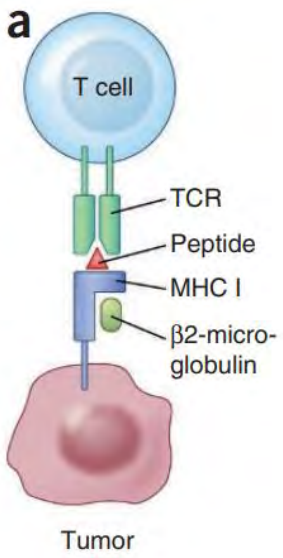
Outline

- **Diffuse large B-cell lymphoma**
  - 3rd line and beyond (ZUMA 1, JULIET, TRANSCEND NHL 001)
  - 2nd line (ZUMA 7, TRANSFORM)
  - Proposed algorithm
- **Mantle cell lymphoma**
  - ZUMA 2
- **Follicular lymphoma**
  - ZUMA 5
  - ELIANA
- **CAR T-cell associated toxicities**
- **CAR T-cell therapy failure mechanism(s)**
  - Treatment options (?)
- **Take home messages**

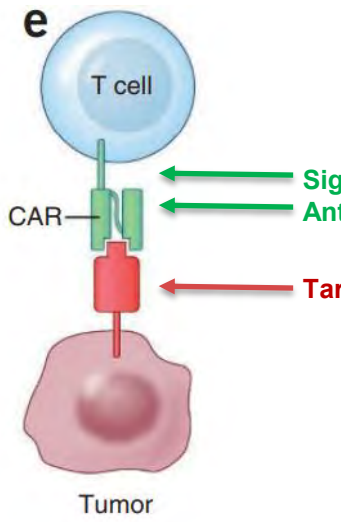
What is CAR T-cell therapy?

- Stands for Chimeric Antigen Receptor T-cell Therapy
- Immunotherapy that uses engineered T lymphocytes to specifically target the intended cancer cell

Normal T-cell



CAR T-cell



Signaling domain
Antigen recognition domain
Target antigen

CAR T-cell benefits
- Localization
- Cytotoxic killing
- Expansion
- Persistence

CD19: B-cell lymphoma/ALL
BCMA: Multiple myeloma

FDA approved

Adapted and modified from Hinrichs CS & Restifo NP. Nat Biotechnol. 2013; 31(11):999-1008

Diffuse large B cell lymphoma

Before availability of CAR-T

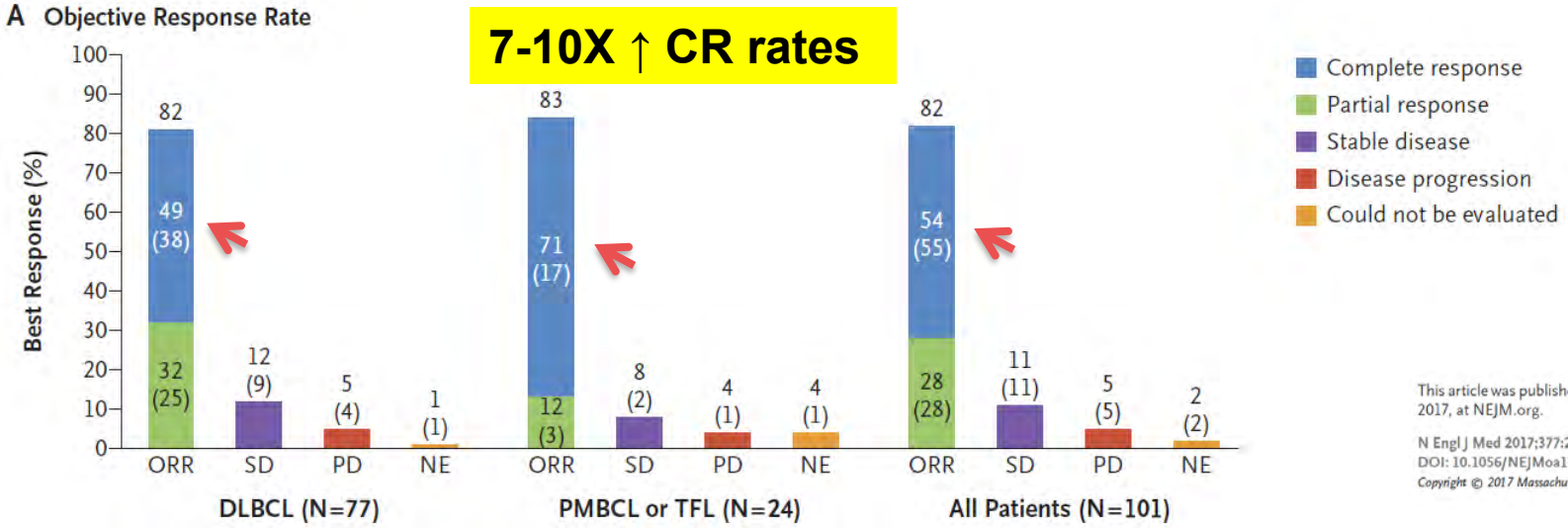
Table 2. Rate of response to chemotherapy after refractory disease

	MDACC (n = 165)	IA/MC (n = 82)	LY.12 (CCTG) (n = 219)	CORAL (LYSARC) (n = 170)	Pooled* (N = 636)
Patients evaluated for response, n†	165	82	106	170	523
Response rate, % (95% CI)	20	26	26	31	26 (21-31)
CR rate	7	7	2	15	7 (3-15)
PR rate	13	18	25	16	18 (13-23)
Response rate by refractory category, % (95% CI)					
Primary refractory					
RR	—	25	27	10	20 (11-34)
CR rate	—	10	1	2	3 (1-11)
Refractory to second-line or later-line therapy					
RR	20	21	20	40	26 (17-39)
CR rate	7	5	20	18	10 (5-20)
Relapse ≤12 mo post-ASCT					
RR	19	35	—	39	34 (24-45)
CR rate	6	10	—	25	15 (6-31)

Crump M, et al. Blood. 2017; 130 (16): 1800-09

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

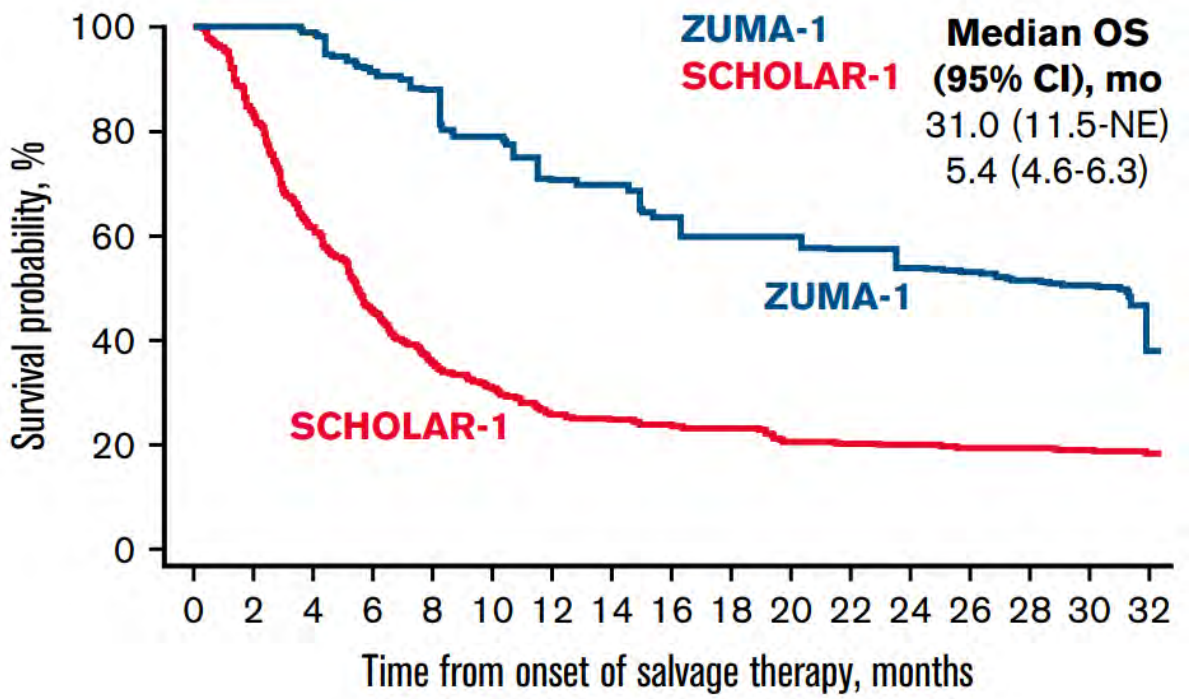
REGULAR ARTICLE

blood advances

Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma

Sattva S. Neelapu,[1] Frederick L. Locke,[2] Nancy L. Bartlett,[3] Lazaros J. Lekakis,[4] Patrick M. Reagan,[5] David B. Miklos,[6] Caron A. Jacobson,[7] Ira Braunschweig,[8] Olalekan O. Oluwole,[9] Tanya Siddiqi,[10] Yi Lin,[11] Michael Crump,[12] John Kuruvilla,[13] Eric Van Den Neste,[14] Umar Farooq,[15] Lynn Navale,[16] Venita DePuy,[17] Jenny J. Kim,[16] and Christian Gisselbrecht[18]

[1]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Department of Blood and Marrow Transplant and Cellular Immunotherapy, Moffitt Cancer Center, Tampa, FL; [3]Siteman Cancer Center, Washington University Medical School, St Louis, MO; [4]Sylvester Comprehensive Care Center, University of Miami Health System, Miami, FL; [5]James P. Wilmot Cancer Institute, University of Rochester School of Medicine, Rochester, NY; [6]Department of Medicine - Blood and Marrow Transplantation, Stanford University School of Medicine, Stanford, CA; [7]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; [8]Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; [9]Division of Hematology/Oncology, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN; [10]Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA; [11]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; [12]Canadian Cancer Trials Group, Queen's University, Kingston, ON, Canada; [13]Princess Margaret Cancer Center, Toronto, ON, Canada; [14]Department of Hematology, Cliniques Universitaires UCL Saint-Luc, Brussels, Belgium; [15]Division of Hematology, Oncology, and Blood and Marrow Transplantation, Department of Internal Medicine, University of Iowa, Iowa City, IA; [16]Kite, a Gilead Company, Santa Monica, CA; [17]Bowden Analytics, Raleigh, NC; and [18]Hôpital Saint Louis, Paris, France



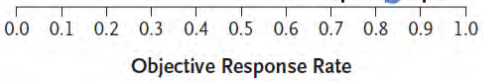
Treatment difference

HR=0.27 (95%CI=0.00-0.38)

73% reduction in risk of death

B Subgroup Analysis

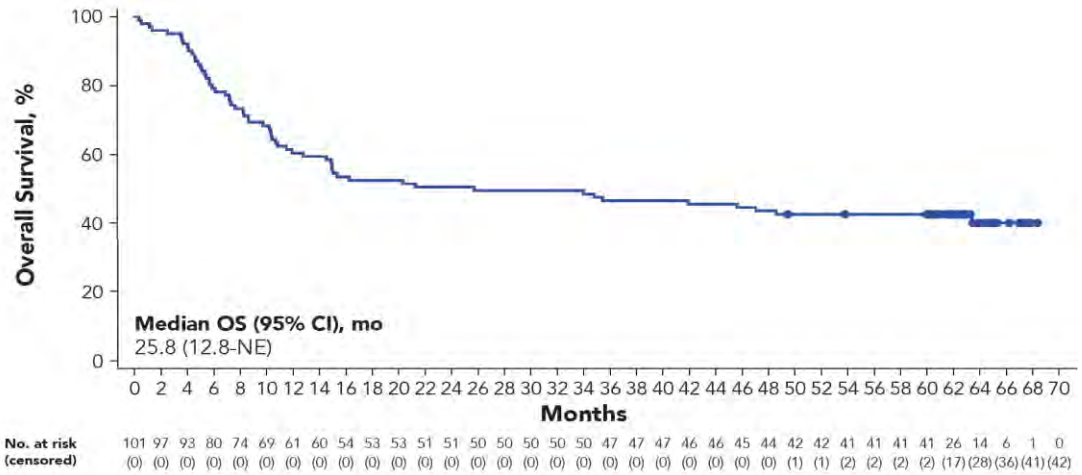
Subgroup	No. of Patients Who Could Be Evaluated	No. of Patients with Event	Objective Response Rate (95% CI)
Overall	101	83	0.82 (0.73–0.89)
Refractory subgroup			
Refractory to ≥second-line therapy	78	65	0.83 (0.73–0.91)
Relapse after ASCT	21	16	0.76 (0.53–0.92)
Age			
<65 yr	77	61	0.79 (0.68–0.88)
≥65 yr	24	22	0.92 (0.73–0.99)
Disease stage			
I or II	15	13	0.87 (0.60–0.98)
III or IV	86	70	0.81 (0.72–0.89)
IPI risk score			
0–2	53	46	0.87 (0.75–0.95)
3 or 4	48	37	0.77 (0.63–0.88)
Extranodal disease			
Yes	70	56	0.80 (0.69–0.89)
No	31	27	0.87 (0.70–0.96)
Bulky disease (≥10 cm)			
Yes	17	12	0.71 (0.44–0.90)
No	84	71	0.85 (0.75–0.91)
Treatment history			
Primary refractory disease	26	23	0.88 (0.70–0.98)
Refractory to two consecutive lines	54	42	0.78 (0.64–0.88)
CD19 status			
Positive	74	63	0.85 (0.75–0.92)
Negative	8	6	0.75 (0.35–0.97)
CD19 histologic score			
≤150	26	22	0.85 (0.65–0.96)
>150	56	47	0.84 (0.72–0.92)
Cell of origin			
Germinal center B-cell–like subtype	49	43	0.88 (0.75–0.95)
Activated B-cell–like subtype	17	13	0.76 (0.50–0.83)
CD4:CD8 ratio			
>1	47	41	0.87 (0.74–0.95)
≤1	52	40	0.77 (0.63–0.87)
Tocilizumab use			
Yes	43	36	0.84 (0.69–0.93)
No	58	47	0.81 (0.69–0.90)
Glucocorticoid use			
Yes	27	21	0.78 (0.58–0.91)
No	74	62	0.84 (0.73–0.91)



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

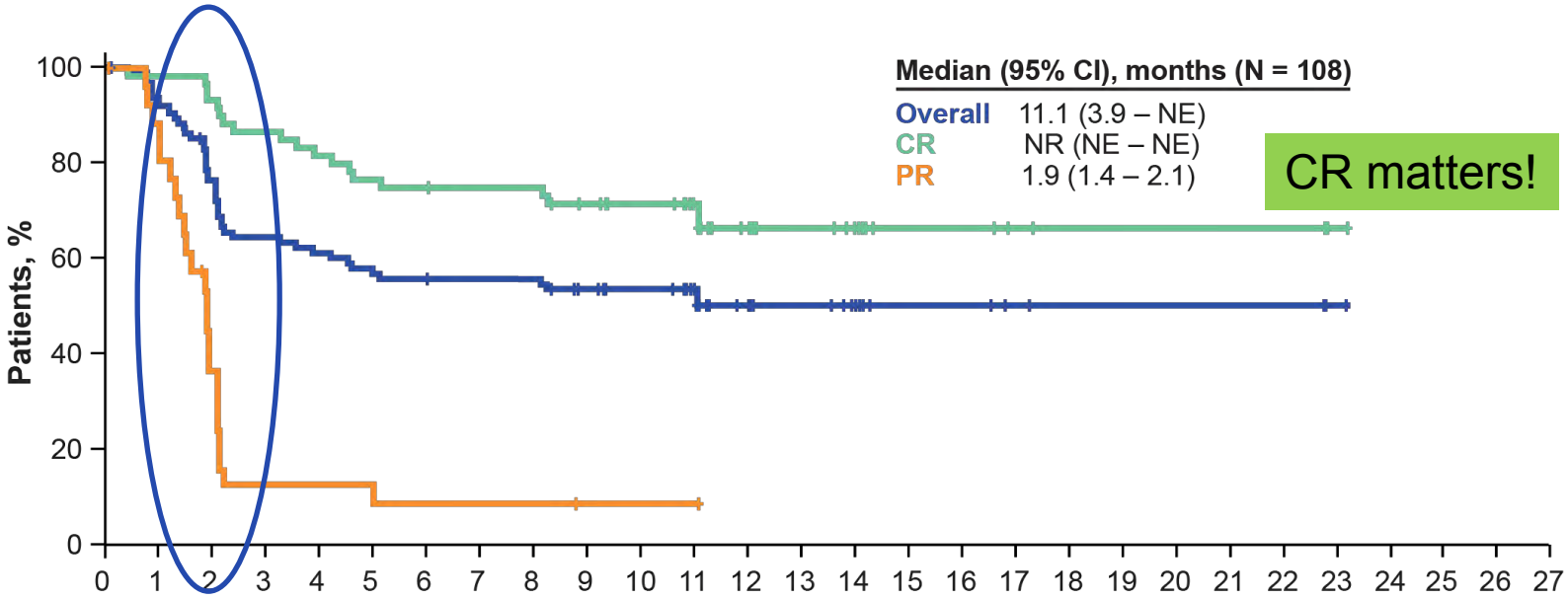
The 5-year OS rate:

- 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

DOR by best objective response (median F/U of 15.4 months)



Patients at Risk

Overall	89	82	67	56	53	49	48	47	47	42	38	31	19	16	12	6	6	4	3	3	3	3	3	1	0
CR	63	61	58	53	50	47	46	45	45	41	37	30	19	16	12	6	6	4	3	3	3	3	3	1	0
PR	26	21	9	3	3	2	2	2	2	1	1	1	0												

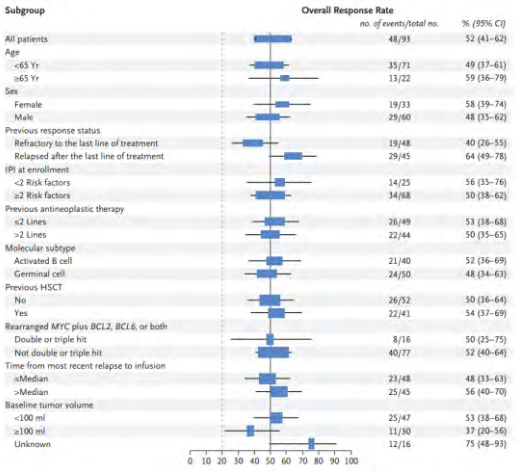
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

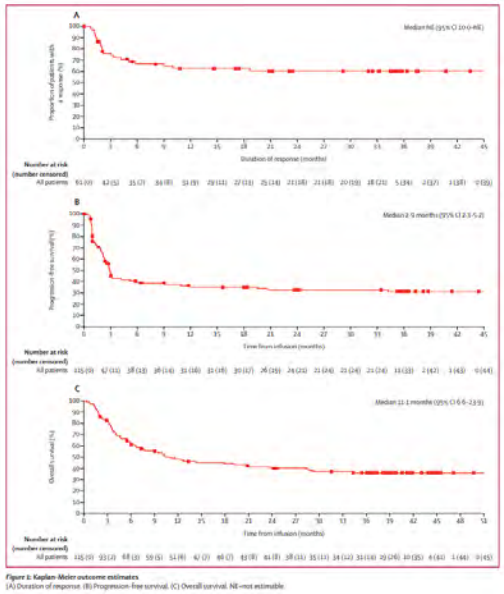
Variables	All pts
N pts enrolled	111
Median (range) age, years	56 (22-76)
Stage III-IV disease	84 (76%)
≥ 3 prior lines of therapy	57 (52%)
Relapsed after auto-HCT	54 (49%)



Schuster SJ, et al. N Engl J Med. 2019; 380:45-56

Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study

Stephen J Schuster, Constantine S Tam, Peter Borchmann, Nina Worel, Joseph P McGuirk, Harald Holte, Edmund K Waller, Samantha Jaglowski, Michael R Bishop, Lloyd E Damon, Stephen Ronan Foley, Jason R Westin, Isabelle Fleury, P Joy Ho, Stephan Mielke, Takanori Teshima, Murali Janakiram, Jing-Mei Hsu, Koji Izutsu, Marie José Kersten, Monalisa Ghosh, Nina Wagner-Johnston, Koji Kato, Paolo Corradini, Marcela Martinez-Prieto, Xia Han, Ranjan Tiwari, Gilles Salles, Richard T Maziarz

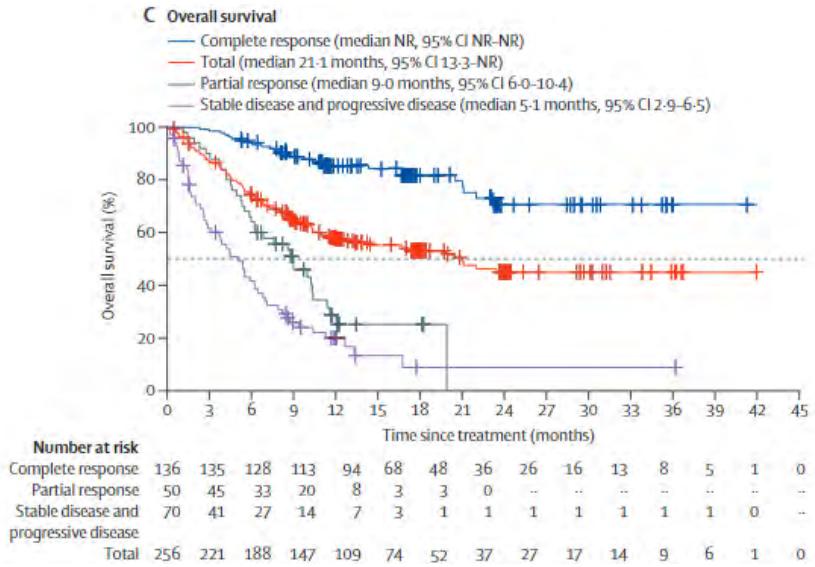


- At a median follow-up of 40.3 months (IQR 37·8–43·8)
- ORR= 53% by IRC-assessed
- CR= 39%
- The median time to first response= 29 (28-31) days

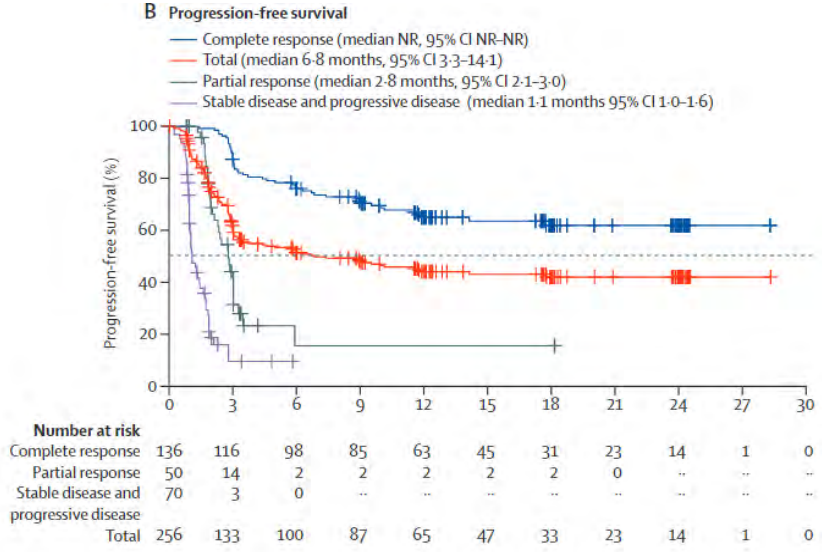
Schuster SJ, et al. Lancet Oncol. 2021; 22:1403-15

TRANSCEND NHL 001 (Lisocabtagene maraleucel)

Overall survival



Progression-free survival



Abramson JS, et al. Lancet. 2020; 396;839-52

Double/triple hit lymphoma

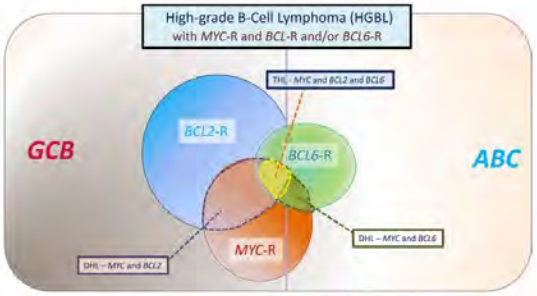


Figure 1. Category of aggressive B-cell lymphomas "HGBLs with *MYC* and *BCL2* and/or *BCL6* rearrangements" described in the 2016 revision to the World Health Organization classification of tumors of hematopoietic and lymphoid tumors. Most cases with *MYC* and *BCL2* rearrangements are of GCB origin, whereas most cases with *BCL6* rearrangements are of ABC origin. This category includes DH lymphomas, which involve *MYC* and *BCL2* or *MYC* and *BCL6*, as well as THLs that involve *MYC*, *BCL2*, and *BCL6*. When translocated, *MYC* may have an *IG* or non-*IG* partner gene, with the former associated with an inferior outcome. In a large study, 7.9% of tumors with DLBCL morphology were assigned to HGBL-DHL/THL, composing 13.3% of GCB and 1.7% of ABC DLBCL.[30]

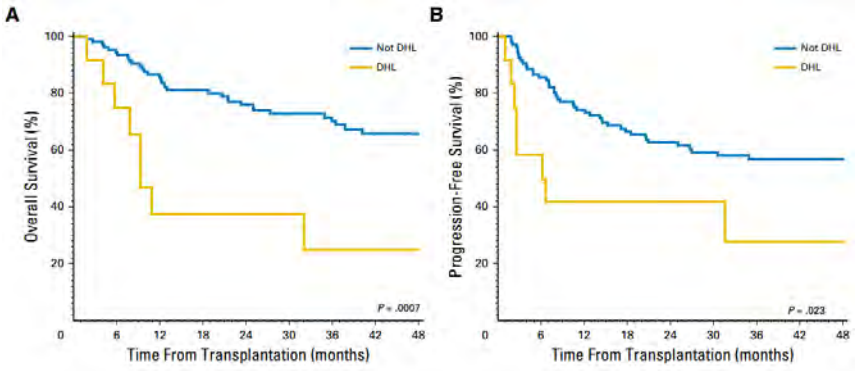
Kieron Dunleavy, Double-hit lymphoma: optimizing therapy, Hematology Am Soc Hematol Educ Program, 2021,

VOLUME 35 · NUMBER 1 · JANUARY 1, 2017

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Relapsed or Refractory Double-Expressor and Double-Hit Lymphomas Have Inferior Progression-Free Survival After Autologous Stem-Cell Transplantation

Alex F. Herrera, Matthew Mei, Lawrence Low, Haesook T. Kim, Gabriel K. Griffin, Joo Y. Song, Reid W. Merryman, Victoria Bedell, Christine Pak, Heather Sun, Tanya Paris, Tracey Stiller, Jennifer R. Brown, Lihua E. Budde, Wing C. Chan, Robert Chen, Matthew S. Davids, Arnold S. Freedman, David C. Fisher, Eric D. Jacobsen, Caron A. Jacobson, Ann S. LaCasce, Joyce Murata-Collins, Auayporn P. Nademanee, Joycelynne M. Palmer, German A. Pihan, Raju Pillai, Leslie Popplewell, Tanya Siddiqi, Aliyah R. Sohani, Jasmine Zain, Steven T. Rosen, Larry W. Kwak, David M. Weinstock, Stephen J. Forman, Dennis D. Weisenburger, Young Kim, Scott J. Rodig, Amrita Krishnan, and Philippe Armand



154 Double Hit/Double Expressor Lymphomas: A Multicenter Analysis of Survival Outcomes with CD19-Directed CAR T-Cell Therapy

Program: Oral and Poster Abstracts
Type: Oral
Session: 627. Aggressive Lymphomas: Clinical and Epidemiological: Treatment of CNS Lymphoma, Neurologic Toxicities, and Relapsed/Refractory DLBCL
Hematology Disease Topics & Pathways:
Research, Biological therapies, adult, Lymphomas, non-Hodgkin lymphoma, Clinical Research, B Cell lymphoma, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Diseases, real-world evidence, aggressive lymphoma, Therapies, Lymphoid Malignancies, Study Population, Human

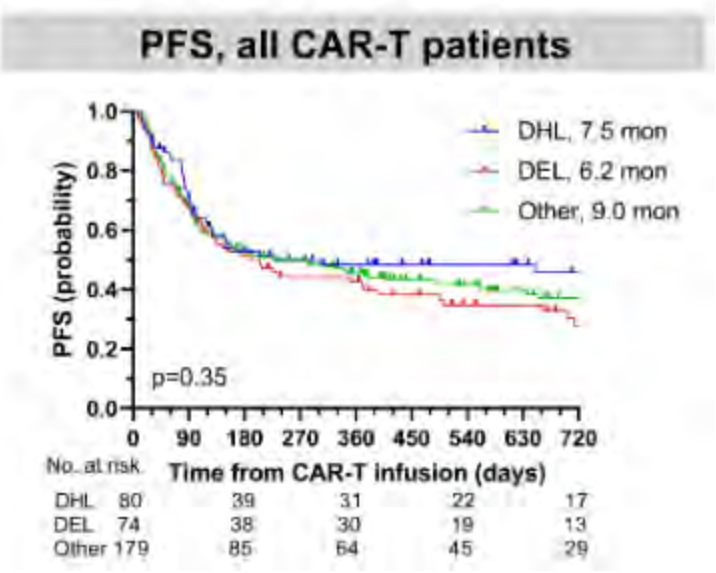
Saturday, December 10, 2022: 12:45 PM

Joanna Zurko, MD[1], Geoffrey Shouse, PhD, DO[2], Pallawi Torka, MD[3], Tamara K. Moyo, MD, PhD[4*], Jason T. Romancik, MD[5], Imran A. Nizamuddin, MD[6], Kaitlin Annunzio, DO[7], Jieqi Liu, MD[8*], Stefan K. Barta, MD[9], Robert Ferdman, MD[3*], Rahul Bhansali, MD[10*], Jonathon B. Cohen, MD, MS[11], Sayan Mullick Chowdhury, DO, PhD[12*], Nirav N. Shah, MD[13], Elyse I. Harris, MD[14], Vaishalee P. Kenkre, MD[1], McKenzie Sorrell, DO[15], Brian T. Hess, MD[15], Deborah M. Stephens, DO[16], Lindsey A. Fitzgerald, MD[17], Thomas A. Ollila, MD[18], Ishan Roy[19*], Shuo Ma, MD[20], Jane N. Winter, MD[21], Barbara Pro, MD[22], Jonathan Moreira, MD[23], Leo I. Gordon, MD[23], Alexey V Danilov, MD[24], Andrew M. Evens, DO, MBA, MMSc[25], Narendranath Epperla, MD, MS[26] and Reem Karmali, MD, MSc[27]

- **536 pts from 13 US centers**
  - **408 pts included (DHL=80; non-DHL=328)**

	DHL	Non-DHL	P-value
ORR	69%	66%	0.7
mPFS	7.5 months	6.2 months	0.2
mOS	NR	21 months	0.6

Predictor of inferior PFS on multivariable analysis
- >2 lines of therapy pre-apheresis
- Bridging therapy
- Elevated LDH at apheresis

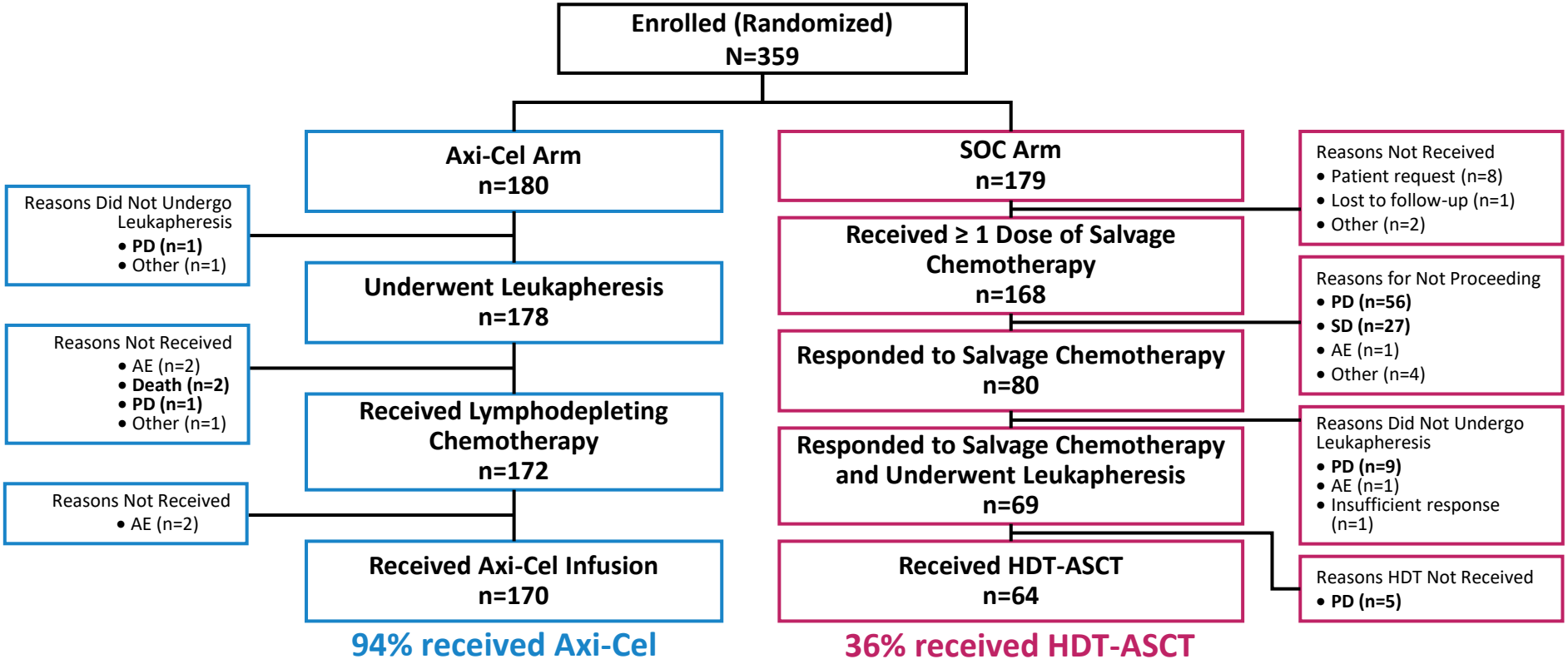


Zurko J, et al. Am Soc Hematol 2022 (Abs 154)

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)

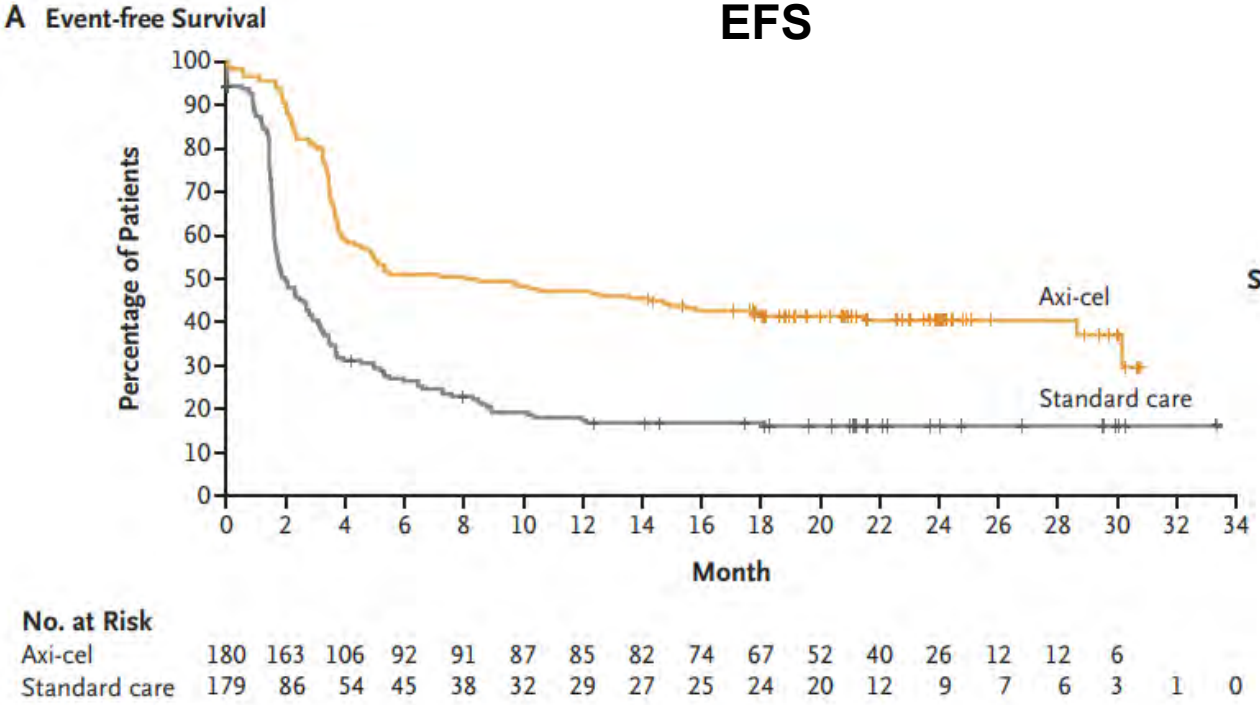
Patient Disposition: Nearly 3× as Many Axi-Cel Patients Received Definitive Therapy Versus SOC Patients



ASH Plenary presentation: courtesy Dr. Frederick Locke

Primary endpoint: EFS

EFS



	No. of Patients	Median Event-free Survival (95% CI)
		mo
Axi-cel	180	8.3 (4.5–15.8)
Standard Care	179	2.0 (1.6–2.8)

Stratified hazard ratio for event or death, 0.40 (95% CI, 0.31–0.51)
P<0.001

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

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

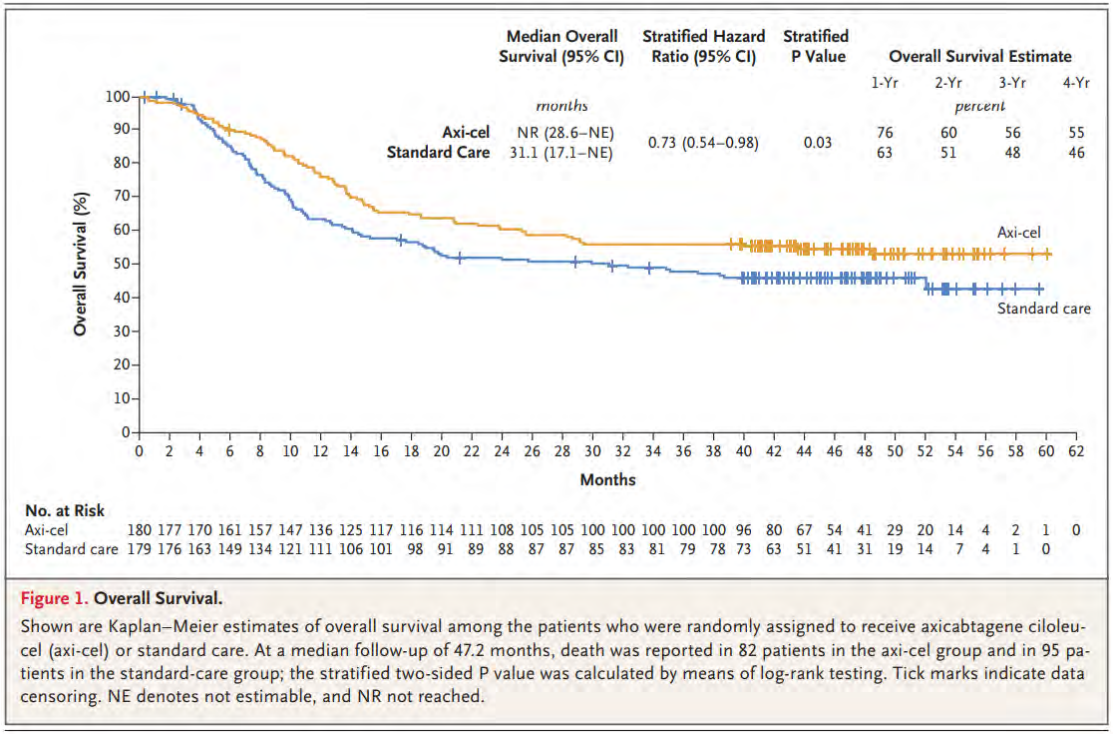


Figure 1. Overall Survival.

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.

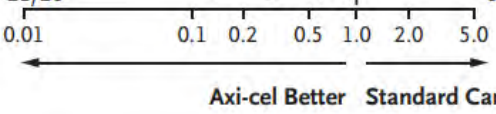
Westin JR, et al. N Engl J Med. 2023; Jun 5. doi: 10.1056/NEJMoa2301665. Online ahead of print

MAYO CLINIC

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)



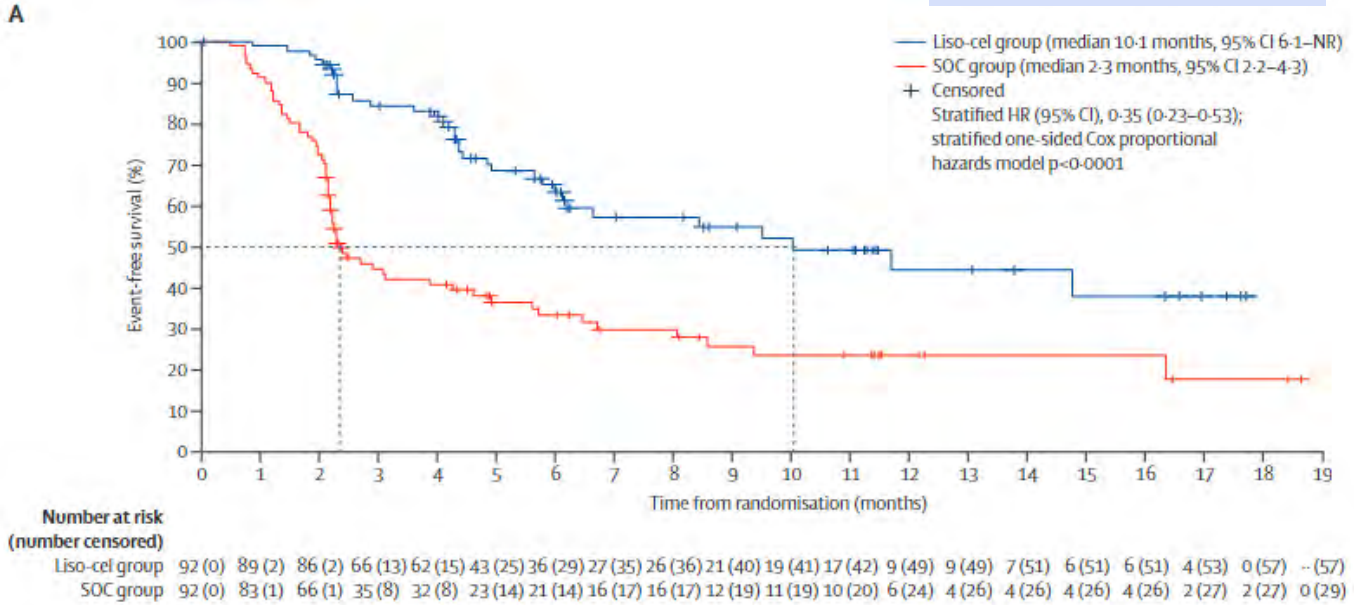
Locke FL, et al. N Engl J Med. 2022;386(7):640-654

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)

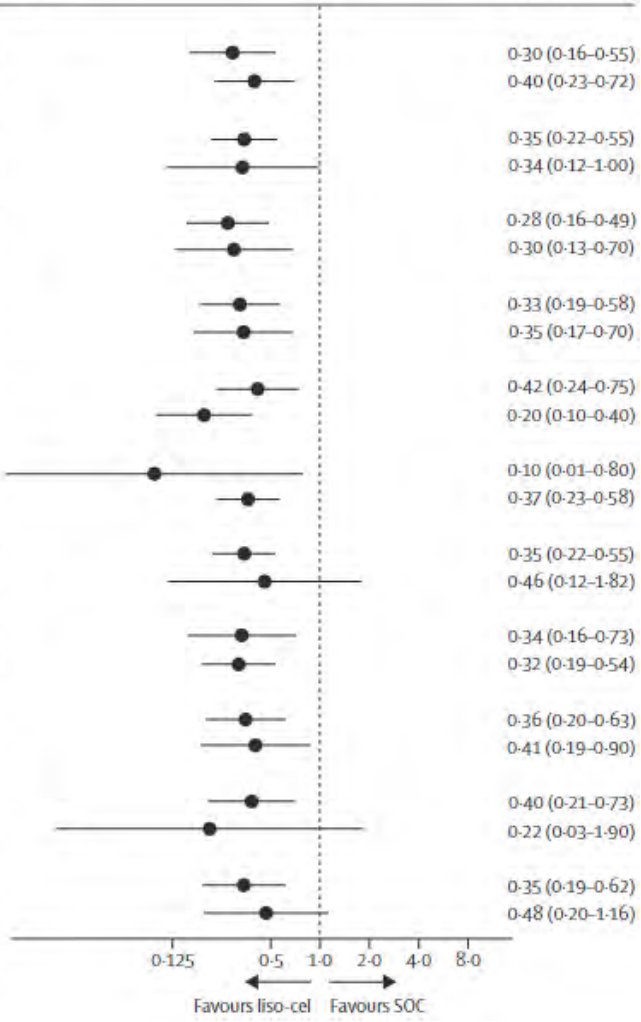


Kamdar M, et al. Lancet 2022; 399: 2294–308

TRANSFORM: subgroup analysis

B

	Liso-cel group Events/patients (%)	SOC group Events/patients (%)	Stratified HR (95% CI)
sAAIPI			
0 or 1	16/56 (29%)	32/55 (58%)	0·30 (0·16–0·55)
2 or 3	19/36 (53%)	31/37 (84%)	0·40 (0·23–0·72)
Previous response status			
Refractory	30/67 (45%)	52/68 (76%)	0·35 (0·22–0·55)
Relapse to last previous therapy	5/25 (20%)	11/24 (46%)	0·34 (0·12–1·00)
Age group, years			
<65	17/56 (30%)	46/67 (69%)	0·28 (0·16–0·49)
≥65 to <75	18/36 (50%)	15/23 (65%)	0·30 (0·13–0·70)
Sex			
Male	19/44 (43%)	44/61 (72%)	0·33 (0·19–0·58)
Female	16/48 (33%)	19/31 (61%)	0·35 (0·17–0·70)
ECOG performance status (at screening)			
0	18/48 (38%)	36/57 (63%)	0·42 (0·24–0·75)
1	17/44 (39%)	27/35 (77%)	0·20 (0·10–0·40)
SPD, cm²			
>50	3/10 (30%)	9/10 (90%)	0·10 (0·01–0·80)
≤50	29/77 (38%)	53/76 (70%)	0·37 (0·23–0·58)
Lactate dehydrogenase, units per L			
<500	30/79 (38%)	53/81 (65%)	0·35 (0·22–0·55)
≥500	4/10 (40%)	10/11 (91%)	0·46 (0·12–1·82)
Previous chemotherapy response status			
Chemo refractory (progressive or stable disease)	15/25 (60%)	16/18 (89%)	0·34 (0·16–0·73)
Chemo sensitive (partial or complete response)	20/67 (30%)	47/74 (64%)	0·32 (0·19–0·54)
NHL type			
DLBCL	21/60 (35%)	36/57 (63%)	0·36 (0·20–0·63)
HGBCL	14/22 (64%)	19/21 (90%)	0·41 (0·19–0·90)
DLBCL subtype			
DLBCL NOS de novo	19/53 (36%)	30/49 (61%)	0·40 (0·21–0·73)
DLBCL transformed from indolent NHL	2/7 (29%)	6/8 (75%)	0·22 (0·03–1·90)
DLBCL subtype based on cell of origin			
GCB	21/45 (47%)	29/40 (73%)	0·35 (0·19–0·62)
ABC, non-GCB	7/21 (33%)	22/29 (76%)	0·48 (0·20–1·16)



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

CIBMTR analysis: CAR-T vs. auto-HCT in chemosensitive disease (PR)

blood
Regular Article

LYMPHOID NEOPLASIA

Autologous transplant vs chimeric antigen receptor T-cell therapy for relapsed DLBCL in partial remission

Mazyar Shadman,[1,2] Marcelo Pasquini,[3] Kwang Woo Ahn,[3,4] Yue Chen,[3] Cameron J. Turtle,[1,2] Peiman Hematti,[5] Jonathon B. Cohen,[6] Farhad Khimani,[7] Siddhartha Ganguly,[8] Reid W. Merryman,[9] Jean A. Yared,[10] Frederick L. Locke,[7] Nausheen Ahmed,[8] Pashna N. Munshi,[11] Amer Beitinjaneh,[12] Patrick M. Reagan,[13] Alex F. Herrera,[14] Craig S. Sauter,[15,16] Mohamed A. Kharfan-Dabaja,[17] and Mehdi Hamadani[3,18]

- Patients in partial response (PR)
  - CAR T=145
  - Auto-HCT=266
- Median age, years
  - CAR T= 60 (24-91) yrs
  - Auto-HCT=58 (18-80), p=0.07
- Median lines of prior therapies
  - CAR T= 3 (2-11)
  - Auto-HCT=2 (1-6), **p<0.001**

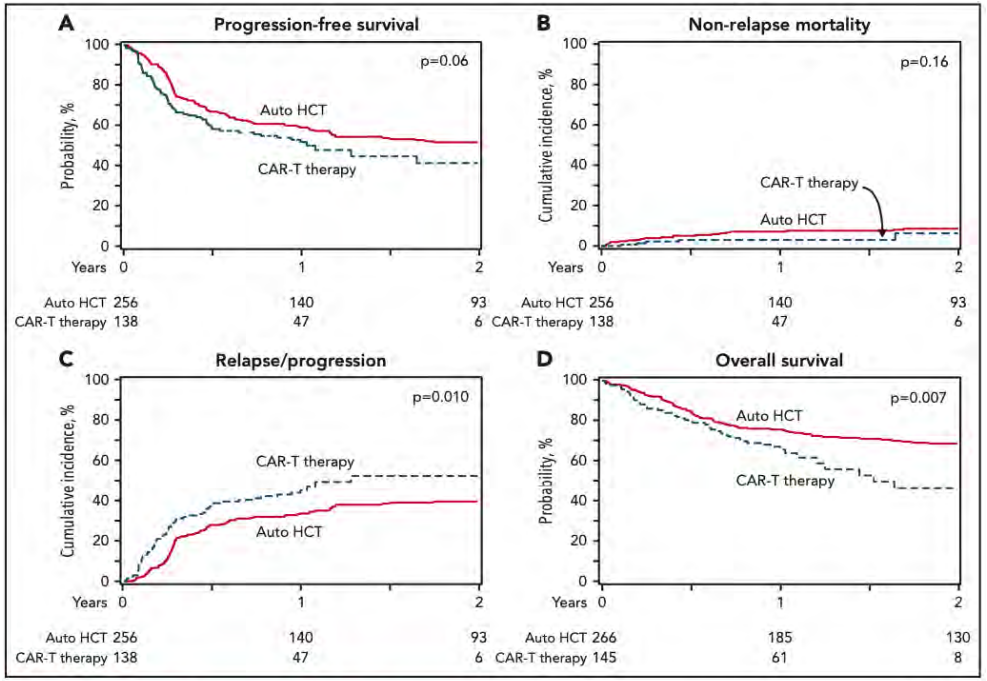


Figure 1. Auto-HCT vs CAR-T in patients with DLBCL in PR (all patients). (A) Progression-free survival. (B) Nonrelapse mortality. (C) Progression/relapse. (D) Overall survival.

Shadman M, et al. Blood. 2022; 139(9):1330-39

CIBMTR analysis: CAR-T vs. auto-HCT in complete remission (CR)

781 Autologous Transplant (auto-HCT) Is Associated with Improved Clinical Outcomes Compared to CAR-T Therapy in Patients (pts) with Large B-Cell Lymphoma (LBCL) Achieving a Complete Remission

Program: Oral and Poster Abstracts
Type: Oral
Session: 731. Autologous Transplantation: Clinical and Epidemiological: Role of Autologous Stem Cell Transplantation in Multiple Myeloma and Lymphomas: A Therapeutic Approach

Monday, December 11, 2023: 10:30 AM

Mazyar Shadman, MD, MPH[1,2], Kwang Wooahn, PhD[3], Manmeet Kaur[4*], Mohamed A. Kharfan-Dabaja, MD, MBA[5], Alex F. Herrera, MD[6], Craig S Sauter, MD[7] and Mehdi Hamadani, MD[8]*

Univariate analysis

	CAR T	Auto-HCT	P-value
Relapse (2-year)	**48%**	27.8% ↓	<0.001
PFS (2-year)	**47.8%**	66.2% ↑	<0.001
OS (2-year)	**66.5%**	78.9% ↑	0.037

Table-1: Selected baseline characteristics

	CAR-T	auto-HCT	P-value
Age, years	64	59	0.14
Extra-nodal disease	58%	63%	0.37
Refractory disease to first-line	29%	20%	0.22
Prior lines of therapy, n	3	2	**<0.01**
Early treatment failure (within 12 months)	72%	58%	**0.02**
Elevated LDH before treatment	37%	31%	**0.04**
high-grade B-cell lymphoma with MYC and BCL2 or BCL6 rearrangement	14%	27%	**0.03**

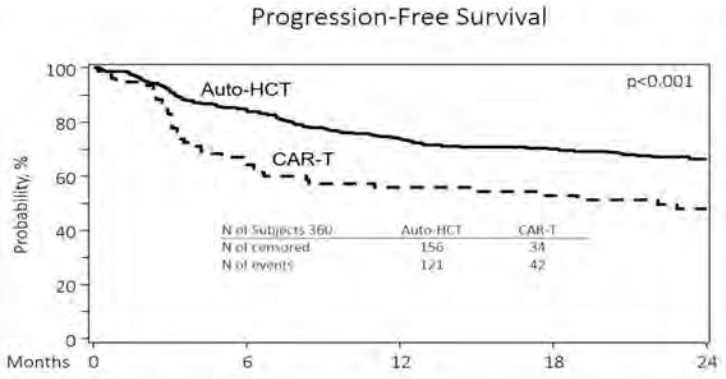
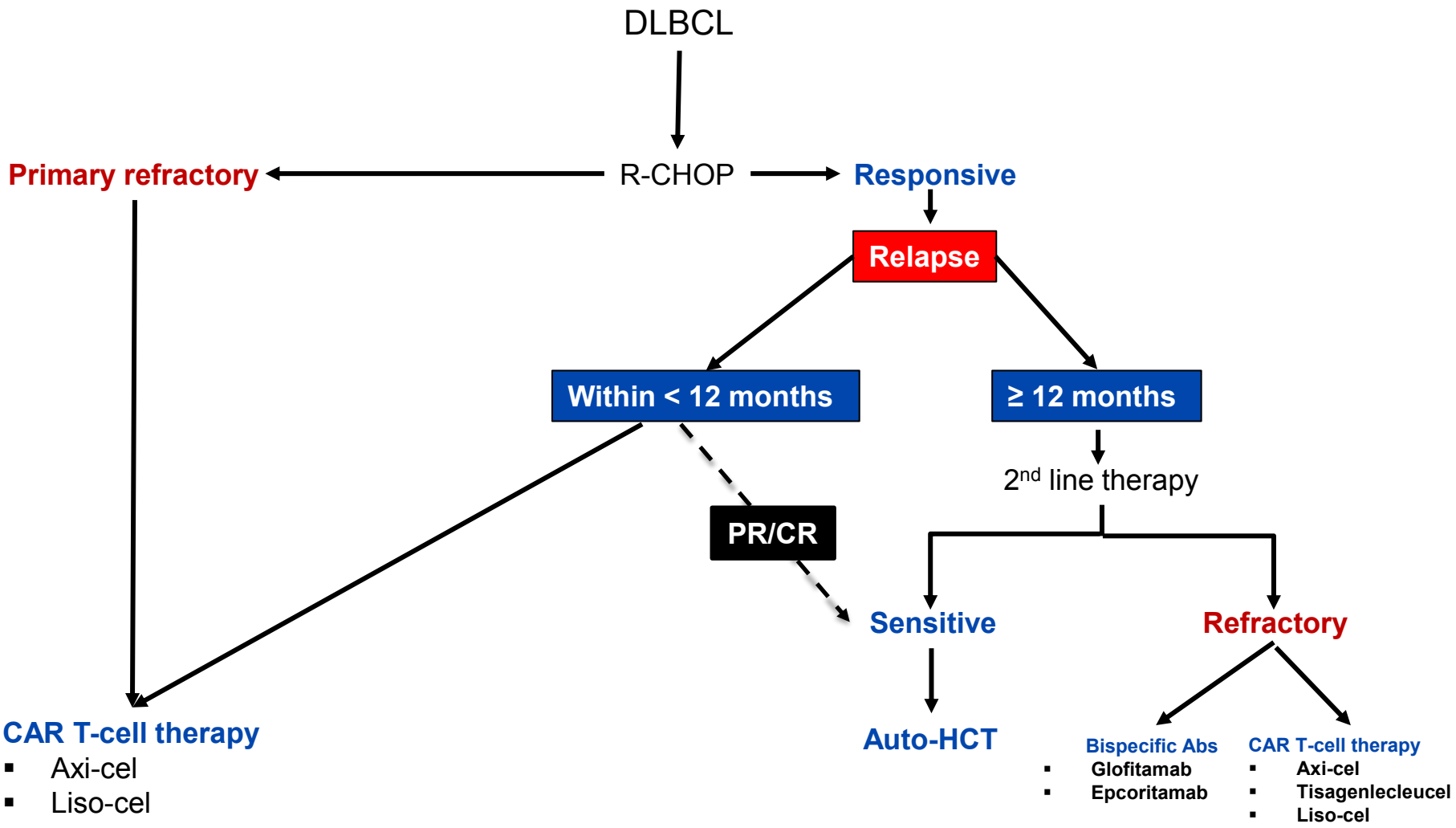


Figure-1: PFS in pts with LBCL who received auto-HCT vs. CAR-T while in CR

MAYO CLINIC

Shadman, et al. Am Soc Hematol 2023 (Abs 781)

Proposed treatment algorithm in DLBCL



ZUMA-2: Baseline characteristics

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)

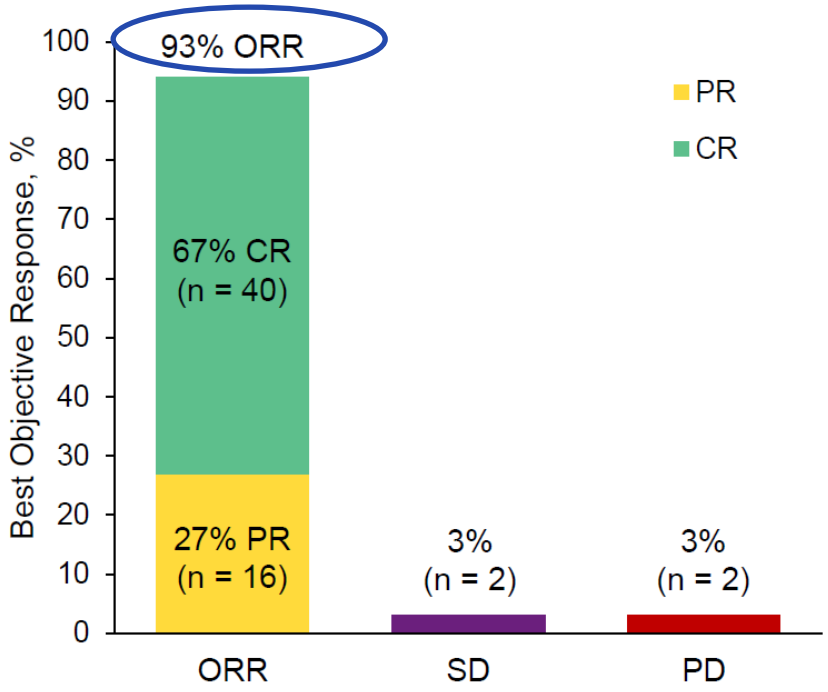
MAYO CLINIC

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.

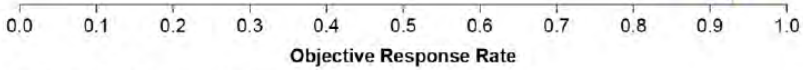
Wang M, et al. ASH 2019. Abs 754
Wang M, et al. NEJM. 2020. 382:1331

ZUMA-2

ASH 2019. Abs 754

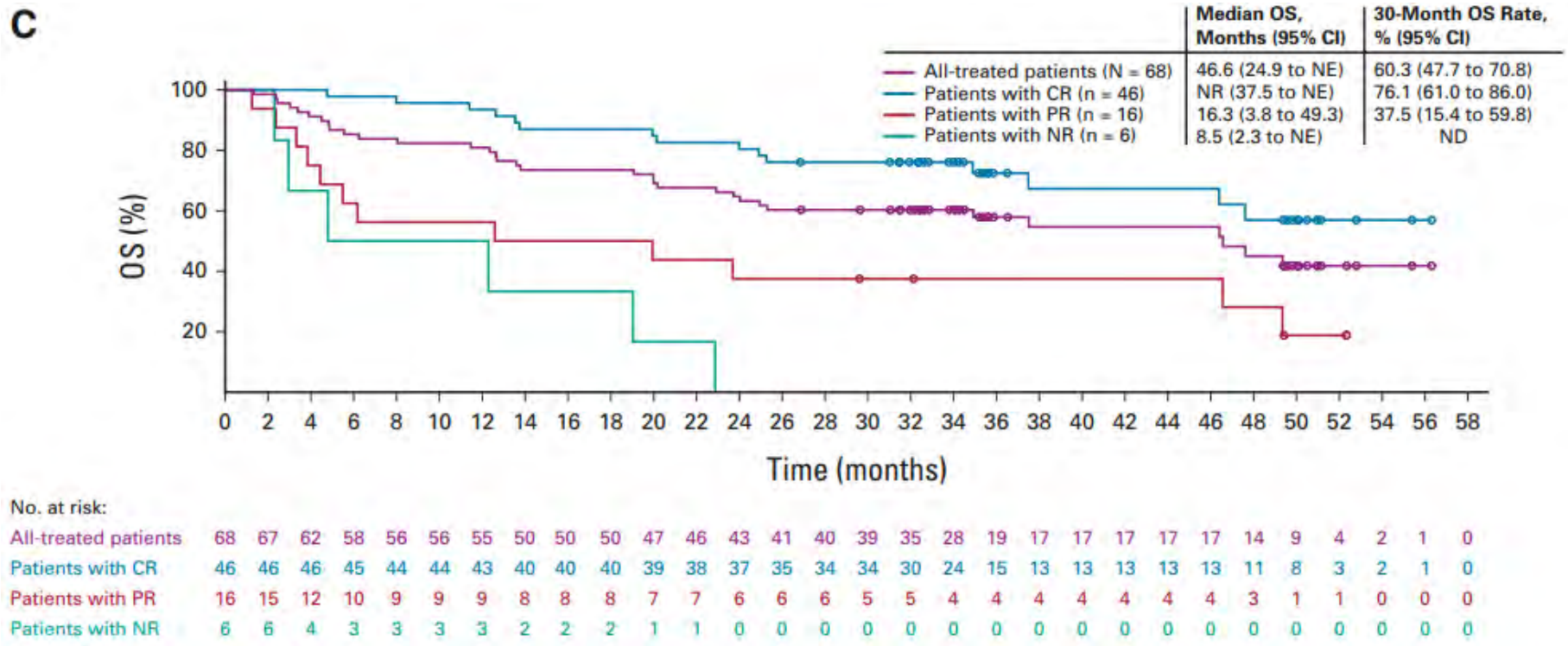
ORR Was Consistent Across Key Subgroups

	Evaluable Patients	Responding Patients	ORR (95% CI)
Overall	60	56	0.93 (0.84, 0.98)
Age			
< 65 Years	28	26	0.93 (0.76, 0.99)
≥ 65 Years	32	30	0.94 (0.79, 0.99)
MCL morphology			
Classical MCL	35	32	0.91 (0.77, 0.98)
Pleomorphic	4	4	1.00 (0.40, 1.00)
Blastoid	14	13	0.93 (0.66, 1.00)
Ki-67 index			
< 50%	14	14	1.00 (0.77, 1.00)
≥ 50%	32	30	0.94 (0.79, 0.99)
Disease stage			
I-II	2	2	1.00 (0.16, 1.00)
III-IV	58	54	0.93 (0.83, 0.98)
Simplified MIPI			
Low risk	25	23	0.92 (0.74, 0.99)
Intermediate/high risk	33	31	0.94 (0.80, 0.99)
Steroid use for AE management			
Yes	35	33	0.94 (0.81, 0.99)
No	25	23	0.92 (0.74, 0.99)
Tocilizumab use			
Yes	42	40	0.95 (0.84, 0.99)
No	18	16	0.89 (0.65, 0.99)
Bridging therapy use			
Yes	21	19	0.90 (0.70, 0.99)
No	39	37	0.95 (0.83, 0.99)



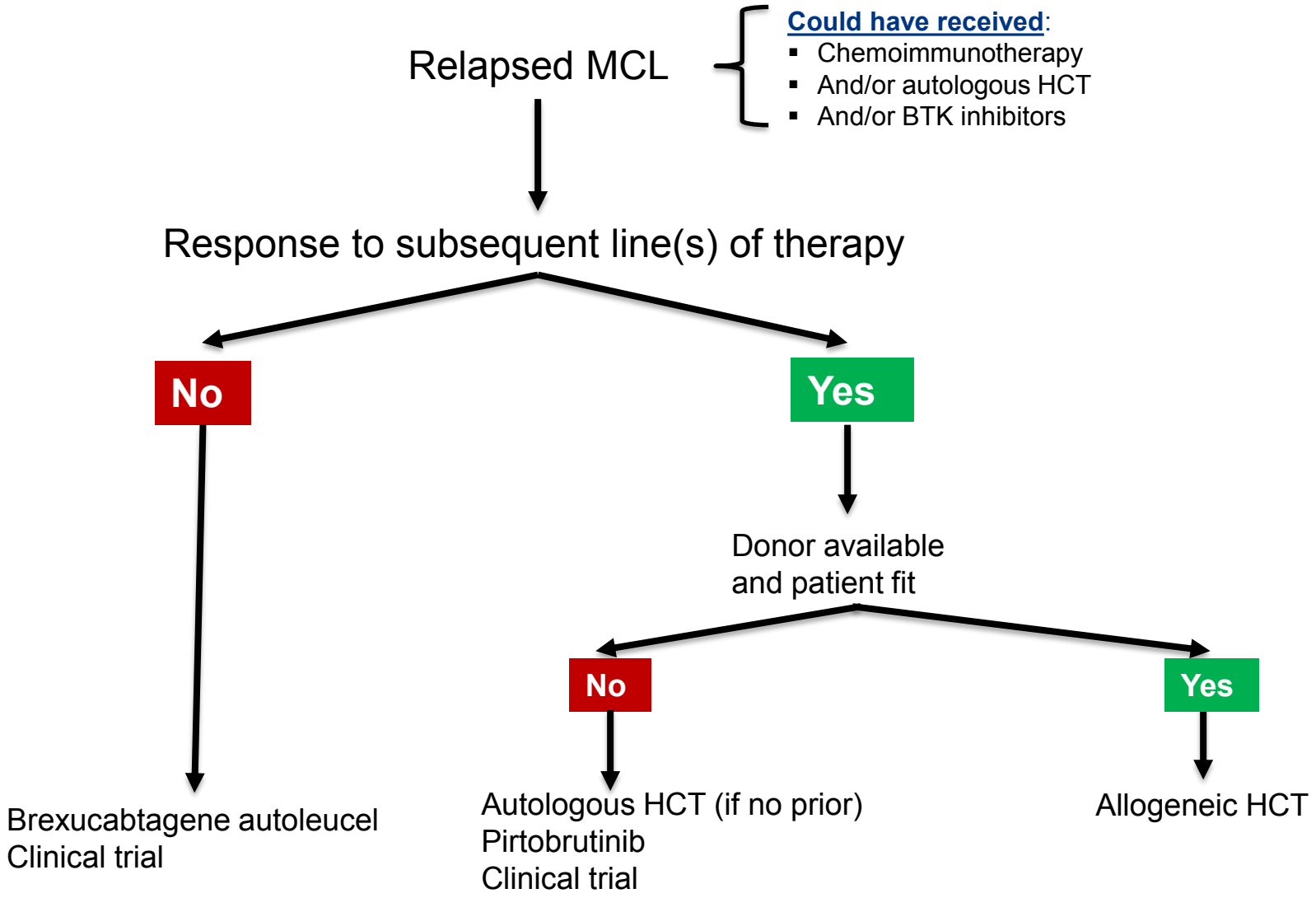
CR, complete response; MCL, mantle cell lymphoma; MIPI, MCL International Prognostic Index; ORR, objective response rate.

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



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

Proposed algorithm for relapsed MCL



Follicular lymphoma

- ~5% of all hematologic neoplasms
- Marked heterogeneity, several morphological variants and specific subtypes
- Usually indolent, with a median overall survival of >15 years
- Yet, remains incurable
- ~20% progress or relapse within 2 years of treatment initiation → **dismal prognosis (POD24)**

Carbone A, et al. Nat Rev Dis Primers. 2019; 5(1):83

Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial

Caron A Jacobson, Julio C Chavez, Alison R Sehgal, Basem M William, Javier Munoz, Gilles Salles, Pashna N Munshi, Carla Casulo, David G Maloney, Sven de Vos, Ran Reshef, Lori A Leslie, Ibrahim Yakoub-Agha, Olalekan O Oluwole, Henry Chi Hang Fung, Joseph Rosenblatt, John M Rossi, Lovely Goyal, Vicki Plaks, Yin Yang, Remus Vezan, Mauro P Avanzi, Sattva S Neelapu

	Patients with follicular lymphoma (n=124)	Patients with marginal zone lymphoma (n=24)	All patients (N=148)
Age, years			
Median	60 (53–67)	65 (61–72)	61 (53–68)
≥65	38 (31%)	13 (54%)	51 (34%)
Sex			
Female	51 (41%)	13 (54%)	64 (43%)
Male	73 (59%)	11 (46%)	84 (57%)
Race			
Asian	2 (2%)	0	2 (1%)
Black or African American	4 (3%)	1 (4%)	5 (3%)
White	115 (93%)	22 (92%)	137 (93%)
Other or missing	3 (3%)	1 (4%)	4 (3%)
Ethnicity			
Hispanic or Latino	6 (5%)	2 (8%)	8 (5%)
Not Hispanic or Latino	118 (95%)	21 (88%)	139 (94%)
Missing	0	1 (4%)	1 (1%)
Follicular lymphoma histological category			
Grade 1	33 (27%)	NA	NA
Grade 2	61 (49%)	NA	NA
Grade 3a	30 (24%)	NA	NA
Marginal zone lymphoma histological category			
Nodal	NA	7 (29%)	NA
Extranodal	NA	17 (71%)	NA
ECOG performance status			
0	78 (63%)	14 (58%)	92 (62%)
1	46 (37%)	10 (42%)	56 (38%)
Disease stage			
Stage I–II	18 (15%)	2 (8%)	20 (14%)
Stage III	45 (36%)	3 (13%)	48 (32%)
Stage IV	61 (49%)	19 (79%)	80 (54%)
Follicular Lymphoma International Prognostic Index			
Low risk (0–1)	22 (18%)	NA	NA
Intermediate risk (2)	48 (39%)	NA	NA
High risk (≥3)	54 (44%)	NA	NA
High tumour bulk (GELF criteria)*	64 (52%)	10 (42%)	74 (50%)
Sum of product diameters, mm²	2790 (1443–4936)	1720 (861–3348)	2723 (1391–4219)

(Table 1 continues in next column)

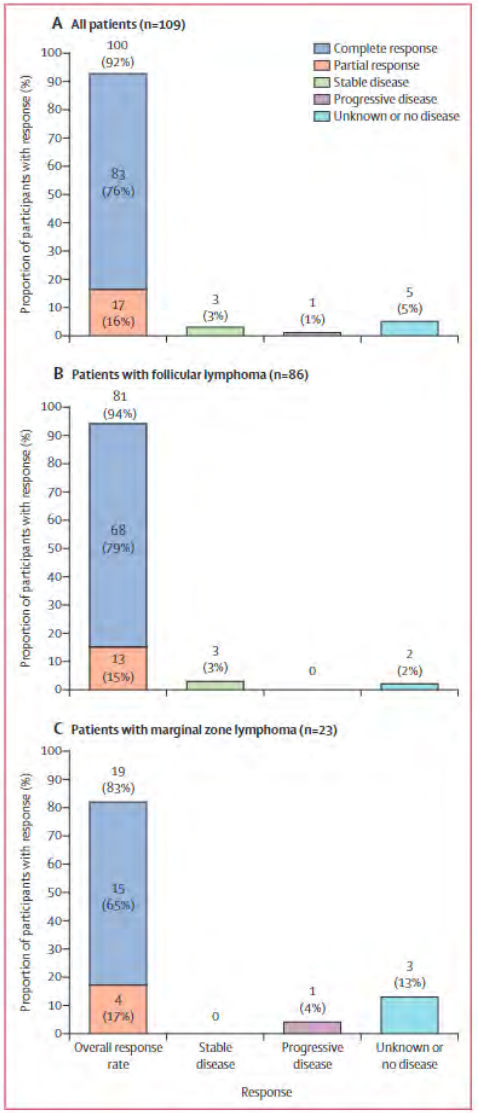
	Patients with follicular lymphoma (n=124)	Patients with marginal zone lymphoma (n=24)	All patients (N=148)
(Continued from previous column)			
Previous lines of therapy			
Median†	3 (2–4)	3 (2–5)	3 (2–4)
≥3 previous lines of therapy	78 (63%)	16 (67%)	94 (64%)
Previous PI3K inhibitor	34 (27%)	9 (38%)	43 (29%)
Previous autologous stem-cell transplantation	30 (24%)	3 (13%)	33 (22%)
Previous anti-CD20 mAb and alkylating agent	123 (99%)	23 (96%)	146 (99%)
Previous anti-CD20 mAb single agent	39 (31%)	10 (42%)	49 (33%)
Previous alkylating single agent	16 (13%)	6 (25%)	22 (15%)
Previous lenalidomide	38 (31%)	8 (33%)	46 (31%)
Relapsed or refractory subgroup‡			
Refractory to last previous therapy	84 (68%)	18 (75%)	102 (69%)
POD24 from initiating first anti-CD20 mAb-containing therapy§	68 (55%)	13 (57%)	81 (55%)
Positive CD19 status¶	93/103 (90%)	15/16 (94%)	108/119 (91%)
Lymphoma present in bone marrow‖	33 (27%)	11 (46%)	44 (30%)

1ry endpoint: ORR by IRRC

Median F/U=17.5 months

Median PFS= Not reached for FL; 12 months for MZL

Median OS= Not reached for FL and MZL



Jacobson CA, et al. Lancet Oncol. 2022 Jan;23(1):91-103

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

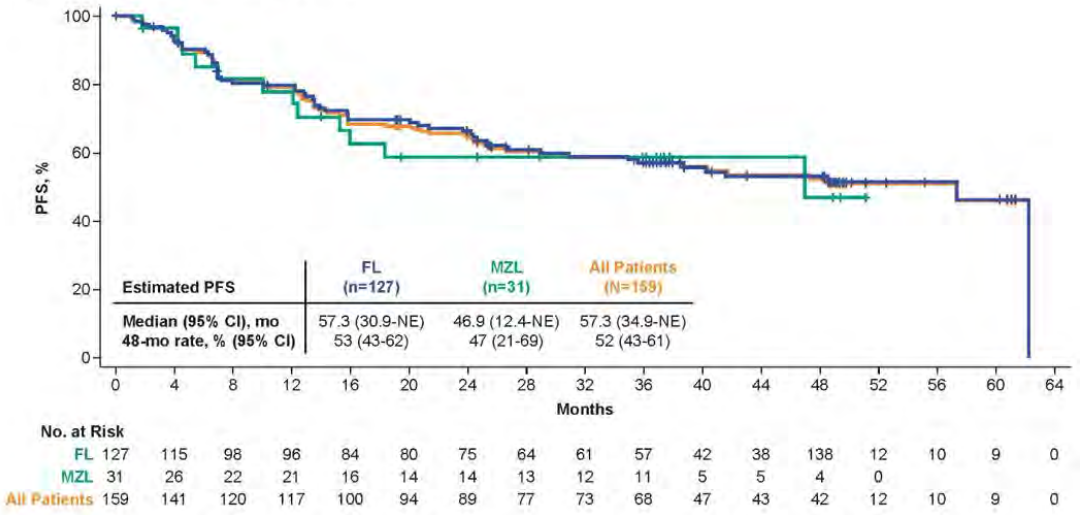
Hematology Disease Topics & Pathways:

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*[6,7], *Pashna N. Munshi, MD*[8], *Carla Casulo, MD*[9], *David G Maloney, MD, PhD*[5], *Sven de Vos, MD, PhD*[10,11], *Ran Reshef, MD, MSc*[12], *Lori A. Leslie, MD*[13], *Olalekan O. Oluwole, MBBS*[13], *Ibrahim Yakoub-Agha, MD, PhD*[14,15], *Rashmi Khanal, MD, MBBS*[16], *Joseph D. Rosenblatt, MD*[16,17], *Weixin Peng, MS*[17,18], *Christine Lui, MS*[17,18], *Jacob Wulff, DrPH*[17,18], *Rhine R. Shen, PhD*[17,18], *Soumya Poddar, PhD*[17,18], *Andrew Lee, MD*[17,18], *Harry Miao, MD, PhD*[17], *Olga Nikolajeva, MD*[17,18] *and Caron A Jacobson, MD, MMSc*[19]

Figure 1. Progression-Free Survival



Estimated PFS	FL (n=127)	MZL (n=31)	All Patients (N=159)
Median (95% CI), mo	57.3 (30.9-NE)	46.9 (12.4-NE)	57.3 (34.9-NE)
48-mo rate, % (95% CI)	53 (43-62)	47 (21-69)	52 (43-61)

No. at Risk																	
FL	127	115	98	96	84	80	75	64	61	57	42	38	138	12	10	9	0
MZL	31	26	22	21	16	14	14	13	12	11	5	5	4	0			
All Patients	159	141	120	117	100	94	89	77	73	68	47	43	42	12	10	9	0

- 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%**

MAYO CLINIC

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

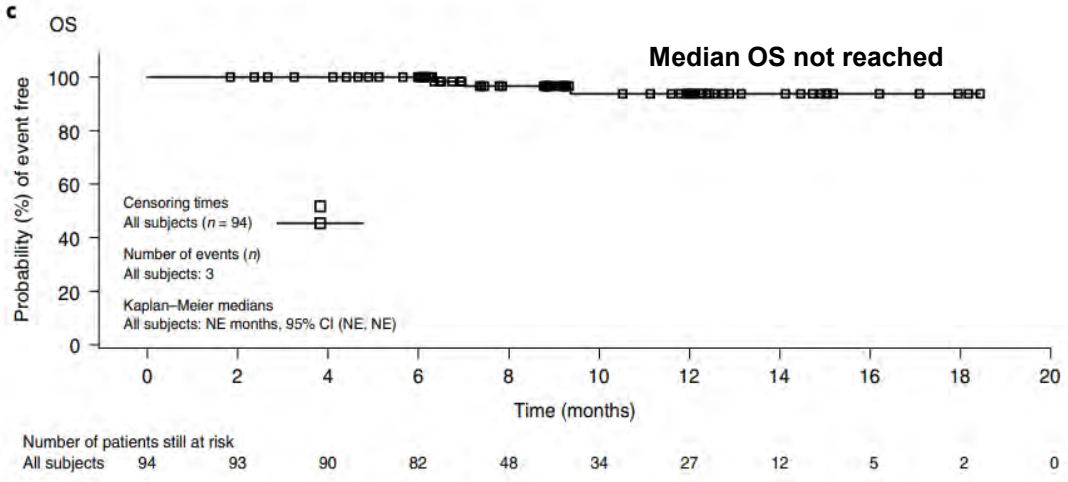
Nathan Hale Fowler[1,2]✉, Michael Dickinson[3], Martin Dreyling[4], Joaquin Martinez-Lopez[5], Arne Kolstad[6], Jason Butler[7], Monalisa Ghosh[8], Leslie Popplewell[9], Julio C. Chavez[10], Emmanuel Bachy[11], Koji Kato[12], Hideo Harigae[13], Marie José Kersten[14], Charalambos Andreadis[15], Peter 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]

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.

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



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.

608 Long-Term Clinical Outcomes and Correlative Efficacy Analyses in Patients (Pts) with Relapsed/Refractory Follicular Lymphoma (r/r FL) Treated with Tisagenlecleucel in the Elara Trial

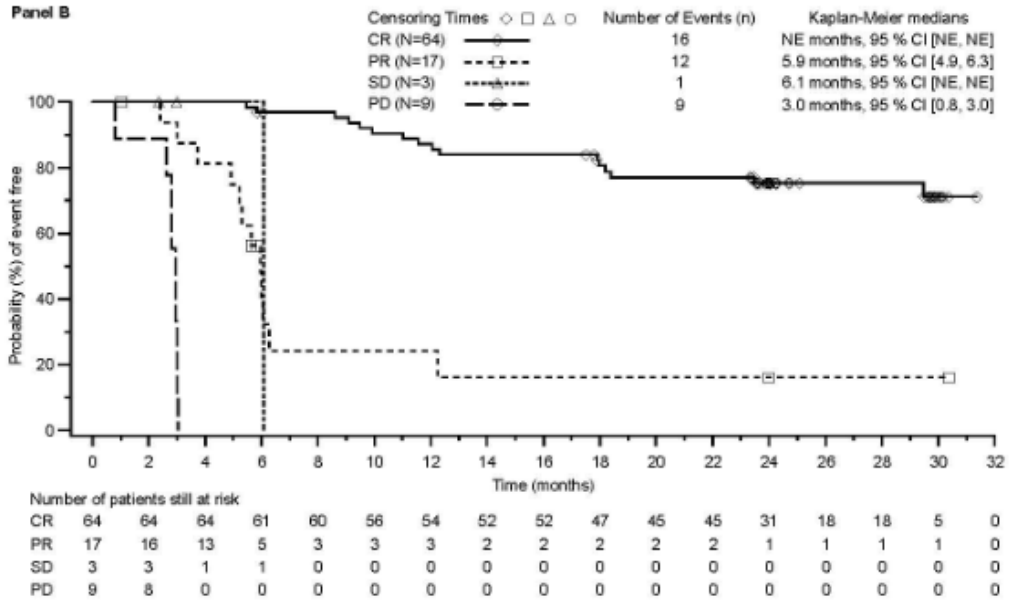
Program: Oral and Poster Abstracts
Type: Oral
Session: 623. Mantle Cell, Follicular, and Other Indolent B Cell Lymphomas: Clinical and Epidemiological IV
Hematology Disease Topics & Pathways:
Research, clinical trials, Biological therapies, Lymphomas, non-Hodgkin lymphoma, Clinical Research, Chimeric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

Sunday, December 11, 2022: 4:45 PM

Martin Dreyling, MD[1], *Michael Dickinson, MD*[2], *Joaquin Martinez Lopez*[3*], *Arne Kolstad, MD, PhD*[4*], *Jason P Butler, MBBS, MMedSc*[5], *Monalisa Ghosh, MD*[6], *Leslie L. Popplewell, MD, FACP, MPH*[7], *Julio Chavez*[8], *Emmanuel Bachy, MD, PhD*[9*], *Koji Kato, MD, PhD*[10*], *Hideo Harigae, MD, PhD*[11], *Marie Jose Kersten, MD, PhD*[12,13], *Charalambos Andreadis, MD, MSCE*[14*], *Peter A. Riedell, MD*[15*], *Phoebe Joy Ho, MBBS(Syd) DPhil(Oxon) FRACP FRCPA FFSc(RCPA)*[16*], *Jose A. Perez-Simon, MD, PhD*[17], *Andy Chen, MD, PhD*[18], *Loretta J. Nastoupil, MD*[19], *Bastian von Tresckow, MD*[20], *Andrés J M Ferreri, MD*[21], *Takanori Teshima, M.D., Ph.D.*[22], *Piers E.M. Patten*[23,24*], *Joseph P. McGuirk, DO*[25], *Andreas Petzer, MD*[26], *Fritz Offner, MD, PhD*[27], *Andreas Viardot, MD*[28], *Pier Luigi Zinzani, MD, PhD*[29,30], *Ram Malladi, MD*[31*], *Ines Paule*[32*], *Aiesha Zia*[32*], *Rakesh Awasthi, PhD*[33*], *Xia Han, MS*[34*], *Davide Germano*[32*], *Darragh O'Donovan, PhD*[35*], *Roberto Ramos, MD*[34*], *Aisha Masood, MD*[34], *Catherine Thieblemont, MD, PhD*[36], *Nathan H. Fowler, MD*[37] *and Stephen J. Schuster, MD*[38*]

- 94 pts evaluable for efficacy
- Median F/U= 28.9 months
- Complete response rate=68%
- Overall response rate= 86.2%
- Median PFS= Not reached
- Estimated 2-year PFS=**57.4%**
- Estimated 2-year OS=**87.7%**

PFS by best overall response



Dreyling M, et al. Am Soc Hematol 2022 (Abs 608)

2121 Comparative Effectiveness of Axicabtagene Ciloleucel Vs Historical Standard-of-Care in Patients with Relapsed or Refractory Follicular Lymphoma: An Analysis of CIBMTR and SCHOLAR-5 Data

Program: Oral and Poster Abstracts
Session: 705. Cellular Immunotherapies: Late Phase and Commercially Available Therapies: Poster I
Hematology Disease Topics & Pathways:
Research, Lymphomas, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Clinical Research, Diseases, real-world evidence, Lymphoid Malignancies
Saturday, December 9, 2023, 5:30 PM-7:30 PM

Swetha Kambhampati, MD[1], *Hai-Lin Wang, MPH*[2], *Jiali Yan, MS*[2], *Alex F. Herrera, MD*[3], *Matthew J. Frank, MD, PhD*[4], *Leslie L. Popplewell, MD, FACP, MPH*[1], *Nausheen Ahmed, MD*[3], *Yi Lin, MD, PhD*[4], *Frederick L. Locke, MD*[7], *Paola Ghione, MD, MSEpi*[8], *John G. Gribben, MD, DSc*[9], *Timothy Best*[2], *Christine Fu, PhD*[2], *Sara Beygi, MD*[2], *Markqayne D Ray, PharmD*[10], *John Bian, PhD*[2], *Zhen-Huan Hu, MPH*[2], *Fang Sun, MD, PhD*[2], *Marcelo Pasquini, MD, MS*[11] *and Caron A Jacobson, MD, MMSc*[12]

Table 1. Summary Statistics of Weighted Descriptive Analysis and Multivariable Regressions

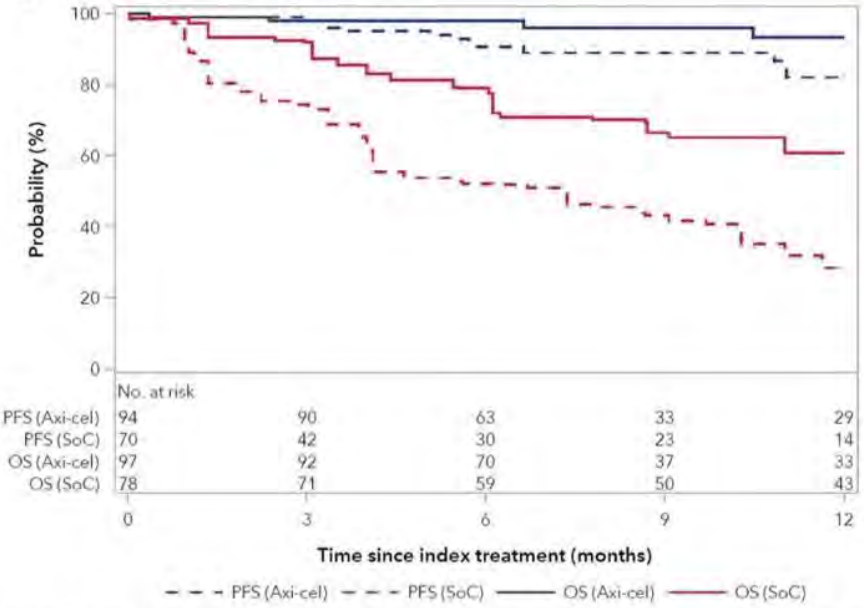
	ORR/CR Rate Analysis[1] N (%)		PFS Analysis[1] N (%)		OS Analysis[1] N (%)	
Treatment (all ages)	**Axi-cel N=256**	**SoC N=177**	**Axi-cel N=251**	**SoC N=171**	**Axi-cel N=256**	**SoC N=175**
Baseline covariates						
Age ≥ 65	97 (38)	88 (50)	94 (37)	84 (49)	97 (38)	87 (50)
Male	149 (58)	95 (53)	146 (58)	92 (54)	149 (58)	94 (54)
Grade 3a (vs 1 or 2)	78 (37)	41 (28)	76 (36)	41 (28)	78 (37)	40 (27)
Elevated LDH at index	62 (34)	48 (36)	61 (34)	46 (35)	62 (34)	48 (36)
Prior ASCT	37 (14)	26 (15)	35 (14)	24 (14)	37 (14)	25 (14)
Time from start of last prior line to index ≥12 months	82 (36)	64 (37)	81 (36)	66 (39)	82 (36)	66 (39)
Refractory to last prior line	168 (79)	144 (81)	163 (79)	134 (79)	168 (79)	141 (81)
	Axi-cel	**SoC**	**Axi-cel vs. SoC (reference)**			
	% (95% CI)	**% (95% CI)**	**OR/HR[2] (95% CI)**			
Effectiveness outcomes						
ORR[3] All ages	92 (88-95)	67 (60-74)	4.93 (2.35-10.34)			
Age ≥ 65	93 (88-98)	65 (54-75)	5.48 (1.80-16.65)			
CR rate[3] All ages	84 (79-88)	37 (30-44)	16.72 (7.03-39.73)			
Age ≥ 65	84 (76-91)	36 (26-47)	8.54 (3.43-21.25)			
PFS at 6 months[4] All ages	88 (83-91)	64 (46-77)	0.41 (0.22-0.77)			
Age ≥ 65	89 (80-94)	60 (41-75)	0.10 (0.03-0.24)			
OS at 6 months[5] All ages	97 (94-99)	85 (73-92)	0.15 (0.06-0.34)			
Age ≥ 65	98 (92-99)	79 (63-89)	0.12 (0.04-0.36)			

[1]Covariates considered in propensity score weighting for all analysis sets: age (< 65 vs ≥ 65 years), sex (male vs female), FL subtype (grade I vs II vs IIIA vs missing), elevated LDH at index (yes vs no vs missing), prior ASCT (yes vs no), time from start of last prior line to index (< 12 vs ≥ 12 months vs missing), response to last prior line of treatment (relapse vs refractory vs missing). [2]OR for ORR and CR rate; HR for PFS and OS. [3]Based on the Response Rate Analysis Set. [4]Based on the Progression Free Survival Analysis Set. [5]Based on the Overall Survival Analysis Set.

ASCT, autologous stem cell transplant; CI, confidence interval; CR, complete response; FL, follicular lymphoma; HR, hazard ratio; LDH, lactate dehydrogenase; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SoC, standard of care.

Historical SOC: chemotherapy, anti-CD20 mAb + chemotherapy, immunomodulatory IMID drugs)

Figure 1. Adjusted Survival Curves within 12 Months post Index in Patients Age ≥ 65 from Weighted Multivariable Cox Regressions



[1]Adjusted PFS and OS was derived from the direct adjusted survival estimates (*Makuch et al. J Chronic Dis.*1982) in the SMR weighted analysis sets. OS, overall survival; PFS, progression-free survival; SoC, standard of care; SMR, standard mortality ratio.

Toxicities associated with CAR T-cell treatments

Short-term toxicity(ies)

Cytokine Release Syndrome (CRS)

ImmunoTargets and Therapy — Dovepress

REVIEW

Cytokine Release Syndrome: Current Perspectives

Hemant Murthy[1]
Madiha Iqbal[1]
Julio C Chavez[2]
Mohamed A Kharfan-Dabaja[1]

[1]Division of Hematology-Oncology and Blood and Marrow Transplantation Program, Mayo Clinic, Jacksonville, FL, USA; [2]Department of Malignant Hematology, Moffitt Cancer Center, Tampa, FL, USA

Abstract: Chimeric antigen receptor T cell (CART) therapy represents a novel and a paradigm-shifting approach to treating cancer. Recent clinical successes have widened the applicability of CD19 CART cells for the treatment of relapsed/refractory B-cell NHL, namely tisagenlecleucel and axicabtagene ciloleucel. Tisagenlecleucel is also approved for relapsed and/or refractory B-ALL up to age 25. CART therapy is associated with unique and potentially life-threatening toxicities, notably cytokine release syndrome (CRS). A better understanding of the pathogenesis of CRS is crucial to ensure proper management. In this review, CRS definitions, profiles, risk factors and grading systems are discussed. Finally, current and novel investigational approaches and therapies for CRS are summarized.

Keywords: cytokine release syndrome, chimeric antigen receptor T-cell therapy

- Potentially serious complication of CAR-T therapy
- Knowledge about exact mechanism continues to evolve
- Cytokine mediated inflammatory response:
  - *In vivo* CAR-T activation and expansion
  - Also, from immune cells (macrophages) that respond to CAR-T activation
- Symptoms: Mild (pyrexia) → severe (hemodynamic compromise and organ failure)
- Median time to onset: varies according to product (2-4 days)
- Rare: Hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS)

Murthy H, et al. Immunotargets Ther. 2019; 8: 43-52

Biol Blood Marrow Transplant 25 (2019) 625–638

ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Guideline

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

Daniel W. Lee[1,#], Bianca D. Santomasso[2,#], Frederick L. Locke[3], Armin Ghobadi[4], Cameron J. Turtle[5], Jennifer N. Brudno[6], Marcela V. Maus[7], Jae H. Park[8], Elena Mead[9], Steven Pavletic[6], William Y. Go[10], Lamis Eldjerou[11], Rebecca A. Gardner[12], Noelle Frey[13], Kevin J. Curran[14], Karl Peggs[15], Marcelo Pasquini[16], John F. DiPersio[4], Marcel R.M. van den Brink[8], Krishna V. Komanduri[17], Stephan A. Grupp[18,*], Sattva S. Neelapu[19,**]

ASTCT consensus grading (CRS)

- **Always rule out a possible infectious cause of the fever**
  Blood and urine cultures, chest X-ray, examine sites of IV lines

Table 2
ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Lee DW, et al. Biol Blood Marrow Transplant. 2019; 25: 625-38

Management of CRS by Grade

- **Grade 1:** r/o sepsis, antimicrobials commonly started, anti-pyretics, consider tocilizumab for fevers lasting >2-3 days or refractory fevers
- **Grade 2:** guided management of hypotension (IV fluids), hypoxia (nasal canula), tocilizumab ± glucocorticoids
- **Grade 3:** ICU consult, vasopressors, high-flow oxygen, non-rebreather mask, glucocorticoids
- **Grade 4:** multiple pressors, mechanical ventilation, glucocorticoids, anakinra (if refractory, off label), siltuximab (if refractory, off label)

Neurotoxicity

Hematol Oncol Stem Cell Ther 13 (2020) 1–6

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/hemonc

REVIEW ARTICLE

Cytokine release syndrome and neurologic toxicities associated with chimeric antigen receptor T-cell therapy: A comprehensive review of emerging grading models

Julio C. Chavez [a], Michael D. Jain [b], Mohamed A. Kharfan-Dabaja [c,*]

Risk factors

- CAR-T product (Axi-cel)
- High tumor burden
- Higher peak of CAR-T cells
- Pre-existing neurologic comorbidities
- Disease burden in the bone marrow (B-ALL)
- Severity of CRS

Chavez JC, et al. Hematol Oncol Stem Cell Ther. 2020 Mar;13(1):1-6

ASTCT Consensus Grading (ICE score*)

ICE

- **Orientation:** orientation to year, month, city, hospital: 4 points
- **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
- **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
- **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
- **Attention:** ability to count backwards from 100 by 10: 1 point

**ICE: Immune Effector Cell-Associated Encephalopathy score*

Lee DW, et al. Biol Blood Marrow Transplant. 2019; 25: 625-38

ASTCT consensus Grading (ICANS*)

Table 6
ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[|]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings[‡]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[§]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

[|] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[‡] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

[§] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

ICANS: Immune effector cell-associated neurotoxicity syndrome

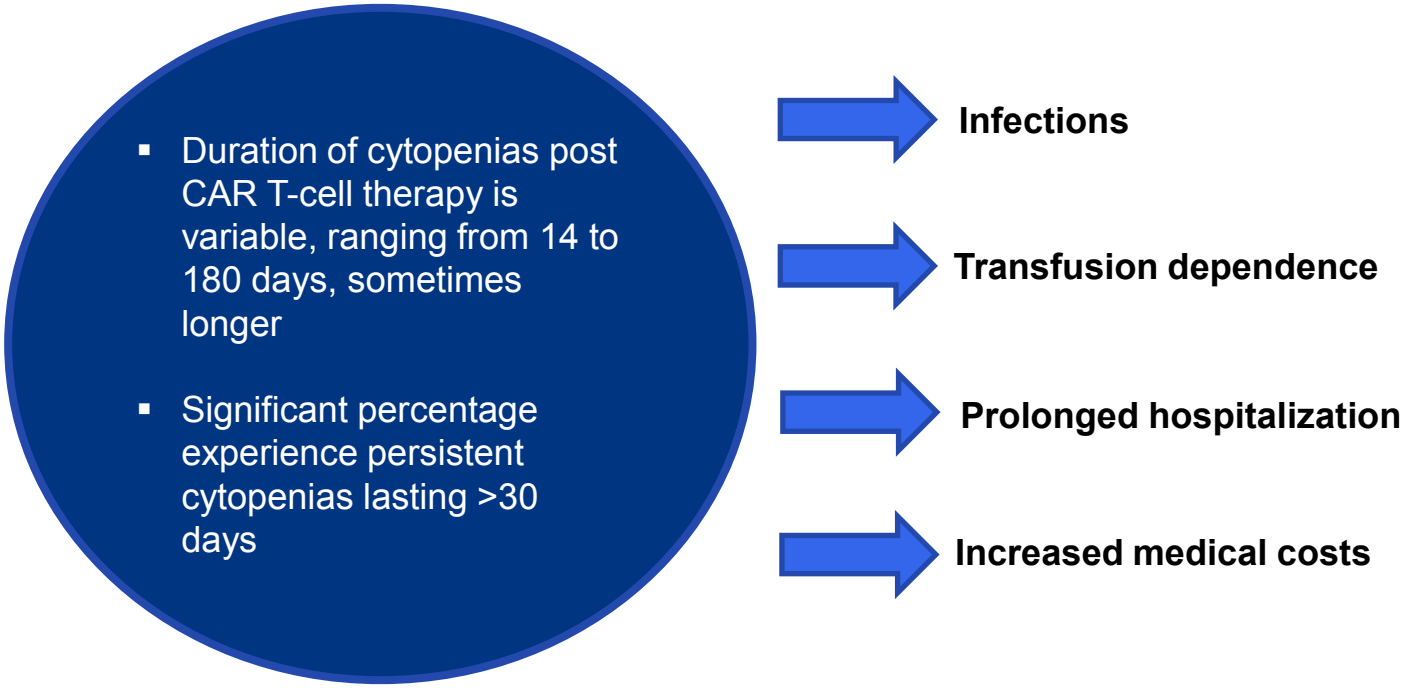
Lee DW, et al. Biol Blood Marrow Transplant. 2019; 25: 625-38

Management of neurotoxicity by Grade

- **Grade 1:** Supportive care, aspiration precautions, avoid CNS acting drugs
- **Grade 2:** Anti-seizure precautions, consider glucocorticoids (dexamethasone or solumedrol), neuro-ICU consult
- **Grade 3:** Continue glucocorticoids (dexamethasone or solumedrol), consider radiologic eval (r/o increased intracranial pressure), airway protection
- **Grade 4:** Continue glucocorticoids, airway protection

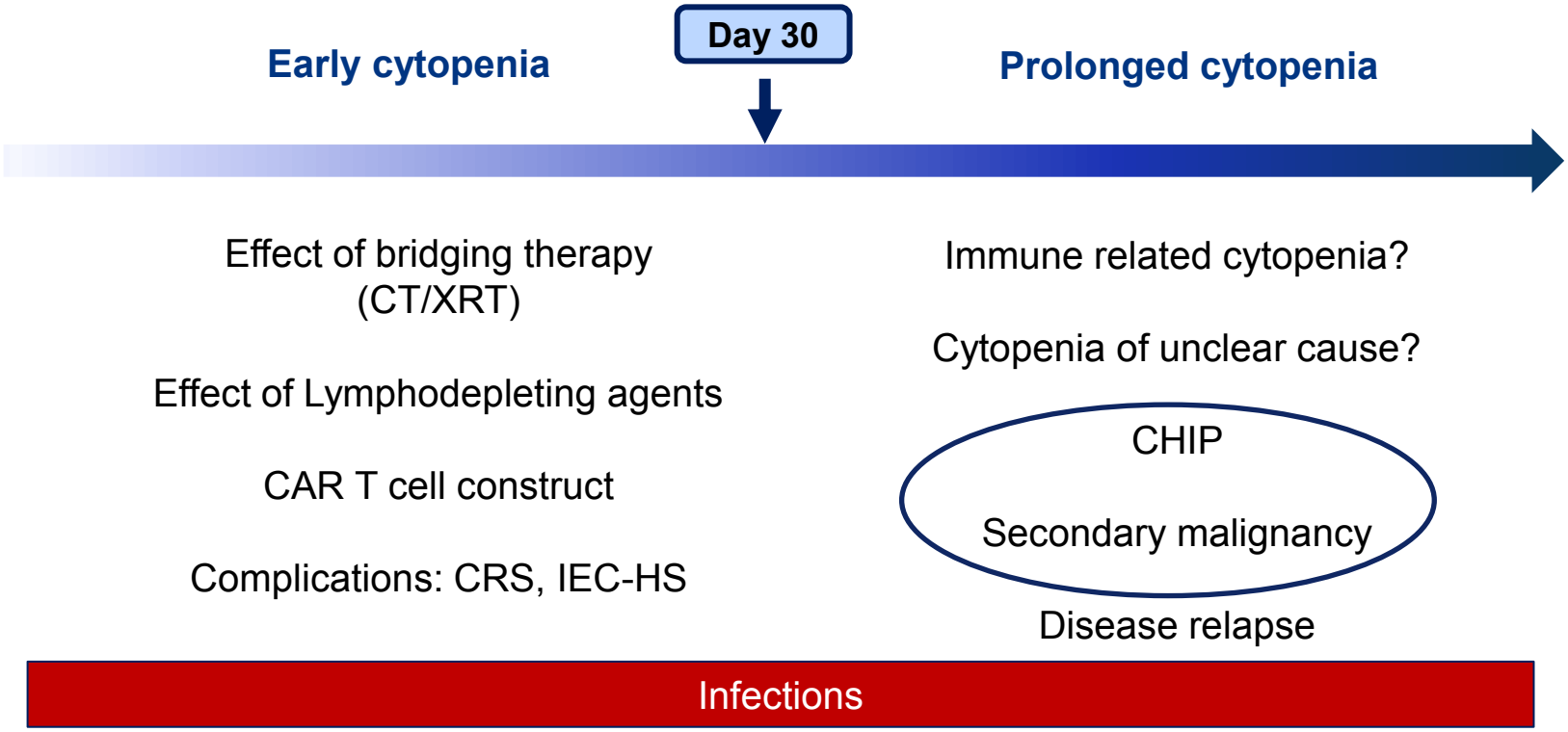
Long-term toxicities

Cytopenia (CAR-to-penia)

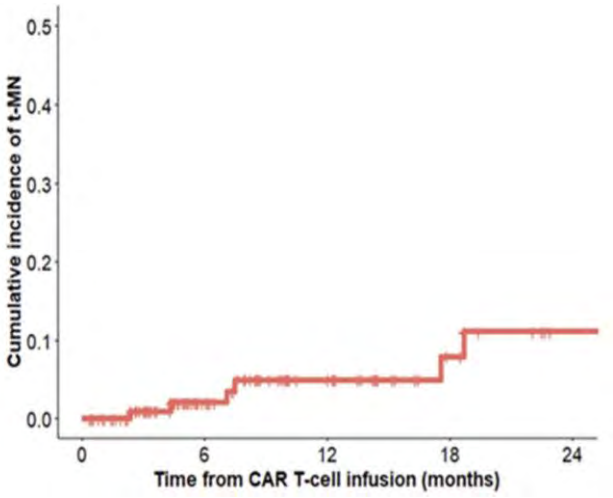


Zhu F et al. Cell Transplant. 2020 Jan-Dec;29:963689720919434
Yassine F et al. Hematol Oncol Stem Cell Ther. 2022; 15(3):122-130

Causes of cytopenia after CAR T cell therapy?



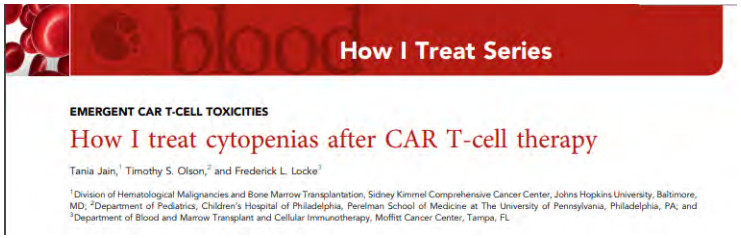
Therapy-related myeloid neoplasms following CAR T-cell therapy

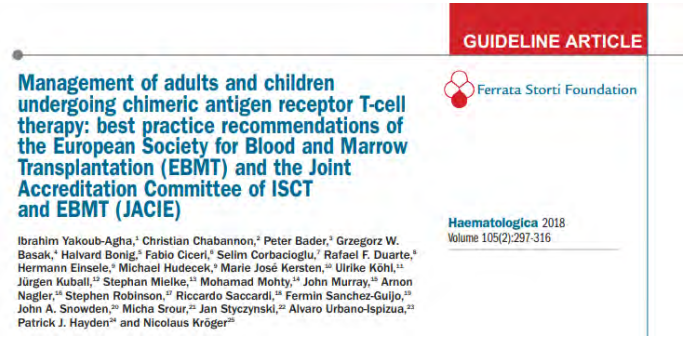


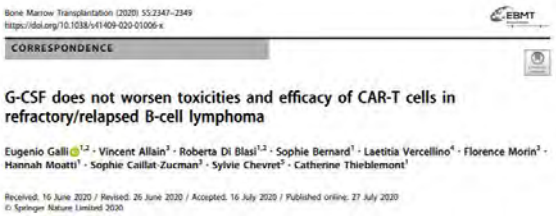
- 189 pts treated with CAR T-cell at Mayo Clinic of whom 10 (5.3%) developed t-MN. Five received prior autologous HCT
- Median interval from CAR T → t-MN 9.8 (IQR 3.6-19.8) mos
- Pre-CAR T BM samples on three patients, NGS:
  - *DNMT3A* (Arg882His, VAF 7%)
  - *DNMT3A* (Met801Val, VAF 8%)
  - *TP53* (Ile254Ser, VAF 40%)

Alkhateeb HB et al. Blood Cancer J. 2022;12(7):113

Management of cytopenias







- Largely relies on supportive care
- G-CSF is used for the management of neutropenia
- The European Society of Blood and Marrow Transplantation practice guidelines recommend waiting at least 14 days post CAR T-cell infusion prior to considering G-CSF for management of neutropenia

Jain T, et al. Blood. 2023; 141 (20): 2460–2469
Yakoub-Agha I, et al. Haematologica. 2018; 105 (2): 297
Galli E, et al. Bone Marrow Transplant. 2020; 55:2347–2349

Management of cytopenias

- Routine anti-bacterial and anti-fungal prophylaxis not recommended
  - ***Targeted based on clinical suspicion***
- Anti-viral and anti-pneumocystis pneumonia prophylaxis recommended from start of lymphodepletion to 1-year post CAR T-cell or until CD4 count >0.2x10^9 /L
- IVIG replacement to be considered in adults who have had infections with encapsulated organisms
- In clinical practice and in trials, IVIG replacement often considered and targeted to trough IgG levels > 400 mg/dL
  - ***But, how often to be checked?***

Yakoub-Agha I et al. Haematologica. 2020; 105(2):297-316

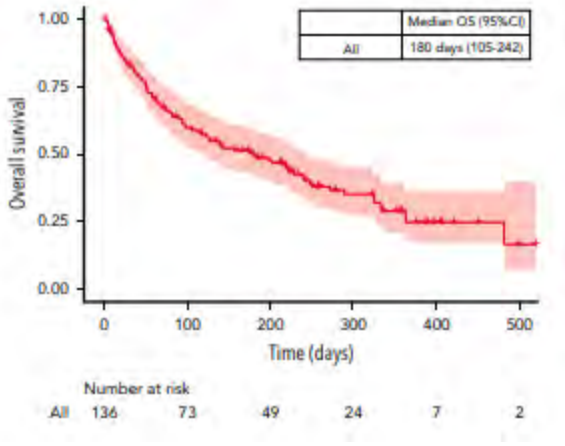
CAR T-cell therapy failure

- 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

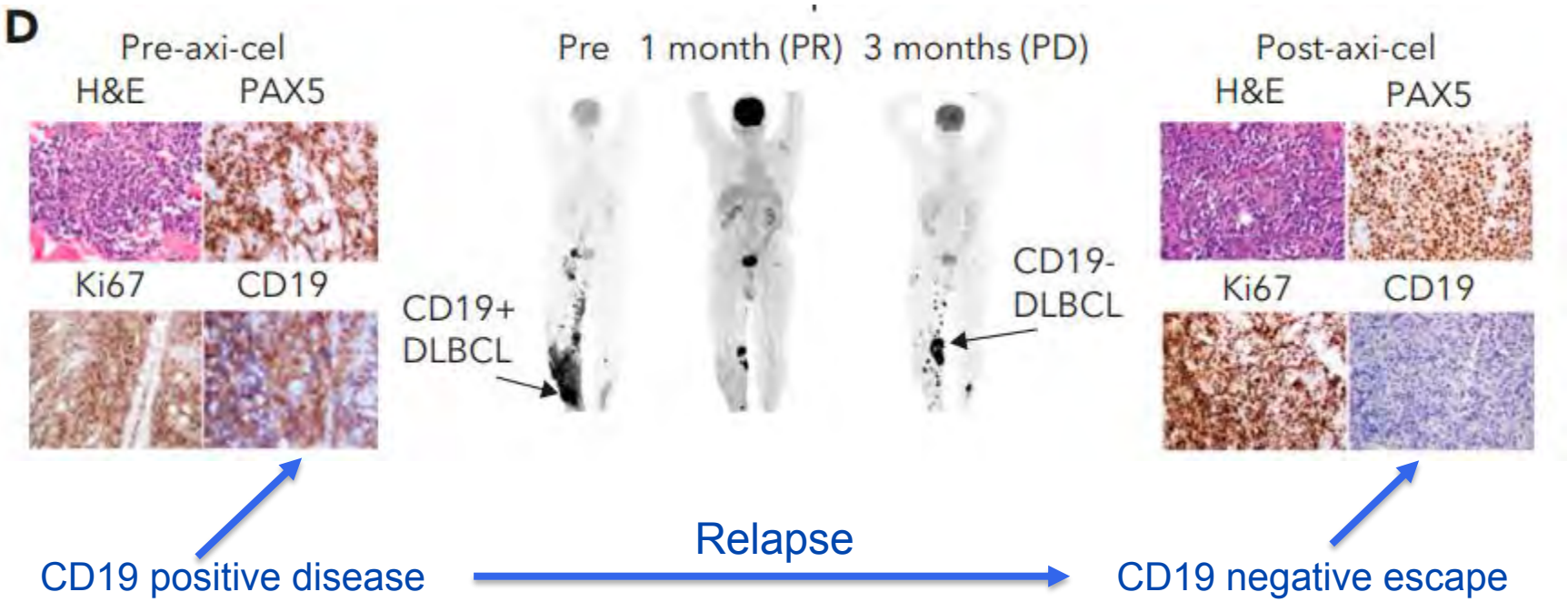
blood
Letter to *Blood*

TO THE EDITOR:

CD19 target evasion as a mechanism of relapse in large B-cell lymphoma treated with axicabtagene ciloleucel

Vicki Plaks,[1] John M. Rossi,[1] Justin Chou,[1] Linghua Wang,[2] Soumya Poddar,[1] Guangchun Han,[2] Zixing Wang,[1] Shao-Qing Kuang,[2] Fuliang Chu,[2] Richard E. Davis,[2] Francisco Vega,[2] Zahid Bashir,[1] Caron A. Jacobson,[3] Frederick L. Locke,[4] Patrick M. Reagan,[5] Scott J. Rodig,[6] Lazaros J. Lekakis,[7] Ian W. Flinn,[8] David B. Miklos,[9] Adrian Bot,[1] and Sattva S. Neelapu[2]

CD19 negative escape= 30%



New approaches needed: New target(s), multi-targets, etc.

Plaks, et al. Blood. 2021; 138 (12): 1081–1085

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

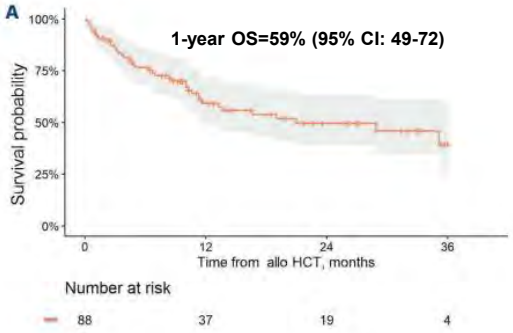


Table 3. Multivariate analysis outcomes after allogeneic hematopoietic cell transplantation.[1]

	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 a new target different from CD19?

Manufactured in Mayo Clinic Florida

- We manufactured a novel CAR-T cell therapy targeting **B-cell activating factor receptor (BAFF-R)**, a key regulator of B-cell proliferation and maturation→ we named it **MC10029**
  - Revised manuscript version submitted to journal (pending decision)
- Pre-clinical data completed
- FDA granted an IND (June 21, 2023)
- Phase I clinical trial anticipated to activate in March 2024
  - Study will allow inclusion of prior CD19-guided CAR T-cell failures

Cancer Immunology, Immunotherapy (2023) 72:4031–4047
https://doi.org/10.1007/s00262-023-03537-w

RESEARCH

Translational development of a novel BAFF-R CAR-T therapy targeting B-cell lymphoid malignancies

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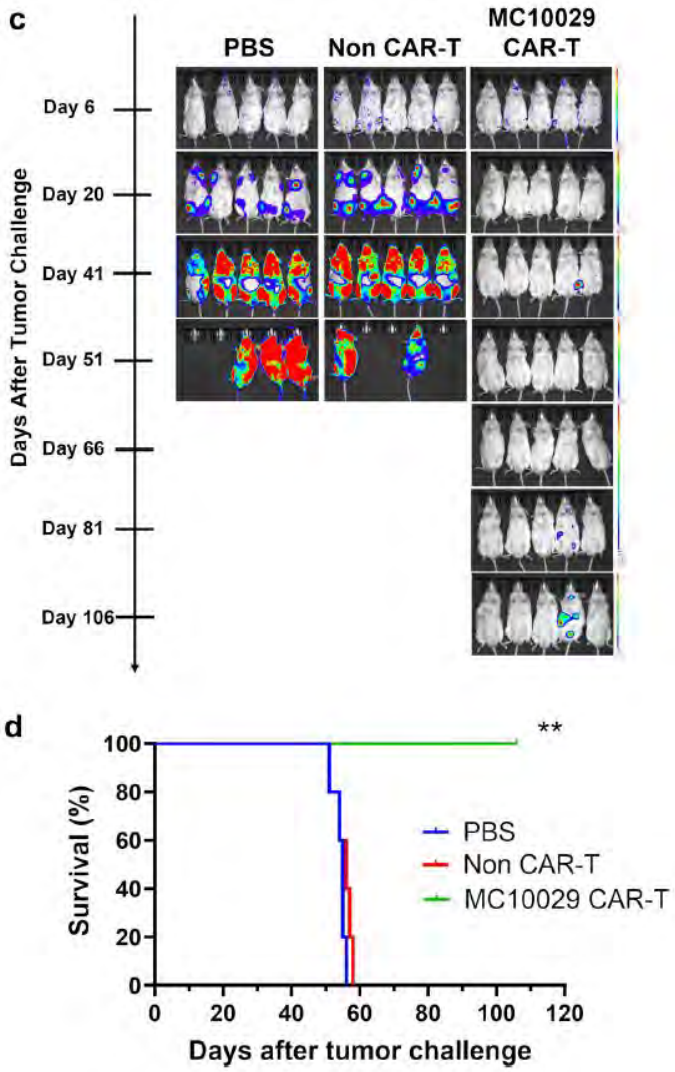
Received: 27 February 2023 / Accepted: 24 August 2023 / Published online: 10 October 2023

Z138 cells: Blastoid variant of MCL



Luo et al. Cancer Immunol Immunother.2023; 72: 4031-47

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

Take home messages

- CAR-T revolutionized Rx of DLBCL, MCL, and FL. Here to stay!
- In relapsed/refractory DLBCL (≥ 3rd line, 5-year OS ≥ **42.6%** (axi-cel))
  - For DLBCL achieving CR, (≥ 3rd line, 5-year OS=**64.4%** (axi-cel))
- In 1ry refractory DLBCL or early relapse (<12 months)
  - Axi-cel better than SOC (PFS, OS); Liso-cel better than SOC (PFS)
- Responses are sustained in MCL and FL
  - For MCL in CR, 30-mos OS=**76.1%** (Brexu-cel)
  - For FL in CR, 3-year OS=**75%** (Axi-cel)
  - For FL in CR, 2-year OS=**87.7%** (Tisa-cel)

Take home messages

- Short-term toxicities are unique (CRS and ICANS), but manageable
- Long-term more challenging
  - Pancytopenia
  - Hypogammaglobulinemia
  - Therapy-related myeloid neoplasms
    - CHIPs prior to CAR T-cell vs. after CAR T-cell?