CAR-T cell Therapy Updates: Aggressive B-cell NHL & Indolent


Jose D. Sandoval-Sus, MD FACP

Assistant member, Department of Malignant Hematology & Cellular Therapy
Moffitt Cancer Center at Memorial Healthcare System
Pembroke Pines, FL

@HemSandoval

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Malignant Hematology & Cellular Therapy

DISCLOSURES:

- Speaker's Bureau: BMS
- Advisory Board: SeaGen, Incyte, Janssen, MassiveBio, TG therapeutics

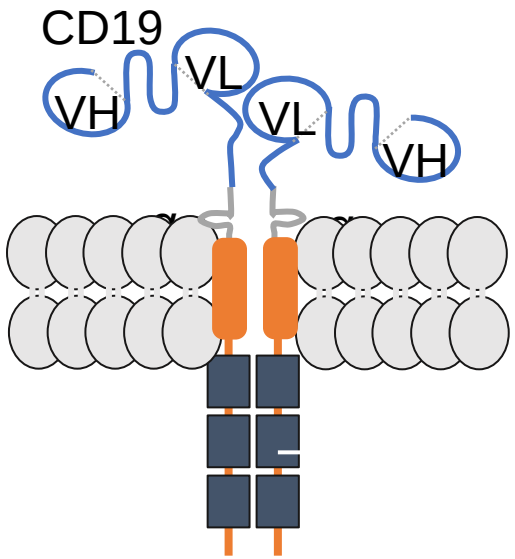
Learning objectives

- Learn about the latest updates regarding CAR-T cell therapy for patients with B-cell aggressive & indolent Non-Hodgkin Lymphomas (NHL):
  - ✓ High grade B cell lymphomas (DLBCL, PMBCL and other HGBCL).
  - ✓ Mantle cell lymphoma (MCL).
  - ✓ Follicular lymphoma and Marginal zone lymphoma (FL/MZL).

- Know about CAR-T cell therapy data outside clinical trials ("real world" data) and identify possible opportunities and roadblocks for wider community implementation.

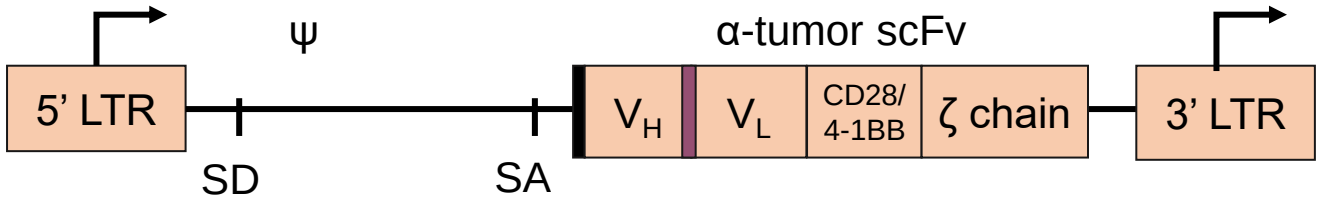
Generation of TAA-Targeted T Cells for Treatment of Cancer

1. Construct a CAR gene

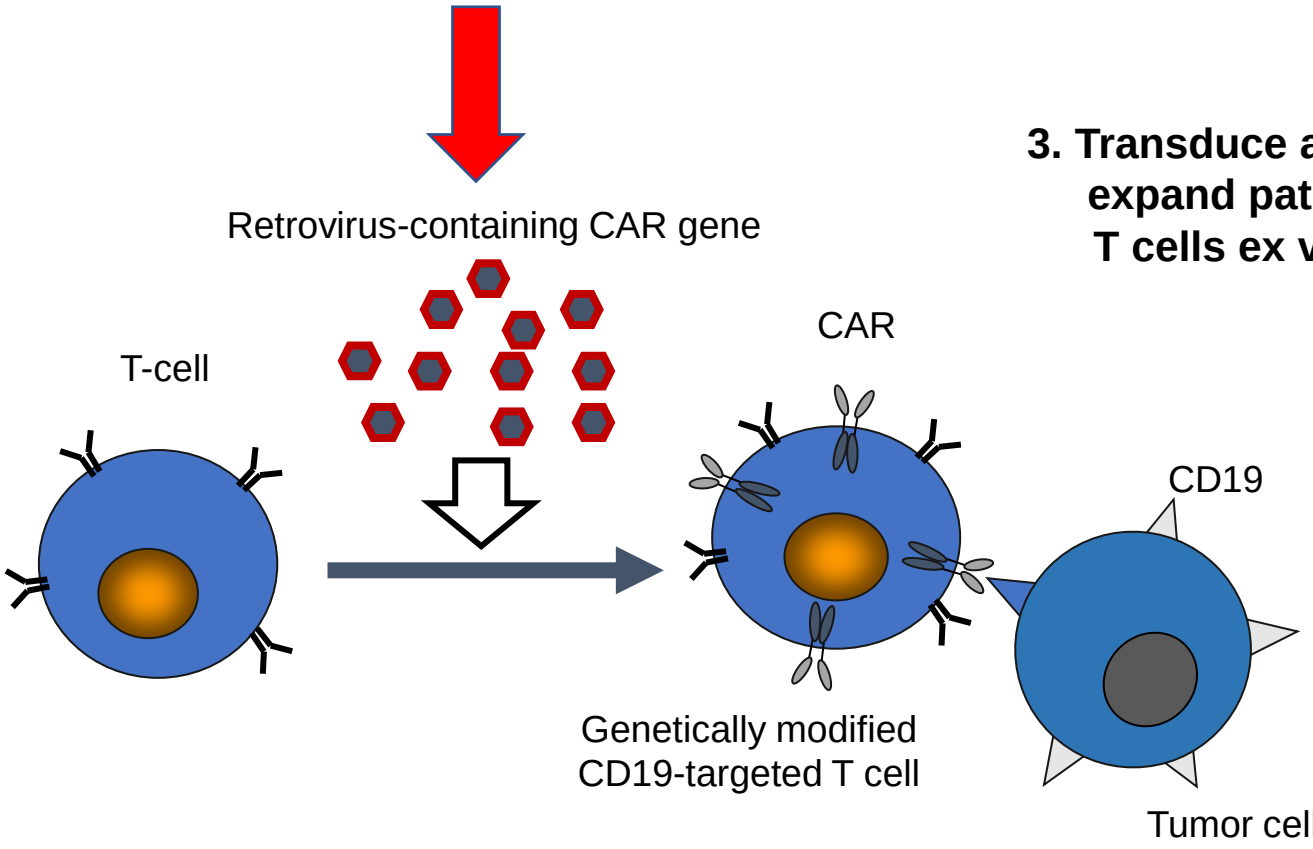


scFv-CD28/4-1BB

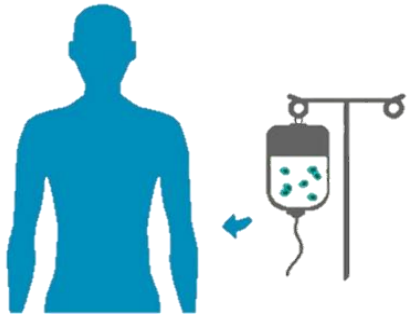
2. Subclone CAR gene into a vector



3. Transduce and expand patient T cells ex vivo



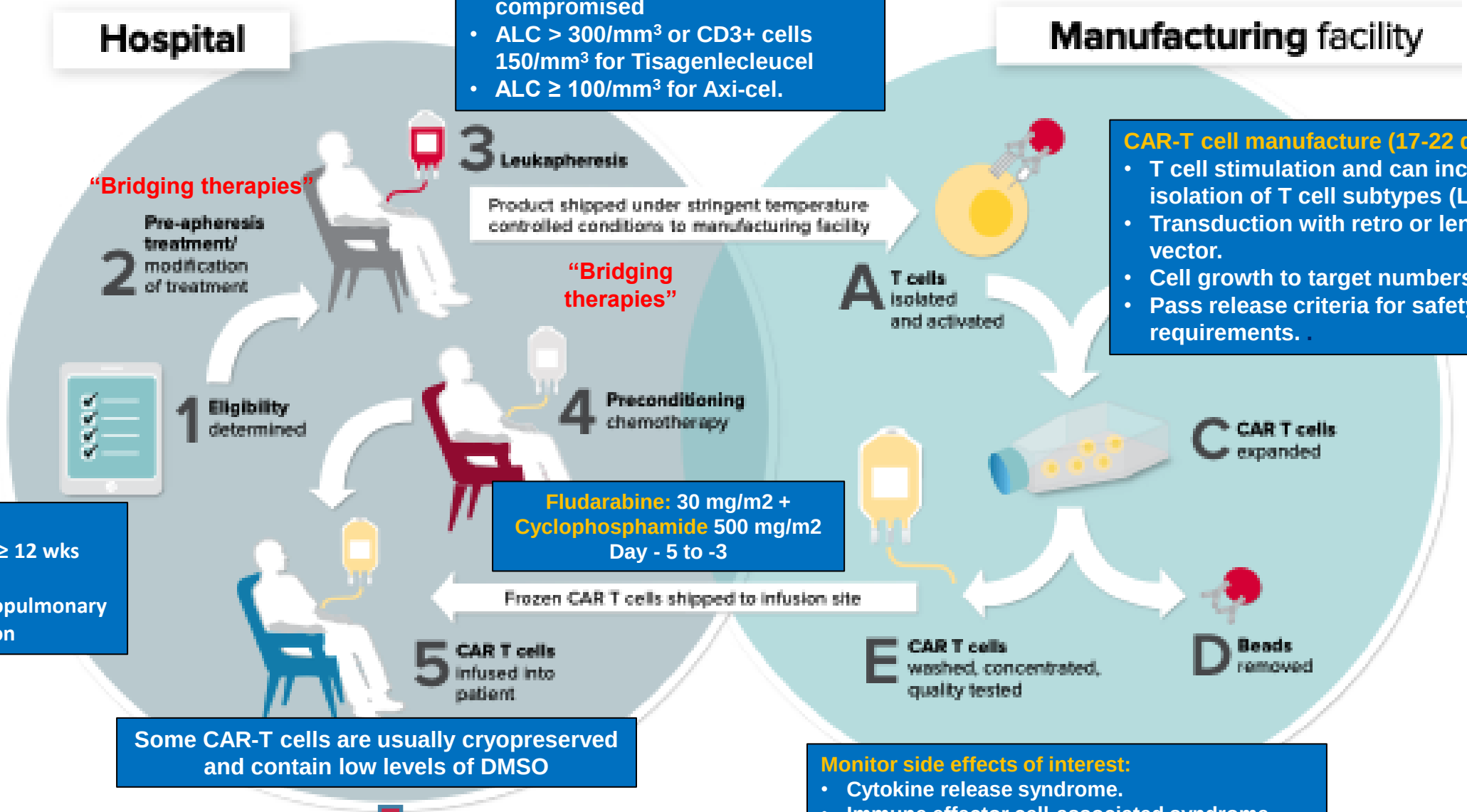
4. Infuse CAR T-cells into patient



Sadelain M, et al. *Nat Rev Cancer*. 2003;3:35-45.,
Brentjens RJ, et al. *Nat Med*. 2003;9:279-286.

Resting state leukapheresis

- No growth factor stimulation.
- Auto T cells usually compromised
- ALC > 300/mm^3 or CD3+ cells 150/mm^3 for Tisagenlecleucel
- ALC ≥ 100/mm^3 for Axi-cel.



CAR-T cell manufacture (17-22 days)

- T cell stimulation and can include isolation of T cell subtypes (Liso-Cel).
- Transduction with retro or lentiviral vector.
- Cell growth to target numbers.
- Pass release criteria for safety and FDA requirements. .

Fludarabine: 30 mg/m2 + **Cyclophosphamide** 500 mg/m2
Day - 5 to -3

- Type of disease
- Life expectancy ≥ 12 wks
- ECOG PS = 0/1
- Adequate cardiopulmonary and organ function

Some CAR-T cells are usually cryopreserved and contain low levels of DMSO

Monitor side effects of interest:

- Cytokine release syndrome.
- Immune effector cell-associated syndrome (ICANS)
- Infections, HLH, cytopenias, B cell aplasia, etc.

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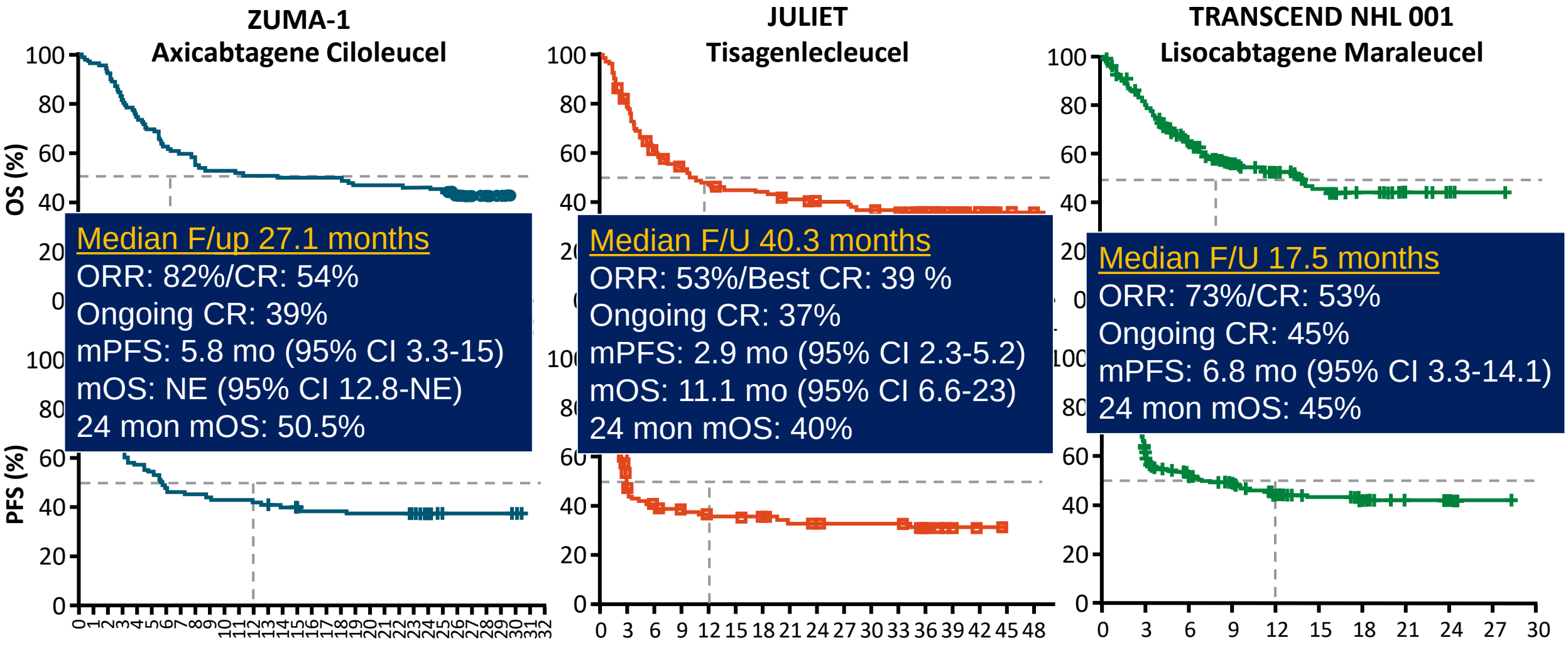
FDA-Approved CD19-Targeted CAR T-Cell Therapies

Therapy	Indications
Axicabtagene ciloleucel	▪ **Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy,** including DLBCL NOS, DLBCL arising from follicular lymphoma ("transformed lymphoma"), primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma. ▪ **Adults with R/R follicular lymphoma ≥ 2 lines (not MZL)**
Brexucabtagene autoleucel	▪ **Adults with R/R Mantle Cell Lymphoma.** ▪ **Adults with R/R B- cell precursor Acute Lymphoblastic Leukemia (10/1/21).**
Lisocabtagene maraleucel	▪ **Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy**, including DLBCL NOS, DLBCL arising from indolent lymphoma (transformed lymphoma"), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.
Tisagenlecleucel	▪ **Patients aged up to 25 yrs with B-cell precursor ALL that is refractory or in second or later relapse.** ▪ **Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy**, including DLBCL NOS, DLBCL arising from follicular lymphoma ("transformed lymphoma"), high-grade B-cell lymphoma.

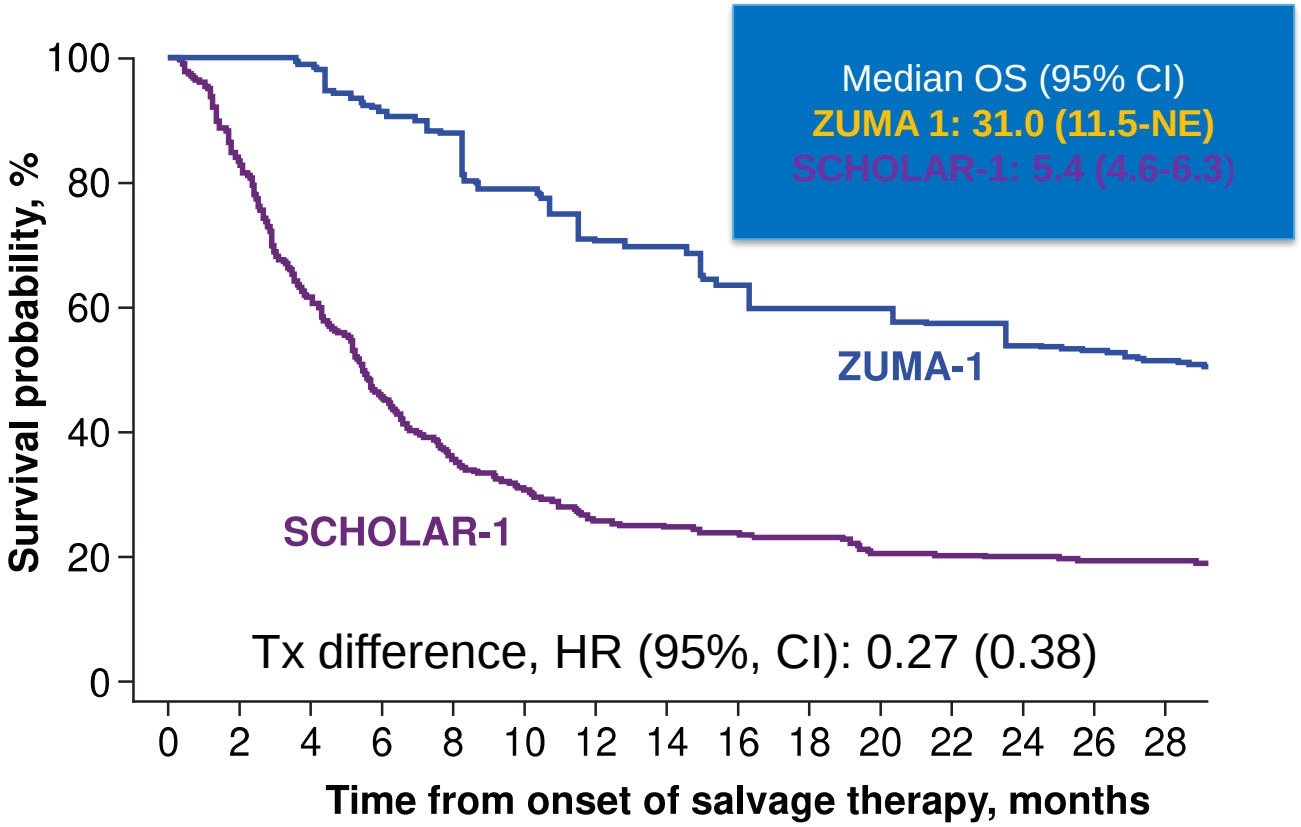
Anti-CD19 CAR T-Cell Therapy in DLBCL & HGBCL



Locke F et al. Lancet Oncol. 2019;20:31; Schuster SJ et al. Lancet Oncol. 2021; 22(10):1403-1415; Abramson J et al. Lancet. 2020;396:839.

Comparison of 2-year Outcomes with CAR-T cells (ZUMA-1) vs. Salvage Chemotherapy in Refractory Large B-cell lymphoma

	ZUMA-1	SCHOLAR-1	Ratio (95% CI)
12-mo OS rate (95% CI), %*	71 (46-91)	26 (22-32)	2.7 (1.7-3.8)
18-mo OS rate (95% CI), %*	60 (37-83)	23 (19-29)	2.6 (1.5-3.9)
24-mo OS rate (95% CI), %*	54 (30-80)	20 (16-26)	2.7 (1.4-4.3)



73% reduction in the risk of death……. (lots of caveats!)

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Neelapu SS, Locke FL, et al. Blood Advances Sept 2021

Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium

"Real World US Experience"

Baseline pt characteristics:

Characteristic	No. (%)
No. of patients	298
Age, years	
< 60	144 (48.3)
≥ 60	154 (51.7)
Median (range)	60 (21-83)
ECOG PS	
0	76 (25.5)
1	164 (55.0)
2	46 (15.4)
3	11 (3.7)
4	1 (< 1.0)
Disease stage	
I or II	52 (17.6)
III or IV	244 (82.4)
International Prognostic Index score[a]	
0-2	136 (45.6)
3-5	162 (54.4)
Disease type	
DLBCL	203 (68.1)
PMBCL	19 (6.4)
TFL	76 (25.5)
GCB-like[b]	158 (59.8)
Non-GCB[b]	106 (40.1)
Double/triple-hit[c]	64 (22.8)
Double expressor[c]	98 (37.4)
LDH > ULN at leukapheresis[e]	157 (60.6)
LDH > ULN at conditioning[e] chemotherapy	155 (59.4)
Bulky disease (≥ 10 cm)	68 (22.7)
Prior therapies	
≥ 3 prior lines of therapy	222 (74.5)
Median No. of prior lines (range)	3 (2-11)
History of primary refractory disease	101 (33.9)
Refractory to most recent therapy	125 (42.0)
Relapsed	72 (24.0)
Prior ASCT	98 (32.9)
Prior allogeneic SCT	7 (2.4)
Prior CD-19–directed therapy[f]	5 (1.7)

ZUMA-1 comorbidity exclusion criteria at the time of leukapheresis	
No. of patients with exclusion criteria	129 (43.0)
1 criterion	76 (58.9)
≥ 2 criteria	53 (41.1)
ECOG PS > 1	58 (19.0)
Platelets < 75,000/μL	34 (11.4)
DVT/PE within 6 months	31 (10.4)
History of CNS disease	21 (7.0)
Renal insufficiency (GFR < 60 mL/min/1.73 m^2)	21 (7.0)
Prior checkpoint inhibitor therapy	17 (5.7)
LVEF < 50%	10 (3.4)
Symptomatic pleural effusion	10 (3.4)
Bilirubin > 1.5 g/dL	7 (2.4)
Prior CD19-directed therapy	5 (1.7)

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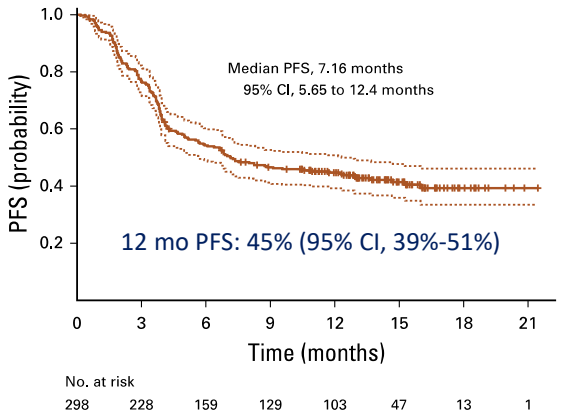
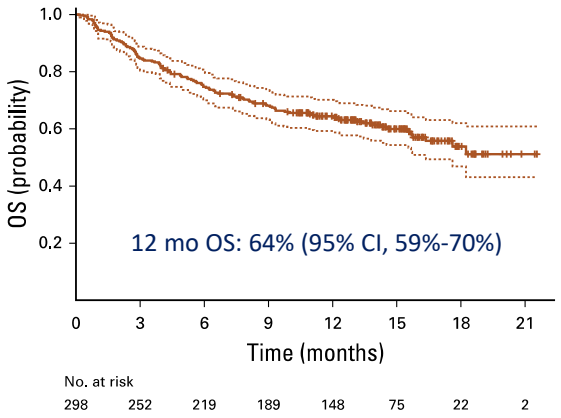
Nastoupil L, Jain M et al. J Clin Oncol. 2020 Sep 20;38(27):3119-3128

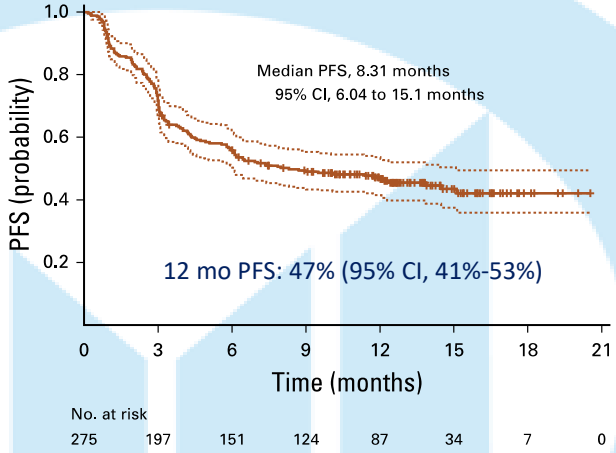
Real World Experience-US CART Consortium: Axi-cel experience

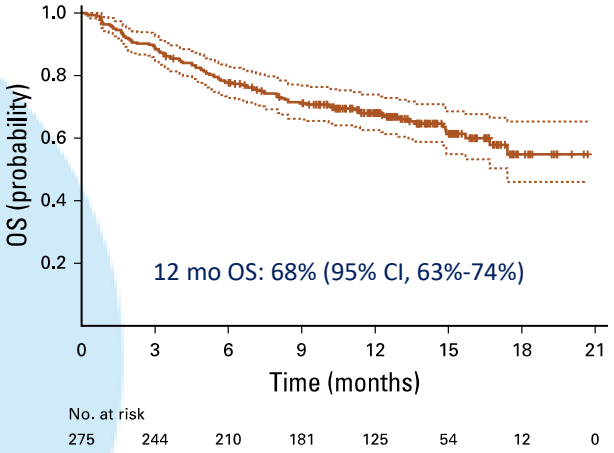
Outcomes of patients who underwent leukapheresis (ITT analysis)





Outcomes of patients who received Axi-cel (Per protocol analysis)





Summery of AEs

Event and Grade	No. (%)
Cytokine release syndrome	
Any	251 (91.2)
1	94 (34.2)
2	138 (50.2)
3	12 (4.4)
4	6 (2.2)
5	1 (0.4)
Median time to maximum severity, days	3
Range	0-37
Interquartile range	1-5
Neurotoxicity	
Any	189 (68.7)
1	49 (17.8)
2	55 (20)
3	66 (24)
4	18 (6.6)
5	1 (0.4)
Median time to maximum severity, days	6
Range	0-27
Interquartile range	5-8
Hospitalization	
Median hospital stay, days (range)	14 (3-66)
Intensive care unit stay	91 (33)
Tocilizumab use	170 (62)
Corticosteroid use	149 (54)

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Nastoupil L, Jain M et al. J Clin Oncol. 2020 Sep 20;38(27):3119-3128

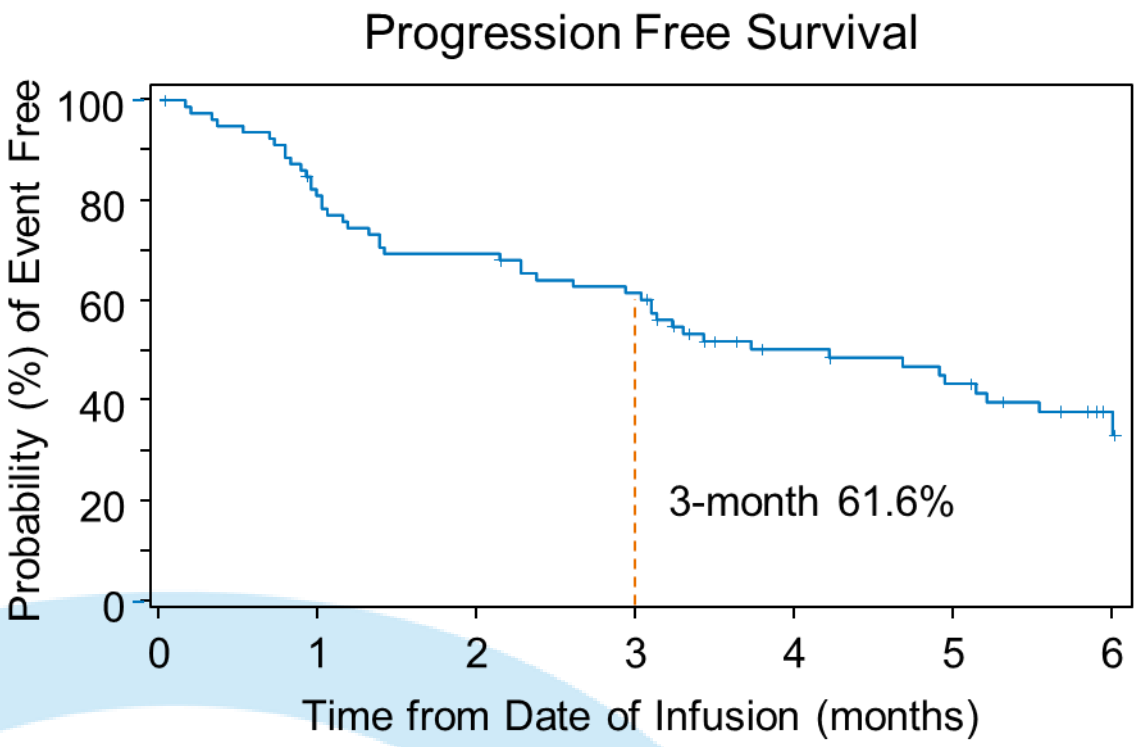
Tisagenlecleucel Chimeric Antigen Receptor (CAR) T-Cell Therapy for Adults with Diffuse Large B-Cell Lymphoma (DLBCL): Real World Experience from the Center for International Blood & Marrow Transplant Research (CIBMTR) Cellular Therapy Registry

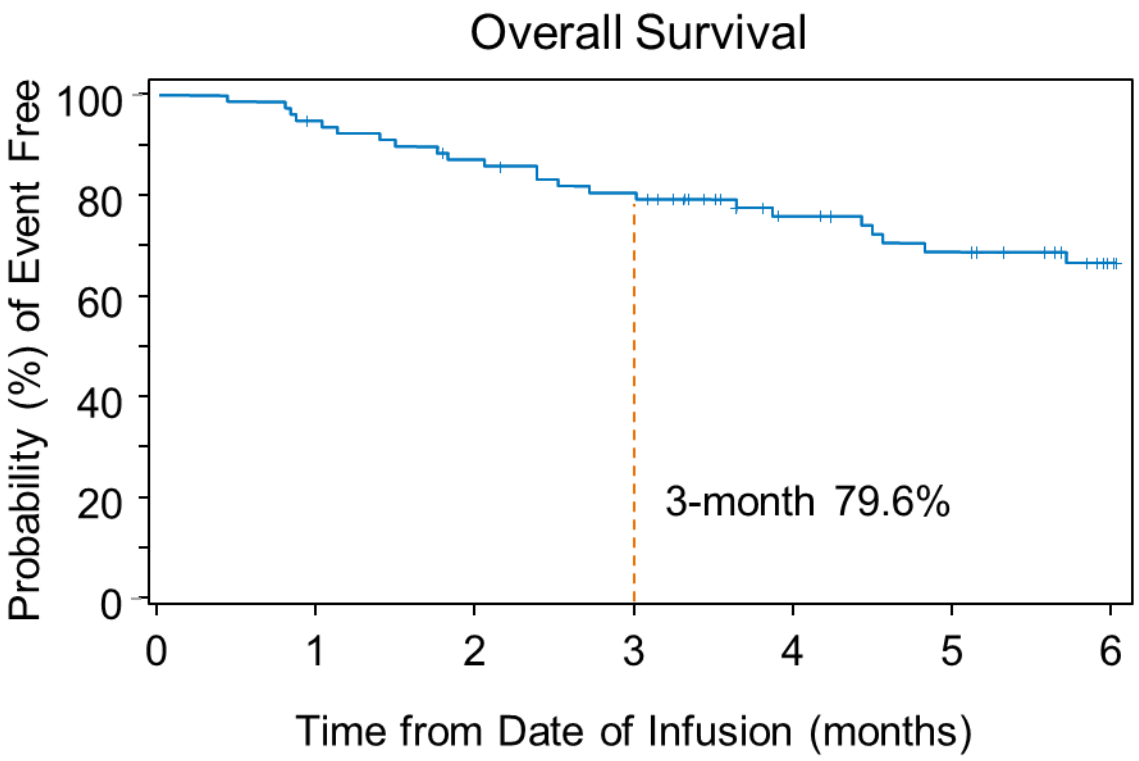
Samantha Jaglowski, Zhen-Huan, Yiyun Zhang, Hu, Manali Kamdar, Monalisa Ghosh, Premal D Lulla, Joshua P Sasine, Miguel-Angel Perales, Peiman Hematti, Sarah Nikiforow, Patricia Steinert, Lan Yi, Raghav Chawla, Lida Pacaud, Mary M Horowitz, Eric Bleickardt, Marcelo C. Pasquini

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

The CIBMTR® (Center for International Blood and Marrow Transplant Research®) is a research collaboration between the National Marrow Donor Program® (NMDP)/Be The Match® and the Medical College of Wisconsin (MCW).

CIDR
CELLULAR IMMUNOTHERAPY DATA RESOURCE





N at Risk							
All subjects	80	63	54	47	30	25	14

N at Risk							
All subjects	80	75	68	61	45	39	24

Courtesy of Dr. Krishna Komanduri

Jaglowski S et al. Nov 2019 Blood 134(Supplement_1):766-766

Comparison to JULIET Pivotal Trial

	CIBMTR Registry N=83[a] (%)	JULIET[b] N=115 (%)
ORR	58	52
CR	40	38
DOR at 3 months	75	76
PFS at 3 and 6 months	62 / 33	46 / 39
OS at 3 and 6 months	80 / 67	83 / 61
CRS (Gr. ≥ 3)	4[c]	23[e]
Neurotoxicity (Gr. ≥ 3)	5[d]	11[f]

Courtesy of Dr. Krishna Komanduri

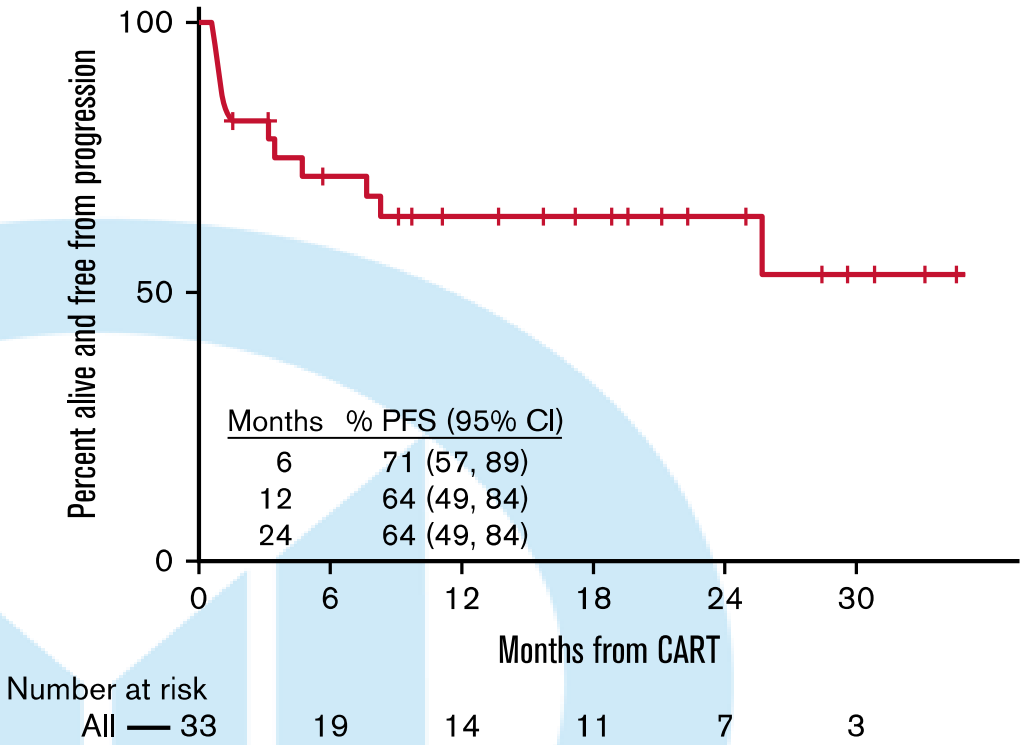
[a]Efficacy set N=80; safety set N=83
[b]Bachanova V, et. al. Clin Lymphoma Myeloma Leuk 2019 Sep. Vol 19; (Suppl 1); S251-S252
[c] ASTCT grading
[d] ICANS Grading
[e] UPenn grading
[f] MedDRA SMQ: non-infectious encephalopathy/delirium

Jaglowski S et al. Nov 2019 Blood 134(Supplement_1):766-766

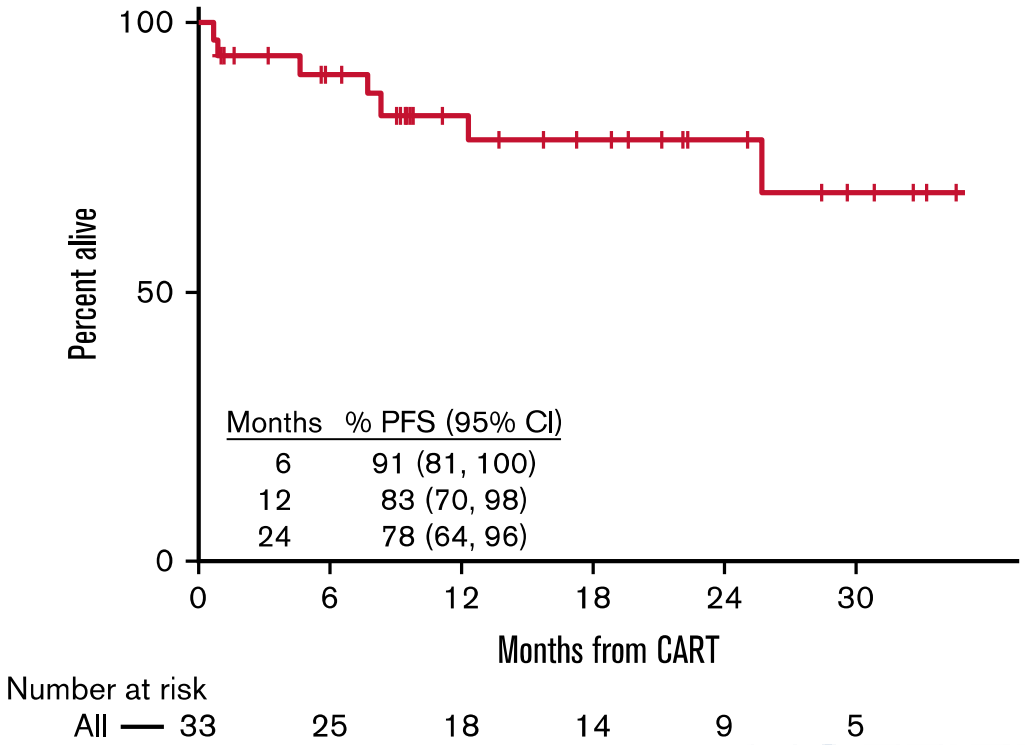
Real-world outcomes of axicabtagene ciloleucel in adult patients with Primary Mediastinal B-cell Lymphoma (N=33 pts)

Median F/up 13.8 months
ORR: 76%/CR: 67% (ITT pts)
24 mon mPFS: 64% (95% CI 49-84)
24 mon mOS: 78% (95% CI 64-96)

Progression free survival (PFS)



Overall survival (OS)



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Crombie JL et al. Blood Adv. 2021 Sep 28;5(18):3563-3567

Current place of CAR-T Therapies in DLBCL/HGBCL

First-line Chemoimmunotherapy

R-CHOP (SOC)

Phase III POLARIX trial (Polatuzumab vedotin + RCHP vs. RCHOP) in 1st line DLBCL met primary endpoint

Relapsed/Refractory HGBCL

- Phase III TRANSFORM trial (Lisa-cel vs. Chemotx followed by AutoHCT in 2nd line in R/R LBCL is positive (?).

- Phase III ZUMA-7 trial is positive: Axi-cel used as 2nd line Tx in pts with R/R LBCL improved EFS by 60%, compared to Chemotx followed by AutoHCT (SCT).

Second-line/Salvage ChemoimmunoTx

CR/PR

HDT/Autologous HSCT

SD/PD

Bridge Tx:
- Clinical trial
- ChemoImmunotx (i.e.PolaV+BR).
- Tafasitamab + Lenalidomide*
- Loncastuximab tesirine*
- Radiation Tx

SD/PD

Bridge Tx:
- Clinical trial
- ChemoImmunotx (i.e.PolaV+BR).
- Tafasitamab + Lenalidomide*
- Loncastuximab tesirine*
- Radiation Tx

CAR T-Cell Therapy

**Anti-CD19 targeted therapies*

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CAR-T cell therapy for Mantle Cell Lymphoma (MCL)

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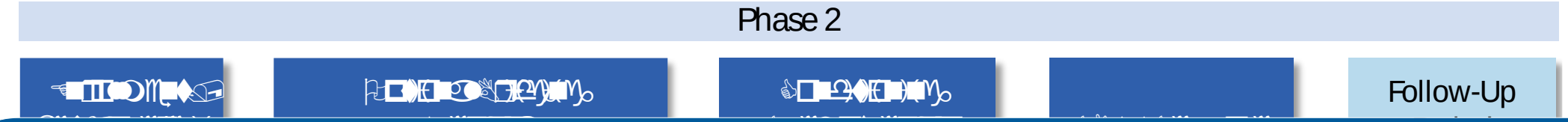
The NEW ENGLAND JOURNAL of MEDICINE

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



What is KTE-X19 (Brexucabtagene autoleucel)?

- Novel manufacturing process that involves T-cell selection and lymphocyte enrichment (XLP ™).

- Removes circulating CD19-expressing malignant cells.
- Reduces the possible activation and exhaustion of anti-CD19 CAR T cells during the ex vivo manufacturing process.
- Used in the MCL, ALL and CLL clinical trials.

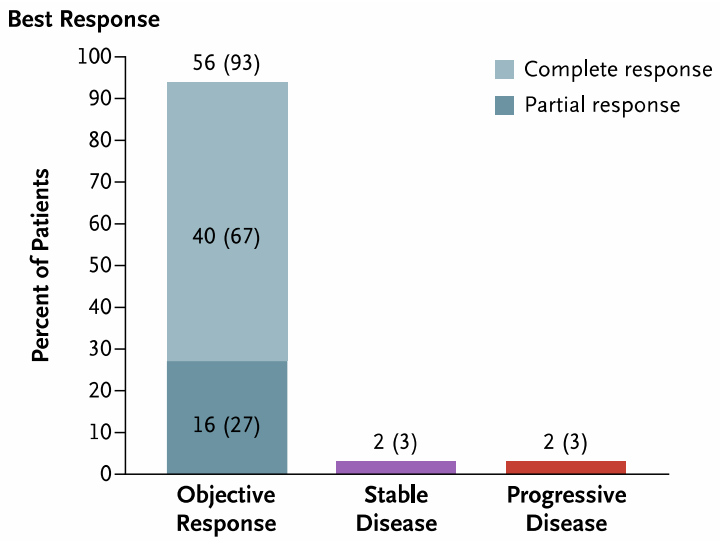
Wang M et al. N Engl J Med 2020;382:1331-42.

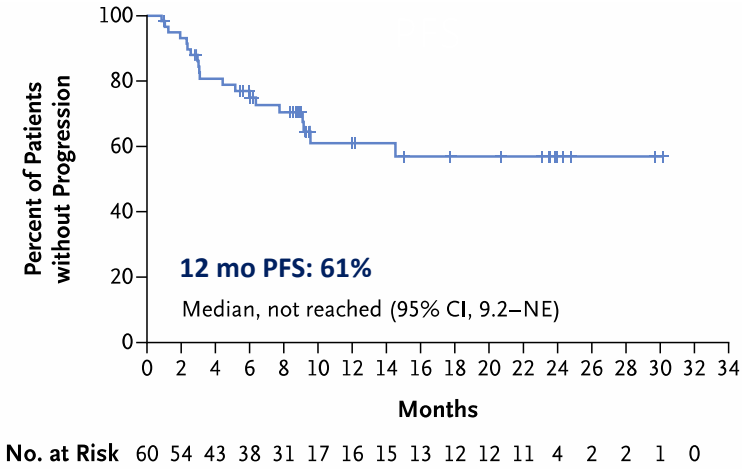
ZUMA-2: Brexucabtagene Autoleucel (KTE-X19) for Patients With R/R MCL

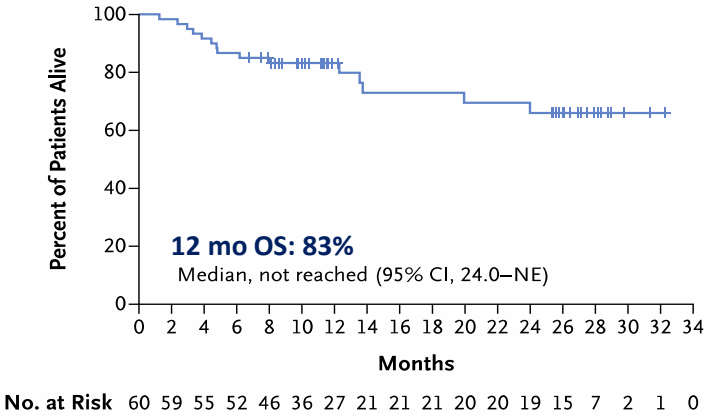
Patient baseline characteristics (N=68)

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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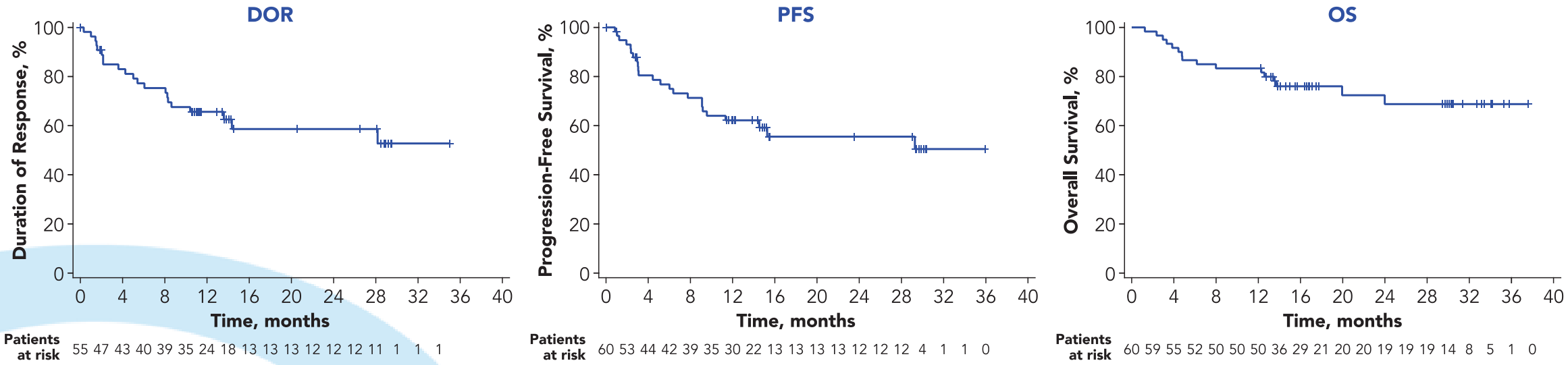
Wang M et al. N Engl J Med 2020;382:1331-42.

ZUMA-2: Long term follow up (2021 TCT update)

- Median follow up: 17 months (12.3 - 37.6 months).
- 29/60 evaluable pts (48%) have an ongoing response.
- 28 of 40 pt who achieved a CR remains in CR (70%



	DOR		PFS		OS	
	Median (95% CI), mo	15-Mo Rate (95% CI), %	Median (95% CI), mo	15-Mo Rate (95% CI), %	Median (95% CI), mo	15-Mo Rate (95% CI), %
Evaluable patients (N=60)	NR (14–NE)[a]	59 (43–72)[a]	NR (10–NE)	59 (45–71)	NR (NE–NE)	76 (63–85)
Patients in CR (n=40)	NR (14–NE)	70 (49–83)	NR (15–NE)	75 (57–87)	NR (NE–NE)	92 (76–97)
Patients in PR (n=15)	2 (1–4)	24 (6–49)	3 (2–5)	24 (6–49)	13 (3–NE)	47 (21–69)

[a] Of 55 total responding patients.
CR, complete response; DOR, duration of response; NE, not estimable; NR, not reached; PFS, progression-free survival; PR, partial response; OS, overall survival.

- The medians for duration of response (DOR), progression-free survival (PFS), and OS were not reached after a median follow-up of 17.5 months (**Figure 3**)

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Safety and Preliminary Efficacy in Patients with Relapsed/Refractory Mantle Cell Lymphoma Receiving Lisocabtagene Maraleucel in TRANSCEND NHL 001

M. Lia Palomba,[1] Leo I. Gordon,[2] Tanya Siddiqi,[3] Jeremy Abramson,[4] Manali Kamdar,[5] Matthew Lunning,[6] David G. Maloney,[7] Charalambos Andreadis,[8] Jon E. Arnason,[9] Nilanjan Ghosh,[10] Amitkumar Mehta,[11] Scott R. Solomon,[12] Thalia Farazi,[13] Jacob Garcia,[13] Christine Dehner,[13] Ken Ogasawara,[14] Jie Gao,[13] Michael Wang[15]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Northwestern University Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL, USA; [3]City of Hope National Medical Center, Duarte, CA, USA; [4]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [5]University of Colorado Cancer Center, Aurora, CO, USA; [6]University of Nebraska Medical Center, Omaha, NE, USA; [7]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [8]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA, USA; [9]Beth Israel Deaconess Medical Center, Boston, MA, USA; [10]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [11]University of Alabama at Birmingham, Birmingham, AL, USA; [12]Immunotherapy Program, Northside Hospital Cancer Institute, Atlanta, GA, USA; [13]Bristol Myers Squibb, Seattle, WA, USA; [14]Bristol Myers Squibb, Princeton, NJ, USA; [15]University of Texas MD Anderson Cancer Center, Houston, TX, USA

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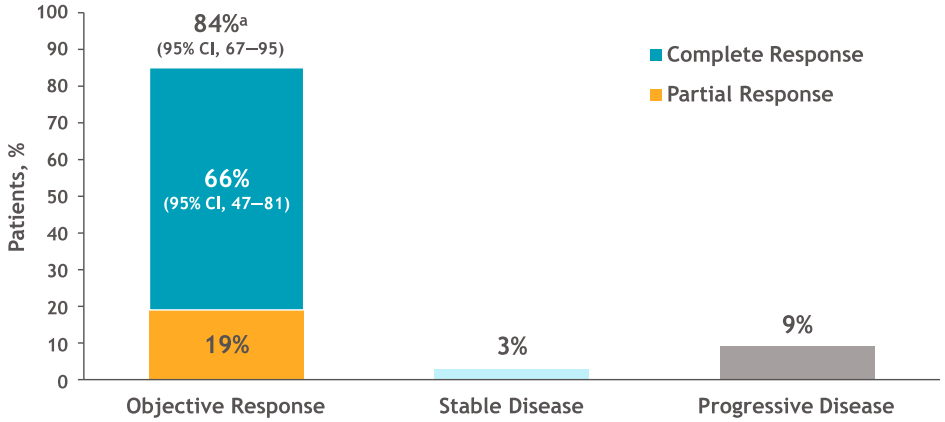
Palomba L et al. ASH 2020; abstract 118

	All liso-cel–Treated Patients (N = 32)
Age, median (range), y ≥65 y, n (%)	67 (36–80) 21 (66)
Male, n (%)	27 (84)
ECOG PS at screening, n (%) 0 1	 16 (50) 16 (50)
Blastoid morphology, n (%)	13 (41)
Ki67 ≥30%, n (%)	23 (72)
TP53 mutations, n (%)	7 (22)
SPD ≥50 cm^2 prior to LDC,[a] n (%)	5 (17)
LDH >ULN prior to LDC, n (%)	16 (50)
CRP ≥20 mg/L at baseline,[b] n (%)	17 (55)
Secondary CNS lymphoma at time of liso-cel administration, n (%)	1 (3)
Bone marrow involvement at infusion,[c] n (%)	8 (25)
No. of prior therapies, median (range) ≥3 prior therapies, n (%)	3 (1–7) 22 (69)
Prior HSCT, n (%) Allogeneic Autologous	11 (34) 3 (9) 10 (31)
Refractory,[d] n (%)	26 (81)
Prior BTK inhibitor, n (%) Prior ibrutinib Refractory to prior ibrutinib[e]	28 (88) 24 (75) 10 (31)
Prior venetoclax, n (%) Refractory to prior venetoclax[e]	8 (25) 5 (16)
Bridging therapy, n (%) Systemic treatment only Radiotherapy only Systemic treatment and radiotherapy	17 (53) 12 (37.5) 1 (3) 4 (12.5)

Best Overall Response by Investigator Assessment



- Median on-study follow-up: 5.9 (range, 0.4–24.8) months
- Median time to first CR or PR: 0.95 (range, 0.9–2.0) months

- ORR and CR rate, respectively, for patients with high-risk features:
  - Ki67 ≥30% (n = 23): 83% and 65%
  - Blastoid morphology (n = 13): 77% and 54%
  - *TP53* mutations (n = 7): 100% and 57%

[a]Based on 32 patients treated; one patient was not evaluable and is not shown in the figure.

✓ **Median duration of response (DoR): Not reached**

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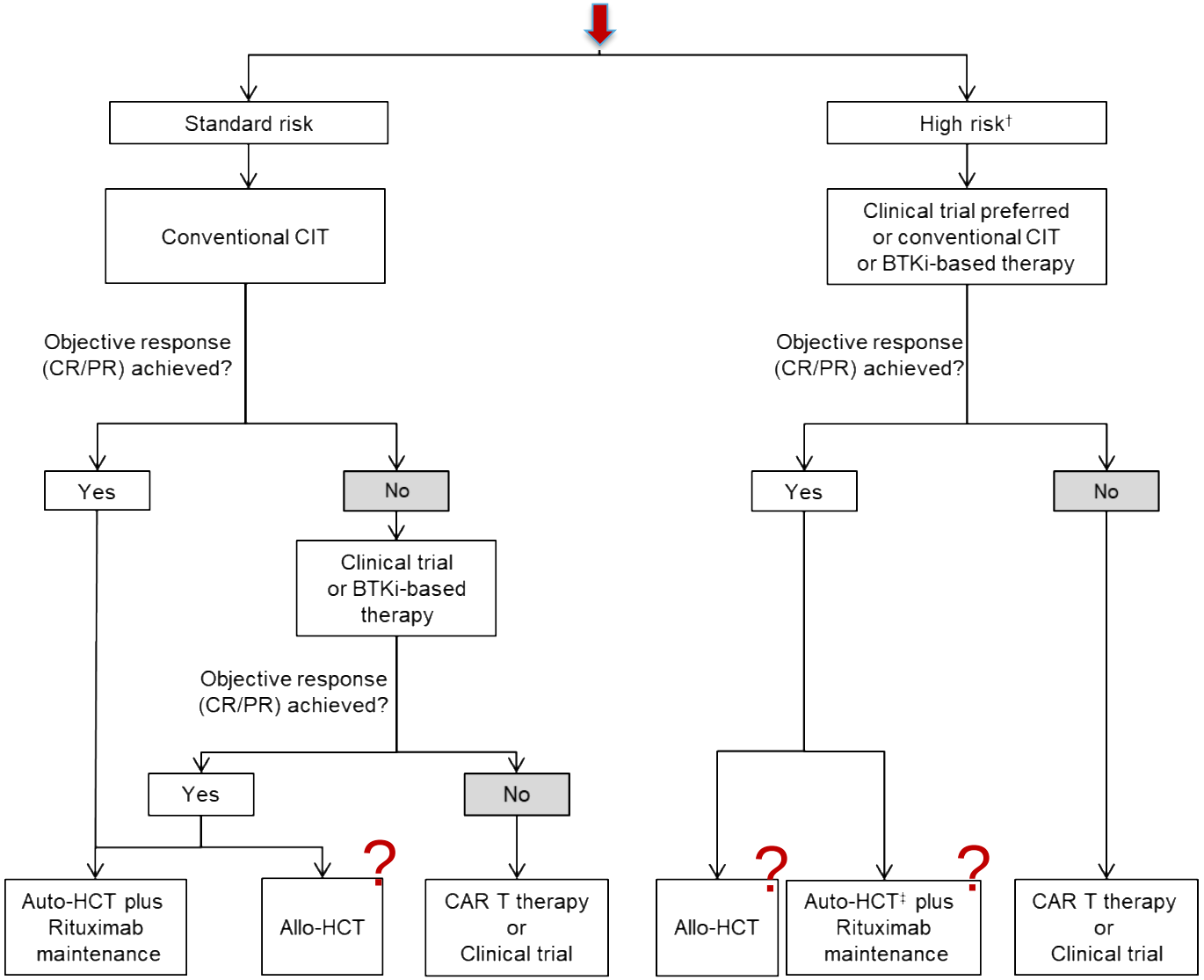
Palomba L et al. ASH 2020; abstract 118

Proposed Tx algorithm for MCL in the ERA of CAR-T cell Therapy

New diagnosis of MCL IN NEED of treatment



†High risk: biallelic Del17p, *TP53* mutations, high-intermediate/high MIPI-C, blastoid variant
‡Limited role in Del17p/*TP53* mutations

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Yassine F, Sandoval-Sus JD, Ayala E, et al. Transplant Cell Ther. May 2021

CAR-T cell therapy for Follicular Lymphoma (FL) & Marginal Zone Lymphoma (MZL)

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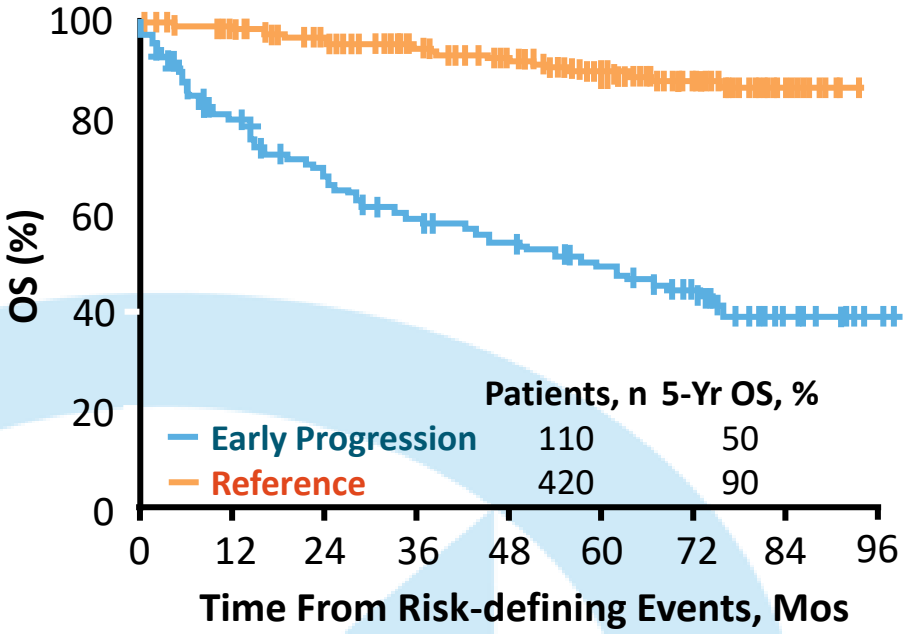
Early Relapse of Patients with FL After First-line Therapy Predicts Poor Prognosis

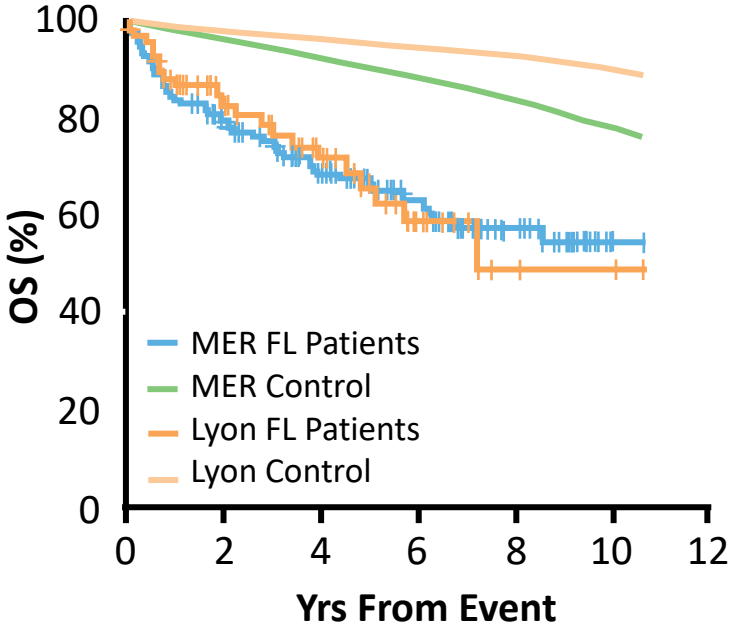
OS of Patients with FL Treated with R-CHOP from NLCS (N = 588)*



*Similar results found for an independent validation set and for first-line R-CVP and R-fludarabine in exploratory analyses.

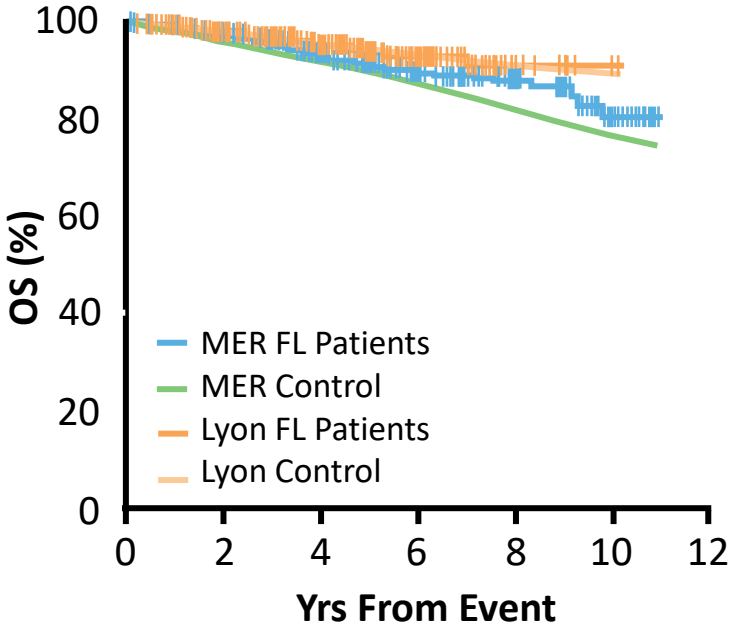
OS of Patients with FL from MER and Lyon vs Age/Sex-Matched Controls (N = 920)

Patients Not Achieving EFS12†



SMR (MER): 3.72 (95% CI: 2.78-4.88)
SMR (Lyon): 8.74 (95% CI: 5.41-13.36)

Patients Achieving EFS12†



SMR (MER): 0.73 (95% CI: 0.56-0.94)
SMR (Lyon): 1.02 (95% CI: 0.58-1.65)

†EFS12: event-free survival at 12 mos.

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Casulo C, et al. J Clin Oncol. 2015;33:2516-2522. Casulo C, et al. Annals of Oncology. 2017;28:2094-2106. Maurer MJ, et al. Am J Hematol. 2016;91:1096-1101.

Primary Analysis of ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

Caron Jacobson, MD[1]; Julio C. Chavez, MD[2]; Alison Sehgal, MD[3]; Basem William, MD[4]; Javier Munoz, MD, MS, FACP[5]; Gilles Salles, MD, PhD[6]; Pashna Munshi, MD[7]; Carla Casulo, MD[8]; David Maloney, MD, PhD[9]; Sven de Vos, MD, PhD[10]; Ran Reshef, MD[11]; Lori Leslie, MD[12]; Ibrahim Yakoub-Agha, MD, PhD[13]; Olalekan Oluwole, MD, MPH, MBBS[14]; Henry Chi Hang Fung, MD[15]; Joseph Rosenblatt, MD[16]; John Rossi, MS[17]; Lovely Goyal, PhD[17]; Vicki Plaks, LLB, PhD[17]; Yin Yang, MS[17]; Jennifer Lee, BS[17]; Wayne Godfrey, MS, MD[17]; Remus Vezan, MD, PhD[17]; Mauro Avanzi, MD, PhD[17]; and Sattva S. Neelapu, MD[18]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]University of South Florida H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [3]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [4]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [5]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [6]Centre Hospitalier Lyon Sud, Pierre-Bénite, France; [7]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA; [8]University of Rochester Medical Center - James P. Wilmot Cancer Center, Rochester, NY, USA; [9]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [10]Ronald Reagan University of California Los Angeles Medical Center, Santa Monica, CA, USA; [11]Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY, USA; [12]John Theurer Cancer Center, Hackensack, NJ, USA; [13]CHU de Lille, Univ Lille, INSERM U1286, Infinite, 59000 Lille, France; [14]Vanderbilt University Medical Center, Nashville, TN, USA; [15]Fox Chase Cancer Center, Philadelphia, PA, USA; [16]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; [17]Kite, a Gilead Company, Santa Monica, CA, USA; and [18]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

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Jacobson C et al. . ASH 2020. Abstr 700. NCT03105336.

ZUMA-5: Axi-cel for refractory Indolent Non-Hodgkin Lymphoma: Study Design

- **Multicenter, single-arm phase II trial**

Patients with R/R FL (grade 1-3a) or MZL (nodal or extranodal), ≥ 2 prior lines of therapy including anti-CD20 mAb + alkylating agent
(N = 153 enrolled)
(N=146 treated)

→

Conditioning CT

Fludarabine 30 mg/m^2 + Cyclophosphamide 500 mg/m^2
Days -5, -4, -3

→

CAR T-Cells

Axi-Cel
2 x 10^6 cells/kg
Day 0

Followed for safety up to 15 yrs

Patients with SD but no relapse > 1 yr from completion of last therapy ineligible. Single-agent anti-CD20 mAb not counted as line of therapy for eligibility. Median time to delivery of axi-cel: 17 days following leukapheresis.

Primary endpoint: ORR (IRRC-assessed per Lugano classification)

Key secondary endpoints: CR rate (IRRC-assessed), ORR (investigator-assessed), DoR, PFS, OS, AEs, CAR T-cell and cytokine levels

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Jacobson C et al. . ASH 2020. Abstr 700. NCT03105336.

ZUMA-5: Baseline Disease Characteristics

Characteristic	FL (n = 124)	MZL (n = 22)	All Patients (N = 146)
Median age (range), years	60 (34 – 79)	66 (48 – 77)	61 (34 – 79)
≥ 65 years, n (%)	38 (31)	13 (59)	51 (35)
Male, n (%)	73 (59)	10 (45)	83 (57)
ECOG 1, n (%)	46 (37)	9 (41)	55 (38)
Stage III-IV disease, n (%)	106 (85)	20 (91)	126 (86)
≥ 3 FLIPI, n (%)	54 (44)	14 (64)	68 (47)
High tumor bulk (GELF criteria), n (%)[a]	64 (52)	8 (36)	72 (49)
Median no. of prior therapies (range)	3 (1 – 10)[b]	3 (2 – 8)	3 (1 – 10)[b]
≥ 3, n (%)	78 (63)	15 (68)	93 (64)
Prior PI3Ki therapy, n (%)	**34 (27)**	**9 (41)**	**43 (29)**
Refractory disease, n (%)[c]	84 (68)	16 (73)	100 (68)
POD24 from first anti-CD20 mAb-containing therapy, n (%)[d]	**68 (55)**	**11 (52)**	**79 (55)**
Prior autologous SCT, n (%)	**30 (24)**	**3 (14)**	**33 (23)**

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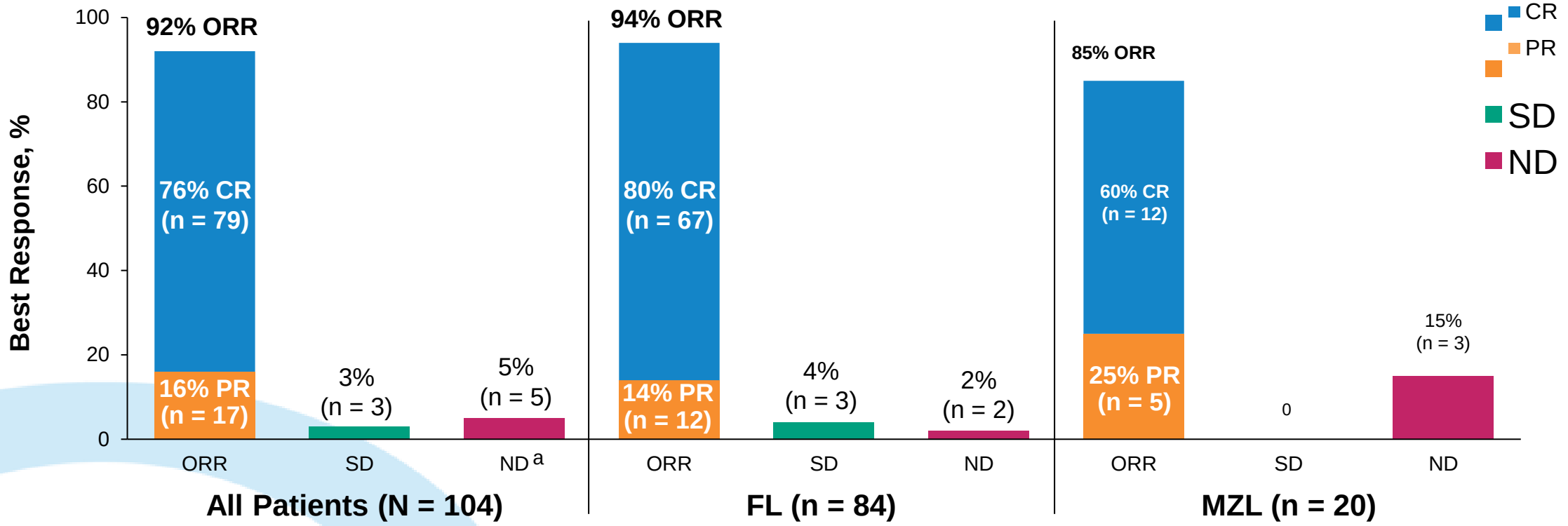
Jacobson C et al. . ASH 2020. Abstr 700. NCT03105336.

ZUMA-5: Efficacy (ORR and CR)



- The median time to first response was 1 month (range, 0.8 – 3.1)
- Among the 25 patients with FL who initially had a PR, 13 (52%) subsequently converted to a CR after a median of 2.2 months (range, 1.9 – 11.2)

The investigator-assessed ORR (N = 104) was 95%, with a CR rate of 77%. Concordance between investigator-assessed and IRRC-assessed ORR was 91%. [a] For the 5 patients reported as ND, 4 (1 FL; 3 MZL) had no disease at baseline and postbaseline per IRRC but were considered with disease by the investigator; 1 patient with FL died before the first disease assessment. CR, complete response; FL, follicular lymphoma; IRRC, Independent Radiology Review Committee; MZL, marginal zone lymphoma; ND, undefined/not done; ORR, overall response rate; PR, partial response; SD, stable disease.

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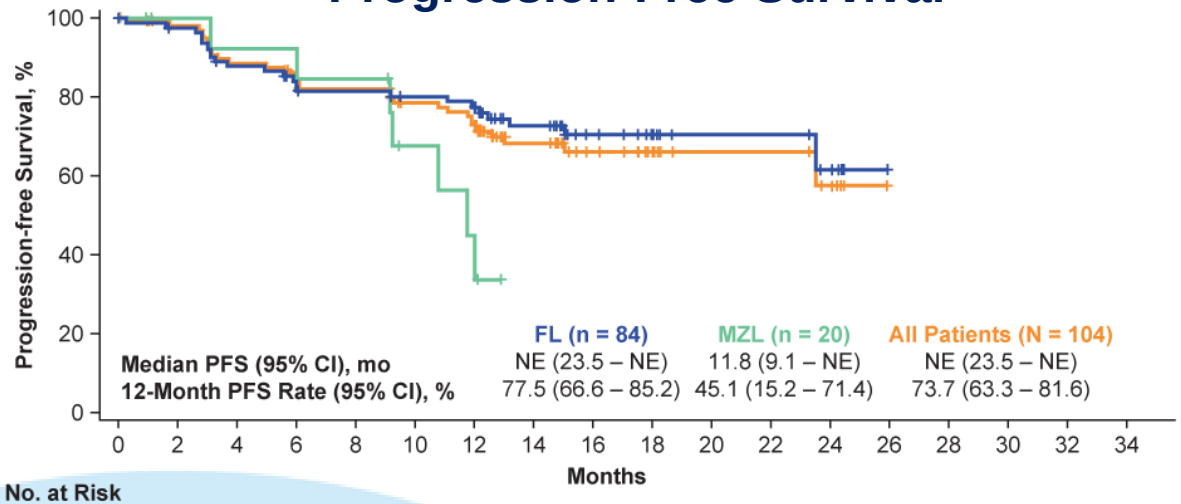
Jacobson C et al. . ASH 2020. Abstr 700. NCT03105336.

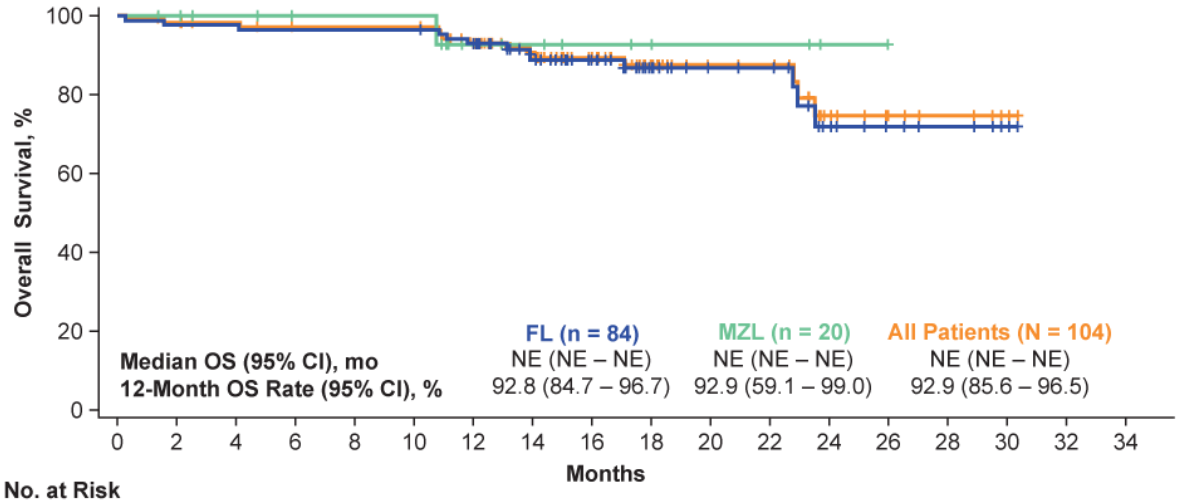
ZUMA-5: Progression Free Survival and Overall Survival

Progression-Free Survival



No. at Risk														
FL	84	80	71	65	62	59	57	40	27	21	9	9	6	0
MZL	20	13	12	12	11	6	4	0						
All Patients	104	93	83	77	73	65	61	40	27	21	9	9	6	0

Overall Survival



No. at Risk																	
FL	84	82	82	81	81	81	77	63	52	35	21	20	11	7	5	2	0
MZL	20	19	16	14	14	14	9	7	5	4	3	3	1	0			
All Patients	104	101	98	95	95	95	86	70	57	39	24	23	12	7	5	2	0

- With a median follow-up of 17.5 months, median PFS and median OS were not reached
  - The 12-month PFS rate was 73.7% (95% CI, 63.3 – 81.6) for all patients
  - The 12-month OS rate was 92.9% (95% CI, 85.6 – 96.5) for all patients

FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; OS, overall survival; PFS, progression-free survival.

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Jacobson C et al. . ASH 2020. Abstr 700. NCT03105336.

ZUMA-5: Cytokine Release Syndrome

Parameter	FL (n = 124)	MZL (n = 22)	All Patients (N = 146)
CRS, n (%)[a]			
Any grade	97 (78)	22 (100)	119 (82)
Grade ≥ 3	**8 (6)**	**2 (9)**	**10 (7)**
Most common symptoms of any grade, n/n (%)			
Pyrexia	94/97 (97)	20/22 (91)	114/119 (96)
Hypotension	39/97 (40)	10/22 (45)	49/119 (41)
AE management, n (%)			
Tocilizumab	56 (45)	15 (68)	71 (49)
Corticosteroids	19 (15)	6 (27)	25 (17)
Median time to onset (range), days	4 (1 – 15)	4 (1 – 9)	4 (1 – 15)
Median duration of events (range), days	6 (1 – 27)	6 (2 – 14)	6 (1 – 27)
Patients with resolved events, n/n (%)	96/97 (99)[b]	22/22 (100)	118/119 (99)[b]

- **Grade 4 and Grade 5 CRS occurred in 1 patient each**
- No patients had ongoing CRS as of the cutoff date[b]

[a] CRS was graded per Lee DW, et al. *Blood*. 2014;124:188-195. Individual symptoms of CRS were graded per National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03. [b] One patient with FL died of multisystem organ failure in the context of CRS (Day 7) prior to the resolution of CRS.
AE, adverse event; CRS, cytokine release syndrome; FL, follicular lymphoma; MZL, marginal zone lymphoma.

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Jacobson C et al. . ASH 2020. Abstr 700. NCT03105336.

ZUMA-5: ICANS

Parameter	FL (n = 124)	MZL (n = 22)	All Patients (N = 146)
Neurologic events, n (%)[a]			
Any grade	70 (56)	17 (77)	87 (60)
Grade ≥ 3	**19 (15)**	**9 (41)**	**28 (19)**
Most common events of any grade, n/n (%)			
Tremor	36/70 (51)	9/17 (53)	45/87 (52)
Confusional state	28/70 (40)	7/17 (41)	35/87 (40)
AE management, n (%)			
Corticosteroids	38 (31)	14 (64)	52 (36)
Tocilizumab	7 (6)	2 (9)	9 (6)
Median time to onset (range), days	7 (1 – 177)	7 (3 – 19)	7 (1 – 177)
Median duration of events (range), days	14 (1 – 452)	10 (2 – 81)	14 (1 – 452)
Patients with resolved events, n/n (%)	67/70 (96)	14/17 (82)	81/87 (93)

- **Grade 4 neurologic events were reported for 3 patients; no Grade 5 events were reported**
- Events were ongoing at the cutoff date in 6 patients: Grade 1 memory impairment (n = 2) and attention disturbance, intermittent paresthesia, and tremor (n = 1 each) and Grade 2 facial paresthesia (n = 1)

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Jacobson C et al. . ASH 2020. Abstr 700. NCT03105336.

Efficacy and Safety of Tisagenlecleucel in Adult Patients With Relapsed/Refractory Follicular Lymphoma: Interim Analysis of 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] Sarah Nagle,[19] Loretta Nastoupil,[1] Bastian von Tresckow,[20,21] Andrés José María Ferreri,[22] Takanori Teshima,[23] Piers EM Patten,[24] Joseph McGuirk,[25] Andreas Petzer,[26] Fritz Offner,[27] Andreas Viardot,[28] Pier Luigi Zinzani,[29] Ram Malladi,[30] Lida Bubuteishvili Pacaud,[31] Alessandra Forcina,[32] Aiesha Zia,[32] Stephen J. Schuster,[33,*] Catherine Thieblemont[34,*]
*Dr Schuster and Dr Thieblemont are co-senior authors.

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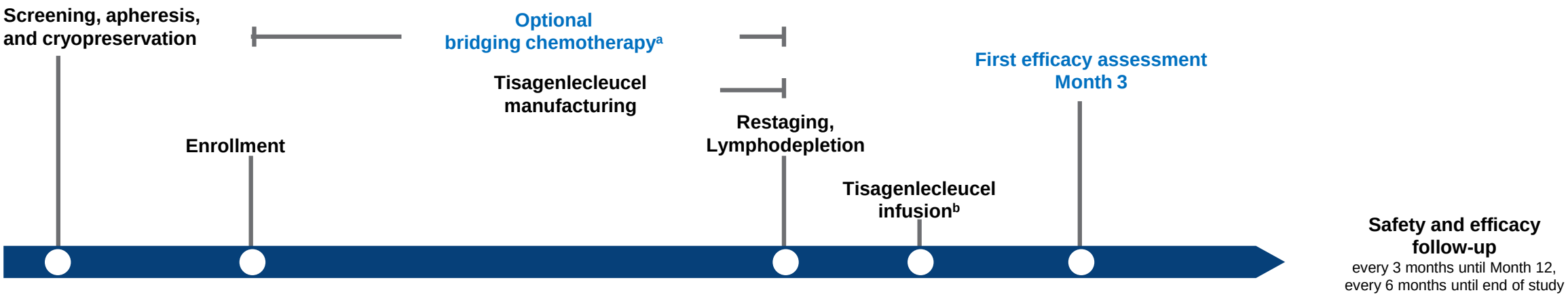
Fowler NH et al. ICML 2021 Virtual, Oral presentation 85.

ELARA: Tisagenlecleucel for R/R Follicular Lymphoma



Key eligibility criteria	Study treatment	Endpoints

• ≥18 years of age
• FL grade 1, 2, or 3A
• Relapsed/refractory disease
• No evidence of histological transformation/FL 3B
• No prior anti-CD19 therapy or allogeneic HSCT
	• Lymphodepleting chemotherapy options were
	  • Fludarabine (25 mg/m^2 IV daily for 3 days) + cyclophosphamide (250 mg/m^2 IV daily for 3 days)
	  • Bendamustine 90 mg/m^2 IV daily for 2 days
	• Tisagenlecleucel dose range (single IV infusion) was: 0.6-6×10^8 CAR-positive viable T cells
		Primary: CR by IRC (Lugano classification 2014)
		
		Secondary: ORR, DOR, PFS, OS, safety

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Fowler NH et al. ICML 2021 Virtual, Oral presentation 85.

ELARA: Demographics and Baseline Disease Status

	All Patients (N=97)*
Median age (range), y ≥ 65 y, %	57.0 (29-73) 24.7
ECOG PS prior to infusion, % 0 1 2	 56.7 39.2 4.1
Stage at study entry III-IV, %	83.5
FLIPI ≥3, %	59.8
Median no. of prior therapies (range) ≥5, %	4 (2-13) 27 (27.8)
POD24 from first anti-CD20 mAb containing therapy,[a] %	**59.8**
Refractory to last line of therapy,[b] %	77.3
Prior autologous HSCT, %	**36.1**
Refractory to ≥2 regimens, %	76.3
Prior therapy, % Anti-CD20 mAb and alkylating agents[c] **PI3K inhibitors** Lenalidomide and rituximab	 64.9 **20.6** 17.3

*Enrolled pts: 98; Infused pts: 97)

- ✓ Median f/up for infused pts (N=97): 10.6 months (4.3-19.7).
- ✓ Median f/up of pts eval for efficacy (N=94): 11 months (4.3-19.7)

- ✓ 18% received Tisa-cel in the outpatient setting.
- ✓ 44% of pts received bridging chemotherapy.
- ✓ Media dose of infused Tisa-cel: 2.06×10^8

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Fowler NH et al. ICML 2021 Virtual, Oral presentation 85.

ELARA: Primary Endpoint

Best Overall Response Rate (by IRC)

Response Rate, %	Patients Evaluable for Efficacy[a] (n=94)
CR	66[a]
PR	20.2
ORR (CR + PR)	86.6

- Investigator-assessed CR rate was 69.1%[b] (ORR 90.4%)
- ORR was consistent across subgroups, including prior SCT, disease status, and high-risk features

- Median follow-up for efficacy (n=94): 11 months (4.3-19.7)
- Probability for a responding patient to remain in response ≥6 months was 79% (95% CI 66-87).
- 12 of 31 PRs (38.7%) converted to CRs; all but 1 occurred between Month 3 and Month 6
- Median time to next antilymphoma treatment was not reached and 69% (36/52) had ongoing responses at the time of data cutoff.
- DOR in pts with CR was 93.7% (95% CI: 81.7-97.9) at 6 months.

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Fowler NH et al. ICML 2021 Virtual, Oral presentation 85.

Adverse Events of Special Interest

	Treated Patients N=97	
AESI (within 8 weeks of infusion)	All grades, %	Grade ≥3, %
Cytokine release syndrome[a,1]	48.5	**0**
Neurological adverse reactions	9.3	**1.0**
Infections	18.6	5.2
Tumor lysis syndrome	1.0	1.0
Prolonged depletion of B cells and/or agammaglobulinemia[b]	10.3	0
Hematologic disorders including cytopenias		
Neutropenia[c,d]	30.9	27.8
Anemia[c]	24.7	13.4
Thrombocytopenia[c]	16.5	9.3

- Median onset of NEs was 8.5 (4-190[e]) days
  - Median time to resolution was 2 days
- Only 1 case of serious ICANS within the first 8 weeks
- CRS median onset was 4.0 (1-14) days and all cases were low grade
- 74.5% of the CRS events and 100% of ICANS occurred in patients with bulky disease
- B-cell recovery at month 6 was 82.6% (95% CI: 66.0-91.6)

All neurological and CRS events resolved with appropriate management

[a]CRS was graded using the Lee scale 2014. [b]Prolonged depletion is defined as lasting ≥ 28 days. Agammaglobulinemia is defined as IgG <4 g/L. Patients were counted here if they had either B cell depletion or agammaglobulinemia or both. [c]One of multiple preferred terms evaluated under the AESI, "Hematologic disorders including cytopenias." [d]Median duration of grade 3/4 neutropenia was 52 days (based on laboratory data). [e]One patient experienced grade 3 delirium with onset on Day 190, occurring after the patient had started new anticancer therapy.

AESI, adverse event of special interest; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; NE, neurological event.

1. Lee DW, et al. Blood. 2014;124(2):188-195.

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Fowler NH et al. ICML 2021 Virtual, Oral presentation 85.

Study/phase	Type of lymphoma	Regimen	Number of patients	ORR%/CR%	PFS, months	OS, months
P III	FL/MZL	B+O; O maintenance	164 FL/28 MZL	69.1/11.2	25.8 months	41 months
Leonard *et al.*[30]/P III	FL/MZL	Rituximab plus Lenalidomide	147 FL/31 MZL	78/34	39.4 months	2 years OS = 95% FL 2 years OS = 82% MZL
Gopal *et al.*[31]/P II	FL/MZL	Idelalisib	72 FL/15 MZL	57/6	11 months FL 7 months MZL	20.3 months
Flinn *et al.*[32]/P II	FL/MZL	Duvelisib	83 FL/18 MZL	40/20 FL 66.7/0 MZL	9.5 mo.	28.9 months
Dreyling *et al.*[33]/P II	FL/MZL	Copanlisib	104 FL/23 MZL	58.7/20.2 FL 78.3/13 MZL	12.5 months 24.1 months	42.6 months 83% at 2 years
Zinzani *et al.*[34]/P II	FL MZL	Umbralisib	117 FL 69 MZL	53/12 FL 55/10.5 MZL	16 months 71% at 12 months	NR NR
Gopal *et al.*[35]/P II Noy *et al.*[36]/P II	FL MZL	Ibrutinib	110 FL 63 MZL	20.9/11 48/3	4.6 months 14.2 months	78% at 2 years 81% at 18 months
Morschhauser *et al.*[37]/P II	FL	Tazemetostat	45 EZH2 mut FL 54 EZH2 wt FL	69/11 35/3	13.8 months 11.1 months	
Jacobson C et al./ Phase II	FL/MZL	Axi-cel	124 FL/22 MZL	94/80 FL/ 85/60 MZL	**12 mo PFS**: 73.7%	**12 mo OS:** All:92.9% FL: 92.8% MZL: 92.9%

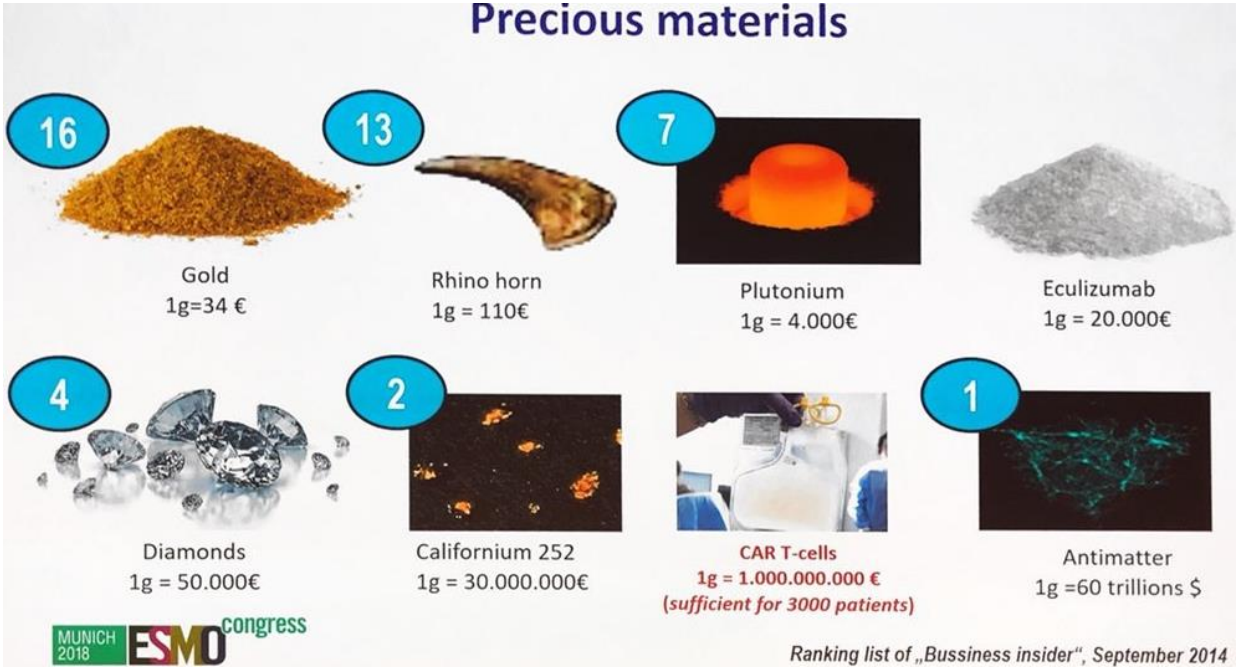
Sandoval-Sus and Chavez JC. Ther Adv Hematol May 2021

CAR-T cell Therapy reality check….. (no pun intended)

TABLE 1. FDA-Approved CAR T-Cell Therapies[5-10]

Therapy and manufacturer	Construct	Indications	WAC	HCPCS code
Tisagenlecleucel	Anti-CD19-4-1BB-CD3z	• Patients aged up to 25 years with B-cell precursor ALL that is refractory or in second or later relapse • Adults with R/R LBCL after ≥2 lines of systemic therapy, including LBCL NOS, LBCL arising from follicular lymphoma, high-grade B-cell lymphoma	ALL: $475,000 B-cell lymphoma: $373,000	Q2042
Axicabtagene ciloleucel	Anti-CD19-CD28-CD3z	• Adults with R/R LBCL after ≥2 lines of systemic therapy, including LBCL NOS, LBCL arising from follicular lymphoma, primary mediastinal LBCL, high-grade B-cell lymphoma • Adults with relapsed or refractory follicular lymphoma after ≥2 lines of systemic therapy	$399,000	Q2041
Lisocabtagene maraleucel	Anti-CD19-4-1BB-CD3z	Adults with R/R LBCL after ≥2 lines of systemic therapy, including LBCL NOS (including LBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal LBCL, and follicular lymphoma grade 3B	$410,300	C9399
Brexucabtagene autoleucel	Anti-CD19-CD28-CD3z	Adults with R/R mantle cell lymphoma	$399,000	Q2053
Idecabtagene vicleucel	Anti-BCMA-4-1BB-CD3z	Adults with R/R multiple myeloma after ≥4 lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody	$419,500	C9399

ALL, acute lymphoblastic leukemia; LBCL, large B-cell lymphoma; HCPCS, healthcare common procedure coding system; NOS, not otherwise specified; R/R, relapsed/refractory; WAC, wholesale acquisition cost.



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Am J Manag Care. 2021;27(13):S253-S261.

Conclusions

- Anti-CD19 CAR- T cell therapy currently is the standard of care (SOC) for patients with R/R DLBCL, PMBCL and other HGBCL after 2 or more therapies.

- There are multiple available anti-CD19 CAR-T cell products approved for R/R DLBCL/HGBCL (Tisa-cel, Axi-cel and Lisa-cel). Hence, we can potentially chose based on:
  - ✓ Age and co-morbidities (as always, age is just a number).
  - ✓ Setting were CAR-T will be administered (outpatient vs. inpatient).
  - ✓ Efficacy: hard to say since there are no head-to-head randomized trials between products.

- Brexucabtagene Autoleucel (and others to come) is currently the SOC in patients with R/R MCL, specially after s/p BTKi disease progression.

- Anti-CD19 CAR- T cell therapy is one of the most active agents against R/R FL, including high risk patients (i.e. POD24), but hard to say if it is SOC in patients with indolent lymphomas.

- Available data suggest anti-CD19 CAR-T cell therapy is less active in R/R MZL and further studies are needed to gain more knowledge about these differences amongst indolent B-cell NHL.

- Best advise for the general Hematologist-Oncologist = **Refer early to CAR-T centers (6 center in FL for adults)**
  - ✓ Active and collegial communication between CAR-T center and treating physical is fundamental

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Thank you very much to:

- All the patients and caregivers.
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- All my mentors.
- To FLASCO and to all my colleagues.

MOFFITT | Memorial Healthcare System
Malignant Hematology & Cellular Therapy

Email: jose.sandoval@moffiitt.org; **jsandovalsus@mhs.net**

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