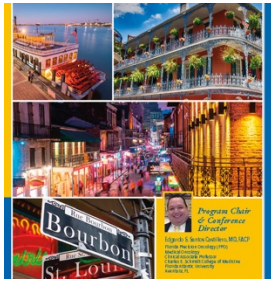
MAYO CLINIC



15th ANNUAL
NEW ORLEANS SUMMER CANCER MEETING
November 20-22, 2020
THE ROOSEVELT NEW ORLEANS

Accredited by: MEC THE MEDICAL EDUCATOR CONSORTIUM
In Collaboration with: Florida Society of Clinical Oncology; Louisiana Oncology Society

Chimeric Antigen Receptor T-cell therapy in 2020: Current Indications

Mohamed A. Kharfan-Dabaja, MD, MBA, FACP
Professor of Medicine
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Director Blood and Marrow Transplantation and Cellular Therapies
Mayo Clinic, Jacksonville, FL

New Orleans, LA
November 22, 2020

Off label discussion(s)

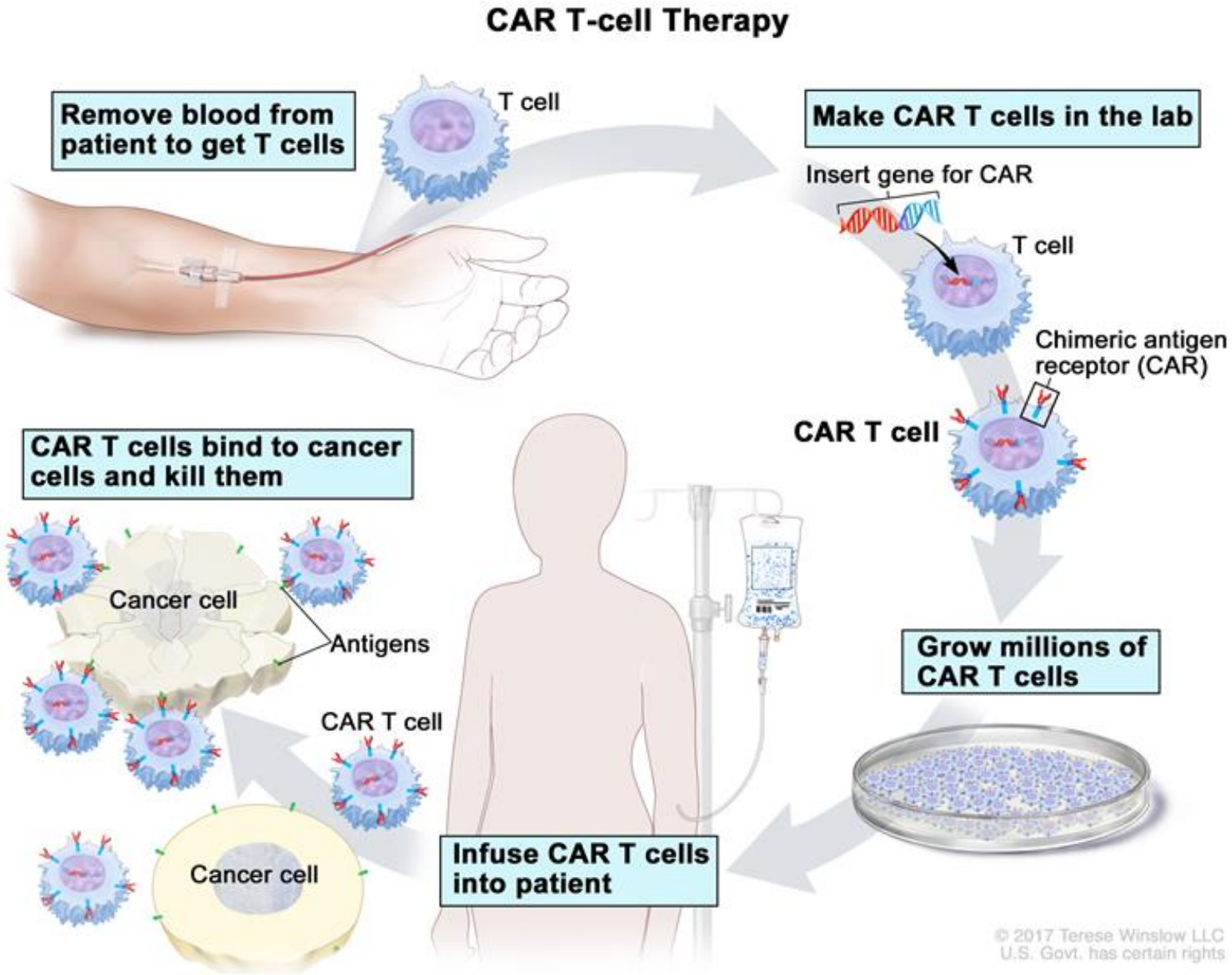
- Lisocabtagene maraleucel (liso-cel; **JCAR017**; Anti-CD19 CAR T-Cell)

Outline

- CAR-T therapy background on FDA approved products
  - B-cell acute lymphoblastic leukemia
  - Diffuse large B cell lymphoma
  - Mantle cell lymphoma (ZUMA-2)

What is CAR T-cell therapy?

- Stands for **C**himeric **A**ntigen **R**eceptor **T**-cell Therapy
- Immunotherapy that uses engineered T lymphocytes to specifically target the intended cancer cell
  - Upon infusion, the receptors may help guide the T cells to identify and attack intended cancer cells throughout the body



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Source: www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy

Approved indications by the US-FDA

- B-cell precursor acute lymphoblastic leukemia, up to 25 years of age, refractory or in second or later relapse
  - Tisagenlecleucel

- Adults with relapsed or refractory large B-cell lymphoma after ≥ 2 lines of systemic therapy, including:
  - Axicabtagene Ciloleucel
  - Tisagenlecleucel
    - DLBCL-NOS
    - Primary mediastinal large B-cell lymphoma (only axicabtagene ciloleucel)
    - High grade B-cell lymphoma
    - DLBCL arising from follicular lymphoma

Approved indications by the US-FDA

- For the treatment of adult patients with relapsed/refractory **mantle cell lymphoma (r/r MCL)**
  - Brexucabtagene autoleucel

Why CAR-T cell therapy in B-cell ALL?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp

N Engl J Med 2018;378:439-48.
DOI: 10.1056/NEJMoa1709866

Study population

- Patients screened= 107
  - Enrolled= 92
  - Treated with Tisagencleucel=75
    - Median age=11 (3-23) years
    - Median prior therapies= 3 (1-8)
    - Median % marrow blasts= 74% (5-99%)
    - **Prior allogeneic transplant= 46 (61%)**

Maude SL, et al. N Engl J Med. 2018; 378: 439-448

Tisagenlecleucel

- In this planned analysis, 75 pts received tisagenlecleucel and were evaluated for efficacy
  - Overall remission rate within 3 months=**81%**
    - All pts who had response had negative MRD
    - 6-months EFS= 73%; OS=90%
    - 12-months EFS=50%; **OS=76%**
    - Median duration of remission **not reached**

MAYO CLINIC

N Engl J Med 2018;378:439-48.
DOI: 10.1056/NEJMoa1709866

Tisagenlecleucel- 18 month updated analysis (ELIANA study)

Median OS was not reached

	RFS	OS
18-month	**66% (95%CI= 52-77%)**	**70% (95%CI=58-79%)**

Grupp SA, et al. ASH 2018. Blood (2018) 132 (Supplement 1): 895

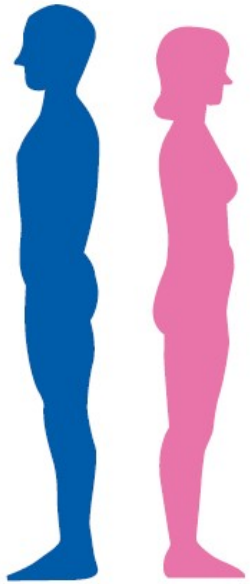
Large B-cell lymphoma

Non-Hodgkin lymphoma

In 2020= 77,240 new cases in the USA
Men= 55%

Estimated New Cases

Males				Females		
Prostate	191,930	21%		Breast	276,480	30%
Lung & bronchus	116,300	13%		Lung & bronchus	112,520	12%
Colon & rectum	78,300	9%		Colon & rectum	69,650	8%
Urinary bladder	62,100	7%		Uterine corpus	65,620	7%
Melanoma of the skin	60,190	7%		Thyroid	40,170	4%
Kidney & renal pelvis	45,520	5%		Melanoma of the skin	40,160	4%
Non-Hodgkin lymphoma	42,380	5%		Non-Hodgkin lymphoma	34,860	4%
Oral cavity & pharynx	38,380	4%		Kidney & renal pelvis	28,230	3%
Leukemia	35,470	4%		Pancreas	27,200	3%
Pancreas	30,400	3%		Leukemia	25,060	3%
All Sites	**893,660**	**100%**		**All Sites**	**912,930**	**100%**



Siegel RL, et al. CA Cancer J Clin. 2020; 70:7-30

Diffuse large B-cell lymphoma

- 77,240 will develop non-Hodgkin lymphoma in the US in 2020[a]
  - Approx. 30-35% will be diffuse large B-cell (DLBCL) type
- 1st line chemo-immunotherapy yields successful outcomes in two-third of cases[b]
- High-dose therapy and autologous HCT cures ~50% of chemosensitive-relapsed cases[c]
  - But outcomes are dismal for those who receive an auto-HCT with relapsed refractory disease (< 15% are cured)[d]

MAYO CLINIC

a. Siegel RL, et al. CA Cancer J Clin. 2020; 70:7-30
b. Feugier P, et al. J Clin Oncol 23:4117-26, 2005
c. Philip T, et al. N Engl J Med 333:1540-5, 1995
d. Philip T, et al. N Engl J Med 316:1493-8, 1987

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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

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

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

N=111 patients

Table 1. Treatment Disposition and Baseline Characteristics of the Patients.*

Variable	Patients with DLBCL	Patients with PMBCL or TFL	All Patients
Treatment disposition			
No. of patients enrolled	81	30	111
Treatment with axi-cel — no. (%)			
Yes	77 (95)	24 (80)	101 (91)
No	4 (5)	6 (20)	10 (9)
Death before treatment†	1 (1)	2 (7)	3 (3)
Adverse event‡	3 (4)	2 (7)	5 (5)
Other§	0	2 (7)	2 (2)
Characteristics at baseline			
No. of patients	77	24	101
Disease type — no. (%)			
DLBCL	77 (100)	0	77 (76)
PMBCL	0	8 (33)	8 (8)
TFL	0	16 (67)	16 (16)
Age			
Median (range) — yr	58 (25–76)	57 (23–76)	58 (23–76)
≥65 yr — no. (%)	17 (22)	7 (29)	24 (24)
Male sex — no. (%)	50 (65)	18 (75)	68 (67)
ECOG performance-status score of 1 — no. (%)	49 (64)	10 (42)	59 (58)
Disease stage — no. (%)			
I or II	10 (13)	5 (21)	15 (15)
III or IV	67 (87)	19 (79)	86 (85)
International Prognostic Index score — no. (%)¶			
0–2	40 (52)	13 (54)	53 (52)
3 or 4	37 (48)	11 (46)	48 (48)
CD-19 status — no./total no. (%)‖			
Negative	7/63 (11)	1/19 (5)	8/82 (10)
Positive	56/63 (89)	18/19 (95)	74/82 (90)
Prior therapies — no. (%)			
≥Three prior lines of therapy	49 (64)	21 (88)	70 (69)
History of primary refractory disease**	23 (30)	3 (12)	26 (26)
History of resistance to two consecutive lines	39 (51)	15 (62)	54 (53)

Table 1. (Continued.)

Variable	Patients with DLBCL	Patients with PMBCL or TFL	All Patients
Refractory subgroup at study entry — no. (%)			
Primary refractory	2 (3)	0	2 (2)
Refractory to second-line or subsequent therapy	59 (77)	19 (79)	78 (77)
Relapse after autologous stem-cell transplantation	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

Before CAR-T

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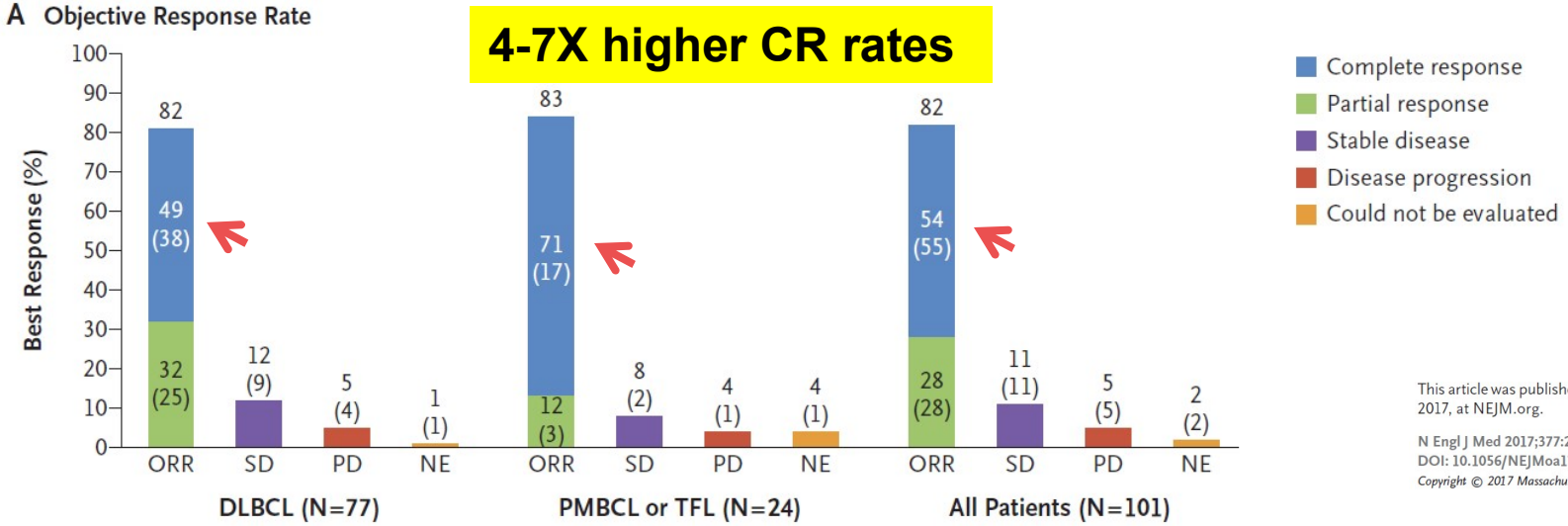
CR rate	7	5	20	18	10 (5-20)
Relapse ≤12 mo post-ASCT					
RR	19	35	—	39	34 (24-45)
CR rate	6	10	—	25	15 (6-31)

Axicabtagene ciloleucel

4-7X higher CR rates



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

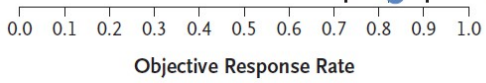
MAYO CLINIC

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

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

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)



4095 A Comparison of Two-Year Outcomes in ZUMA-1 (Axicabtagene Ciloleucel) and SCHOLAR-1 in Patients with Refractory Large B Cell Lymphoma

Program: Oral and Poster Abstracts
Session: 626. Aggressive Lymphoma (Diffuse Large B-Cell and Other Aggressive B-Cell Non-Hodgkin Lymphomas)—Results from Prospective Clinical Trials: Poster III
Hematology Disease Topics & Pathways:
Adult, Biological, Diseases, CRS, neurotoxicity, Therapies, CAR-Ts, Adverse Events, Non-Hodgkin Lymphoma, DLBCL, Study Population, Clinically relevant, Lymphoid Malignancies

Monday, December 9, 2019, 6:00 PM-8:00 PM
Hall B, Level 2 (Orange County Convention Center)

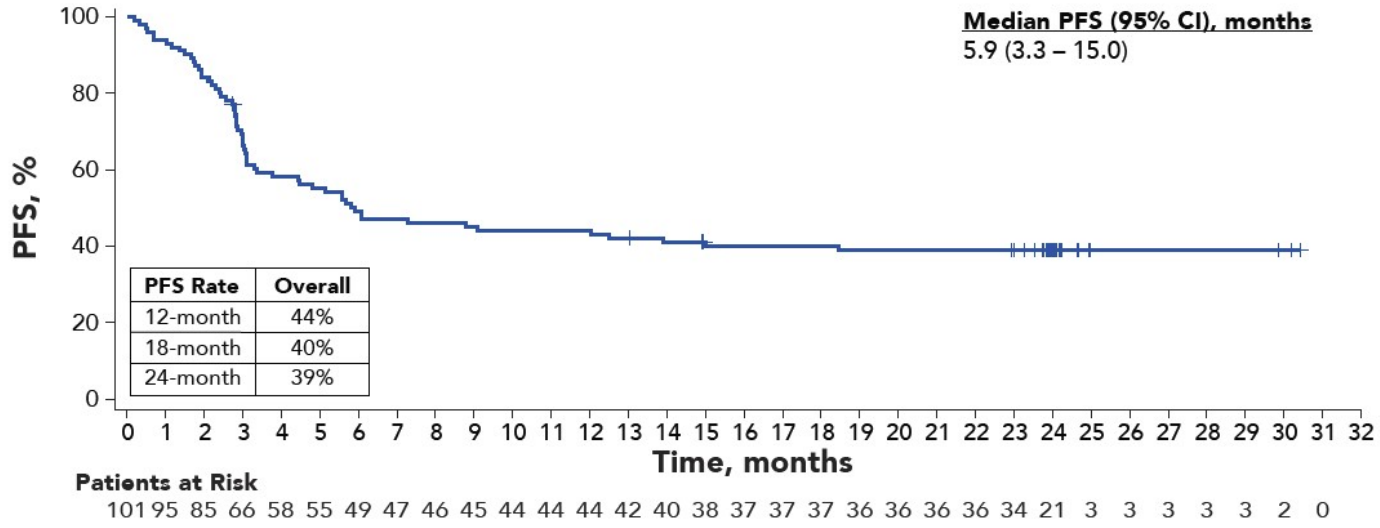
Sattva S Neelapu, MD[1], Frederick L. Locke, MD[2], Nancy L Bartlett, MD[3*], Lazaros J Lekakis, MD[4*], Patrick M Reagan, MD[5], David B. Miklos, MD, PhD[6], Caron A. Jacobson, MD, MMSc[7*], Ira Braunschweig, MD[8*], Olalekan O. Oluwole, MBBS, MPH[9], Tanya Siddiqi, MD[10*], Yi Lin, MD, PhD[11], Michael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

<u>The 2-year survival rate after standardization was</u>:

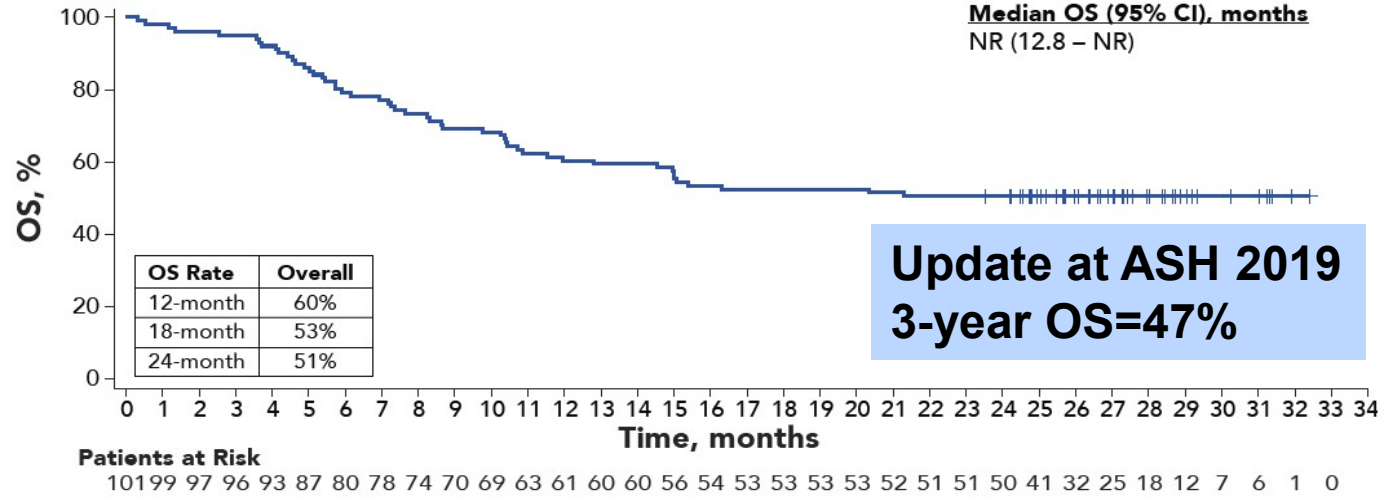
- ***ZUMA-1 =50% (95% CI, 40% – 59%)***
- SCHOLAR-1=12% (95% CI, 9% – 15%)

Translated to a **<u>73% reduction in risk of death</u>** in ZUMA-1 vs. SCHOLAR-1 (HR, 0.27; *P*< .0001)

Axicabtagene ciloleucel: survival update



NR, not reached; PFS, progression-free survival.

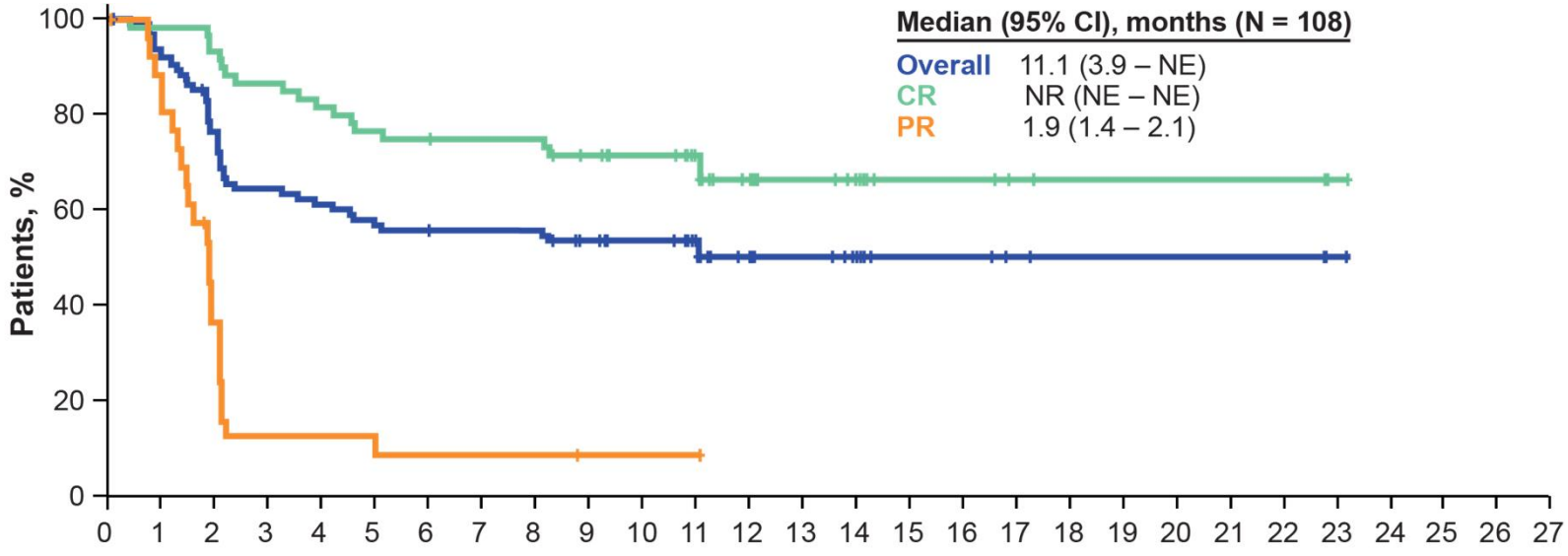


Update at ASH 2019
3-year OS=47%

NR, not reached; OS, overall survival.

Neelapu SS, et al. N Engl J Med. 2017; 377:2531-44
Neelapu et al. ASH 2018 (data update)
Topp MS. Et al. ASH 2019. Abs 243

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												

JULIET

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*

This article was published on December 1, 2018, at NEJM.org.

N Engl J Med 2019;380:45-56.
DOI: 10.1056/NEJMoa1804980

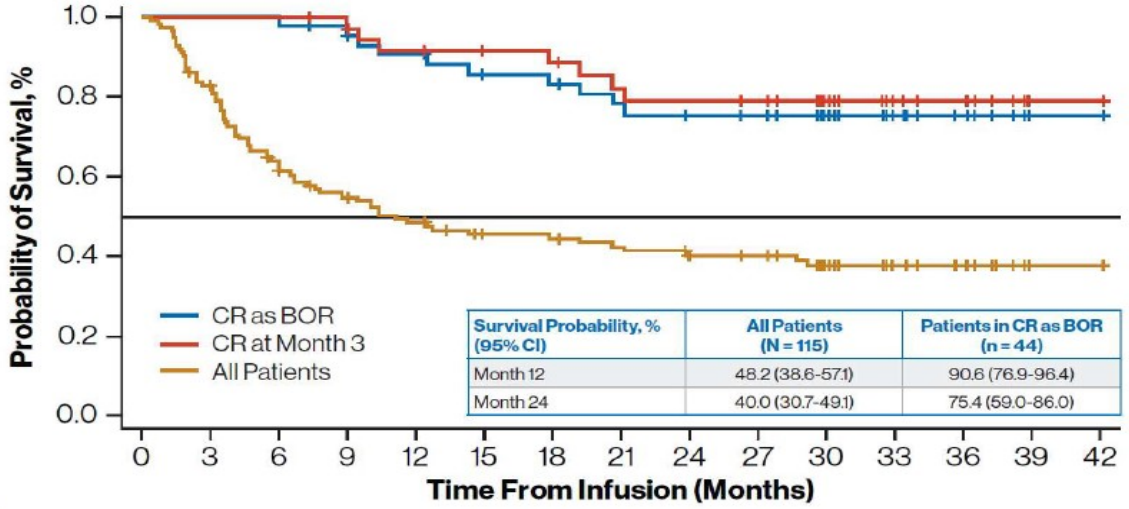
N=111 patients

Table 1. Demographic and Clinical Characteristics of the Patients in the Full Analysis Set at Baseline.*

Characteristic	Patients (N=111)
Median age (range) — yr	56 (22–76)
Age ≥65 yr — no. (%)	25 (23)
ECOG performance status — no. (%)†	
0	61 (55)
1	50 (45)
Disease stage at study entry — no. (%)‡	
Stage I	8 (7)
Stage II	19 (17)
Stage III	22 (20)
Stage IV	62 (56)
Bone marrow involvement at study entry — no. (%)	8 (7)
Diagnosis on central histologic review — no. (%)	
Diffuse large B-cell lymphoma, not otherwise specified	88 (79)
Transformed follicular lymphoma	21 (19)
Other	2 (2)
Double- or triple-hit rearrangement: *MYC* plus *BCL2*, *BCL6*, or both — no./total no. (%)§	19/70 (27)
Cell of origin of cancer — no. (%)	
Germinal center B-cell type	63 (57)
Non–germinal center B-cell type	45 (41)
Missing data	3 (3)
No. of previous lines of antineoplastic therapy — no. (%)¶	
1	5 (5)
2	49 (44)
3	34 (31)
4–6	23 (21)
Relapse after last therapy — no. (%)‖	50 (45)
Refractory diffuse large B-cell lymphoma — no. (%)**	61 (55)
Previous autologous hematopoietic stem-cell transplantation — no. (%)	54 (49)

Tisagenlecleucel: JULIET update

Results: Overall Survival For Patients in CR and All Patients in Full Cohort



At Risk															
CR as BOR	44	44	43	41	38	34	33	30	28	27	21	12	8	1	1
CR at Month 3	37	37	37	35	32	30	29	26	25	24	18	9	7	1	1
All Patients	115	93	68	59	51	44	43	40	36	35	24	14	9	1	1

- Median OS in the full cohort was 11.1 months (95% CI, 6.6-23.9 months) and not reached for patients in CR

Westin JR, et al. ASH 2019. Poster 4103

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

Table 1: Patient Demographics and Baseline Characteristics

	NHL N=70 n (%)
Age at infusion (years)	
Median (range)	65.11 (18.5-88.9)
Sex - n (%)	
Female/Male	27 (38.6) / 43 (61.4)
Race - n (%)	
White	60 (85.7)
African-American	2 (2.9)
Asian	3 (4.3)
More than one race	0 (0)
Unknown / Not reported	5 (7.1)
ECOG performance status -- n (%)	
0	24 (34.3)
1	33 (47.1)
2	3 (4.3)
Not reported	10 (14.3)
Lymphoma type	
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	22 (31.4)
DLBCL	21 (30)
DLBCL - germinal center B-cell type	13 (18.6)
DLBCL – activated B-cell type	10 (14.3)
T-cell/histiocytic rich large B-cell lymphoma	2 (2.9)
Follicular, mixed small cleaved and large cell	1 (1.4)
Follicular (grade unknown)	1 (1.4)
Histologic transformation	
No transformation	51 (72.9)
Transformation from a different lymphoma histology	15 (21.4)
Transformation from CLL	4 (5.7)
Stage at diagnosis	
I	4 (5.7)
II	6 (8.6)
III	14 (20.0)
IV	23 (32.9)
Prior auto transplant	16 (22.9)
Prior allo transplant	4 (5.7)
Number of prior lines	
Median (range)	3 (0-9)
0	1 (1.4)
1	4 (5.7)
2	12 (17.1)
≥ 3	47 (67.1)
Not reported	6 (8.6)
Disease status prior to CT	
Primary induction failure – resistant	22 (31.4)
Second or later complete remission	4 (5.7)
First relapse	18 (25.7)
Second relapse	22 (31.4)
≥ Third relapse	2 (2.9)
Not reported / unknown	2 (2.9)

Table 2: Cell Viability vs Best Overall Responses

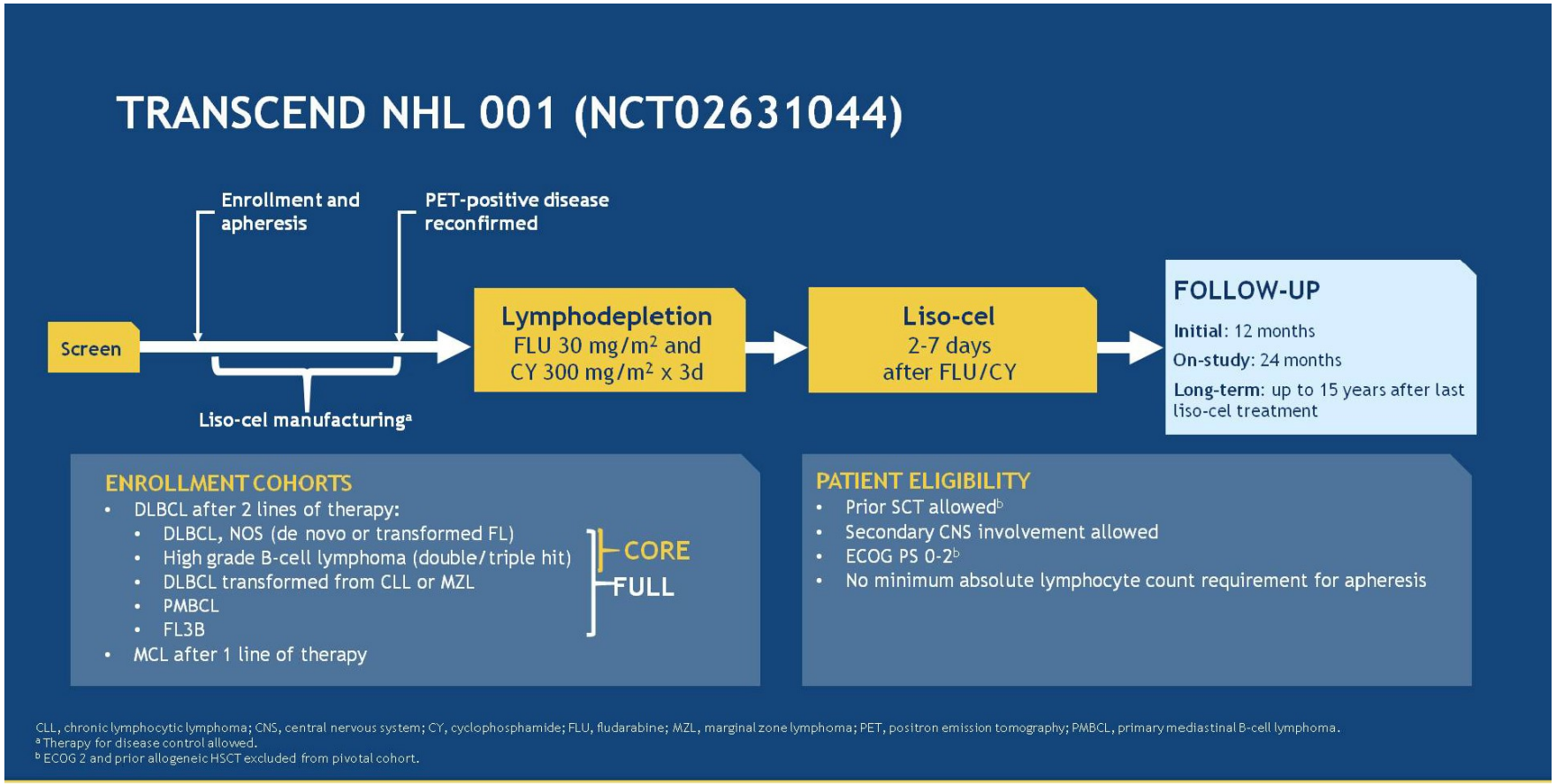
Best Overall Response	Viability ≥ 80% (N=23)	Viability60 - 80% (N=21)
CR	9 (39)	8 (38)
PR	5 (22)	4 (19)
Overall response (CR + PR)	14 (61)	12 (57)
No response/stable disease	2 (9)	0 (0)
Progressive disease	7 (30)	7 (33)
Not assessed	0 (0)	2 (10)

All patients received cells in the approved range for their weight.

Viability data missing for 3 patients due to incomplete batch number identification

Jaglowski S, et al. ASH 2019. Abs 766

TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017)



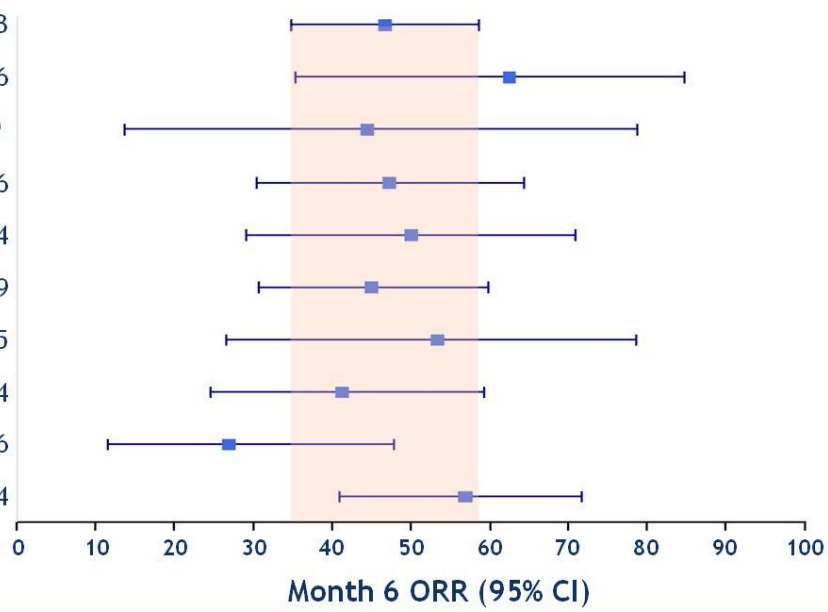
MAYO CLINIC

Abramson JS, et al. J Clin Oncol 36, 2018 (suppl; abstr 7505)

TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017)

High Durable ORR in Poor-Risk DLBCL Subgroups

Population	ORR (95% CI)	n
CORE patient population[a]	46.6 (34.8-58.6)	73
Double/triple hit	62.5 (35.4-84.8)	16
Double expressor	44.4 (13.7-78.8)	9
Never in CR	47.2 (30.4-64.5)	36
Chemosensitive	50 (29.1-70.9)	24
Chemorefractory	44.9 (30.7-59.8)	49
Relapse < 12 mo from ASCT	53.3 (26.6-78.7)	15
SD/PD to last chemotherapy	41.2 (24.6-59.3)	34
IPI 3-5	26.9 (11.6-47.8)	26
IPI 0-2	56.8 (41-71.7)	44



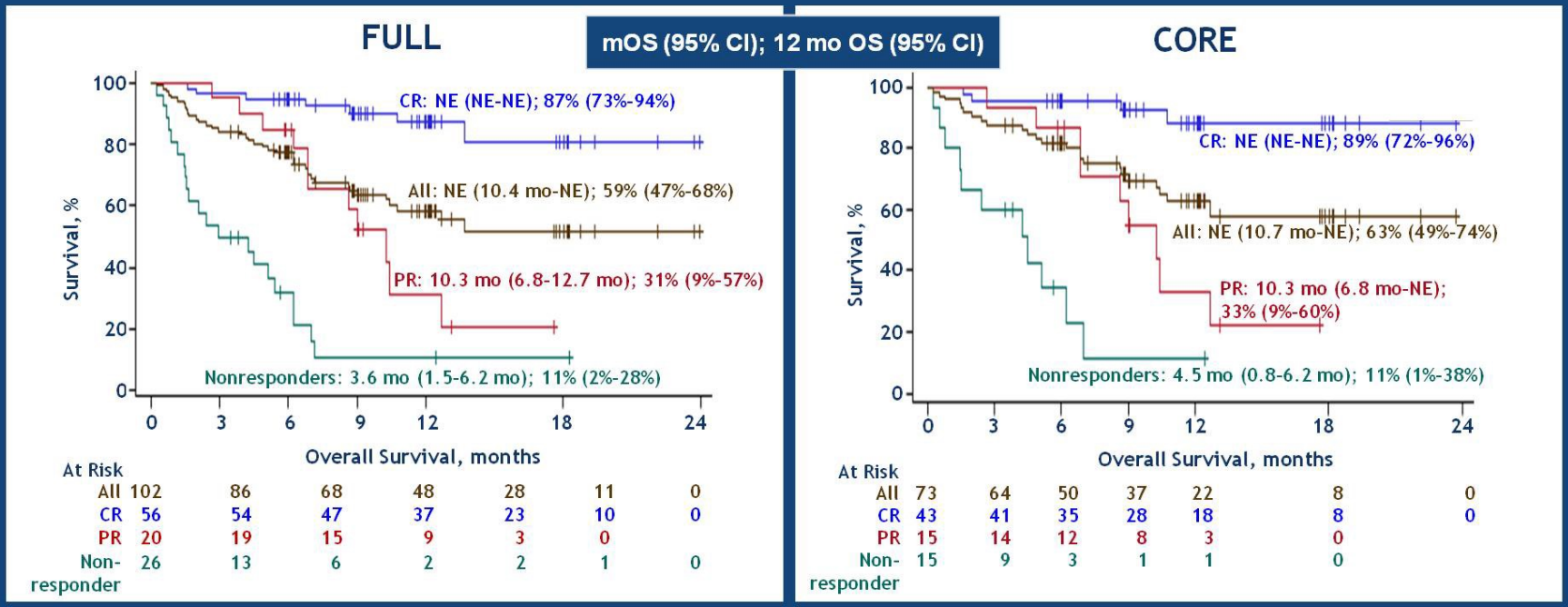
[a] Includes all DLBCL patients treated at all dose levels in CORE.

Abramson JS, et al. J Clin Oncol 36, 2018 (suppl; abstr 7505)

TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017)

Overall Survival (OS)

Early OS Encouraging in High-Risk DLBCL Patient Population (Median Follow-up 12 Months)



NE, not estimable.

Abramson JS, et al. J Clin Oncol 36, 2018 (suppl; abstr 7505)

Mantle cell lymphoma

ZUMA-2

The NEW ENGLAND JOURNAL of MEDICINE

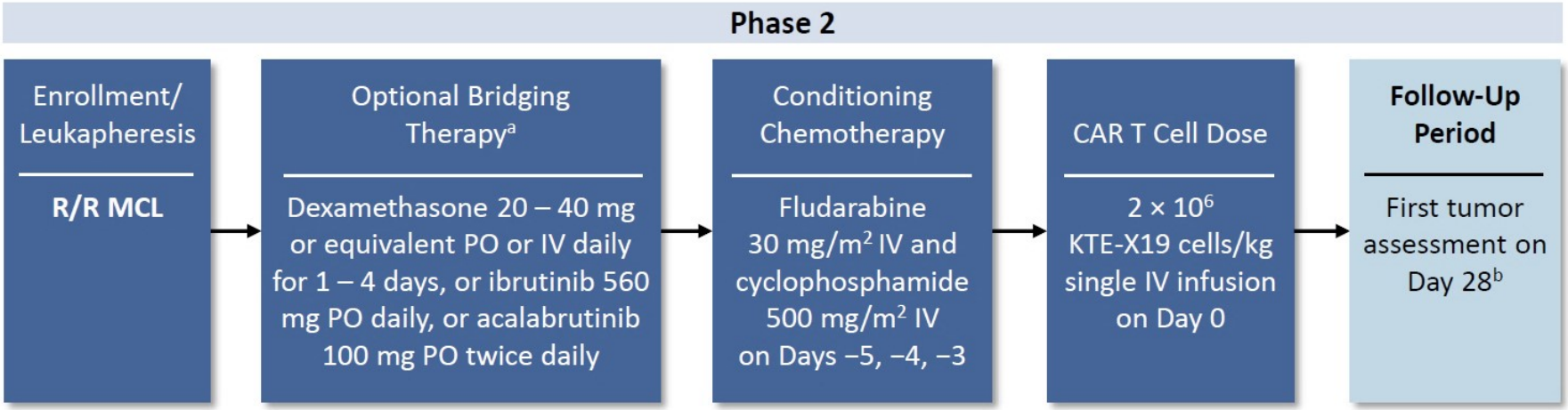
ORIGINAL ARTICLE

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

ZUMA-2: Study design

ASH 2019. Abs 754



Primary Endpoint

- ORR (IRRC-assessed per the Lugano classification[1])

Key Secondary Endpoints

- DOR
- PFS
- OS
- AEs
- ORR (Investigator-assessed per revised IWG criteria[2])
- EQ-5D
- Levels of CAR T cells in blood and cytokines in serum

[a] Administered after leukapheresis and completed ≤ 5 days before initiating conditioning chemotherapy; PET-CT was required post-bridging.
[b] Bone marrow biopsy was done at screening and if positive, not done, or indeterminate, a biopsy was needed to confirm CR.
AE, adverse event; CAR, chimeric antigen receptor, DOR, duration of response; EQ-5D, European Quality of Life-5 Dimensions; IRRC, Independent Radiology Review Committee; IWG, International Working Group; MCL, mantle cell lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral; R/R, relapsed/refractory.
1. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068. 2. Cheson BD, et al. *J Clin Oncol.* 2007;25:579-586.

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

ZUMA-2: Baseline characteristics

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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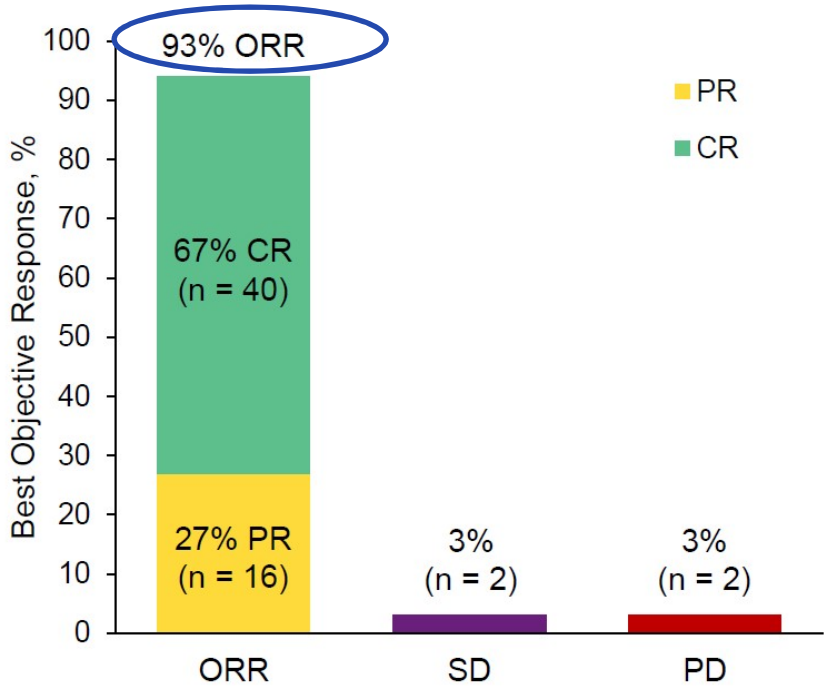
Wang M, et al. NEJM. 2020. 382:1331

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.

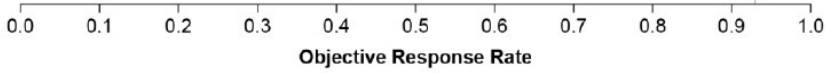
Wang M, et al. ASH 2019. Abs 754
Wang M, et al. NEJM. 2020. 382:1331

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.

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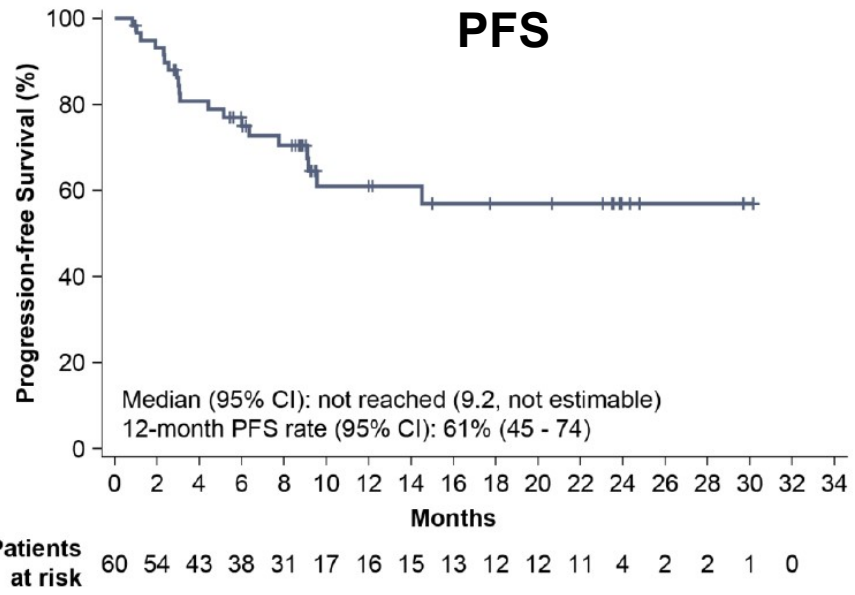
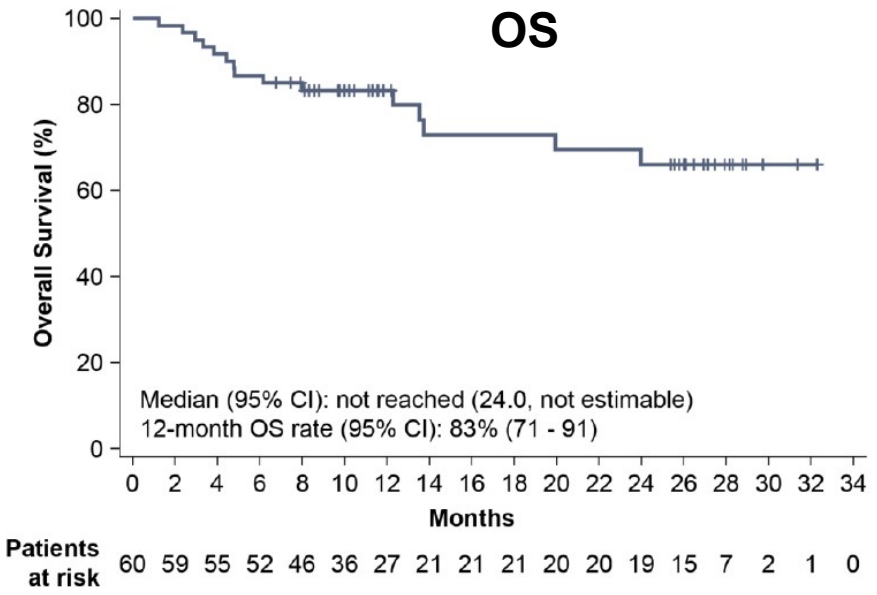
Wang M, et al. ASH 2019. Abs 754
Wang M, et al. NEJM. 2020. 382:1331

ZUMA-2: Survival

ASH 2019. Abs 754

- Median PFS and median OS were not reached after a median follow-up of 12.3 months



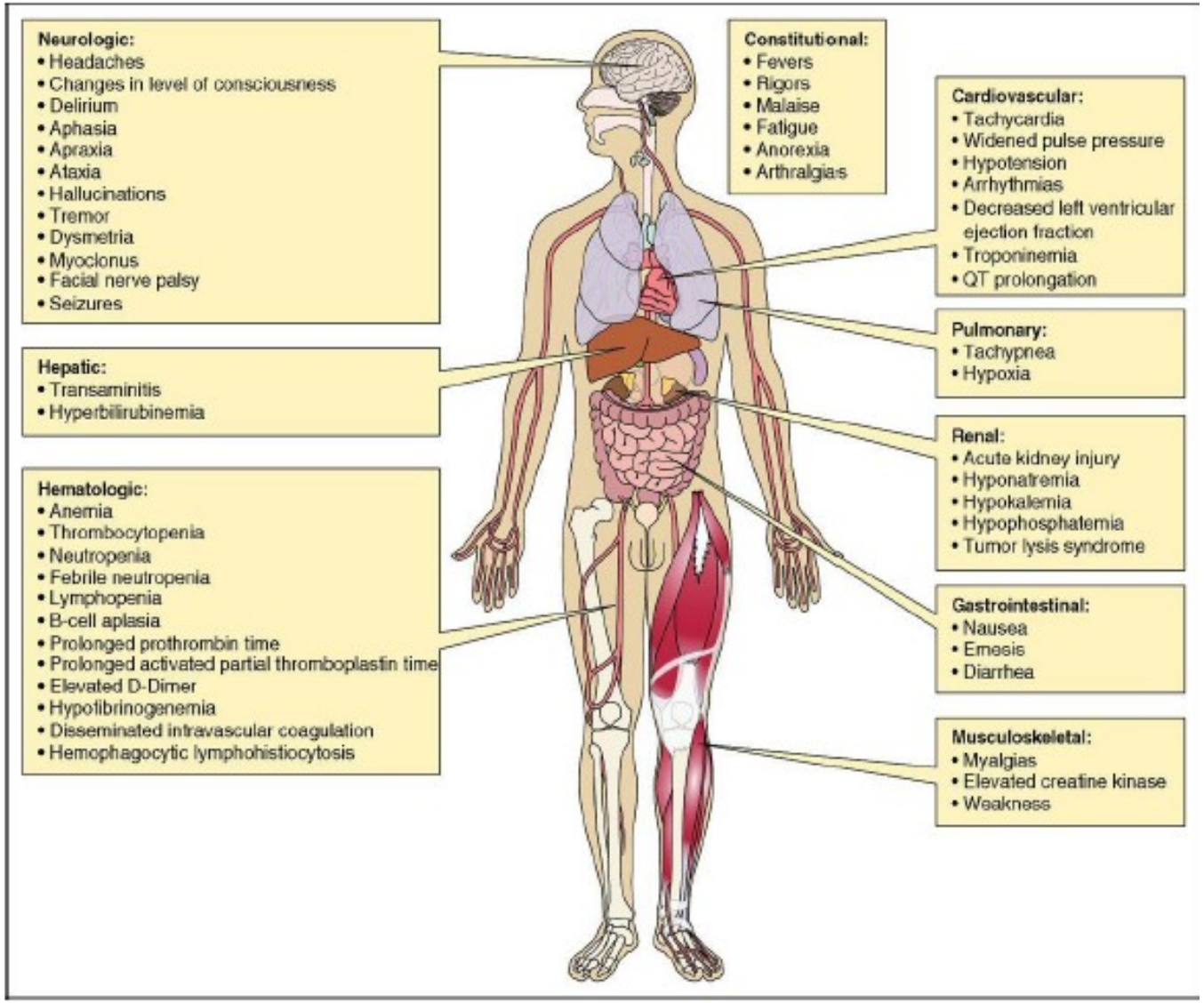


OS, overall survival; PFS, progression-free survival.

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

Toxicities associated with CAR T-cell treatments

Cytokine release syndrome (CRS): A systemic inflammatory response caused by cytokines released by infused CAR T cells and other immune cells and results in reversible organ dysfunction.



MAYO CLINIC

Bruno and Kochenderfer. Blood. 2016: 127:3321

Risk factors for severe CRS

Patient	Disease	CAR-T
▪ Baseline inflammatory state ↑ baseline serum ferritin ↑ C-reactive protein ▪ <u>Other</u> Biomarkers of endothelial cell activation Angiopoietin-2 von Willebrand factor	▪ B-cell ALL > lymphomas (?) ▪ Marrow involvement ▪ Burden/bulkiness ▪ Thrombocytopenia	▪ CAR-T design Axicabtagene ciloleucel Tisagenlecleucel Lisocabtagene maraleucel ▪ Higher CAR-T dose ▪ Lymphodepletion (Flu-CY)

CRS with anti-CD19 CAR T-cell therapy for DLBCL

Parameter	Axicabtagene Ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Histology	DLBCL	DLBCL	DLBCL (FULL)
Study	ZUMA-1	JULIET	TRASNCEND NHL01
Grading criteria	Lee et al. 2014	Penn Grading Scale	Lee et al. 2014
CRS (any grade), %	93	58	39
CRS (Grade ≥ 3), %	13	22	1



MAYO CLINIC

Neelapu. NEJM. 2017;377:2531
Schuster. NEJM. 2019;380:45.
Abramson, ASCO 2018

Differences Between Various CRS Grading Scales

Clinical parameter	Lee DW, et al.	U Penn.	CTCAE v5
Constitutional symptoms	Grade 1	Grade 1	Grade 1
Hypotension responsive to IV fluids	Grade 2	Grade 3	Grade 2
<40% FiO2	Grade 2	Grade 3	Grade 2
High dose vasopressors	Grade 3	Grade 4	Grade 3
Mechanical ventilation	Grade 4	Grade 4	Grade 4

- CTCAE v5 borrows and simplifies the Lee et al. criteria
- ASTCT 2018: project to harmonize CAR T CRS and neurotoxicity grading

MAYO CLINIC

Lee DW, et al. Blood. 2014; 124: 188
Porter DL, et al. Sci Transl Med. 2015 Sep 2;7(303):303ra139

Biol Blood Marrow Transplant 25 (2019) 625–638

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

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

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.

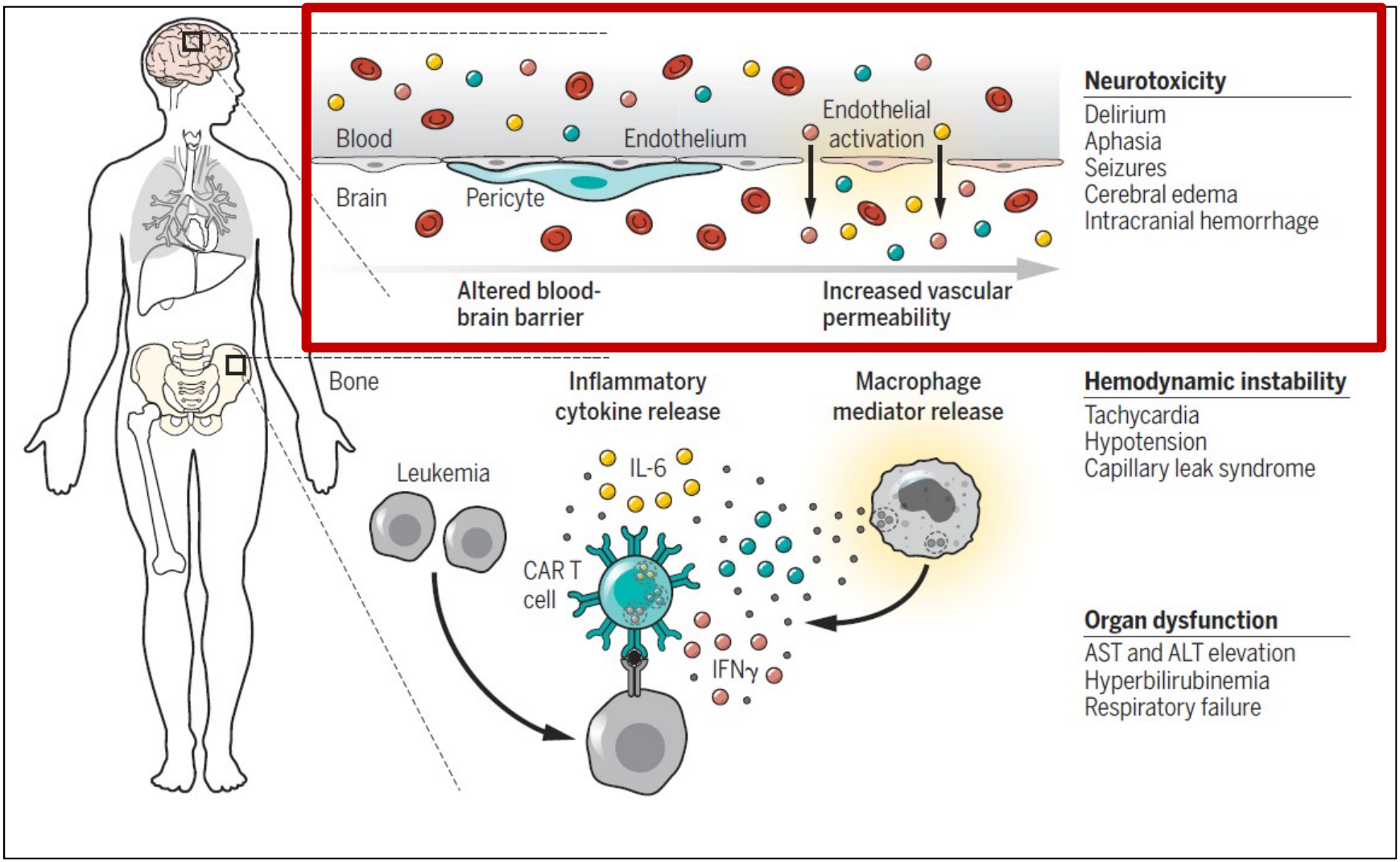
* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or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

Neurotoxicity



June C, et al. Science. 2018; 359:1361-65

Risk factors for neurotoxicity

- CAR-T product (Axi-cel)
- High tumor burden
- Higher peak of CAR-T cells
- Lymphodepleting chemotherapy with fludarabine
- 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

Neurotoxicity

- Generally, manifests as a toxic encephalopathy
  - Confusion, disorientation, difficulty finding words, etc.
  - In more severe cases, seizures, elevated intracranial pressure, cerebral edema
- May last few hours to several days
- It is generally reversible, although deaths have been reported
- Biphasic presentation
  - Phase 1: Days 0-5, may have concurrent CRS
  - **Phase 2: After day +5, by then CRS has generally subsided**

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.

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

Take home messages

- CAR-T revolutionized treatment of DLBCL, B-cell ALL, and MCL. Here to stay!
- In relapsed/refractory DLBCL, 2-year OS ≥ 40%
  - For patients in CR >70%
- Anti-CD19 CAR T-cell therapies are being evaluated in earlier stages of DLBCL (*de novo* or transformed)
  - CAR T-cell vs. autologous HCT
- Toxicities are unique (CRS and ICANS) but manageable

Thank you