Data + Perspectives: Clinical Investigators Discuss the Role of CAR T-Cell Therapy for Patients with Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

Part 1 of a 2-Part CME Satellite Symposium Series During the Society of Hematologic Oncology 2024 Annual Meeting

Wednesday, September 4, 2024

11:46 AM – 12:46 PM CT

Faculty

Joshua Brody, MD

Jason Westin, MD, MS

Moderator

Matthew Lunning, DO

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Faculty

Joshua Brody, MD
Director, Lymphoma Immunotherapy Program
The Tisch Cancer Institute at Mount Sinai
Faculty Member, Icahn Genomics Institute
Icahn School of Medicine at Mount Sinai
New York, New York

Jason Westin, MD, MS
Director, Lymphoma Clinical Research
Section Chief, Aggressive Lymphoma
Professor, Department of Lymphoma
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Moderator

Matthew Lunning, DO
Associate Professor of Medicine
Medical Director, Cellular Therapy
Associate Vice Chair of Research
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Department of Internal Medicine
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RTP
RESEARCH TO PRACTICE

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Virtual/Zoom Attendees: Submit challenging cases or questions for discussion using the Zoom chat room.

The program moderator will address as many cases or questions as possible with the faculty panel during the program.

Download Program Slides Here

https://asset.researchtopractice.com/2024/Webinar/SOHO2024_CAR-T_Sep4.pdf

Slides are also available on our RTPLive app.

For Zoom attendees, the slides link is posted in the chat room.

About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

Data + Perspectives: Clinical Investigators Discuss the Current and Future Management of Diffuse Large B-Cell Lymphoma

Part 2 of a 2-Part CME Satellite Symposium Series During the Society of Hematologic Oncology 2024 Annual Meeting

Wednesday, September 4, 2024
7:30 PM – 8:30 PM CT

Faculty

Grzegorz S Nowakowski, MD
Laurie H Sehn, MD, MPH

Moderator

Christopher R Flowers, MD, MS

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Data + Perspectives: Clinical Investigators Discuss the Role of CAR T-Cell Therapy for Patients with Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

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Faculty

Joshua Brody, MD

Jason Westin, MD, MS

Moderator

Matthew Lunning, DO

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Agenda

Module 1: Integration of Chimeric Antigen Receptor (CAR) T-Cell Therapy into the Management of Diffuse Large B-Cell Lymphoma — Dr Westin

Module 2: Current Role of CAR T-Cell Therapy for Other B-Cell Lymphomas — Dr Lunning

Module 3: Tolerability and Other Practical Considerations with CAR T-Cell Therapy — Dr Brody

Agenda

Module 1: Integration of Chimeric Antigen Receptor (CAR) T-Cell Therapy into the Management of Diffuse Large B-Cell Lymphoma — Dr Westin

Module 2: Current Role of CAR T-Cell Therapy for Other B-Cell Lymphomas — Dr Lunning

Module 3: Tolerability and Other Practical Considerations with CAR T-Cell Therapy — Dr Brody

Integration of Chimeric Antigen Receptor (CAR) T-Cell Therapy into the Management of Diffuse Large B-Cell Lymphoma (DLBCL)

Jason Westin, MD, MS

Dr Westin — Disclosures

Consulting Agreements	AbbVie Inc, Allogene Therapeutics, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Genentech, a member of the Roche Group, Genmab US Inc, Incyte Corporation, Janssen Biotech Inc, Kite, A Gilead Company, MorphoSys, Novartis, Nurix Therapeutics Inc, Pfizer Inc

ZUMA-7: Study Schema and Endpoints: Axi-Cel Versus SOC as Second-Line Therapy in Patients With R/R LBCL

R/R LBCL
N=359
77 Sites

Key Eligibility:
- Aged ≥18 y
- LBCL[1]
- R/R ≤12 mo of 1L therapy[a]
- Intended to proceed to HDT-ASCT

Stratification:
- Response to 1L therapy
- Second-line age-adjusted IPI (sAAIPI)

Optional Steroid-Only Bridging (No Chemotherapy)

1:1 Randomization

Axi-Cel (n=180)
Conditioning Chemotherapy + Axi-cel[b]

SOC (n=179)
Investigator-Selected Platinum-Based Chemoimmunotherapy[c]

Initial Disease Assessment (Day 50)

Responders (CR or PR)
Proceed to HDT-ASCT

Nonresponders
Additional Treatment Off Protocol[d]

Day 100 Assessment

Day 150 Assessment

LTFU Assessment

Primary Endpoint
- Event-free survival[e] (EFS) by blinded central review

Key Secondary Endpoints
- ORR
- OS

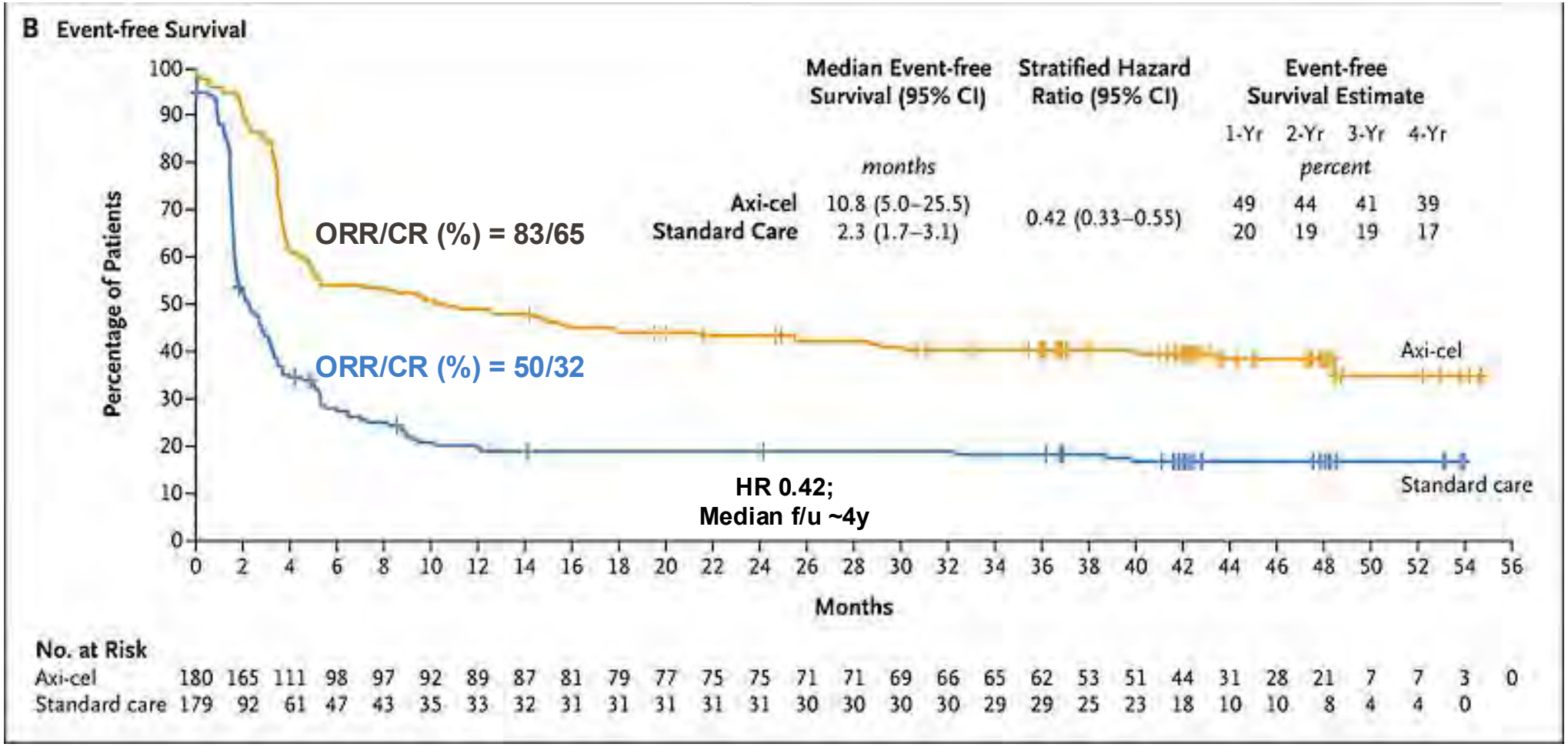
Secondary Endpoints
- PFS
- Safety
- PROs

No Protocol-Specified Crossover

[a] Refractory disease was defined as no CR to 1L therapy; relapsed disease was defined as CR followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy. [b] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10^6 CAR+ T cells/kg). [c] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [d] 56% of patients received subsequent cellular immunotherapy. [e] EFS was defined as time from randomization to the earliest date of disease progression per Lugano Classification,[2] commencement of new lymphoma therapy, or death from any cause.

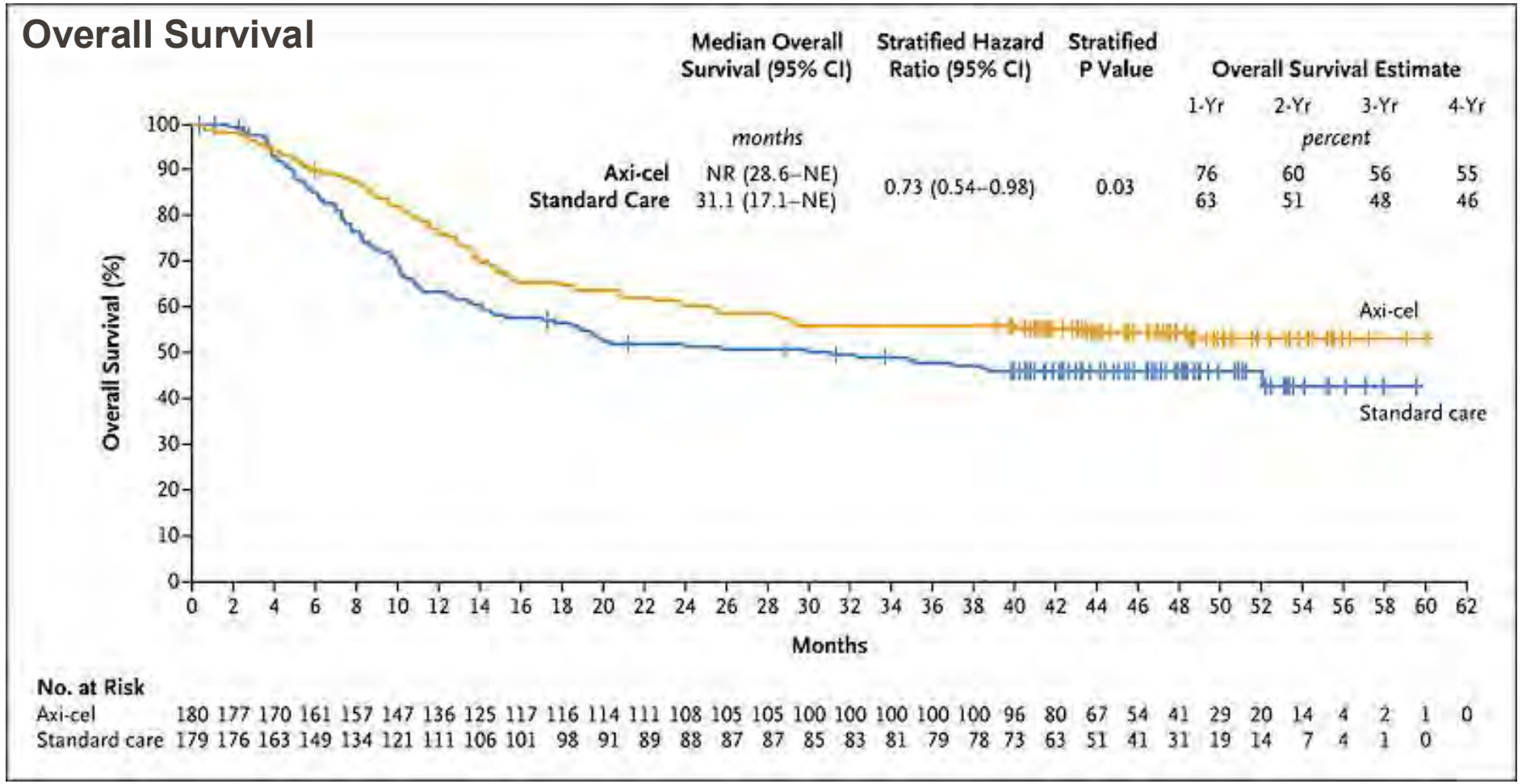
1. Swerdlow SH, et al. *Blood*. 2016;127:2375-2390. 2. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

Axi-cel improves event free survival compared with chemotherapy in 2L R/R LBCL



Westin JR et al, NEJM 2023

Axi-cel improves overall survival compared with chemotherapy in 2L R/R LBCL

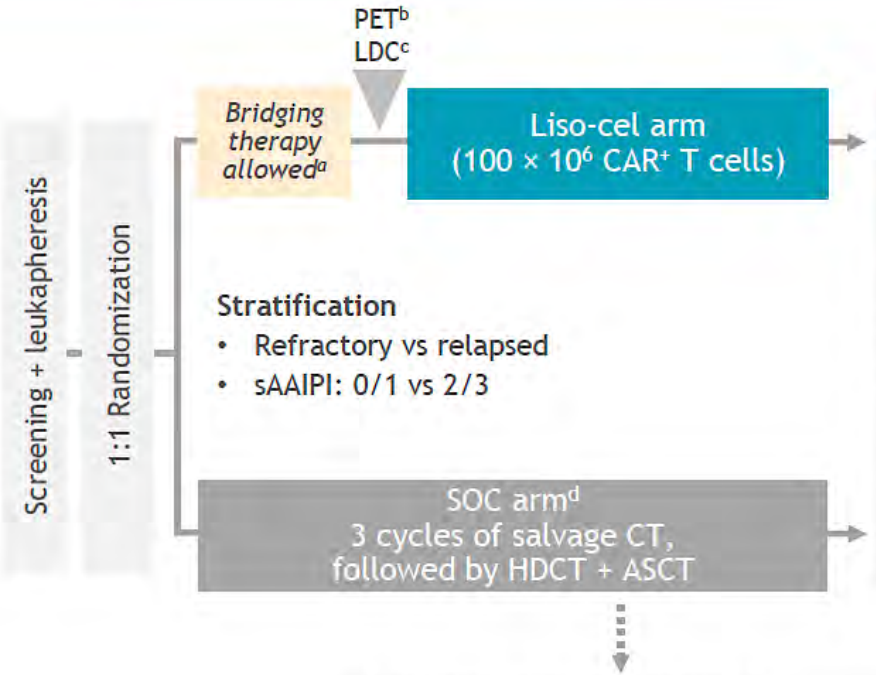


Westin JR et al, NEJM 2023

TRANSFORM study design

Key eligibility

- Age 18–75 years
- Aggressive NHL
  - DLBCL NOS (de novo or transformed from indolent NHL), HGBCL (double/triple hit) with DLBCL histology, FL3B, PMBCL, THRBCL
- Refractory or relapsed ≤ 12 months after 1L treatment containing an anthracycline and a CD20-targeted agent
- ECOG PS ≤ 1
- Eligible for HSCT
- Secondary CNS lymphoma allowed
- LVEF > 40% for inclusion
- No minimum absolute lymphocyte count



Response assessments

- Weeks 9 and 18
- Months 6, 9, 12, 18, 24, and 36

Primary endpoint

- EFS (per IRC)

Key secondary endpoints

- CR rate, PFS, OS

Other secondary endpoints

- Duration of response, ORR, PFS on next line of treatment
- Safety, PROs

Exploratory endpoints

- Cellular kinetics
- B-cell aplasia

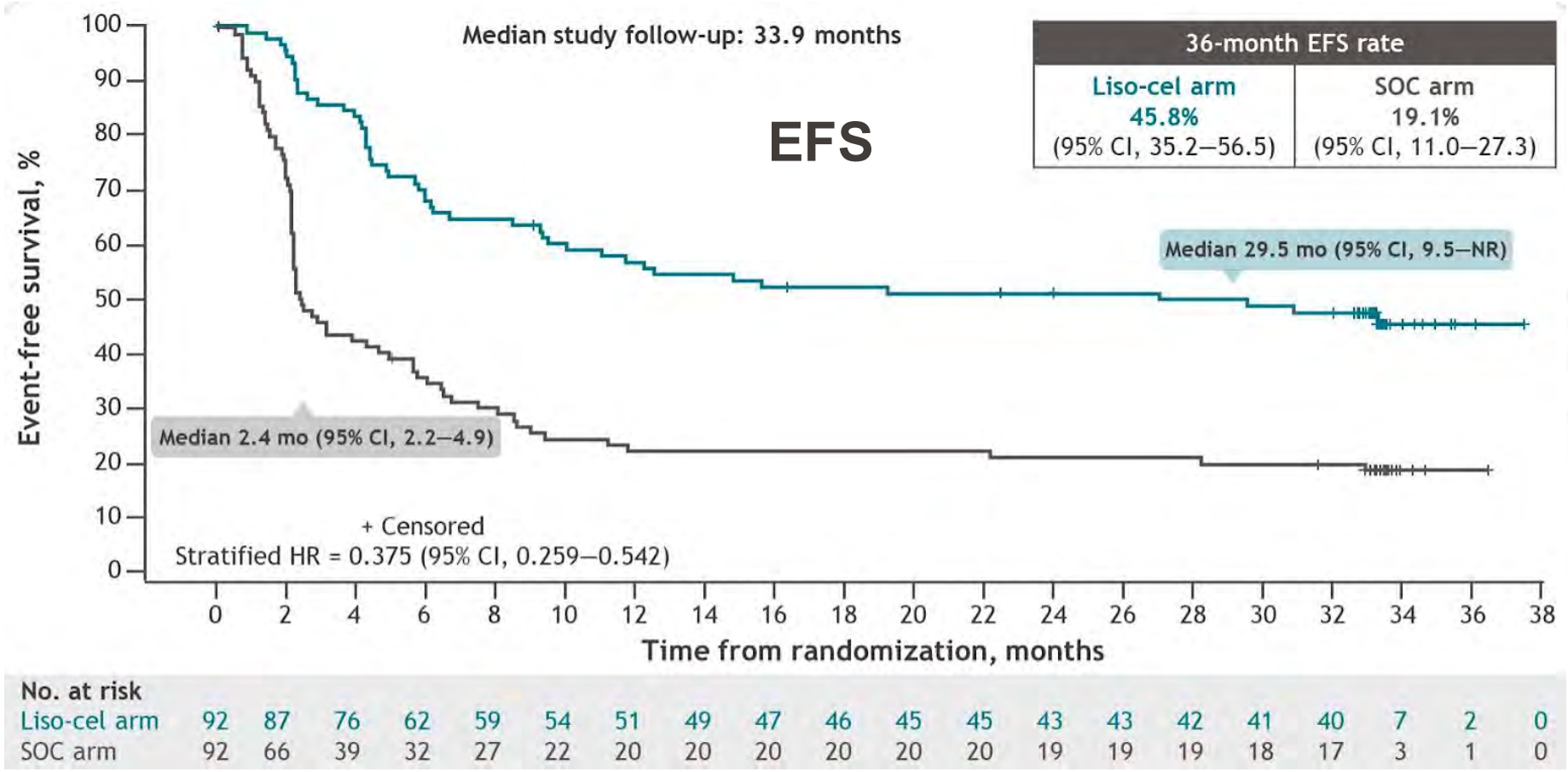
TRANSFORM PRO data
Poster (Abs 3845)
Abramson et al.
Dec 13, 2021, 6:00 pm (EST)

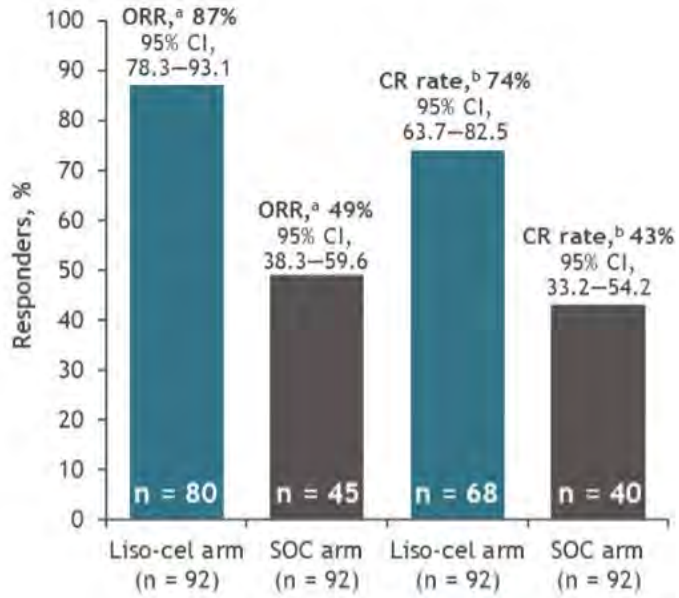
- **EFS is defined as time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy, whichever occurs first**

[a]Patients may have received a protocol-defined SOC regimen to stabilize their disease during liso-cel manufacturing; [b]Only for patients who received bridging therapy; [c]Lymphodepletion with fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 for 3 days; [d]SOC was defined as physician's choice of R-DHAP, R-ICE, or R-GDP.
DLBCL, diffuse large-B cell lymphoma; FL3B, follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; LDC, lymphodepleting chemotherapy; NOS, not otherwise specified; PD, progressive disease; PMBCL, primary mediastinal large B-cell lymphoma; PRO, patient-reported outcome; sAAIPI, secondary age-adjusted International Prognostic Index; THRBCL, T-cell/histiocyte-rich large B-cell lymphoma.

Kamdar M, et al. ASH 2021 [Abstract #91]

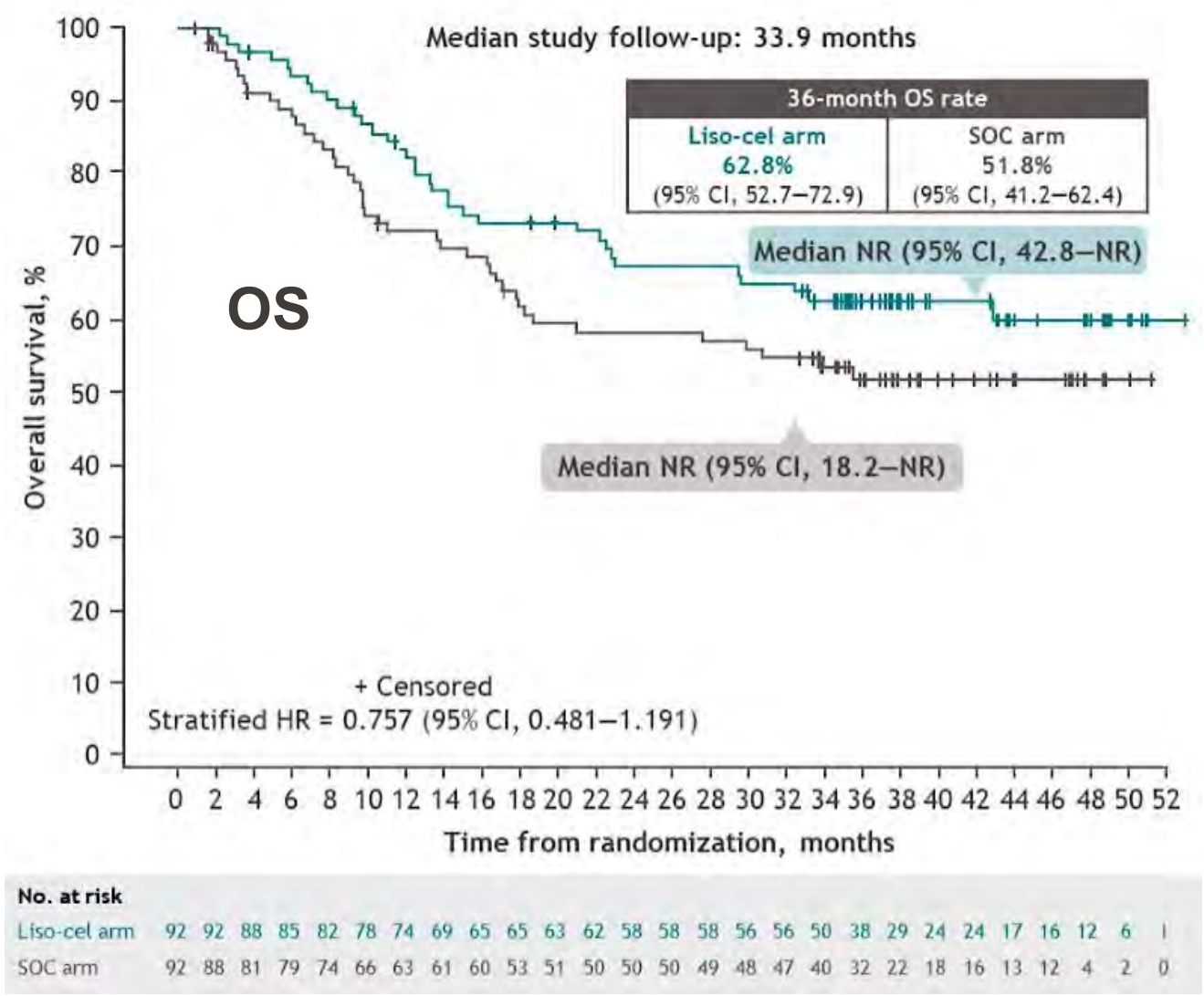
Liso-cel improves event free survival and response rate compared with chemotherapy in 2L R/R LBCL





Kamdar MK et al. ASCO 2024;Abstract 7013.

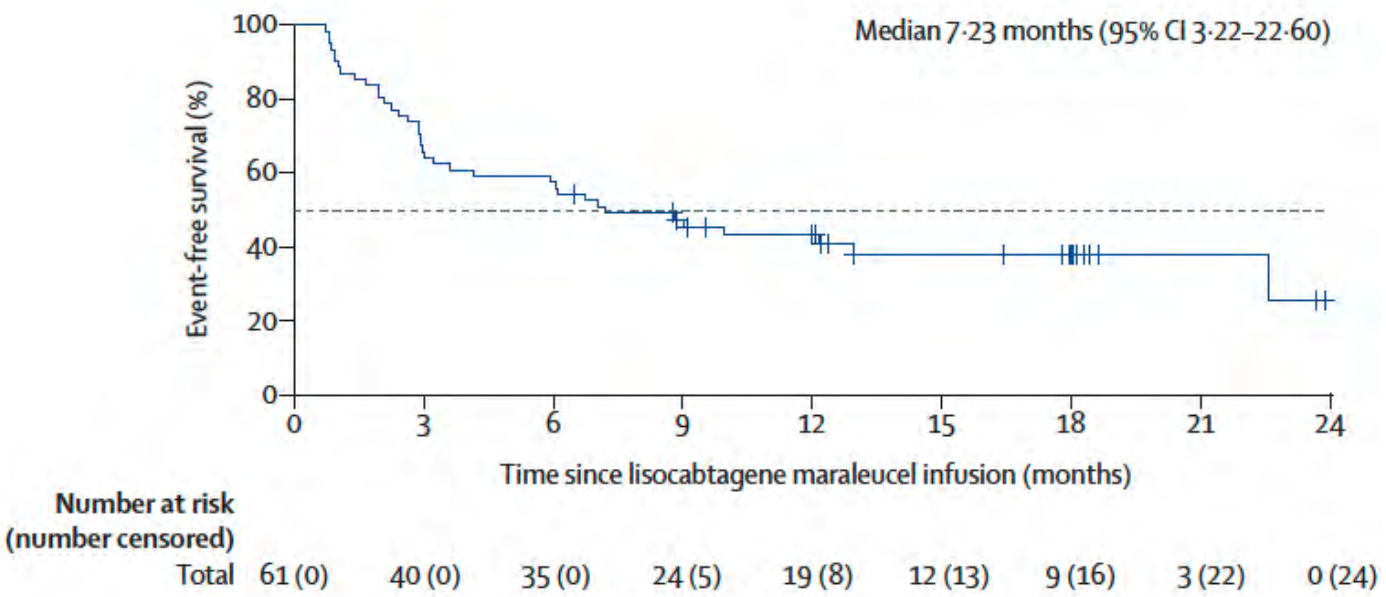
Liso-cel trends toward overall survival improvement compared with chemotherapy in 2L R/R LBCL



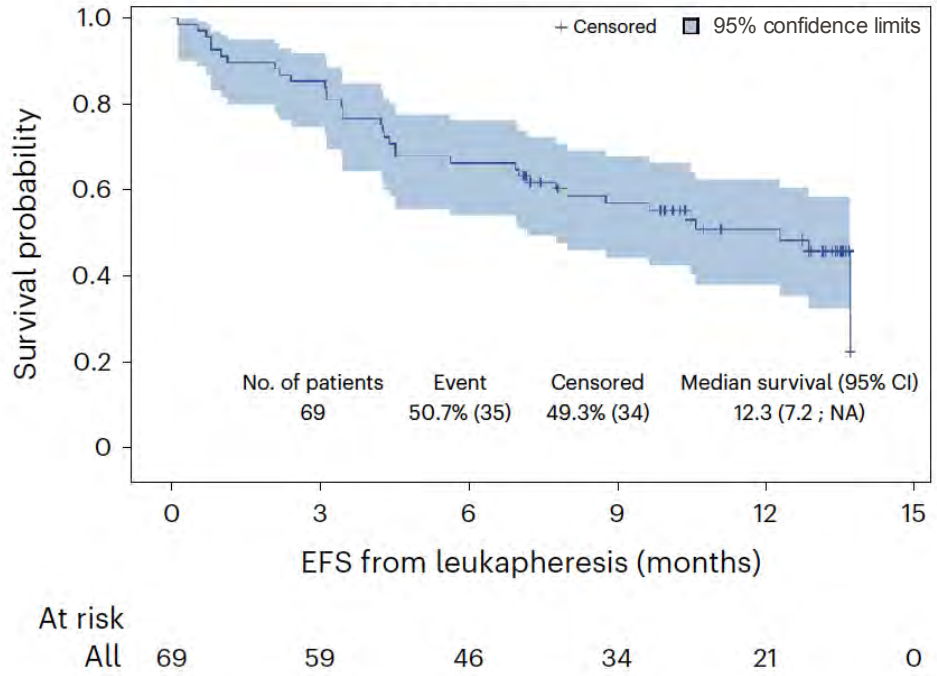
Kamdar MK et al. ASCO 2024;Abstract 7013.

Transplant ineligible 2L

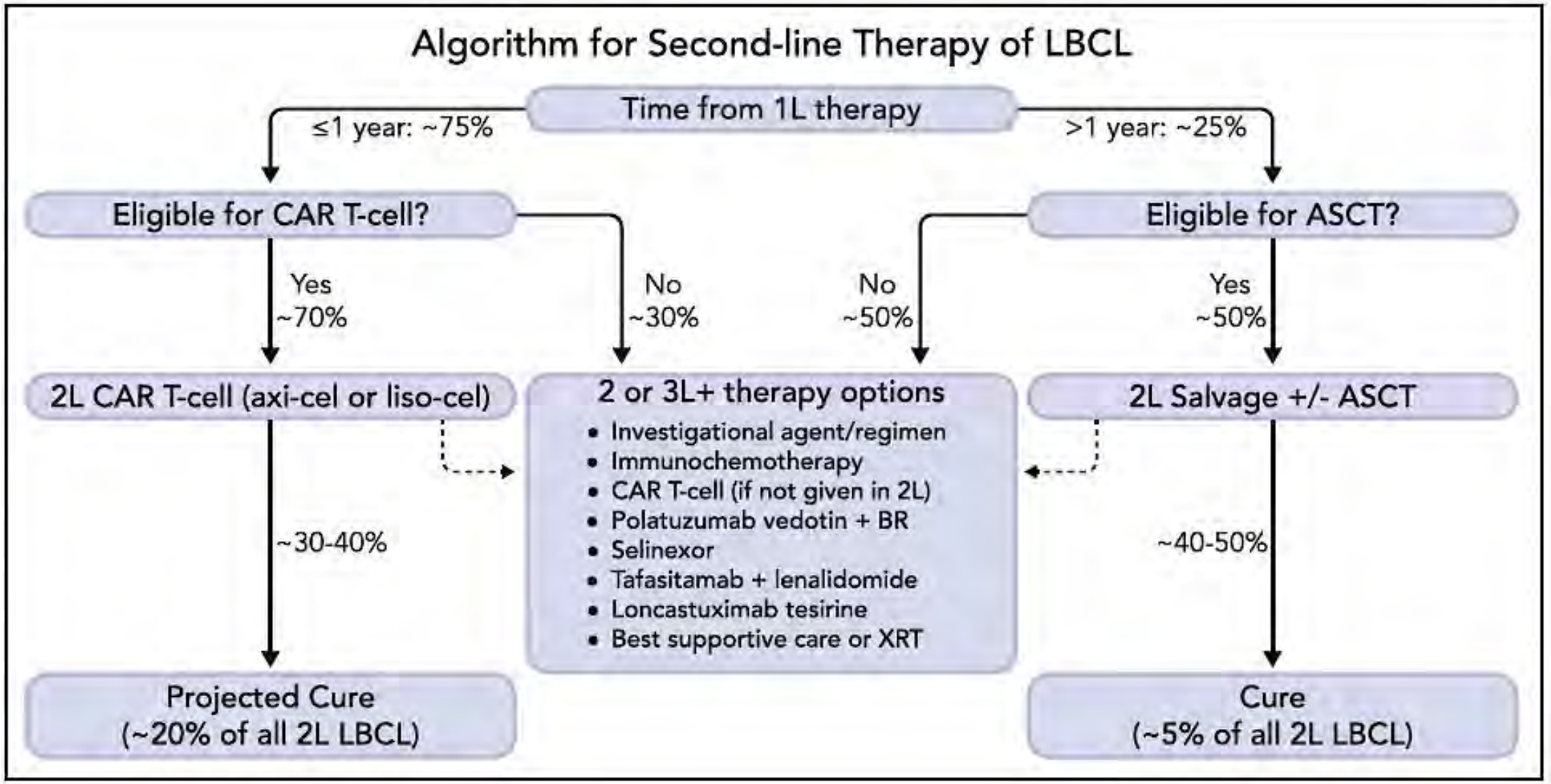
Liso-cel



Axi-cel



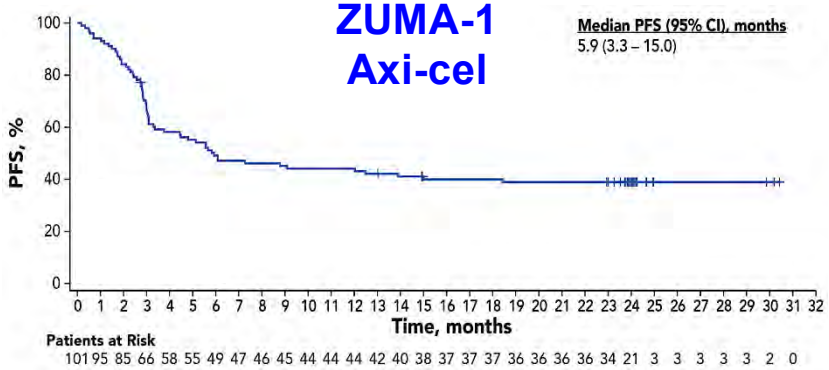
Sehgal A, et al. *Lancet Oncol*. 2022;23(8):1066-1077. Houot R, et al. *Nat Med.* 2023



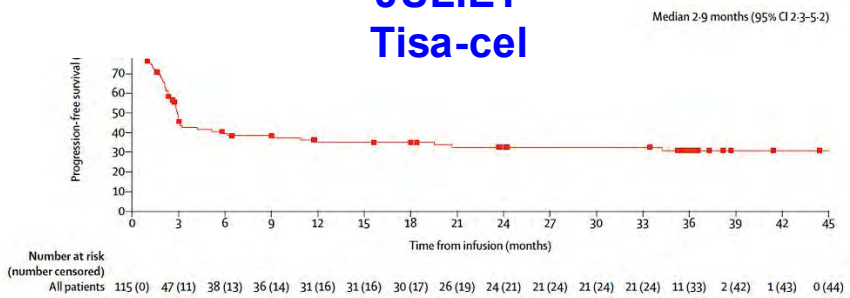
Westin and Sehn, Blood 2022

CAR T-cells in ≥3L for LBCL: PFS and OS

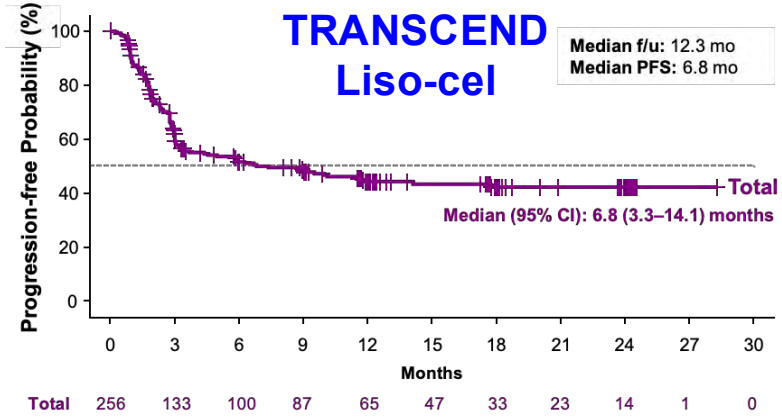
ZUMA-1 Axi-cel

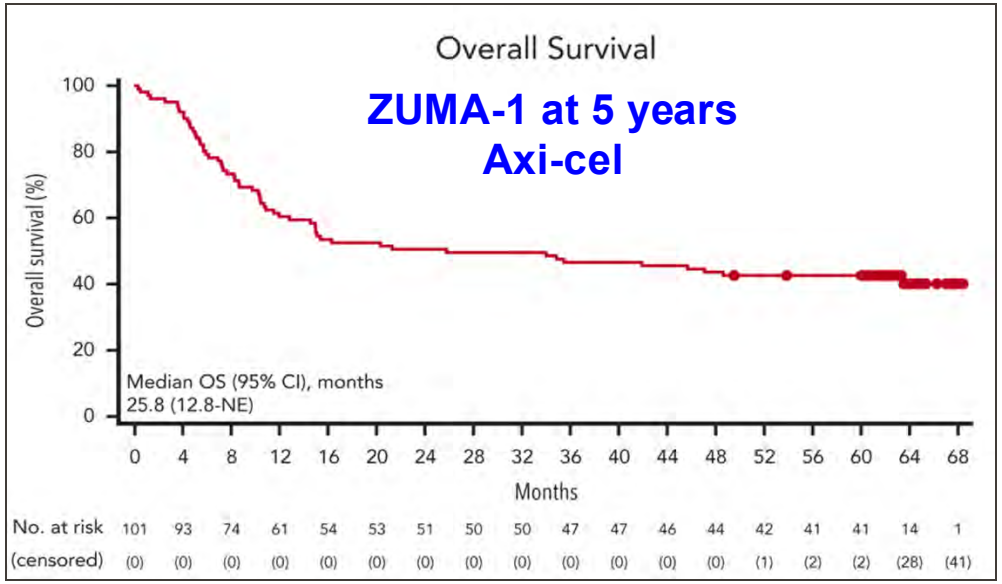


JULIET Tisa-cel



TRANSCEND Liso-cel





Approval

Axi-cel, tisa-cel, and liso-cel for adult patients with r/r LBCL after 2 or more lines of systemic therapy

Neelapu SS et al. *N Engl J Med.* 2017;377:2531-2544. Locke FL et al. *Lancet Oncol.* 2019;20(1):31-42. Schuster SJ et al. *N Engl J Med.* 2019;380:45-56. Schuster SJ et al. *Lancet Oncol.* 2021;22(10):1403-1415. Abramson JS et al. *Lancet.* 2020;396(10254):839-852. Neelapu et al, *Blood* 2023

nature medicine

FOCUS | ARTICLES

https://doi.org/10.1038/s41591-022-01731-4

OPEN

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

Sattva S. Neelapu[1]✉, Michael Dickinson[2], Javier Munoz[3], Matthew L. Ulrickson[3], Catherine Thieblemont[4,5], Olalekan O. Oluwole[6], Alex F. Herrera[7], Chaitra S. Ujjani[8], Yi Lin[9], Peter A. Riedell[10], Natasha Kekre[11], Sven de Vos[12], Christine Lui[13], Francesca Milletti[13], Jinghui Dong[13], Hairong Xu[13] and Julio C. Chavez[14]

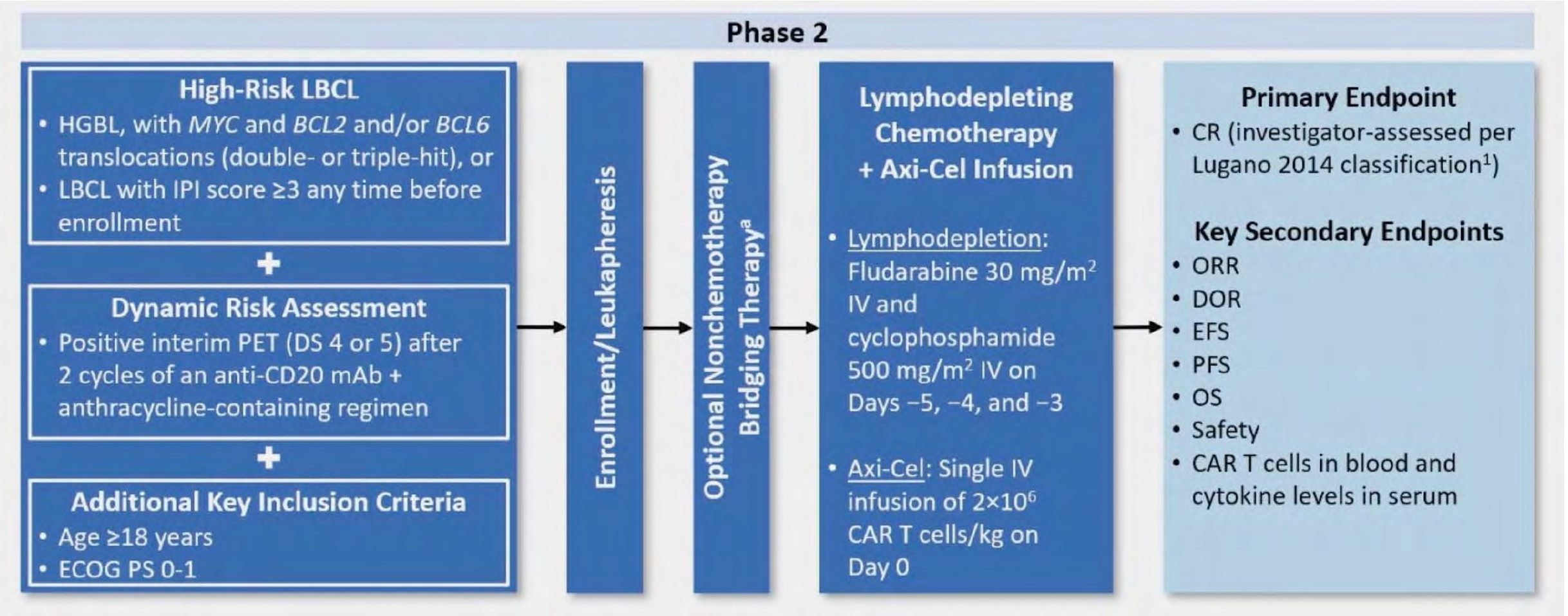
3-Year Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel as First-Line Therapy in Patients with High-Risk Large B-Cell Lymphoma

Julio C. Chavez, MD[1]; Michael Dickinson, MBBS, D Med Sci, FRACP, FRCPA[2]; Javier Munoz, MD, MS, MBA, FACP[3]; Matthew L. Ulrickson, MD[3]; Catherine Thieblemont, MD, PhD[4]; Olalekan O. Oluwole, MD, MPH, MBBS[5]; Alex F. Herrera, MD[6]; Chaitra S. Ujjani, MD[7]; Yi Lin, MD, PhD[8]; Peter A. Riedell, MD[9]; Natasha Kekre, MD, MPH, FRCPC[10]; Sven de Vos, MD, PhD[11]; Christine Lui, MS[12]; Jacob Wulff, DrPH[12]; Chad M. Williams, PhD[12]; Weixin Peng, MS[12]; Ioana Kloos[12]; Hairong Xu, MD, PhD[12]; and Sattva S. Neelapu, MD[13]

ZUMA-12: Study Design

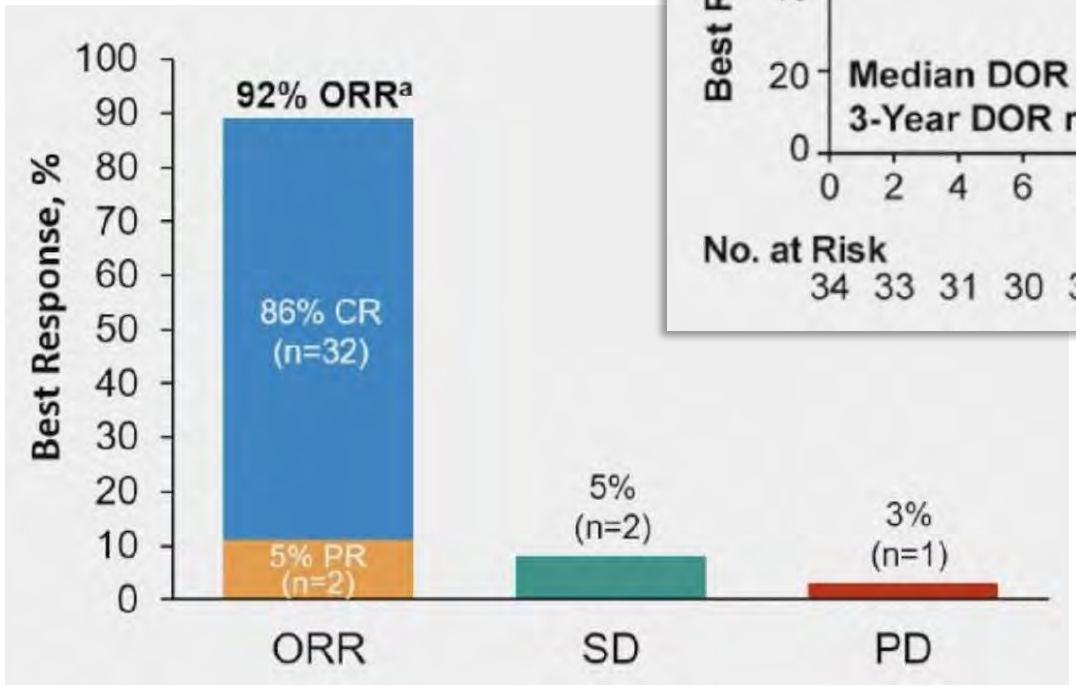
High risk population
- IPI 3-5 or DHL

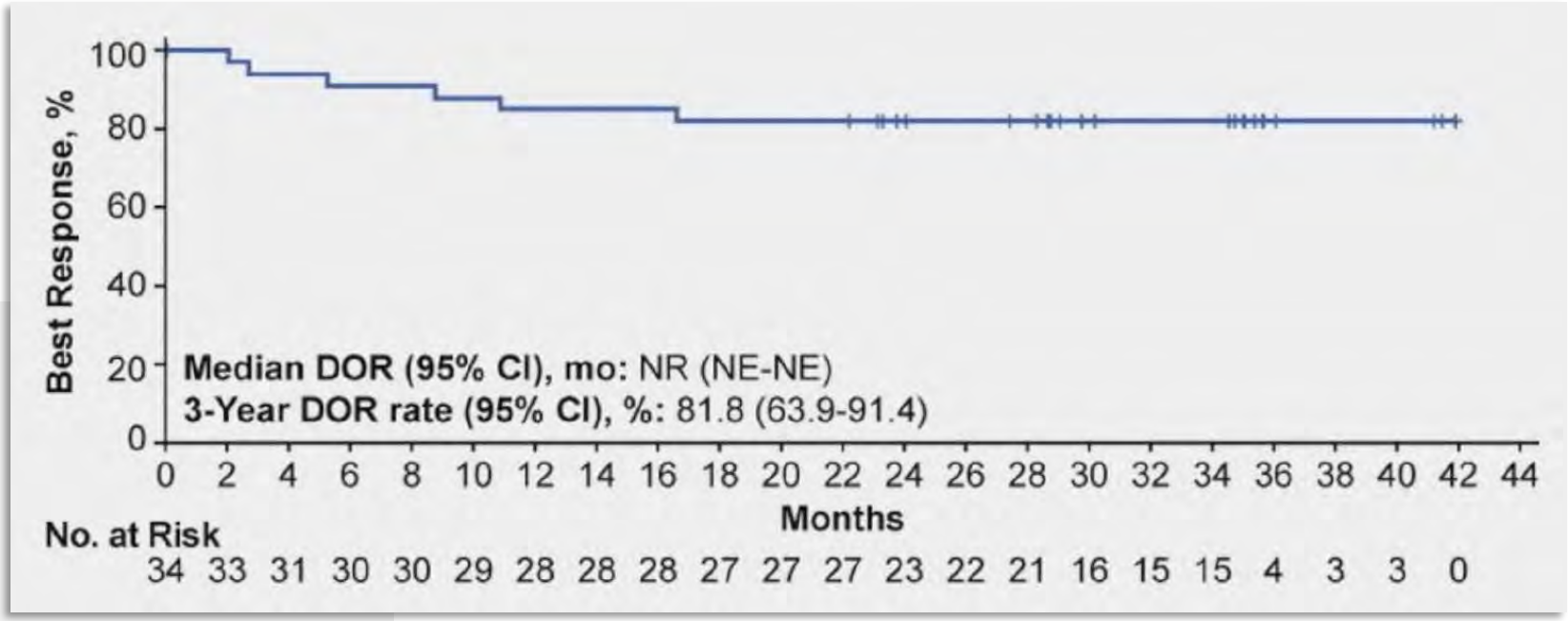
AND
- iPET2 with 5PS of 4 or 5



Chavez JC et al. ASH 2023;Abstract 894.

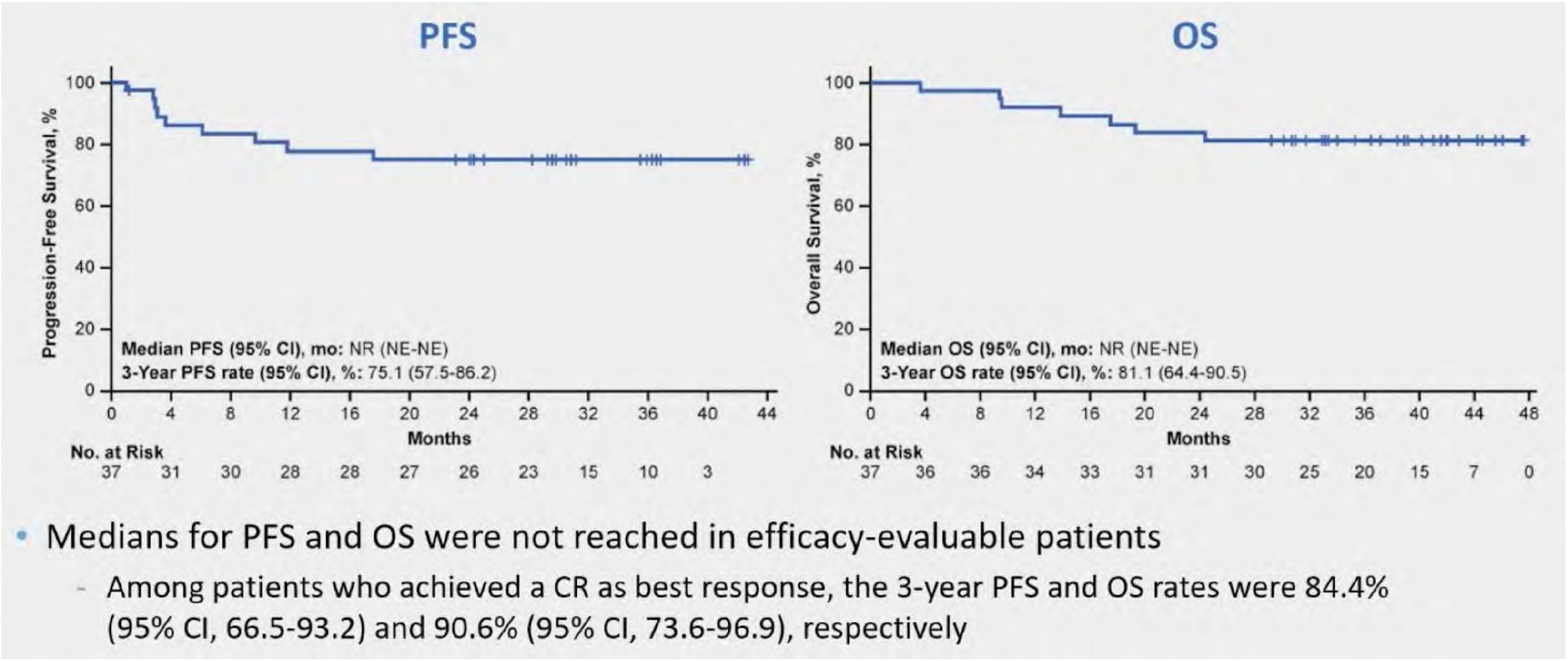
ZUMA-12: ORR and DOR





Chavez JC et al. ASH 2023;Abstract 894.

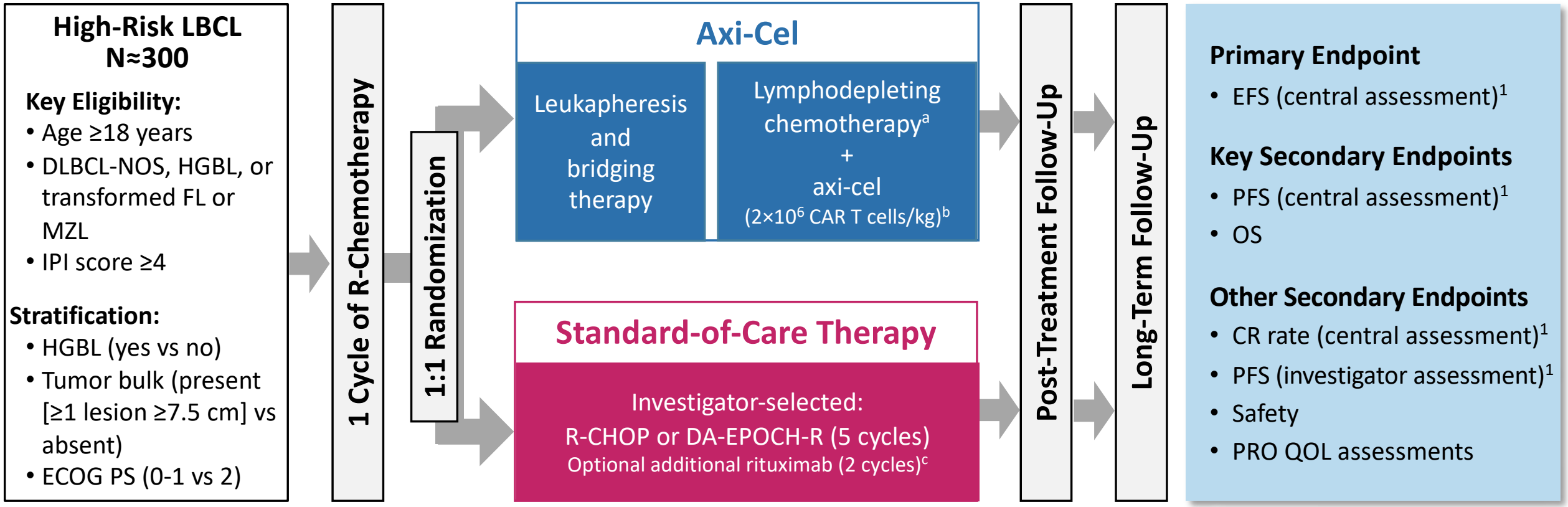
ZUMA-12: Survival Outcomes



- Medians for PFS and OS were not reached in efficacy-evaluable patients
  - Among patients who achieved a CR as best response, the 3-year PFS and OS rates were 84.4% (95% CI, 66.5-93.2) and 90.6% (95% CI, 73.6-96.9), respectively

Chavez JC et al. ASH 2023;Abstract 894.

ZUMA-23 Phase 3 Study Design



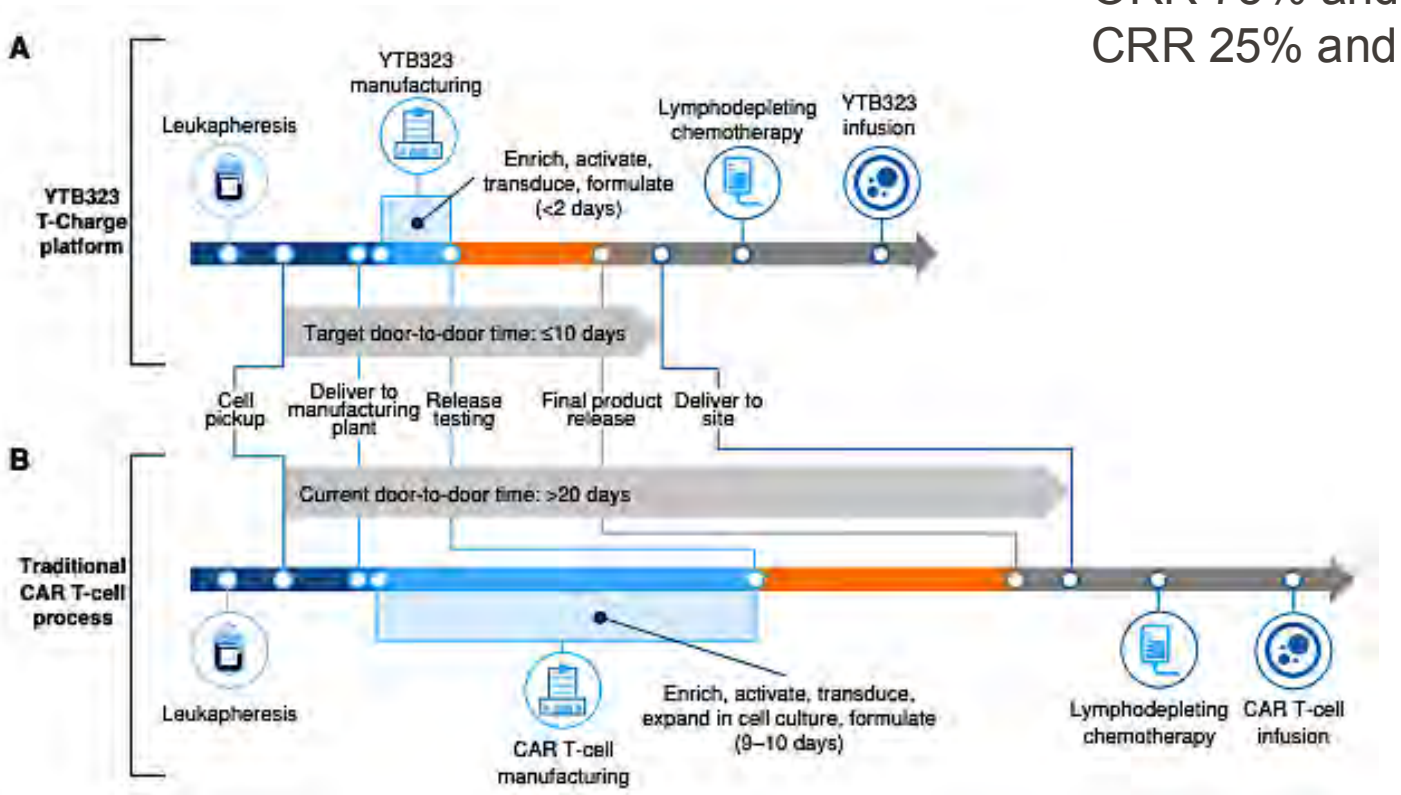
1. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068.

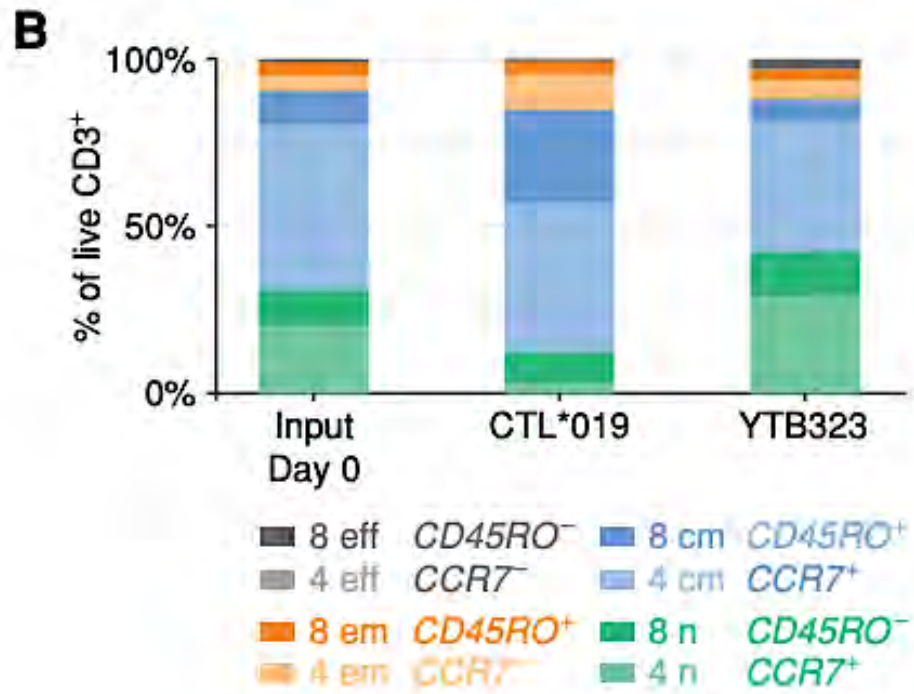
[a] Lymphodepleting chemotherapy will consist of cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day), received Days –5 through –3 before receiving axi-cel. [b] Prophylactic corticosteroids may be administered after axi-cel infusion per investigator discretion. [c] If standard of care per local clinical practice, patients may also receive 2 additional cycles of rituximab monotherapy.

Axi-cel, axicabtagene ciloleucel; CR, complete response; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; FL, follicular lymphoma; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; MZL, marginal zone lymphoma; NOS, not otherwise specified; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; R-chemotherapy, rituximab plus chemotherapy; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone; QOL, quality of life.

Novel CAR T-cell platform for DLBCL: Rapcabtagene autoleucel

ORR 75% and 80% at dose level 1 and 2
CRR 25% and 73% at dose level 1 and 2

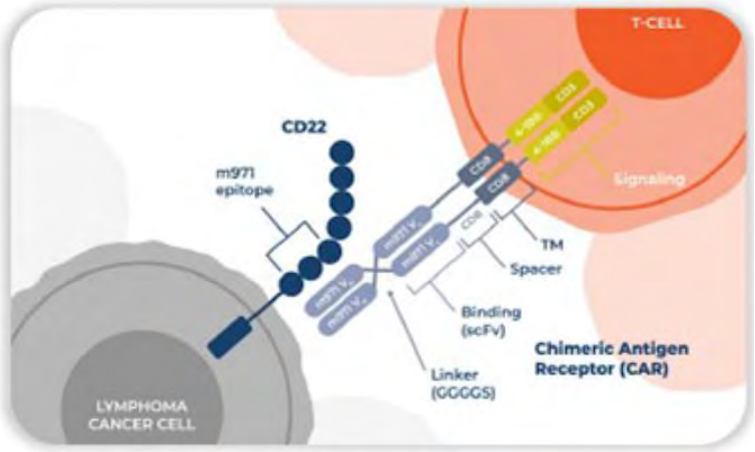


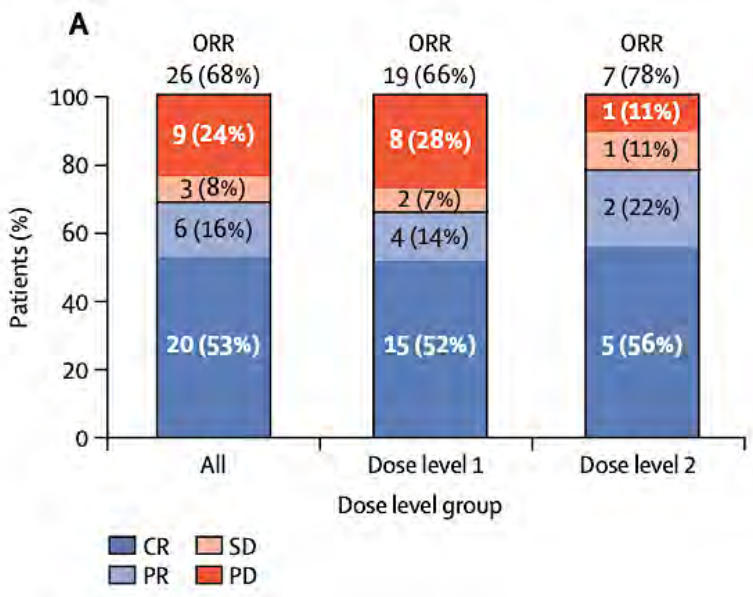


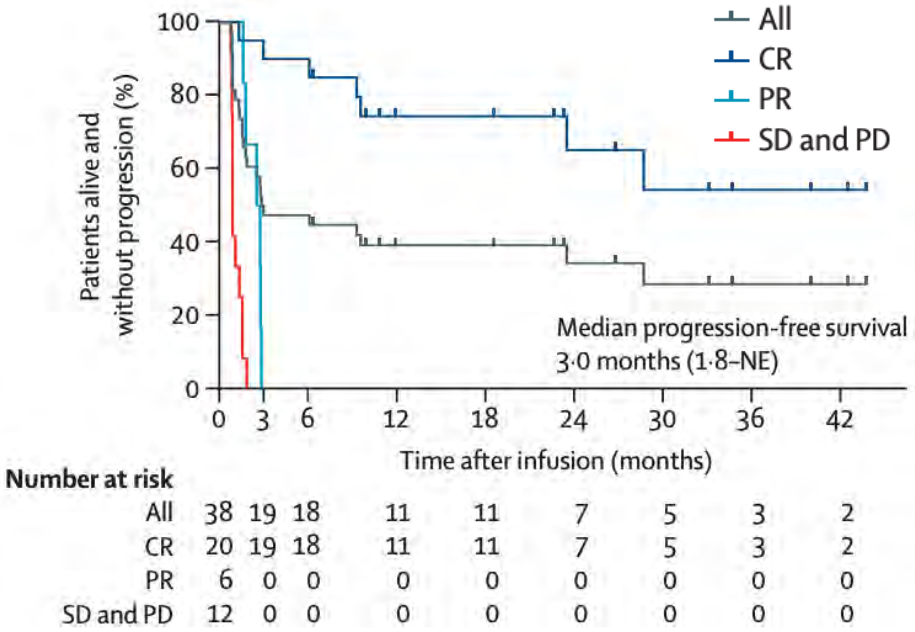
Ongoing trial in 1L high risk LBCL patients

Dickinson et al, Cancer Discovery 2023

Novel CAR T-cell platform for DLBCL: Firicabtagene autoleucel

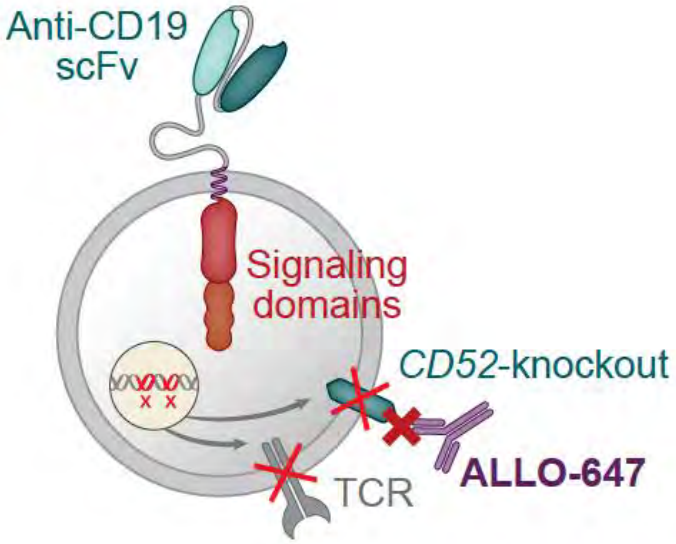


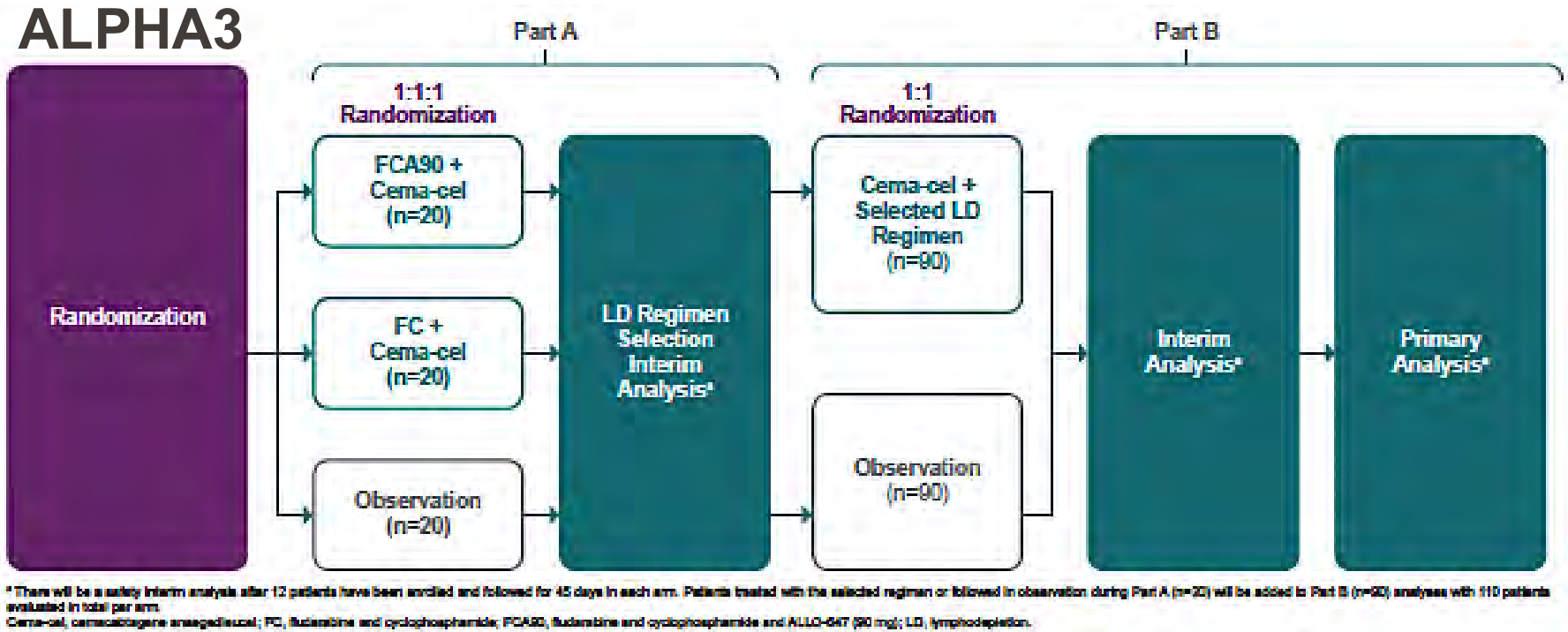




Ghobadi et al, ASCO 2024, Frank et al, Lancet 2024

Novel CAR T-cell platform for DLBCL: Cemacabtagene ansegedleucel



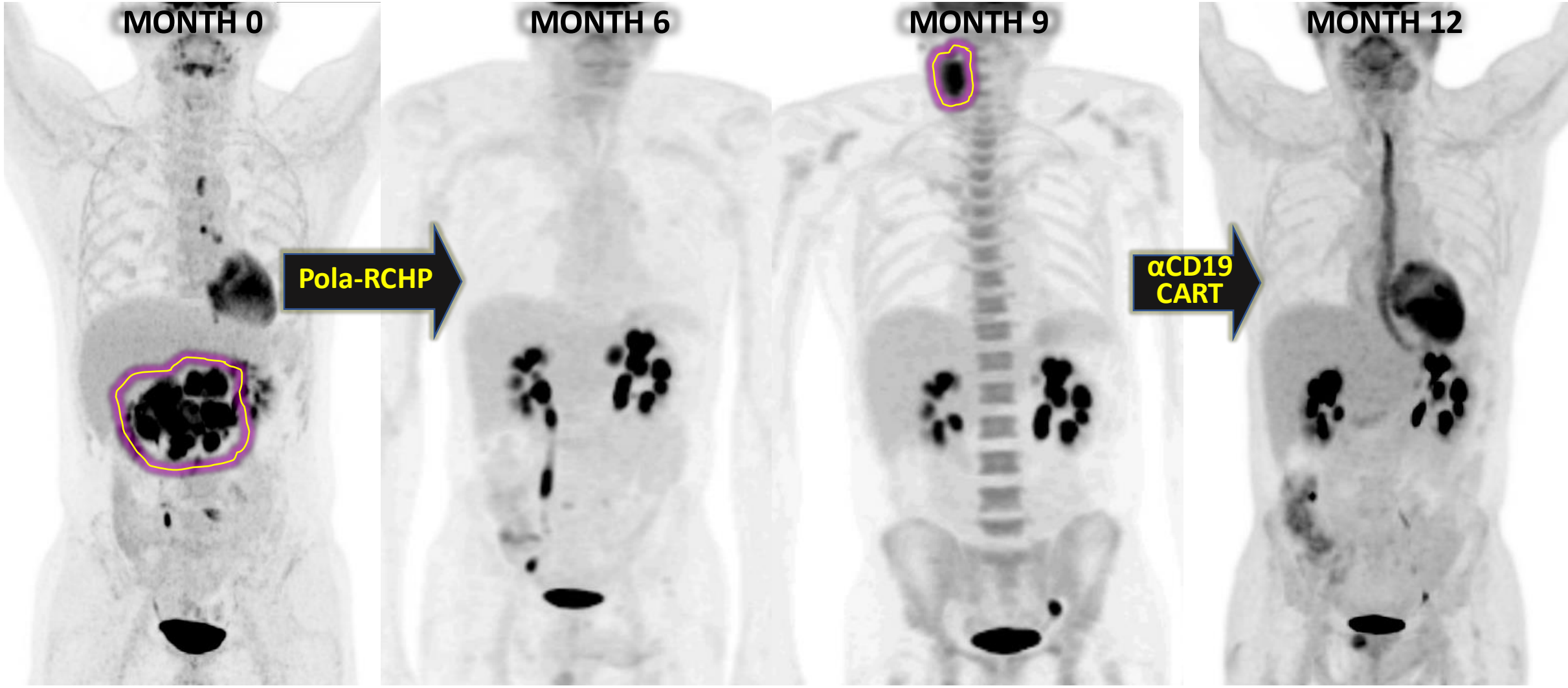


Westin et al, SOHO 2024

Faculty Case Presentations

Case Presentation: Dr Brody

71 yo man w DM2, HTN, COPD, dx w DLBCL, non-GC → Pola-RCHP → CR x 6 months → relapse → XRT+ Liso-cel αCD19 CART



QUESTIONS FOR THE FACULTY

In general, what is your preferred CAR T-cell therapy to administer to a 71-year-old patient with DLBCL after relapse on first-line treatment? What if the patient were 55 years old? What if the patient were 83 years old?

How do you sequence bispecific antibodies and CAR T-cell therapy for a patient with DLBCL who is eligible to receive both? Do you believe CAR T-cell therapy is more effective the earlier it is given? Is CAR T-cell therapy as effective after a bispecific antibody as it is before?

Case Presentation: Dr Lunning

- A man who was initially diagnosed at age 72 with LBCL-NOS, leg type presented with multiple papular skin lesions, but no adenopathy on staging PET/CT. He was treated initially with R-CHOP X 6 with evidence of metabolic CR. He tolerated induction therapy well with minimal fatigue and G1 peripheral neuropathy.
- At age 75 he had evidence of relapse with multiple diffuse skin lesions that was c/w DLBCL-NOS, non-GCB. He was now treated with tafasitamab-lenalidomide. His CrCl was 50. He tolerated dose adjusted lenalidomide (10 mg) and tafasitamab with minimal cytopenias and infections.
- He had evidence of POD 18 months after initiation, but now with diffuse adenopathy, pleural lesions, and skin lesions. He wishes to consider curative therapy as he has tolerated therapy to date well. He proceeded towards CAR-T with tisa-cel.
- He had pre-apheresis bridging with pola-rituximab X 1 with a second cycle post apheresis with evidence of responsive disease.
- He completed dose adjusted flu/cy followed by tisa-cel. He experienced G1 CRS without ICANS.
- His D+100 PET/CT was consistent with mCR with mild residual normocytic anemia. No intercurrent infections but CD4 count remains < 250.

QUESTIONS FOR THE FACULTY

In general, how do you sequence CD19-directed treatment (eg, tafasitamab and CAR T-cell therapy) for patients who are eligible to receive both?

Do you believe that a second CD19-targeted treatment is as effective in a patient who has previously received anti-CD19 therapy as in one who has not?

Agenda

Module 1: Integration of Chimeric Antigen Receptor (CAR) T-Cell Therapy into the Management of Diffuse Large B-Cell Lymphoma — Dr Westin

Module 2: Current Role of CAR T-Cell Therapy for Other B-Cell Lymphomas — Dr Lunning

Module 3: Tolerability and Other Practical Considerations with CAR T-Cell Therapy — Dr Brody

A Blitz of CAR T-Cell Therapies for Rel/Ref FL, MCL, and CLL

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Associate Vice Chair of Research, Department of Internal Medicine

Assistant Vice Chancellor of Clinical Research

University of Nebraska Medical Center

Nebraska Medicine

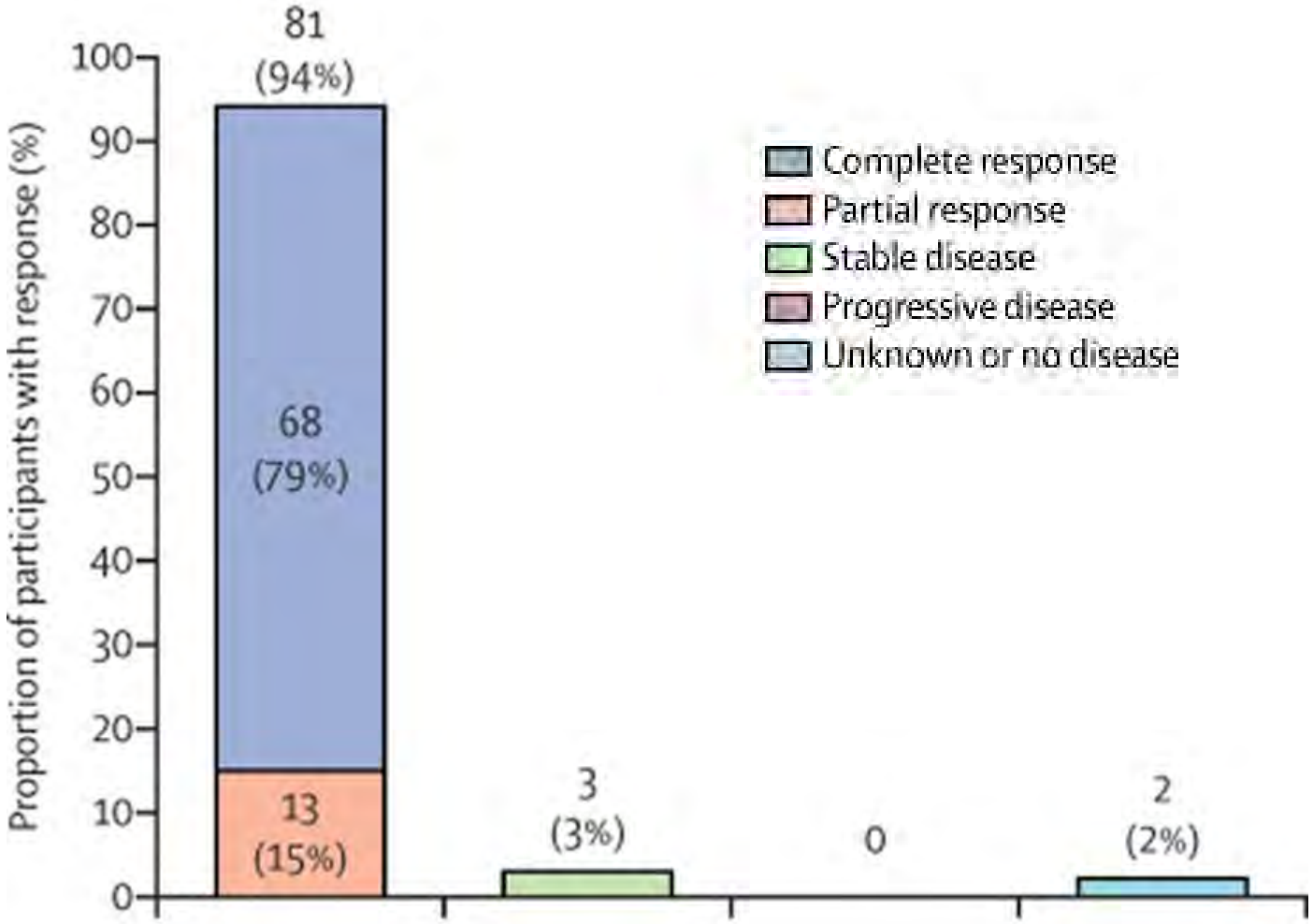
Dr Lunning — Disclosures

Consulting Honoraria	AbbVie Inc, Acrotech Biopharma, ADC Therapeutics, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Caribou Biosciences Inc, CRISPR Therapeutics, Daiichi Sankyo Inc, Fate Therapeutics, Genentech, a member of the Roche Group, Genmab US Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, Kite, A Gilead Company, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Nurix Therapeutics Inc, Recordati, Regeneron Pharmaceuticals Inc, Sanofi, Seagen Inc, Vittoria Biotherapeutics
Research Funding	Bristol Myers Squibb, Fate Therapeutics, Sana Biotechnology

Objectives

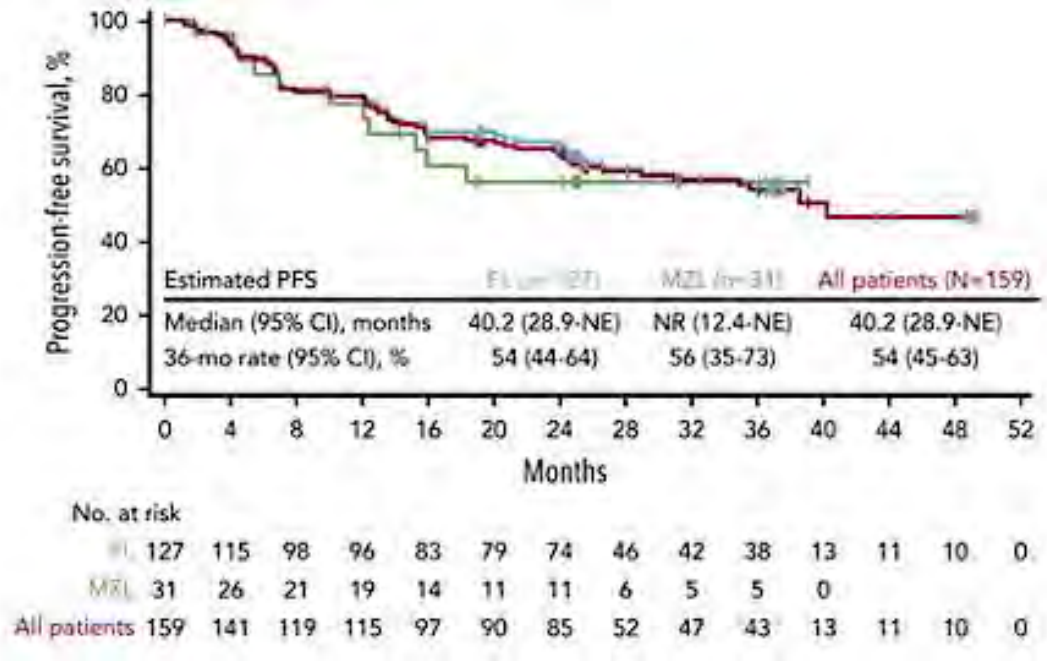
- Discuss the outcomes with axi-cel, tisa-cel and liso-cel for relapsed/refractory (R/R) follicular lymphoma
- Discuss the outcomes with brexu-cel and liso-cel for R/R mantle cell lymphoma
- Discuss the outcomes of liso-cel for R/R chronic lymphocytic leukemia (CLL)

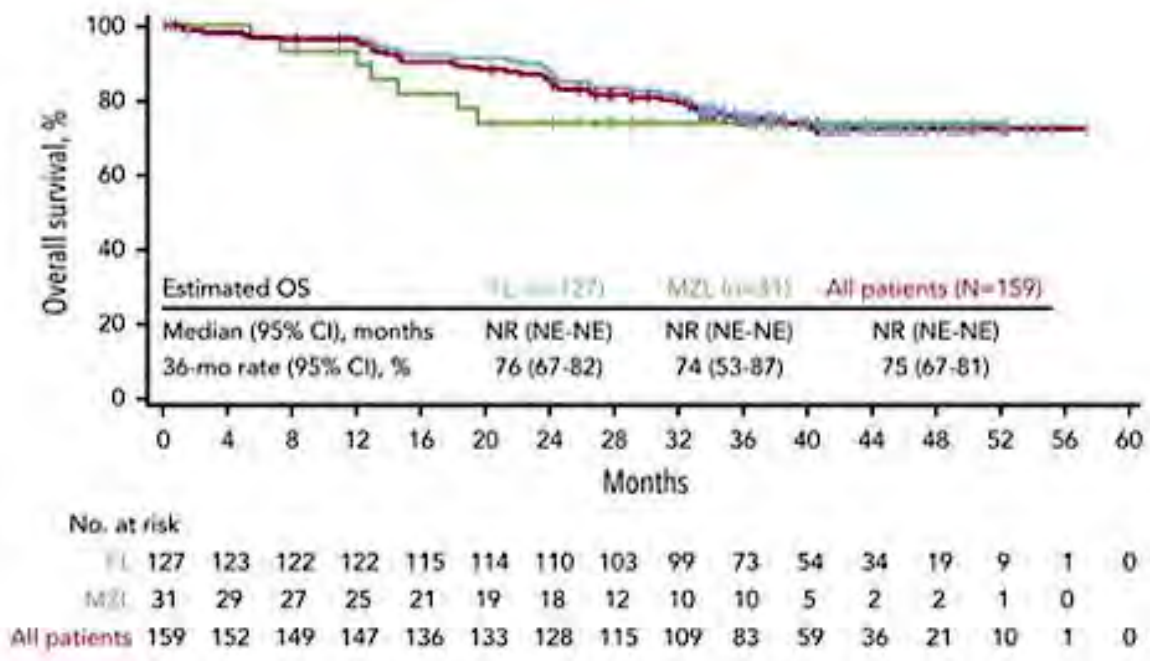
Axi-cel in Rel/Ref FL: ZUMA-5



Jacobsen et al. 2022

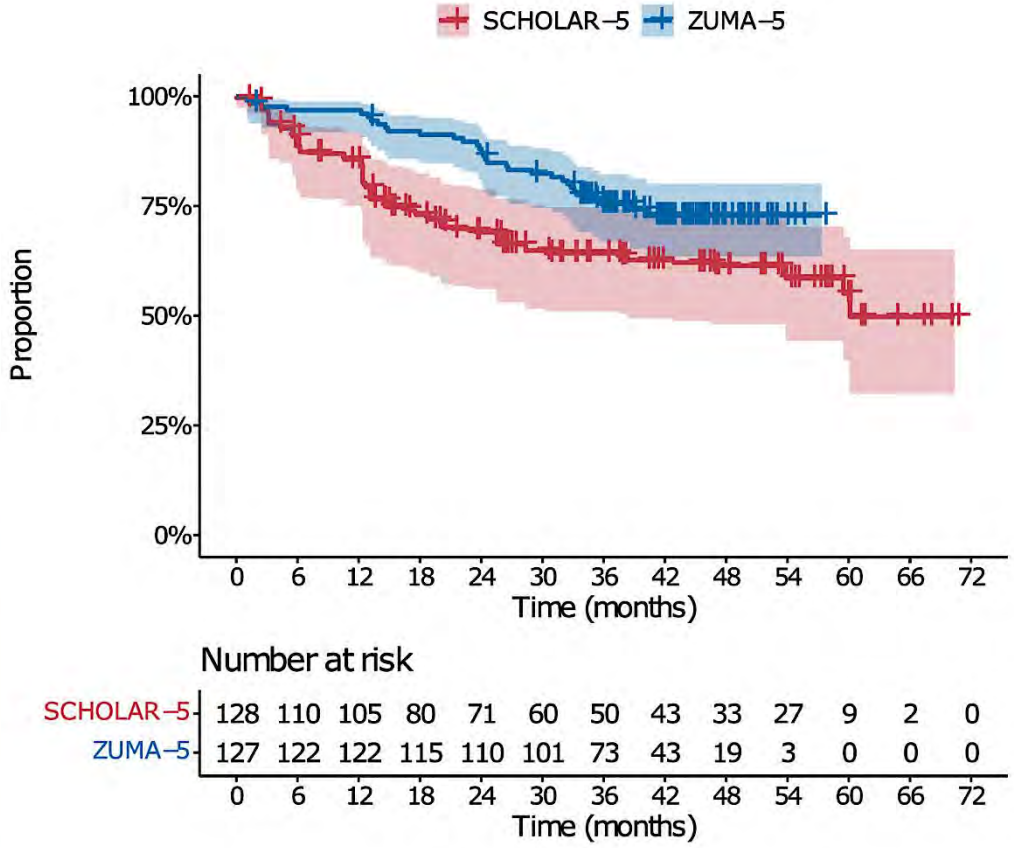
Axi-cel in Rel/Ref FL: ZUMA-5

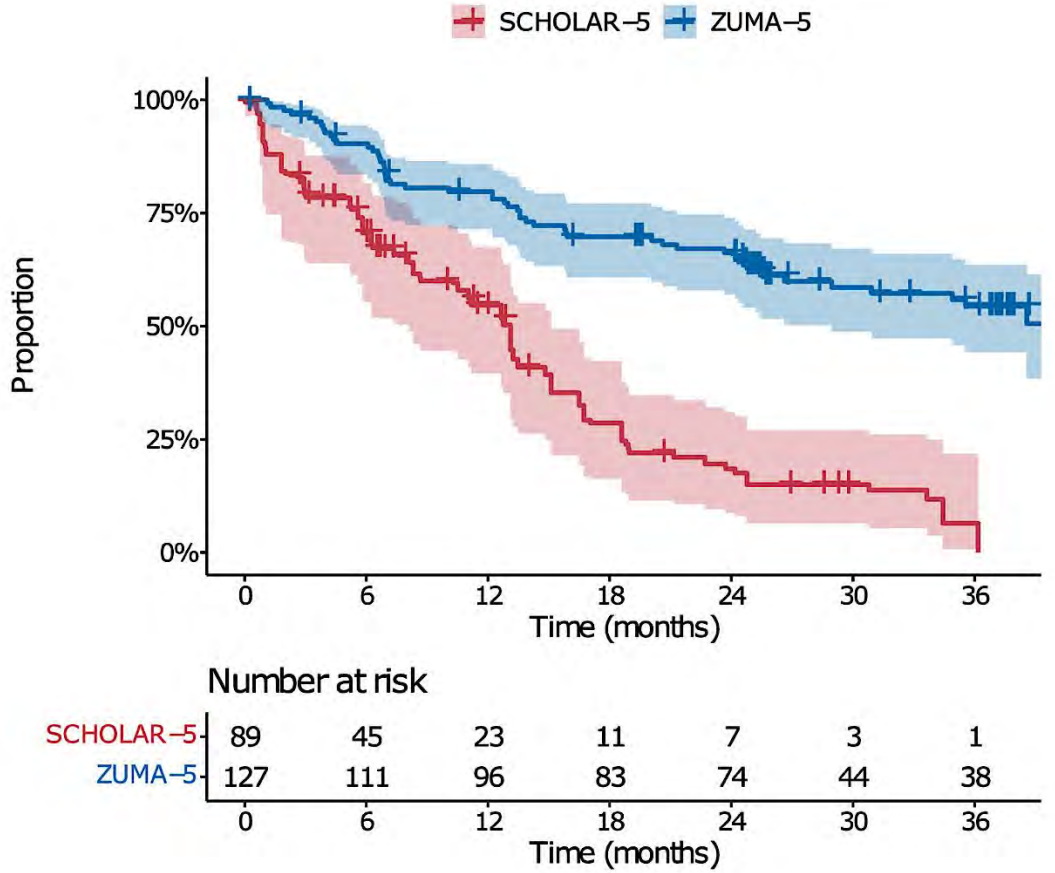




Jacobsen Lancet 2022; Neelapu et al. Blood 2024

Axi-cel in Rel/Ref FL: ZUMA-5





Ghione et al. Blood 2022

Tisa-cel in Rel/Ref FL: ELARA

BACKGROUND. The primary analysis of the Phase II ELARA trial (NCT03568461, median follow-up of 17 months) showed:

86%	69%	67%
Overall response rate (ORR)	Complete response rate (CRR)	12-mo progression-free survival rate

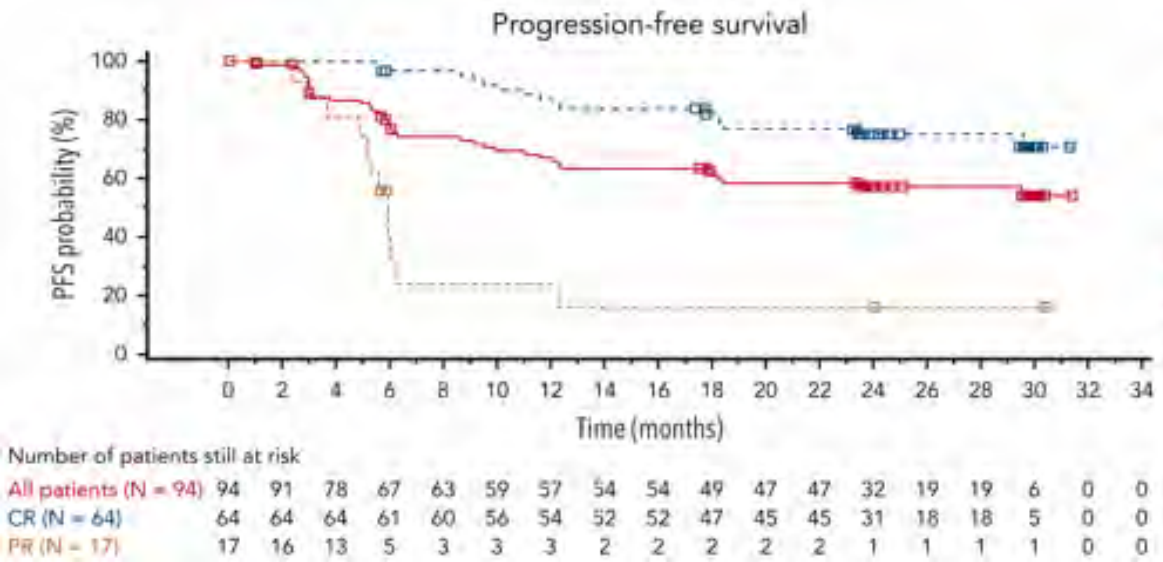
With a median follow-up of 29 months, high response rates were confirmed in patients with high-risk disease:

	ORR	CRR
POD24	82%	59%
High TMTV	75%	40%
Bulky Disease	86%	65%
High FLIPI	81%	61%
Double Refractory	85%	66%

POD24, progression of disease within 24 months from 1st immunochemotherapy TMTV, total metabolic tumor volume

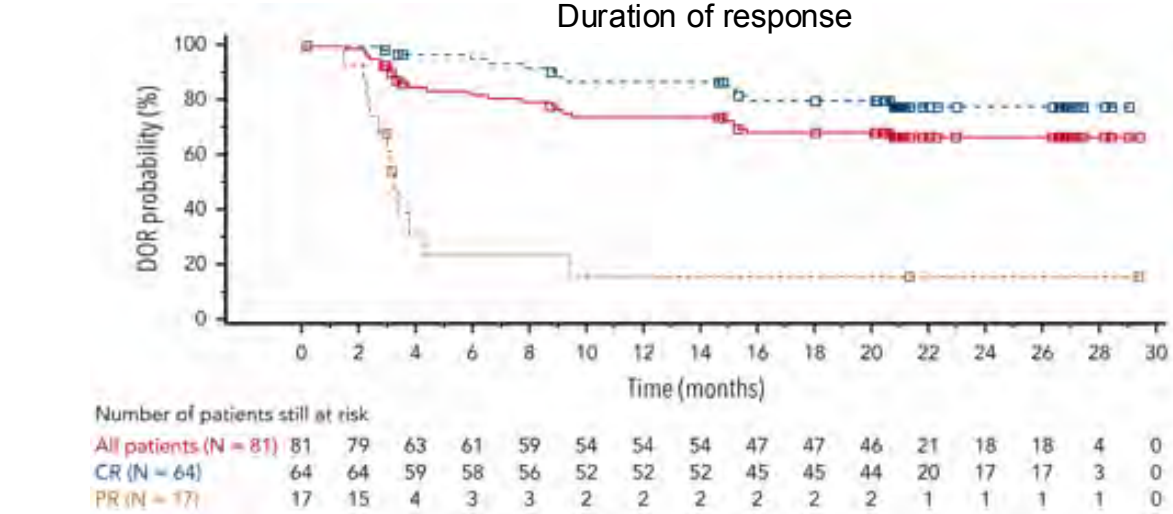
Dreyling et al. Blood 2024

Tisa-cel in Rel/Ref FL: ELARA



PFS Probability	% (95% CI)
12 months, all patients	67.2 (56.3-75.9)
24 months, all patients	57.4 (46.2-67.0)
12 months, patients in CR	87.2 (76.0-93.4)
24 months, patients in CR	75.3 (62.4-84.3)

Kaplan-Meier medians
All patients: NE months, 95% CI [18.2-NE]
CR: NE months, 95% CI [NE-NE]
PR: 5.9 months, 95% CI [4.9-6.3]

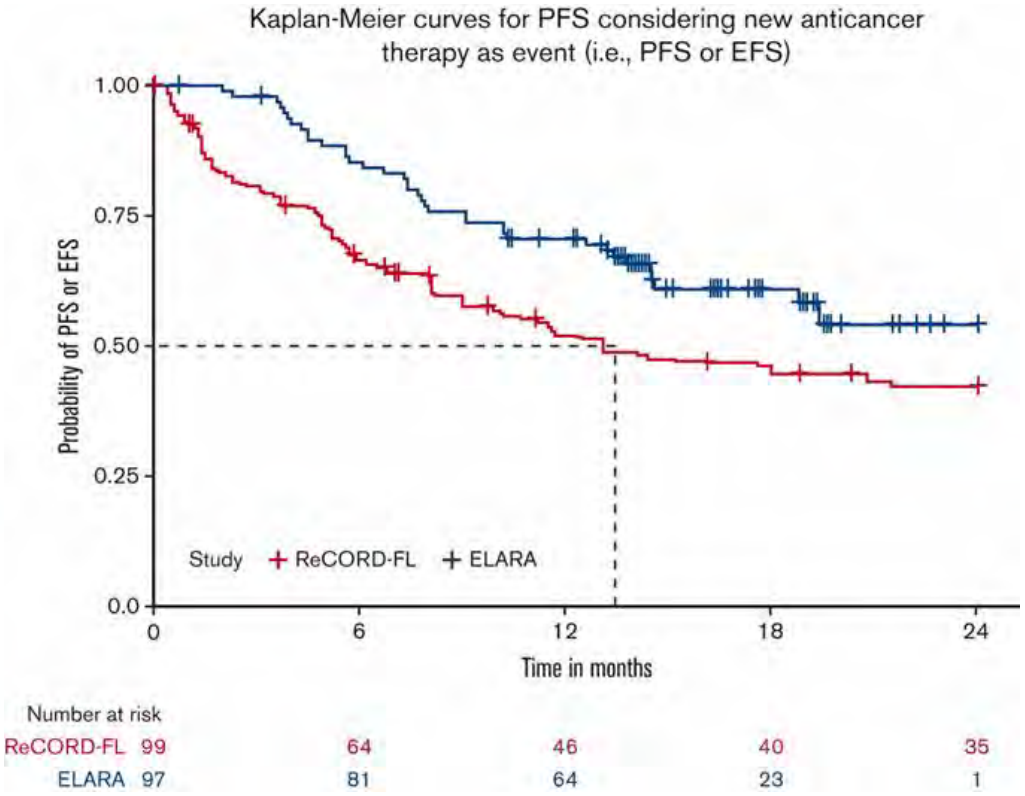


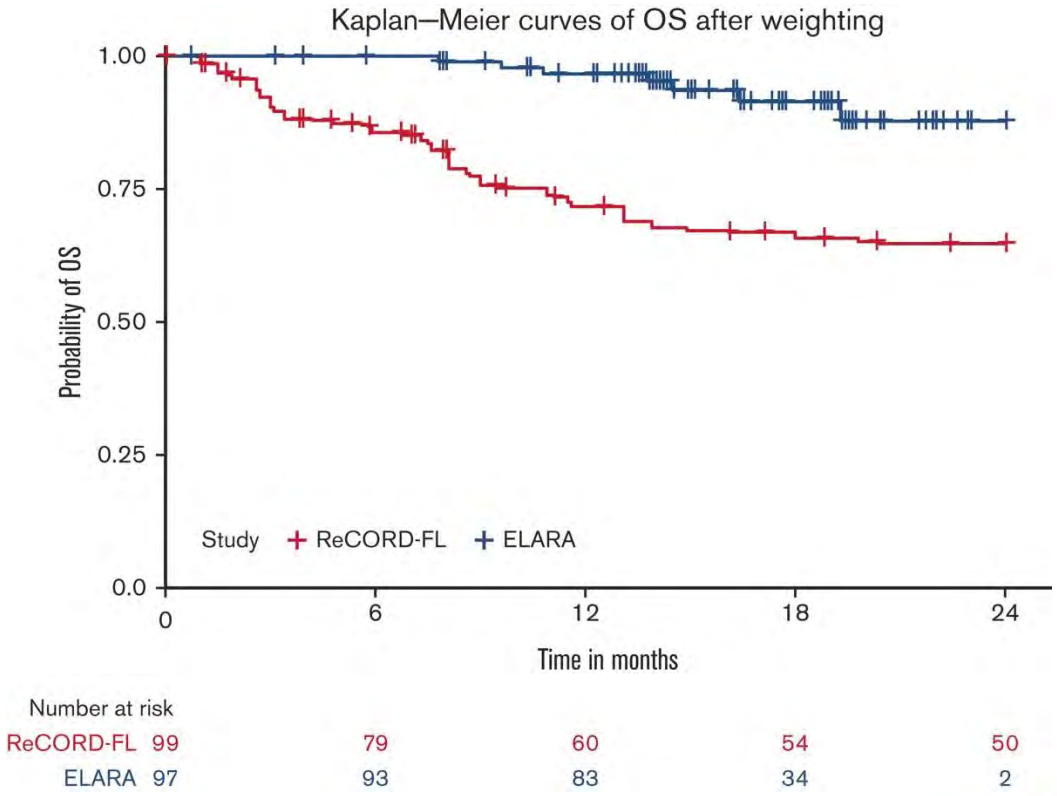
DOR Probability	% (95% CI)
12 months, all patients	73.8 (62.4-82.3)
24 months, all patients	66.4 (54.3-76.0)
12 months, patients in CR	86.9 (75.6-93.2)
24 months, patients in CR	77.8 (64.7-86.5)

Kaplan-Meier medians
All patients: NE months, 95% CI [NE-NE]
CR: NE months, 95% CI [NE-NE]
PR: 3.2 months, 95% CI [2.3-4.3]

Dreyling et al. Blood 2024

Tisa-cel in Rel/Ref FL: ELARA





Salles et al. Blood Advances 2022

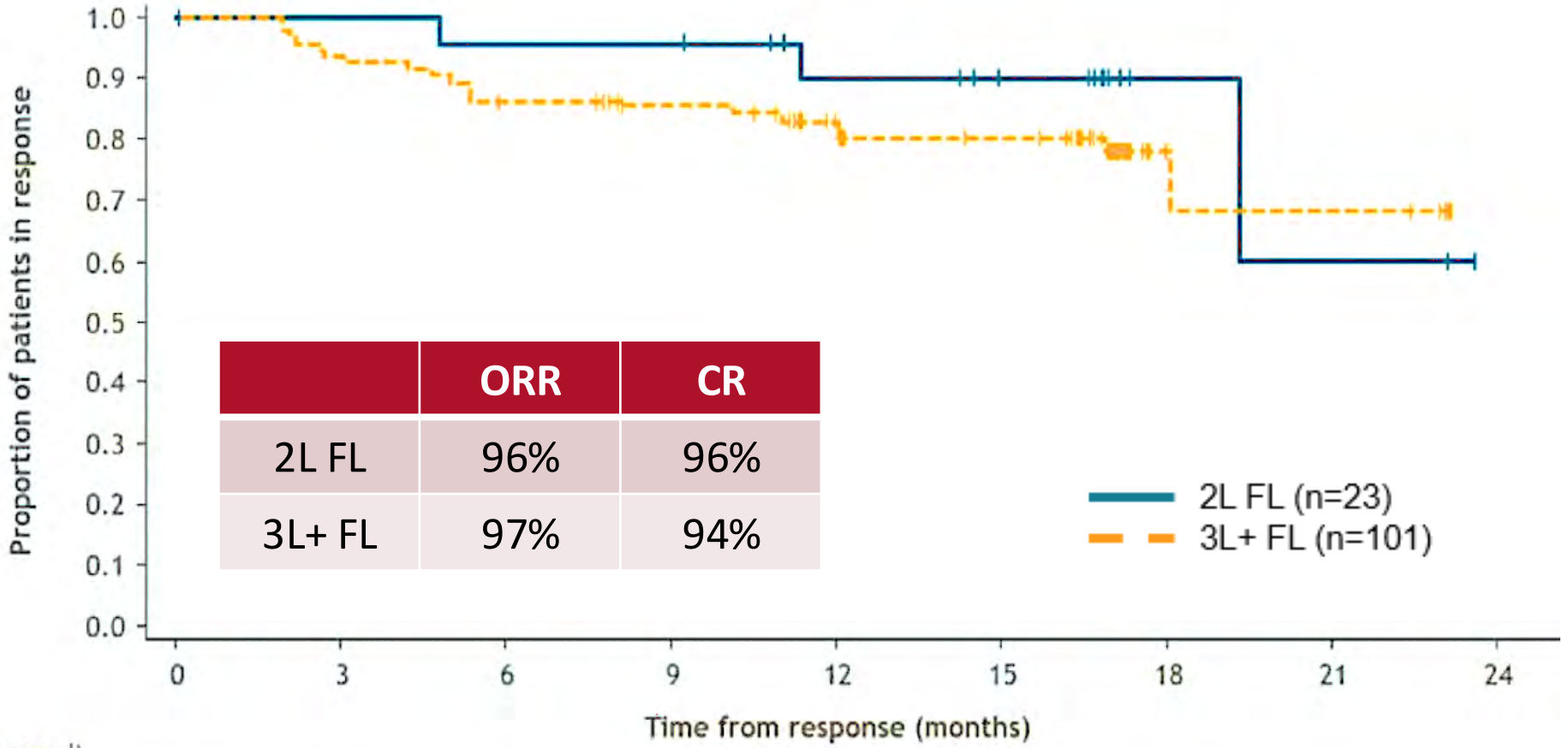
Liso-cel in Rel/Ref FL: TRANSCEND-FL

Patient Characteristics		2L FL (n=23)	3L+ FL (n=107)
Median age (range), y		53 (34–69)	62 (23–80)
FL grade 1 or 2/3a at screening,[b] n (%)		17 (74)/6 (26)	81 (76)/25 (23)
Ann Arbor stage at screening, n (%)	I/II	6 (26)	12 (11)
	III/IV	17 (74)	95 (89)
FLIPI at screening, n (%)	0–1/2	11 (48)/4 (17)	12 (11)/34 (32)
	3–5	8 (35)	61 (57)
LDH>ULN before lymphodepletion, n (%)		6 (26)	47 (44)
Met mGELF criteria at most recent relapse, n (%)		16 (70)	57 (53)
Median (range) prior lines of therapy		1 (1–1)	3 (2–10)
Prior HSCT, n (%)		0	33 (31)
Received prior rituximab and lenalidomide, n (%)		0	23 (21)
Refractory to last systemic therapy,[c] n (%)		15 (65)	72 (67)
Double refractory (anti-CD20 & alkylator),[d] n (%)		11 (48)	69 (64)
POD24 from initial immunochemotherapy, n (%)		15 (65)	58 (54)
POD24 from diagnosis, n (%)		12 (52)	46 (43)
Received bridging therapy, n (%)		5 (22)	44 (41)

Morschhauser et al. Nat Med 2024

Liso-cel in Rel/Ref FL: TRANSCEND-FL

	ORR	CR
2L FL	96%	96%
3L+ FL	97%	94%



No. at risk (censored)

2L FL	22 (0)	22 (0)	21 (0)	21 (0)	16 (4)	13 (3)	3 (10)	2 (0)	0 (2)
3L+ FL	98 (0)	91 (1)	83 (1)	77 (5)	62 (12)	49 (12)	8 (40)	7 (0)	0 (7)

Morschhauser et al. Nat Med 2024

Putting it Together

	Axi-cel	Tisa-cel	Liso-cel (3L+)
Patients	127	97	101
ORR	94%	86%	97%
CR	79%	68%	94%
mF/U	41m	29m	17m
Median PFS	40m (54%@36m)	NR @29m (57%@24m)	NR @17m (81%@12m)

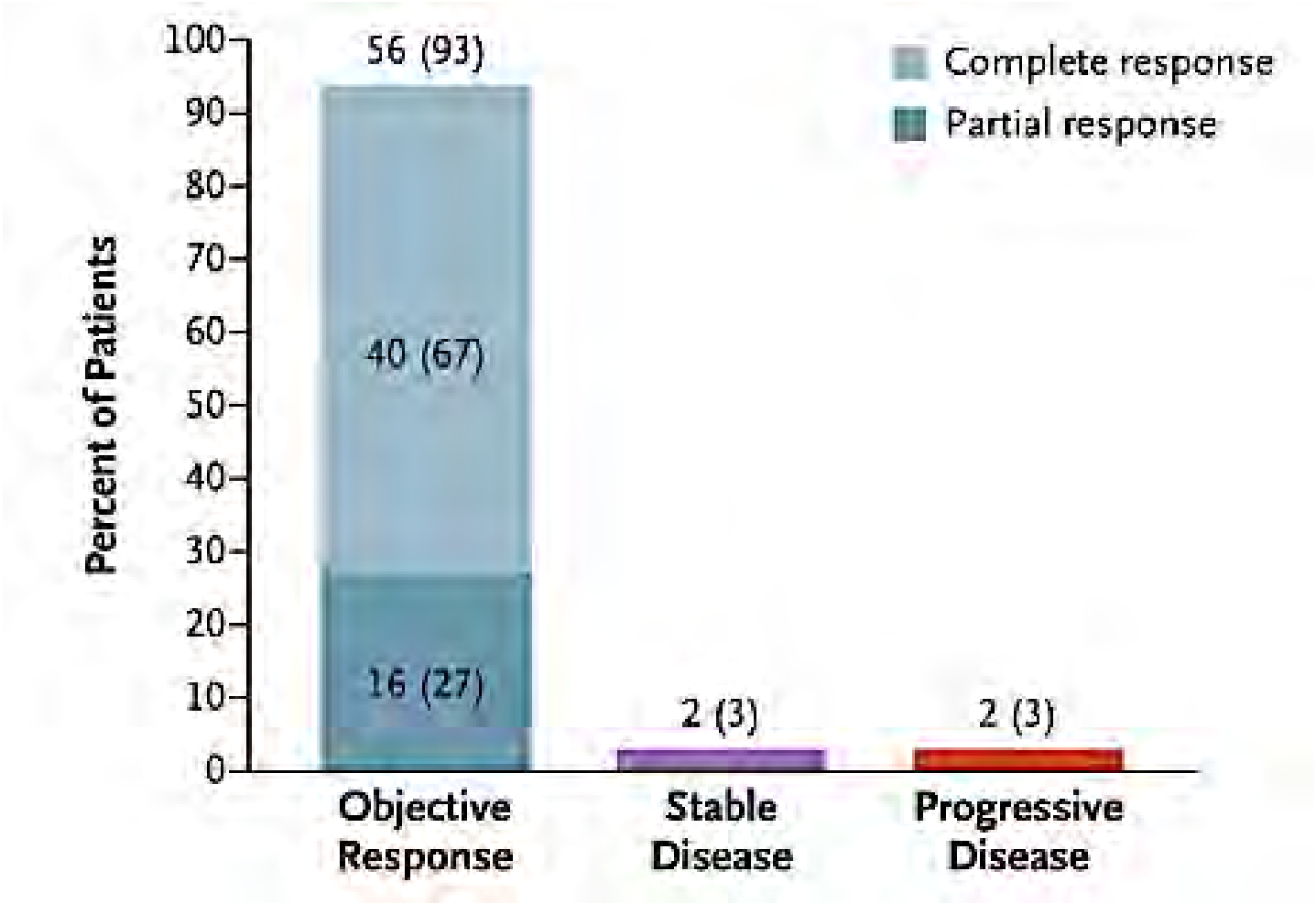
Neelapu et al. *Blood* 2024; Dreyling et al. *Blood* 2024; Morschhauser et al. *Nat Med* 2024

Putting it Together

	Axi-cel	Tisa-cel	Liso-cel
CRS (All Grade)	78%	49%	58%
CRS (Grade ≥3)	6%	0%	1%
ICANS (All Grade)	56%	23%	15%
ICANS (Grade ≥3)	18%	1%	2%

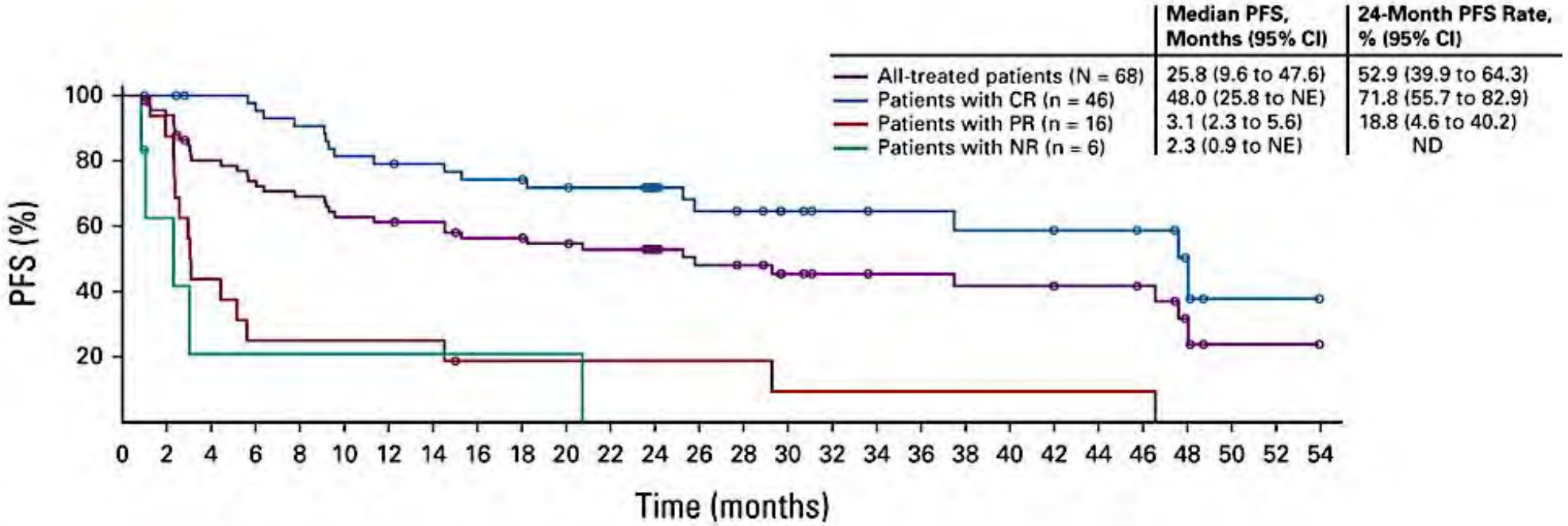
Neelapu et al. Blood 2024; Dreyling et al. Blood 2024; Morschhauser et al. Nat Med 2024

Brexu-cel in Rel/Ref MCL: ZUMA-2



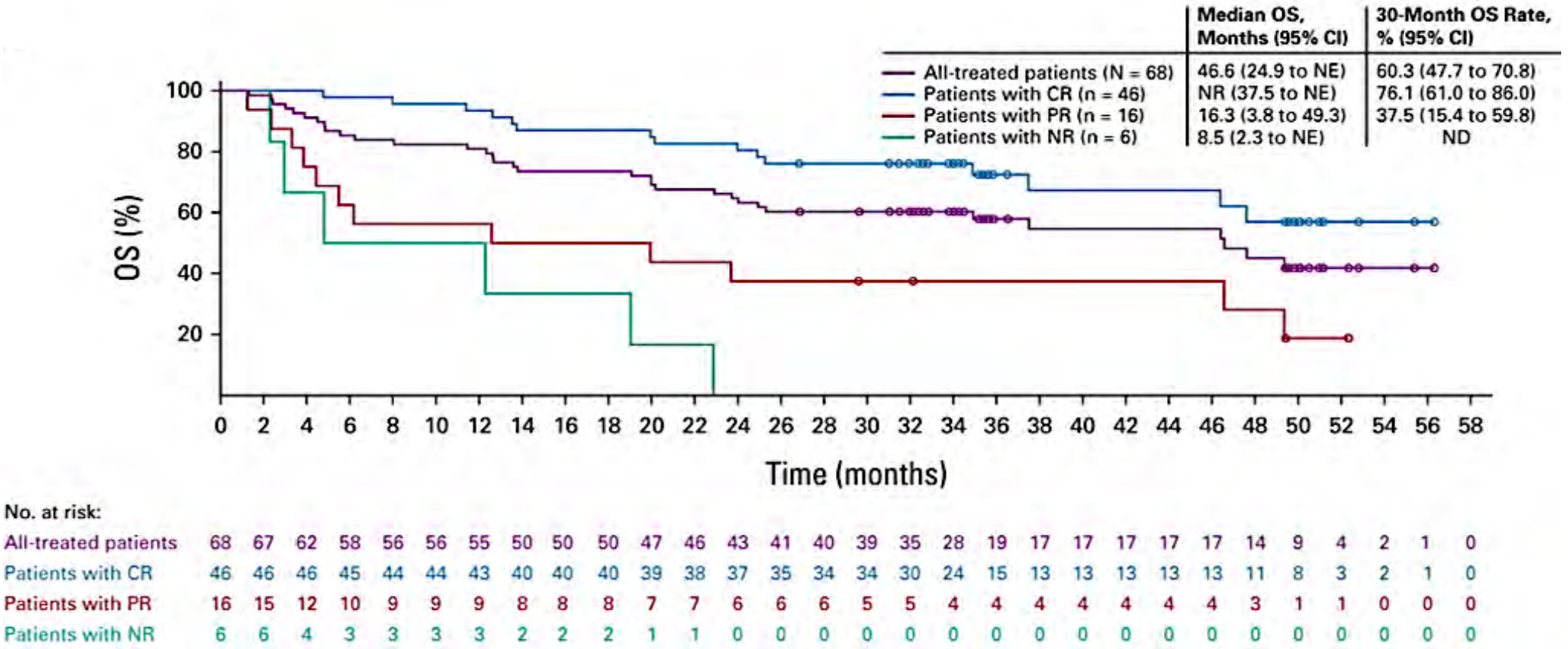
Wang et al. NEJM 2020

Brexu-cel in Rel/Ref MCL: ZUMA-2



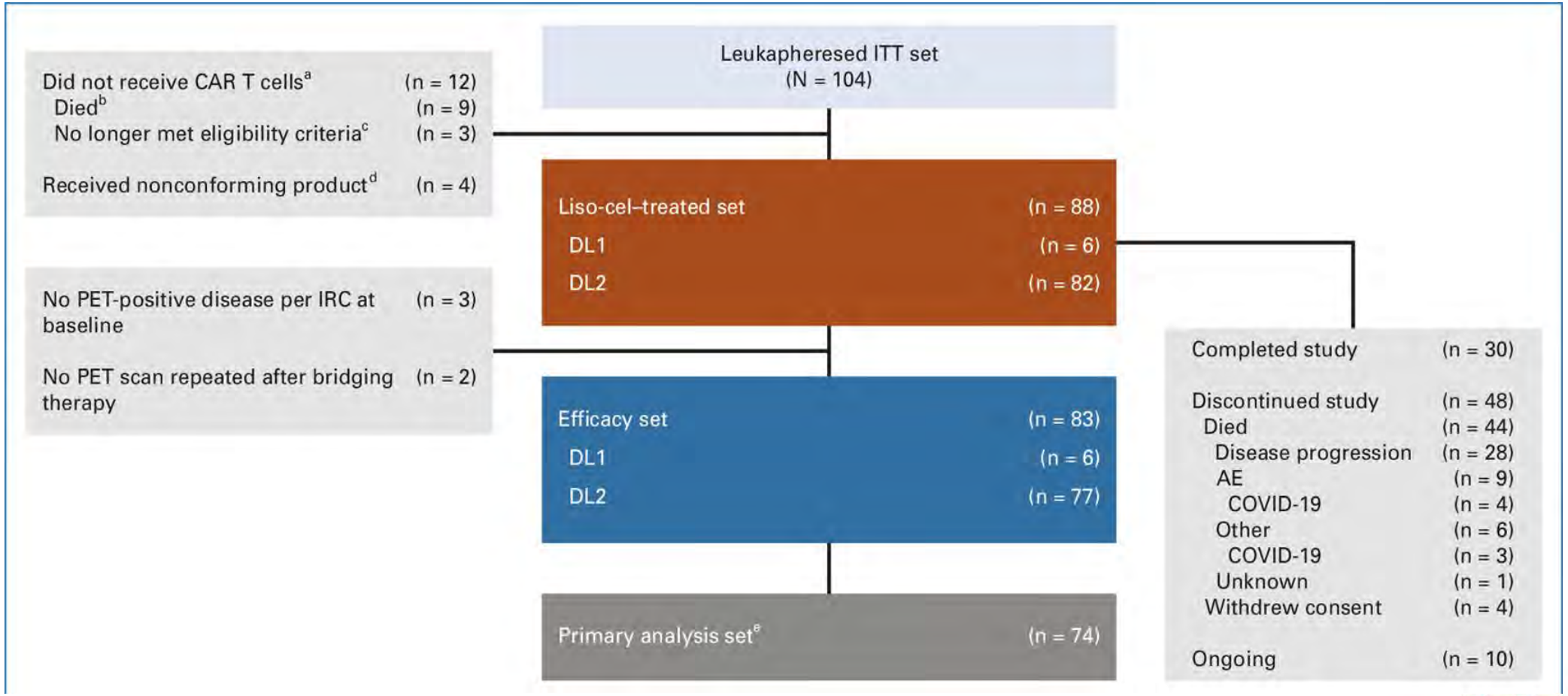
Wang M et al. *J Clin Oncol* 2023;41(3):555-567.

Brexu-cel in Rel/Ref MCL: ZUMA-2



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

Liso-cel in Rel/Ref MCL: TRANSCEND-MCL



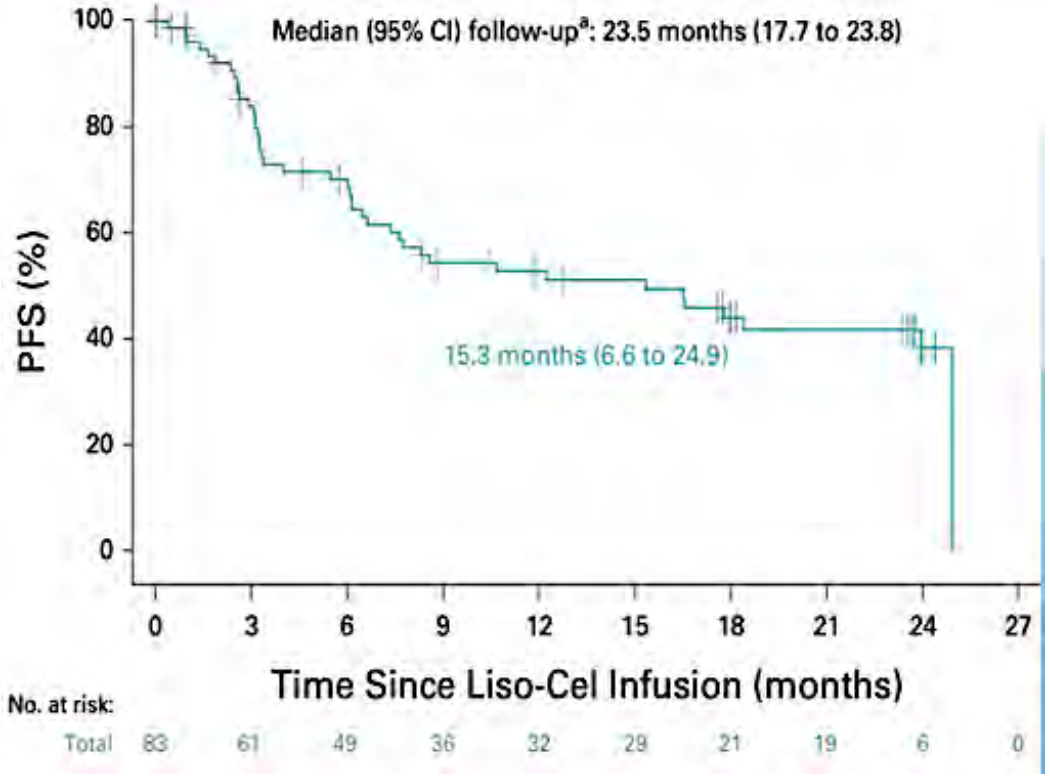
Wang et al. JCO 2024

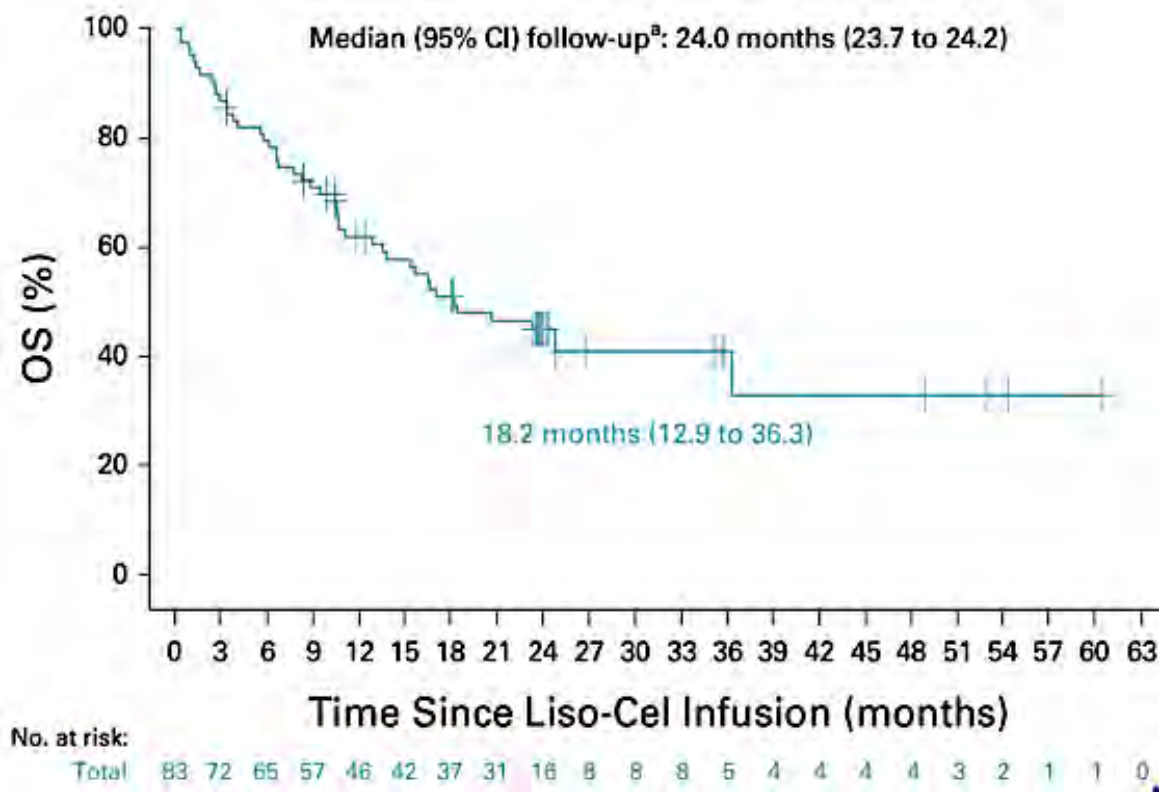
Liso-cel in Rel/Ref MCL: TRANSCEND-MCL

		Ki-67 proliferation index		*TP53* mutation		Blastoid morphology	
	Overall population (N = 88)	≥ 30% (n = 66)	< 30% (n = 15)	Yes (n = 20)	No (n = 34)	Yes (n = 27)	No (n = 48)
Median (range) age, y	68.5 (36–86)	68 (36–86)	71 (57–79)	71 (54–84)	69 (36–80)	68 (36–84)	70.5 (48–86)
≥ 65 y, n (%)	64 (73)	46 (70)	12 (80)	16 (80)	27 (79)	20 (74)	37 (77)
Median (range) prior lines of systemic therapy	3 (1–11)	3 (1–11)	3 (1–9)	3 (2–11)	3 (1–9)	3 (1–9)	3 (2–11)
≥ 5 prior lines of systemic therapy, n (%)	26 (30)	21 (32)	2 (13)	7 (35)	9 (26)	10 (37)	12 (25)
Prior HSCT, n (%)	29 (33)	22 (33)	3 (20)	4 (20)	11 (32)	13 (48)	11 (23)
Prior BTKi, n (%)	83 (94)	62 (94)	14 (93)	20 (100)	32 (94)	25 (93)	47 (98)
Refractory disease,[d] n (%)	61 (69)	48 (73)	9 (60)	11 (55)	21 (62)	24 (89)	26 (54)
Refractory to BTKi,[e] n (%)	47 (53)	37 (56)	6 (40)	7 (35)	21 (62)	18 (67)	24 (50)
Ki-67 proliferation index ≥ 30%, n (%)	66 (75)	66 (100)	0	14 (70)	25 (74)	24 (89)	33 (69)
TP53 mutation, n (%)	20 (23)	14 (21)	4 (27)	20 (100)	0	3 (11)	14 (29)
Blastoid morphology, n (%)	27 (31)	24 (36)	2 (13)	3 (15)	12 (35)	27 (100)	0
Secondary CNS lymphoma, n (%)	7 (8)	5 (8)	2 (13)	1 (5)	3 (9)	1 (4)	4 (8)
Complex karyotype, n (%)	26 (30)	21 (32)	3 (20)	7 (35)	16 (47)	10 (37)	13 (27)
Received bridging therapy, n (%)	58 (66)	49 (74)	5 (33)	13 (65)	21 (62)	19 (70)	30 (62.5)

Palomba et al. ASTCT 2024

Liso-cel in Rel/Ref MCL: TRANSCEND-MCL





Wang et al. JCO 2024

Putting it Together

	Brexu-cel	Liso-cel
Patients	68	83
ORR	91%	83%
CR	68%	72%
Median PFS	26m	15m
Median OS	47m	18m

Wang M et al. *J Clin Oncol* 2023;41(3):555-567; Wang et al. JCO 2024

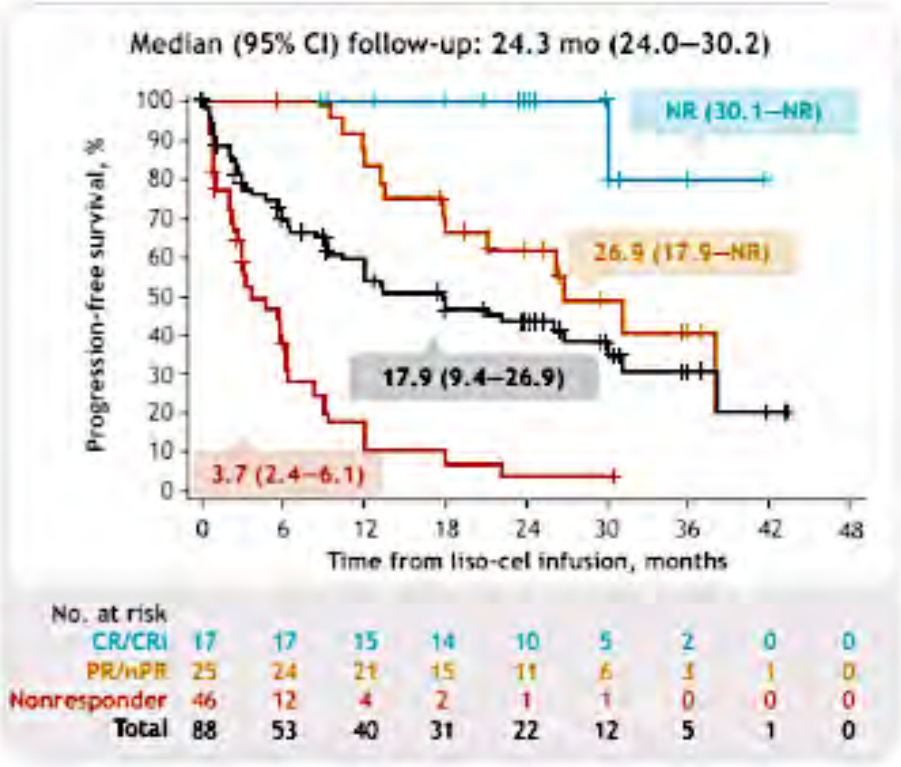
Putting it Together

	Brexu-cel	Liso-cel
CRS (All Grade)	91%	61%
CRS (Grade ≥3)	15%	1%
ICANS (All Grade)	63%	31%
ICANS (Grade ≥3)	31%	9%

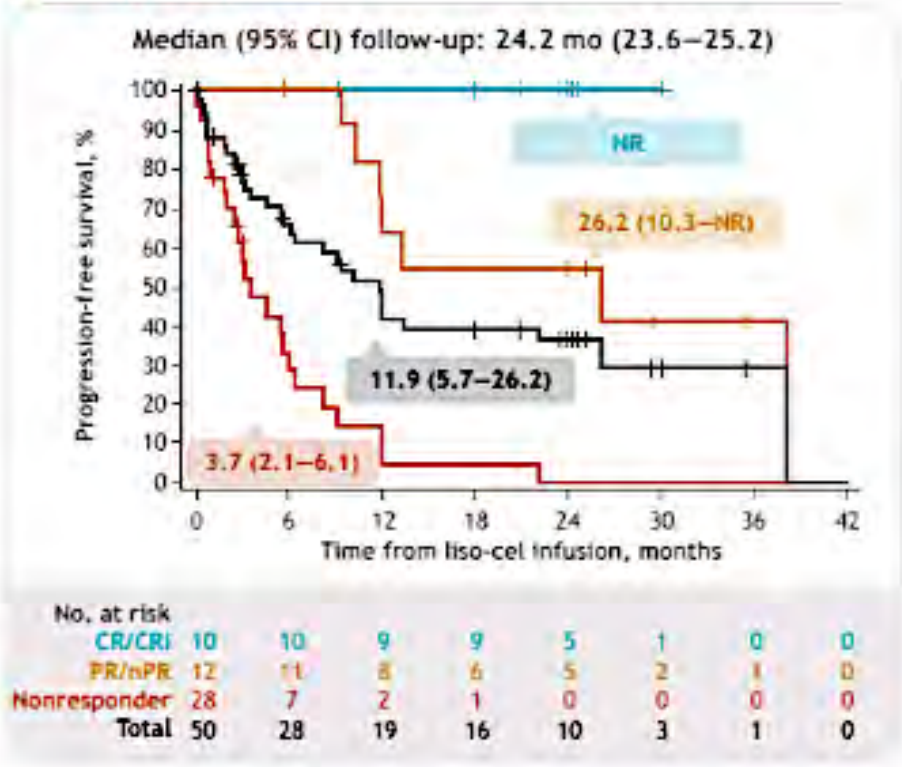
Wang NEJM 2020; Wang et al. JCO 2024

Liso-cel in Rel/Ref CLL: TRANSCEND-CLL

(A) Full study population at DL2 (n = 88)



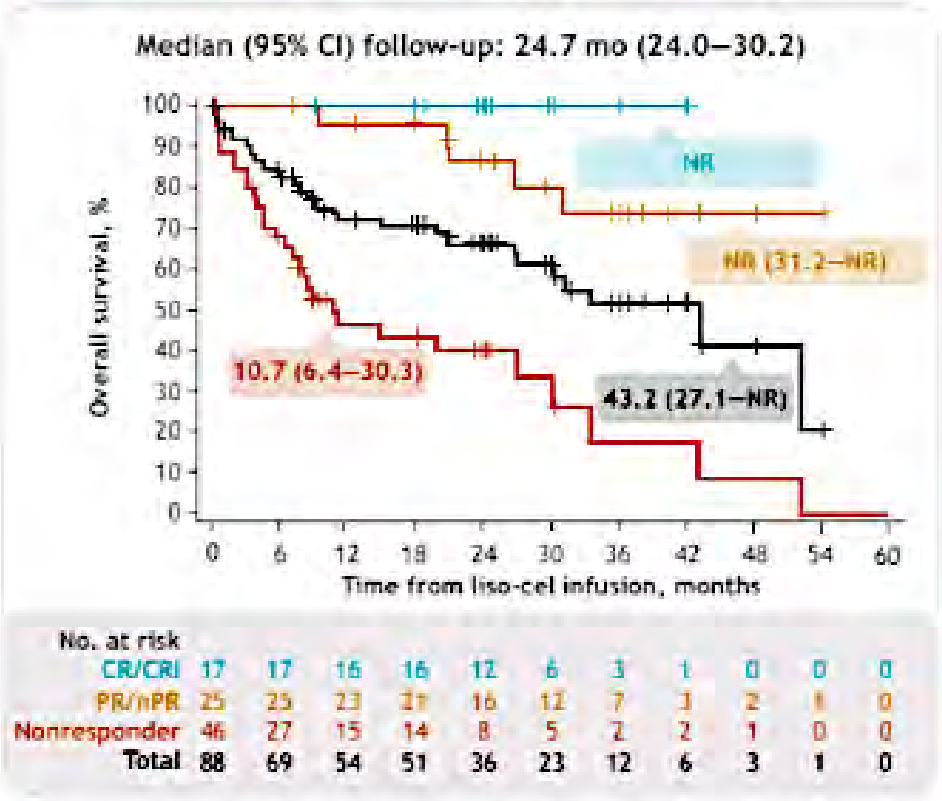
(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n = 50)



Shah et al. ASTCT 2024

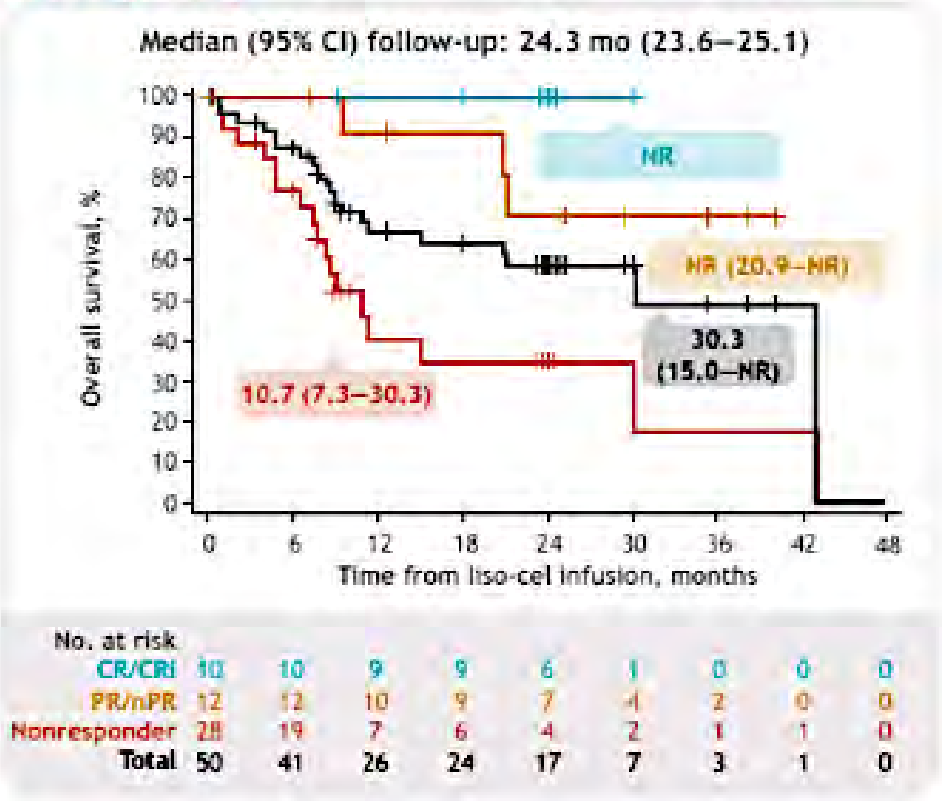
Liso-cel in Rel/Ref CLL: TRANSCEND-CLL

(A) Full study population at DL2 (n = 88)



No. at risk											
CR/CRi	17	17	16	16	12	6	3	1	0	0	0
PR/nPR	25	25	23	21	16	12	7	3	2	1	0
Nonresponder	46	27	15	14	8	5	2	2	1	0	0
Total	88	69	54	51	36	23	12	6	3	1	0

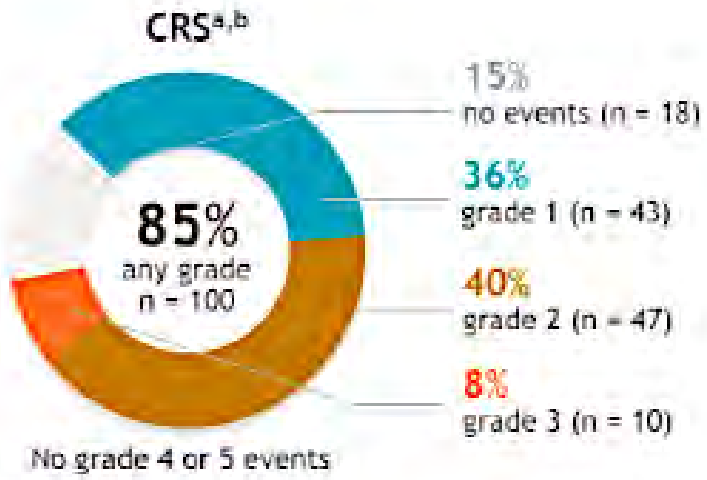
(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n = 50)

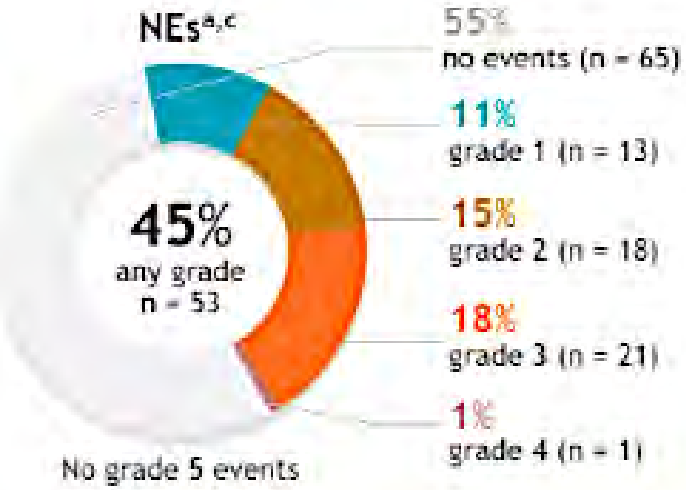


No. at risk											
CR/CRi	10	10	9	9	6	1	0	0	0		
PR/nPR	12	12	10	9	7	4	2	0	0		
Nonresponder	28	19	7	6	4	2	1	1	0		
Total	50	41	26	24	17	7	3	1	0		

Shah et al. ASTCT 2024

Liso-cel in Rel/Ref CLL: TRANSCEND-CLL





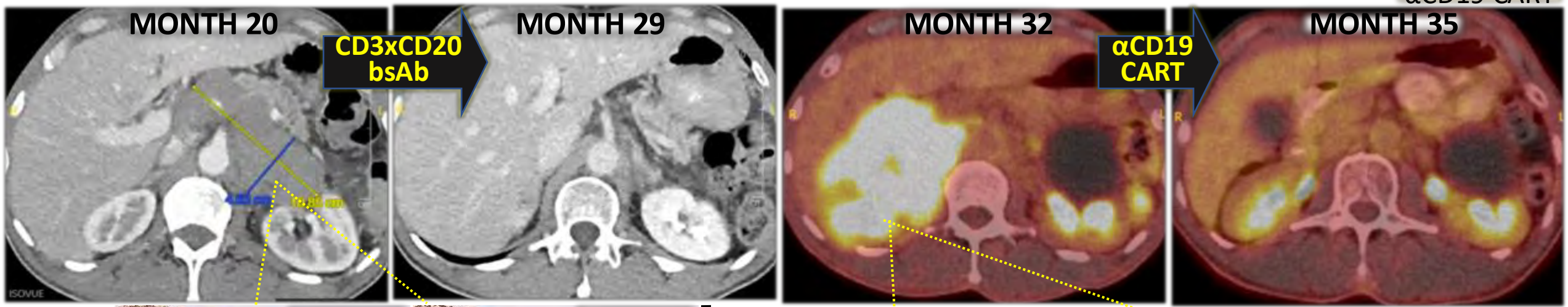
	Total (n = 118)	
	CRS	NE
Patients with an event, n (%)	100 (85)	53 (45)
Median (range) time to onset, days	4 (1–18)	7 (1–21)
Median (range) time to resolution, days	6 (2–37)	7 (1–83)
Received tocilizumab and/or corticosteroids for CRS and/or NE, n (%)	82 (69)	

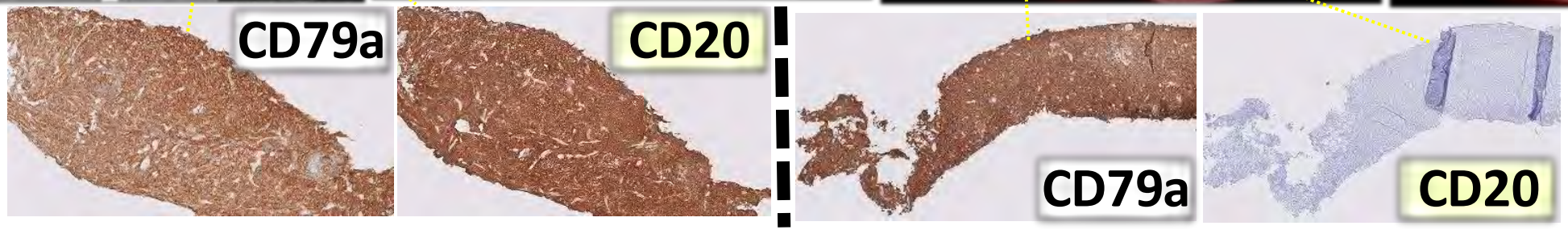
Shah et al. ASTCT 2024

Faculty Case Presentations

Case Presentation: Dr Brody

51 yo woman w Follicular Lymphoma s/p **R-Benda**→ CR x 20 months → **CD3xCD20** bsAb → CR x 9 months → relapse → Axi-cel αCD19 CART





QUESTIONS FOR THE FACULTY

Regulatory and reimbursement issues aside, what is your preferred CAR T-cell therapy for a patient with relapsed FL?

In general, in which line of therapy do you administer CAR T-cell therapy for patients with relapsed FL? In which line of therapy would you like to use CAR T-cell therapy for patients with FL?

Case Presentation – Dr Westin

72M with MCL, dx in 2017, TP53 wild type: treated with BR x 6 cycles = CR

Relapsed 4 years later: treated with BTKi x 16 months = CR then PD

Now with bulky adenopathy, LDH is 4x ULN, weight loss of 15 pounds

Treated with brexu-cel: grade 2 CRS, grade 3 ICANS, resolved = CR

QUESTIONS FOR THE FACULTY

What would you recommend for a younger patient with MCL who experienced disease progression on first-line chemoimmunotherapy and second-line BTK (Bruton tyrosine kinase) inhibition? What if the patient received a BTK inhibitor as first-line treatment with progression?

Regulatory and reimbursement issues aside, what is your preferred CAR T-cell therapy for a patient with relapsed MCL?

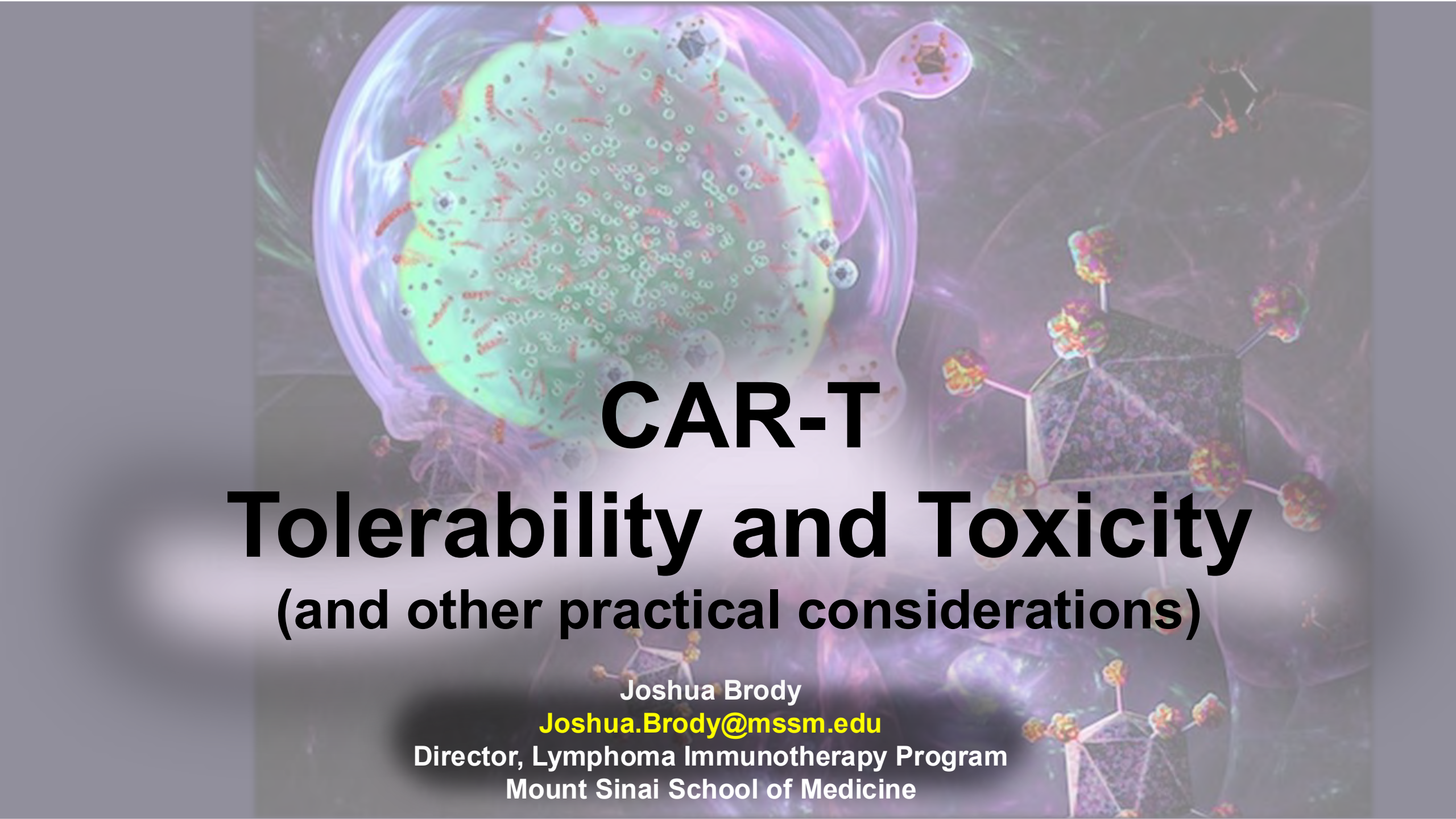
What would be your treatment approach for a younger patient with CLL who progresses on a BTK inhibitor and then a BCL2 inhibitor?

Agenda

Module 1: Integration of Chimeric Antigen Receptor (CAR) T-Cell Therapy into the Management of Diffuse Large B-Cell Lymphoma — Dr Westin

Module 2: Current Role of CAR T-Cell Therapy for Other B-Cell Lymphomas — Dr Lunning

Module 3: Tolerability and Other Practical Considerations with CAR T-Cell Therapy — Dr Brody



CAR-T
Tolerability and Toxicity
(and other practical considerations)

Joshua Brody
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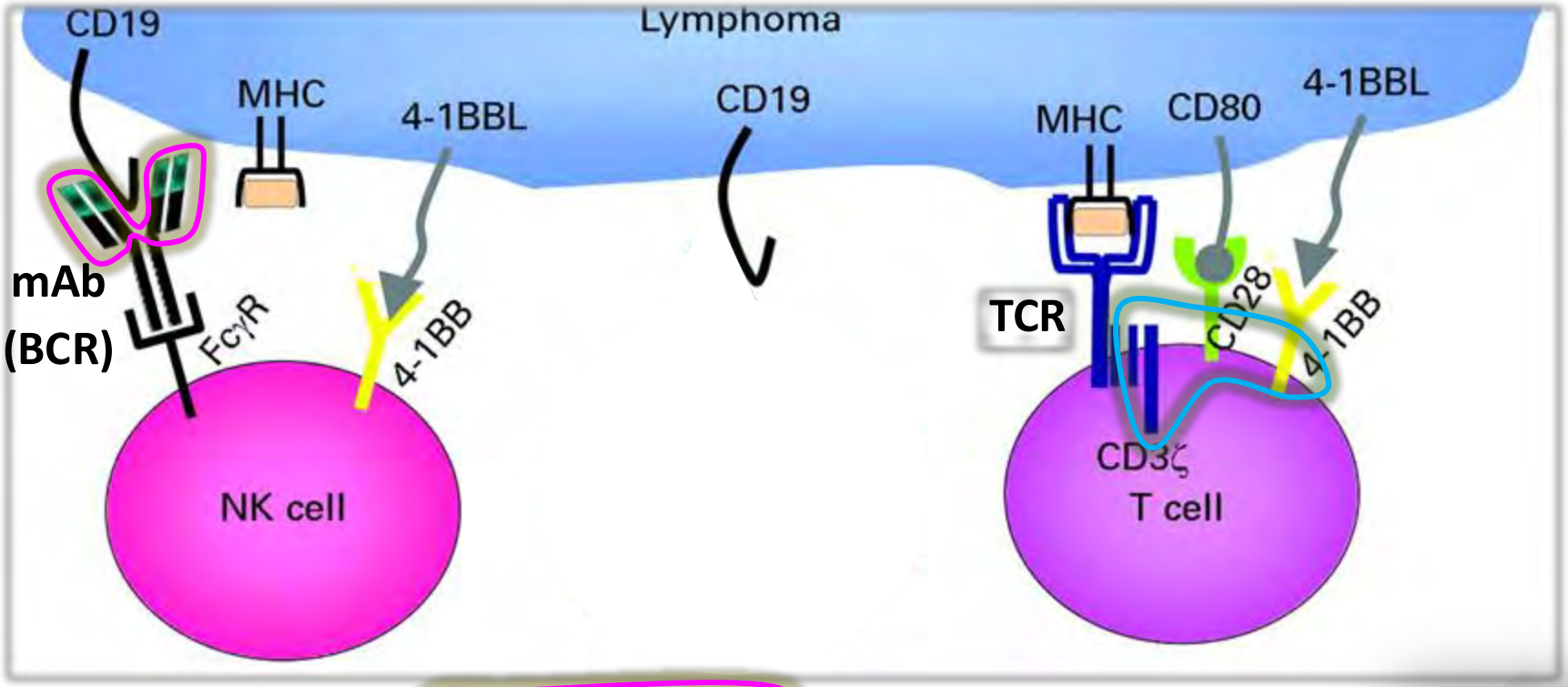
Director, Lymphoma Immunotherapy Program
Mount Sinai School of Medicine

Dr Brody — Disclosures

No relevant conflicts of interest to disclose.

CAR: Chimera of 2 Antigen Receptors



-Antigen Receptor 1: antibody (recognition)

-Antigen Receptor 2: TCR (signaling)

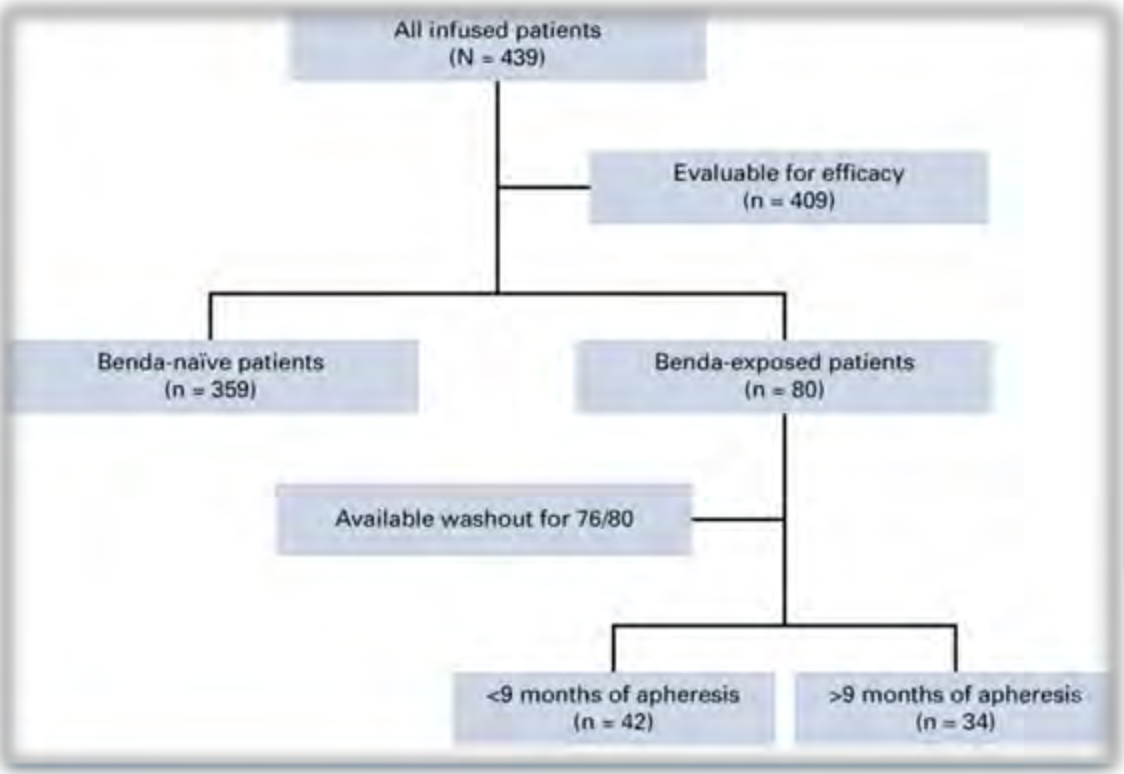
-CAR-T: a T cell with a CAR shoved into it

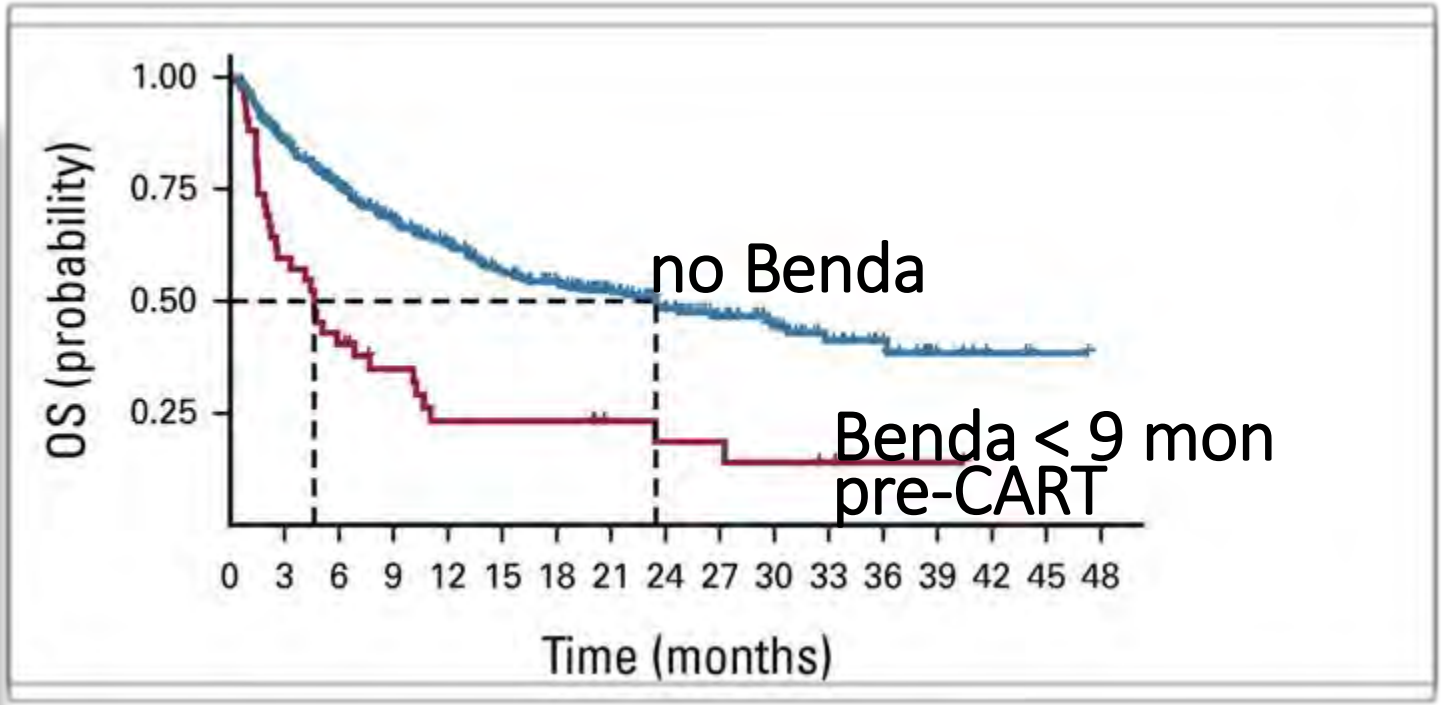
Brody J, et al., J Clin Oncol. 2011

Prior rx effect on CAR-T: Bendamustine ~ ↓ survival

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

Recent Bendamustine Treatment Before Apheresis Has a Negative Impact on Outcomes in Patients With Large B-Cell Lymphoma Receiving Chimeric Antigen Receptor T-Cell Therapy



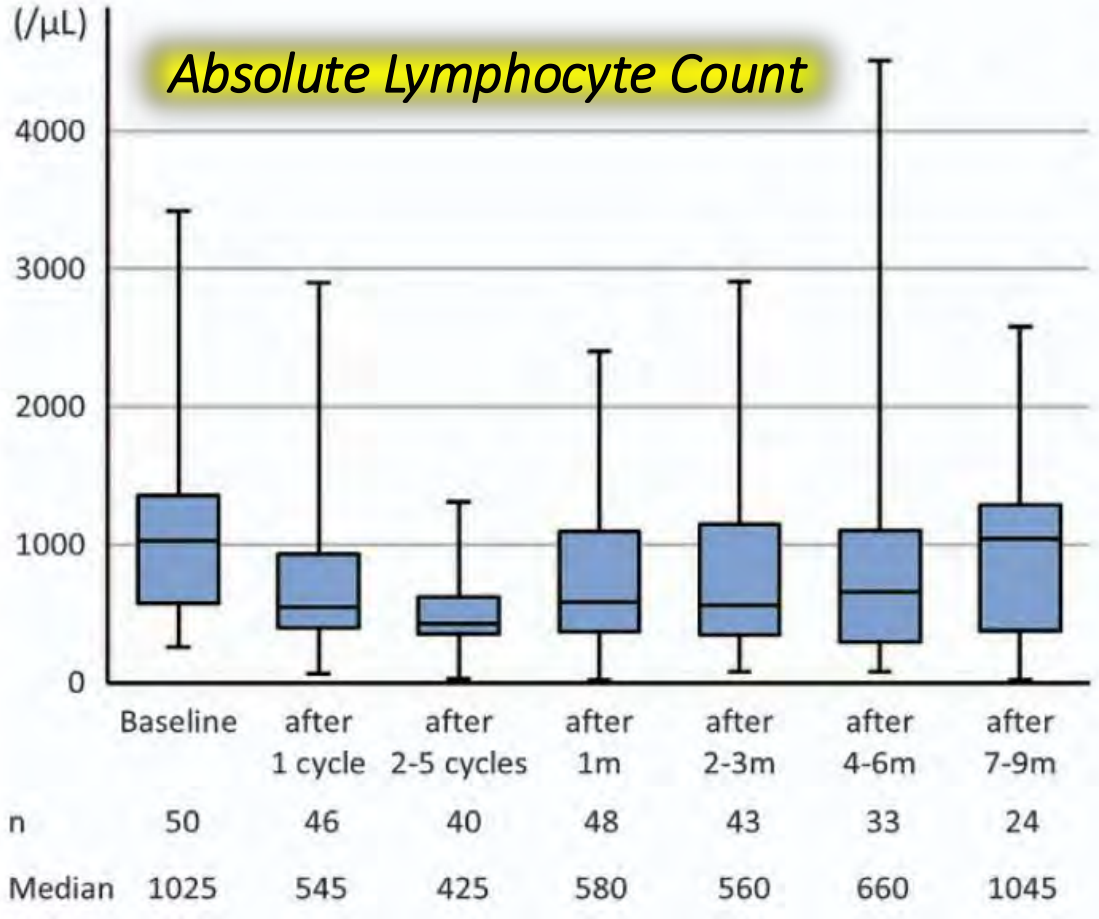


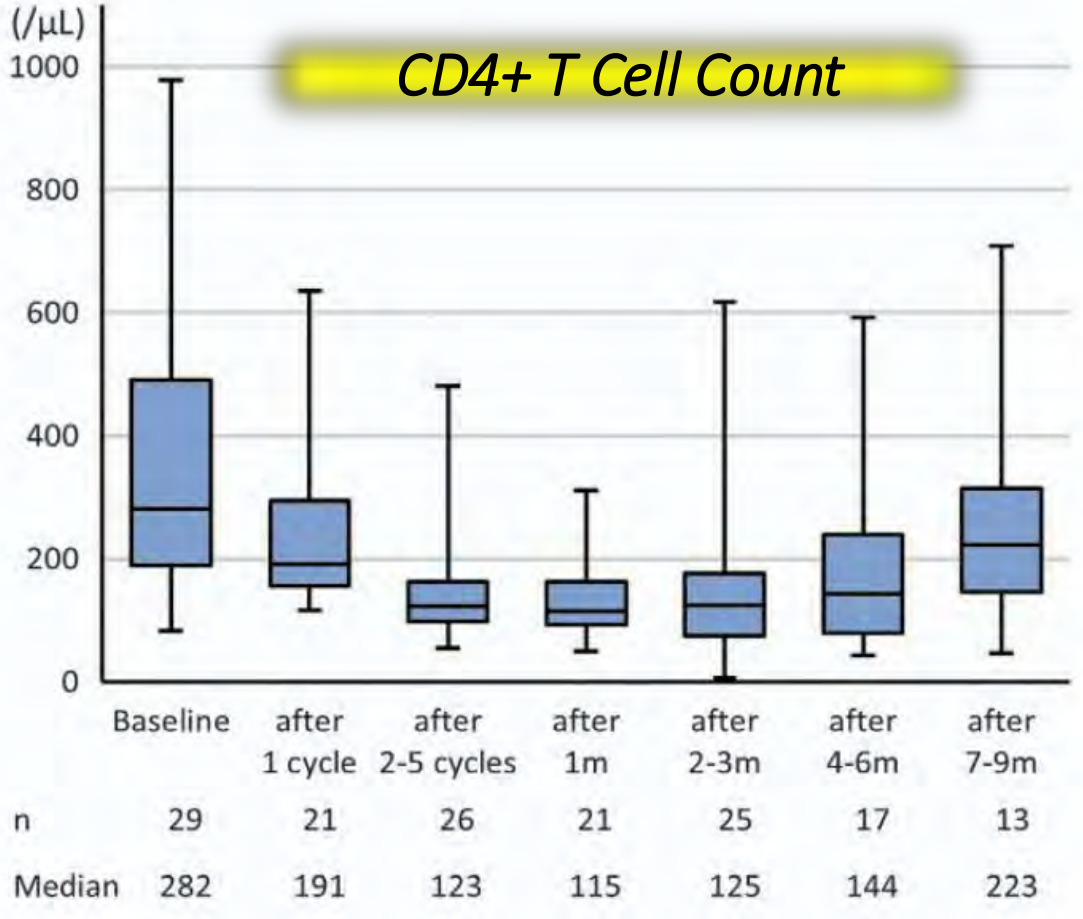
Iacoboni, G et al., *J Clin Oncol* 2024

Prior rx effect on CAR-T: Bendamustine ~ ↓ T cells

Citation: Blood Cancer Journal (2015) 5, e362; doi:10.1038/bcj.2015.86
www.nature.com/bcj

Prolonged lymphocytopenia after bendamustine therapy in patients with relapsed or refractory indolent B-cell and mantle cell lymphoma





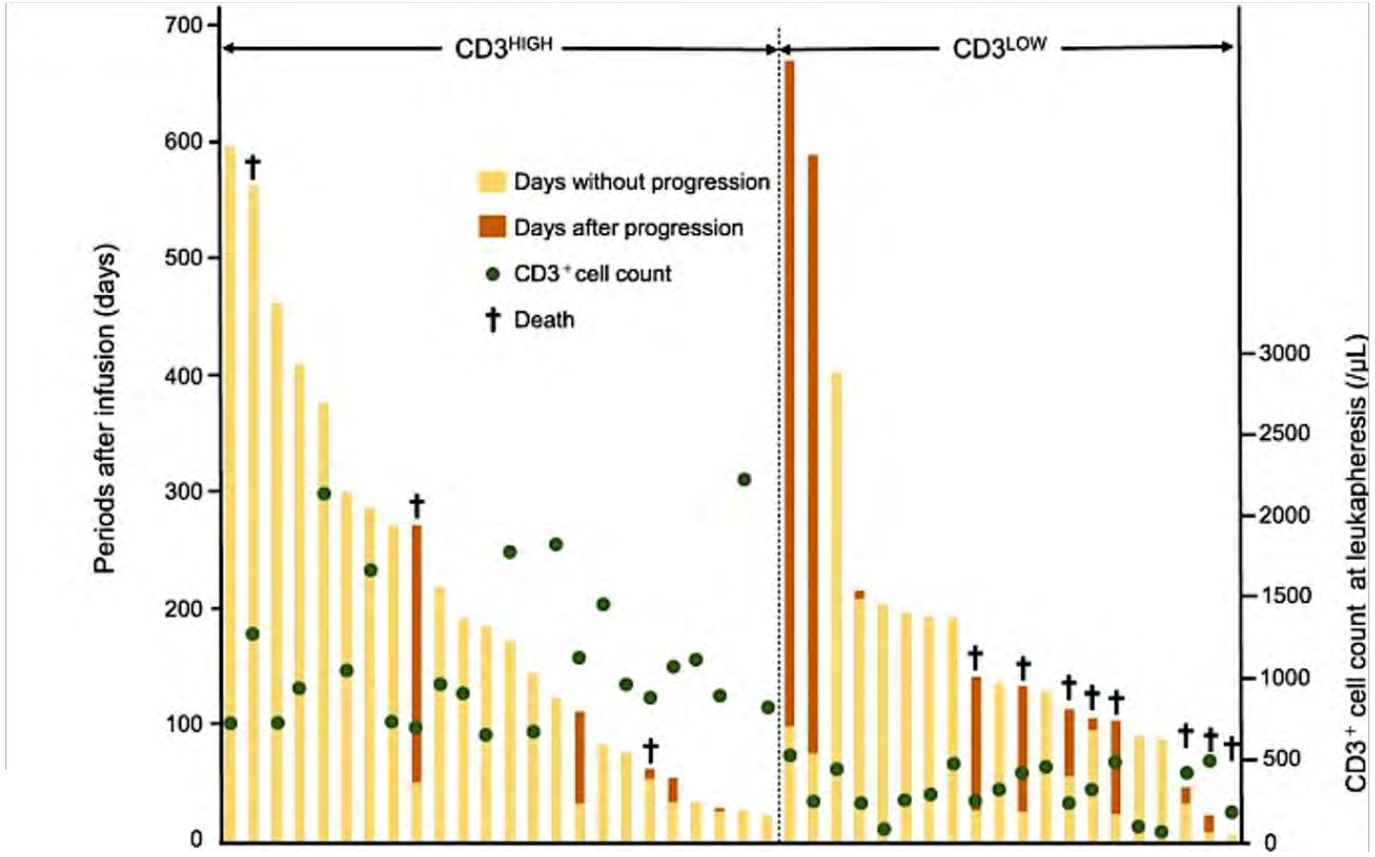
Saito H et al., Blood Cancer J . 2015

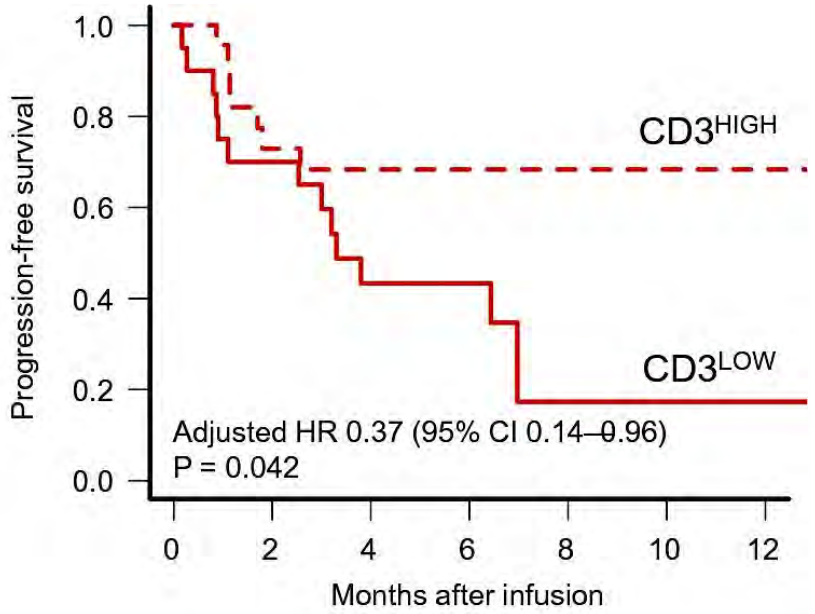
Prior rx effect on CAR-T: low T cells ~ ↓ outcomes

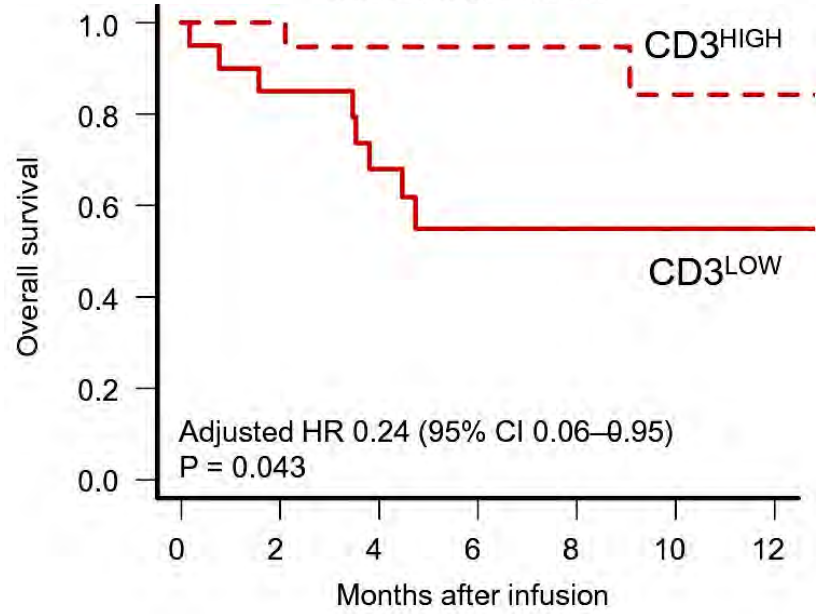
www.nature.com/scientificreport

scientific reports

T-cell counts in peripheral blood at leukapheresis predict responses to subsequent CAR-T cell therapy

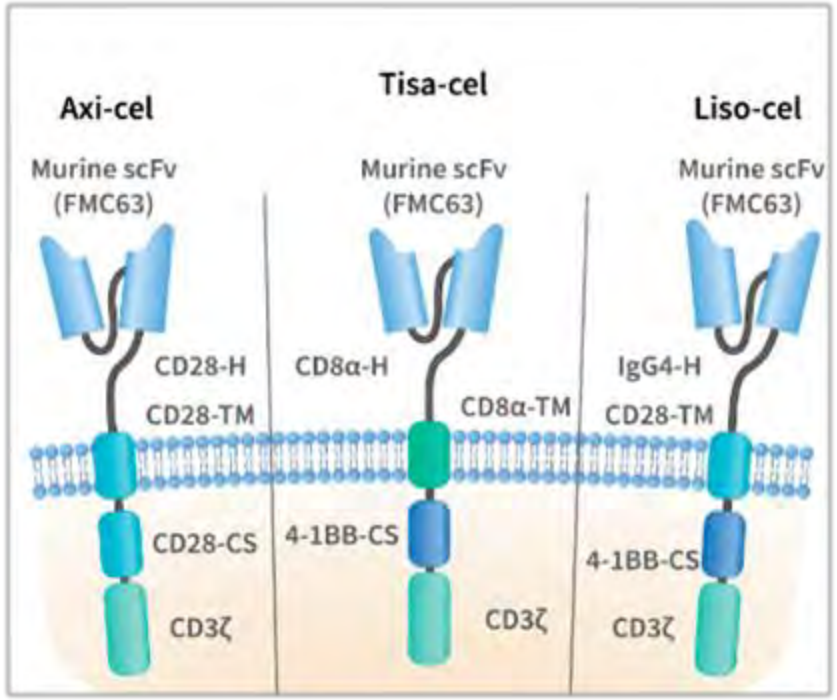


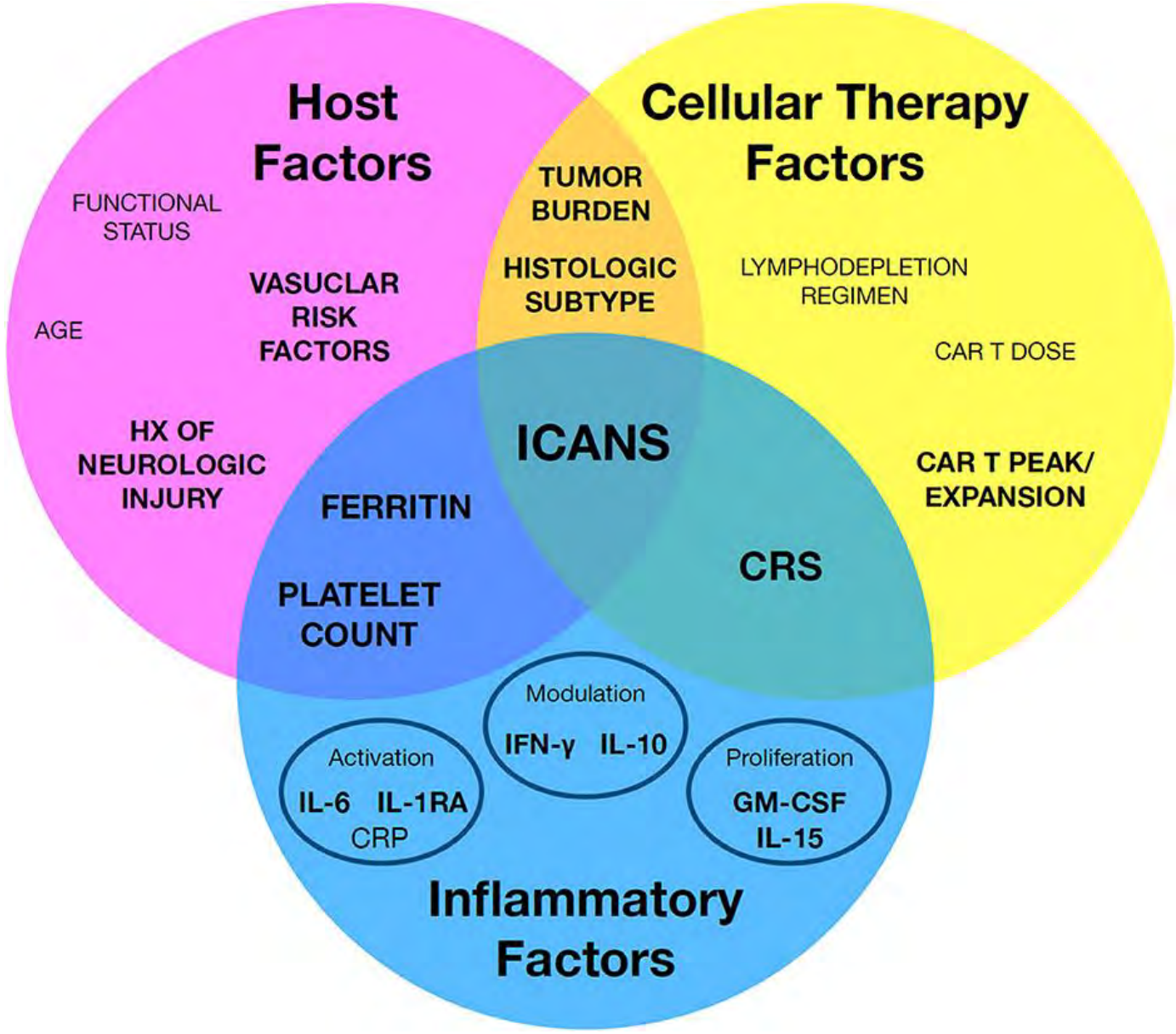




Wada F et al., Scientific Reports 2022

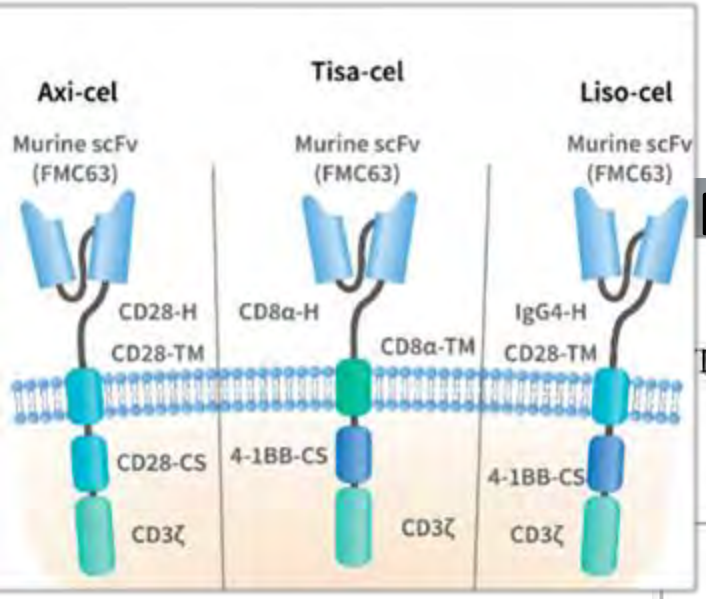
Patient vs Product effects on CAR-T toxicity





Butt OH et al., Front Neurol. 2023

Patient vs Product effects on CAR-T toxicity

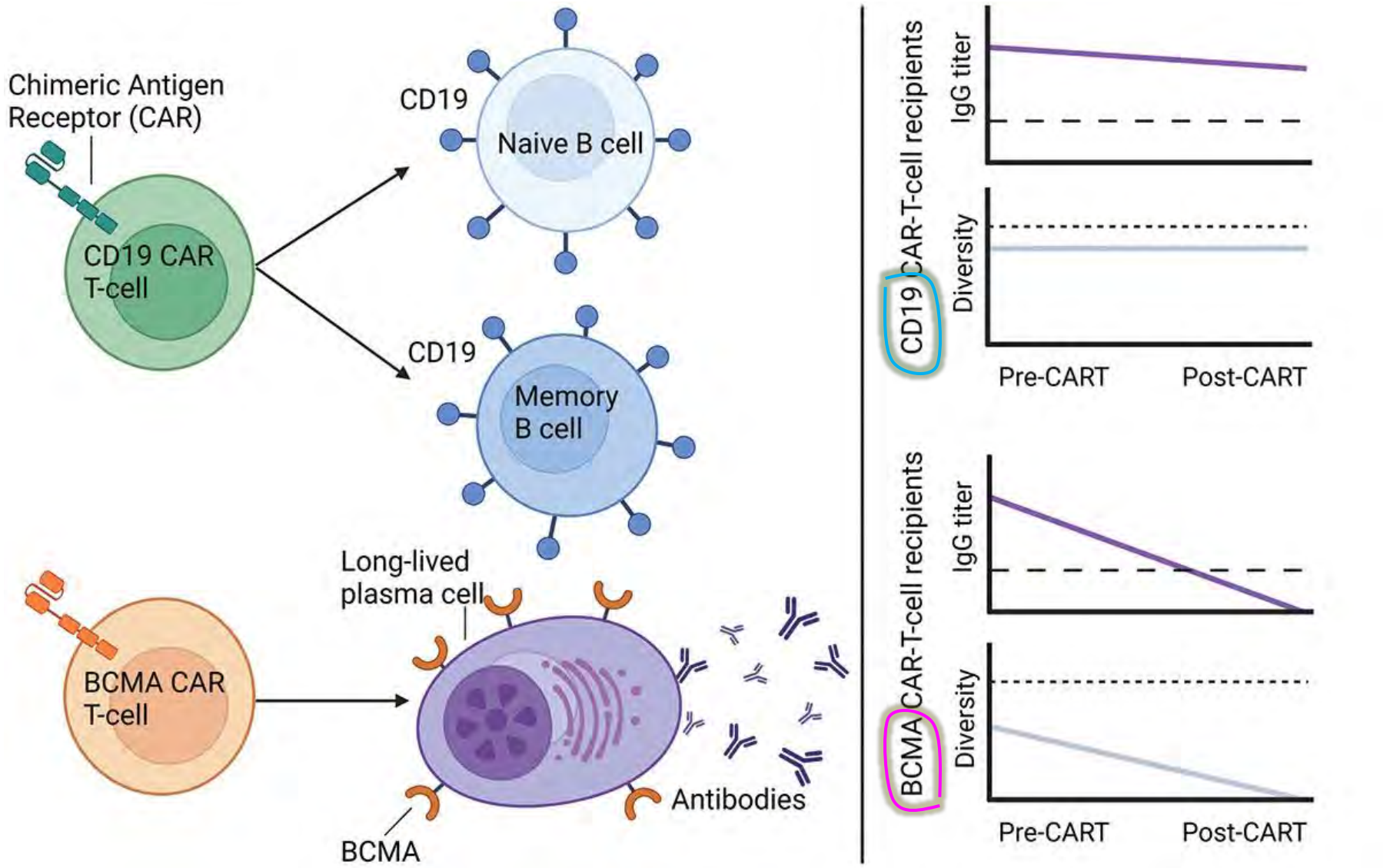


Product	Dx	Trial	CRS	CRS≥3	ICANS	ICANS≥3
Tisagenlecleucel	B-ALL	ELIANA	77	21	40	13
	DLBCL	JULIET	58	22	21	12
	FL	ELARA	48.5	0	4.1	1
Axicabtagene ciloleucel	DLBCL	ZUMA-1	93	13	64	28
	FL	ZUMA-5	82 (78% in FL subgroup)	7 (6% in FL subgroup)	59 (56% in FL subgroup)	19 (15% in FL subgroup)
	LBCL (2nd line)	ZUMA-7	92	6	60	21
Brexucabtagene autoleucel	MCL	ZUMA-2	91	15	63	31
	B-ALL		89	24	60	25
Lisocabtagene maraleucel	DLBCL		42	2	30	10
	DLBCL (2nd line)	T	49	1	12	4

monitor & manage

Butt OH et al., Front Neurol. 2023

Late CAR-T toxicities: hypogammaglobulinemia



Kampouri E et al., *Expert Rev Hematol*. 2022

Late CAR-T toxicities: cytopenias

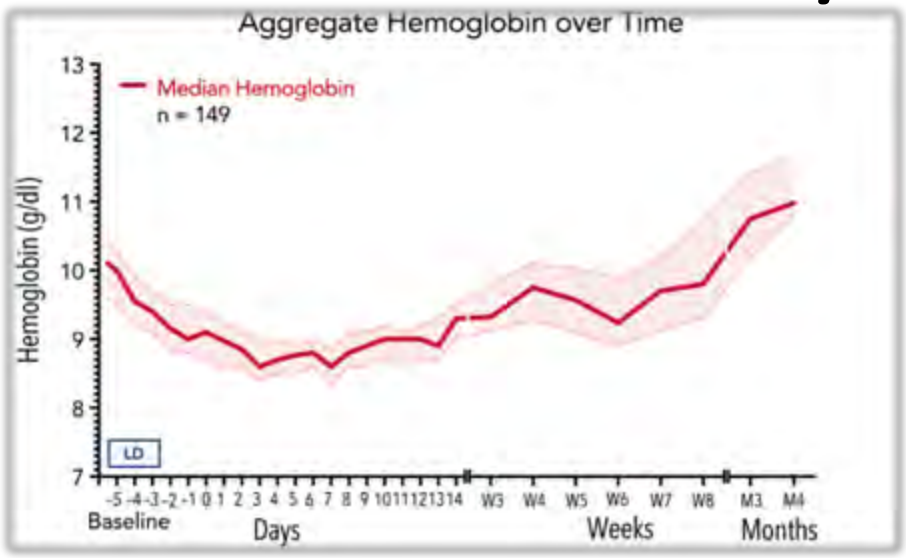
blood

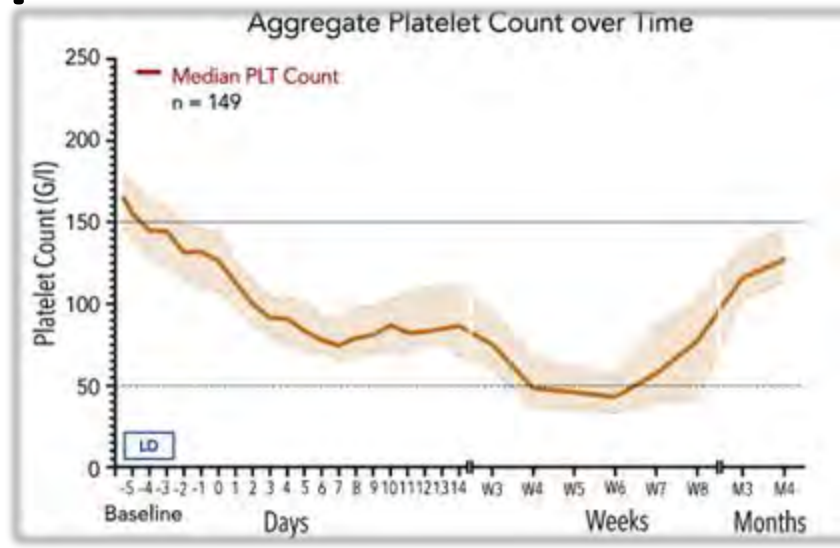
CAR-HEMATOTOX: a model for CAR T-cell–related hematologic toxicity in relapsed/refractory large B-cell lymphoma

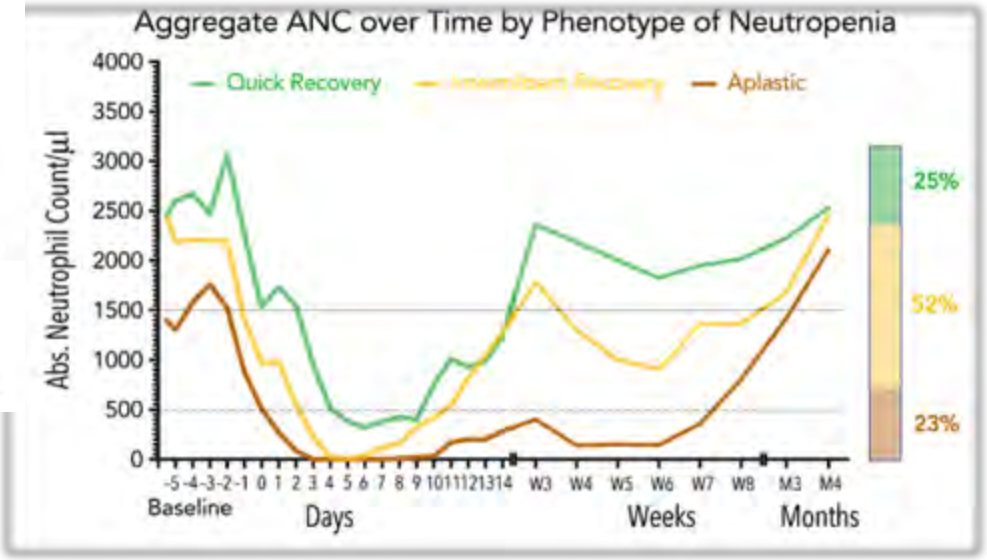
www.german-lymphoma-alliance.de/Scores.html

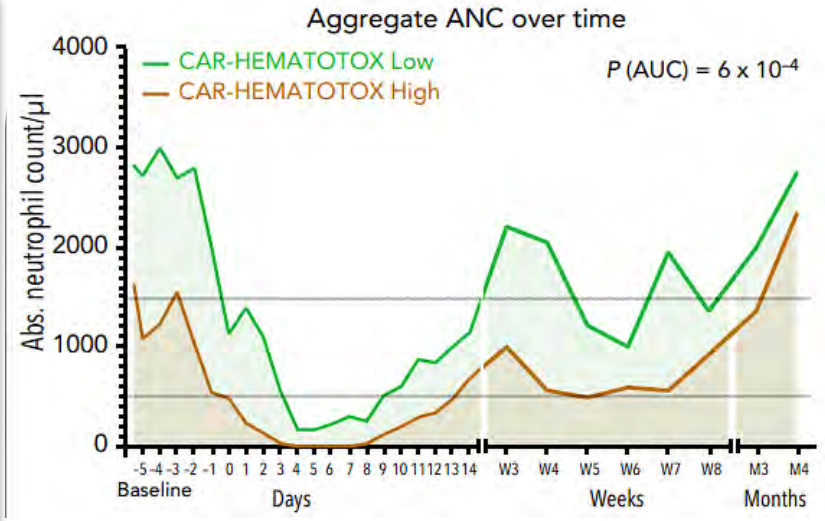
Platelet Count	< 75,000 /µl
Absolute Neutrophil Count (ANC)	< 1,200 /µl
Hemoglobin	< 9.0 g/dl
C-reactive protein (CRP)	< 3.0 mg/dl
Ferritin	> 2,000 ng/ml
CAR-HEMATOTOX score	6

Patient belongs to CAR-HEMATOTOX *high* risk group.









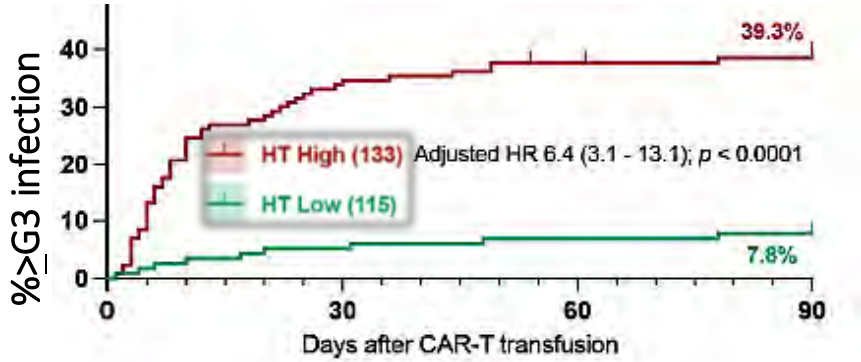
Rejeski K et al., Blood. 2021

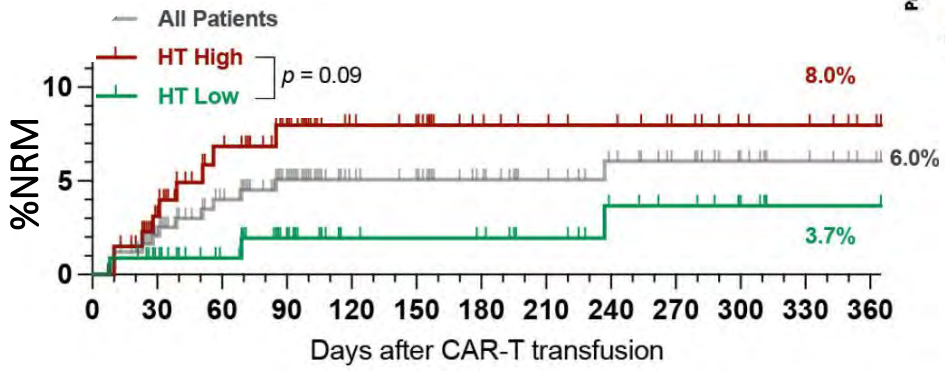
Late CAR-T toxicities: infections

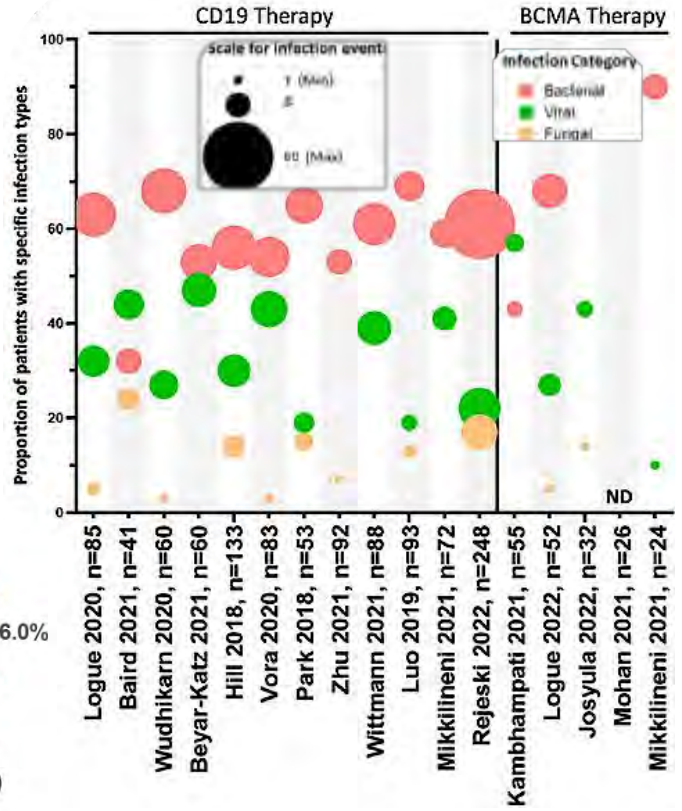
The CAR-HEMATOTOX risk-stratifies patients for severe infections and disease progression after CD19 CAR-T in R/R LBCL

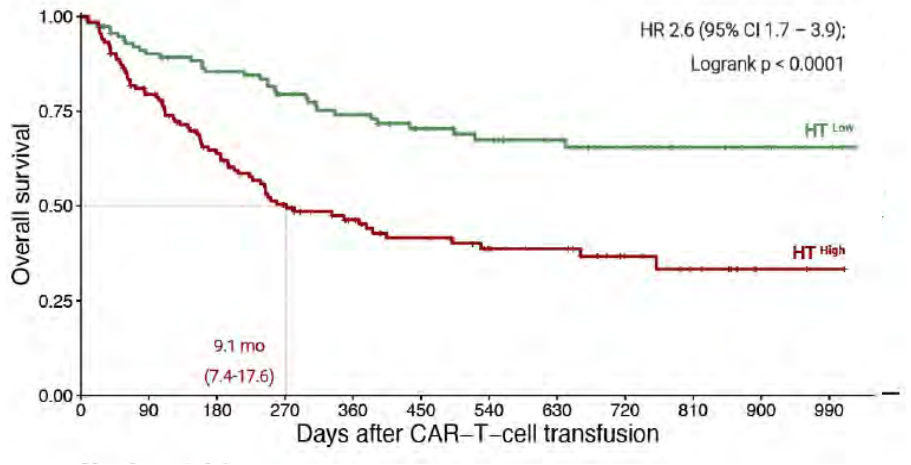
Journal for ImmunoTherapy of Cancer

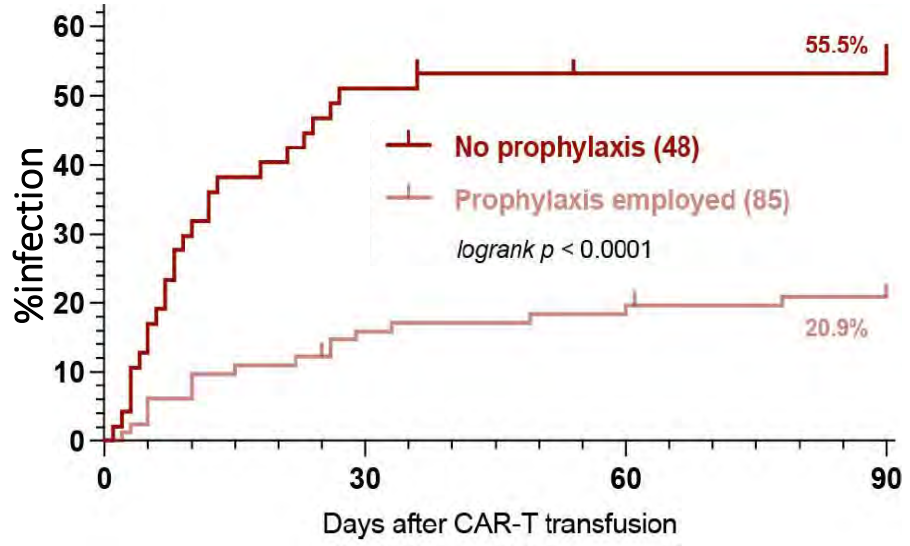
Kai Rejeski [1,2,3] Ariel Perez,[4,5] Gloria Iacoboni,[6] Olaf Penack,[7,8] Veit Bücklein,[1,2]











Rejeski K et al., *J Immunother Cancer*. 2022

Kampouri E et al., *Transpl Infect Dis*. 2023

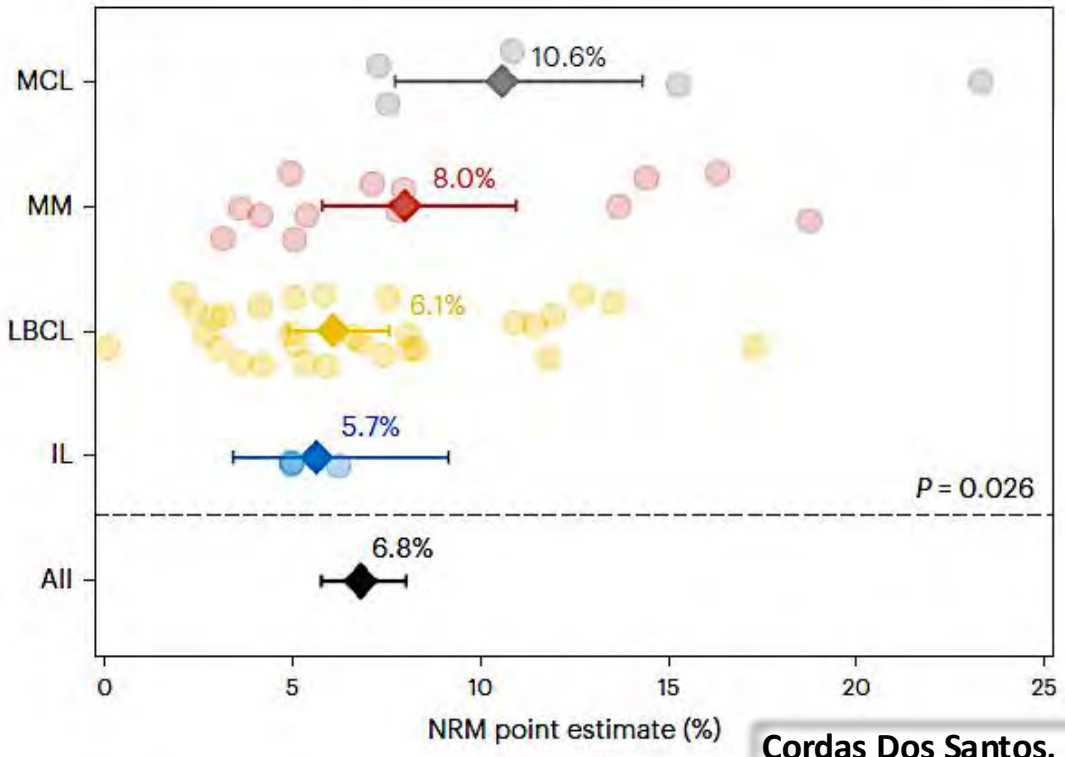
Late CAR-T toxicities: infections

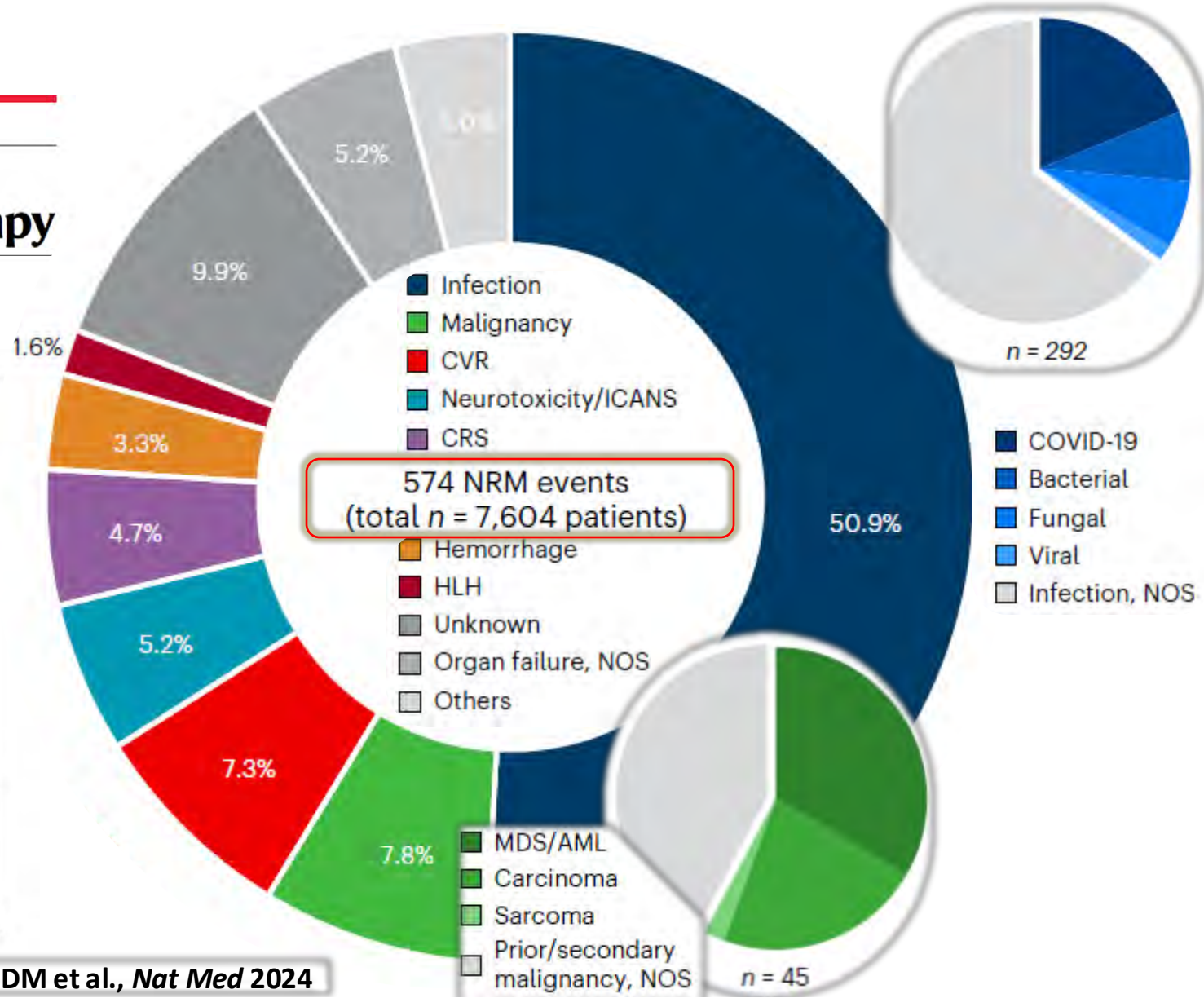
nature medicine

A systematic review and meta-analysis of nonrelapse mortality after CAR T cell therapy

Received: 28 January 2024

David M. Cordas dos Santos[1,2,3,4,11], Tobias Tix[4,11], Roni Shouval[5,6],





Cordas Dos Santos, DM et al., *Nat Med* 2024

T-cell malignancies after CAR-T

~20 TCLs / ~8,000 AERS CAR-T patients = 0.25%

The NEW ENGLAND JOURNAL of MEDICINE

Secondary Cancers after Chimeric Antigen Receptor T-Cell Therapy

Authors: Nicole Verdun, M.D., and Peter Marks, M.D., Ph.D. Author Info & Affiliations

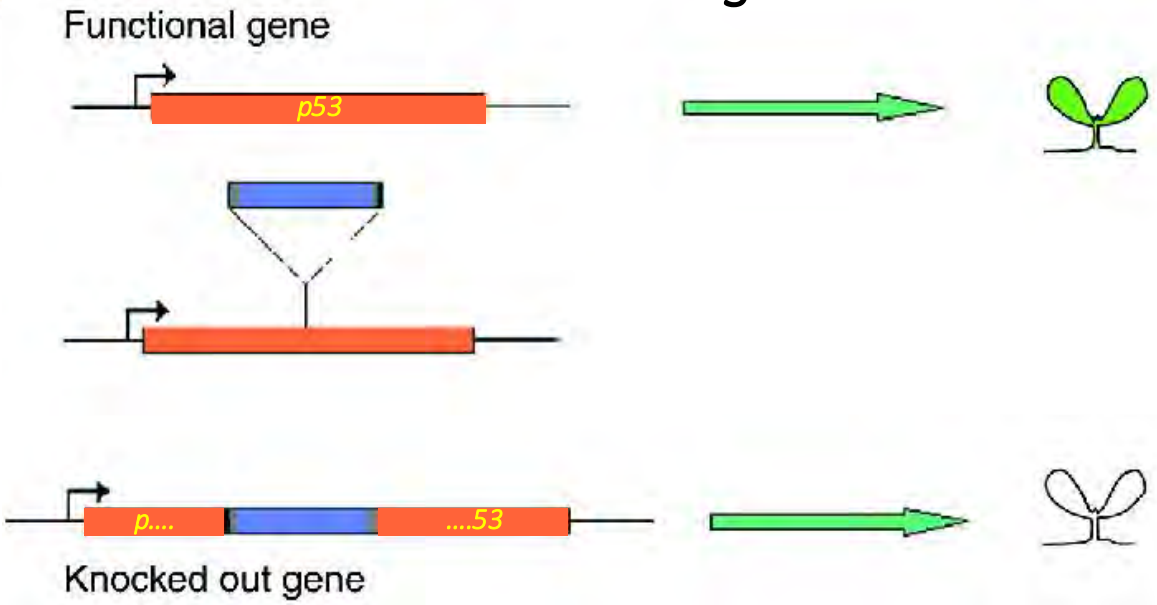
Published January 24, 2024 | N Engl J Med 2024;390:584-586 | DOI: 10.1056/NEJMp2400209 | VOL. 390 NO. 7

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA Requires Boxed Warning for T cell Malignancies Following Treatment with BCMA-Directed or CD19-Directed Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies

Possible mechanisms:

insertional mutagenesis



T-cell malignancies after CAR-T

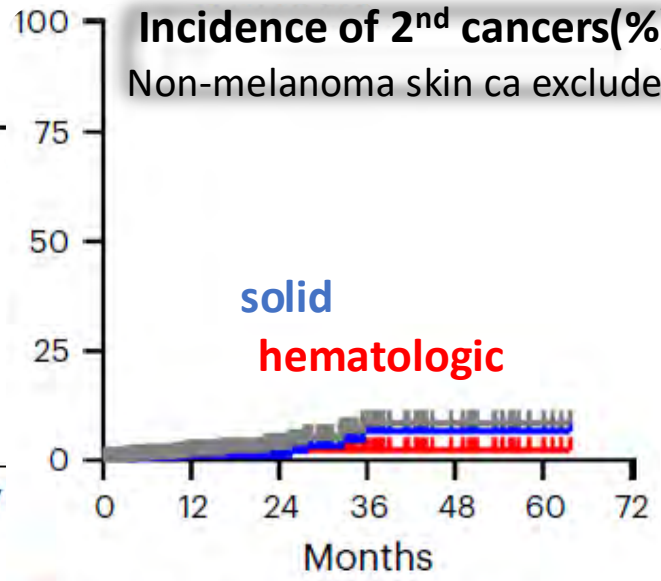
The NEW ENGLAND JOURNAL of MEDICINE

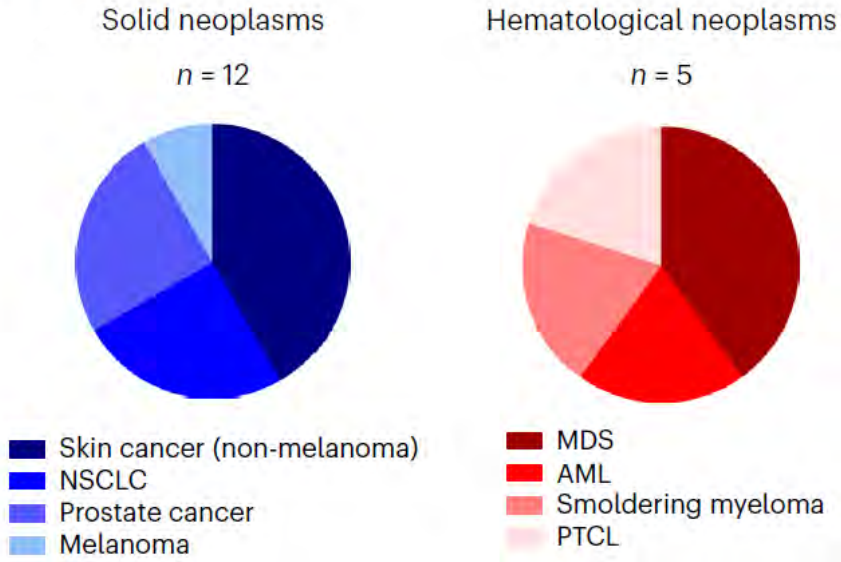
T-Cell Neoplasms after B-Cell Neoplasms — The Pre–CAR T-Cell Era

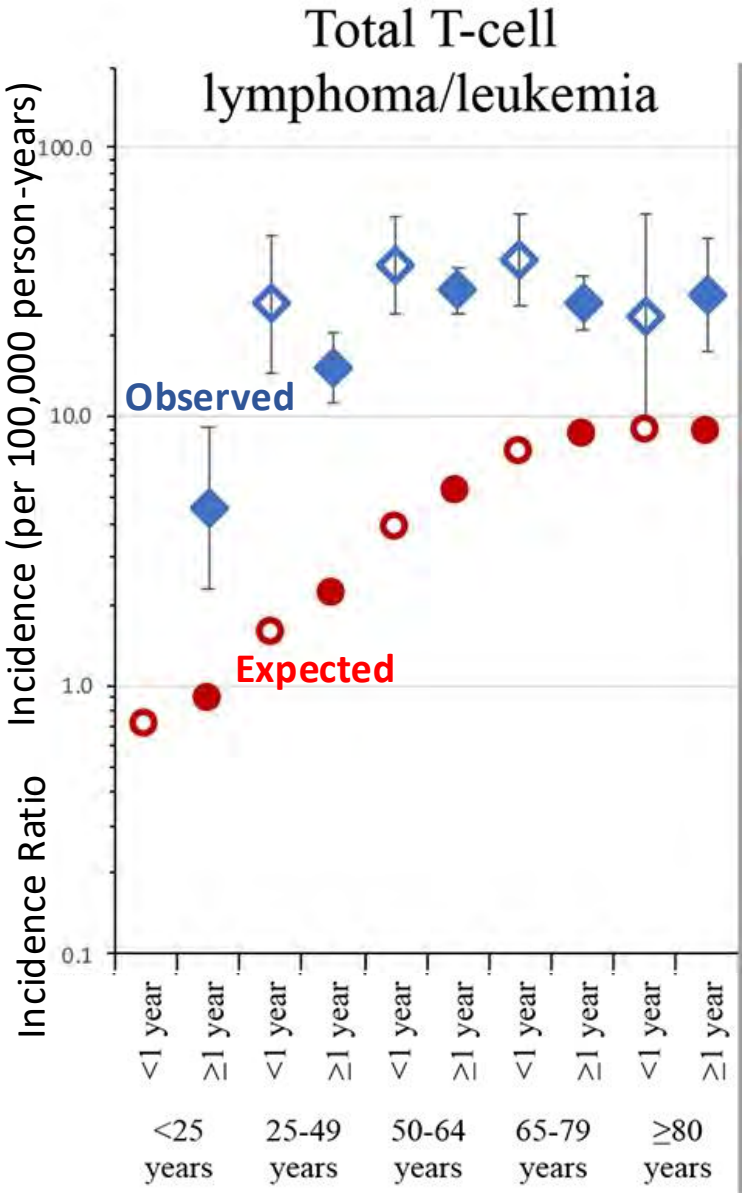
Published August 14, 2024 | N Engl J Med 2024;391:662-664 | DOI: 10.1056/NEJMc2408029
VOL. 391 NO. 7

nature medicine

T cell lymphoma and secondary primary malignancy risk after commercial CAR T cell therapy







Dores, GM and Morton, LM, *NEJM* 2024 Aug

Ghilardi, G et al., *Nat Med* 2024

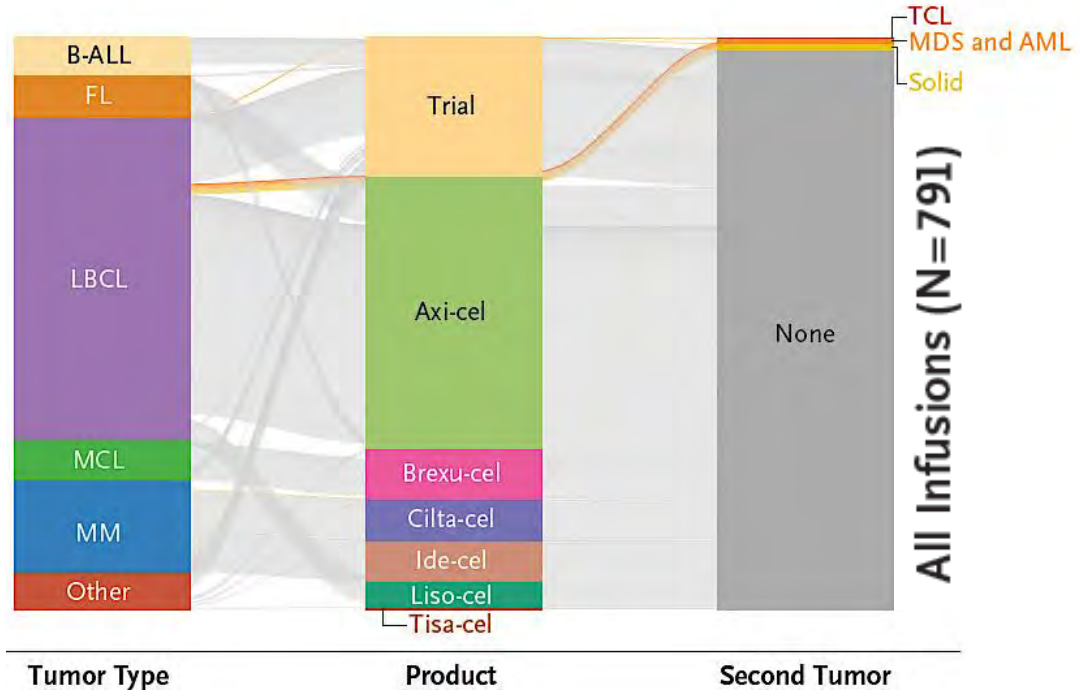
T-cell malignancies after CAR-T

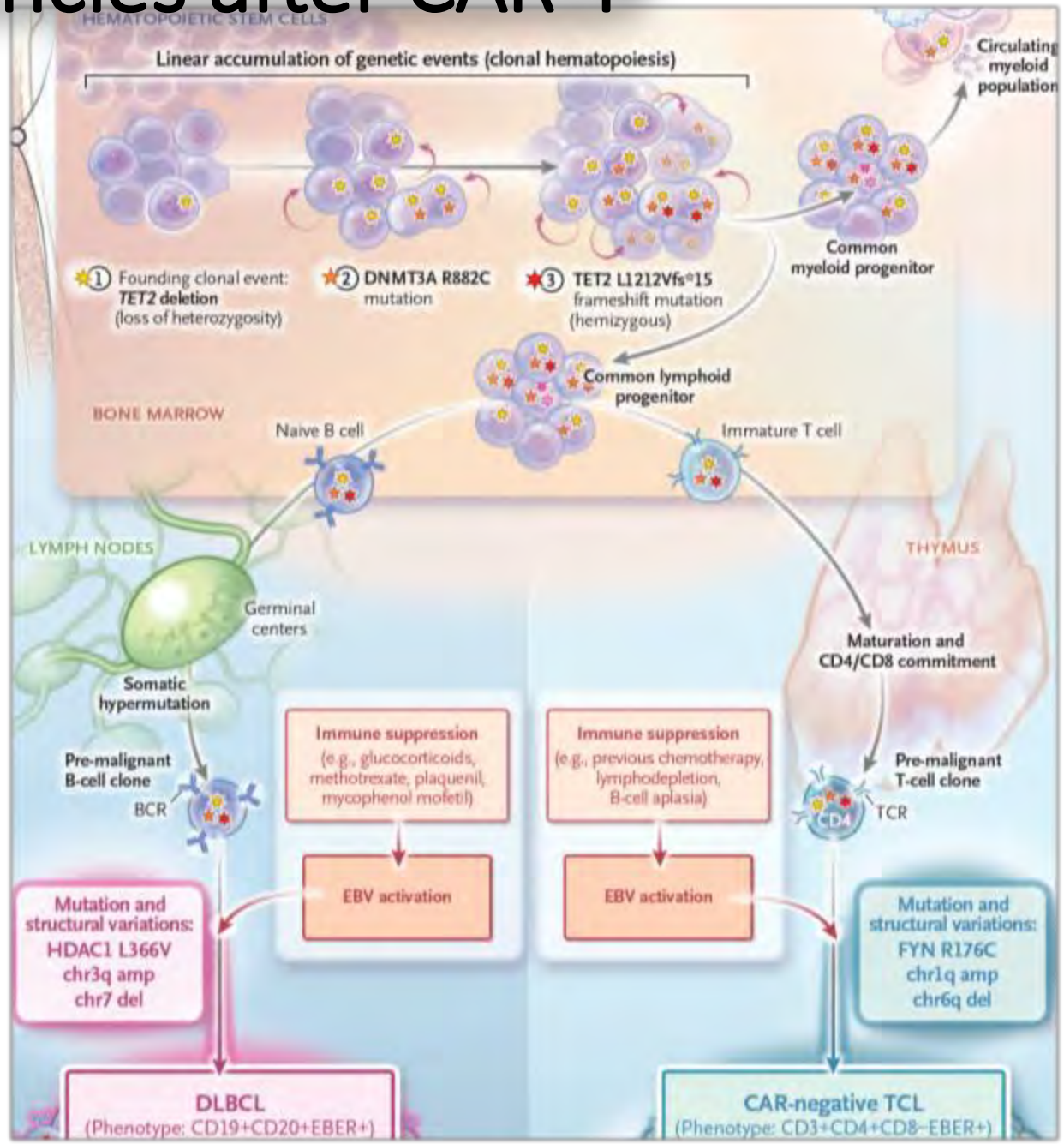
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 13, 2024 VOL. 390 NO. 22

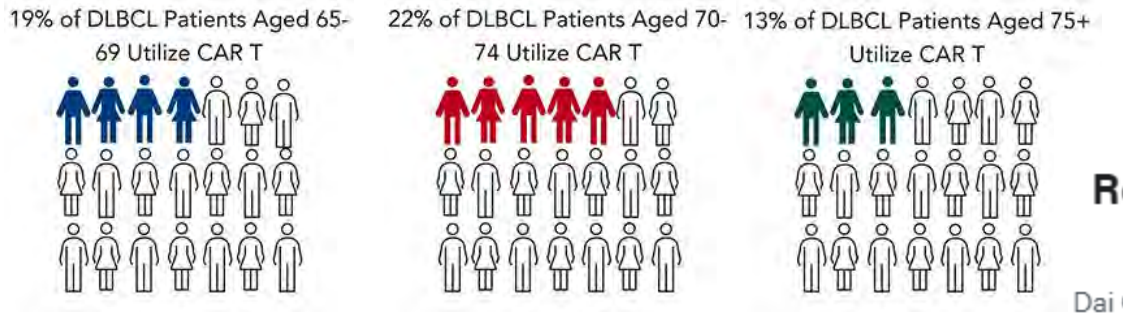
Risk of Second Tumors and T-Cell Lymphoma after CAR T-Cell Therapy

Mark P. Hamilton, M.D., Ph.D., Takeshi Sugio, M.D., Ph.D., Troy Noordenbos, M.D., Ph.D., Shuyu Shi, B.Med.,





Practical considerations: CAR-T in older patients



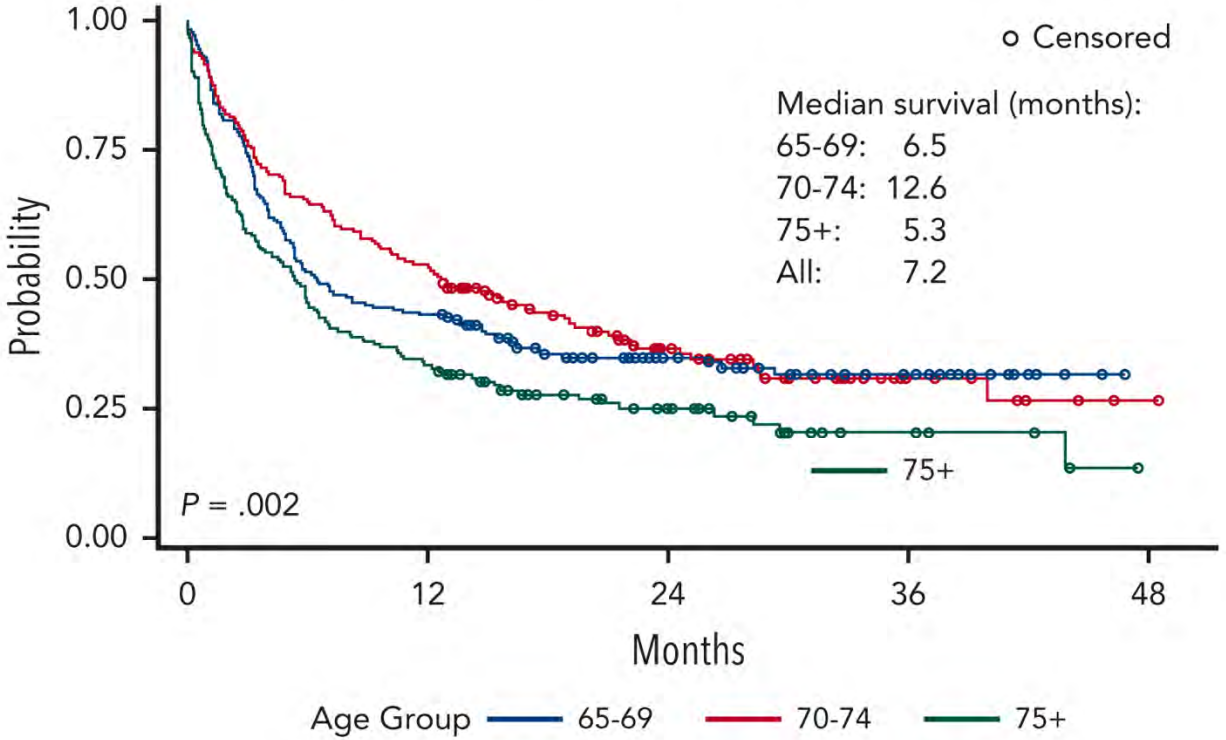
LYMPHOID NEOPLASIA | SEPTEMBER 21, 2023

blood

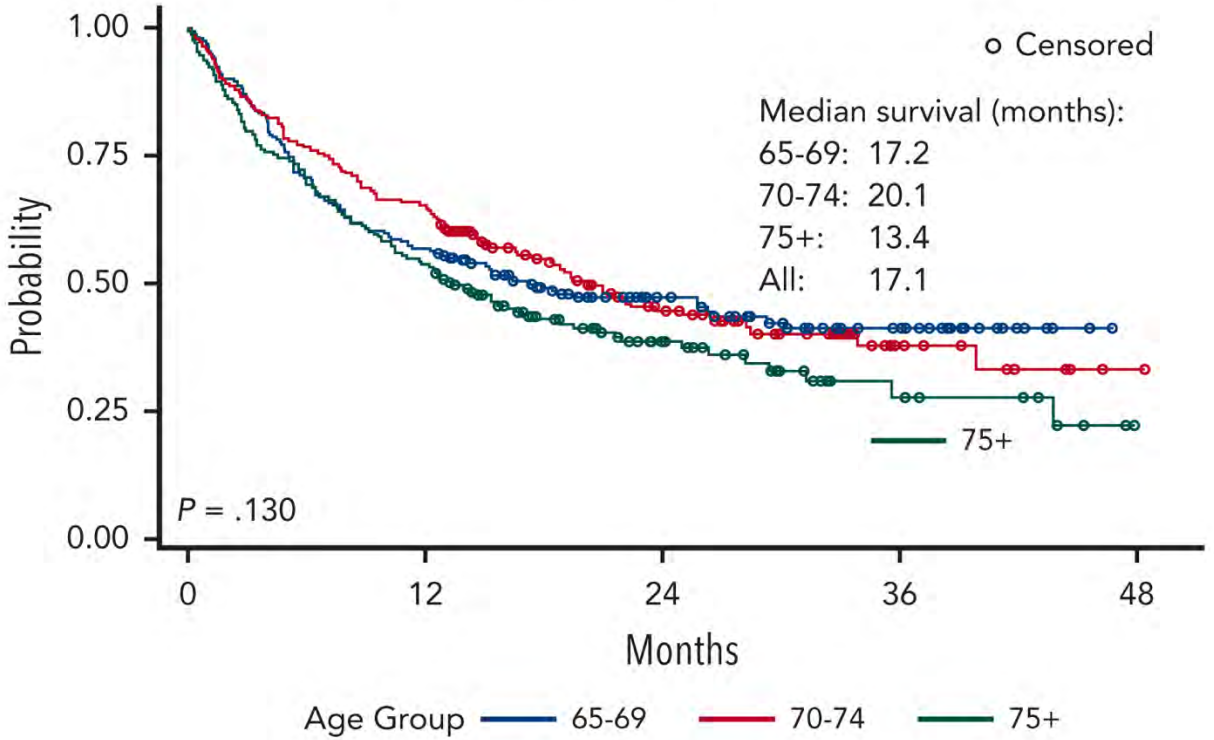
Real-world experience of CAR T-cell therapy in older patients with relapsed/refractory diffuse large B-cell lymphoma

Dai Chihara, Laura Liao, Joseph Tkacz, Anjali Franco, Benjamin Lewing, Karl M. Kilgore, Loretta J. Nastoupil, Lei Chen

Event-free survival by age category



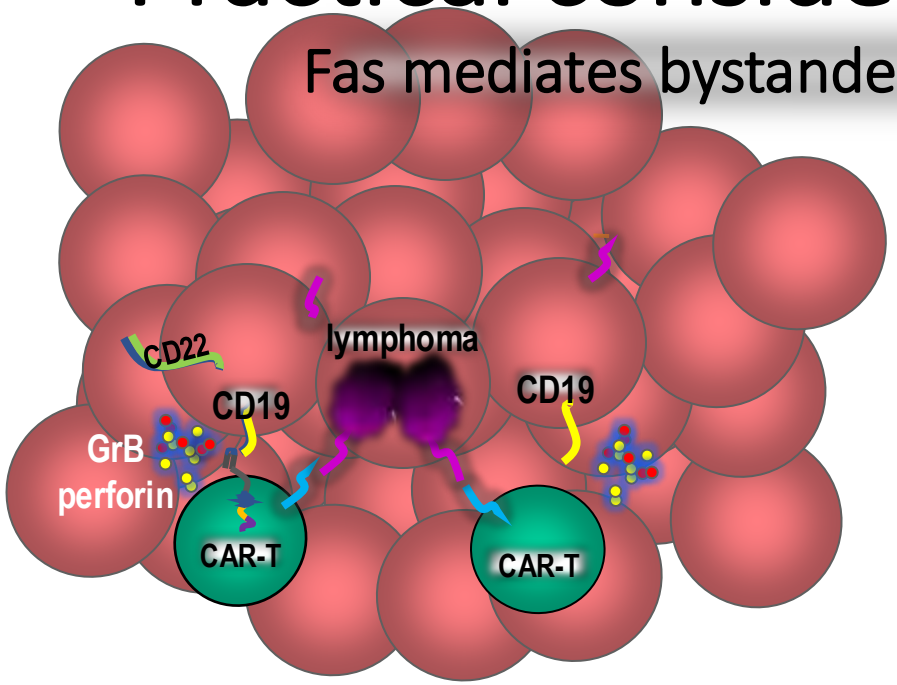
Overall survival by age category

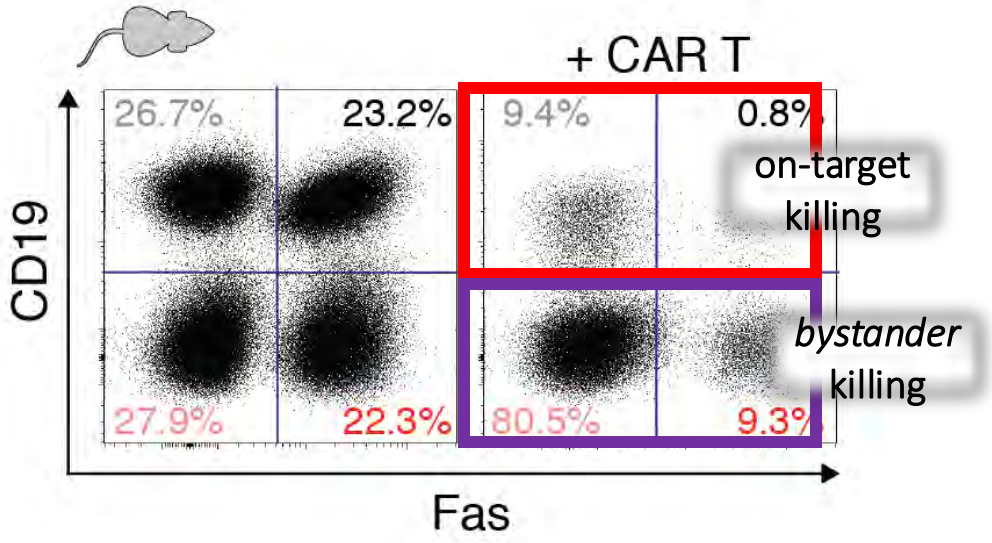


Chihara D et al., *Blood* 2023

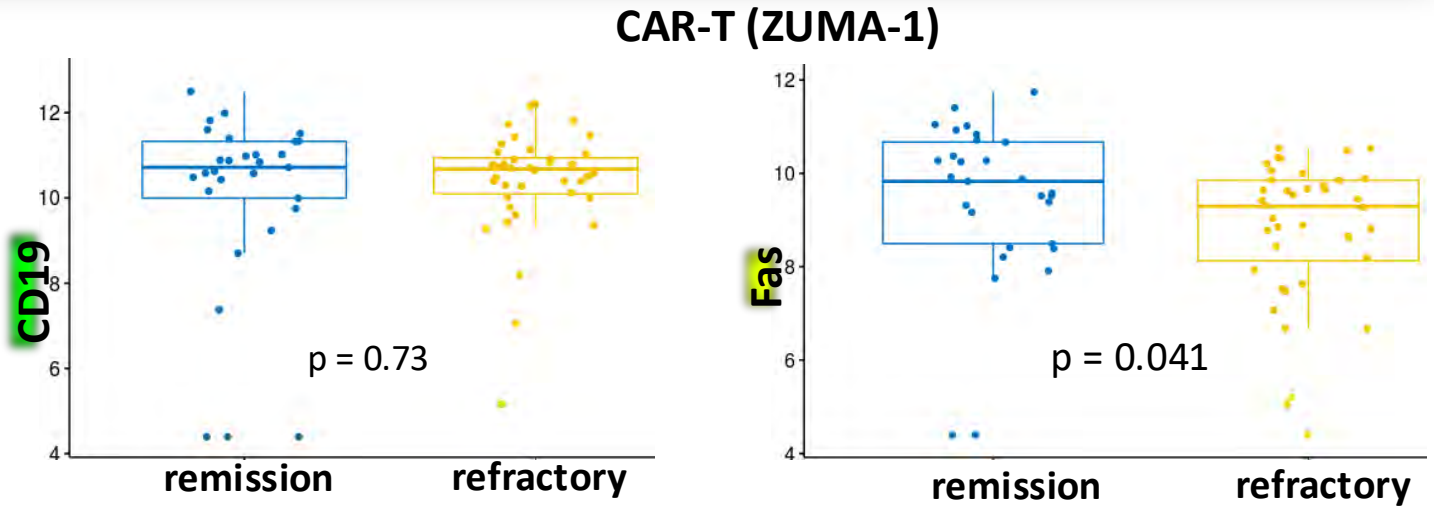
Practical considerations: CAR-T induces Ag escape

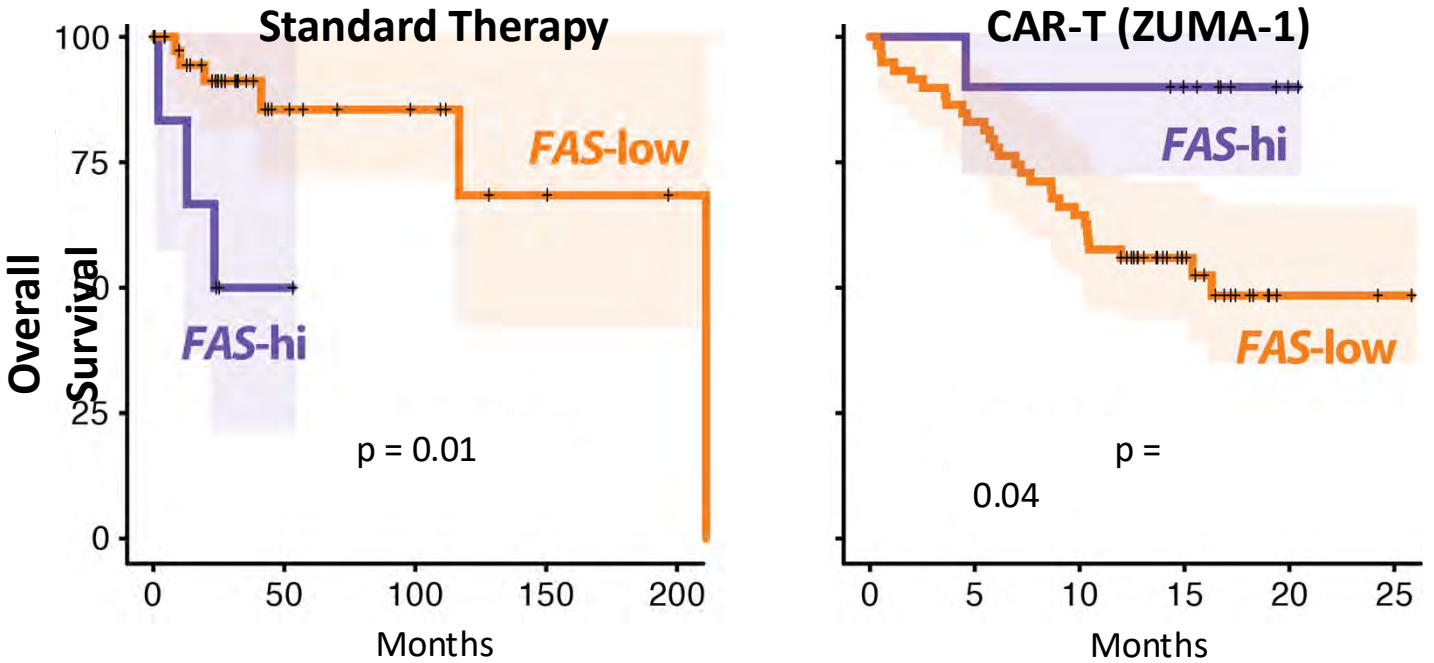
Fas mediates bystander killing, prevents Ag escape and predicts survival.





Upadhyay R, et al., *Cancer Discovery*, 2021.





Faculty Case Presentations

Case Presentation – Dr Westin

64M with LBCL treated with RCHOP x 6 cycles with initial response but refractory disease. PET = abdominal mass 8x10cm, LDH = 5x ULN, multiple FDG avid EN sites, PS is 2.

He received bridging followed by axi-cel and develops grade 1 CRS 24h after infusion, evolving to grade 2 CRS on day 3. He receives tocilizumab and dexamethasone, with improvement in fever and blood pressure, but fever returns 12 hours later, toci given again which resolves the fever.

On day 5, he is less verbal and appears confused, ICE score changes from 10/10 in the morning to 3/10 in the afternoon, and 0/10 in the evening. He is transferred to ICU, EEG shows no seizure, CT head shows no obvious change, high dose steroids (methylprednisolone 500mg q12 for 3d, then taper) started. On day 6, ICE score is 2/10. On day 7, ICE is 7/10 with continued improvement.

Discharged to rehab on day 13.

QUESTIONS FOR THE FACULTY

Do you believe there is a relationship between CAR T-cell therapy-associated toxicity and treatment benefit?

What is the typical course of recovery from Grade 3 ICANS related to CAR T-cell therapy?

How, if at all, do you explain the risk of developing secondary T-cell lymphoma to your patients who are about to receive CAR T-cell therapy?

Case Presentation: Dr Lunning

- A 44-year-old woman who presented to the ER with severe RUQ pain, darkening of urine, and progressive fatigue.
- After admission she had an US noted a 5X5 cm liver lesion with regional adenopathy causing obstructive jaundice
- An US guided biopsy demonstrated HGBCL with MYC and BCL-2 rearrangement.
- PET/CT noted diffuse adenopathy with extranodal avid disease in liver and adrenal glands bilaterally. LDH elevated 3X ULN. ECOG 2. IPI was 4.
- CNS/CSF evaluation were unremarkable.
- Started on DA-EPOCH-R in hospital with resolution of hyperbilirubinemia. IT MTX given.
- PET/CT after 2 cycles noted Deauville 4.
- PET/CT after 6 cycles noted Deauville 5 (new liver lesions) and residual adenopathy above liver background.
- Biopsy confirmed DLBCL, GCB subtype

Case Presentation: Dr Lunning (continued)

- She had pre-apheresis bridging with pola-rituximab X 1 with a second cycle post apheresis with evidence of stable disease.
- She completed flu/cy followed by axi-cel. She experienced G2 CRS and G3 ICANS treated per institutional guidelines with toci X 1 with a total dex equivalent over 30 days of ~300 mg. She was on prophylactic acyclovir, levofloxacin, sulfamethoxazole and trimethoprim, and voriconazole.
- She had post axi-cel cytopenias requiring transfusions and prn GCSF. IgG level 150.
- Her D+30 PET/CT was mCR but evidence of LLL consolidation. Fungal workup negative. Bronchoscopy with pneumonia panel positive for pseudomonas. Treated with antibiotics.
- Started on monthly IVIG without event.
- PET/CT at D+100 and 6 months c/w mCR. Multiple viral infections but not further high-grade bacterial infections.
- Resolution of cytopenias.
- Returned to work 6 months post CAR-T

QUESTIONS FOR THE FACULTY

What is your general approach to antimicrobial prophylaxis for patients who are receiving CAR T-cell therapy?

How do you counsel patients regarding vaccinations after CAR T-cell therapy?

How useful do you find monitoring immunoglobulin levels and administering IVIG as needed for patients who are receiving CAR T-cell therapy?

Data + Perspectives: Clinical Investigators Discuss the Current and Future Management of Diffuse Large B-Cell Lymphoma

Part 2 of a 2-Part CME Satellite Symposium Series During the Society of Hematologic Oncology 2024 Annual Meeting

Wednesday, September 4, 2024
7:30 PM – 8:30 PM CT

Faculty

Grzegorz S Nowakowski, MD
Laurie H Sehn, MD, MPH

Moderator

Christopher R Flowers, MD, MS

RTP RESEARCH TO PRACTICE

Thank you for joining us!
Your feedback is very important to us.

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The CME credit link is posted in the chat room.