CAR T-cell therapy in patients with aggressive B-cell lymphoma

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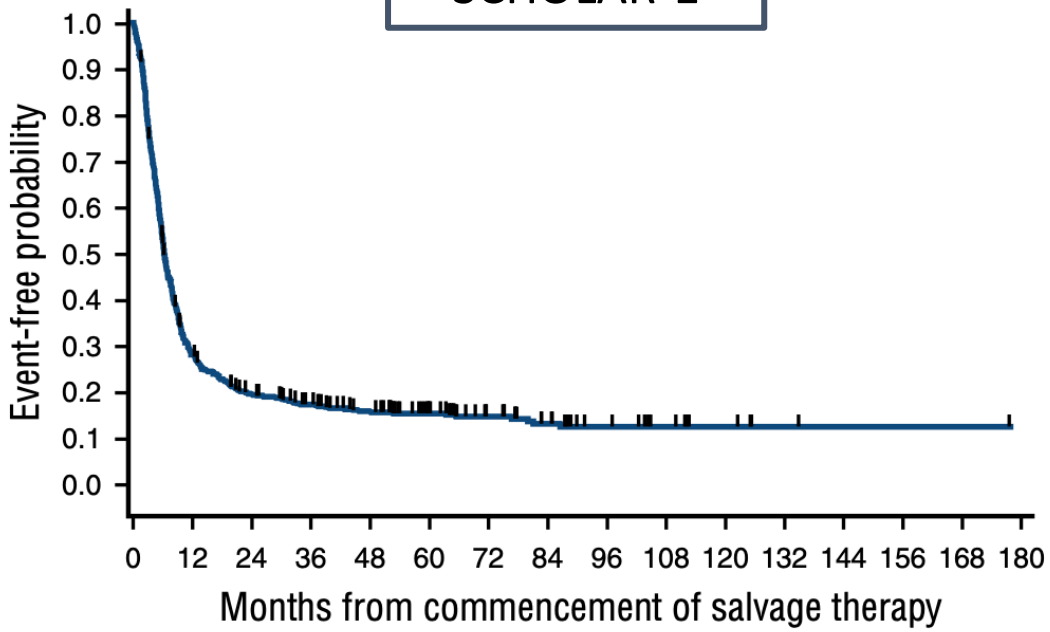
Disclosures

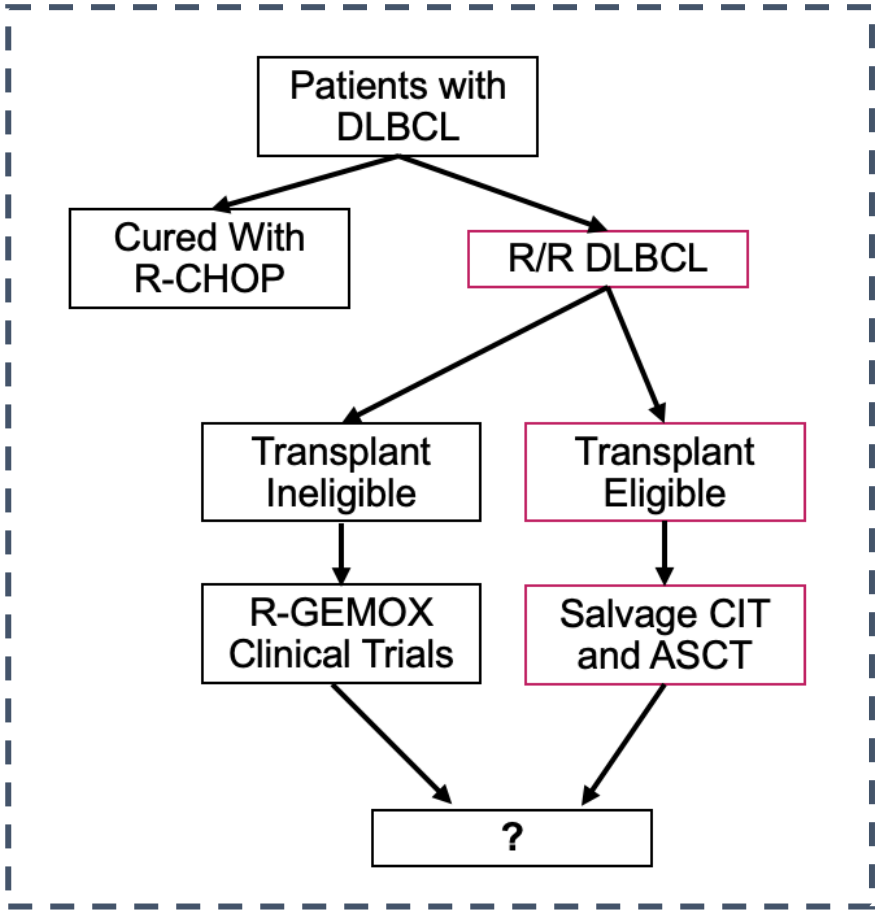
- **Consultancy:** Allogene, Amgen, Autolus, BMS, Gilead, Nektar, Miltenyi Novartis, Pierre Fabre, Pfizer.
- **Speaker**: Amgen, BMS, Gilead, Novartis, Pfizer.
- **Travel and accommodation**: Kite-Gilead, Novartis, Pierre Fabre, Pfizer.

Chimeric antigen receptor T-cell therapy – *Rationale*

SCHOLAR-1

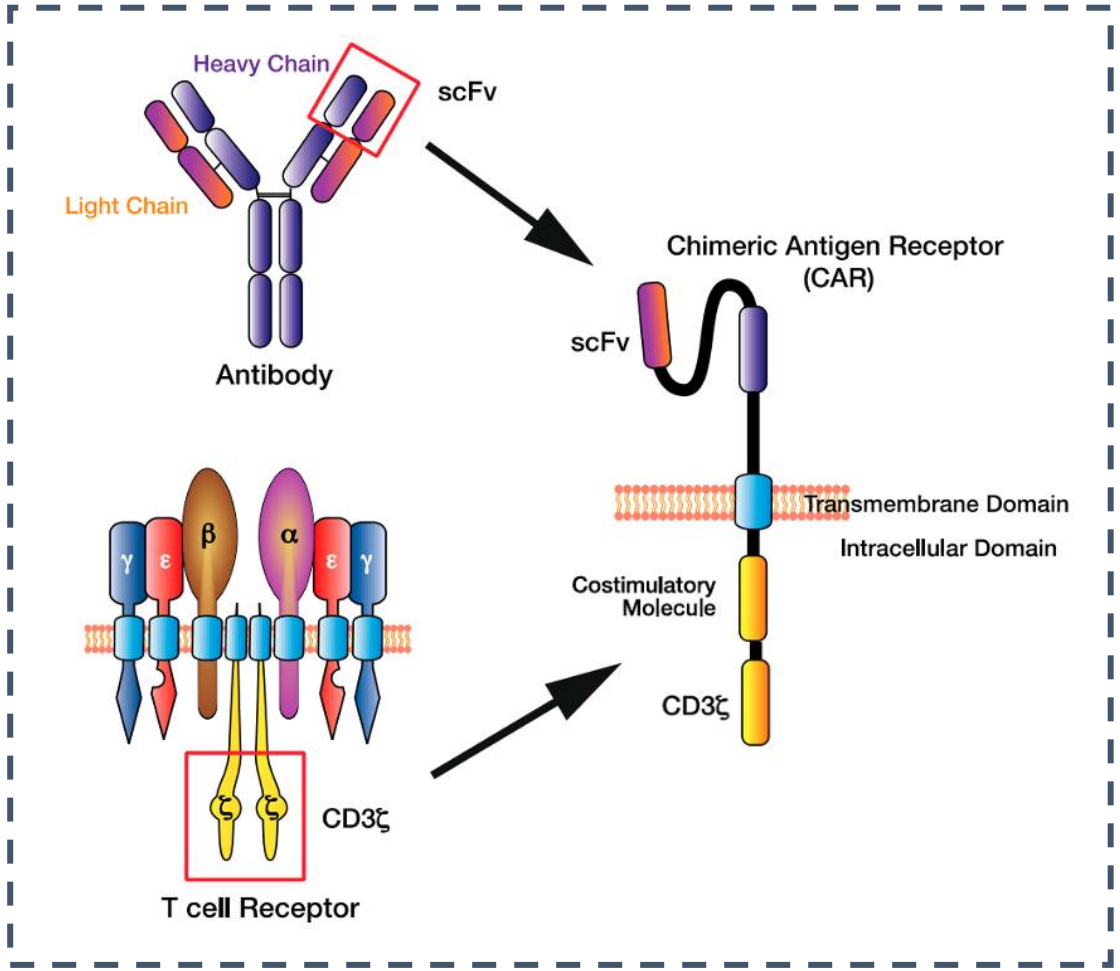


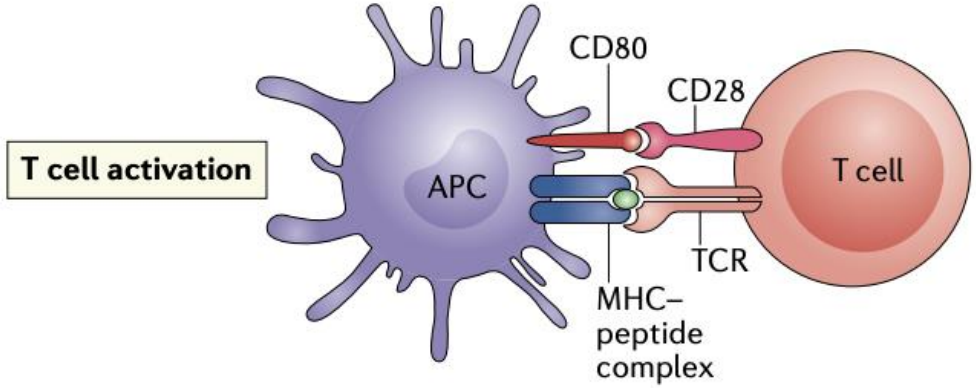
Pooled response rate of 26% (CR 7%)
Median OS of 6.3 months



Crump M et al, Blood. 2017

Chimeric Antigen Receptor (CAR) T-cell therapy – *Concept*

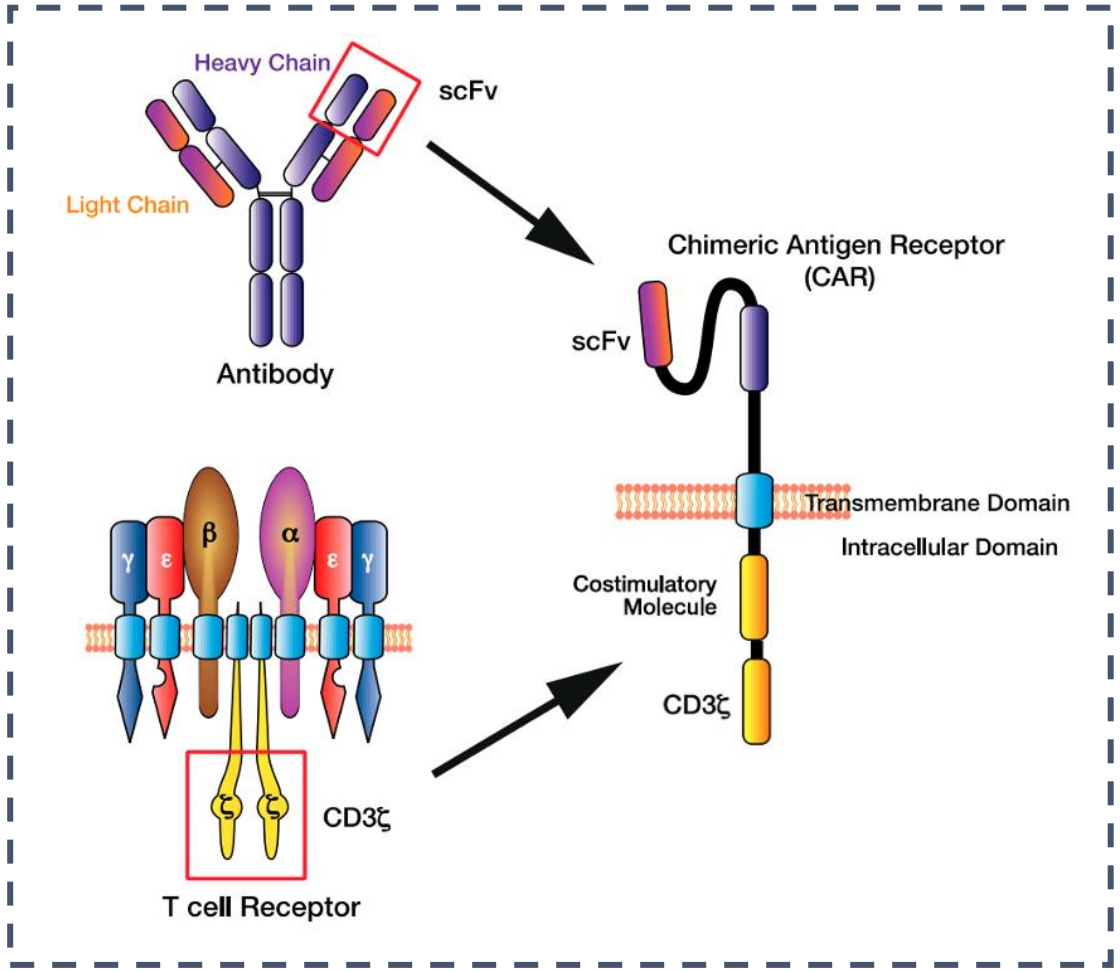


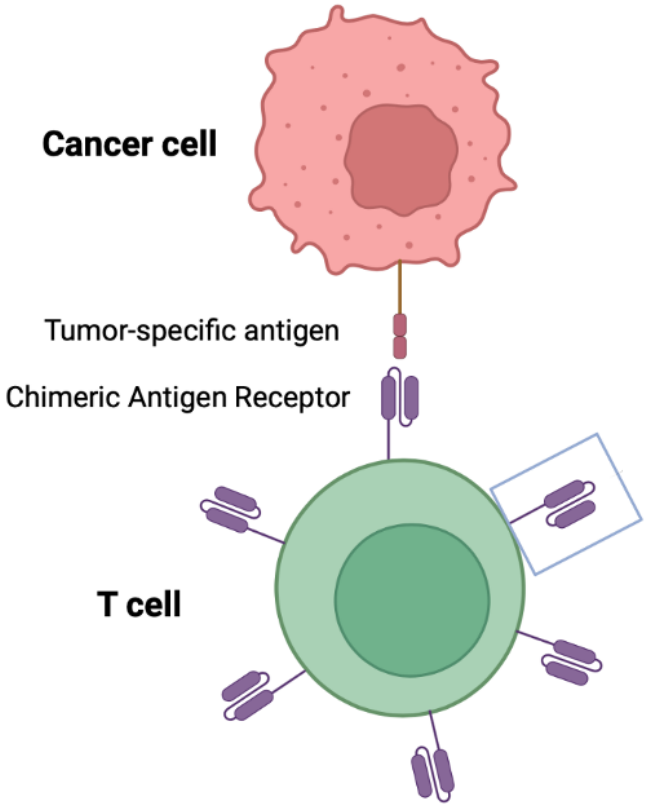


APC, antigen-presenting cell
MHC, major histocompatibility complex
TCR, T cell receptor

Hannah E. Hughes-Parry, Int. J. Mol. Sci. 2020
Cappell KM, Nat Rev Clin Oncol 2021

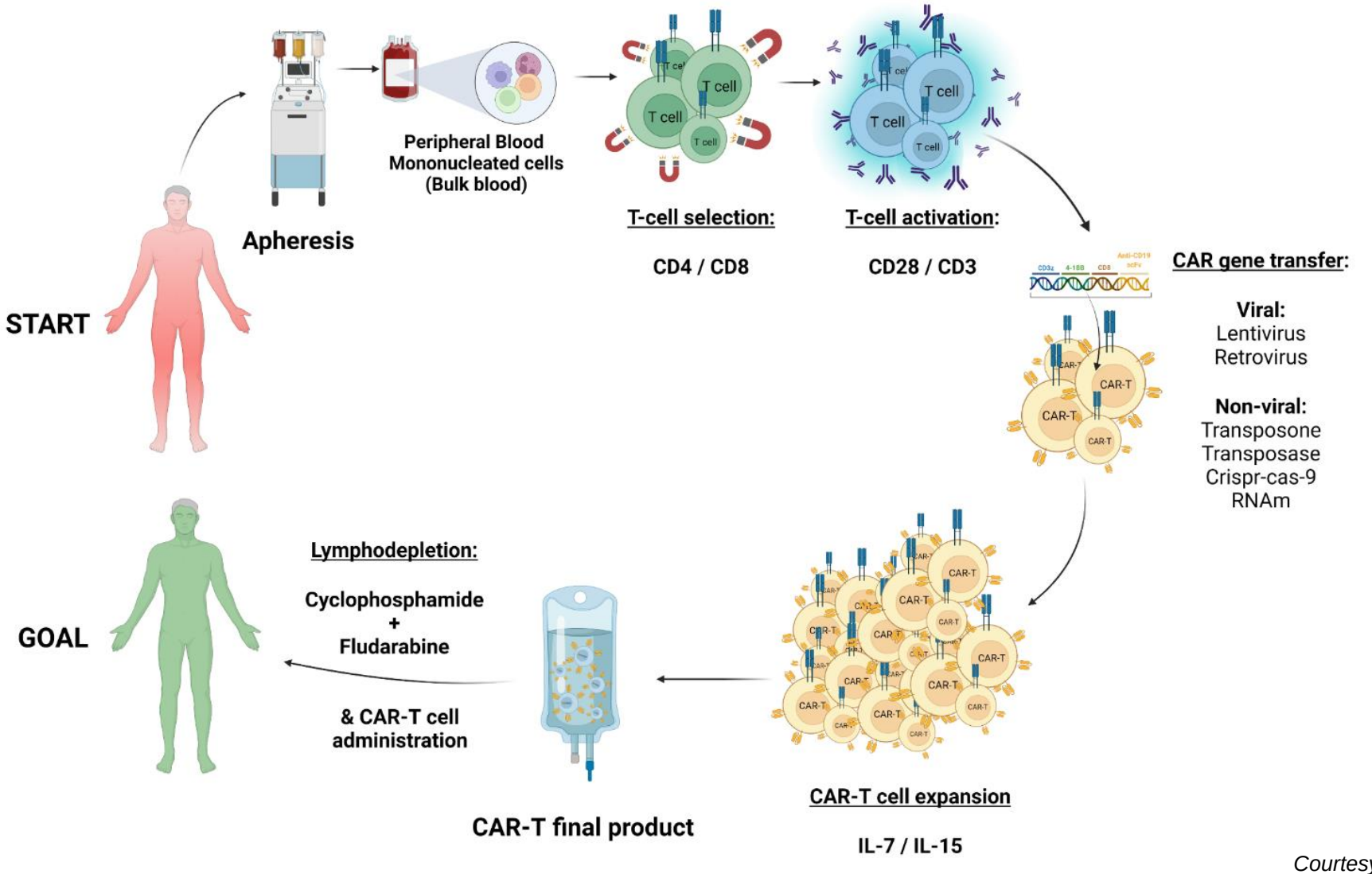
Chimeric Antigen Receptor (CAR) T-cell therapy – *Concept*





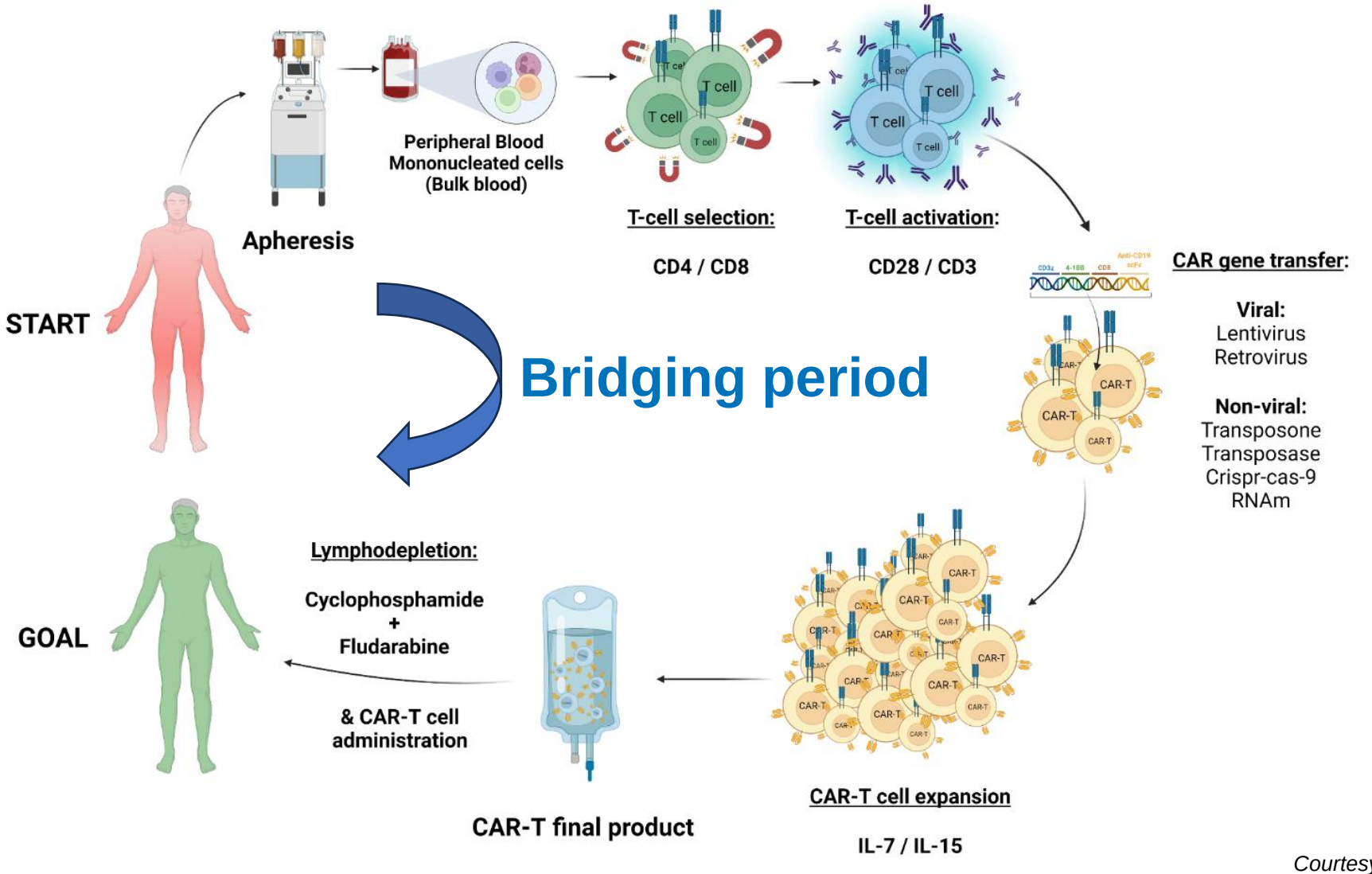
Hannah E. Hughes-Parry, Int. J. Mol. Sci. 2020
Cappell KM, Nat Rev Clin Oncol 2021

Patient journey – *CAR T-cell therapy*



Courtesy of Valentín Ortiz

Patient journey – *CAR T-cell therapy*



Courtesy of Valentín Ortiz

CAR T-cell therapy – *Short term toxicity*

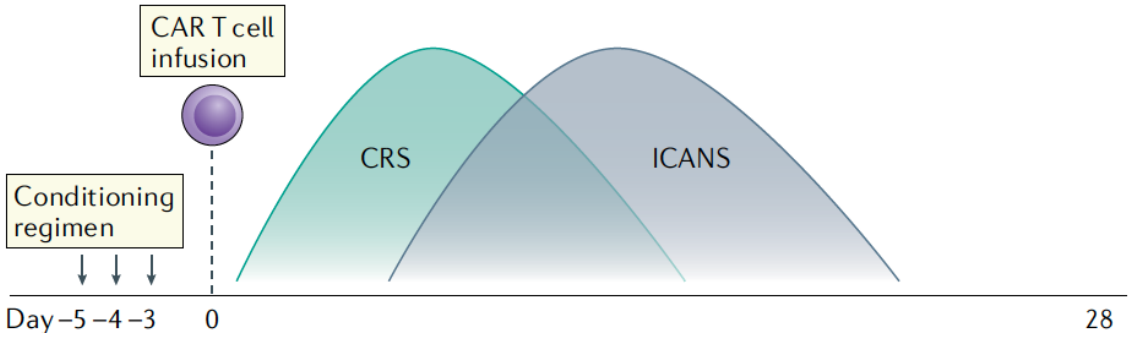
CRS

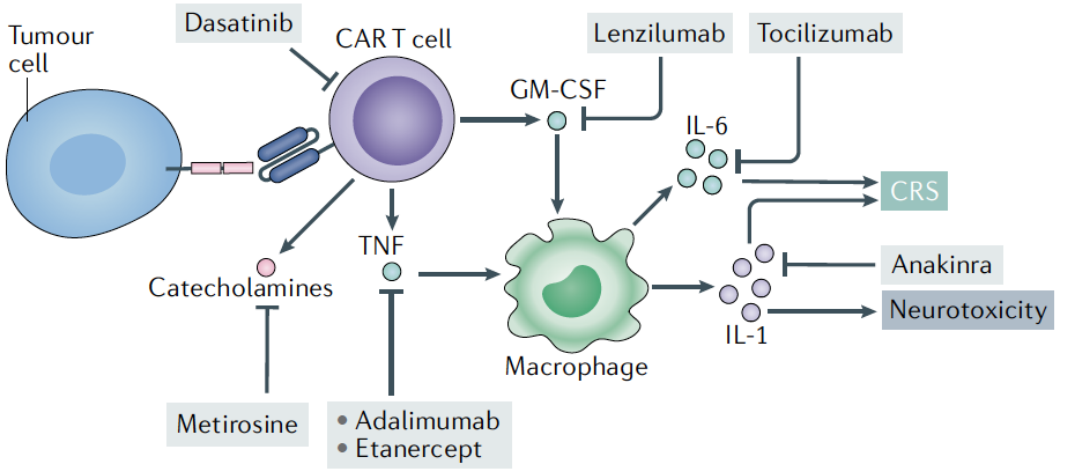
- **Cause**: CAR-T expansion, ↑ cytokines
- **Onset**: 1-3 days
- **Features**: Fever/Hypotension/Hypoxia

ICANS

- **Cause**: Impaired BBB integrity
  - High CSF:blood cytokine levels
  - CAR-positive T-cells in CSF
- **Onset**: 5-7 days; later than CRS
- **Features**: Aphasia/Confusion/Seizures

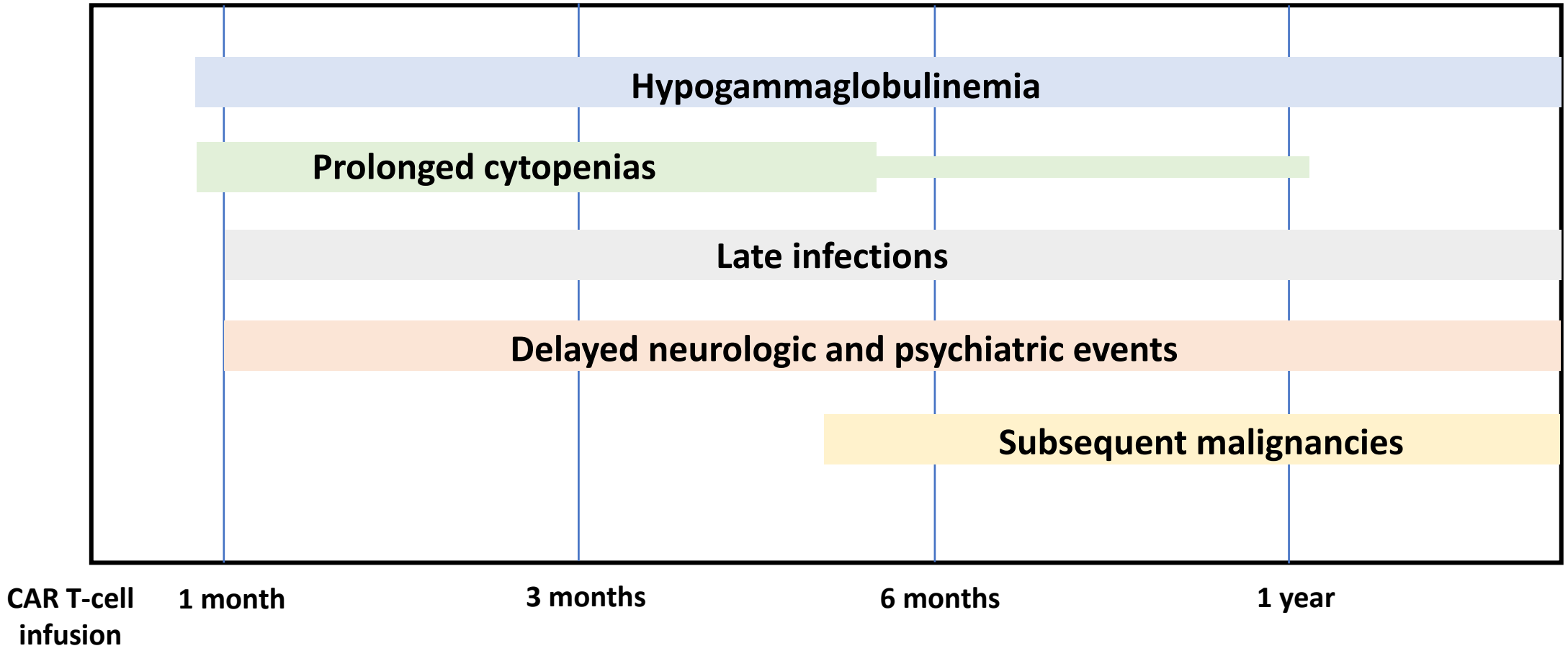
- **Common risk variables**
  - Disease burden
  - Peak CAR T-cell and cytokine levels
  - Early and severe CRS (for ICANS)





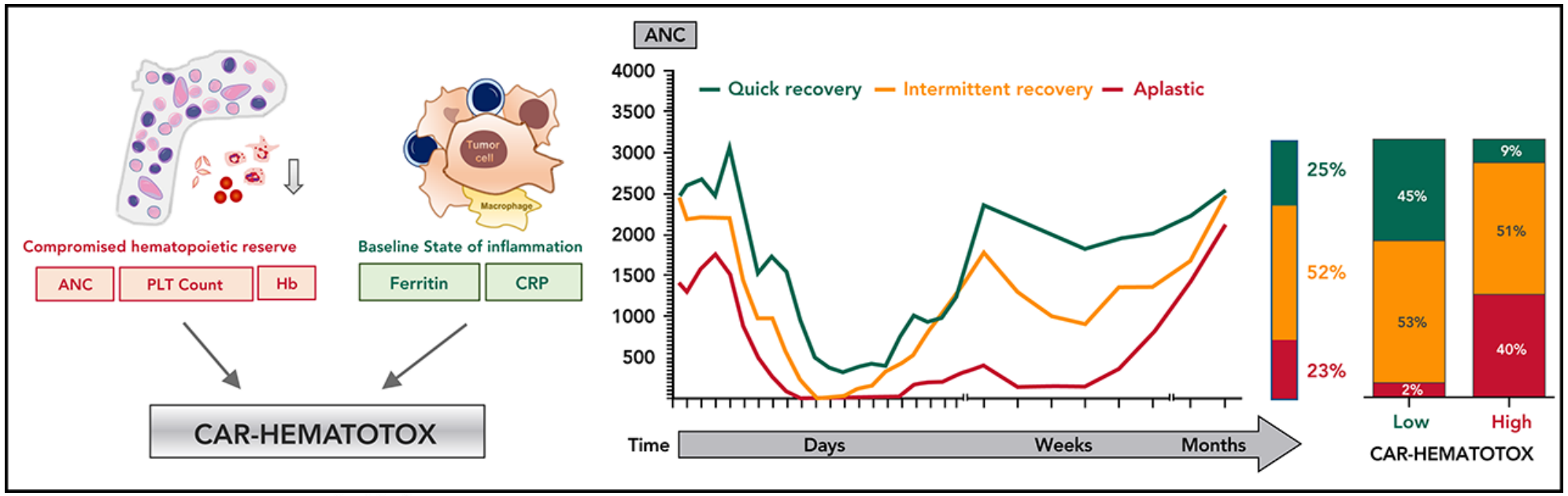
Morris EC, Nature Reviews – Immunology, 2022

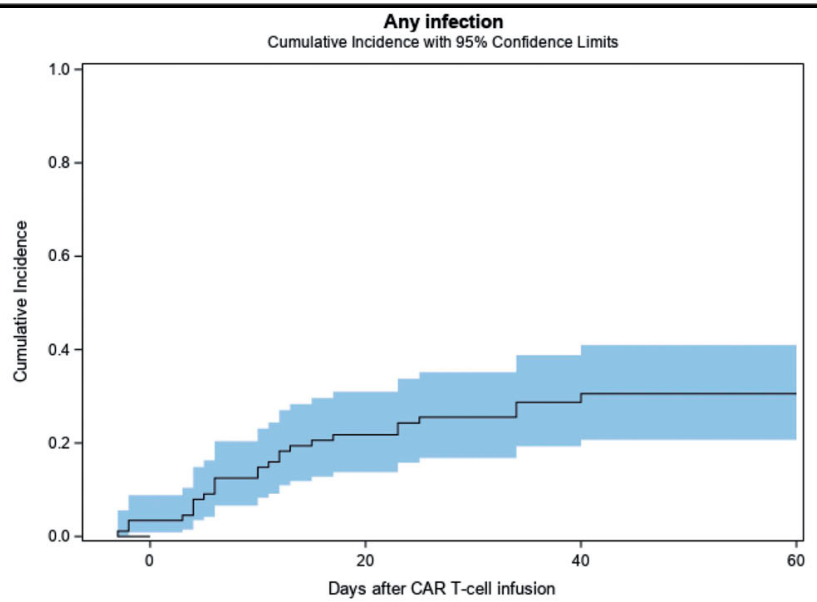
CAR T-cell therapy – *Long term toxicity*

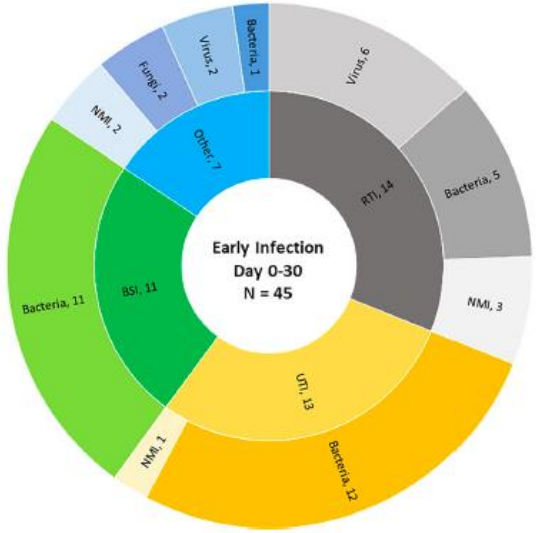


Chakraborty R, Transplant Cell Ther. 2021 (adapted)

Cytopenias and infections after CAR T-cell therapy







Rejeski K. Blood.2021
Pernas B. Eur J Haem. 2024
Dayagi et al. Leukemia lymphoma.2021;

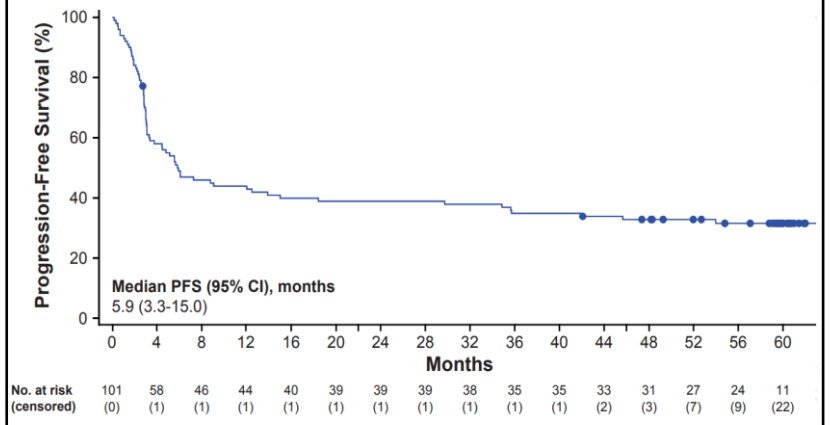
Mortality after CAR T-cell therapy

Meta-analysis	Non-relapse mortality	Cause of death
• N= 7,604 (18 trials, 28 RW studies)	• MCL: 10.6% • MM: 8% • LBCL: 6.1% • FL: 5.7%	• **Infections: 50.9%** • Other malignancies: 7.8% • Cardiovascular/respiratory: 7.3% • CRS + ICANS + HLH: 11.5%

Cordas do Santos DM. et al., Nature Medicine.2024

Long-term follow-up of pivotal clinical trials in 3rd line

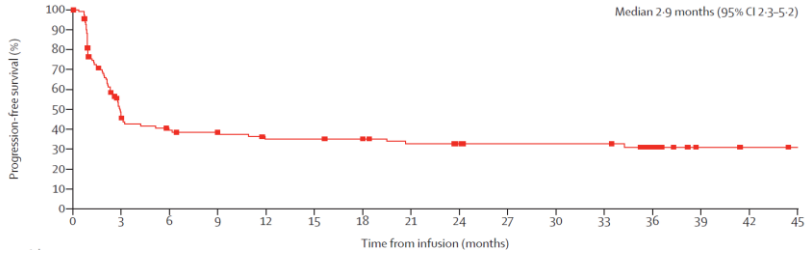
ZUMA-1: Axi-cel



mPFS 5.9 months
(mFU 63.1 mo)

Neelapu SS et al, Blood 2023

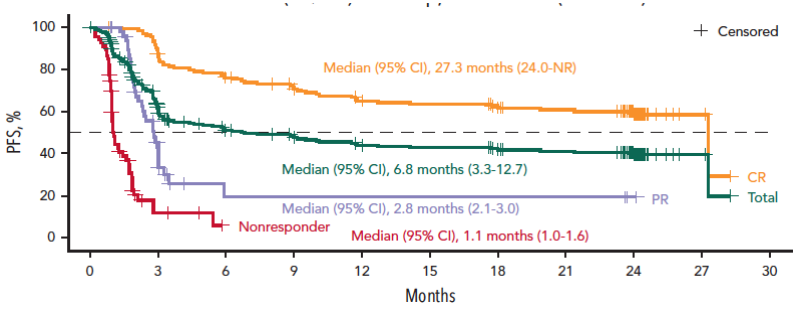
JULIET: Tisa-cel



mPFS 2.9 months
(mFU 40.3 mo)

Schuster SJ et al, Lancet Oncol 2021

TRANSCEND: Liso-cel

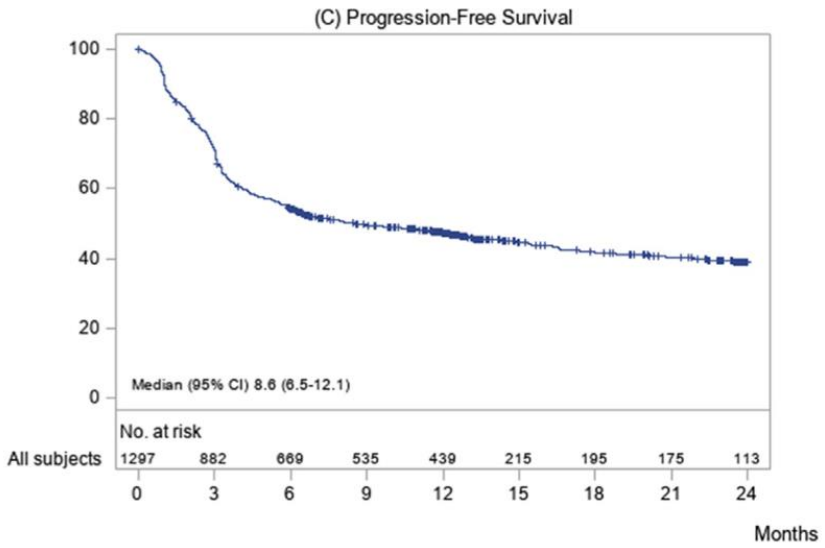


mPFS 6.8 months
(mFU 23.9 mo)

Abramson JS et al, Blood 2024

Real-world evidence in ≥3rd line (US + European)

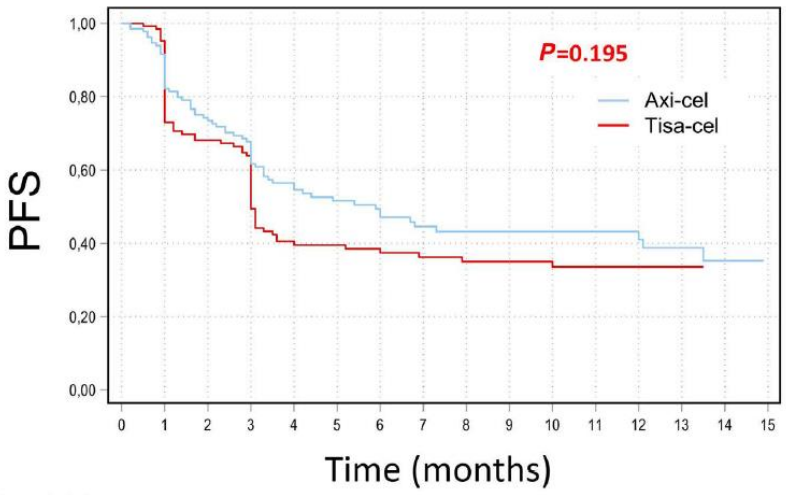
Axi-cel (CIBMTR)



12-month PFS: 47%

Jacobson CA, TCT 2022

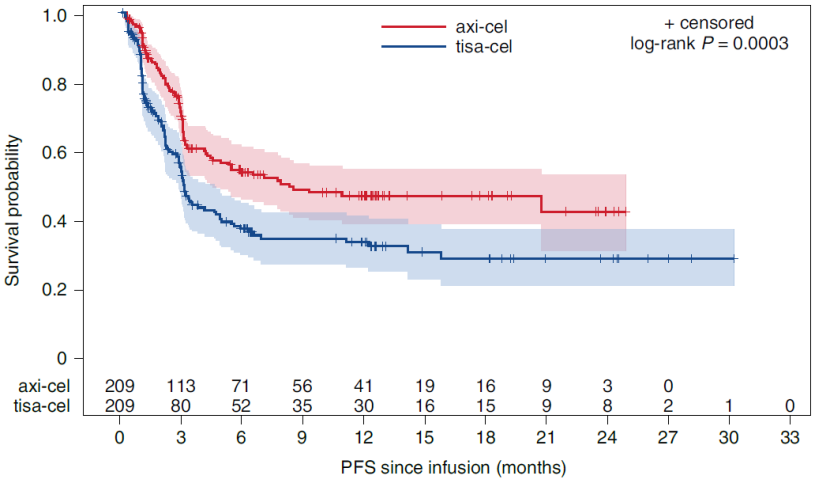
Spain (GETH/GELTAMO)



12-mo PFS: 41% (A) and 33% (T)

Kwon M*, Iacoboni G*, Haematologica 2022

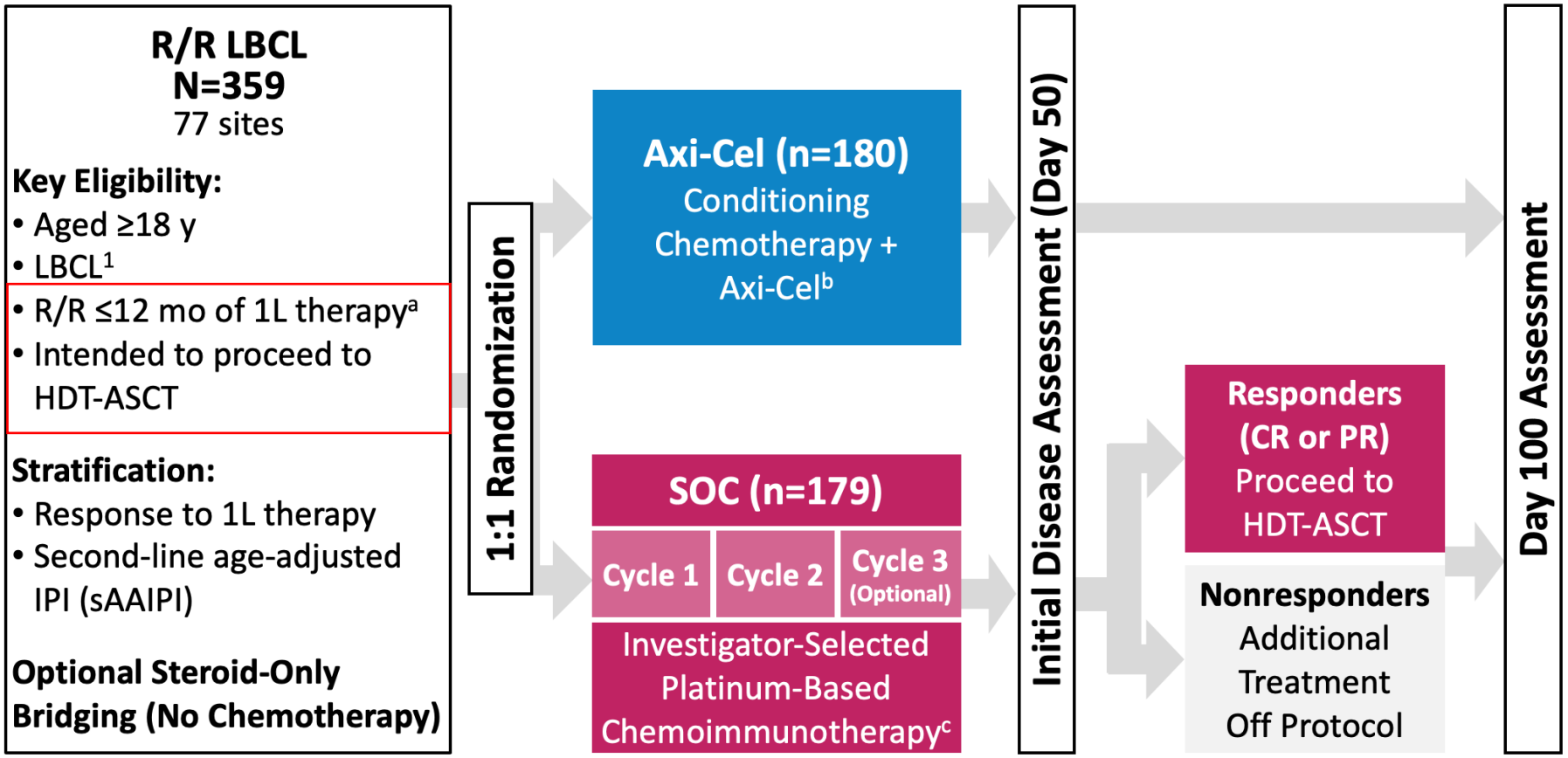
France (DESCAR-T)



12-mo PFS: 47% (A) and 33% (T)

Bachy E, Nature Medicine 2022

CAR T-cells vs Standard of Care in 2L Transplant-Eligible Patients

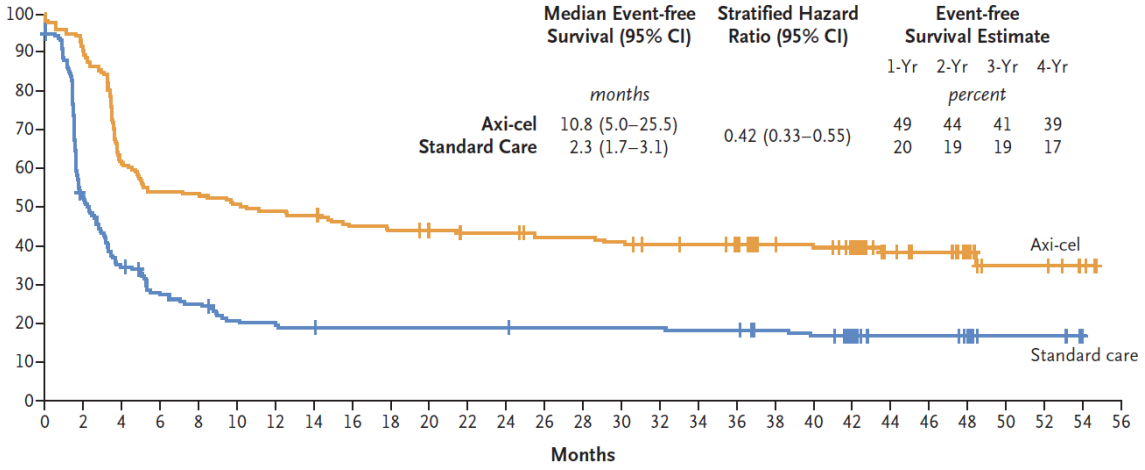


Westin JR, NEJM 2023

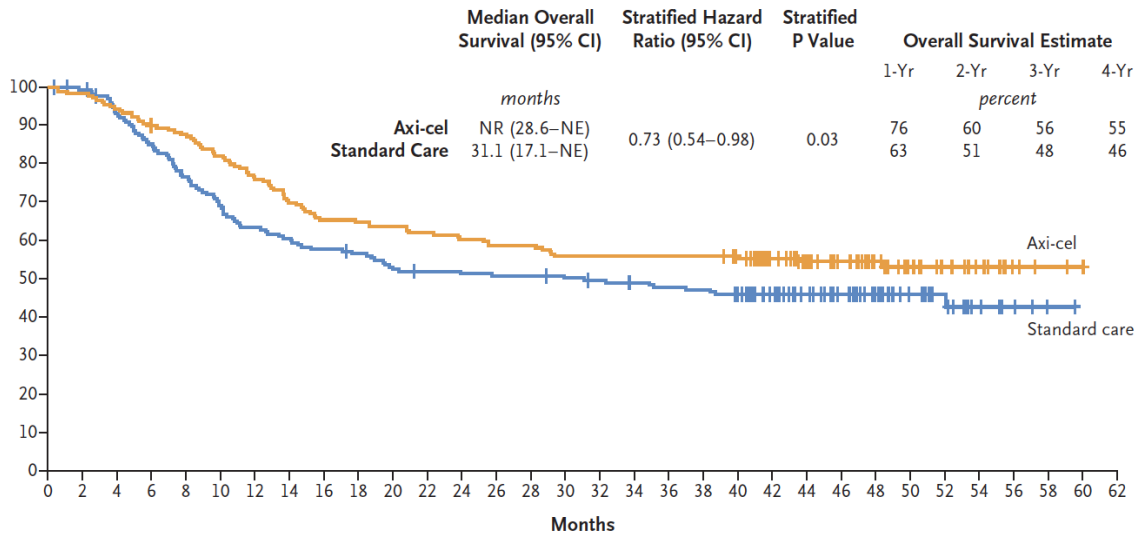
Axi-cel and Liso-cel improved EFS vs Standard of Care

Axi-cel

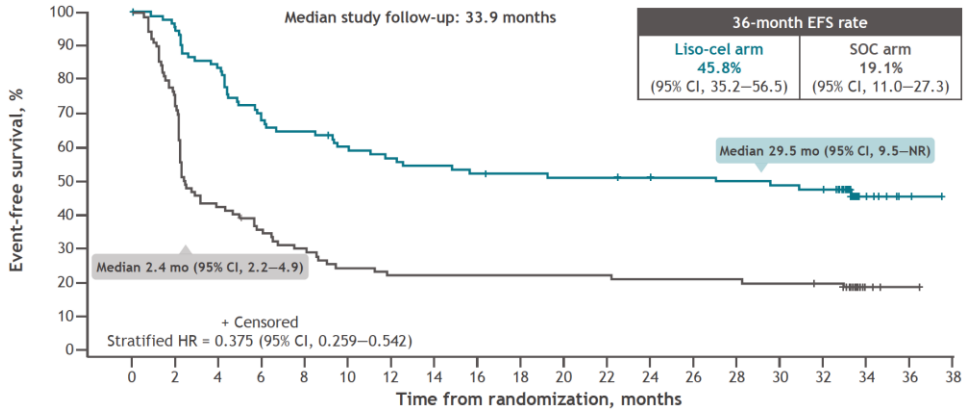
EFS

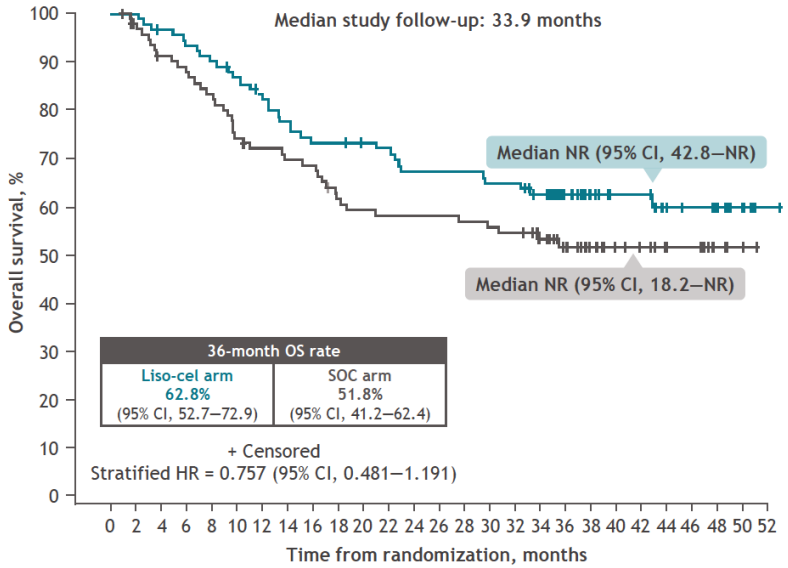


OS



Liso-cel





Westin JR, NEJM 2023; Locke FL, NEJM 2022; Abramson JS, Blood 2023; Abramson JS, EHA 2024, #S272

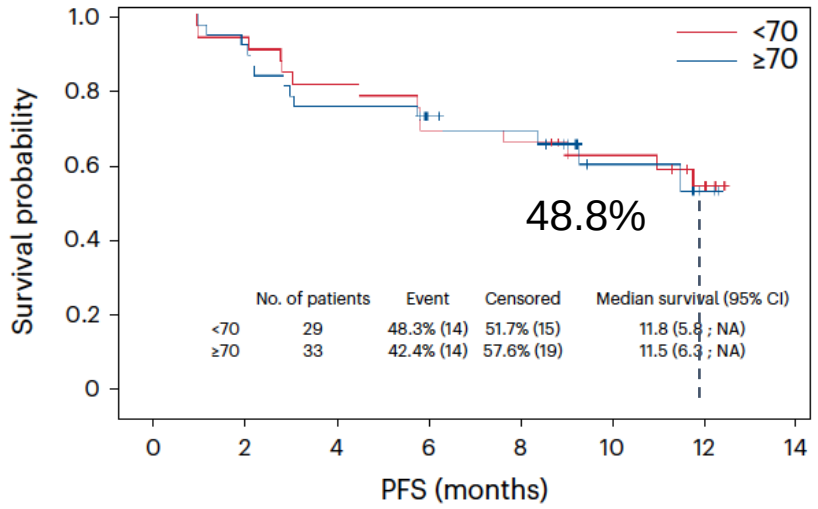
Toxicity across pivotal 2L and 3L+ trials

	Axi-cel		Tisa-cel		Liso-cel	
Trial	**ZUMA-1**	**ZUMA-7**	**JULIET**	**BELINDA**	**TRANSCEND**	**TRANSFORM**
Line	3L+	2L	3L+	2L	3L+	2L
CR	58%	65%	40%	28%	53%	66%
PFS (median)	5.9 mo	14.7 mo	2.9 mp	-	6.8 mo	14.8 mo
OS (median)	25.8 mo	NR	11.1 mo	-	27.3 mo	NR
CRS, ≥G3	11%	6%	23%	5%	2%	1%
ICANS, ≥G3	32%	21%	12%	2%	10%	4%
	Locke, F – Lancet 2019	*Locke, F – NEJM 2021*	*Schuster, SJ Lancet 2021*	*Bishop, M – NEJM 2021*	*Abramson, J – Lancet 2020*	*Kamdar, M – Lancet 2022*

Clinical Trials in Second-Line for Transplant-Ineligible Patients

ALYCANTE
Axi-cel 2L TNE (<12 mo)

mFU 12 mo
90% ORR - 79% CR
12-mo OS 78%

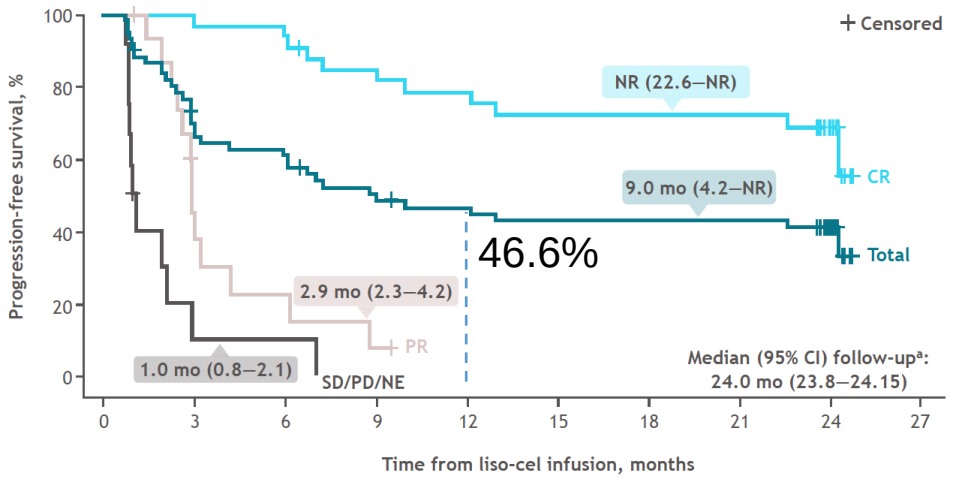


sCRS 8% - sICANS 15%
Toci 77%- Steroids 65%
ICU 26% - Infections G5 10%

Houot R, Nature Medicine 2023

PILOT
Liso-cel 2L TNE

mFU 18 mo
80% ORR - 54% CR
12-mo OS 68%



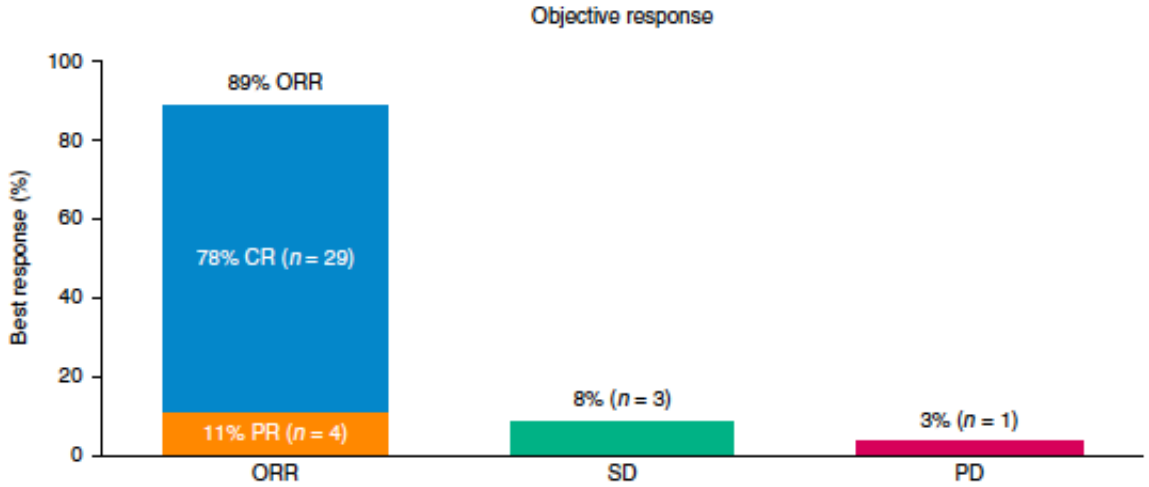
sCRS 2% - sICANS 5% (all G3)

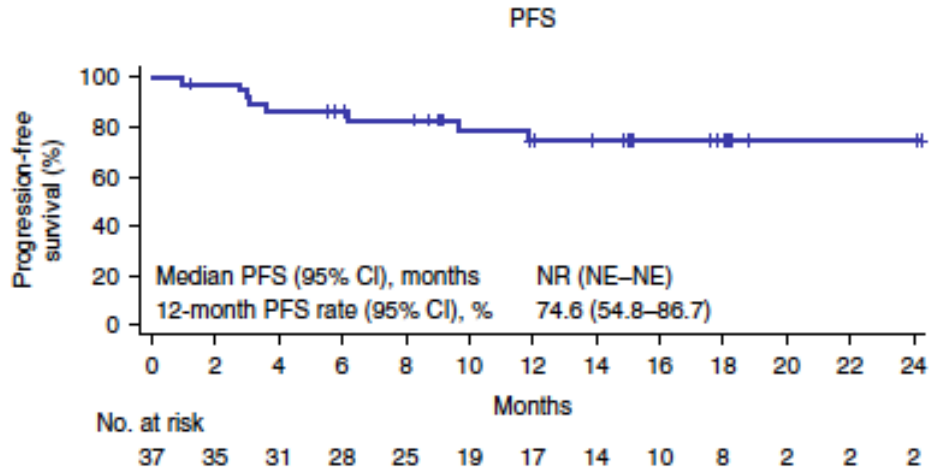
Sehgal A, Lancet Oncol 2022
Sehgal A, ASH Meeting 2023, Presentation #105

ZUMA-12
Axi-cel as first-line therapy for high risk LBCL

- **High-grade B cell lymphoma, with MYC and BCL2 and/or BCL6 translocations** (40%)
- **LBCL with IPI score ≥ 3** (78%)

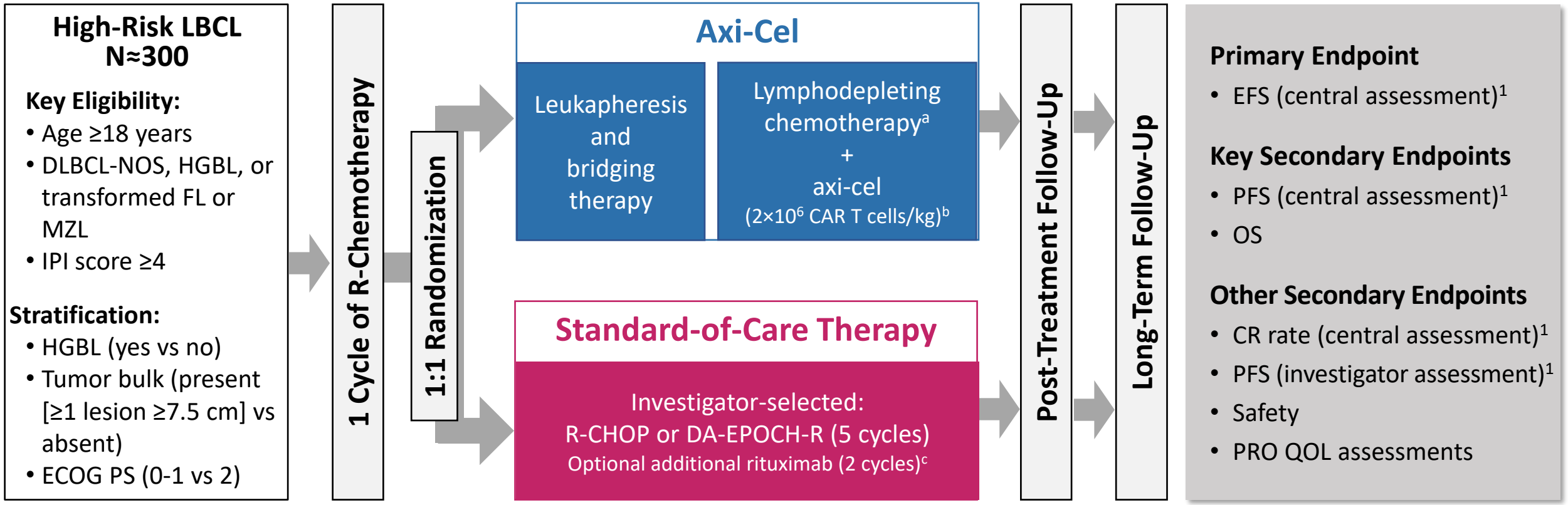
Outcomes in ZUMA-12 (N=40) *(DS 4 or 5 after 2 cycles or R-CT)*	
ORR, %	90
CR, %	80
Any Gr CRS, %	40 (100)
Any Gr NE, %	29 (73)
Gr ≥3 CRS, %	3 (8)
Gr ≥3 NE, %	9 (23)





Neelapu S, Nature Medicine. 2022

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.

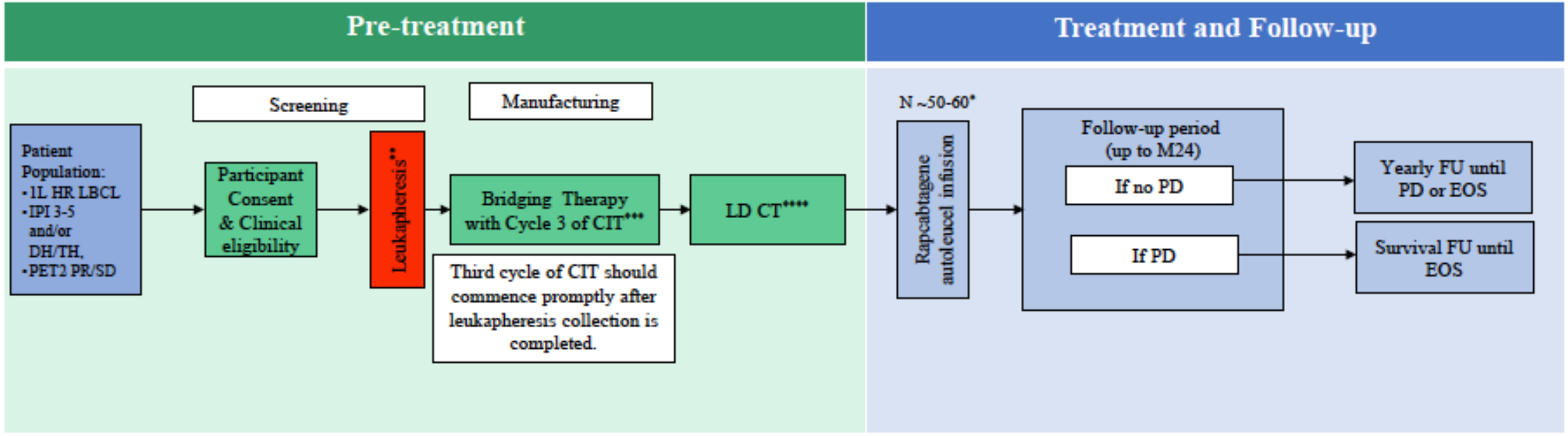
Axi-cel, axicabtagene ciloleucel; CR, complete response; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; FL, follicular 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.

YTB323 1L LBCL Cohort

CYTB323A12101 Study Flow for 1L HR LBCL Cohort

Pre-Screening requirement:

Positive PET per Lugano classification (Deauville score 4 or 5) and overall response of PR/SD after 2 cycles of CIT. PET scan must be performed no earlier than Day 14 of Cycle 2.



* Approximately 40 participants planned for the primary efficacy analysis based on the efficacy analysis set for 1L HR LBCL
- IPI 4-5 or DH/TH, n=20
- IPI 3 not DH/TH, n=20

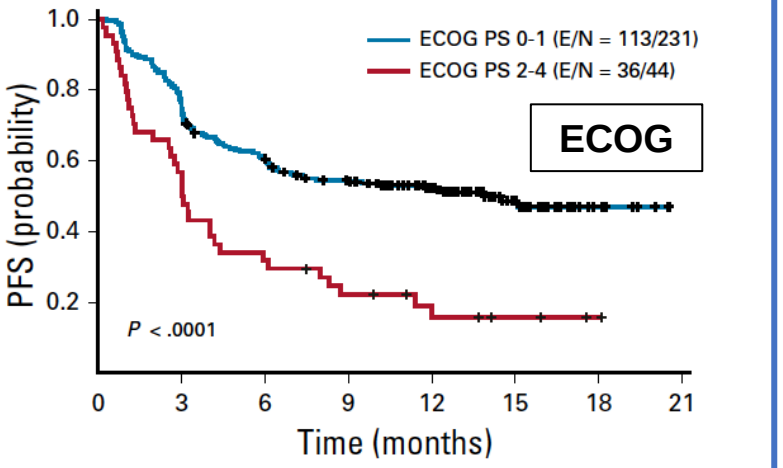
** **Leukapheresis** should be performed within 5 days from signing the main ICF. Refer to Section 8.1.2.1 for more details

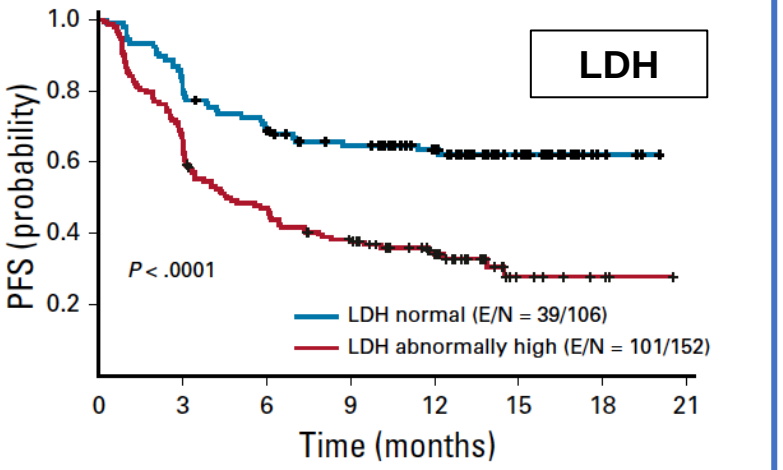
*** All 1L HR LBCL participants **must** receive a third cycle of CIT as bridging therapy and a lymphodepleting chemotherapy regimen of fludarabine 25 mg/m^2 daily plus cyclophosphamide 250 mg/m^2 daily for 3 days. Refer to Section 6.1.7.2 for more details

**** Prior to **Lymphodepleting chemotherapy**, at least 11 days should have passed since the last dose of bridging CIT. Refer to Section 6.1.7.3 and Section 6.1.8 for more details.

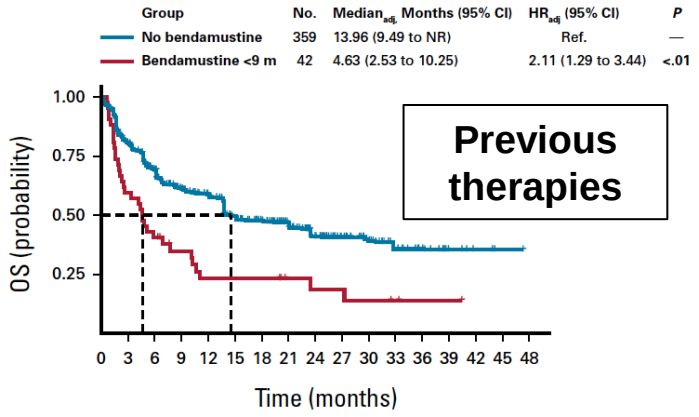
IPI: International Prognostic Index; DH: Double Hit; TH: Triple Hit; PR/SD: Partial Response/Stable Disease; CIT: Chemoimmunotherapy; LD CT: Lymphodepleting Chemotherapy; PD: Progression of Disease; EOS: End of Study; FU: Follow-Up

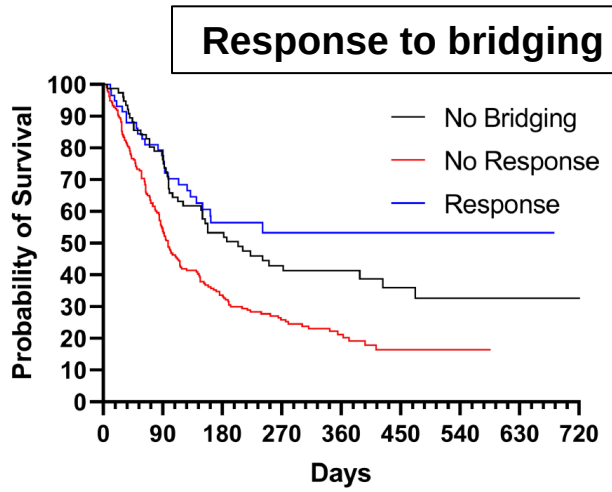
Prognostic factors for CAR T-cell efficacy in LBCL



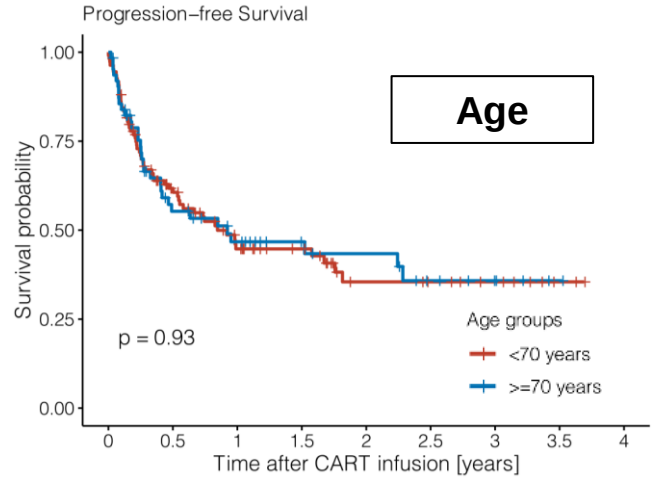


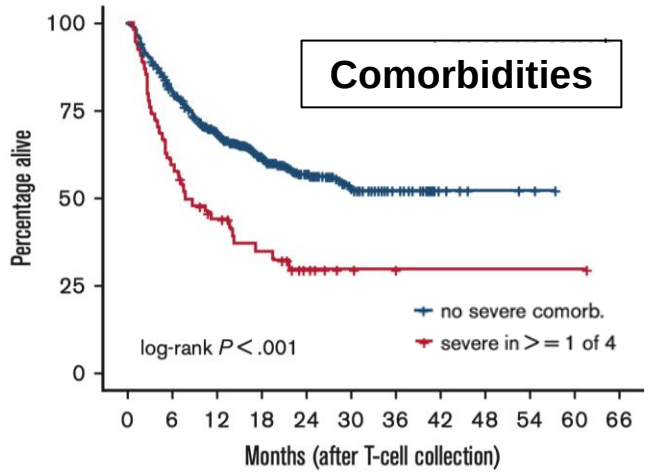
Nastoupil LJ, JCO 2020





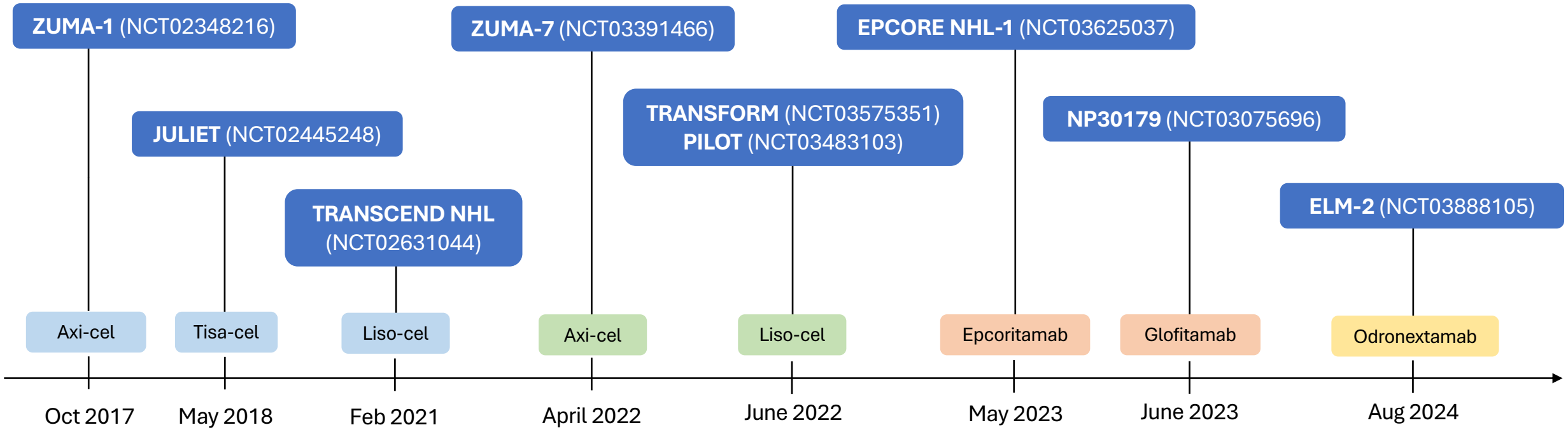
Iacoboni G, JCO 2023
Bethge WA, Blood 2022





Berning P, Hemasphere 2024
Shouse G, Blood Advances 2023

FDA approvals of TCEs in large B-cell lymphoma



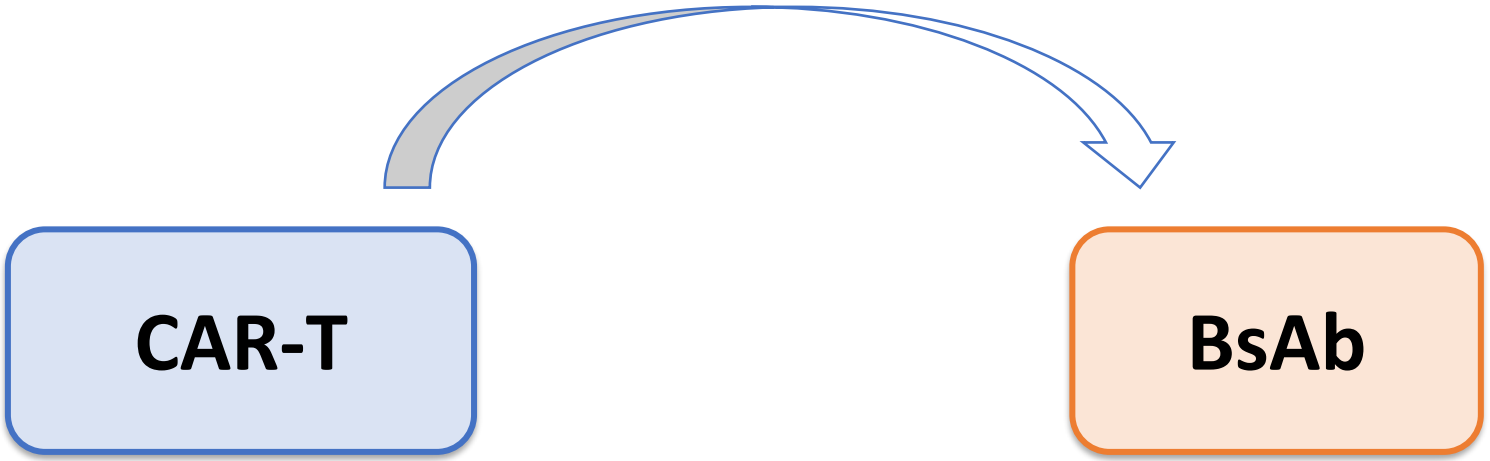
3L+ CART approvals

2L CART approvals

3L+ BsAb approvals

3L+ BsAb approvals (only EMA)

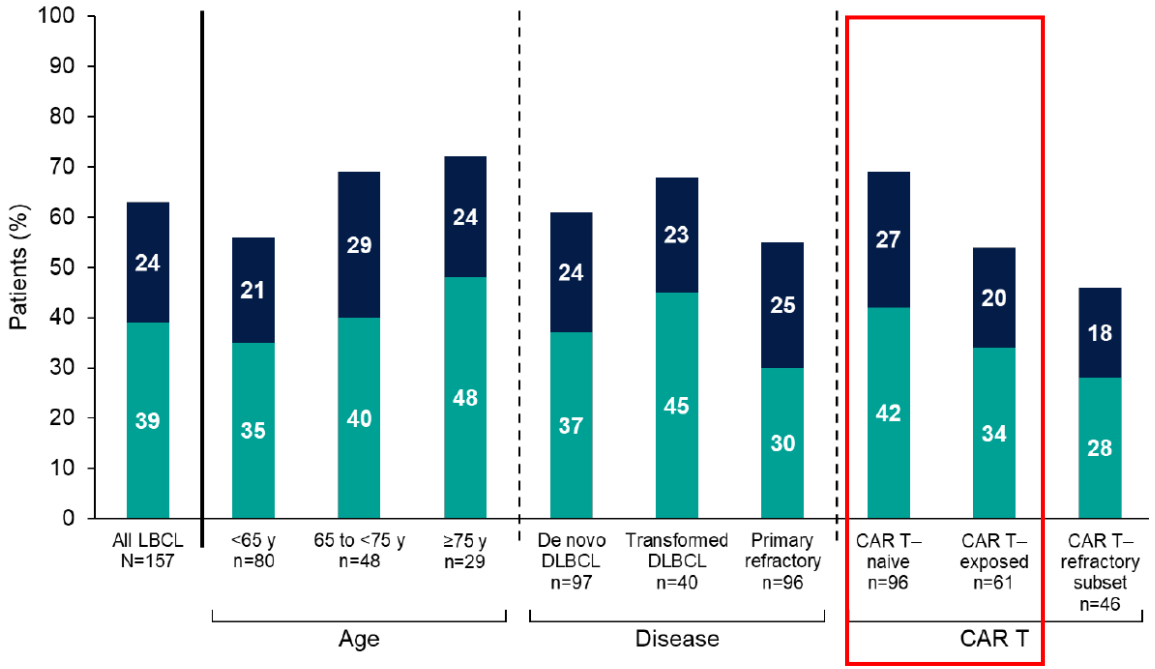
What about treatment sequencing?



Comparable response rates in CART-exposed patients

Epcoritamab

61 pts (39%)



Thieblemont C, et al.
J Clin Oncol 2023

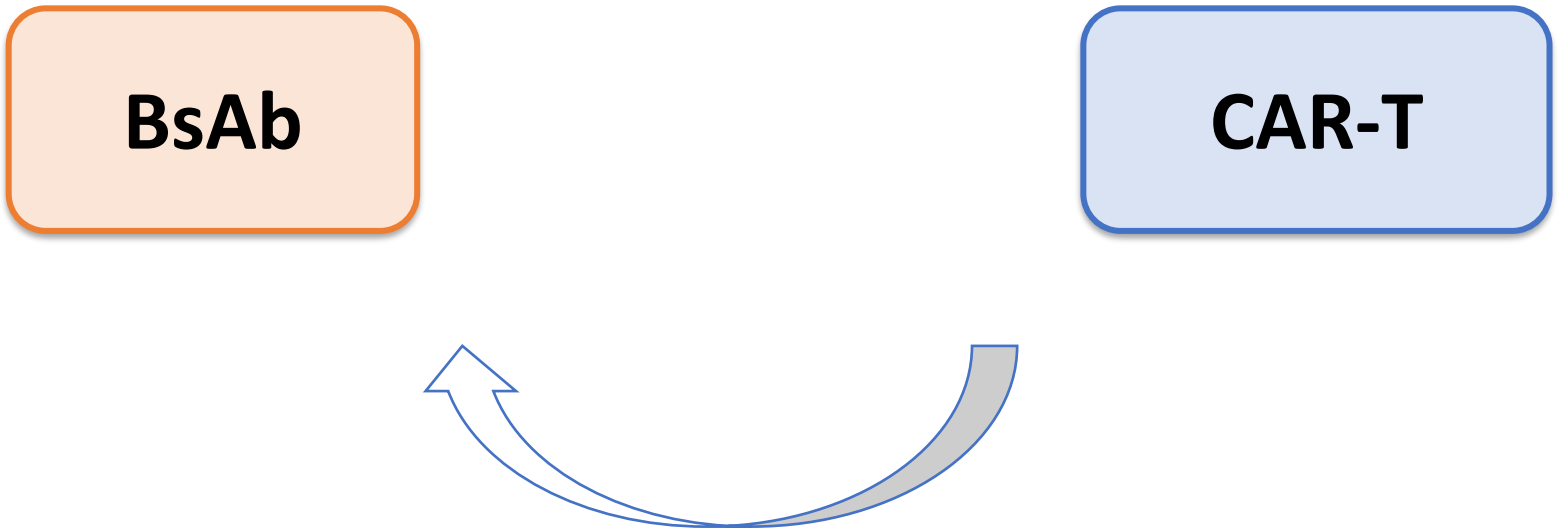
Glofitamab

51 pts (33%)

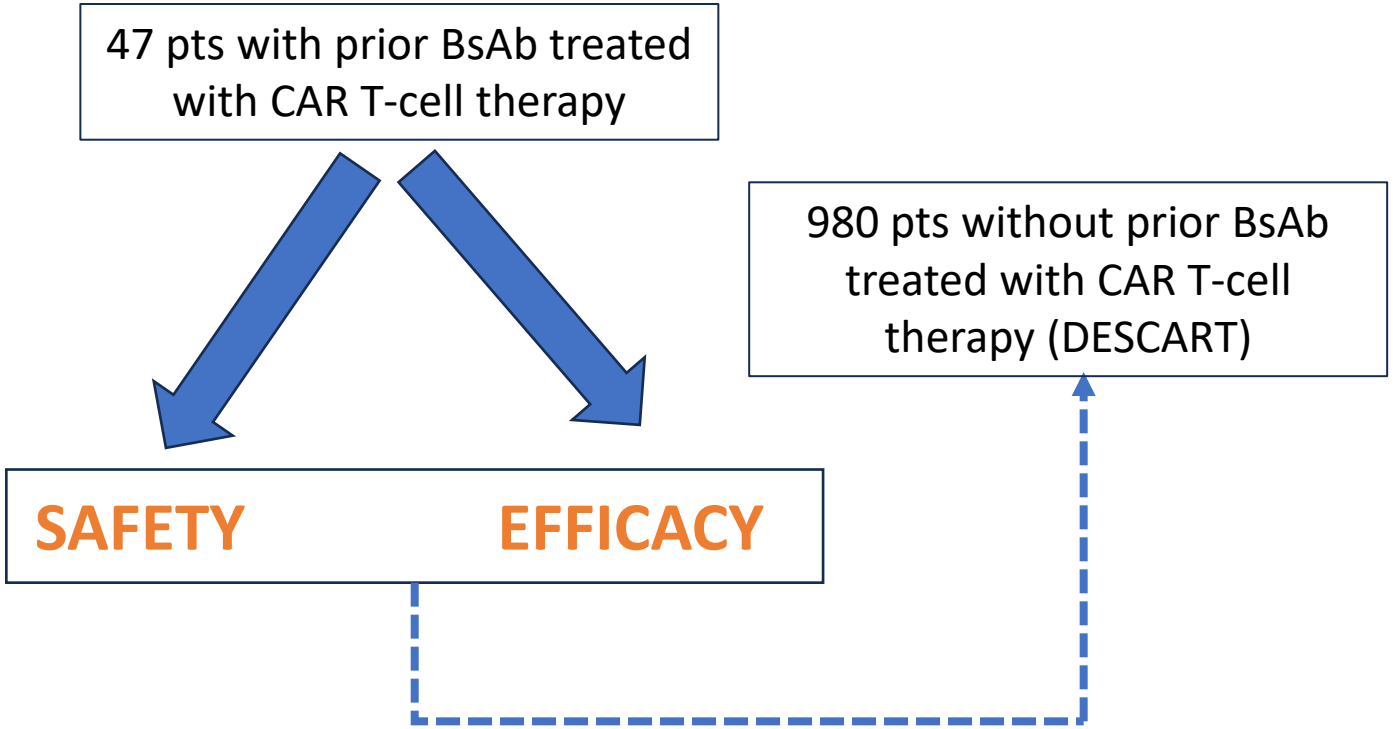
Subgroup	No. of Patients	Complete Response (95% CI) *percent*
Overall	155	39 (32–48)
Sex		
Female	54	52 (38–66)
Male	101	33 (24–43)
Age		
<65 yr	71	41 (29–53)
≥65 yr	84	38 (28–49)
Previous CAR T-cell therapy		
Yes	52	35 (22–49)
No	103	42 (32–52)

Dickinson M, NEJM 2022

What about treatment sequencing?



What about treatment sequencing?



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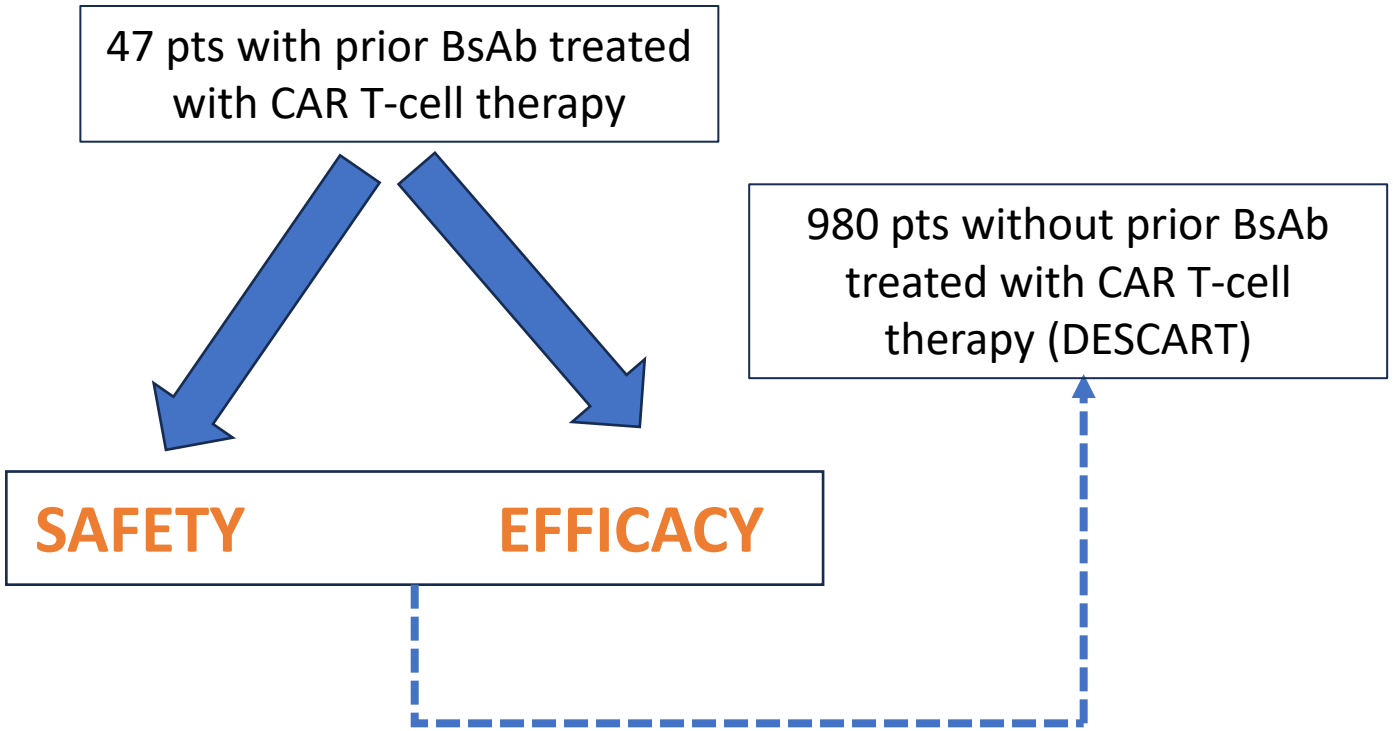
What about treatment sequencing?



Toxicity	N=47
CRS any, n (%)	37 (79)
- Grade ≥3, n (%)	3 (6)
ICANS any, n (%)	11 (23)
- Grade ≥3, n (%)	1 (2)

CRS		BsAb†		p-value
		No†	Yes	
CAR-T	No	21% (4/19)	22% (6/27)	1.0
	Yes	79% (15/19)	78% (21/27)	

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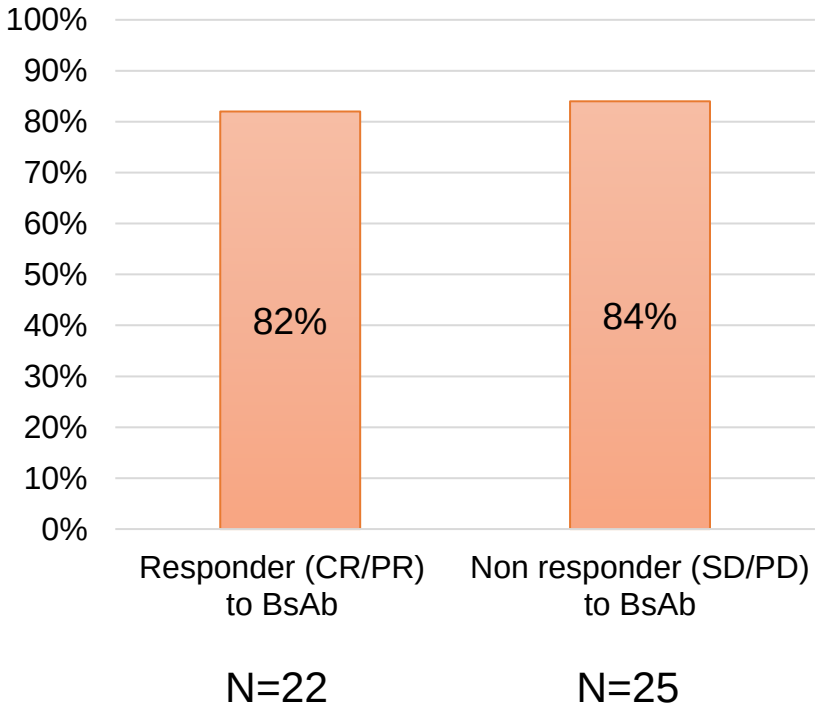
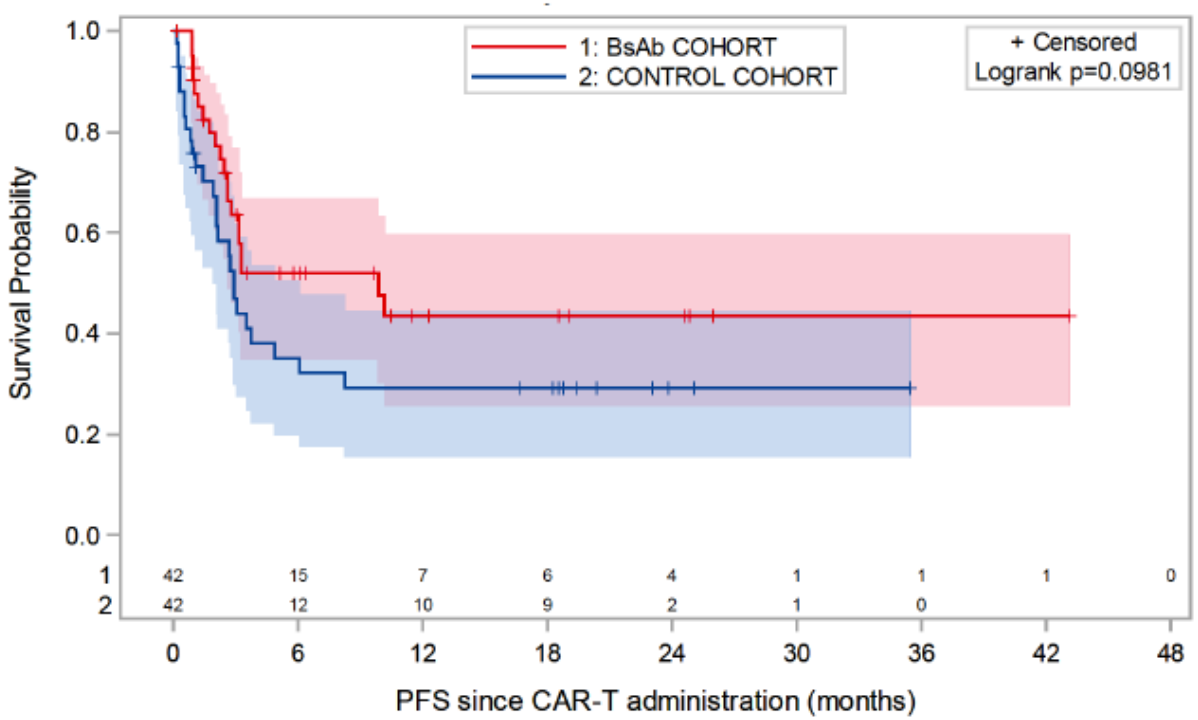
CAR-T Efficacy is Not Impaired by Previous BsAb Treatment

Efficacy	N=47
Best ORR (CR), %	85 (43)
1-year PFS	42%
1-year OS	55%

ORR to CAR T-cell therapy according to prior response to BsAb



PFS to CAR T-cell therapy according to prior exposure to BsAb



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Conclusions

- CAR T-cell therapies show superior outcomes in third line and in transplant eligible second line patients (and probably in NTE) compared with standard therapy.
- Identifying pre-treatment predictive factors is key to deliver the therapy to the best patients at the appropriate time.
- CAR T-cell efficacy and toxicity is not modified by previous use of bispecific antibodies in patients with large B-cell lymphoma, although the optimal treatment sequencing is yet to be determined

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