GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

Convegno Educazionale GITMO

LE TERAPIE CELLULARI IN EMATOLOGIA
TRA PASSATO, PRESENTE E FUTURO

Brescia, 28-29 novembre 2025

Centro Paolo VI

Nei linfomi aggressivi: possiamo definire un algoritmo nell'era dei bi-specifici?

Unit of Blood Disease and Bone Marrow Transplantation
Program of Cell Therapies and Research in Hematology

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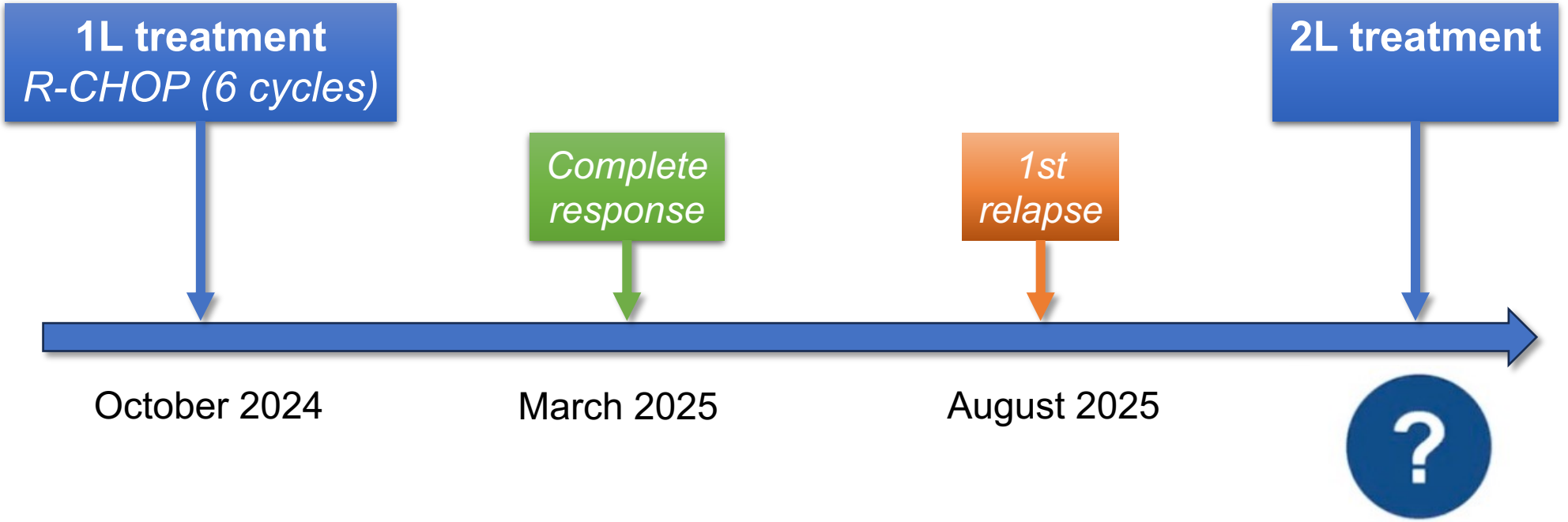
Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili

Disclosures of Mirko Farina

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

Clinical Case

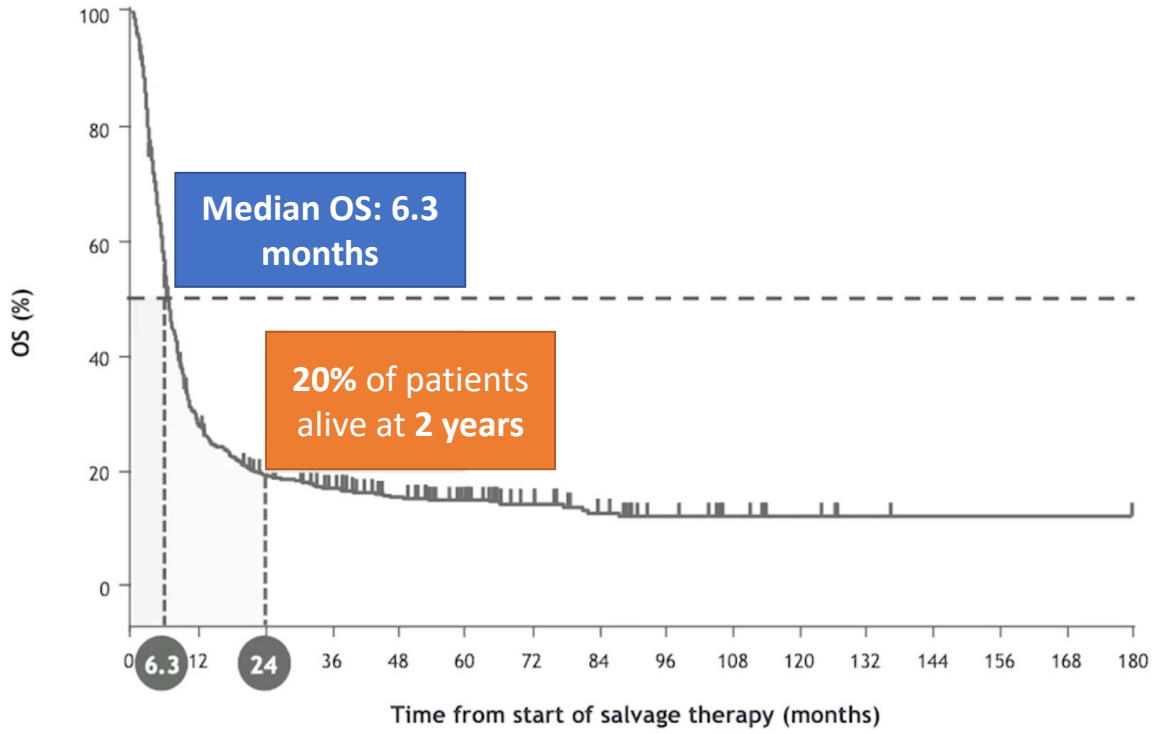
F.R. is a 67-year-old, male patient diagnosed with DLBCL nos, stage IV, IPI intermediate-high



Treatment algorithm of Large B-cell Lymphoma

R-CHOP/Pola-R-CHP
DA-EPOCH-R

2L treatment



SCHOLAR-1
(N=636)

Included patients with:

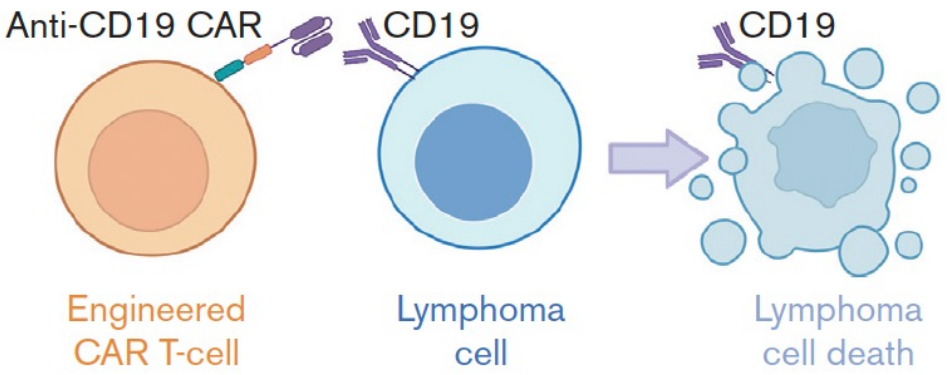
- **Primary refractory disease**
- **Refractory to ≥2 lines of therapy**
- **Relapse ≤12 months post ASCT**

Crump et al., Blood 2017

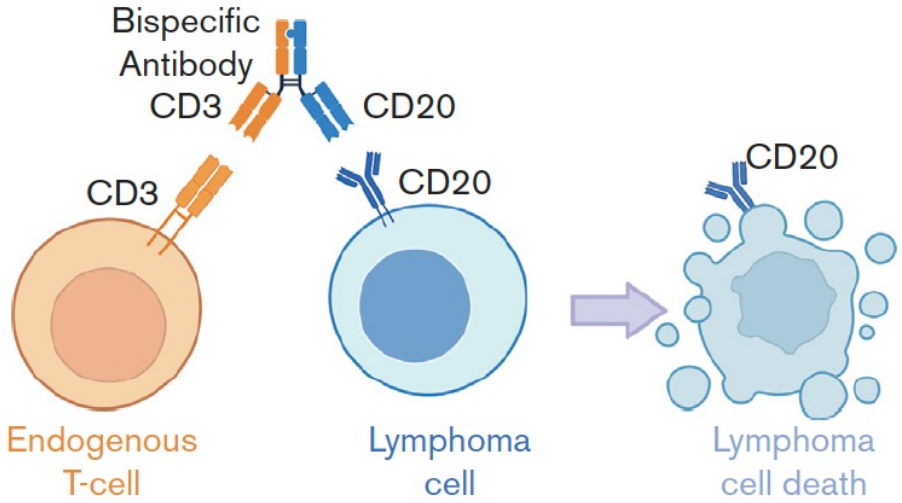
T-cell redirecting strategies have revolutionised LBCL treatment

T-cell engaging therapies have delivered unprecedented efficacy in B-cell lymphomas and revolutionised the management of early-relapsed and multiply-relapsed chemo-refractory LBCL

CAR T cells recognize and kill CD19-expressing cancer cells[1]



CD3 × CD20 bsAbs bring together T cells and CD20+ tumor cells to induce T cell-mediated killing of the tumor cell[2]



Haydu and Abramson, Blood Adv 2024

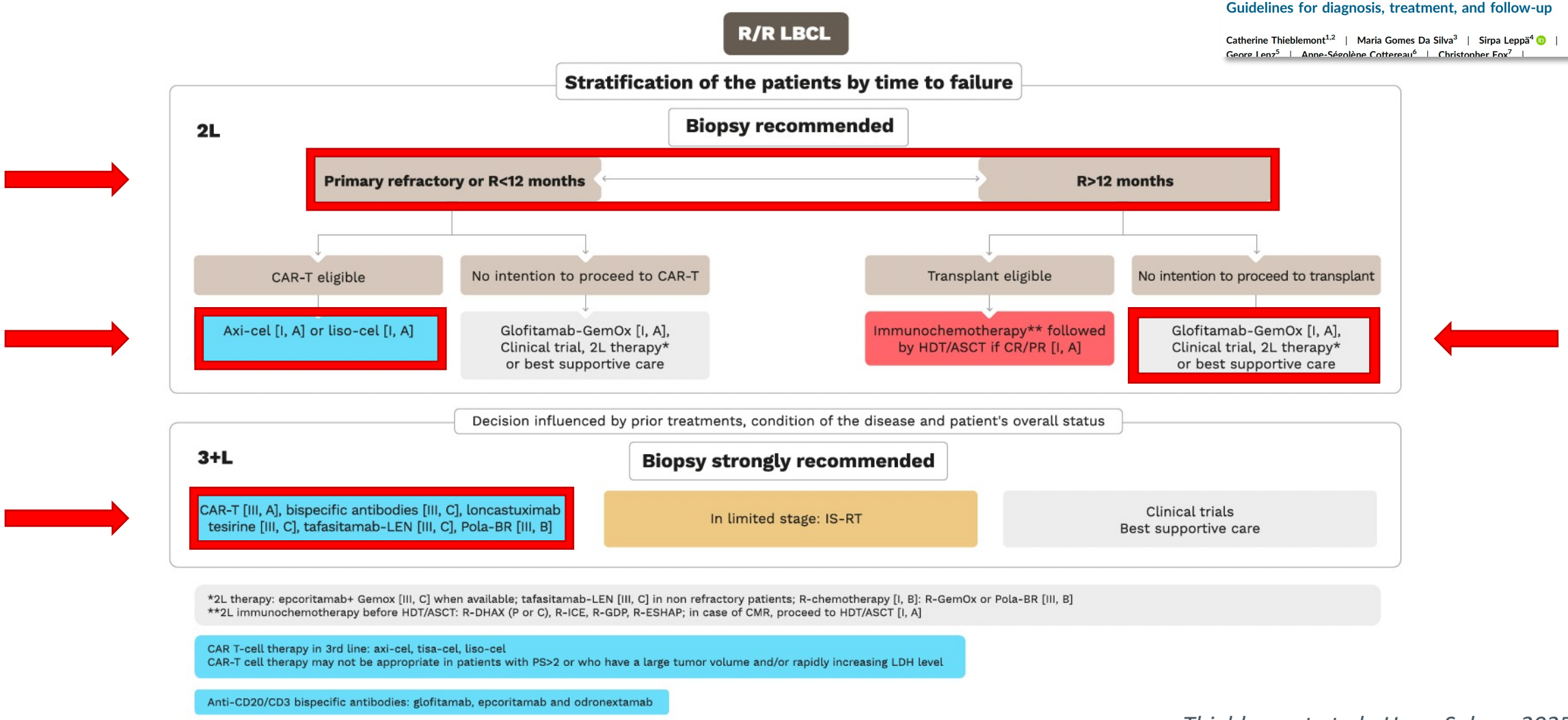
1. Abramson JS, et al. Lancet. 2020;396:839-852. 2. Schuster SJ. Hematological Oncology. 2021;39(S1):113–116.

LBCL EHA Clinical Practice Guidelines

Received: 13 March 2025 | Accepted: 6 August 2025
DOI: 10.1002/hem3.70207
GUIDELINES - EXPERT OPINION
HemaSphere eha

Large B-cell lymphoma (LBCL): EHA Clinical Practice Guidelines for diagnosis, treatment, and follow-up

Catherine Thieblemont[1,2] | Maria Gomes Da Silva[3] | Sirpa Leppä[4] | Georg Lenz[5] | Anne-Ségolène Cottereau[6] | Christopher Fox[7]

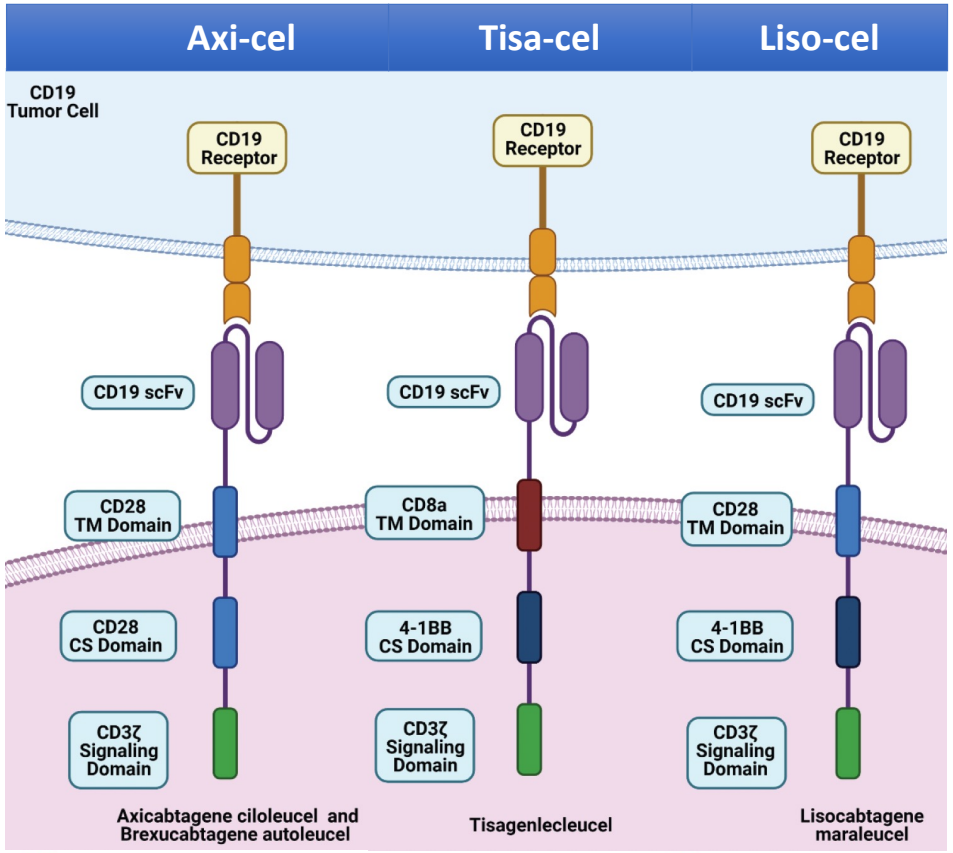


Thieblemont et al., HemaSphere 2025

Currently, the Approval Status determines sequence of BiABs & CART

	BCP-ALL	Lymphoma	MM
BsAb	1st Line, MRD^{+}	3rd Line	4th Line
CART	2nd Line	2nd Line	4th Line
Data Availability on Sequencing			
BsAb => CART	+++	+	+
CART => BsAb	+	++	+

CAR-T cells and BiABs approved in LBCL



3L+ DLBCL October 2017
2L April 2022

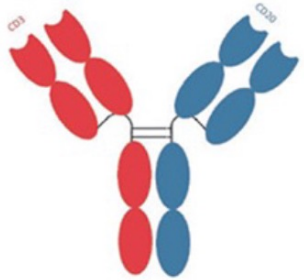
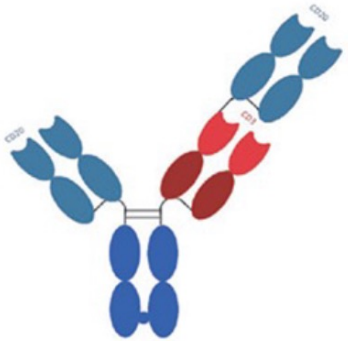
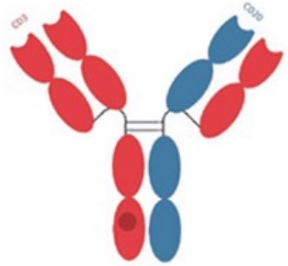
3L+ DLBCL August 2018
2L October 2022

3L+ DLBCL May 2018

3L+ DLBCL August 2018

3L+ DLBCL February 2021
2L June 2022

3L+ DLBCL April 2022
2L April 2022

EPCORITAMAB	GLOFITAMAB	ODRONEXTAMAB
CD3xCD20	CD3x$(CD20)_2$	CD3xCD20
		
• Monovalent CD3 and monovalent CD20 binding • Humanized mouse IgG1-based antibody	• Monovalent CD3 and bivalent CD20 binding • Humanized mouse IgG1-based antibody	• Monovalent CD3 and monovalent CD20 binding • Fully human IgG4-based antibody

3L+ DLBCL May 2023, FL June 2024

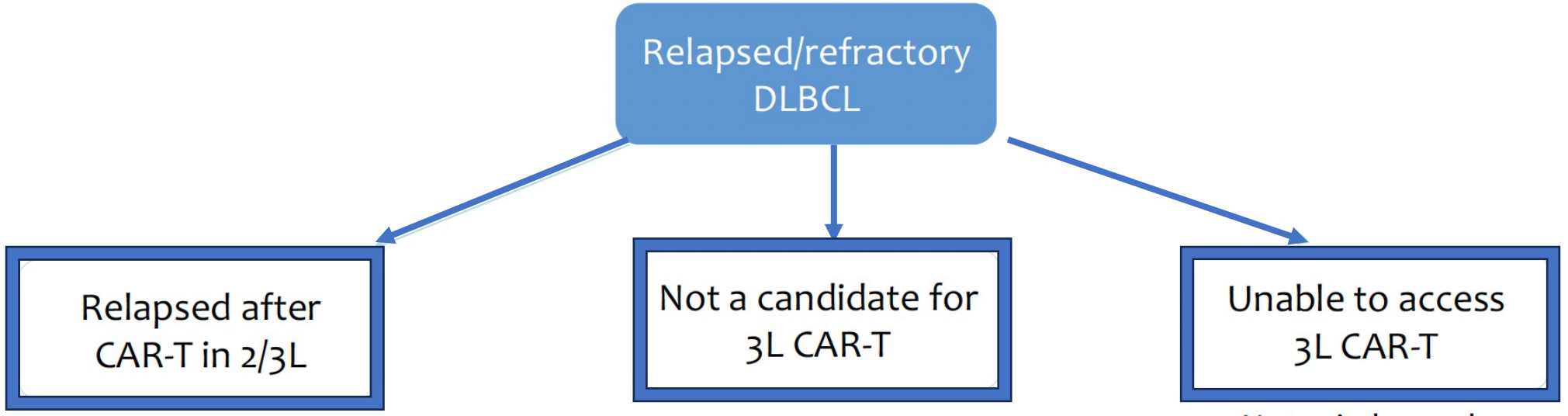
3L+ DLBCL or FL Sep 2023[4]

3L+ DLBCL June 2023

3L+ DLBCL July 2023

3L+ DLBCL or FL June 2024

Who is the typical DLBCL candidate for 3L+ BiABs?



- Relapsed < 1 year of 1L and had 2L CAR-T
- Relapsed after 3L CAR-T

- Ineligible histology, loss of CD19
- Comorbidity
- Features predicting poor response e.g. rapid PD, tumour bulk
- Failed apheresis or product manufacture
- Patient preference

- Not reimbursed
- Patient unable to travel for treatment

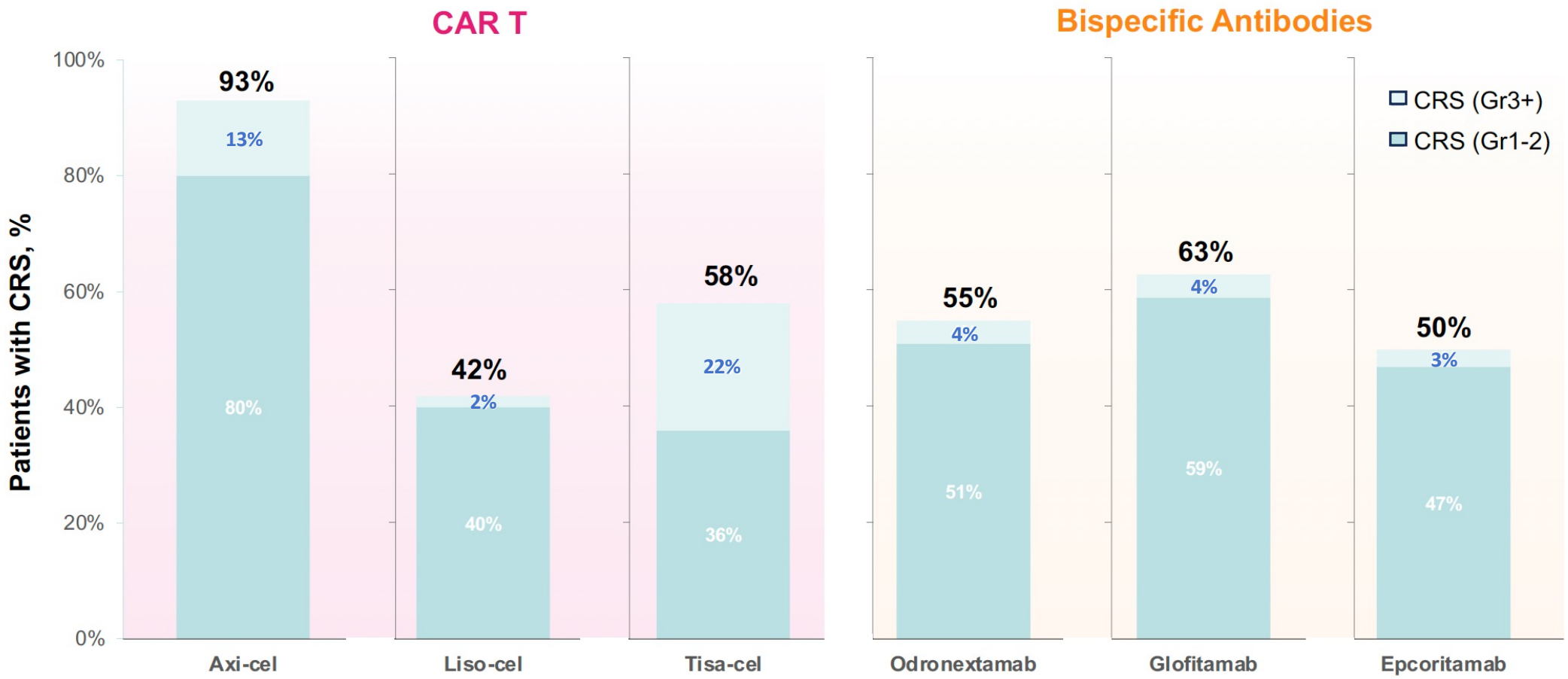
Zurko J, et al Haematologica. 2023;108(1):98-109.

Summary of Clinical trials for CAR T vs BiABs in R/R LBCL, 3rd Line

	Axi-cel	Tisa-cel	Lisocel	Glofitamab	Epcoritamab
Median follow-up (mo)	63	49	24	24	20
ORR (%)	**82**	**52**	**73**	**67**	**71**
CR (%)	**58**	**39**	**53**	**39**	**39**
Median DOR (mo)	62	Not reached	26	NR	20.8
Ongoing CR	30 %	2 6%	26 %	31 %	27 %

Karmali, ASH Education program 2021

Clinical trials for and BiABs vs CD19 CARTs: toxicity



Thieblemont et al. JCO 2022; Dickinson et al. NEJM 2022; Neelapu et al. NEJM 2017, Abramson et al. Lancet 2020, Shuster et al. NEJM 2019

BiABs & CAR-T in LBCL, 3rd Line: Meta-analysis

- *Sixteen studies comprising 1347 patients were included in the pooled analysis*

blood Regular Article

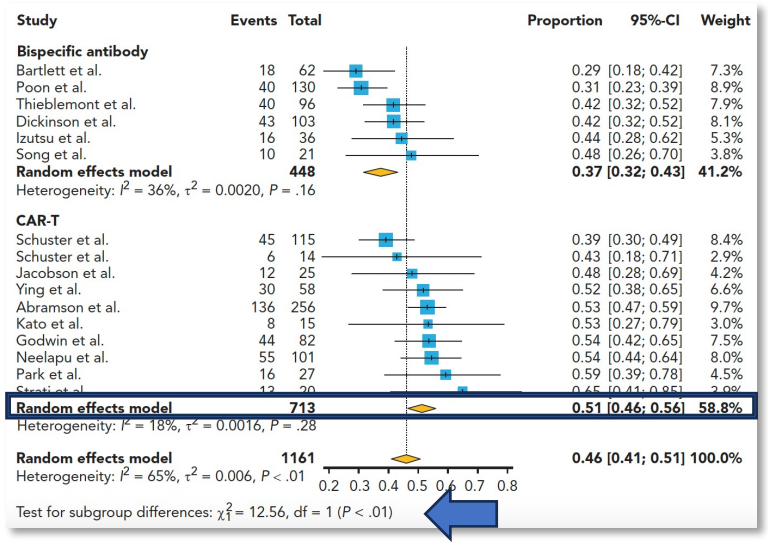
LYMPHOID NEOPLASIA

CAR T cells vs bispecific antibody as third- or later-line large B-cell lymphoma therapy: a meta-analysis

Jinchul Kim,[1] Jinhyun Cho,[1] Moon Hee Lee,[1] Sang Eun Yoon,[2] Won Seog Kim,[2,3] and Seok Jin Kim[2,3]

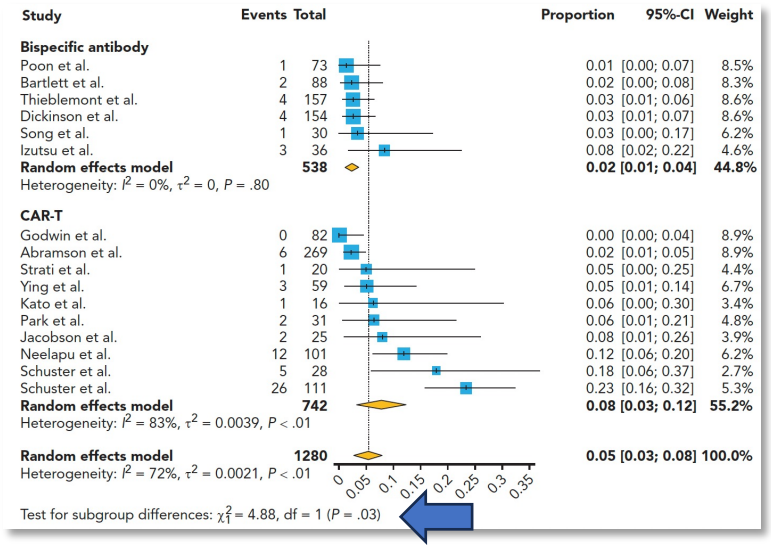
[1]Department of Hematology-Oncology, Inha University College of Medicine and Hospital, Incheon, Korea; [2]Division of Hematology-Oncology, Department of

CR rate

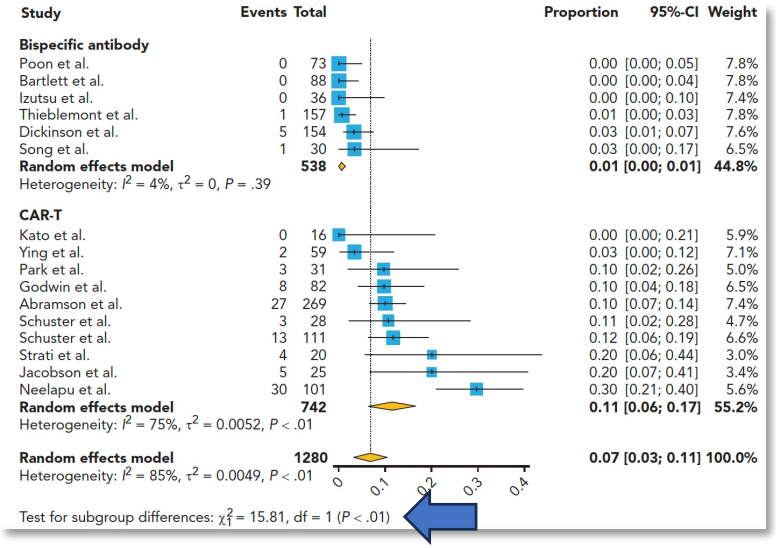


Adverse events of grade ≥3

CRS



ICANS



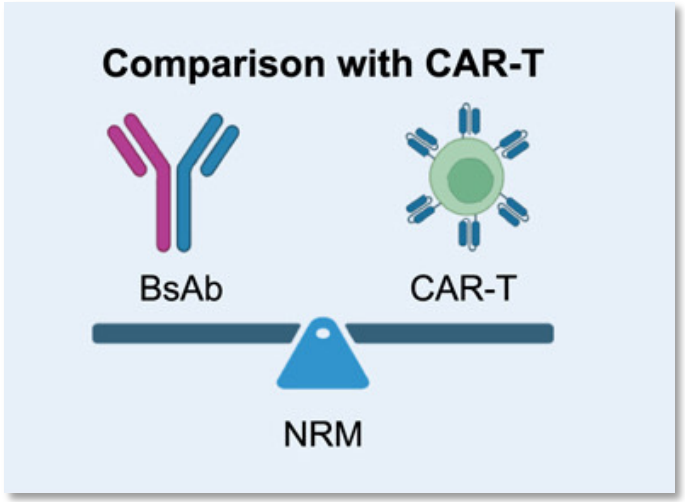
CR rate (CAR-T vs. BiABs):
51% *(95%CI 46-56)* **vs. 37%** *(95% CI, 32-43)*
p-valure < 0.01

CRS severe (CAR-T vs. BiABs): 8% vs 2%
ICANS severe (CAR-T vs. BiABs): 11% vs 1%
INFECTIONS: NO DIFFERENCE!

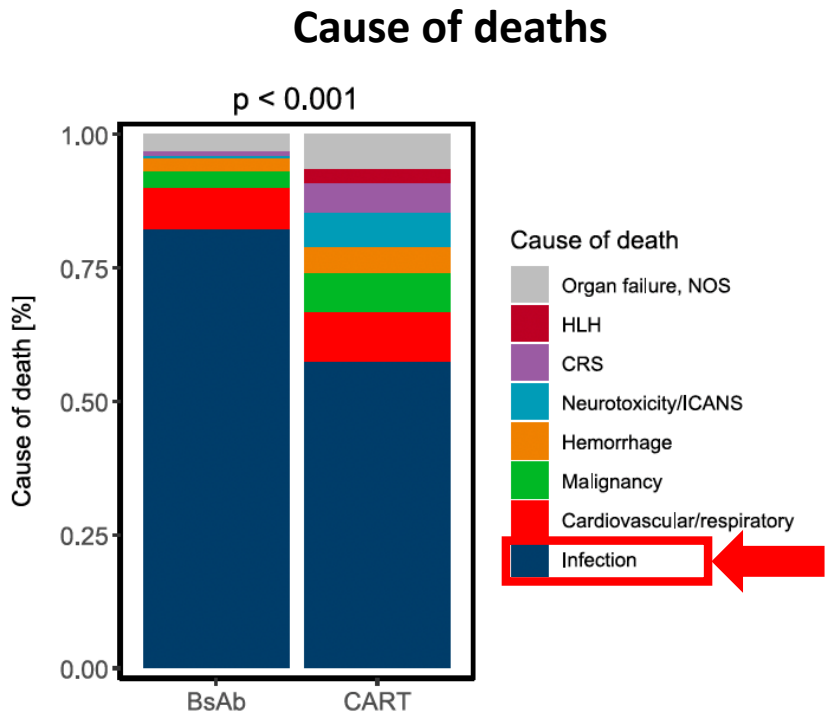
Kim et al. Blood 2024

BiABs & CART in LBCL, 3rd Line: NRM

- Meta-regression comparing BsAb and CAR-T therapies (*n* = 8,592) showed **no significant NRM difference when accounting for key study-level confounders (*p* = 0.96).**



	Studies	Patients	Estimate (95%CI)	p value
Mechanism				
CAR-T [ref.]	45	6692		
BsAb	23	1900	0.01 (-0.39;0.41)	0.96

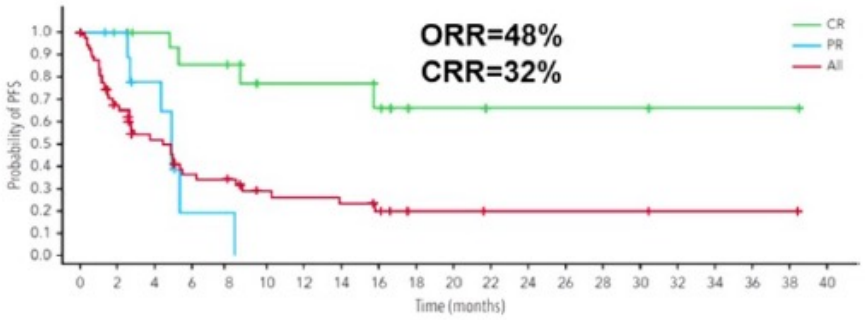


Tix et al. Mol Ther 2025

Efficacy of BiABs after CAR-T cell therapy

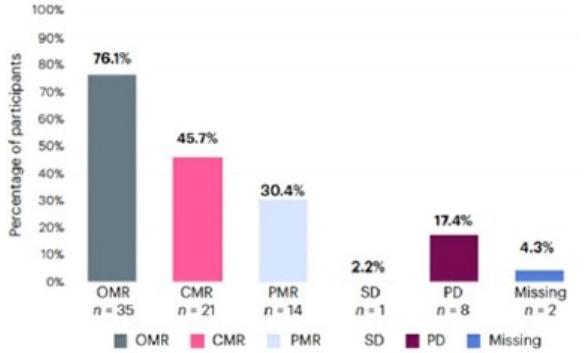
Odronextamab expansion cohort (ELM-1, N=60)
48% relapsed <3 mo after CAR-T, 27% HGBL

12-mo PFS 27% and 12-mo OS 46%; CRS 48%



Glofitamab (BICAR study, N=46)
26% relapsed <3 mo after CAR-T

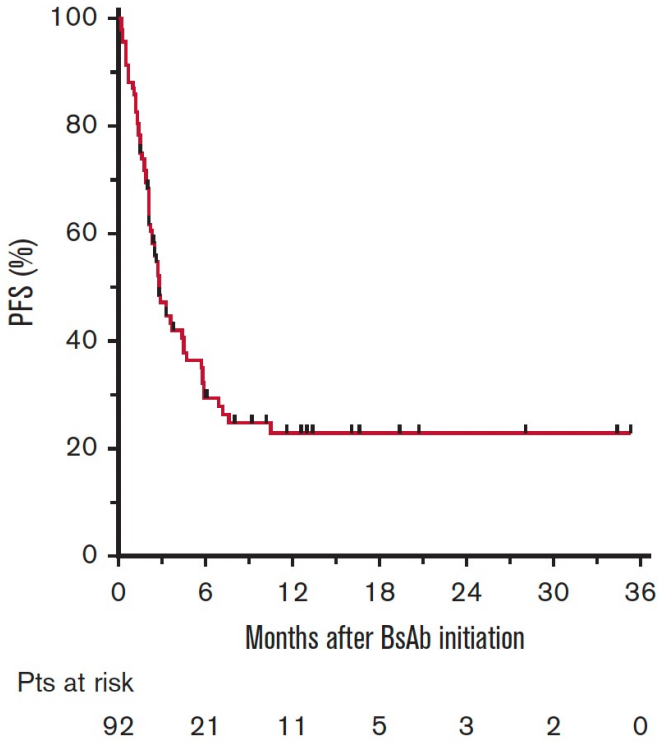
12-mo PFS 37% and 12-mo OS 56%, CRS 13%

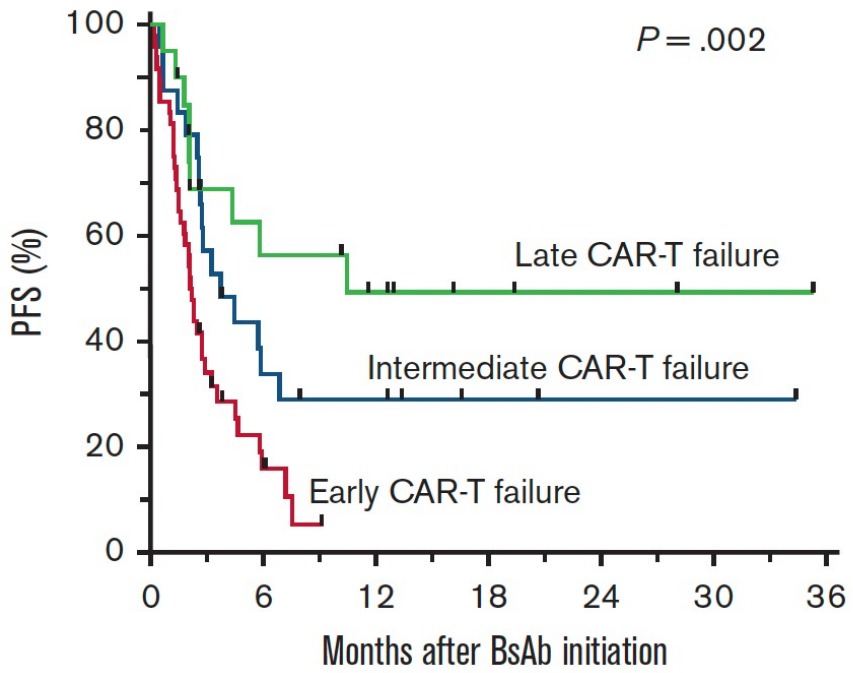


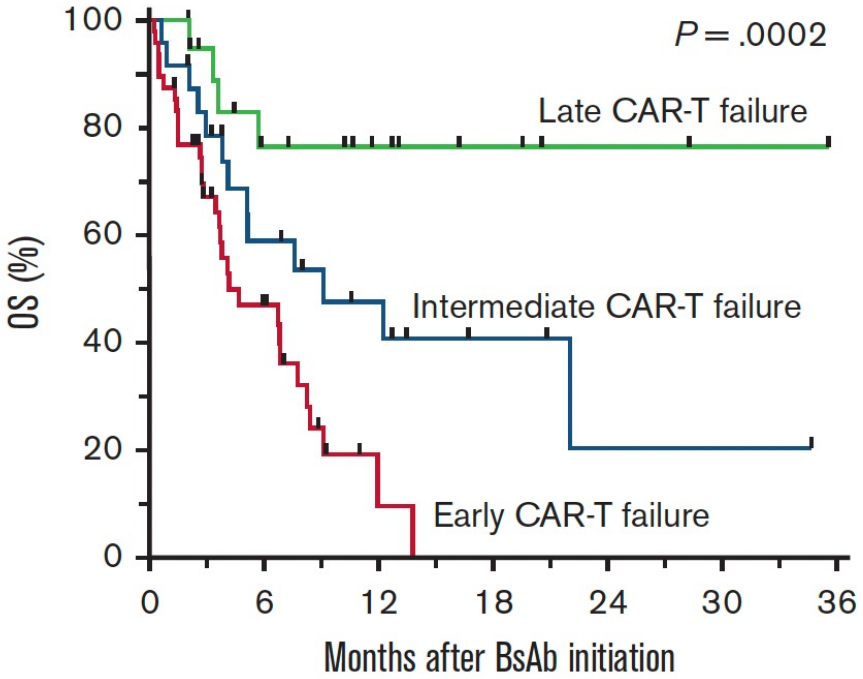
	Trial	N patients	N patients after CAR-T	Outcome
Glofitamab[1]	NP30179	154	51 (33%)	**35% CRR**
Epcoritamab[2]	EPCORE NHL-1	128	61 (39%)	**36% CRR**
Odronextamab[3]	ELM-1	85 (LBCL)	35 (41%)	**27% CRR**

Topp et al. Blood 2024; Cartron et al. Nat Cancer 2025; Dickinson et al, NEJM 2022; Thieblemont et al. Leukemia 2024; Bannerji et al. Lanct Haematol 2022

Outcome of BiABs after CAR-T failure in R/R LBCL







ORR 43% (CR 22%)
PFS = 2.8 months

Shumilov et al. Blood Adv 2025

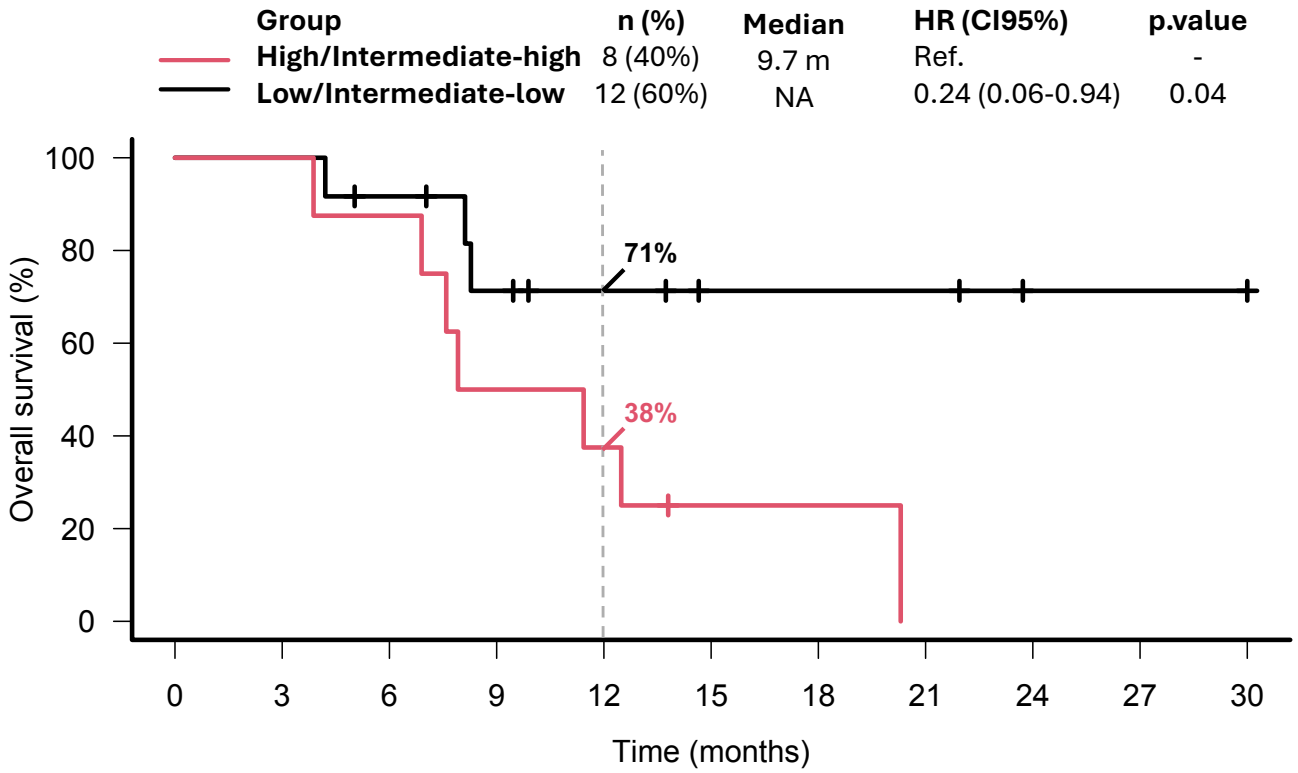
Outcome of BiABs after CAR-T failure in R/R LBCL

CAR-T BiABs

PC-PI score

Table 2 Multivariate modeling in the training cohort

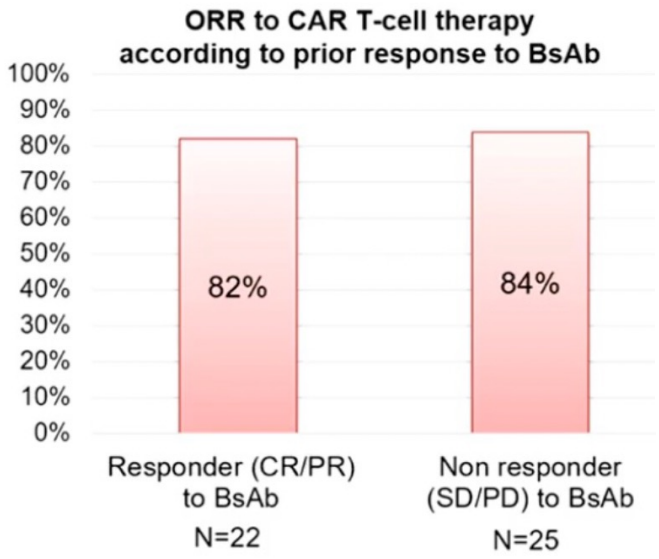
Variable	1 point	% pts	HR	95% CI	*p*
ECOG	≥ 1	76	1.77	1.11–2.81	0.02
LDH (x ULN)	≥ 2	30	1.56	1.10–2.22	0.01
Hemoglobin (g/dL)	< 10	45	1.48	1.03–2.13	0.03
Number extranodal sites	≥ 2	43	1.54	1.09–2.19	0.02
Months from CAR-T to PD	< 4	81	1.71	0.97–3.00	0.06



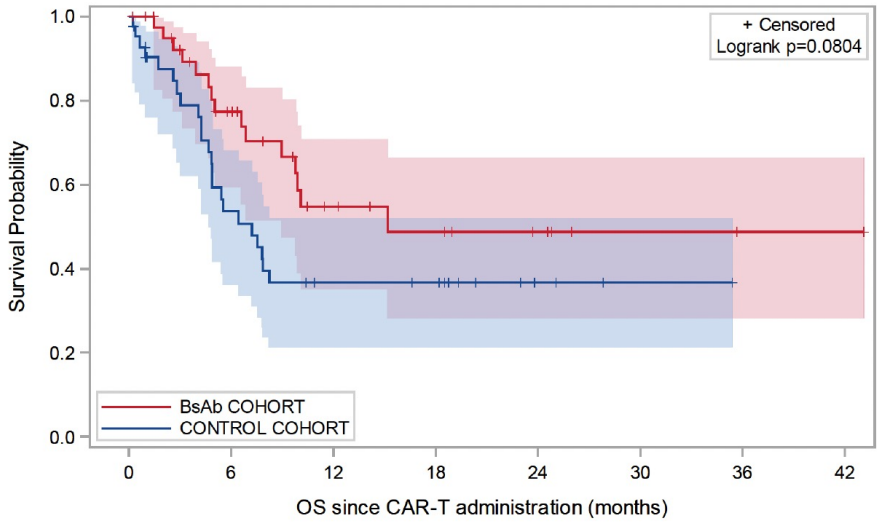
Iacoboni et al., J Hematol Oncol 2024,
Farina et al. Accepted for pubblication, J Hematol Oncol 2025

CAR T cell Therapy remained effective after BiABs

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



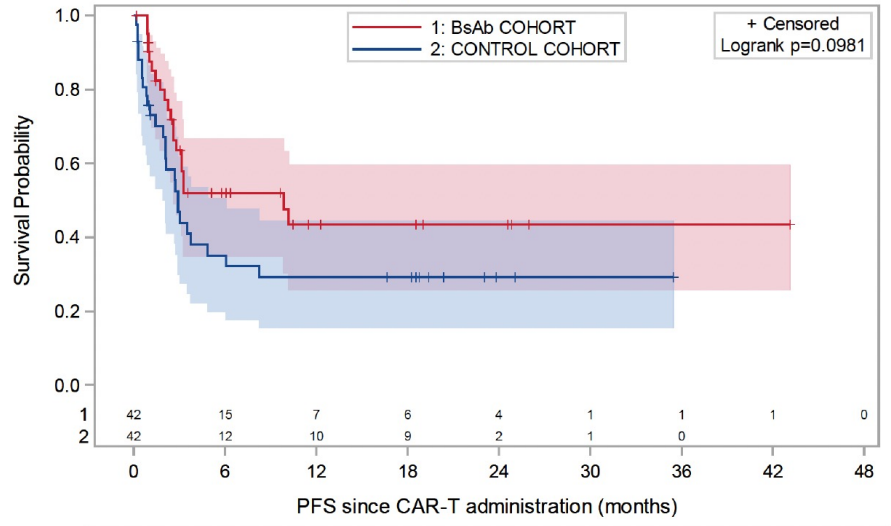
OS



	No. of Subjects	Event	Censored	Median Survival (95%CL)
BsAb COHORT	42	35.7 % (15)	64.3 % (27)	15.2 (9 ; NA)
CONTROL COHORT	42	54.8 % (23)	45.2 % (19)	7.2 (4.9 ; NA)

BiABs cohort: 1-year OS 55%
Control cohort: 1-year OS 37%

PFS



	No. of Subjects	Event	Censored	Median Survival (95%CL)
BsAb COHORT	42	47.6 % (20)	52.4 % (22)	9.9 (2.6 ; NA)
CONTROL COHORT	42	61.9 % (26)	38.1 % (16)	2.9 (2.1 ; 6)

BiABs cohort: 1-year PFS 43%
Control cohort: 1-year PFS 29%

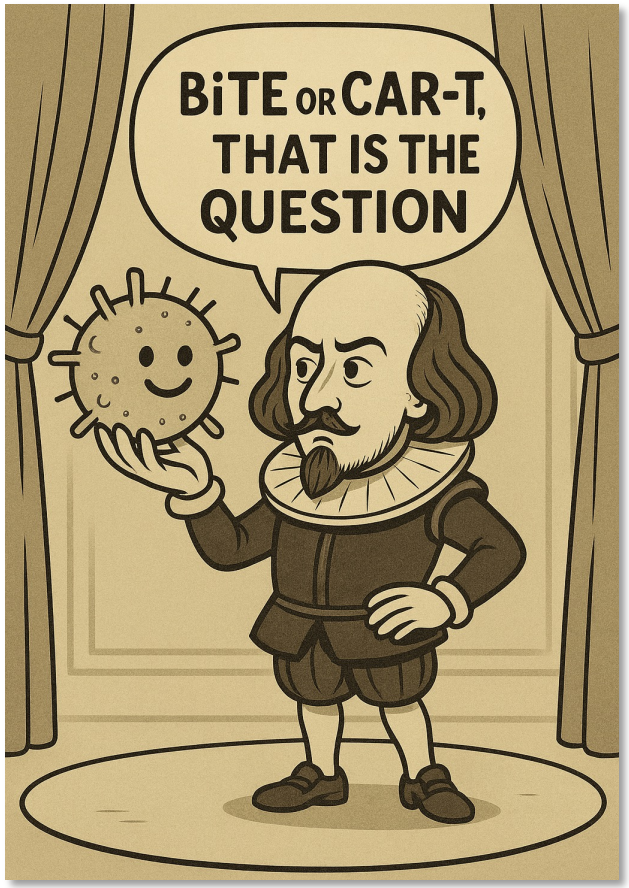
Crochet G et al. Blood 2024

Sequencing BiABs & CAR-T: key questions on clinical relevance

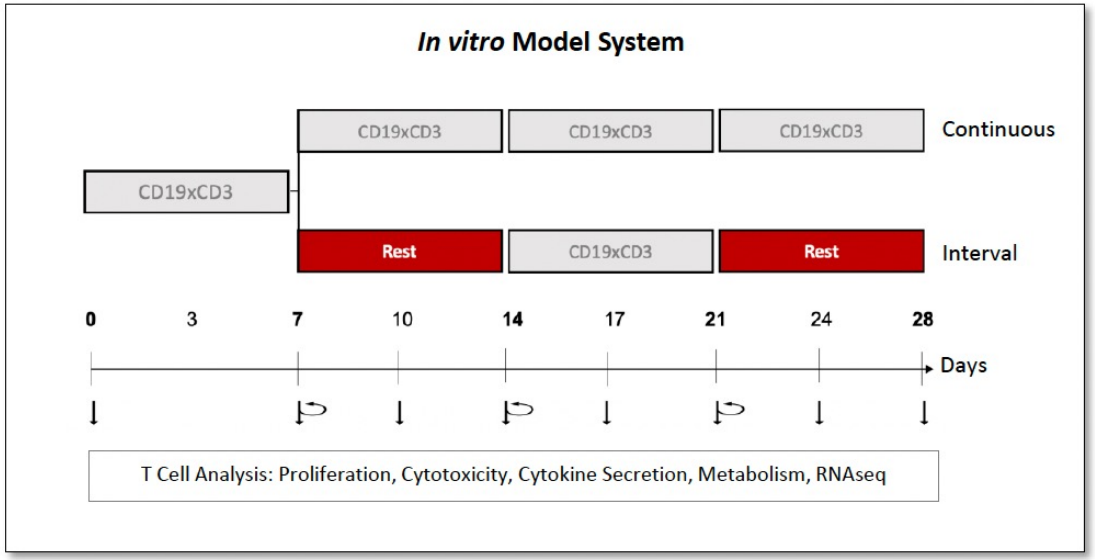
T cell exhaustion:
continous bispecific exposure can lead to T cell exhaustion
→ compromising CART efficacy?

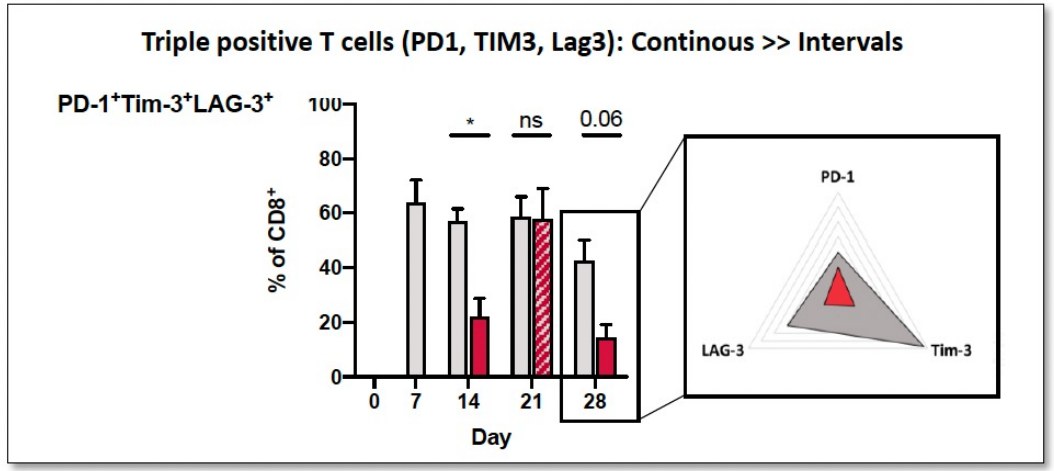
Loss of Target Antigen
Antigen Escape and/or selection of pre-existing Antigen negative/dim cells:
- **CD19 (CAR-T: Axi-cel, Liso-cel, Tisa-cel; Tafasitamab)**
- **CD20 (BiABs: Glofitamab, Epcoritmab)**

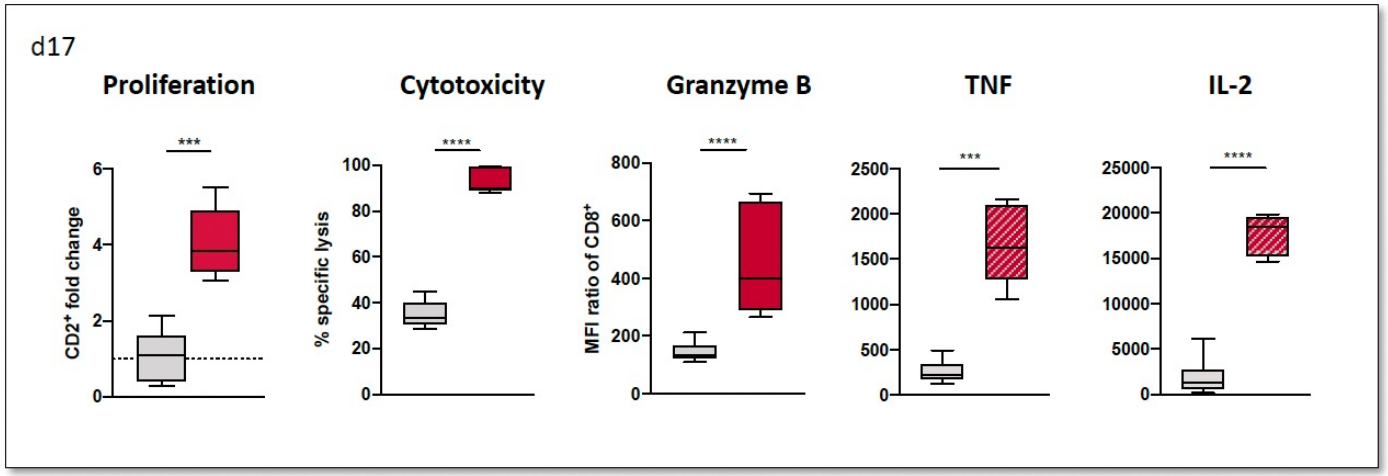
Size of disease
- Need urgent treatment/patient can wait

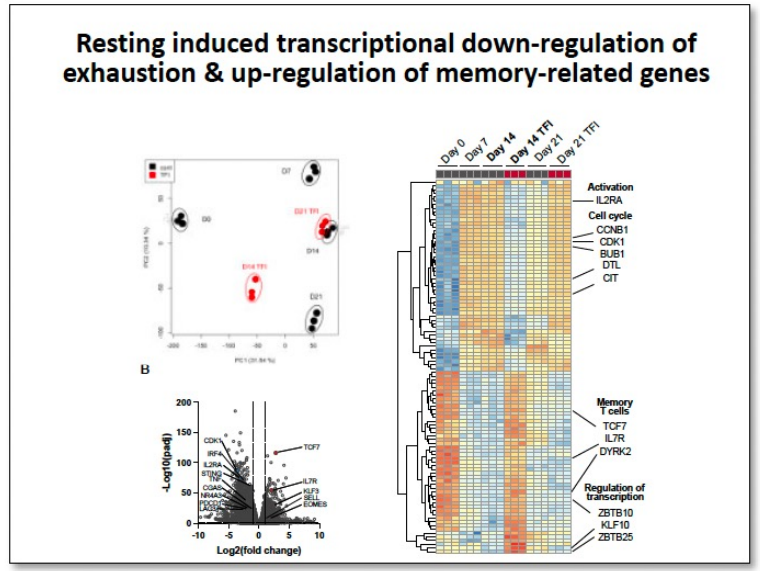


Continous CD19 BiABs exposure induced T cell exhaustion Reversed by Resting



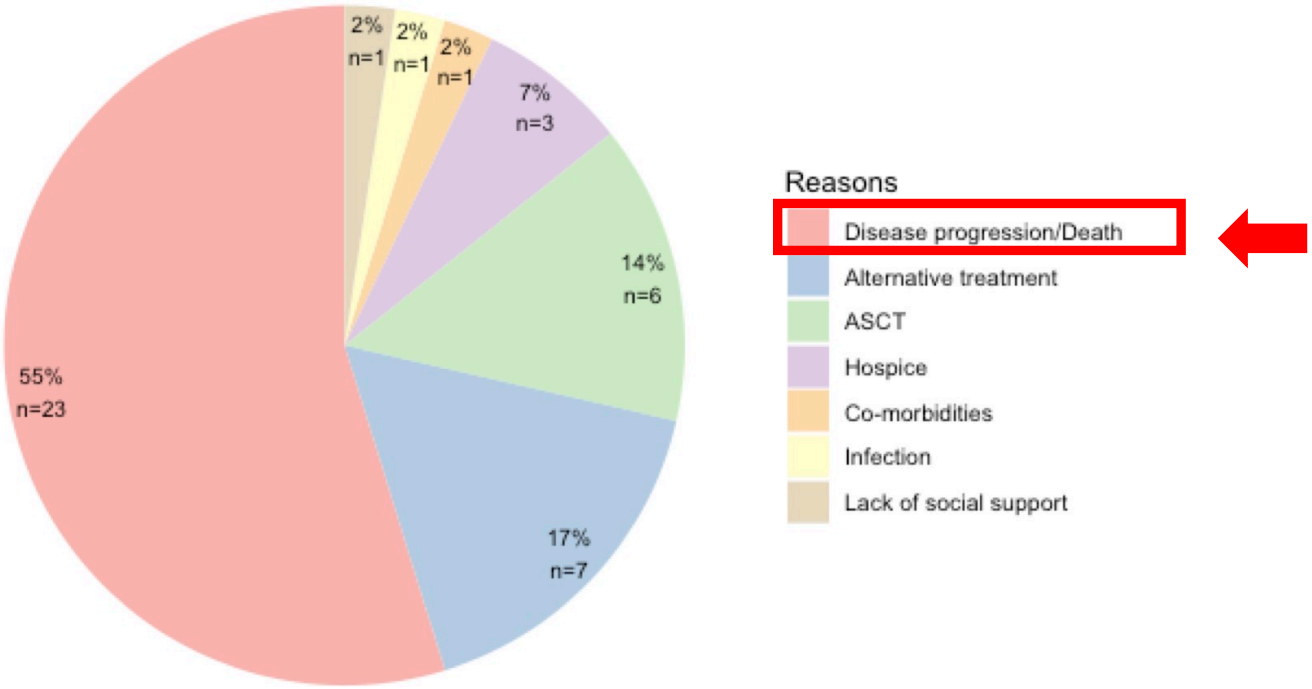






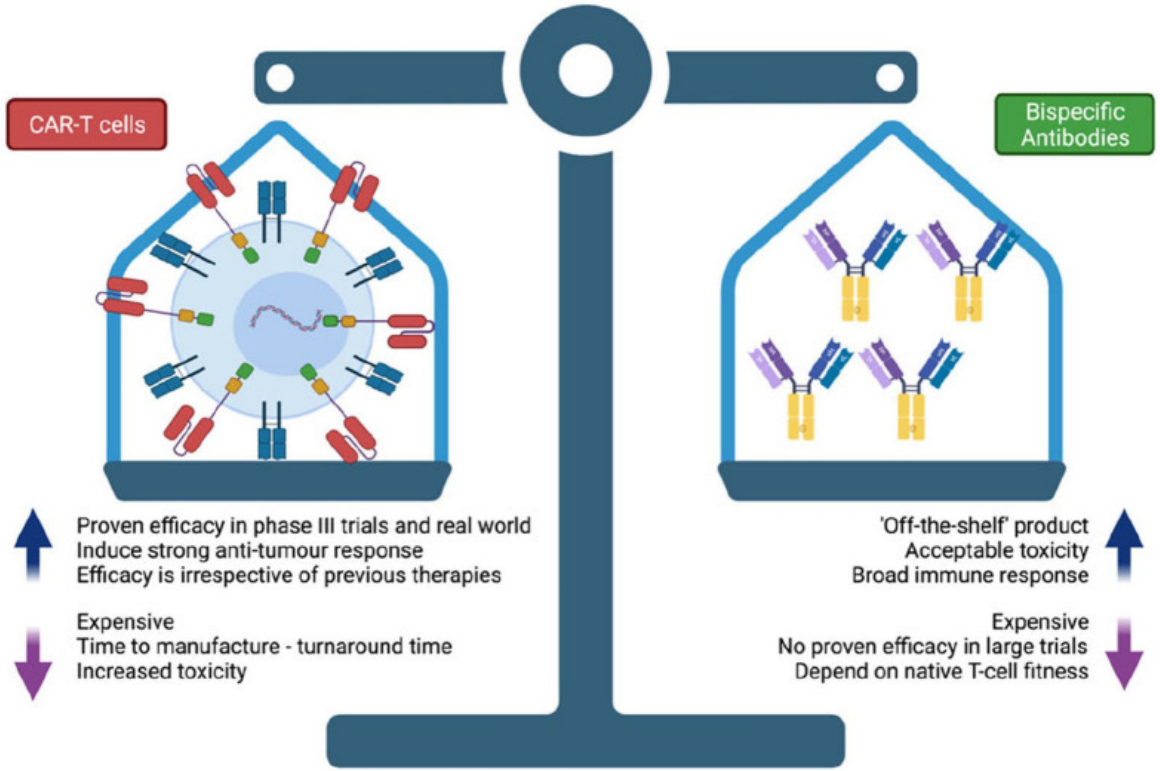
Philipp et al, Blood 2022

Why CAR-T Was Not Given in Second Line



Wuliji et al., Transpl & Cell Therapy 2024

CAR-T vs. BiABs



CAR T-cells	Bispecific Antibodies
Excellent efficacy	Excellent efficacy
Manufacturing process (3-4 weeks)	Available off-the-shelf
Usually inpatient, followed by period of time proximal to administering center for monitoring	Usually outpatient, initially with weekly visits that ultimately space out depending on product
"One and done"	Months (fixed duration) or continuous treatment
Requires lymphodepleting chemotherapy +/– bridging	No lymphodepleting chemotherapy or bridging
Higher risk of, and less predictable, CRS and NT	Less risk of, and more predictable, CRS and NT
Infections and cytopenias are common; likely higher rates and more prolonged	Infections and cytopenias are common; potentially lower rates but more follow up needed
Durable responses with years of follow up	Longer follow up needed for response durability

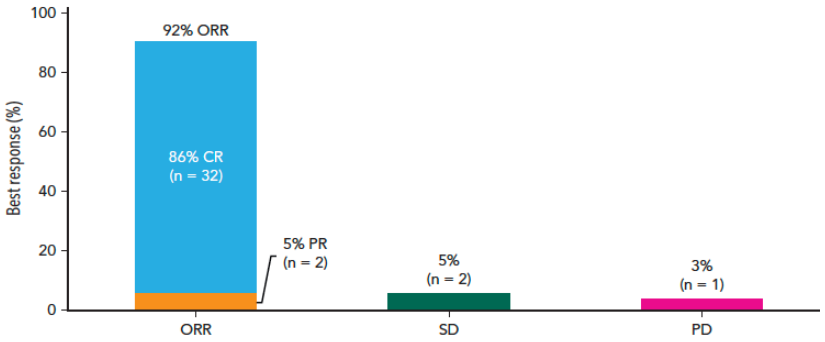
Haydu and Abramson, Blood Adv 2024

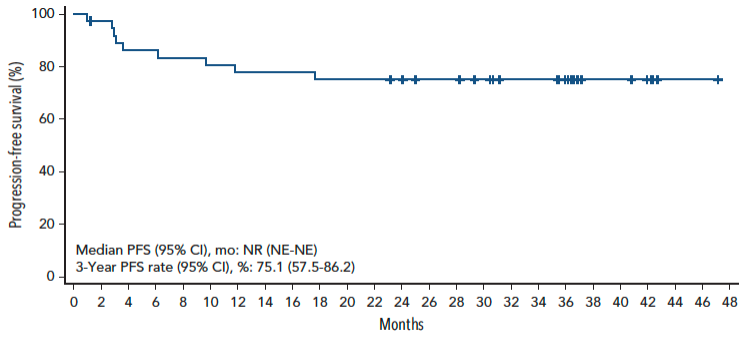
This is what we know so far – but the story is still unfolding

CAR-T & BiABs are moving up the line…

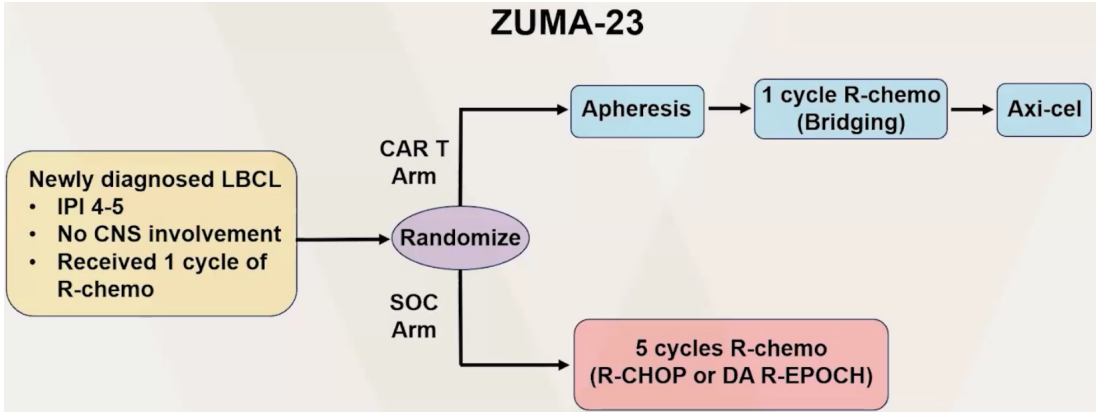
ZUMA12

IPI 3-5 or DH/TH
iPET with DS 4 or 5

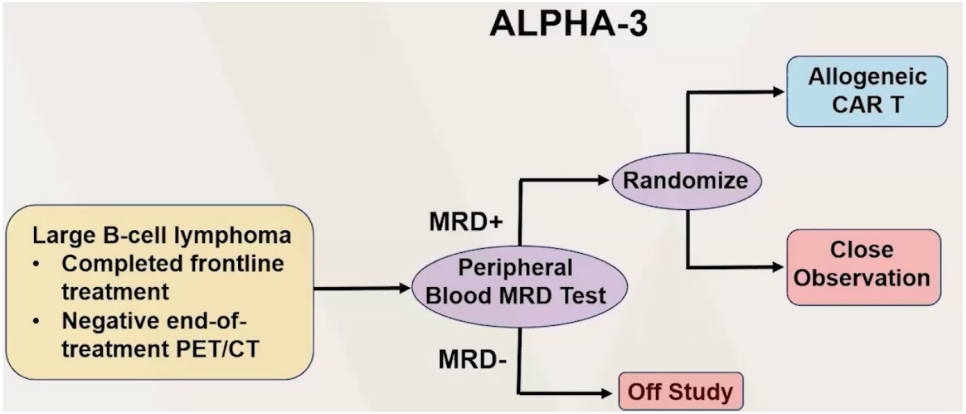




CAR-T in 1st line



Allogeneic CAR-T as consolidation Therapy



Neelapu et al. Nat Med 2022, Chavez JC Blood 2025

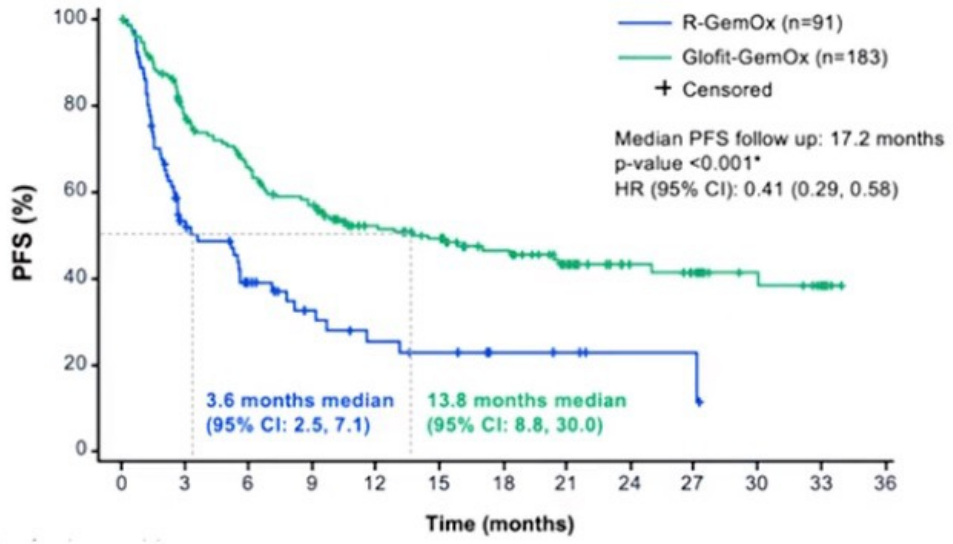
BiABs Development in DLBCL

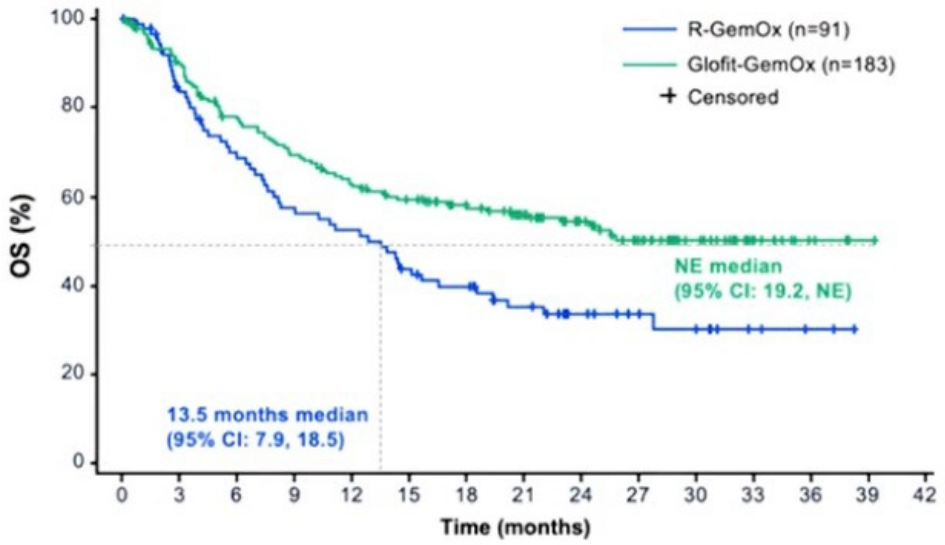
	Epcoritamab	Glofitamab	Odronextamab
1L	**Ph3 EPCORE-DLBCL-2**[1] Epcor + R-CHOP vs R-CHOP **Ph2 EPCORE-DLBCL-3**[2] Epcor +/- Len (frail/unfit) **Ph 2 NHL-2**[3] **and NHL-5**[4] Epcor + (R-CHOP, R-mini-CHOP, Pola-R-CHP)	**Ph3 SKYGLO**[7] Glofit + Pola-R-CHP vs Pola-R-CHP **Ph 2 GO43075**[8] Glofit + R-CHOP (high-risk) **Ph 1 NP40126**[9] Glofit + (R-CHOP, Pola-R-CHP)	**Ph 3 OLYMPIA-3**[17] Odro + CHOP vs R-CHOP
2L	**Ph3 EPCORE DLBCL-1**[5] Epcor monotherapy **Ph3 EPCORE DLBCL-4**[6] Epcor + Len **Ph 2 NHL-2**[3] **and NHL-5**[4] Epcor + (R-DHAX/C, GemOx, R-ICE, Len, Ibr-Len, golcadomide)	**Ph3 STARGLO**[10] Glofit + R-GemOx vs GemOx **Ph 1/2 NP39488**[11] Glofit + Pola Glofit + Atezolizumab **Ph 1 BP41072**[12] Glofit + Englumafusp alfa	**Ph3 OLYMPIA-4**[18] Odro monotherapy **Ph 1 CLIO-1**[19] Odro + cemiplimab **Ph 1 ATHENA-1**[20] Odro + REGN5837
3L			

1. NCT05578976 2. NCT05660967. 3. NCT04663347. 4. NCT05283720. 5. NCT04628494. 6. epcore-trials.com/dibcl-4/ 7. NCT06047080 8. NCT04980222. 9. NCT03467373. .10. NCT04408638 11. NCT03533283. 12. NCT04077723. 13 NCT03677154. 14. NCT05171647. 15. NCT05207670 16. NCT03671018. 17. NCT06091865 18. NCT06230224. 19. NCT02651662. 20. NCT05685173

STARGLO: randomized Ph3 trial in transplant-ineligible R/R DLBCL pts

Glofitamab + Chemo in 2L





Outcome	R-GemOx	Glofit-GemOx
PFS, median mo	**3.6**	**13.8**
18-month PFS	**23%**	**47%**

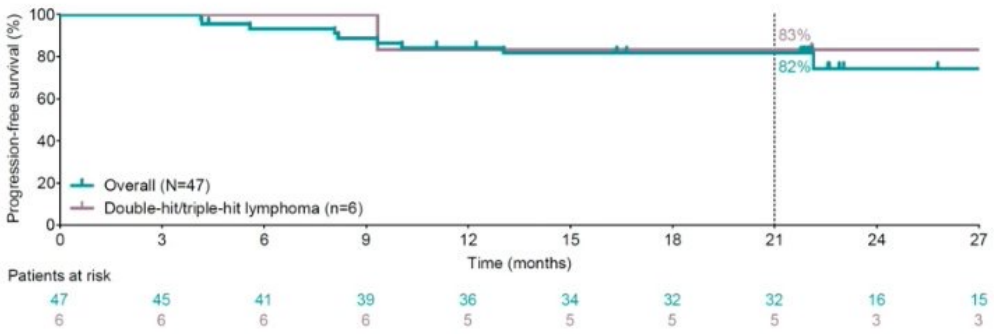
Outcome	R-GemOx	Glofit-GemOx
OS, median mo	**13.5**	**NR**
24-month OS	**34%**	**54%**

Abramson JS et al. ASCO Meeting 2025

BiABs + chemo in 1L LBCL

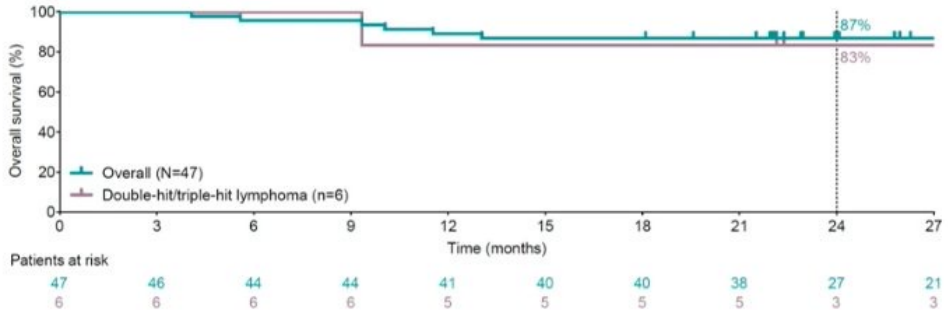
Epcortimab + Chemo in 1L
High risk (IPI 3-5) DLBCL

High Rates of Progression-Free Survival

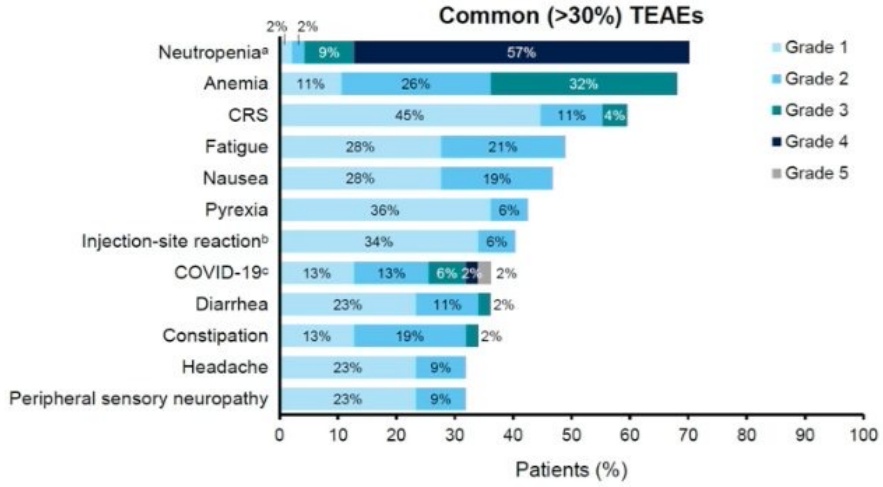


Median follow-up for PFS: 22.9 months. Kaplan–Meier estimated probability of remaining progression free.

Encouraging 2-Year Overall Survival



Manageable Safety Profile

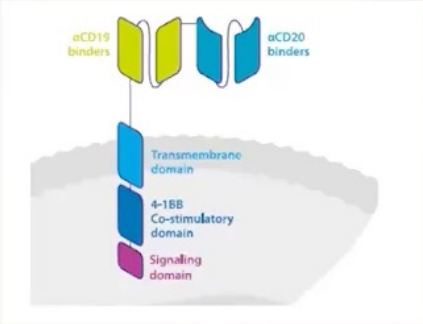


- 8 pts (18%) experienced severe infectious including 4(9%) COVID
- Neutropenia was observed in only 4 pts (9%)
- 8 pts (18%) discontinued Epcoritimab for severe TEAEs
- 5 pts had a fatal TEASs (2 COVID)

Falchi er al. ASH 2024, oral presentation (Abs #581)

CD19/CD20 Dual Targeting

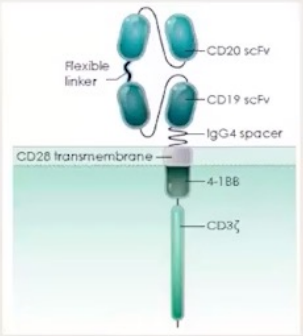
Zamtocabtagene autoleucel



- Tandem CD19/CD20 CAR
- Administered fresh, not cryopreserved

Shah et al. ASTCT 2023

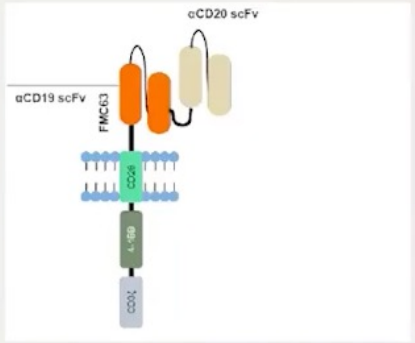
LYL314



- Tandem CD19/CD20 CAR
- Selection of CD62L+ cells prior to manufacturing

Larson et al. ASH 2024

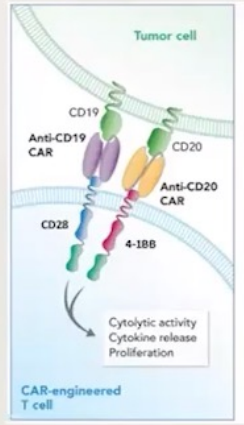
JNJ-4496



- Tandem CD19/CD20 CAR
- Anti-CD20 scFv recognizing noncontiguous regions on CD20

Patel et al. EHA 2025

KITE-363

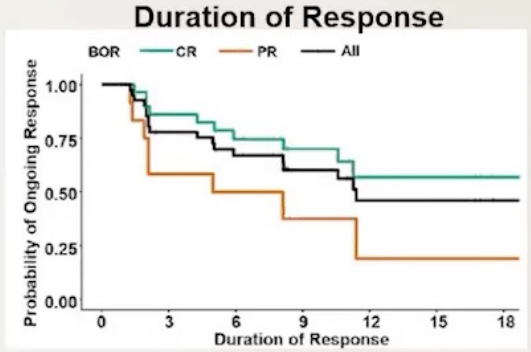


- Bicistronic CD19/CD20 CAR
- CD19 and CD20 CARs have distinct costimulatory domains

Dahiya et al. ASCO 2025

CD19/CD20 Dual Targeting

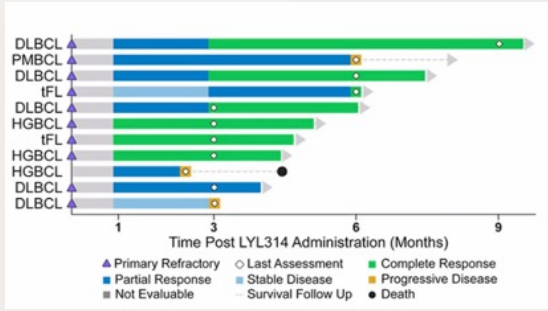
Zamtocabtagene autoleucel



ORR: 73%
CRR: 49%
12-month PFS: 42%
Grade ≥3 CRS: 0%
Grade ≥3 ICANS: 4%

Shah et al. ASTCT 2025

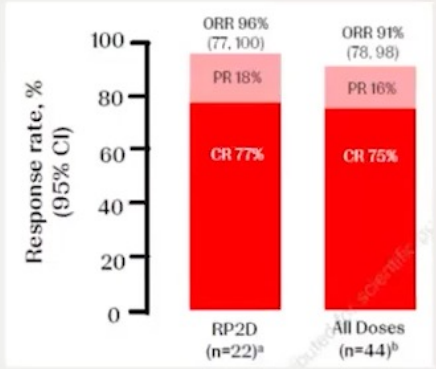
LYL314



ORR: 88% (3L+)
CRR: 72% (3L+)
Grade ≥3 CRS: 0%
Grade ≥3 ICANS: 14%

Merchant et al. ICML 2025

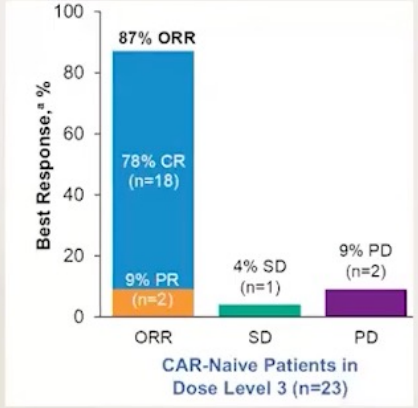
JNJ-4496



At RP2D:
ORR: 96%
CRR: 77%
Grade ≥3 CRS: 0%
Grade ≥3 ICANS: 4%

Patel et al. EHA 2025

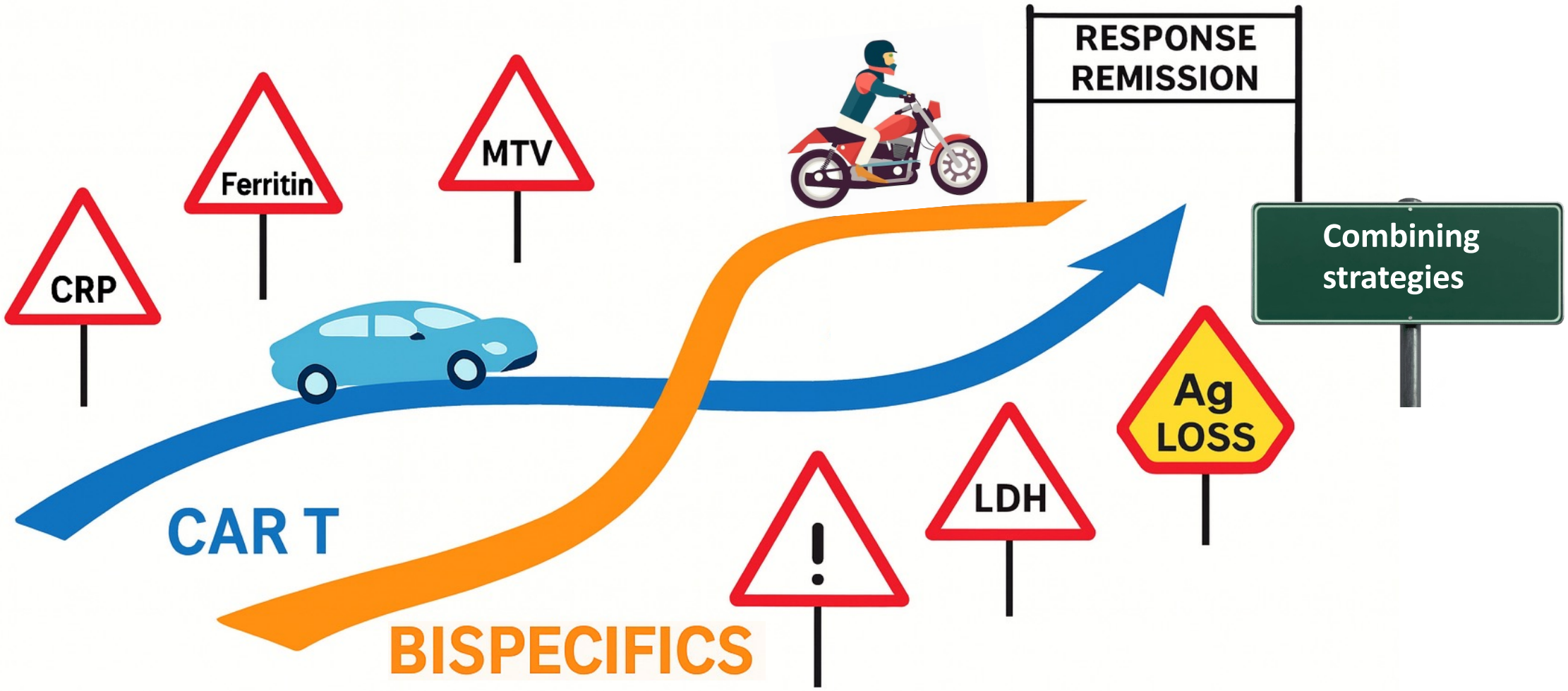
KITE-363



At DL3:
ORR: 87% (CAR-naïve)
CRR: 78% (CAR-naïve)
Grade ≥3 CRS: 4%
Grade ≥3 ICANS: 8%

Dahiya et al. ASCO 2025

The Road determines the Success of CAR-T cells & BiABs in LBCL



Take home messages

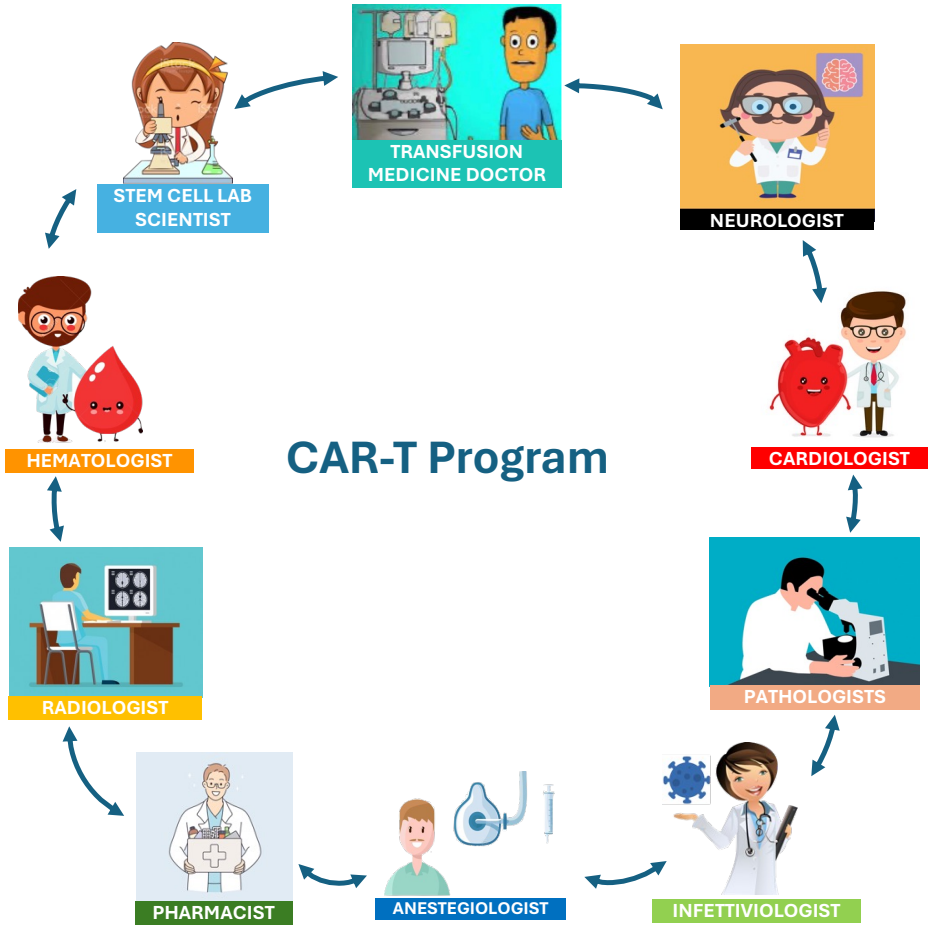
- **Current sequencing in LBCL is driven by approval status:** *CAR-T first, BiABs second*
  - *CAR-T cells: proven durable remissions in 3L and emerging benefit in 2L.*
  - *CD20 BiABs: good responses and acceptable safety, but limited long-term FU/RWE and infections emerging as a key concern.*

- Ongoing trials are evaluating CAR-T cells and BsABs in the first-line setting, with the **potential to significantly reshape the standard of care.**

- Evidence still insufficient to define optimal sequencing between CAR-T & BiABs.

- **Future view**: new CAR-T products, combined strategies, and patient-specific integrated pathways, with CAR-T and BiABs acting as complementary therapies.

Acknowledgments



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