Debate: Bispecific antibodies are a better therapeutic option than CAR-T therapies for early relapsing FL

Moderator: Professor Christian Buske

Pro: Professor Pier Luigi Zinzani | *Con*: Professor Wojciech Jurczak

CAR-T, chimeric antigen receptor T-cell; FL, follicular lymphoma.

Bispecific antibodies are a better therapeutic option than CAR-T therapies for early relapsing FL

Pro

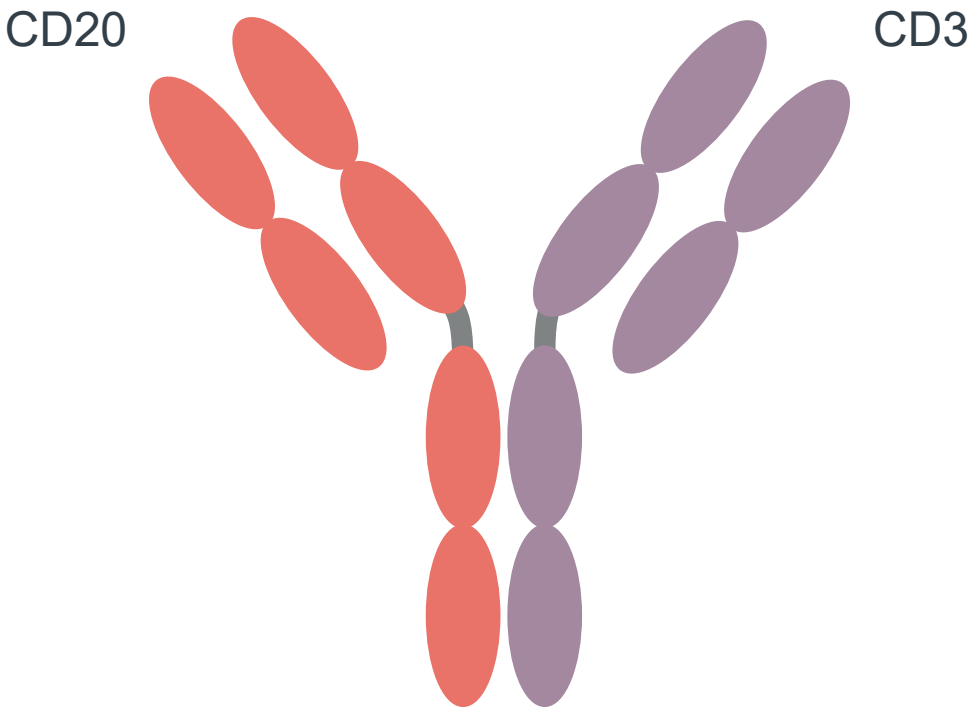
Professor Pier Luigi Zinzani
University of Bologna, Italy

CAR-T, chimeric antigen receptor T-cell; FL, follicular lymphoma.

Disclosures

Company name	Consultant	Speakers bureau	Advisory board
Verastem Oncology	X	X	X
Celltrion Healthcare		X	X
Gilead Sciences		X	X
Janssen-Cilag		X	X
Bristol Myers Squibb		X	X
Servier		X	X
Sandoz			X
Merck Sharp & Dohme	X	X	X
TG Therapeutics		X	X
Takeda Pharmaceuticals		X	X
Roche		X	X
EUSA Pharma	X	X	X
Kyowa Kirin		X	X
Novartis	X	X	X
ADC Therapeutics			X
Incyte		X	X
BeiGene		X	X

Anti-CD20×CD3 bispecific mAbs have shown great activity across B-cell lymphomas[1]



Mosunetuzumab monotherapy is approved for the treatment of adult patients with R/R FL who have received ≥2 prior lines of systemic therapy[2–4]

Response rates observed with mosunetuzumab in patients with R/R FL:[2]
ORR: 80%
CR: 60%

CD, cluster of differentiation; CR, complete response; FL, follicular lymphoma; mAb, monoclonal antibody; ORR, objective response rate; R/R, relapsed/refractory.

1. Falchi L *et al*. *Blood* 2023; 141 (5): 467–480. 2. Budde LE *et al*. *Lancet Oncol* 2022; 23 (8): 1055–1065. 3. FDA grants accelerated approval to mosunetuzumab-axgb for relapsed or refractory follicular lymphoma. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mosunetuzumab-axgb-relapsed-or-refractory-follicular-lymphoma. Accessed February 2024.
4. Roche Registration GmbH. Lunsumio – summary of product characteristics; November 2023.

Bispecific mAbs are ‘off-the-shelf’ drugs[1]

Bispecific mAbs can be administered to the patient as soon as the treatment decision is made[1]

Patients who are treated with CAR-T therapy have to wait for its manufacture and may require bridging therapy prior to treatment[1–3]

CAR-T, chimeric antigen receptor T-cell; mAb, monoclonal antibody.

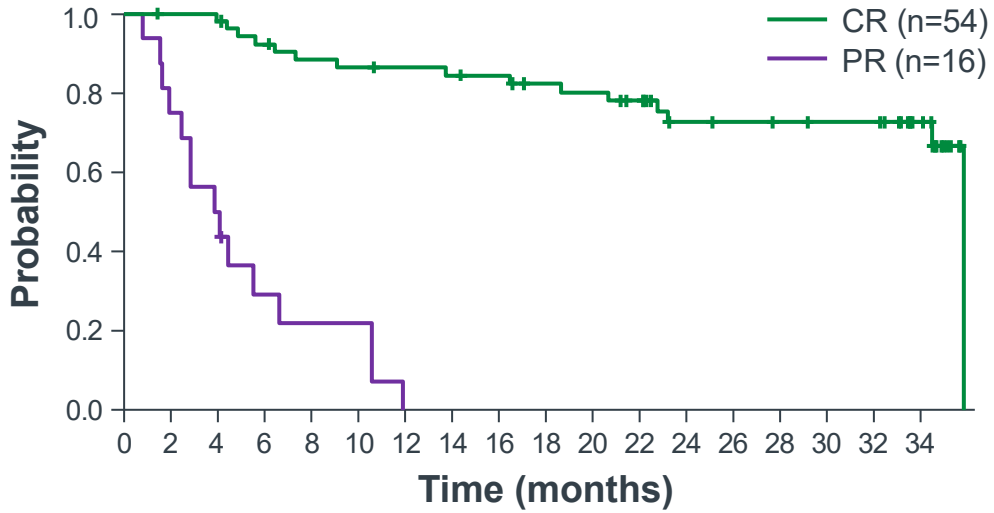
1. Patel A *et al*. *Br J Haematol* 2021; 195 (5): 689–697. 2. Jacobson CA *et al*. *Lancet Oncol* 2022; 23 (1): 91–103. 3. Fowler NH *et al*. *Nat Med* 2022; 28 (2): 325–332.

With bispecific mAbs, CRs are common and may be durable for years beyond discontinuation of treatment

Mosunetuzumab monotherapy: Durability of responses

- R/R FL
- ≥2 prior lines of therapy

DoR for CR vs. PR (May 2023 data cut-off)



Patients at risk

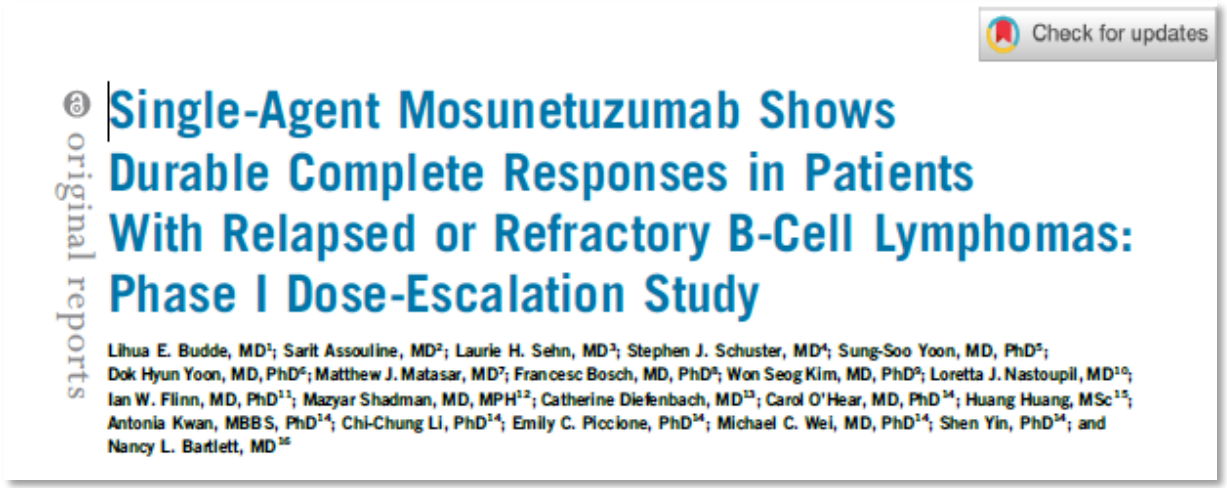
CR	54	53	52	48	45	44	43	42	41	38	37	34	26	25	24	23	23	15
PR	16	12	8	4	3	3	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Median (95% CI) DoR in patients with CR (n=54*), months	36 (NE–NE)
Median (95% CI) DoR in patients with PR (n=16*), months	4 (2.5–6.7)

73% (95% CI: 60.8–86.8) of patients who achieved CR were estimated to be alive and progression-free 30 months after their first response

Fixed-duration treatment with mosunetuzumab: 8 cycles if CR was observed after Cycle 8 and 17 cycles if PR/SD was observed after Cycle 8. *Responders per INV assessment.
CI, confidence interval; CR, complete response; DoR, duration of response; FL, follicular lymphoma; INV, investigator; mAb, monoclonal antibody; NE, not estimable; PR, partial response; R/R, relapsed/refractory; SD, stable disease.
Schuster SJ *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 603).

Bispecific mAbs are effective in patients failing CAR-T therapy[1,2]



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Single-Agent Mosunetuzumab Shows Durable Complete Responses in Patients With Relapsed or Refractory B-Cell Lymphomas: Phase I Dose-Escalation Study

Lihua E. Budde, MD[1]; Sarit Assouline, MD[2]; Laurie H. Sehn, MD[3]; Stephen J. Schuster, MD[4]; Sung-Soo Yoon, MD, PhD[5]; Dok Hyun Yoon, MD, PhD[6]; Matthew J. Matasar, MD[7]; Francesc Bosch, MD, PhD[8]; Won Seog Kim, MD, PhD[9]; Loretta J. Nastoupil, MD[10]; Ian W. Flinn, MD, PhD[11]; Mazyar Shadman, MD, MPH[12]; Catherine Diefenbach, MD[13]; Carol O'Hear, MD, PhD[14]; Huang Huang, MSc[15]; Antonia Kwan, MBBS, PhD[14]; Chi-Chung Li, PhD[14]; Emily C. Piccione, PhD[14]; Michael C. Wei, MD, PhD[14]; Shen Yin, PhD[14]; and Nancy L. Bartlett, MD[16]

Mosunetuzumab has led to CRs in patients with R/R B-NHL who have received prior CAR-T therapy[1,2]

B-NHL, B-cell non-Hodgkin lymphoma; CAR-T, chimeric antigen receptor T-cell; CR, complete response; mAb, monoclonal antibody; R/R, relapsed/refractory.

1. Schuster SJ *et al*. *Blood* 2019; 134 (Suppl 1): 6. 2. Budde LE *et al*. *J Clin Oncol* 2022; 40 (5): 481–491.

Serious CRS events are less common with bispecific mAbs than with CAR-T therapies, and high-grade ICANS is almost never seen

	CRS, %		Neurologic AEs, %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Mosun[1]	44	2	6	0
Axi-cel[2]	78	6*	56	15
Tisa-cel[3]	49	0	37	3†

This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

*One Grade 5 event occurred. †Three Grade 3 and one Grade 4 event occurred.

AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; mAb, monoclonal antibody; mosun, mosunetuzumab; tisa-cel, tisagenlecleucel.

1. Budde LE *et al*. *Lancet Oncol* 2022; 23 (8): 1055–1065. 2. Jacobson CA *et al*. *Lancet Oncol* 2022; 23 (1): 91–103. 3. Fowler NH *et al*. *Nat Med* 2022; 28 (2): 325–332.

The MoA and toxicity profile of bispecific mAbs make them ideal combination partners[1]

- Ongoing trials in patients with R/R FL:[1]

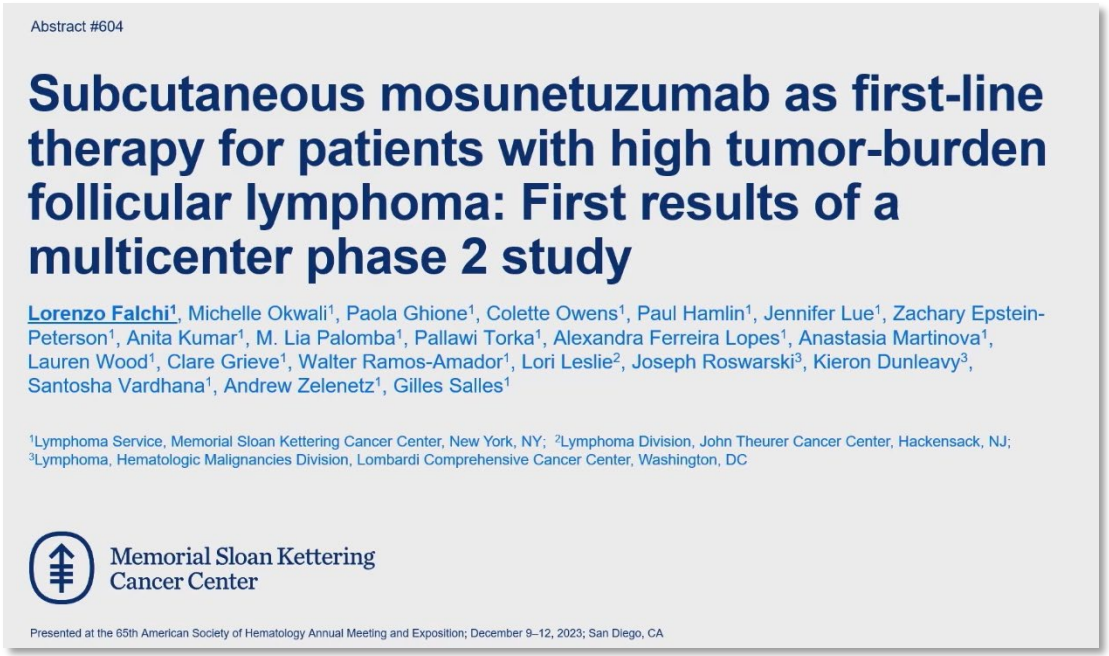
Mosunetuzumab plus lenalidomide
- NCT04246086
- Phase Ib study

Epcoritamab plus R²
- NCT04663347
- Phase Ib/II study

Glofitamab plus obinutuzumab
- NCT03075696
- Phase I/II study

Glofitamab plus R-CHOP
- NCT03467373
- Phase Ib study

Bispecific mAbs are also being investigated in 1L FL[2]



Abstract #604

Subcutaneous mosunetuzumab as first-line therapy for patients with high tumor-burden follicular lymphoma: First results of a multicenter phase 2 study

Lorenzo Falchi[1], Michelle Okwali[1], Paola Ghione[1], Colette Owens[1], Paul Hamlin[1], Jennifer Lue[1], Zachary Epstein-Peterson[1], Anita Kumar[1], M. Lia Palomba[1], Pallawi Torka[1], Alexandra Ferreira Lopes[1], Anastasia Martinova[1], Lauren Wood[1], Clare Grieve[1], Walter Ramos-Amador[1], Lori Leslie[2], Joseph Roswarski[3], Kieron Dunleavy[3], Santosha Vardhana[1], Andrew Zelenetz[1], Gilles Salles[1]

[1]Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Lymphoma Division, John Theurer Cancer Center, Hackensack, NJ; [3]Lymphoma, Hematologic Malignancies Division, Lombardi Comprehensive Cancer Center, Washington, DC

Memorial Sloan Kettering Cancer Center

Presented at the 65th American Society of Hematology Annual Meeting and Exposition; December 9–12, 2023; San Diego, CA

1L, first-line; FL, follicular lymphoma; mAb, monoclonal antibody; MoA, mechanism of action; R², rituximab plus lenalidomide; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristin, prednisone; R/R, relapsed/refractory.

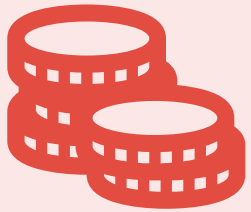
1. Falchi L *et al*. *Blood* 2023; 141 (5): 467–480. 2. Falchi L *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 604).

Why should bispecific mAbs be the 3L treatment for FL?

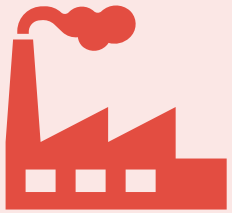
- Anti-CD20×CD3 bispecific mAbs have shown great activity across B-cell lymphomas
- They are ‘off-the-shelf’ drugs
- CRs are common and durable for years beyond discontinuation of treatment
- Bispecific mAbs are effective in patients failing CAR-T therapy
- Serious CRS and ICANS are less common with bispecific mAbs than with CAR-T therapy
- The MoA and toxicity profile of bispecific mAbs make them ideal combination partners

3L, third-line; CAR-T, chimeric antigen receptor T-cell; CD, cluster of differentiation; CR, complete response; CRS, cytokine release syndrome; FL, follicular lymphoma; ICANS, immune effector cell–associated neurotoxicity syndrome; mAb, monoclonal antibody; MoA, mechanism of action.
Slide courtesy of Pier Luigi Zinzani.

Finally, bispecific mAbs are a more sustainable option than CAR-T therapy



Reduced upfront costs



Fewer manufacturing delays

Usability in community practice

CAR-T, chimeric antigen receptor T-cell; mAb, monoclonal antibody.

Patel A *et al*. *Br J Haematol* 2021; 195 (5): 689–697.

Bispecific antibodies are a better therapeutic option than CAR-T therapies for early relapsing FL

Con

Professor Wojciech Jurczak
Maria Skłodowska-Curie National Research Institute of Oncology, Poland

CAR-T, chimeric antigen receptor T-cell; FL, follicular lymphoma.

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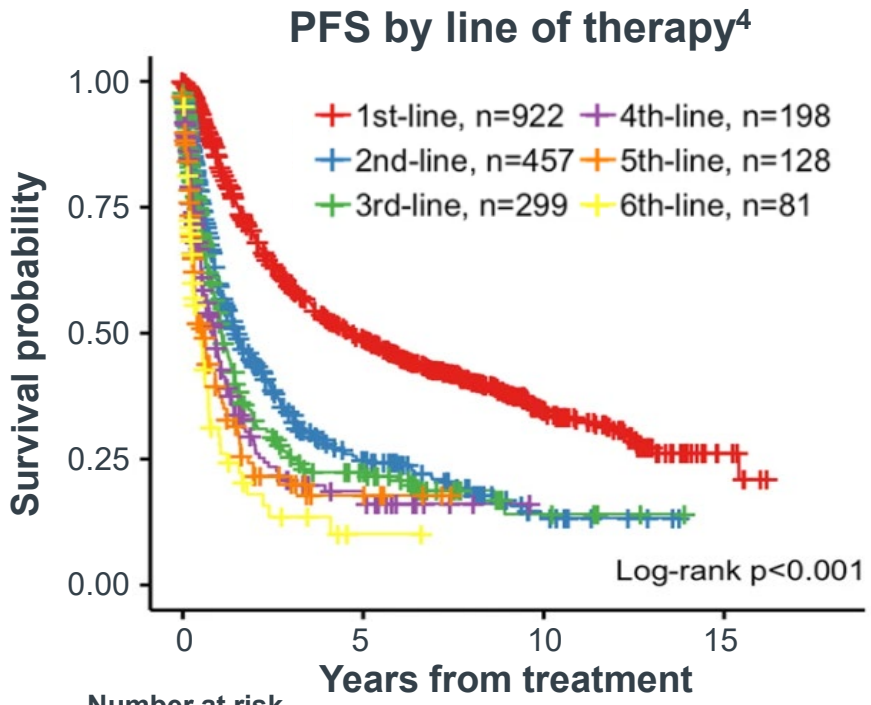
- **Research funding:** AbbVie, AstraZeneca, Bayer, BeiGene, Celgene, Celltrion, Debiopharm, Epizyme, Incyte, Janssen, Loxo Oncology, MEI Pharma, Merck, MorphoSys, Novo Nordisk, Roche, Sandoz, Takeda, TG Therapeutics

Challenges in R/R FL

- FL is a chronic, indolent, and incurable disease with frequent relapses[1–3]
- It is characterized by long survival, with R/R disease often requiring multiple lines of therapy[1–3]
- **Survival outcomes decrease with each line of therapy[4]**

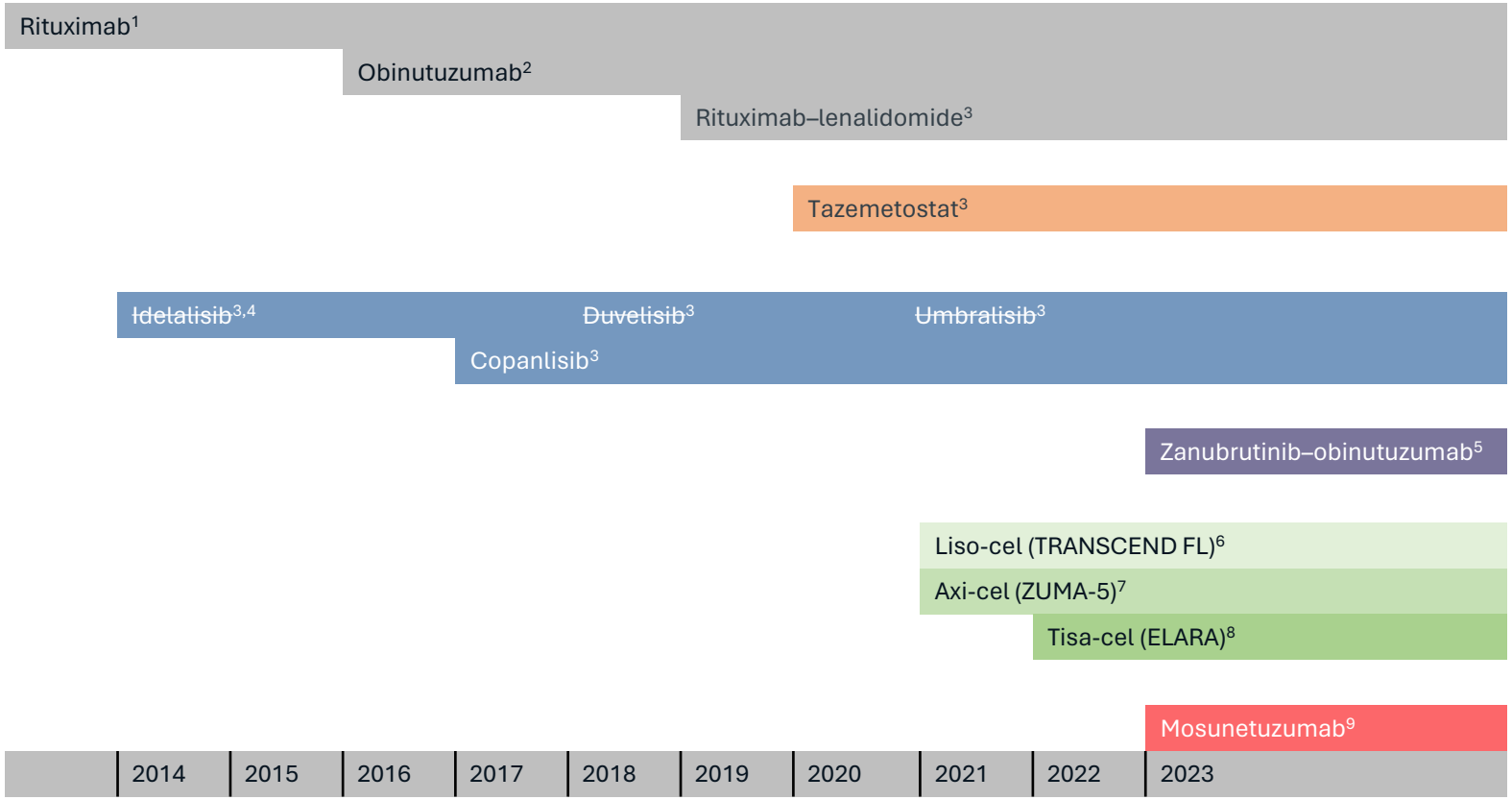
Multiple therapies are available for patients with R/R FL, but there is currently no universally defined treatment approach[3]



1L, first-line; 2L, second-line; 3L, third-line; 4L, fourth-line; 5L, fifth-line; 6L, sixth-line; FL, follicular lymphoma; PFS, progression-free survival; R/R, relapsed/refractory.

1. Skarbnik AZ *et al*. *Front Oncol* 2023; 13: 1120358. 2. Hanel W *et al*. *Hematol Oncol* 2021; 14 (1): 104. 3. Gupta G *et al*. *Am J Blood Res* 2022; 12 (4): 105–124. 4. Batlevi CL *et al*. *Blood Cancer J* 2020; 10 (7): 74.

Therapies approved in R/R FL



February 2021
The FDA approved liso-cel for adult patients with R/R LBCL after ≥2 lines of systemic therapy, including patients with Grade 3B FL[6]

March 2021
The FDA granted accelerated approval to axi-cel for adult patients with R/R FL after ≥2 lines of systemic therapy[7]

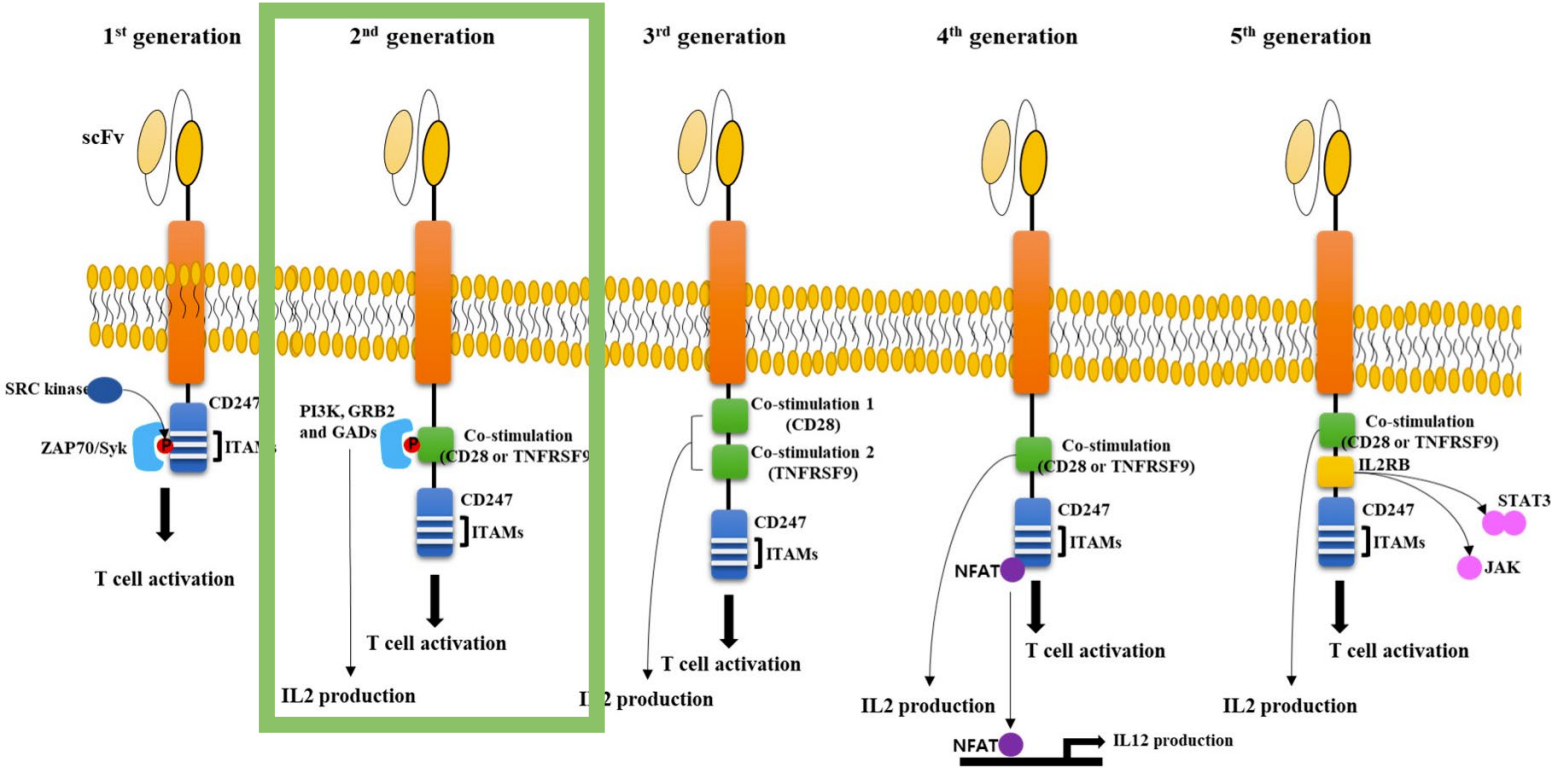
May 2022
The FDA approved tisa-cel for adult patients with R/R FL after ≥2 lines of systemic therapy[8]

axi-cel, axicabtagene ciloleucel; FDA, Food and Drug Administration; FL, follicular lymphoma; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; R/R, relapsed/refractory; tisa-cel, tisagenlecleucel.

1. Roche Registration GmbH. MabThera – summary of product characteristics; November 2023. 2. Obinutuzumab. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/obinutuzumab. 3. Lopedote P *et al*. *Cancer Manag Res* 2023; 15: 257–264. 4. FDA approves PI3K inhibitor, idelalisib for treatment of relapsed CLL, FL and SLL. Available at: https://www.esmo.org/oncology-news/archive/fda-approves-pi3k-inhibitor-idelalisib-for-treatment-of-relapsed-cll-follicular-lymphoma-and-sll. 5. CHMP post-authorisation summary of opinion for Brukinsa. Available at: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-positive-summary-opinion-brukinsa_en.pdf. 6. FDA approves lisocabtagene maraleucel for relapsed or refractory large B-cell lymphoma. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lisocabtagene-maraleucel-relapsed-or-refractory-large-b-cell-lymphoma. 7. FDA grants accelerated approval to axicabtagene ciloleucel for relapsed or refractory follicular lymphoma. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-axicabtagene-ciloleucel-relapsed-or-refractory-follicular-lymphoma. 8. FDA approves tisagenlecleucel for relapsed or refractory follicular lymphoma. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tisagenlecleucel-relapsed-or-refractory-follicular-lymphoma. 9. FDA grants accelerated approval to mosunetuzumab-axgb for relapsed or refractory follicular lymphoma. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mosunetuzumab-axgb-relapsed-or-refractory-follicular-lymphoma. All websites accessed February 2024.

CAR T cells have evolved, with each generation better armed than the last

Axi-cel
Liso-cel
Tisa-cel



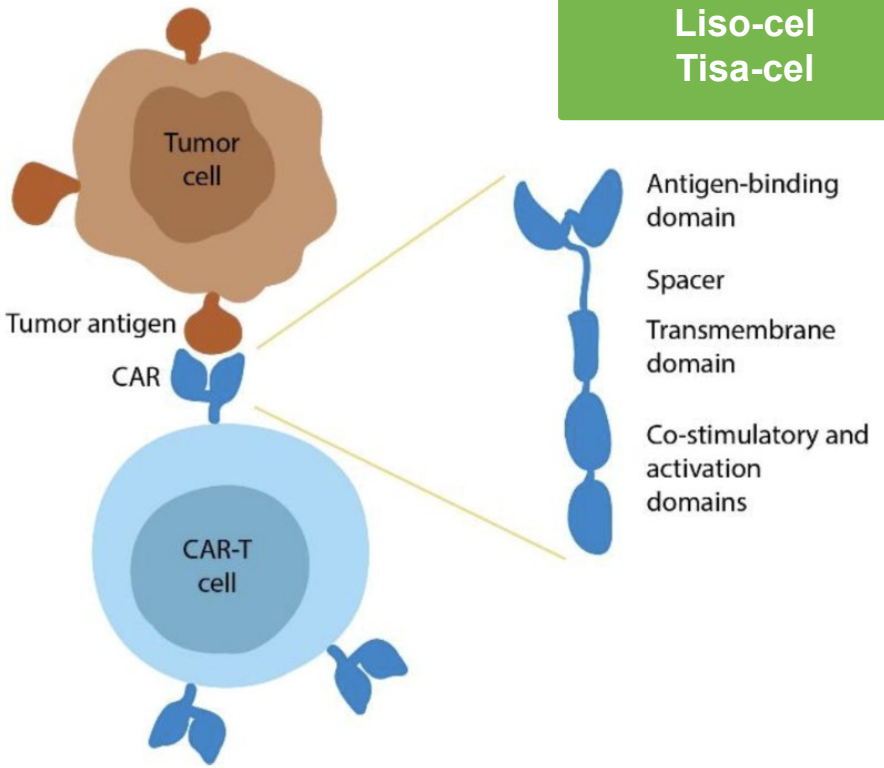
1st generation: CD247 ITAM domain
2nd and 3rd generation: CD247 ITAM domain + 1–2 co-stimulation domains
4th generation: CD247 ITAM domain + co-stimulation domains + genes enhancing IL-12 production
5th generation: TRUCK

axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CD, cluster of differentiation; ITAM, immunoreceptor tyrosine-based activation motif; liso-cel, lisocabtagene maraleucel; tisa-cel, tisagenlecleucel; TRUCK, T cell redirected for universal cytokine-mediated killing.
Kim DW *et al*. *Biomolecule*s 2020; 10 (2): 263.

Special ops vs. conscript army

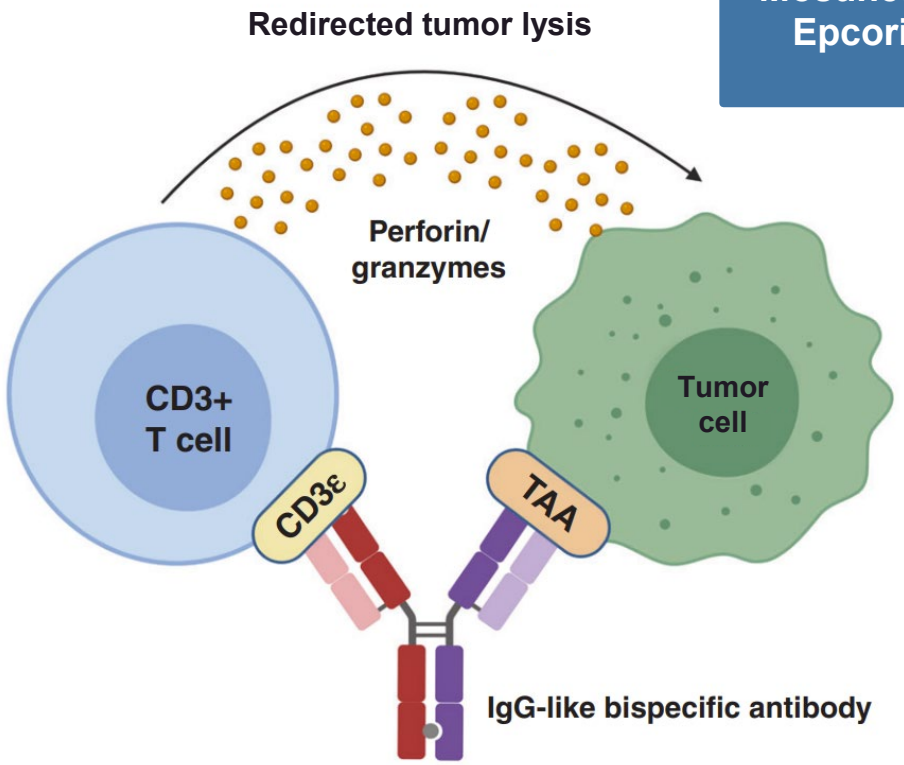
CAR T cell[1]

Axi-cel
Liso-cel
Tisa-cel



Bispecific mAb[2]

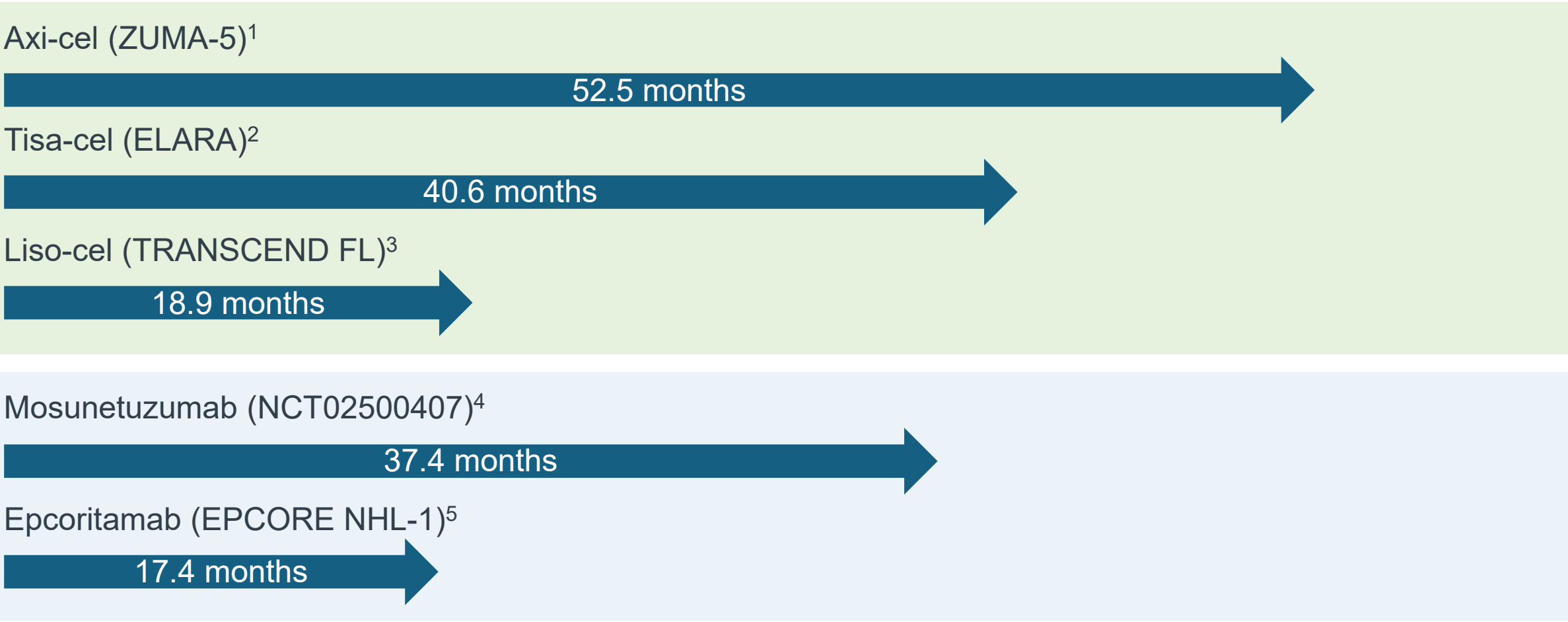
Mosunetuzumab
Epcoritamab



axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CD, cluster of differentiation; Ig, immunoglobulin; liso-cel, lisocabtagene maraleucel; mAb, monoclonal antibody; TAA, tumor-associated antigen; tisa-cel, tisagenlecleucel.

1. Titov A *et al*. *Cancers (Basel)* 2020; 12 (1): 125. 2. Singh A *et al*. *Br J Cancer* 2021; 124 (6): 1037–1048.

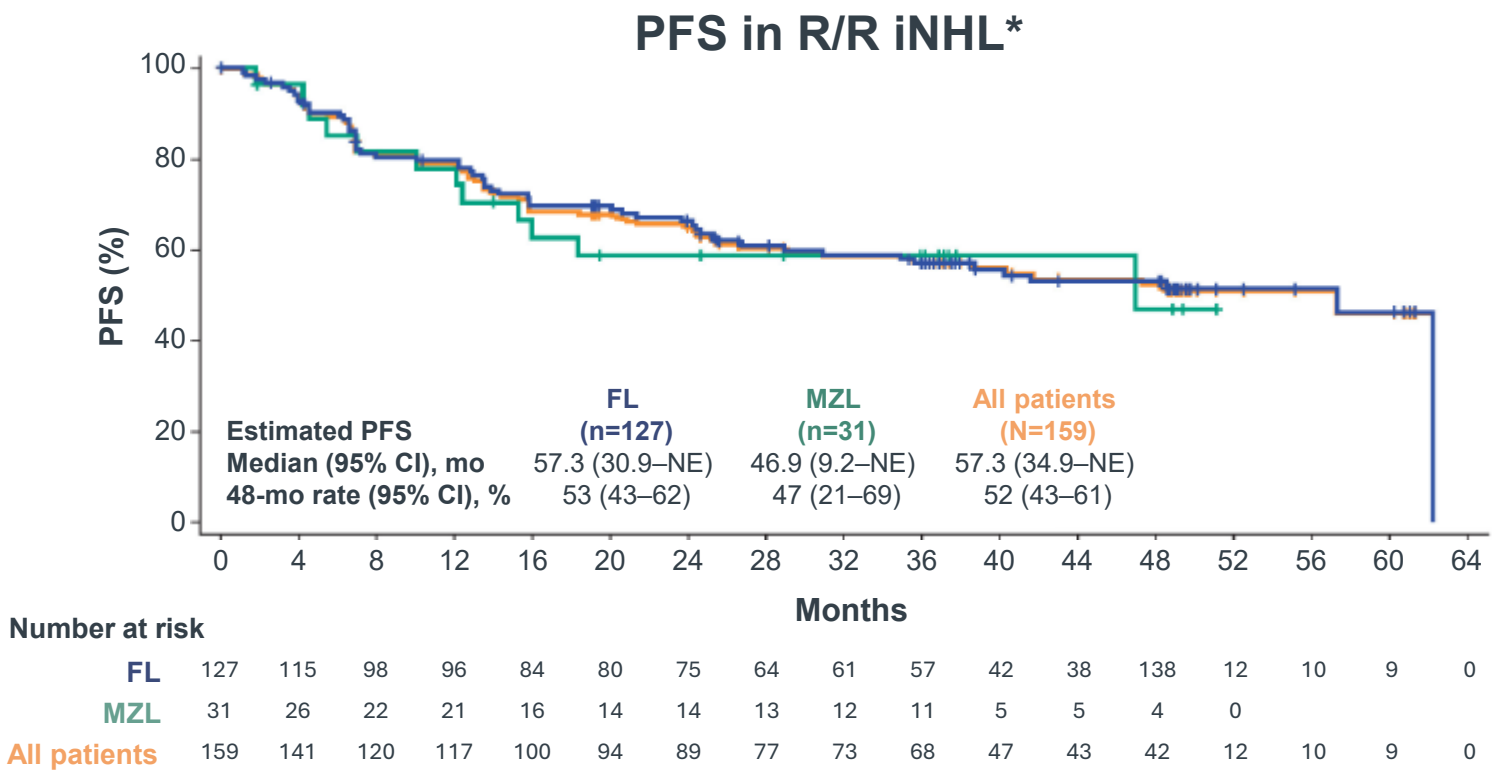
Median follow-up of CAR-T therapies and bispecific mAbs in clinical studies



axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; FL, follicular lymphoma; liso-cel, lisocabtagene maraleucel; mAb, monoclonal antibody; NHL, non-Hodgkin lymphoma; tisa-cel, tisagenlecleucel.

1. Neelapu SS *et al*. Poster presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 4868). 2. Schuster SJ *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 601). 3. Morschhauser F *et al*. Oral presentation at ICML 2023; Lugano, Switzerland, June 13–17, 2023 (Abstract LBA4). 4. Schuster SJ *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 603). 5. Linton K *et al*. Poster presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 1655).

In ZUMA-5, good long-term survival outcomes were achieved with axi-cel in patients with R/R iNHL, including R/R FL



R/R FL

48-month PFS
53%

48-month OS
72%

Data cut-off: March 31, 2023.
*Eligible patients had R/R FL or MZL after ≥2 lines of therapy, including an anti-CD20 mAb plus an alkylating agent.
axi-cel, axicabtagene ciloleucel; CD, cluster of differentiation; CI, confidence interval; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; mAb, monoclonal antibody; mo, months; MZL, marginal zone lymphoma; NE, not estimable; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.
Neelapu SS *et al*. Poster presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 4868).

CAR-T therapies have comparable efficacy and safety to bispecific mAbs in R/R FL

	Patients, n	ORR, %	CR, %	PFS, %	Grade ≥3 AEs, %	Serious AEs, %
Axi-cel[1,2]	124	94*	79*	18-month PFS: 69	85	46
Tisa-cel[3,4]	97	86	68	24-month PFS: 57†	78	28‡
Liso-cel[5]	130	97	94	12-month PFS: 81	NR	NR
Mosunetuzumab[6,7]	90	80§	60	18-month PFS: 47	72	47
Epcoritamab[8]	128	82	63	18-month PFS: ~50‖	69	NR

This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

*ORR and CR data based on n=86. †Estimated PFS. ‡Serious AE within 8 weeks after infusion. §Objective response rate. ‖18-month PFS estimated based on Kaplan–Meier curve.

AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CR, complete response; FL, follicular lymphoma; liso-cel, lisocabtagene maraleucel; mAb, monoclonal antibody; NR, not reported; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; tisa-cel, tisagenlecleucel.

1. Jacobson CA *et al*. *Lancet Oncol* 2022; 23 (1): 91–103. 2. Palomba ML *et al*. *Expert Rev Anticancer Ther* 2023; 23 (2): 199–206. 3. Dreyling M *et al*. *Blood* 2024: blood.2023021567. 4. Fowler NH *et al*. *Nat Med* 2022; 28 (2): 325–332. 5. Morschhauser F *et al*. Oral presentation at ICML 2023; Lugano, Switzerland, June 13–17, 2023 (Abstract LBA4). 6. Budde LE *et al*. *Lancet Oncol* 2022; 23 (8): 1055–1065. 7. Schuster SJ *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 603). 8. Linton K *et al*. Poster presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 1655).

Real-world safety and efficacy outcomes observed with CAR-T therapies are similar to clinical trial data

The rate of severe toxicities observed in the DESCAR-T registry was comparable with that from the ELARA trial (tisa-cel)

	Patient population* (N=70)
CRS, n (%)	
Any	52 (74.3)
Grade 1–2	51 (72.9)
Grade 3–4	1 (1.4)
Neurotoxicity, n (%)	
Any	19 (27.1)
Grade 1–2	16 (22.9)
Grade 3–4	3 (4.3)
MAS (any grade), n (%)	0
Persistent Grade ≥3 cytopenia (>1 month), n (%)	
Anemia	6 (8.6)
Thrombocytopenia	13 (18.6)
Neutropenia	35 (50.0)

Real-world data confirmed very high response rates to CAR-T treatment in patients with R/R FL

ORR: 96%

CRR: 86%

*Patients treated with tisa-cel (n=62) or axi-cel (n=8).

axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CRR, complete response rate; CRS, cytokine release syndrome; FL, follicular lymphoma; MAS, macrophage activation syndrome; ORR, overall response rate; R/R, relapsed/refractory; tisa-cel, tisagenlecleucel.

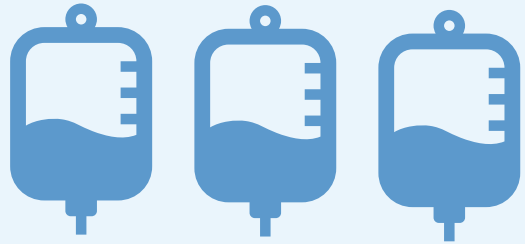
Bachy E *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 296).

Both CAR-T therapies and bispecific mAbs are time-limited therapies, but…[1–3]

CAR-T

Single IV infusion[1–3]

Bispecific mAbs



Multiple treatment cycles[4]

CAR-T, chimeric antigen receptor T-cell; IV, intravenous; mAb, monoclonal antibody.

1. Jacobson CA *et al*. *Lancet Oncol* 2022; 23 (1): 91–103. 2. Morschhauser F *et al*. Oral presentation at ICML 2023; Lugano, Switzerland, June 13–17, 2023 (Abstract LBA4).
3. Fowler NH *et al*. *Nat Med* 2022; 28 (2): 325–332. 4. Budde LE *et al*. *Lancet Oncol* 2022; 23 (8): 1055–1065.

CAR-T therapies vs. bispecific mAbs in early relapsing FL

- Special ops vs. conscript army
- Trial data are more mature, with longer follow-up compared with bispecific mAbs
- CAR-T therapies have comparable efficacy and safety to bispecific mAbs
- Real-world outcomes with CAR-T therapies are similar to clinical trial data
- Single IV infusion vs. prolonged treatment with bispecific mAbs

CAR-T, chimeric antigen receptor T-cell; FL, follicular lymphoma; IV, intravenous; mAb, monoclonal antibody.
Slide courtesy of Wojciech Jurczak.