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Anticorpi bispecifici e CAR-T a confronto nel trattamento delle malattie linfoproliferative

Carlo Visco

Disclosures of Carlo Visco

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie			x		X	X	
Kite-Gilead						X	
Janssen	x		X		X	X	
Gentili					X	X	
Lilly			X		X	X	
Novartis						X	
Pfizer			X		x	x	
Roche						X	
Incyte						x	
Kyowa-Kirin					x		

Bispecifics versus CAR-T cells

-background and history-

The concept of **immunotherapy** goes back to 1880 [*Fred Stein*]. One immigrant with neck tumor and erysipela infection

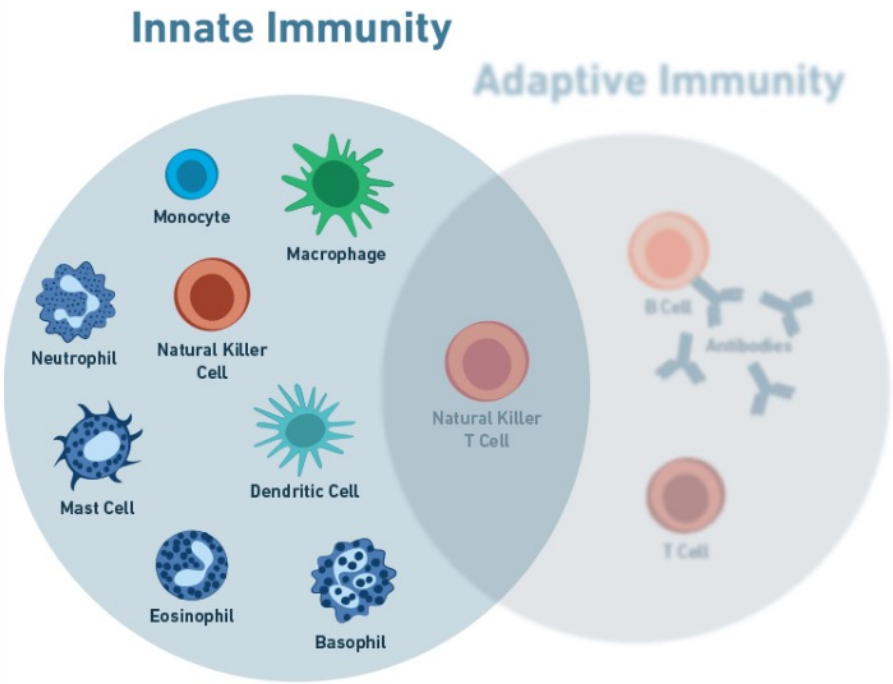
Years later *Coley* injected live bacteria, and then heat-killed pathogens into tumors to enhance immmunity, and had some responses, particularly in sarcomas [*Coley's vaccine*]

In the late 90s, *Beutler* demonstrated that bacterial lipopolysaccharides stimulate TLR, thus activating the immune system against cancer

Coley WB, Ann Surg 1891; Poltorak A et al, Science 1998; Stroll WR, Antibodies 2019

Bispecifics versus CAR-T cells

-background and history-



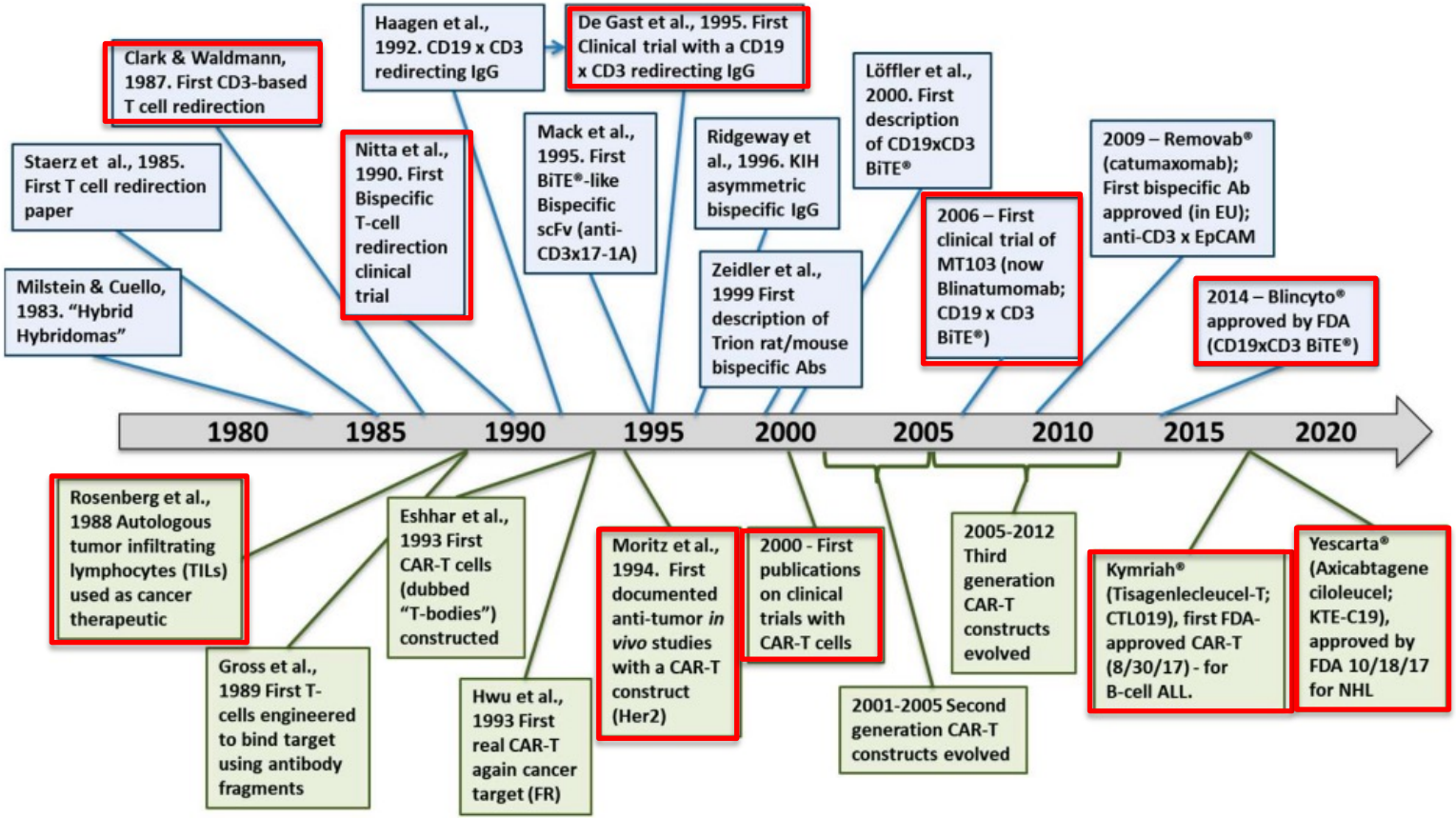
The native immune system prevents and combats malignancies

immune surveillance

senescence

checkpoints

GVL



Bispecifics

CAR-T cells

Bispecifics versus CAR-T cells

-what they are-

- Bispecific antibodies are recombinant proteins that bind 2 antigens; CAR-T cells are re-directed autologous T lymphocytes
- Over years bispecifics have been engineered in >50 different formats, with the BiTEs* that are largely the most used
- Both BiTE and CAR approaches are independent of the endogenous T-cell receptor and of MHC system on tumor cells

*Bispecific T-cell engagers

Subkleve M, Blood Adv 2021

Bispecifics versus CAR-T cells

-PROs and CONs-

BiTEs

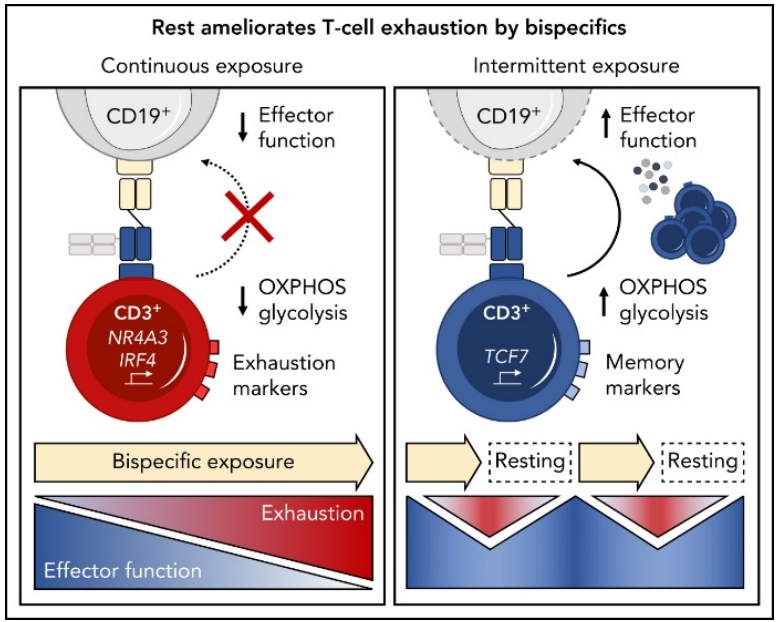
- Off the shelf, no turn-around time
- Less hospitalization
- Quite lower CRS and ICAN
- Combination possible
- Prolonged Tx but all moving to fixed
- Independent of T-cell count (?)

CAR-T

- Engineered for each individual patient, complex process, but one shot
- In the Juliet, 54 days turn around, 111 of 165 received the cells; some % not enough lymphocytes, manufactoring failure
- Need sufficient T-cell count

Subkleve M, Blood Adv 2021

T-cell exhaustion induced by continuous bispecific molecule exposure is ameliorated by treatment-free intervals



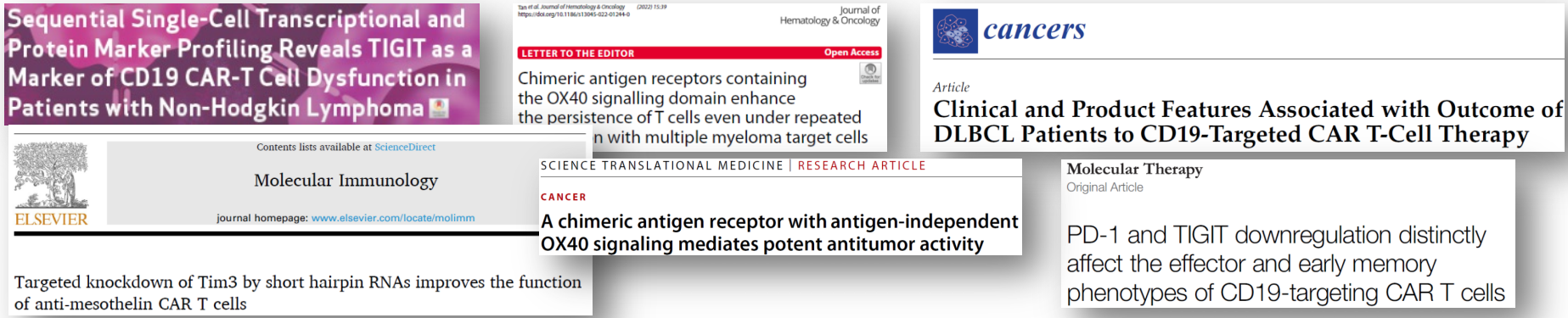
Continuous exposure to a CD19xCD3 bispecific molecule induces T-cell exhaustion

Treatment-free intervals transcriptionally reprogram and functionally reinvigorate T cells

Philipp N, Blood 2022

T-cell exhaustion and CAR-T failure

- CAR-T cell exhaustion and reduced function of endogenous immune system are main reasons causing CAR-T treatment failure
- T-cell exhaustion is characterized by loss of effector functions and reduced proliferating capacities
  - Increased expression of inhibitory checkpoint receptors is a common feature



Bispecifics versus CAR-T cells

-PROs and CONs-

	BiTEs	CAR-T
Manufacturing and dosing variability	Not applicable	CAR T-cell product variability due to differences in T-cell subset composition, CAR transduction efficacy, number of viable CAR T cells; number of transfused CAR T cells differs from 0.2×10^6 to 6×10^8[8,26]
Effector cell	Endogenous CD4 and CD8 T cells	Engineered, commonly using autologous CD4 and CD8 T cells
Effector cell function	Relies on endogenous T-cell composition and function at time of infusion	Relies on T-cell composition and function at time of leukapheresis; further modulation of CAR T function after transfusion through patient- and disease-related parameters (eg TME)[26]
Lymphodepletion prior to start of therapy	No lymphodepletion required But premedication….	Lymphodepletion with cyclophosphamide and fludarabine prior to CAR T-cell transfusion mandatory (tisa-cel: exceptions in case of WBCs $<1\times10^9$/L within 1 wk prior to transfusion)[39]
B-cell aplasia	Recovery after completion of infusion: 6-18 mo[41]	Months to years depending on persistence of functional CAR T cells; hypogammaglobulinemia for months to years[15]

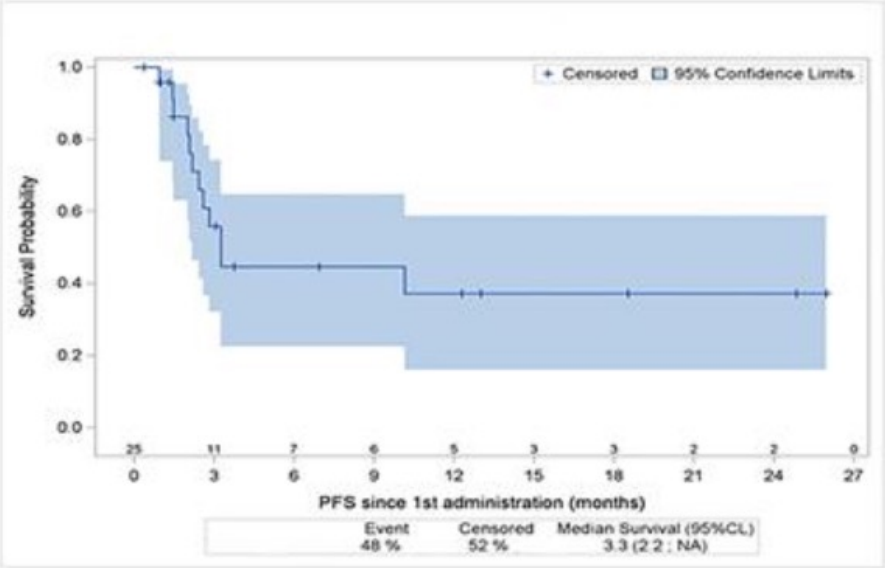
Financial Toxicity

Subkleve M, Blood Adv 2021

Bispecifics versus CAR-T cells
-clinical data-

- No face to face comparison
- We have data on bispecifics post CarT, not much in the pre-CarT setting, or less pretreated patients
- Soon we will need to consider combos (Glofi-Gemox, Pola-Glofi, Epco-Zanu, Epco-ICE etc)

CAR T-Cell Therapy Remain Effective in Patients with Relapse/Refractory B-Cell Non-Hodgkin Lymphoma after Bispecific Antibodies Exposure: Results of a Lysa Study Based on the Descar-T Registry



32 pts in the DESCAR-T registry mainly receiving Glofitamab

The efficacy of CART preserved in B-NHL patients progressing after prior treatment with bispecific antibodies.

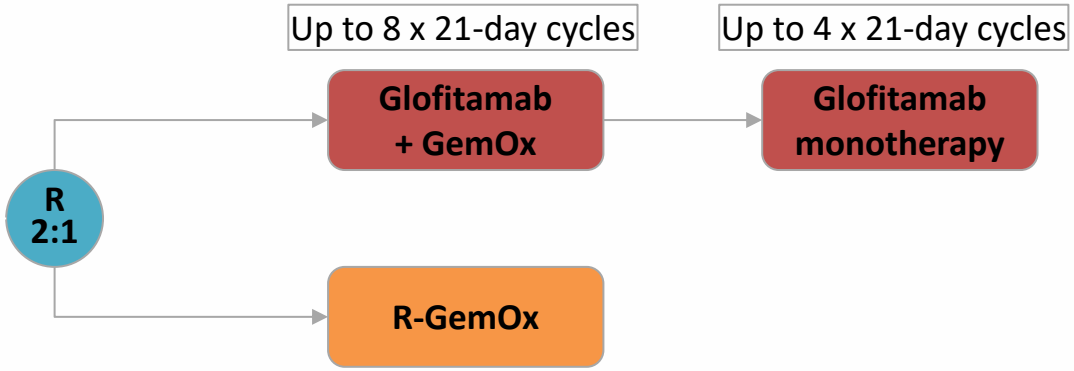
No new toxicity signals have been identified.

Crochet G, ASH 2022

Glofitamab plus R-GemOx vs R-GemOx is under investigation in the Phase 3 GO41944 STARGLO study

Patients

- Aged ≥18 years
- Histologically confirmed DLBCL
- R/R disease after ≥1 prior therapy
- ≥1 bi-dimensionally measurable lesion
- Ineligible for ASCT
- ECOG PS 0–2
- Adequate hematologic and renal function



Endpoints

Primary: OS

Secondary: Other efficacy and safety endpoints

Hertzberg M, et al. ASCO 2021

Bispecifics versus CAR-T cells
-clinical activity-

- This debate applies to:
  - DLBCL
  - FL
  - MCL
  - Multiple Myeloma

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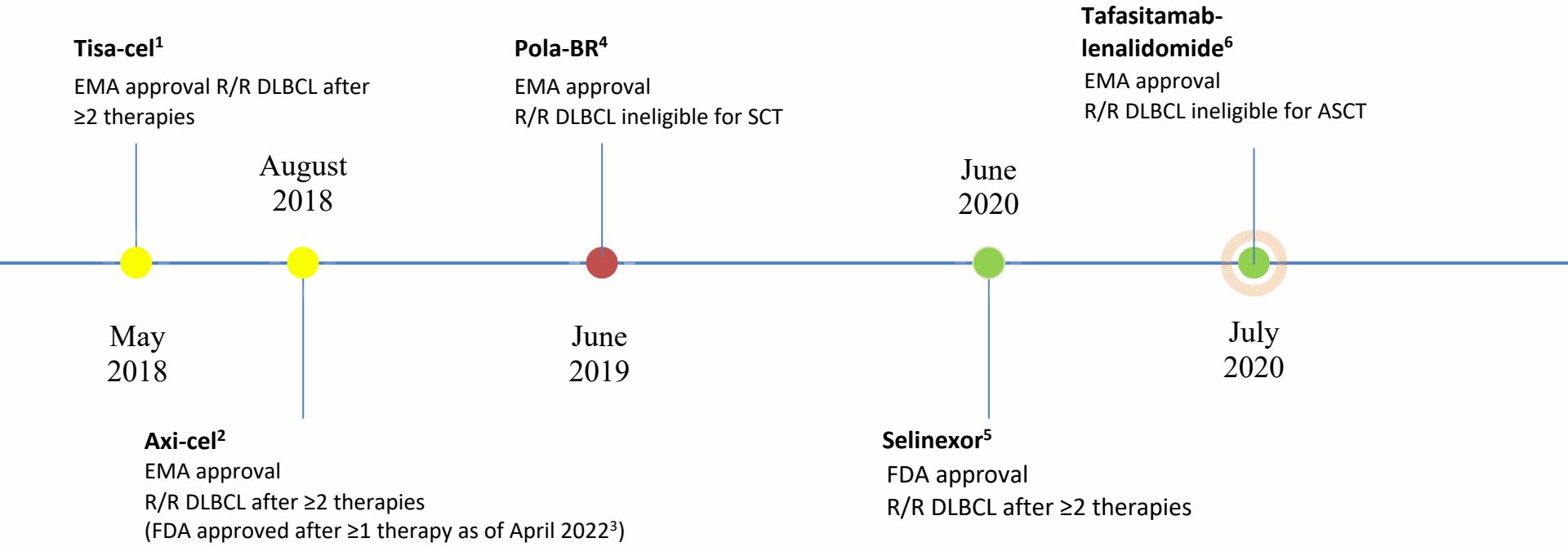
The treatment landscape is evolving in R/R DLBCL



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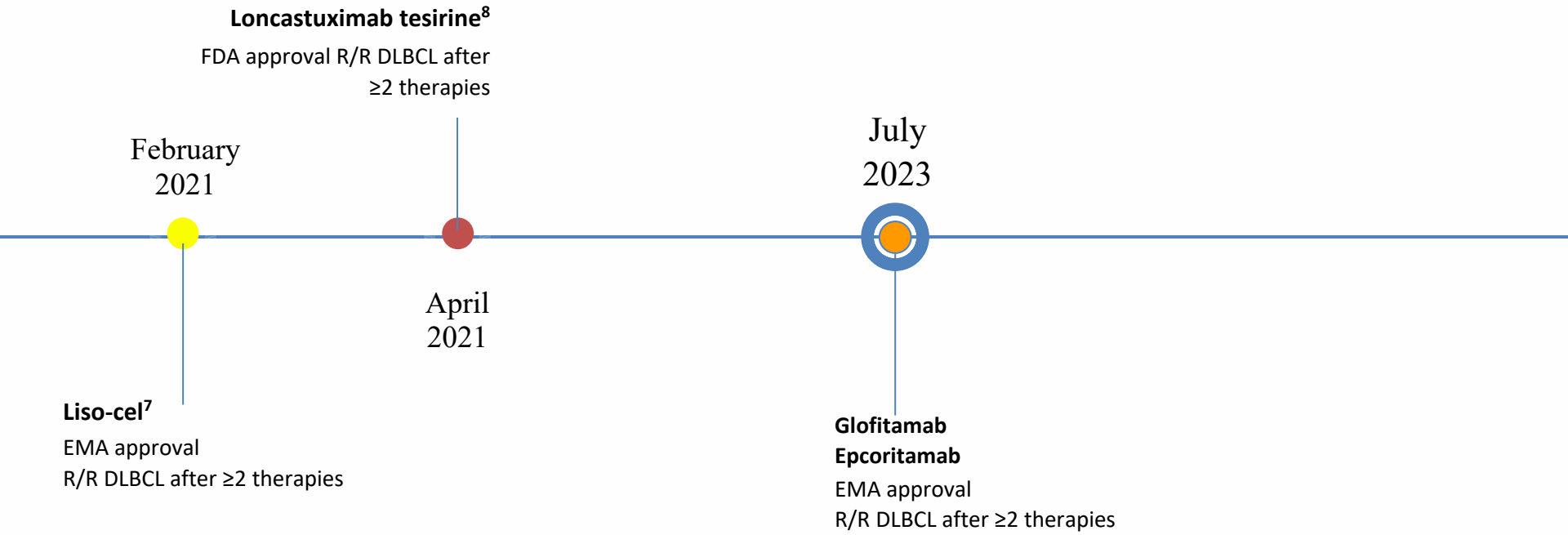


CD20/CD3 bispecific antibodies approved or under development in R/R DLBCL

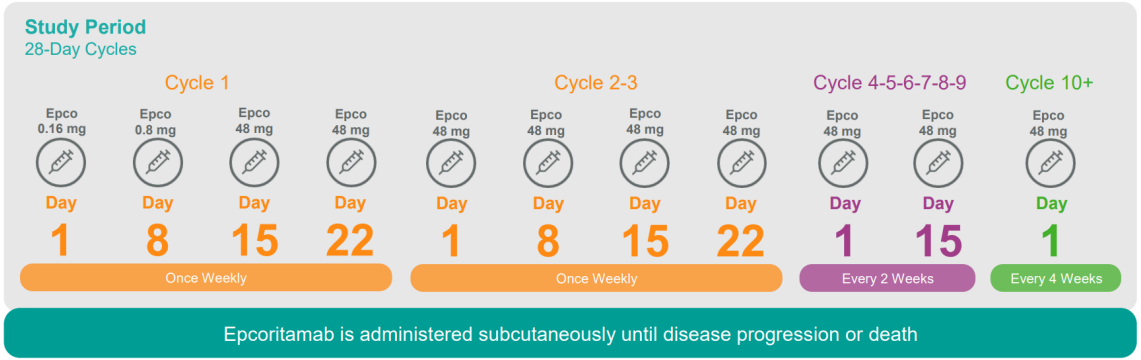
Treatment	Structure	Description	Continuous or fixed	Treatment schedule
Mosunetuzumab[1]	1:1 format 	Fully humanized, IgG1-like with modified Fc region	Fixed	IV 8 or 17 cycles based on response
Epcoritamab[2]		DuoBody full-length, human IgG1 with a silent Fc region	Continuous	Subcutaneous Until PD or unacceptable toxicity
Odronextamab[3]		Hinge-stabilized, fully humanized, full-length IgG4 with a modified Fc region	Continuous	IV Until PD or unacceptable toxicity
Glofitamab[4]	2:1 format 	Fully humanized, IgG1-like with modified Fc region	Fixed	IV Maximum 12 cycles, unless PD or unacceptable toxicity

Budde LE, et al. J Clin Oncol 2022;40:481–91; Clausen MR, et al. J Clin Oncol 2021;39(15_suppl):7518; Bannerji R, et al. Lancet Haematol 2022;9:E327-39; Hutchings M, et al. J Clin Oncol 2021;39:1959–70

Glofitamab, fixed schedule i.v.

Ciclo e giorno	C1D1	C1D8	C1D15	C2D1	C3D1	C4D1	C5D1	C6D1	C7D1	C8D1	C9D1	C10D1	C11D1	C12D1
Obinutuzumab	1000 mg													
Glofitamab		2.5 mg	10 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg

Epcoritamab, until progression s.c.

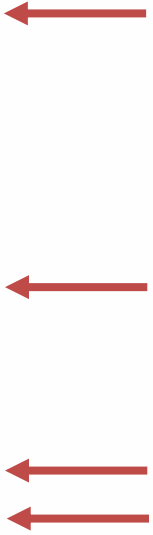


Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Characteristic	Value
Median age (range) — yr	66 (21–90)
Male sex — no. (%)	100 (65)
ECOG performance-status score — no. (%)†	
0	69 (45)
1	84 (55)
Ann Arbor stage at time of study entry — no. (%)	
I	10 (6)
II	25 (16)
III	31 (20)
IV	85 (55)
Missing data	3 (2)
Non-Hodgkin's lymphoma subtype — no. (%)	
Diffuse large B-cell lymphoma, not otherwise specified	110 (71)
Transformed follicular lymphoma	27 (18)
High-grade B-cell lymphoma	11 (7)
Primary mediastinal B-cell lymphoma	6 (4)

Dickinson MJ, NEJM 2022

Bulky disease at study entry	
>6 cm	64 (42)
>10 cm	18 (12)
Previous lines of therapy	
Median no. of lines (range)	3 (2–7)
Only 2 previous lines — no. (%)	62 (40)
≥3 previous lines — no. (%)	92 (60)
Previous therapy for lymphoma — no. (%)	
Anti-CD20 antibody	154 (100)
Anthracycline	149 (97)
CAR T-cell therapy	51 (33)
Autologous stem-cell transplantation — no. (%)	28 (18)
Relapsed or refractory status — no. (%)‡	
Refractory to any previous therapy	139 (90)
Refractory to last previous therapy	132 (86)
Primary refractory	90 (58)
Refractory to any previous anti-CD20 therapy	128 (83)
Refractory to previous CAR T-cell therapy	46 (30)

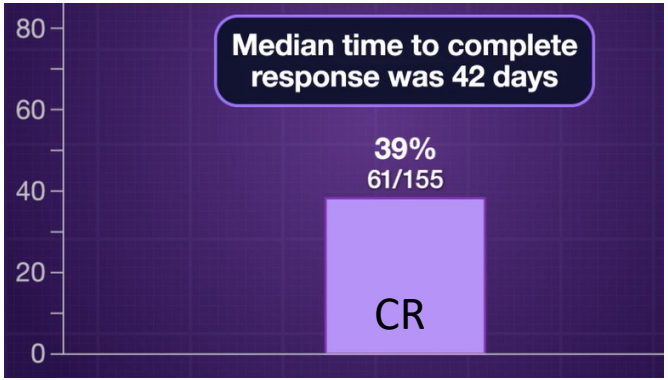


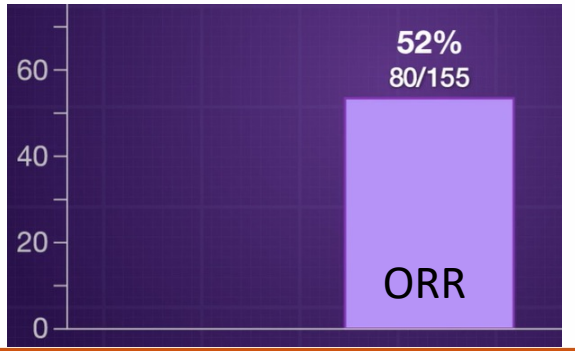
Dickinson MJ, NEJM 2022

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)
Non-Hodgkin's lymphoma subtype at study entry		
DLBCL	110	40 (31–50)
HGBCL	11	0 (NC–NC)
PMBCL	6	50 (12–88)
Transformed follicular lymphoma	28	50 (31–69)
Relapsed or refractory to last previous therapy		
Refractory	132	34 (26–43)
Nonrefractory	23	70 (47–87)
Disease status after ASCT		
Refractory	7	71 (29–96)
Nonrefractory	21	67 (43–85)
Cell of origin		
Germinal-center B cell	66	36 (25–49)
Activated B cell	17	59 (33–82)
Non–germinal-center B cell	34	32 (17–51)
Missing or unclassified	38	42 (26–59)
No. of previous lines of therapies		
2	62	32 (21–45)
≥3	92	44 (34–55)
Double-hit lymphoma		
Yes	20	25 (9–49)
No	134	41 (33–50)
Unknown or missing data	1	100
Double-expressor lymphoma		
Yes	15	20 (4–48)
No	139	41 (33–50)
Unknown or missing data	1	100

Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma

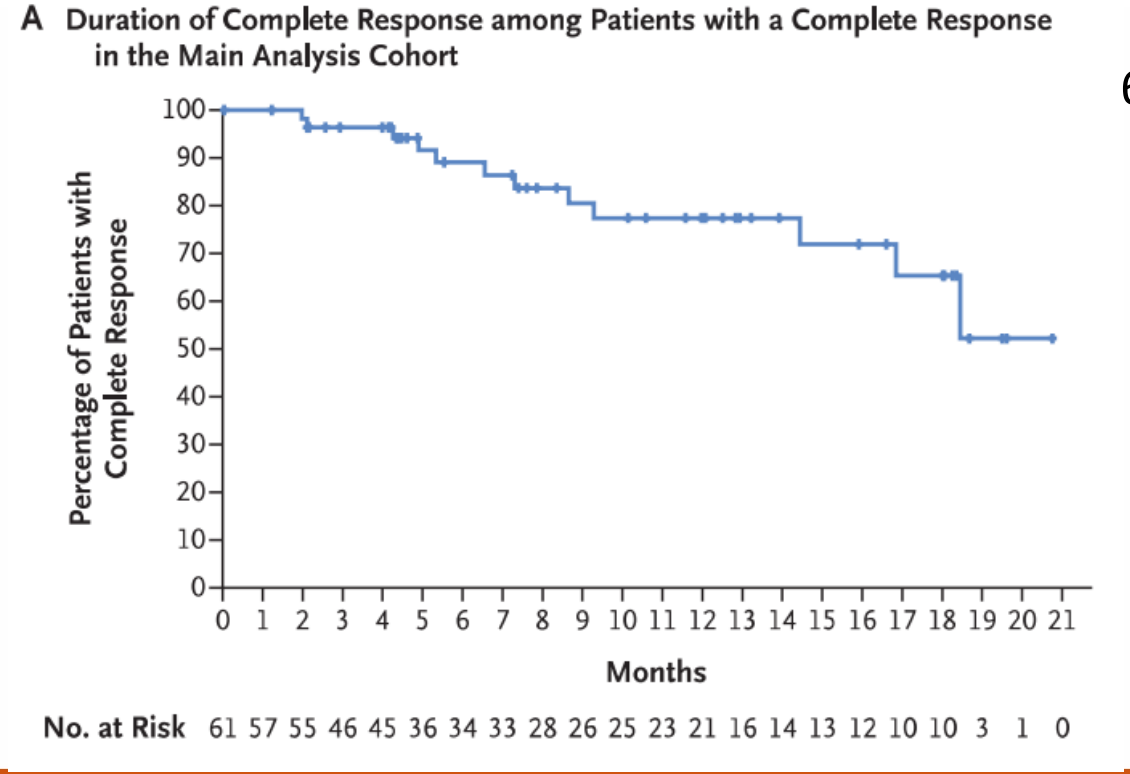
Primary Endpoint: CR rate





Dickinson MJ, NEJM 2022

Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma



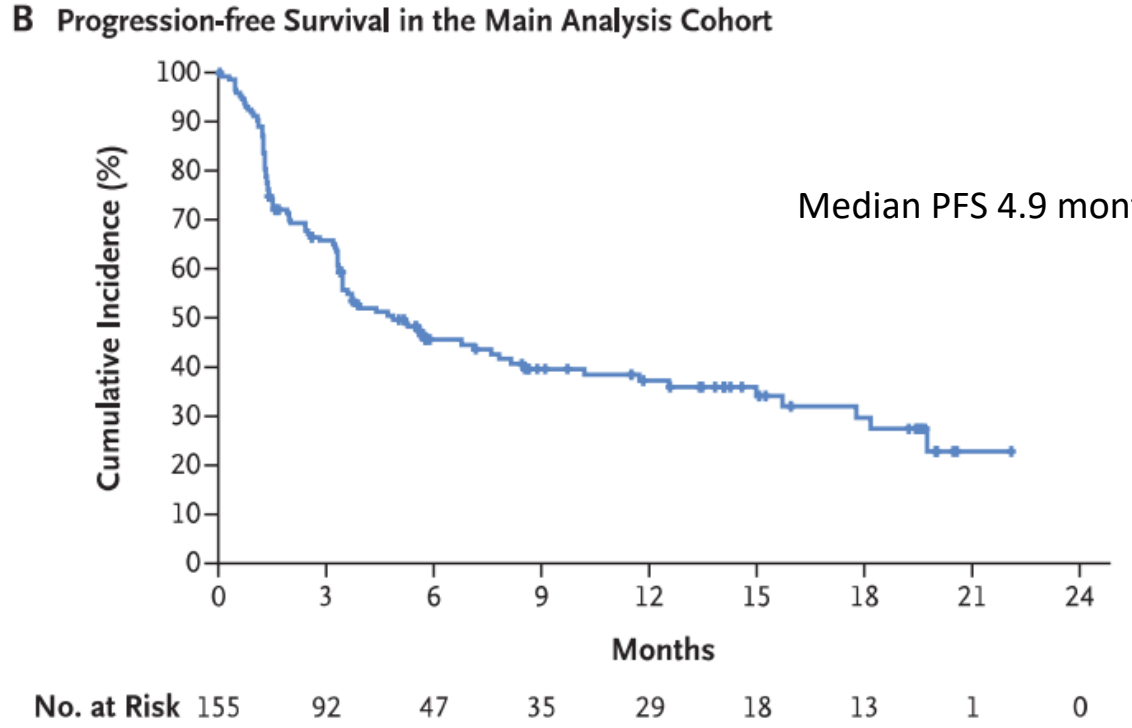
61/155 (39%)

12-months

46/155 (30%) projected

Dickinson MJ, NEJM 2022

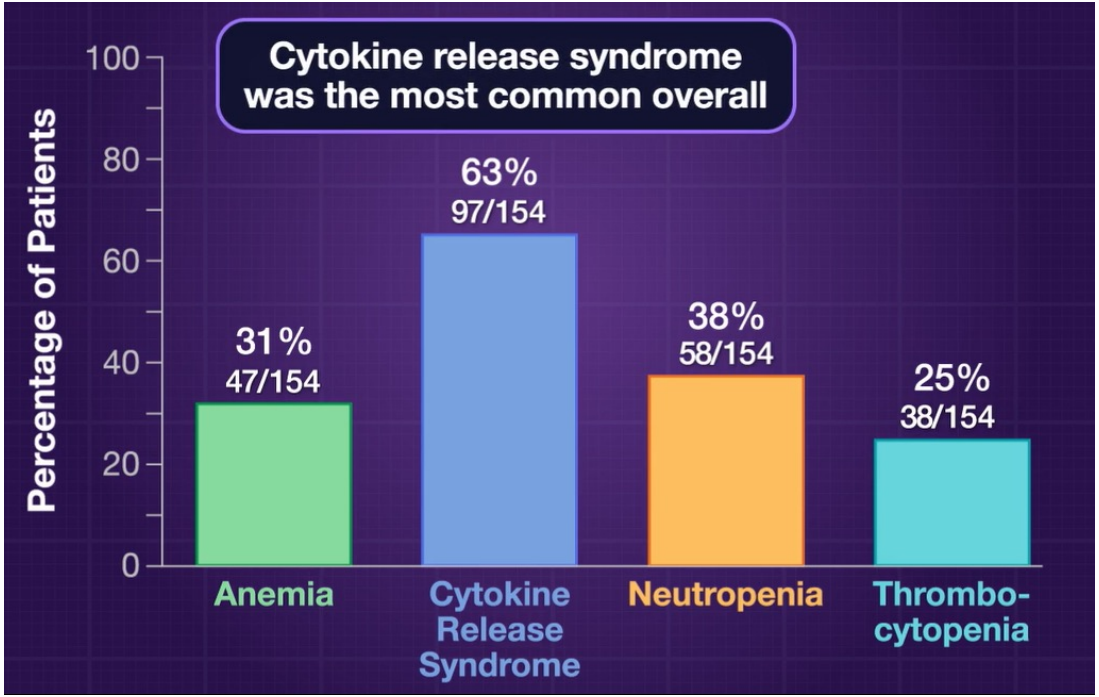
Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma



Median PFS 4.9 months (3.4-8.1)

Dickinson MJ, NEJM 2022

Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma



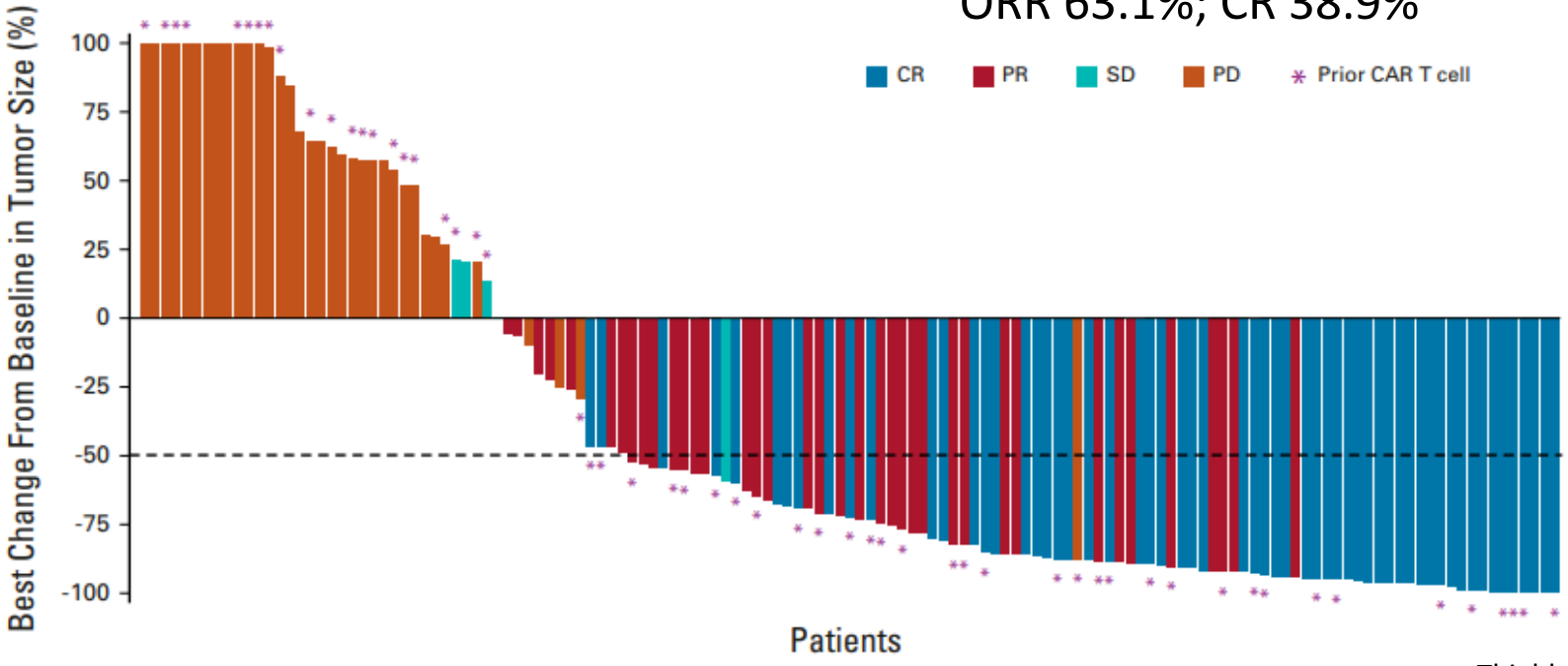
Dickinson MJ, NEJM 2022

Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell–Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial

Thieblemont C, et al. JCO 2022

Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell–Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial

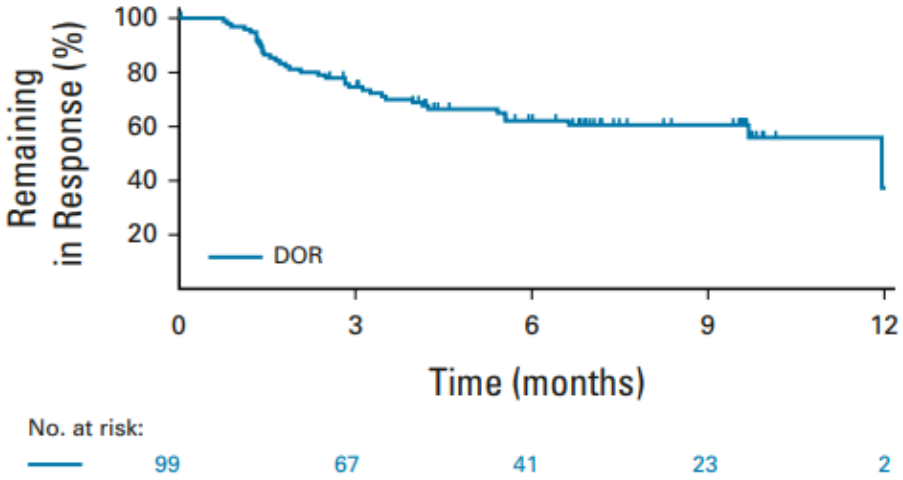
ORR 63.1%; CR 38.9%

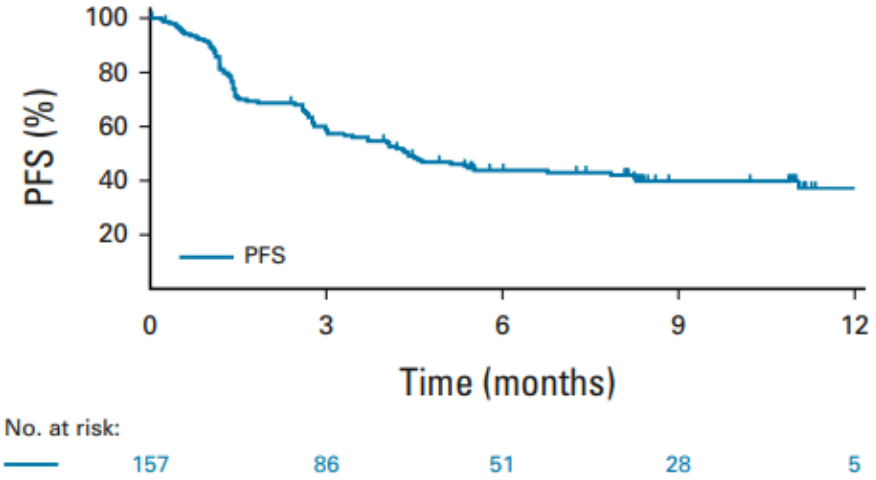


Thieblemont C, JCO 2022

Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell–Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial

Median PFS 4.4 months (3-7.9)





Thieblemont C, JCO 2022

Bispecific antibodies

	Glofitamab n=154	Epcoritamab n=157
Histology	DLBCL ≥2 lines	DLBCL ≥2 lines
PS	0-1	0-2 (n=5 PS2)
Age	66.0 (21–90)	64 (20–83)
Median prior lines of therapy (range)	3 (2–11)	3 (2–7)
Prior CAR T therapy, n (%)Refractory/progressed within 6mo	**51 (33.1)** 132 (85.7)	**61 (39)** 46/61 (75)
Median Follow-up (months)	12.6 (0–22)	10.7 (0.3–17.9)
ORR CR	**80 (51.6%) ORR 61 (39.4%) CR**	**99 (63%) ORR 61 (39%) CR**
Median OS	**NR**	**11.5 (7.9, 15.7)**
Median PFS	**4.4 (3.0–7.9) NR for pts in CR**	**4.9 (3.4, 8.1)**
Gr ≥ 3 CRS / ICANS	2,5%/0,6%	3,9% /2,6%

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

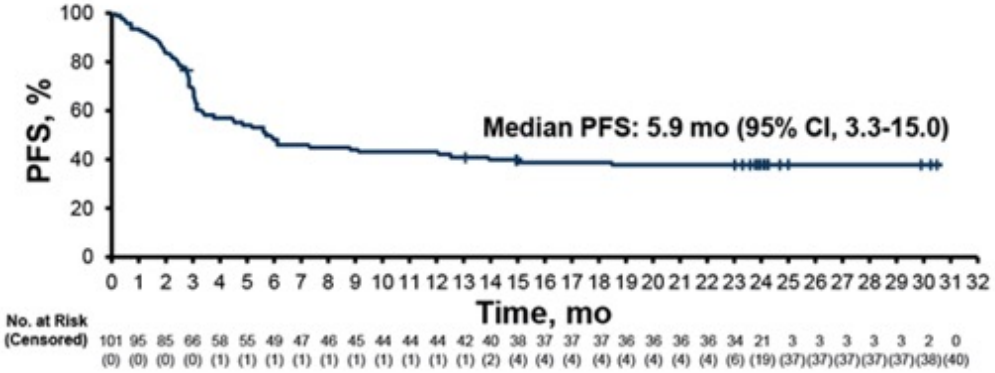
The NEW ENGLAND JOURNAL of MEDICINE S.S. Neelapu et al. Dec 10, 2017

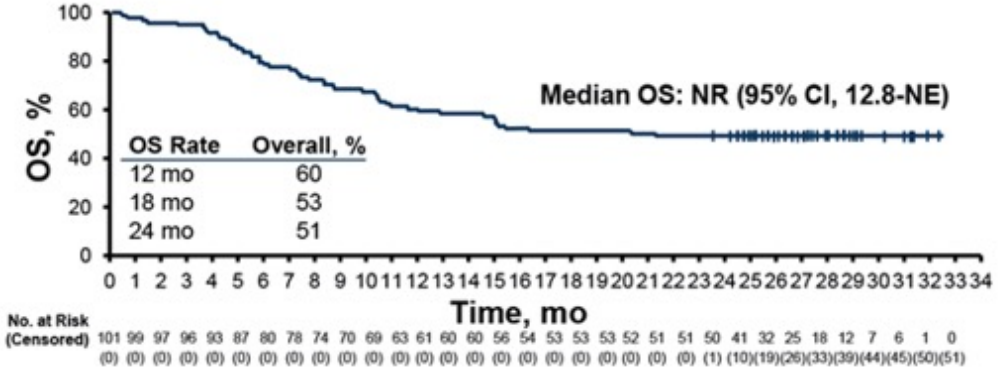
ZUMA-1 is a prospective, registrational, single arm, phase 1-2 study at 22 Medical centers in USA and Israel

119 patients enrolled (median age 58, range 34-69)

Previous therapies	Phase 1 (n=7)	Phase 2 (n=101)
Median (IQR)	3 (3–4)	3 (2–4)
1	0	3 (3%)
2	1 (14%)	28 (28%)
≥3	6 (86%)	70 (69%)
History of primary refractory disease†	1 (14%)	26 (26%)
History of resistance to two consecutive lines	1 (14%)	54 (53%)

Phase 2 ZUMA-1: Long-Term Follow-Up (Median of 27.1 Months)[1]

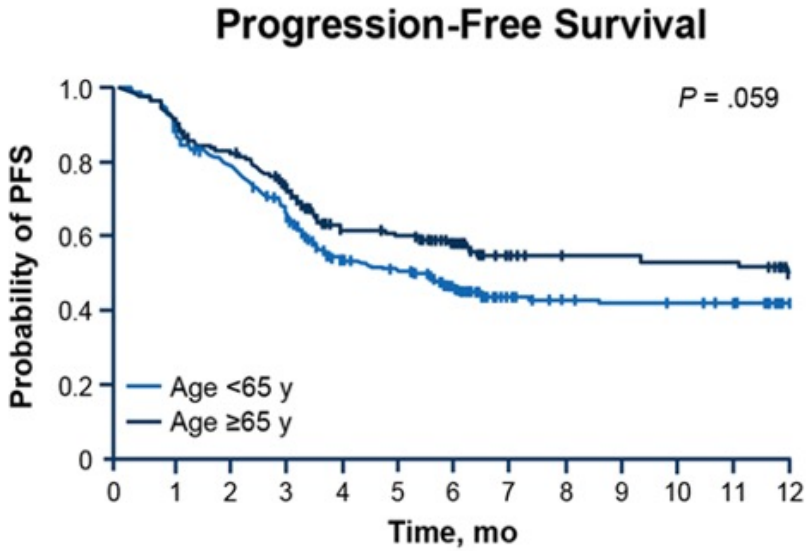


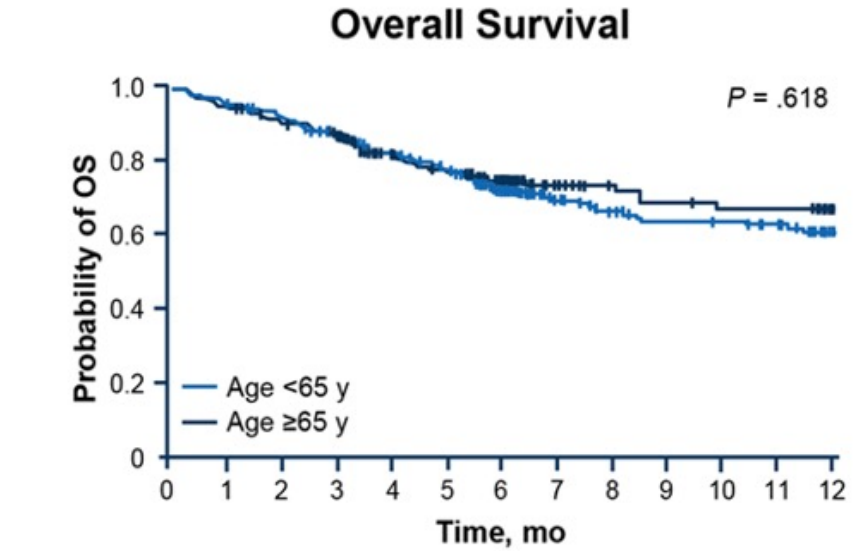


Objective response, n (%)	84 (83)
CR, n (%)	59 (58)
Median DOR, mo	11.1
Median OS, mo	NR
Median PFS, mo	5.9

Locke et al, Lancet Oncol 2019

Axi-Cel CIBMTR Registry for Large B-Cell Lymphoma: Survival Outcomes[1]





Pasquini et al, Transpl Cell Th 2023

Summary of CRS and Neurotoxicity From Major CAR-T Cell Trials in DLBCL[1-3]

Study	CRS All Grades	CRS Grade ≥3	Neurotoxicity All Grades	Neurotoxicity Grade ≥3
ZUMA-1	93%	13%	65%	31%
JULIET	57%[a]	17%[a]	21%	12%
TRANSCEND	37%	1%	23%	13%

Notes

1. Lee criteria used for CRS grading on ZUMA-1 and TRANSCEND
2. U Penn criteria used for CRS grading on JULIET
3. CTCAE criteria used for neurotoxicity grading

[a] Post hoc regrading per Lee criteria.

1. Neelapu SS et al. *N Engl J Med*. 2017;377:2531-2544. 2. Schuster SJ et al. *N Engl J Med*. 2019;380:45-56.
3. Abramson JS et al. *HemaSphere*. 2018;2(suppl 1): Abstract S800.

Bispecifics versus CAR-T cells

-Conclusions in DLBCL-

Early toxicity favours BiTEs, but long time evaluation needed

Efficacy favours CAR-Ts, especially because of plateau

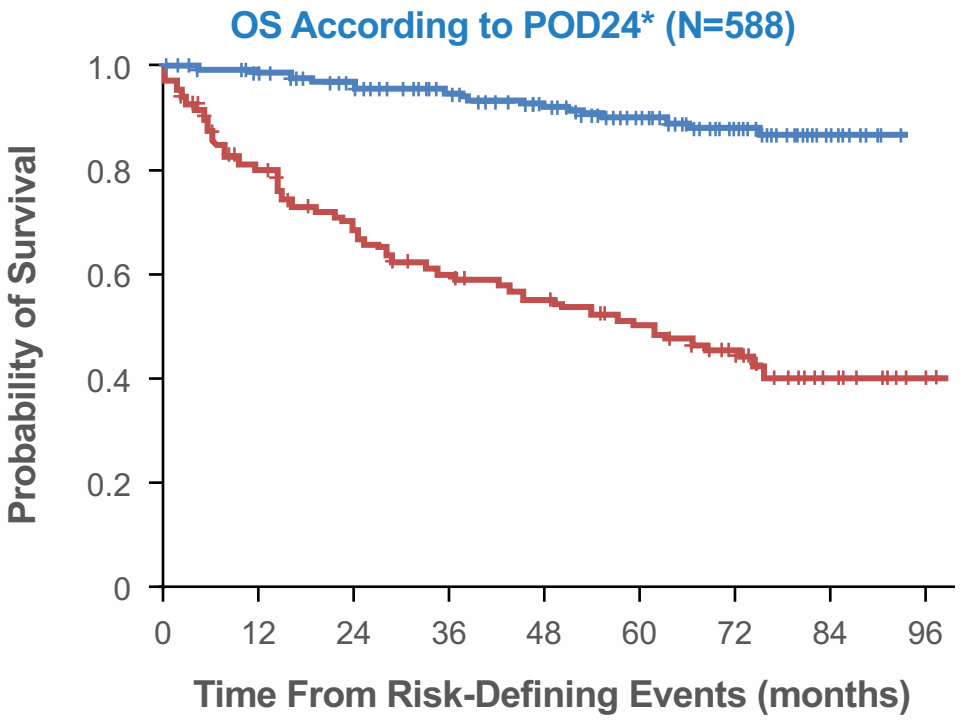
Use of BiTEs before CAR-T to improve response as bridging might be the future, but combinations coming

On both sides, failure to achieve CR remains an unmet need

Bispecifics versus CAR-T cells
-clinical activity-

- This debate applies to:
  - DLBCL
  - FL
  - MCL
  - Multiple Myeloma

Early Relapsed Patients Represent an Unmet Need and Lack Consensus on Their Therapy Following R-CHOP



POD24

- 15% to 20% after 1L
- High risk of transformation (up to 80%)
- Chemorefractoriness
- Undefined role for ASCT
- Rapidly get to 3L+ of therapy

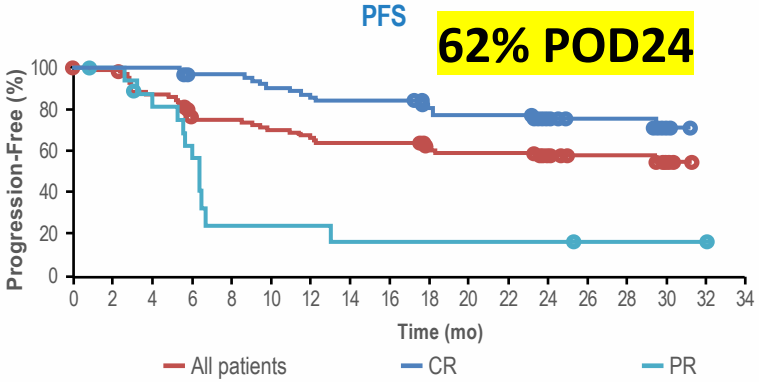
	Patients, n	5-year OS, %
POD24*	110	50
Reference	420	90

Patients With R/R FL Receiving Tisa (ELARA) or Axicell (ZUMA-5)

ELARA

Characteristics	Patients (N=97)
Median age, years, (range)	57 (49–64)
Stages 3–4 disease, n (%)	83 (85.6)
Median prior lines, n (range)	4 (2–13)
Refractory to last line of therapy, n (%)	76 (78.4)
Prior HSCT, n (%)	35 (36.1)

TEAEs of Interest	Tisa-cel
Grades ≥3 CRS, %[a]	0
Grades ≥3 neurological toxicity, n (%)	3 (3.1)



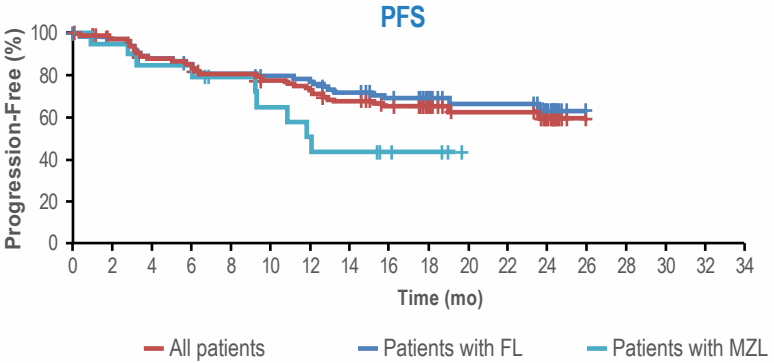
- ORR: 86%
- CRR: 69%
- Median DoR, PFS, and OS were not reached
- 24-mo DoR: 66%

Event-Free Probability % (95% CI)
12-mo PFS, all patients 67 (56–76)
24-mo PFS, all patients 57 (46–67)
12-mo PFS, patients in CR 87 (76–93)
24-mo PFS, patients in CR 75 (62–84)

ZUMA-5

Characteristics	Patients (N=148)
Median age, years (range)	60 (53–67)
Tumor type, n (%)	
FL	124 (83.8)
MZL	24 (16.2)
Stages 3–4 disease, n (%)	106 (85)
Median prior lines, n (range)	3 (2–4)
Refractory disease, n (%)	84 (68)
Prior HSCT, n (%)	33 (22)

TEAEs of interest	Axi-cel
Grades ≥3 CRS, n (%)[a]	8 (6)
Grades ≥3 neurological toxicity, n (%)	19 (15)

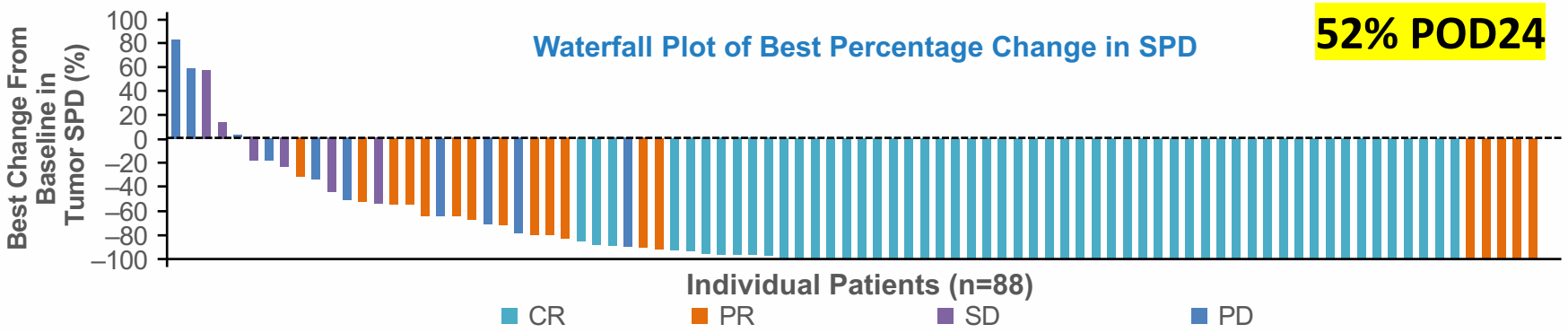


- ORR: 94%
- CRR: 79%
- 12-mo DoR: 72%
- 18-mo OS: 87.4% (median OS not reached)

Median PFS		
FL (n= 86)	MZL (n=23)	All patients (n=109)
NR (23.5–NE)	12.0 (9.1–NE)	NR (23.5–NE)

Fowler NH, et al. *Nat Med*. 2022;28(2):325-332; Jacobson CA, et al. *Lancet Oncol*. 2022;23(1):91-103.

Mosunetuzumab Efficacy Profile

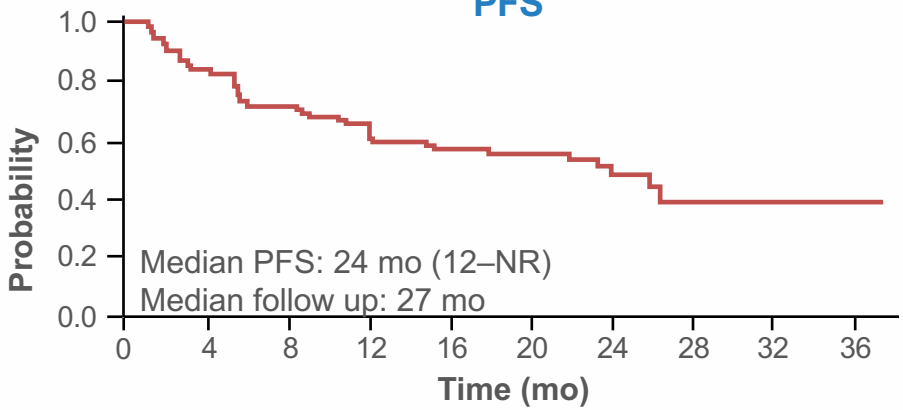


52% POD24

Response

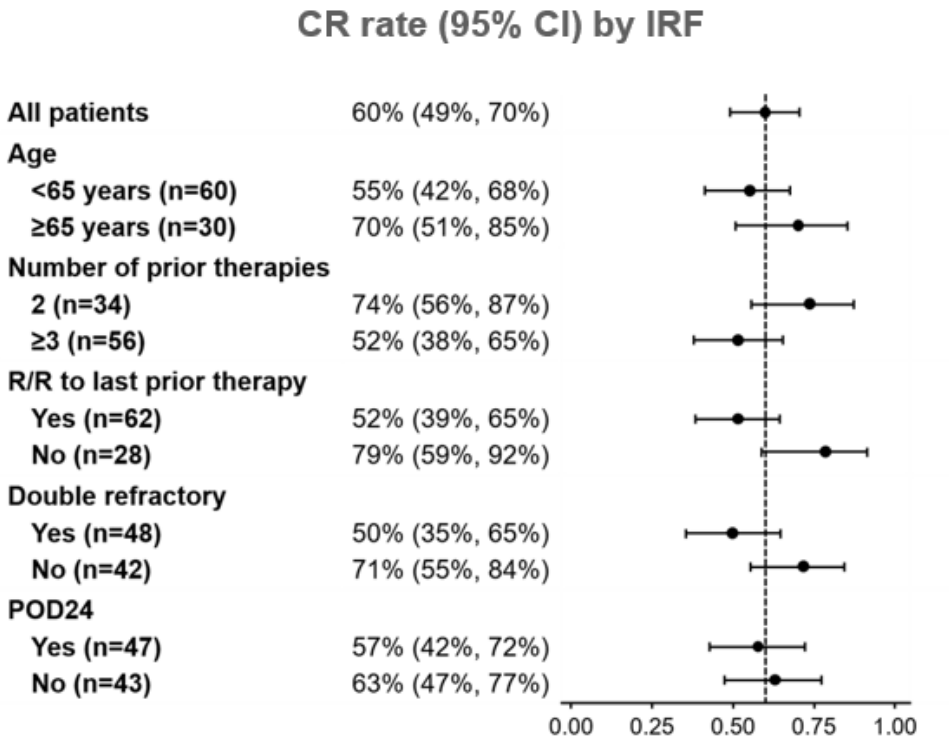
Endpoint	
ORR, % (95% CI)	**78%** (68–86)
CR, % (95% CI)	**60%** (49–70)
Time to first response, median (range)	**1.4 mo** (1.0–11)
Time to first CR, median (range)	**3.0 mo** (1.0-19)

PFS



Budde LE. *Lancet Oncol*. 2022;23(8):1055-1065.

Mosunetuzumab Efficacy Profile



Budde LE. *Lancet Oncol*. 2022;23(8):1055-1065.

Mosunetuzumab Safety Profile

CRS by ASTCT criteria	N=90
CRS (any grade)	44%
Grade 1	26%
Grade 2	17%
Grade 3	1%
Grade 4	1%
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–24)
C1D15	27 (0.1–391)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	11%
Tocilizumab for CRS management	8%
Events resolved	100%

- **CRS was predominantly grade ≤2 and during Cycle 1**
- **All CRS events resolved**
- **No new events reported within 10 months of additional follow-up**

N (%)	N=90	Additional Details
ICANS*	4 (4.4%)	• Confusional state (3.3%; all grades 1–2), disturbance in attention and cognitive disorder (1.1% each; all grade 1); all resolved
Grade 3	0	• No cases of aphasia, seizures, encephalopathy, or cerebral edema

ICANS events were infrequent and all grades 1–2

Budde LE. *Lancet Oncol*. 2022;23(8):1055-1065.

Bispecifics versus CAR-T cells
-Conclusions in FL-

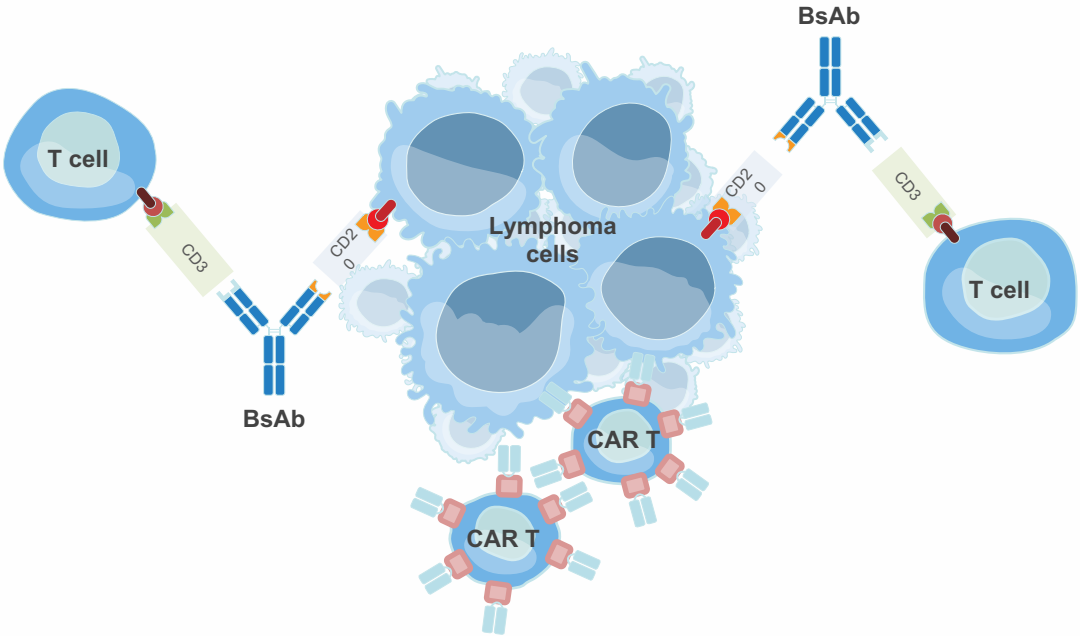
Toxicity seems low for both (outpatient?)

Efficacy looks similar, but we need more follow-up

POD-24 patients will benefit, not clear in which order

Again, on both sides, failure to achieve CR an unmet need

New Hopes by Engaging T cells in lymphomas



Adapted from Khurana A, et al. *Ann Lymphoma*. 2021;5:9. http://dx.doi.org/10.21037/aol-20-48.

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