Bispecific antibodies in Lymphoma : Another win for T cells

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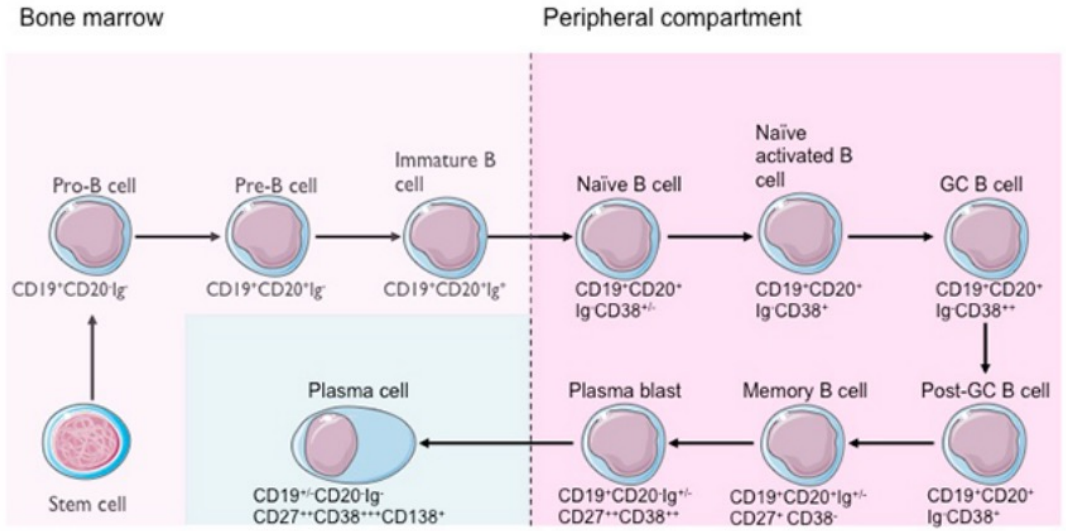
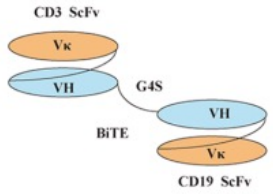
Bispecific Abs in B-NHL

- To harness the **power of a patient's own T cells** is a **revolution** in the treatment of B-cell lymphomas
- **off-the-shelf** products
- T-cell engaging bispecific antibodies **simultaneously binds**
  - to **tumor- associated antigens (TAA)** expressed on tumor cells
  - to **CD3 on T-cells**, resulting in T-cell activation and triggering target-dependent tumor cell killing
- in B-NHL, Bispecific Abs target an antigen that we already know is a **successful target**, thanks to rituximab
- **CD20 is present on all malignant B cells, making for an attractive target**



Bispecific Abs in B-NHL under clinical development

CD3 x CD19

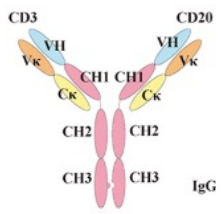


Blinatumomab

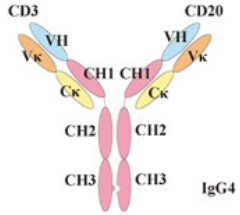
CD3 x CD20

Ig G-based

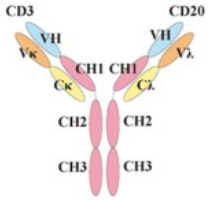
Advanced development



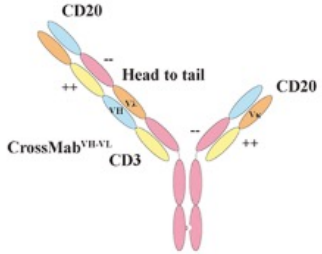
Mosunetuzumab



Odronextamab

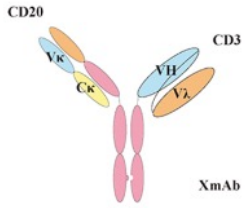


Epcoritamab



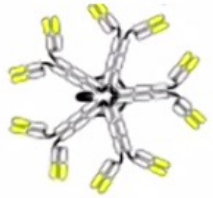
Glofitamab

Under development



Plamotamab

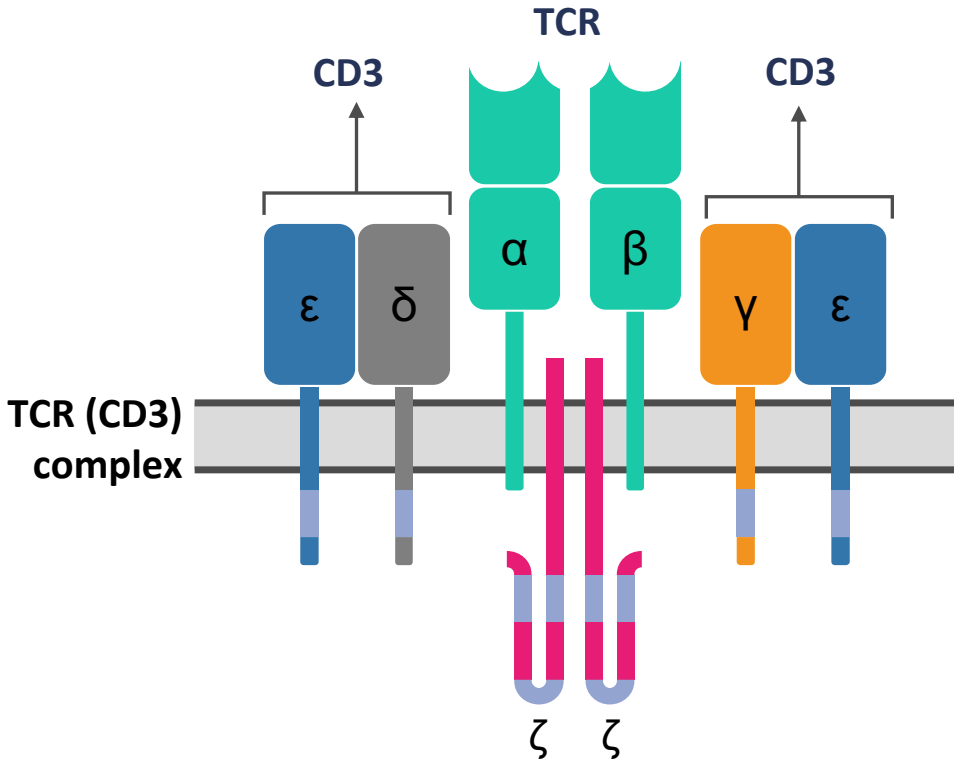
Ig M-based



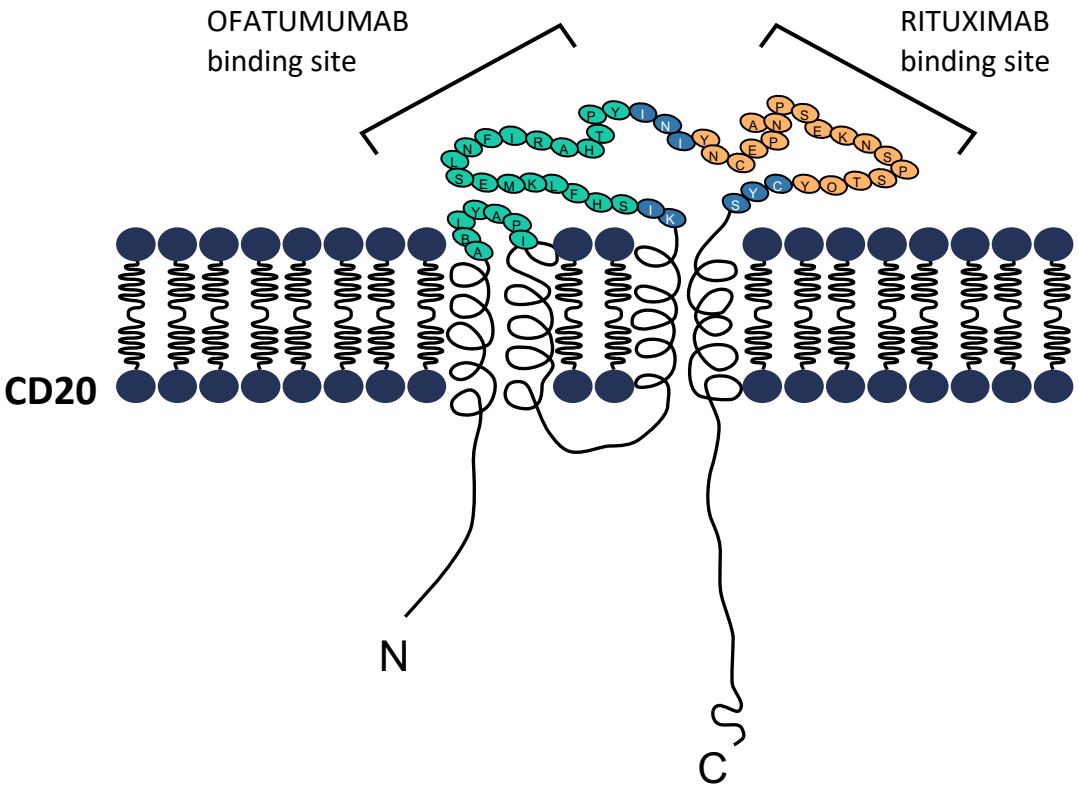
Imvotamab

Adapted Ma et al. Frontiers in Immunology 2021

Binding sites of CD3xCD20 antibodies



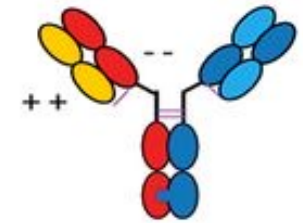
Franco R, *et al. Front Pharmacol* 2016

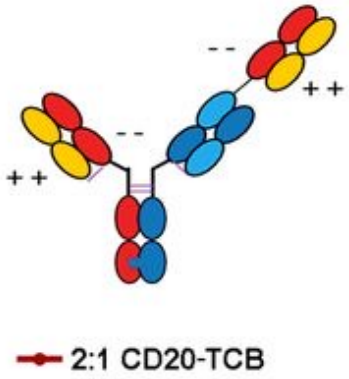


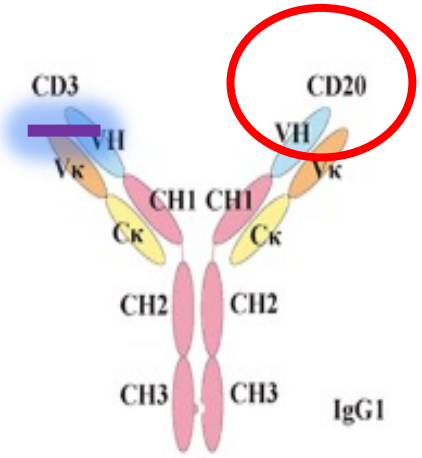
Klein C, *et al. Mabs* 2013

Structure of CD3xCD20 antibodies

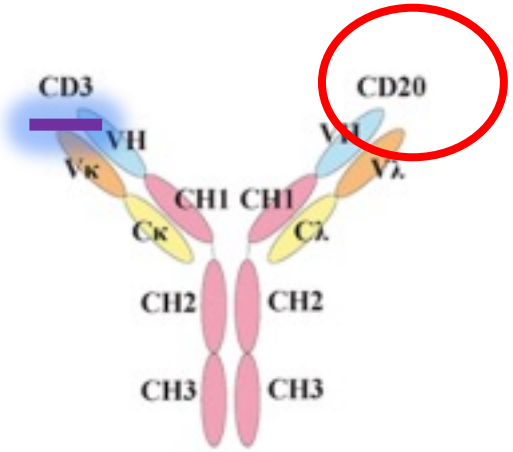
Avidity binding to CD20
1:1 format or 2:1 format



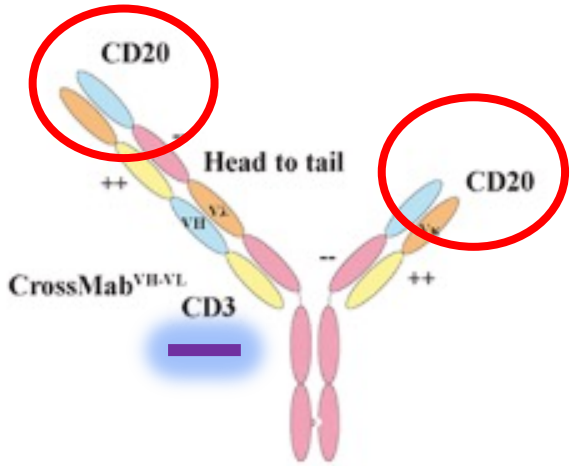




Mosunetuzumab



Epcoritamab



Glofitamab

Bacac M, *et al. Clin Cancer Res* 2018; **24**;4785–97

Single-agent phase 1/2 studies of bispecific antibodies in B-NHL

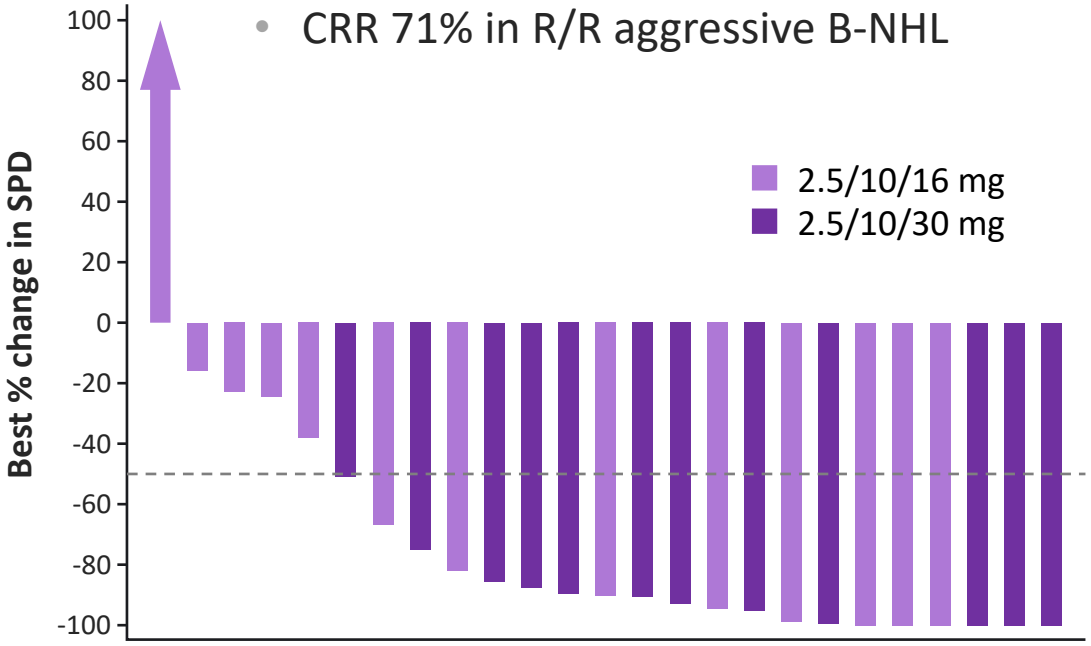
Activities in single agent phase 1-2 in aggressive B-cell lymphomas

Target	Drug	Phase	No*	Efficacy	Références
CD19/CD3	Blinatumomab	2	25	ORR 43% CR 19%	Viardot et al. Blood 2016
CD20/CD3	Glofitamab D-7obinutuzumab	1b	171	ORR 79% CR 71%	Hutchings M, *et al. J Clin Oncol* 2021
CD20/CD3	Mosunetuzumab	1/1b	171	ORR 37.1% CR 19.4%	Schuster SJ, et al. ASH 2019: Abstract 6
CD20/CD3	Odronextamab	1	53	ORR 55% CR 55%	Bannerji R ASH 2019 #762
CD20/CD3	Epcoritamab subcutaneous	1/2	73	ORR 91% CR 55%	Hutchings M, *et al. Lancet* 2021

Activity of glofitamab and epcoritamab in r/r aggressive B-NHL

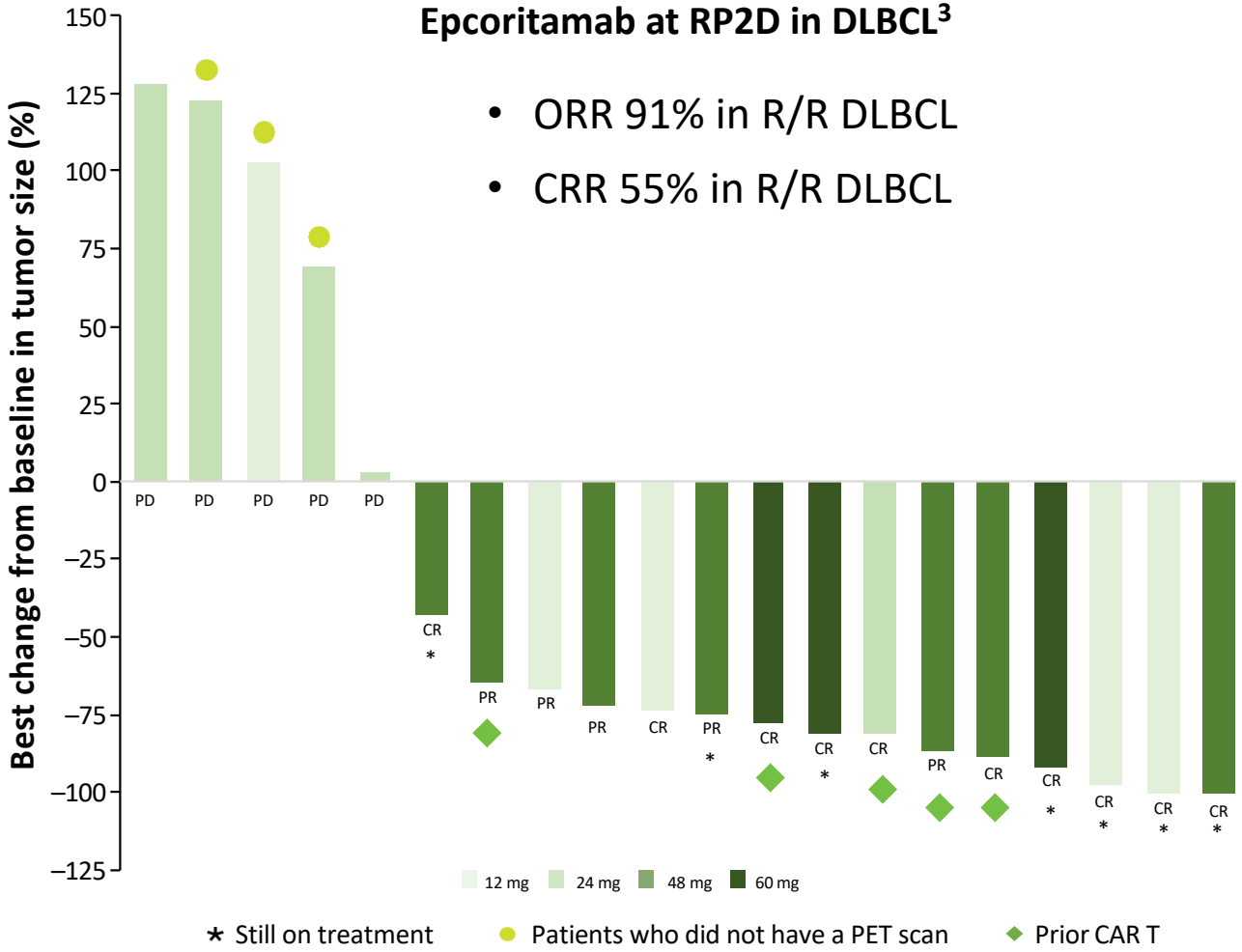
Glofitamab at RP2D in aggressive NHL[1,2]

- ORR 79% in R/R aggressive B-NHL
- CRR 71% in R/R aggressive B-NHL



Epcoritamab at RP2D in DLBCL[3]

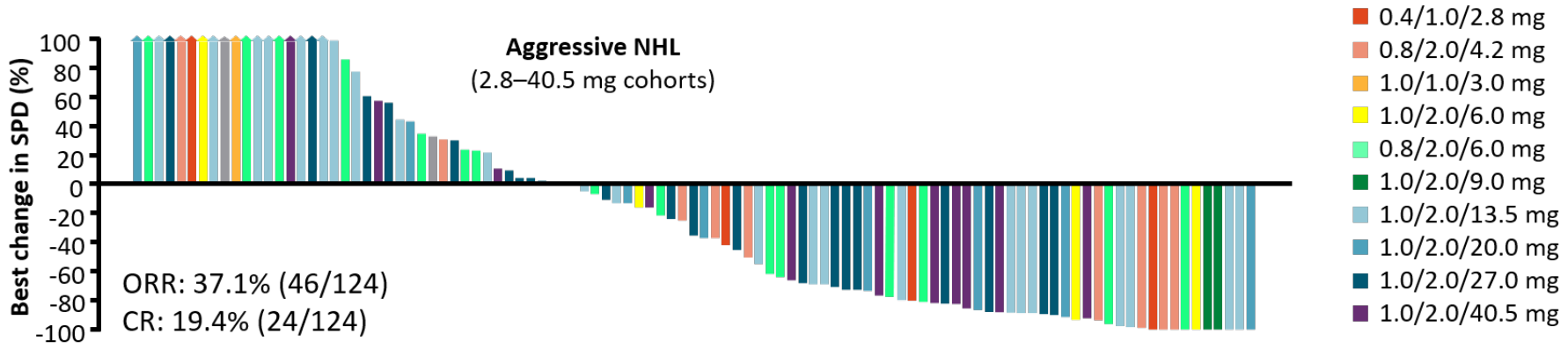
- ORR 91% in R/R DLBCL
- CRR 55% in R/R DLBCL



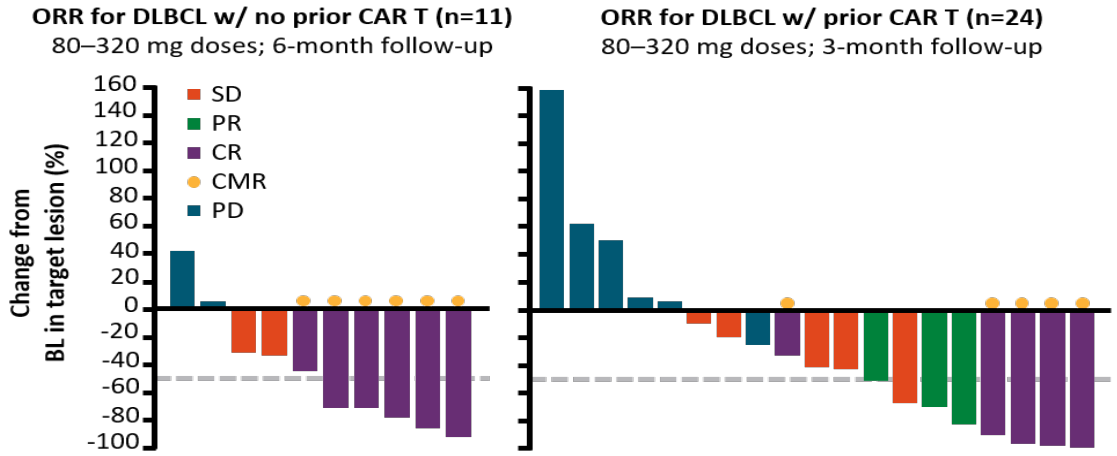
1. Hutchings M, *et al. J Clin Oncol* 2021; **39**:1959–1970; 2. Carlo-Stella C, *et al.* ICML 2021. Abstract 15 (oral); 3. Hutchings M, *et al. Lancet* 2021; 398(10306): 1157-1169.

Activity of mosunetuzumab and odronextamab in r/r aggressive B-NHL

Mosunetuzumab in aggressive NHL[1]



Odronextamab in DLBCL[2]



R/R DLBCL w/no prior CAR T

- ORR: 55% (6/11); CR: 55% (6/11)
- Median duration of CR: NR
- 83% of CRs durable (≥3 months; ≤21 months)

R/R DLBCL w/ prior CAR T

- ORR: 33% (8/24); CR: 21% (5/24)
- Median duration of CR: NR
- 100% of CRs ongoing at last assessment (≤20 months)

1. Schuster SJ, et al. ASH 2019: Abstract 6 (oral presentation) 2. Bannerji R, et al. ASH 2020: Abstract 400 (oral presentation).

Recent data from the DLBCL phase 2 expansion cohorts of the glofitamab and epcoritamab studies

Glofitamab – expansion cohort

Pivotal Phase II expansion in patients with R/R DLBCL and ≥2 prior therapies (NP30179)

Key inclusion criteria

- DLBCL NOS, HGBCL, transformed FL or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - anti-CD20 antibody
  - anthracycline

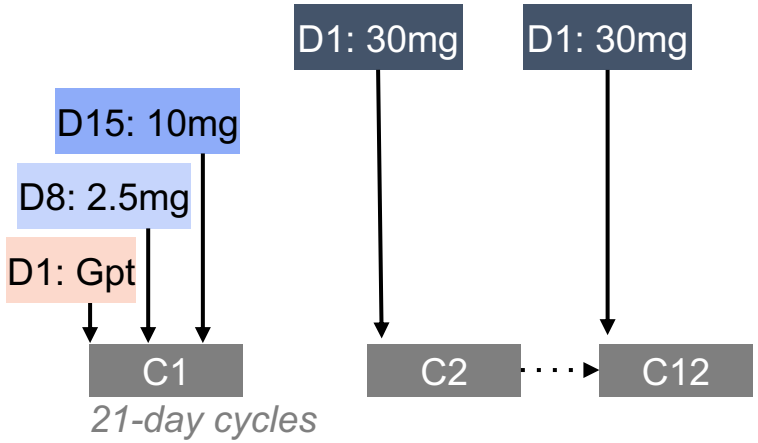
Glofitamab IV administration

Fixed-duration treatment

- max. 12 cycles

CRS mitigation:

- obinutuzumab pretreatment (1 x 1000mg)
- C1 step-up dosing
- monitoring after first dose (2.5mg)



- **Primary: CR (best response) rate by IRC***
- **Key secondary:** ORR rate,† DoR, DoCR,† PFS, and OS

Michael Dickinson,et al. NEJM 2022 & EHA 2022 oral presentation

Baseline characteristics

n (%)*		N=154†
Median age, years (range)		66.0 (21–90)
Male		100 (64.9)
ECOG PS‡	0	69 (44.8)
	1	84 (54.5)
Ann Arbor stage	I	10 (6.5)
	II	25 (16.2)
	III	31 (20.1)
	IV	85 (55.2)
NHL subtype	DLBCL	110 (71.4)
	trFL	27 (17.5)
	HGBCL	11 (7.1)
	PMBCL	6 (3.9)
Bulky disease	>6cm	64 (41.6)
	>10cm	18 (11.7)

n (%)*	N=154
Median no. of prior lines, n (range)	3 (2–7)
2 prior lines	62 (40.3)
≥3 prior lines	92 (59.7)
Prior anti-CD20 Ab	154 (100.0)
Prior anthracycline	149 (96.8)
Prior CAR-T	51 (33.1)
Prior ASCT	28 (18.2)
Refractory to any prior therapy	139 (90.3)
Refractory to last prior therapy	132 (85.7)
Primary refractory	90 (58.4)
Refractory to prior CAR-T	46 (29.9)
Refractory to any prior anti-CD20	128 (83.1)

Heavily pre-treated, highly refractory population

Clinical cut-off date: March 14, 2022; *unless otherwise specified; †safety-evaluable population (all treated patients);
‡ECOG PS 2, n=1 (0.6%); Ab, antibody; ASCT, autologous stem cell transplant; trFL, transformed follicular lymphoma.

Michael Dickinson,et al. NEJM 2022 & EHA 2022 oral presentation

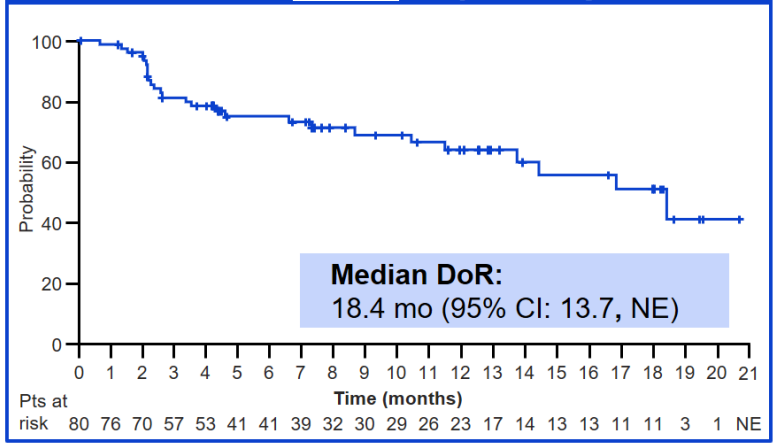
Glofitamab – expansion cohort
Response and duration of response

Efficacy endpoint[1]	Glofitamab 2.5/10/30mg (n=155)
CR rate*	**61 (39.4%)** [95% CI: 31.6%, 47.5%]
ORR*	**80 (51.6%)** [95% CI: 43.5%, 59.7%]

- Median duration of follow-up: 12.6 months (range: 0–22)
- Responses were achieved early: median time to first CR was 42 days (95% CI: 42, 44)

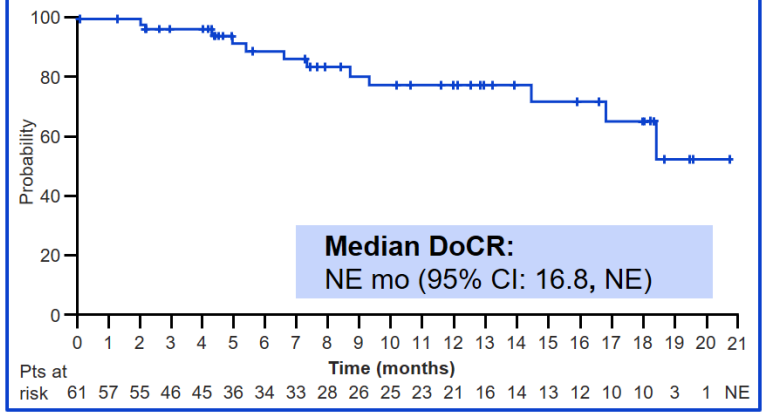
Prior CART : 33%

Duration of overall response by IRC



	N=80
Median DoR follow-up, mo (range)	10.6 (0–21)
12-months DoR, % (95% CI)	**63.6 (51.1, 76.2)**
ORs ongoing at CCOD, n (%)	53 (66.3)

Duration of complete response by IRC



	N=61
Median DoCR follow-up, mo (range)	10.6 (0–21)
12-months DoCR, % (95% CI)	**77.6 (64.3, 90.8)**
CRs ongoing at CCOD, n (%)	49 (80.3)

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Epcoritamab – in aggressive BCL

Dose escalation

Dose expansion data cutoff: January 31, 2022
Median follow-up: 10.7 mo

B-NHL:

- ✓ No DLTs
- ✓ MTD not reached
- ✓ RP2D identified
- ✓ Manageable safety profile
- ✓ Encouraging antitumor activity

Key inclusion criteria:

- R/R CD20^{+} mature B-cell neoplasm
- ECOG PS 0–2
- ≥2 prior lines of antineoplastic therapy including ≥1 anti-CD20 mAb
- FDG PET–avid and measurable disease by CT/MRI
- Prior CAR T allowed

Step-up dosing[a]

Epcoritamab SC RP2D 48 mg
QW C1–3,
Q2W C4–9,
Q4W C10+

→

Treatment until PD[b,c] or unacceptable toxicity

→

LBCL Cohort N=157
DLBCL, HGBCL, PMBCL, and FL Gr3B

- To ensure patient safety and better characterize CRS, inpatient monitoring was required at first full dose for 24 h in this part of the study
- **Primary endpoint:** ORR by Investigator Review Committee (IRC)
- **Key secondary endpoints:** DOR, TTR, PFS, OS, CR rate, and safety/tolerability

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Patients Were Challenging to Treat and Highly Refractory

Demographics	LBCL, N=157
Median age (range), y	64 (20–83)
<65 y, n (%)	80 (51)
65 to <75 y, n (%)	48 (31)
≥75 y, n (%)	29 (18)
ECOG PS, n (%)	
0	74 (47)
1	78 (50)
2	5 (3)
Disease Characteristics[a]	**LBCL, N=157**
Disease type, n (%)	
DLBCL	139 (89)
De novo	97/139 (70)
Transformed	40/139 (29)
Unknown	2/139 (1)
HGBCL	9 (6)
PMBCL	4 (3)
FL Gr3B	5 (3)

Prior Treatments	LBCL, N=157
Median time from initial diagnosis to first dose, y	1.6
Median time from end of last therapy to first dose, mo	2.4
Median prior lines of therapy (range)	3 (2–11)
≥3 Lines of therapy, n (%)	111 (71)
Primary refractory[b] disease, n (%)	96 (61)
Refractory[b] to last systemic therapy, n (%)	130 (83)
Refractory[b] to ≥2 consecutive lines of therapy, n (%)	119 (76)
Prior ASCT, n (%)	31 (20)
Prior CAR T therapy, n (%)	61 (39)
Progressed within 6 mo of CAR T therapy	46/61 (75)

[a]Double/triple-hit patients included, many with responses. [b]Refractory disease is defined as disease that either progressed during therapy or progressed within <6 months of completion of therapy.

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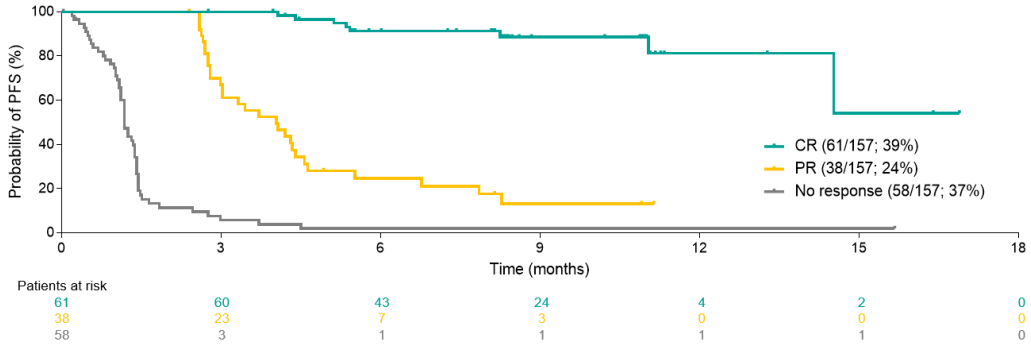
Epcoritamab – expansion cohort
Response rate

Best Overall Response by IRC, n(%)[a]	LBCL N=157
Overall response	**99 (63)** [95% CI: 55–71]
Complete response	**61 (39)** [95% CI: 31–47]
Partial response	38 (24)
Stable disease	5 (3)
Progressive disease	37 (24)

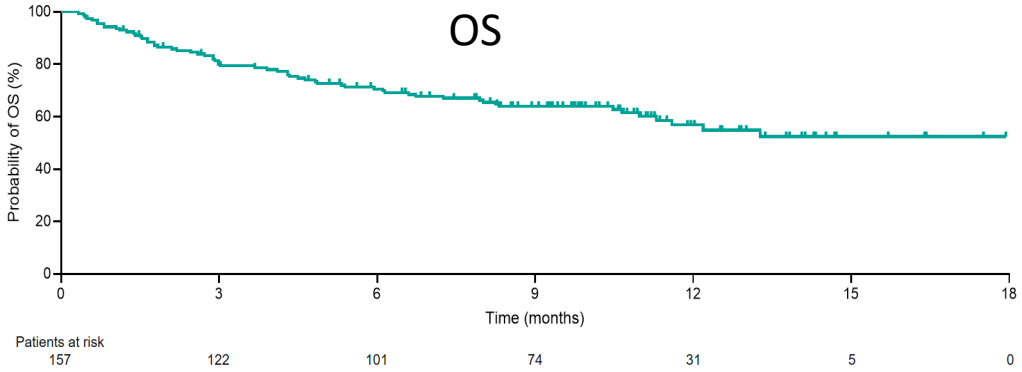
Prior CART : 39%

PFS



Kaplan–Meier Estimate	
Median PFS for complete responders	**Not reached**
Complete responders remaining in complete response at 9 mo	**89%**
Median PFS, mo (95% CI)	4.4 (3.0–7.9)
PFS at 6 mo, % (95% CI)	43.9 (35.7–51.7)

OS



Kaplan–Meier Estimate	N=157
Median OS	**Not reached**
OS at 6 mo, % (95% CI)	70.6 (62.7–77.2)
OS at 12 mo, % (95% CI)	56.9 (47.3–65.4)

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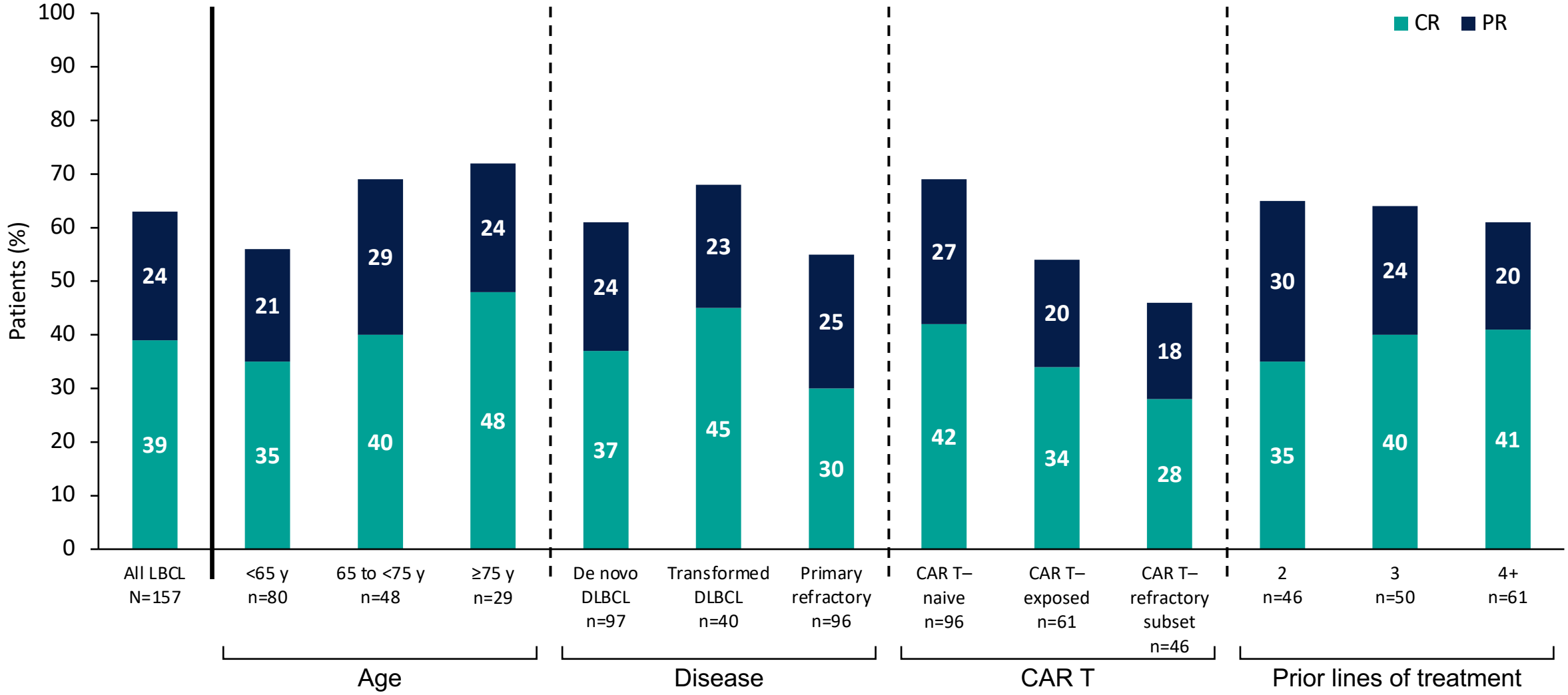
Deep Responses Consistent Across Key Subgroups

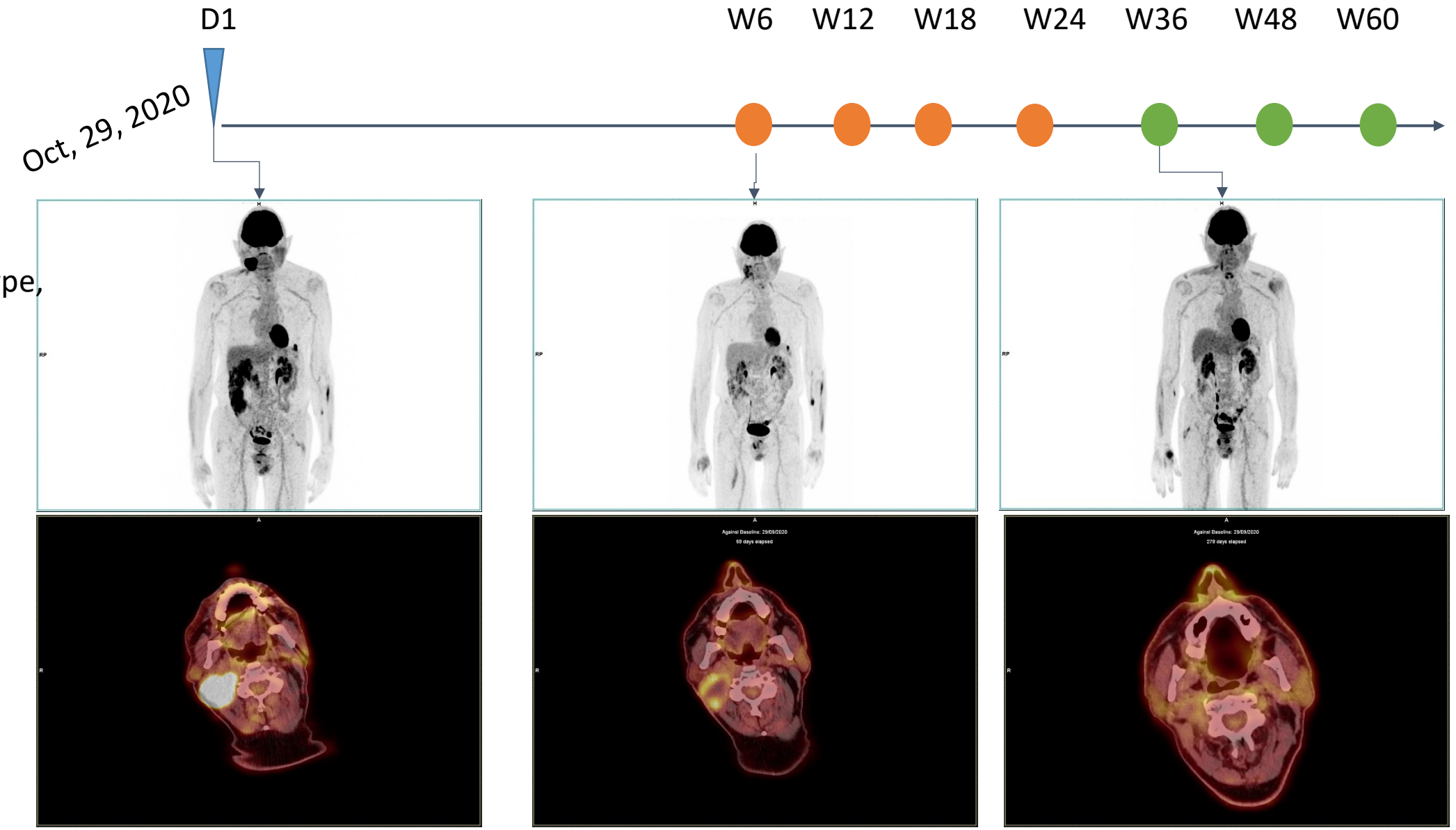


Based on IRC assessment and Lugano criteria.

Thieblemont C, et al. J Clin Oncol 2022

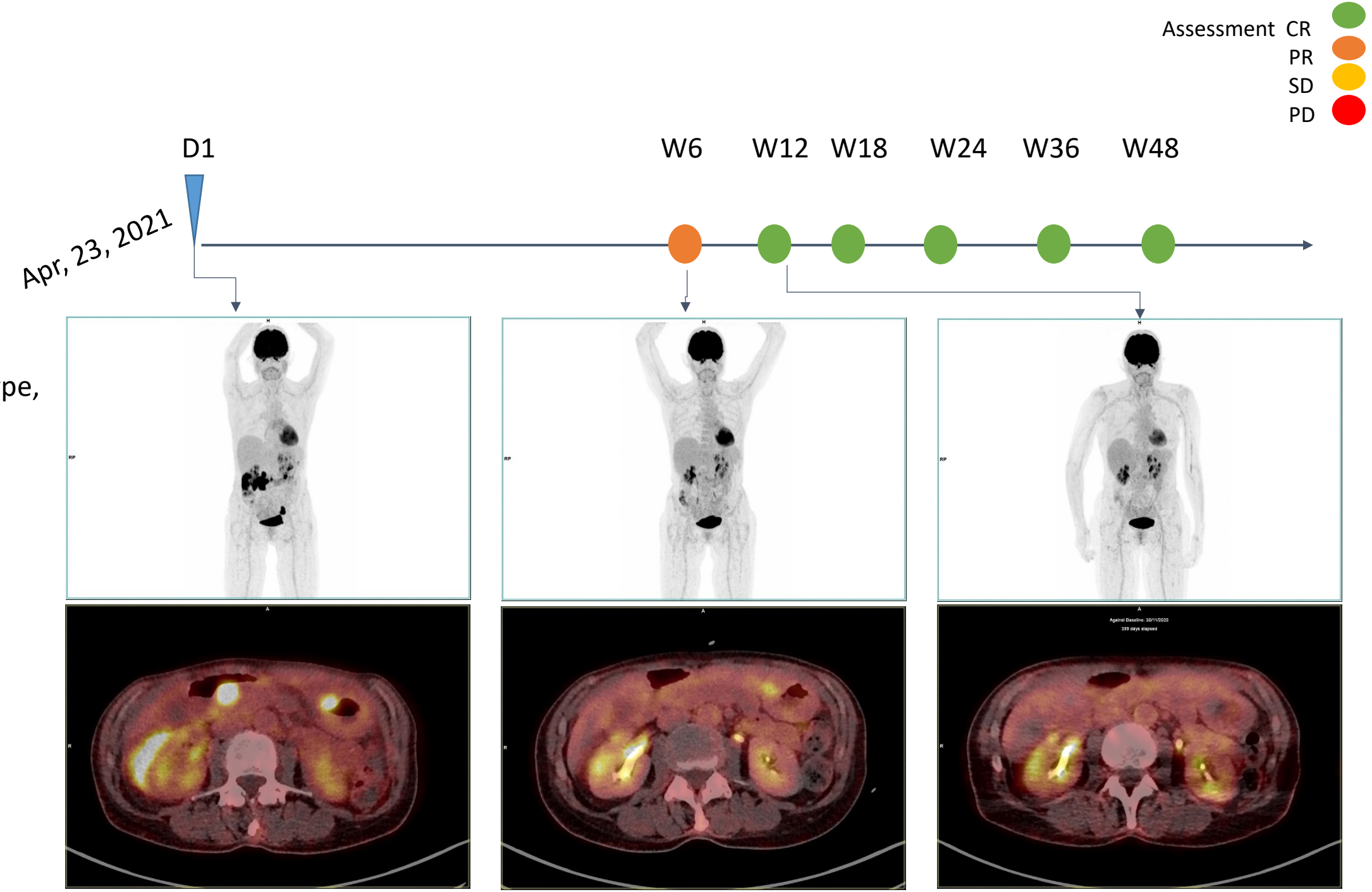
Patient 1. FET

79 y o
PS = 1, No B symptoms
DLBCL GC subtype,
Ki67 90%
Prior lines, n=7
No prior CAR T
Stage III
LDH level :Nl



Patient 2. LEF

59 y o
PS = 1, No B symptoms
DLBCL GC subtype, Ki67 80%
Double HIT
Prior lines, n=5
Prior CAR T
Stage III
Elevated LDH



CRS/neurologic AEs with CD3xCD20 BS Abs

Administration

Bi-specific Anti-body	Targets	Administration
Mosunetuzumab	CD20 x CD3	IV or SC Step-up doses on C1 (D1, D8, D15) → 1mg 2mg 30mg Subsequent 21-day cycles for 8 cycles for patients in CR and up to 17 cycles for those with PR or SD
Glofitamab	$(CD20)_2$ x CD3	IV 21-day cycles up to 12 cycles → Obinutuzumab D-7 2.5mg 10mg 30mg Seven days before 1,000 mg obinutuzumab
Epcoritamab	CD20 x CD3	SC → 0.16mg 0.8mg 24mg or 48mg Weekly dosing in C1-C2 (D1,D8, D15, D22); every 2 weeks in C3–C6 (D1, D15), every 4 weeks from C7 onward Until disease progression or unacceptable toxicity
Odronextamab	CD20 x CD3	IV → 0.2 +0.5 mg 4 +20mg 80mg or 160mg or 320mg Step-up doses on C1 (D1, D2, D8, D9, D15, D16) Weekly dosing C2–C4 (D1,D8, D15), in 21-day cycles After C4, maintenance treatment every 2 weeks Until disease progression or unacceptable toxicity

For review. Barca et al. Frontiers in Immunology 2022 (modified)

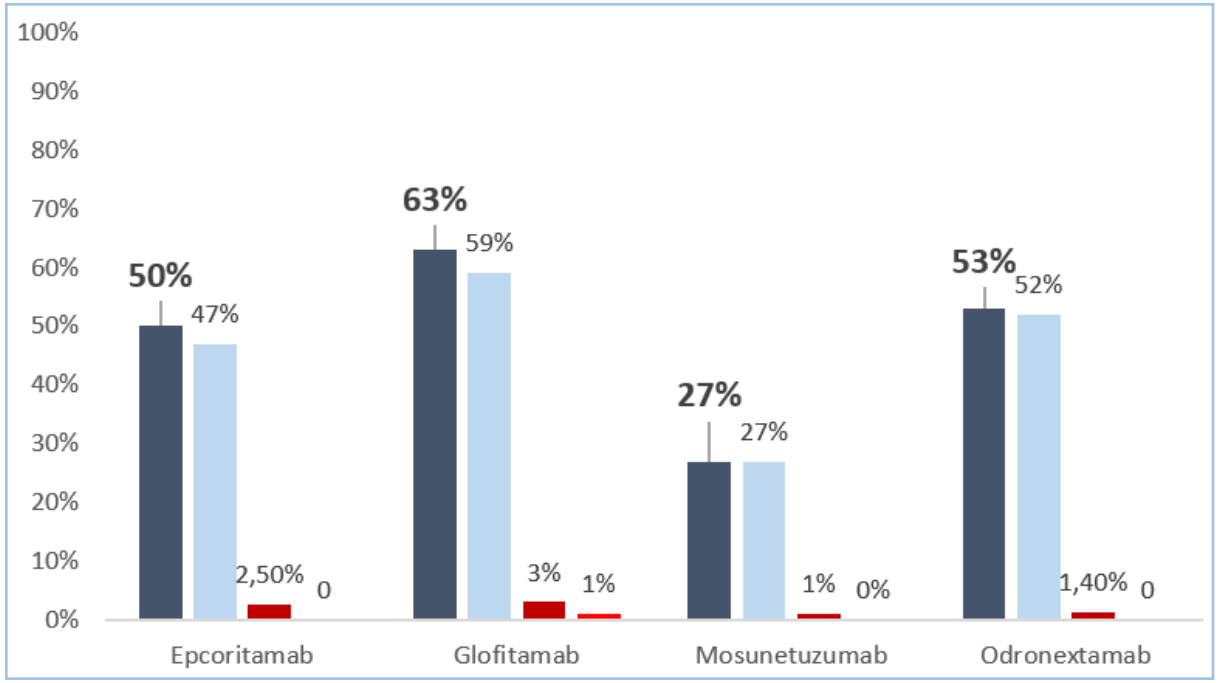
Timing of CRS

Study	Bispecific	Treatment Day	Median time to CRS	Median duration CRS
NCT03625037[1]	**Epcoritamab**	C1D1 (5.8%) C1D8 (11.8%) **C1D15 (42.8%)** C1D22 (4.9%) C2D1+ (3%)	**20 hrs**	**48 hrs**
NCT03075696[2]	**Glofitamab**	**C1D8 (42.8%)** **C1D15 (25.2%)** **C2 (26%)** C3+ (0.9%)	**13.5 hrs (range: 6-52 hrs)**	**30.5 hrs (range 0.5-317)**
NCT02500407[3]	**Mosunetuzumab**	**C1D1 (14.7%)** C1D8 (6.2%) **C1D15 (16.1%)** C2 (1.2%) C3+ (2.9%)	**24 hrs**	**48 hrs (1-20 days)**
NCT03888105[4]	**Odronextamab**	C1 step up	**NA**	**48 hrs (1-133 days)**

1. Thieblemont C, et al *J Clin Oncol.* 2022:JCO2201725. 2.Dickinson MJ, et al. *N Engl J Med.* 2022;387(24):2220-2231. 3.Budde LE, et al *J Clin Oncol.* 2022;40(5):481-491. 4Kim W-S, et al. *Blood.* 2022;140(Supplement 1):1070-1071.

Reported incidence

CRS



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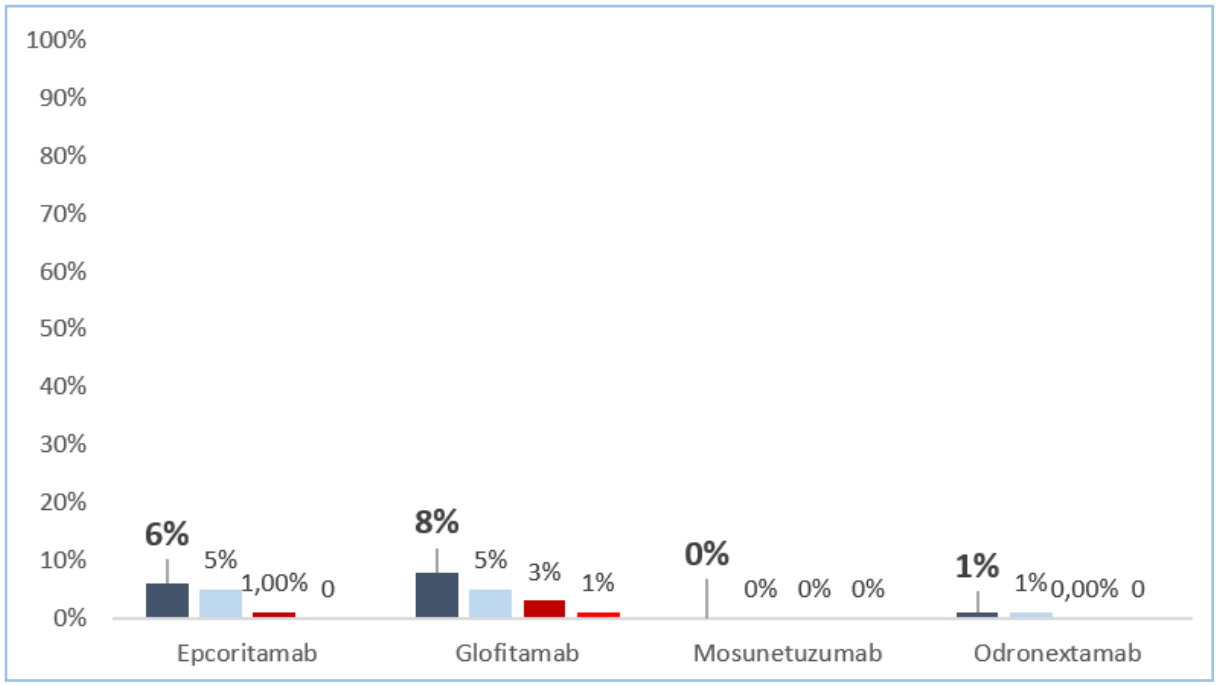


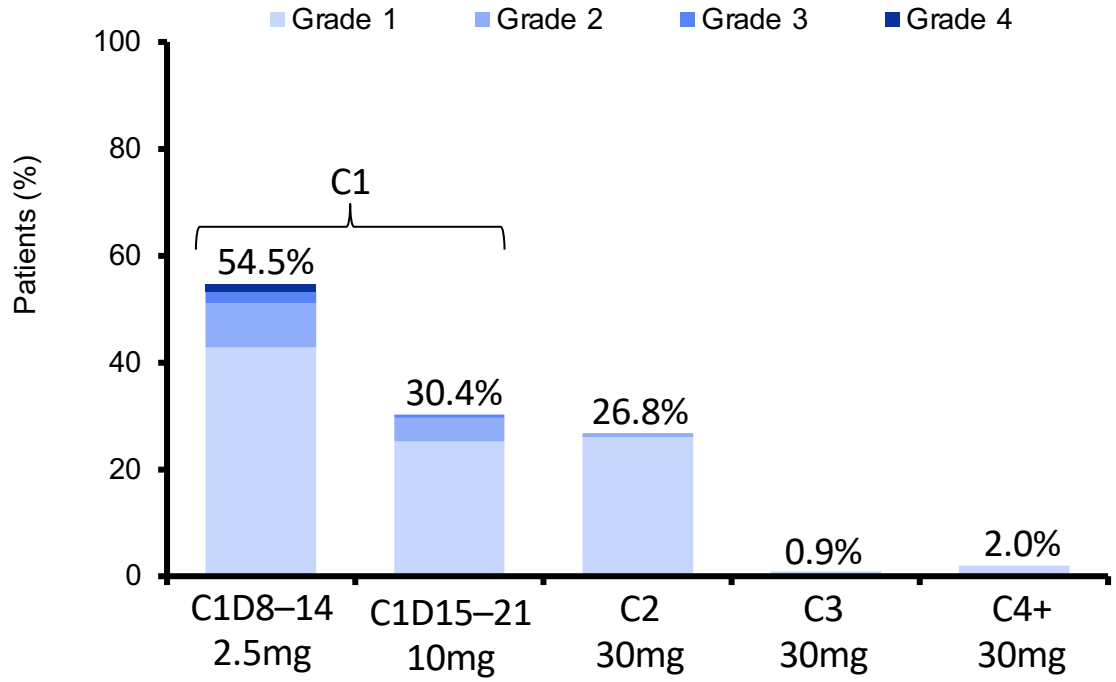
all Grade 1-2 Grade 3 Grade 4-5

Thieblemont C, et al *J Clin Oncol.* 2022:JCO2201725. Dickinson MJ, et al. *N Engl J Med.* 2022;387(24):2220-2231. Budde LE, et al *J Clin Oncol.* 2022;40(5):481-491.Kim W-S, et al. *Blood.* 2022;140(Supplement 1):1070-1071.

Cytokine release syndrome - Glofitamab

n (%)	N=154
CRS (any grade)*	97 (63.0)
Grade 1 (fever)	73 (47.4)
Grade 2	18 (11.7)
Grade 3	4 (2.6)
Grade 4	2 (1.3)
Median time to CRS onset from C1D8 dose, hours (range)	13.6 (6.2–51.8)
Corticosteroids for CRS management	27/97 (27.8)
Tocilizumab for CRS management	31/97 (32.0)

CRS by cycle and grade†



CRS was mostly low grade, time of onset was predictable, and most events occurred during C1

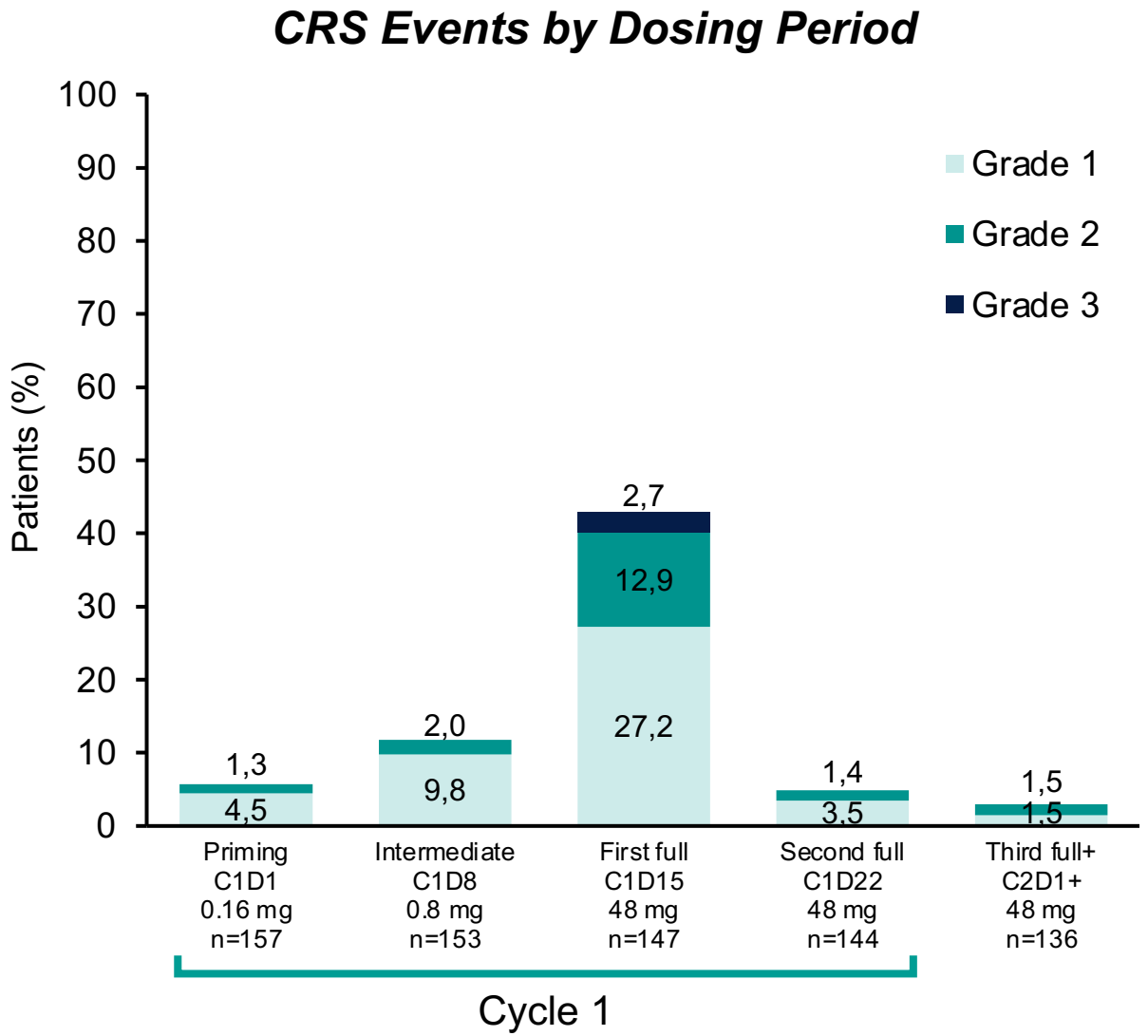
Dickinson M, et al. NEJM 2022 & EHA 2022 oral presentation

Cytokine release syndrome - Epcoritamab

	LBCL N=157
CRS events, n (%)[a]	78 (49.7)
Grade 1	**50 (31.8)**
Grade 2	24 (15.3)
Grade 3	4 (2.5)
Median time to onset from first full dose, d	**0.8 (20 h)**
CRS resolution, n (%)	77 (98.7)
Median time to resolution from first full dose, d	**2 (48 h)**
Treated with tocilizumab, n (%)	22 (14.0)
Treated with corticosteroids, n (%)	16 (10.2)
Leading to treatment discontinuation, n (%)	**1 (0.6)**

[a]Graded by Lee et al. 2019 criteria.

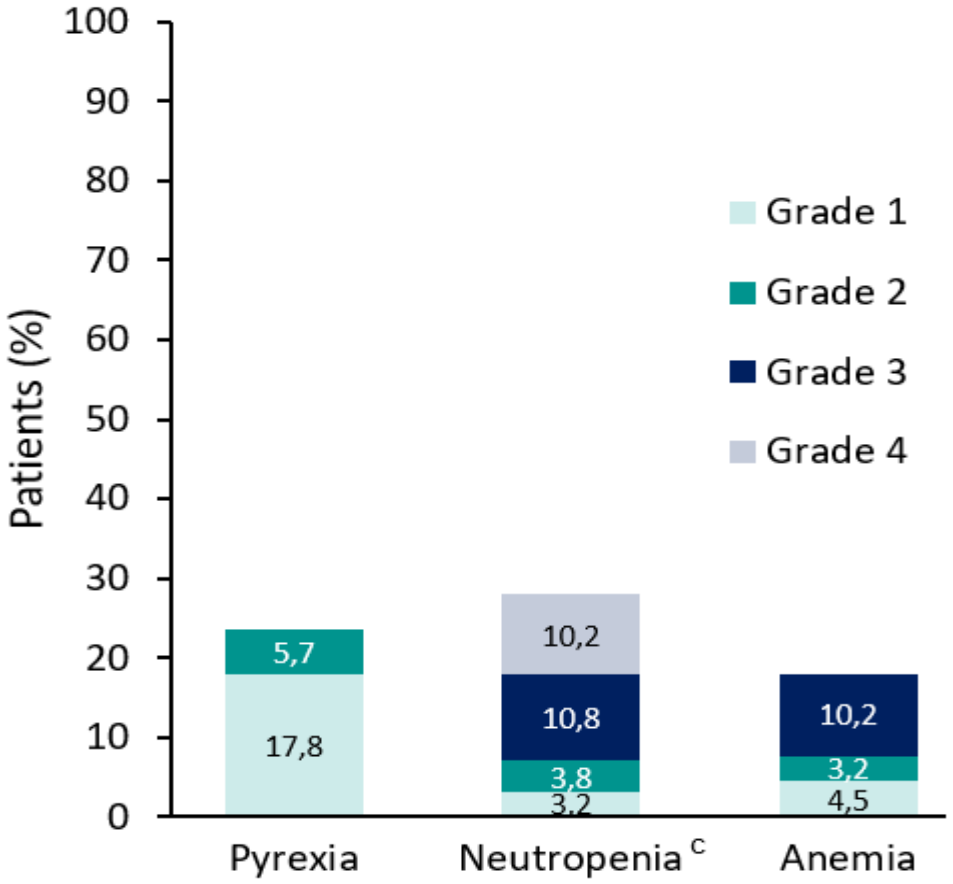
CRS was primarily low grade and predictable: most events occurred following the first full dose



Thieblemont C, et al. J Clin Oncol 2022 and EHA oral presentation

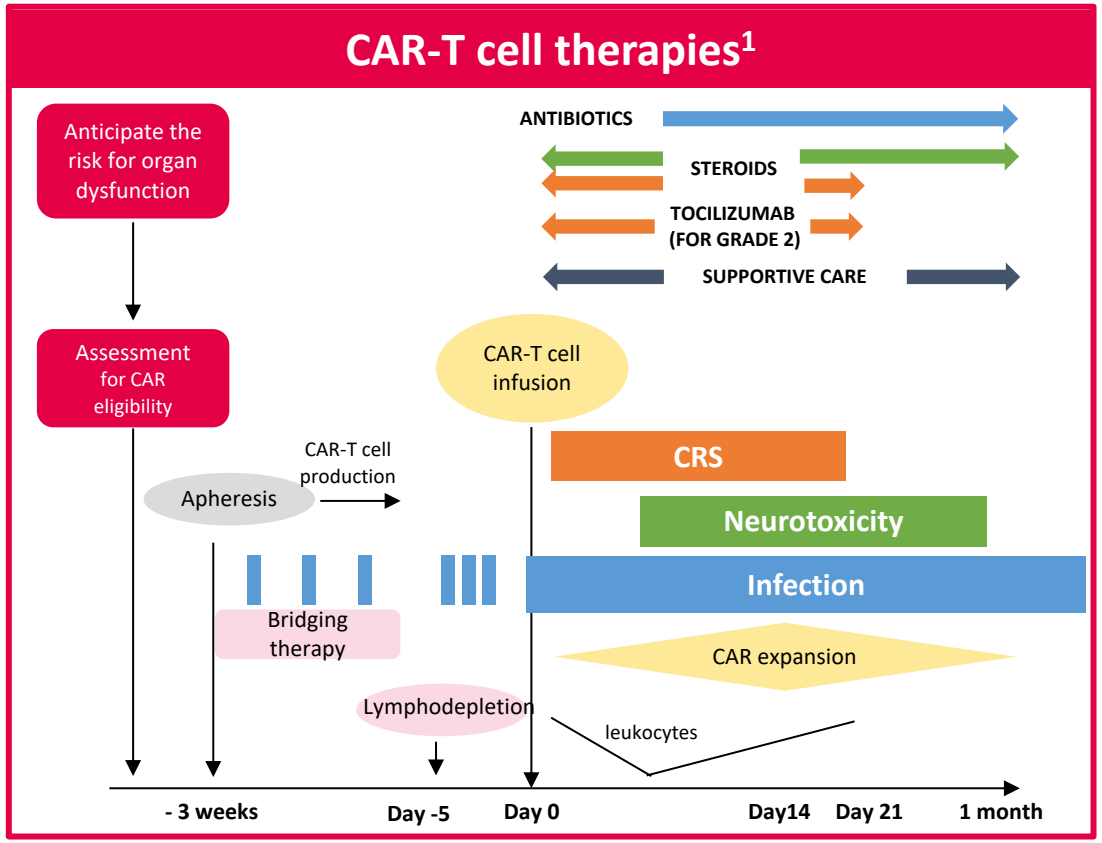
Neutropenia

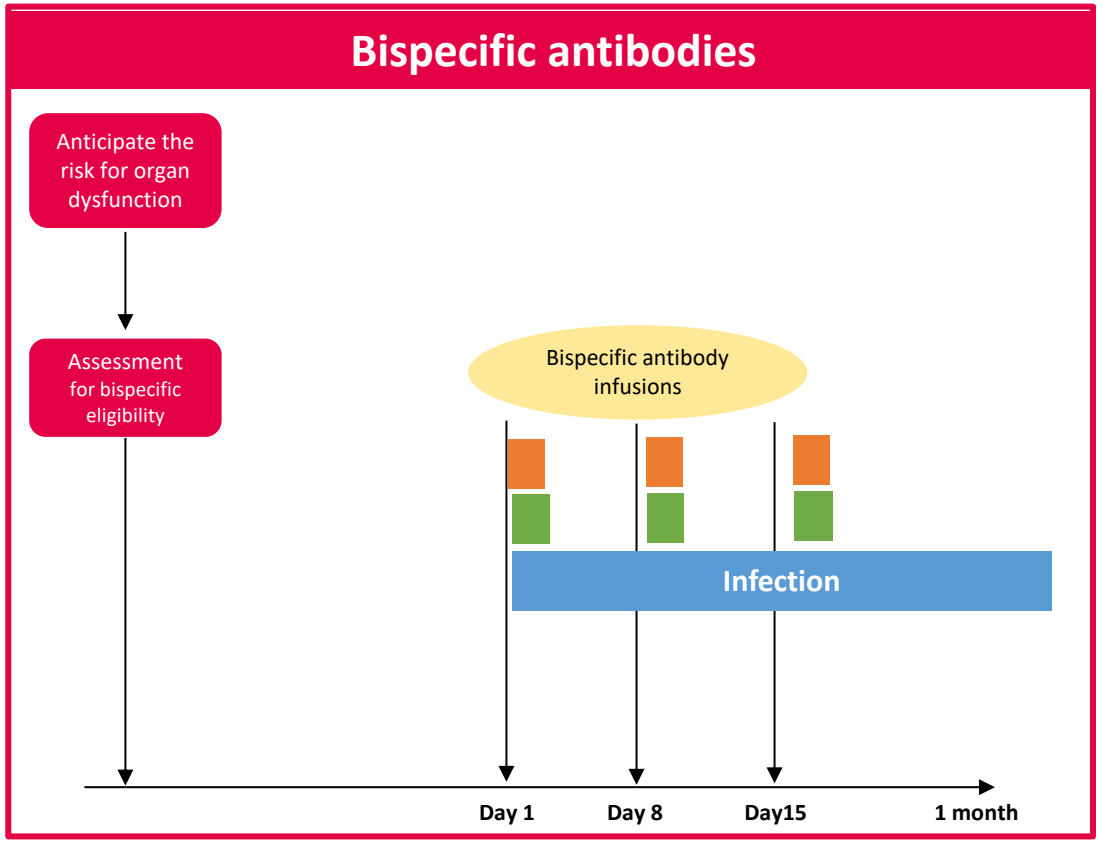
		Grade ≥ 3 neutropenia
Schuster GO29781	Mosunetuzumab N=270	**42 (16%)**
Thieblemont GCT3013-01	Epcoritamab N=157	**33 (21%)**
Hutchings	Glofitamab N=171	**43 (25%)**
Bannerji	Odornextamab N=127	**NR**



Thieblemont C, et al. J Clin Oncol 2022 and EHA oral presentation

Toxicities and management following treatment with T-cell engaging therapies





4 days (IQR 1-6)	CRS	24–48 h after the first full dose
9 days (IQR 7-22)	ICANS	24–48 h after the first full dose
during bridging therapy, after infusion	Infections	throughout treatment

1.Adapted from Azoulay E *et al. Intensive Care Med* 2020;46:1723–6

Management de patients treated with Bispecific Abs

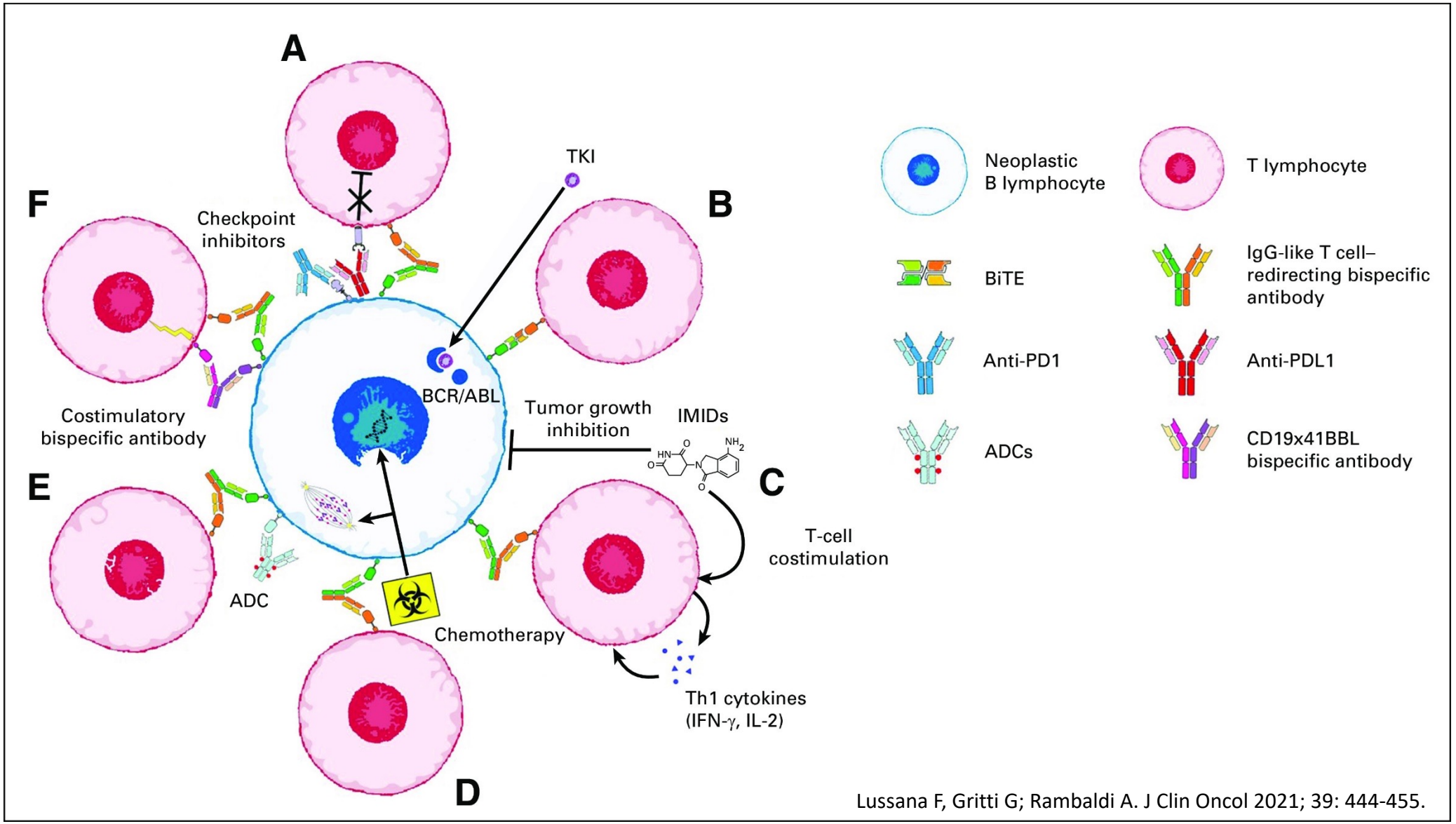
- **Baseline evaluation before administration**
- **Premedication with cortisteroids + dephenydramine + paracetamol**
- **Monitoring for toxicities**
- **Patient education and responsabilities**

Combination studies

MOSUN	**First line**	**Aggressive NHL**	Mosunetuzumab + CHOP or polatuzumab vedotin- CHP	Untreated NHL	Phase 1b/2	NCT03677141
		Indolent NHL	Mosunetuzumab (SC) + lenalidomide	FL and MZL	Phase 2	NCT04792502
GLOFI	**First line**	**Aggressive NHL**	Glofitamab + R-CHOP or Polatuzumab vedotin- R-CHP	Untreated DLBCL (young, high risk)	Phase 1/2	NCT04914741
	R/R in combination	**Indolent NHL**	Mosunetuzumab + lenalidomide vs glofitamab + **lenalidomide** ± obinutuzumab	R/R FL	Phase 1/2	NCT04246086
		Aggressive NHL	Mosunetuzumab **+ GemOx** or glofitamab + **GemOx**	R/R DLBCL or high grade DLBCL	Phase 1b	NCT04313608
			Glofitamab + **GemOx** vs R-GemOx	R/R DLBCL	Phase 3	NCT04408638
		NHL	Glofitamab + **atezolizumab** or **polatuzumab vedotin**	R/R NHL	Phase 1b	NCT03533283
			Glofitamab + **RO7227166**	R/R NHL	Phase 1	NCT04077723
			Mosunetuzumab or glofitamab in combination with **CC-220 and CC-99282**	R/R NHL	Phase 1b	NCT05169515
EPCO	**R/R or first line in combination**	**NHL**	Epcoritamab + R-DHAX/C Epcoritamab + GemOx Epcoritamab + R-Lenalidomide Epcoritamab + R-CHOP Epcoritamab + R-B	R/R DLBCL R/R DLBCL R/R FL Untreated DLBCL Untreated FL	Phase 1b/2	NCT04663347
	R/R in combination	**Aggressive NHL**	Epcoritamab vs R-GemOx or R-B	R/R DLBCL	Phase 3	NCT04628494
ODRO	**R/R in combination**	**NHL**	Odronextamab + cepilimab	R/R NHL	Phase 1	NCT02651662

For review. Barca et al. Frontiers in Immunology 2022

How to get deeper and more durable responses



Lussana F, Gritti G; Rambaldi A. J Clin Oncol 2021; 39: 444-455.

Conclusions

- The CD3/CD20 bispecific antibodies show an antitumor activity which is unprecedented in heavily pretreated r/r B-NHL
- Data from DLBCL phase 2 expansion cohorts (35-40% with prior CAR-T):
  - Glofitamab: ORR 52%, CRR 39%
  - Epcoritamab: ORR 63%, CRR 39%
- The toxicity profile is favourable:
  - Very little CRS > grade 2
  - Very little treatment-related CNS toxicity
- CRS is highly predictable and almost always confined to the cycle 1
- The toxicity profile and mechanism of action make the bispecifics ideal for combination strategies