ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

POLICLINICO DI
SANT'ORSOLA

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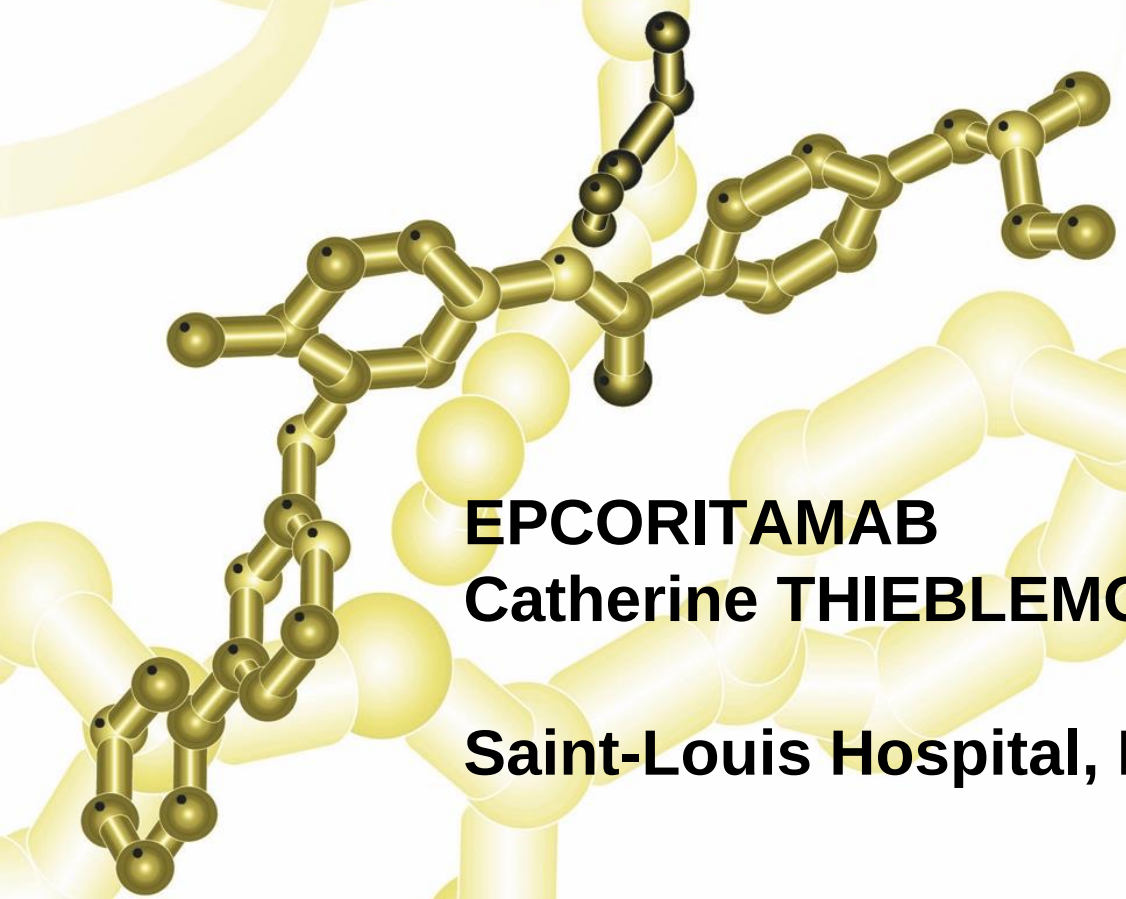
New Drugs in Hematology



EPCORITAMAB

Catherine THIEBLEMONT

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Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
January 15-17, 2024

Disclosures of Catherine Thieblemont

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche						x	travel
BMS						x	travel
Kyte/Gilead						x	travel
Novartis						x	travel
Incyte						x	travel
Takeda						x	travel
Abbvie						x	travel

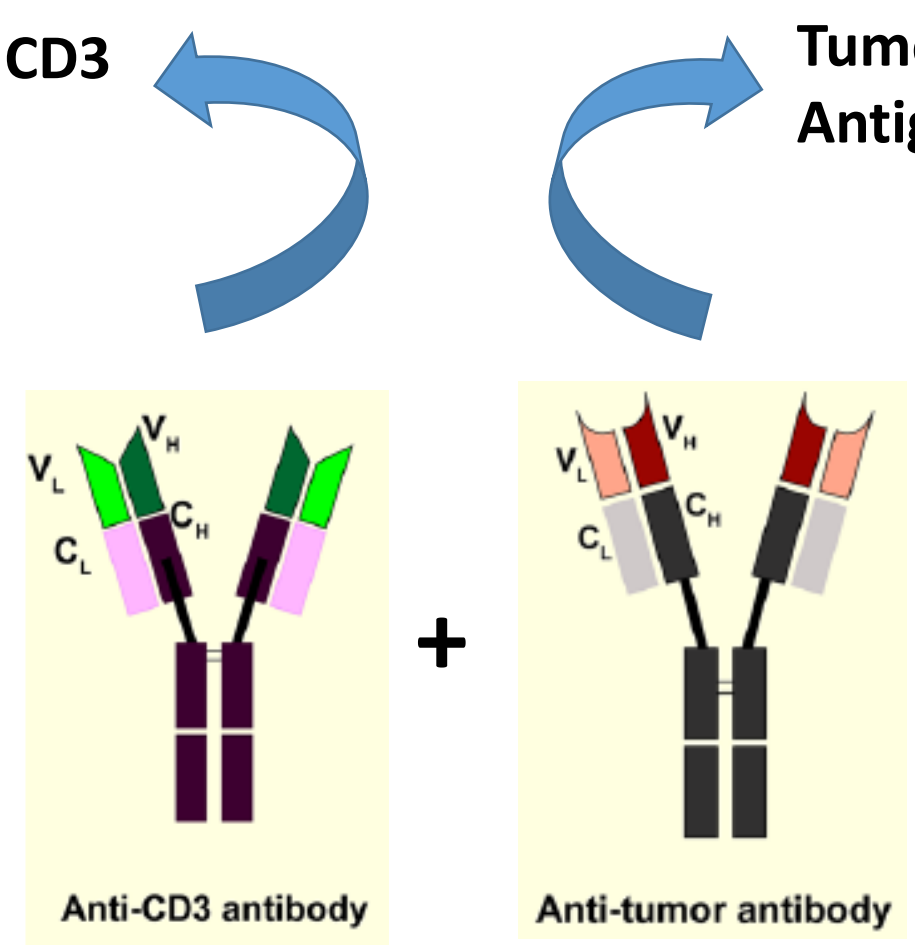
Immunotherapy in oncology

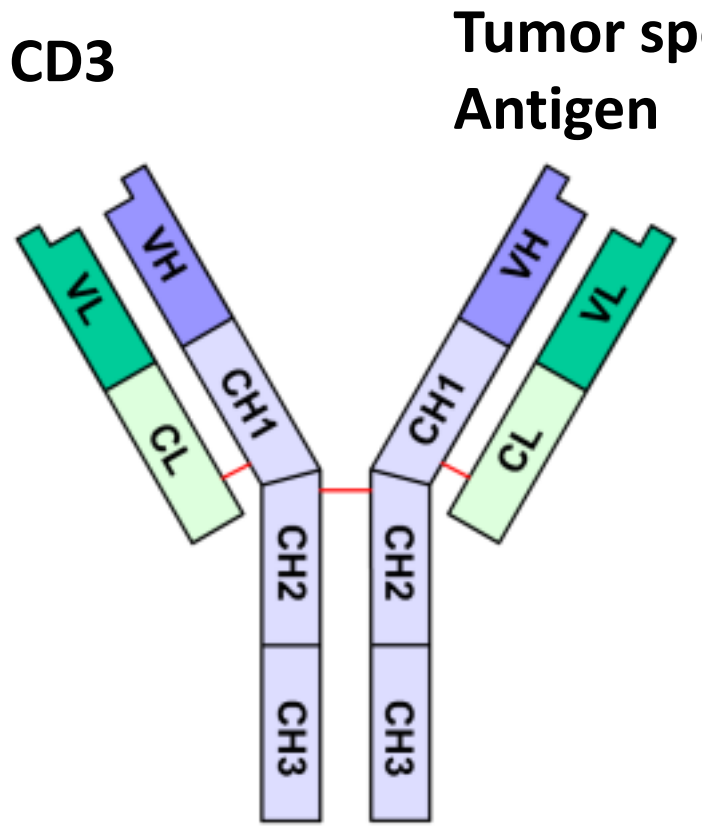
includes a broad range of agents, including

- **antibodies**
- **vaccines**
- **cytokines**
- **oncolytic viruses**
- **bispecific antibodies (BsAbs)**
- **cellular therapies : CAR T-cells**

June C & Sadelain M. N Engl J Med 2018;379:64-73.

Structure of Bs Abs



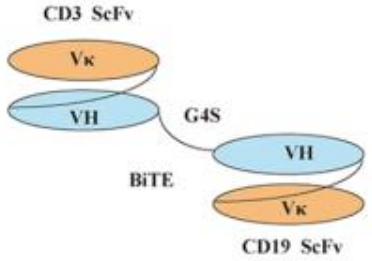


designed to target simultaneously

Tian et al J Hematol Oncol 2021

In hematology, Bispecifics T-cell Engagers (BiTEs) under clinical development

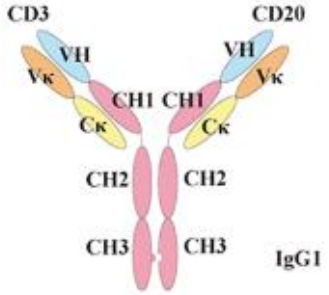
CD3 x CD19



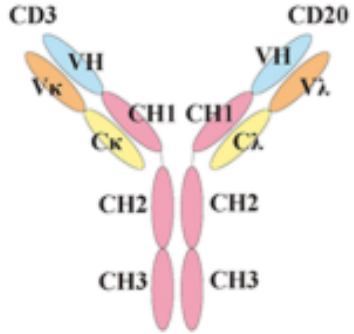
Blinatumomab

CD3 x CD20

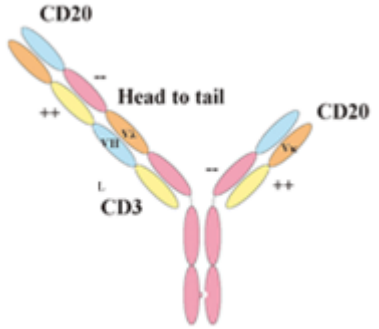
Ig G-based



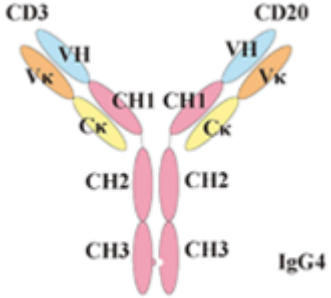
Mosunetuzumab



Epcoritamab

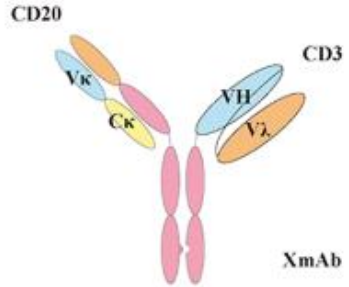


Glofitamab



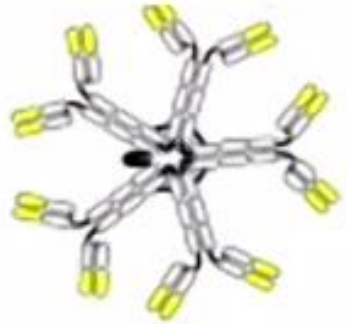
Odronextamab

Under development



Plamotamab

Ig M-based

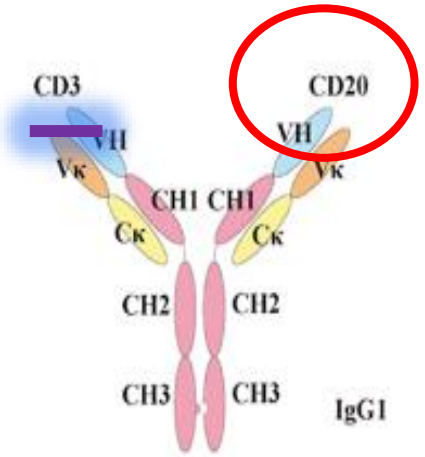


Imvotamab

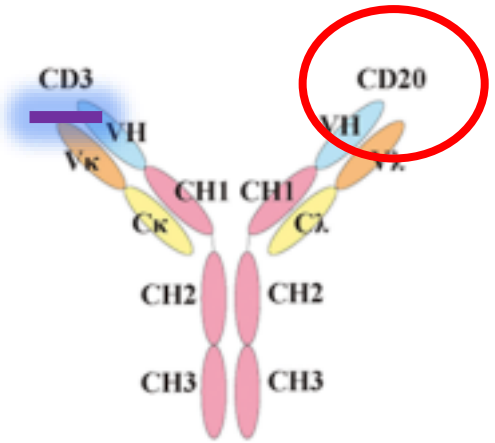
Adapted Ma et al. Frontiers in Immunology 2021

Avidity binding to CD20

1:1 format

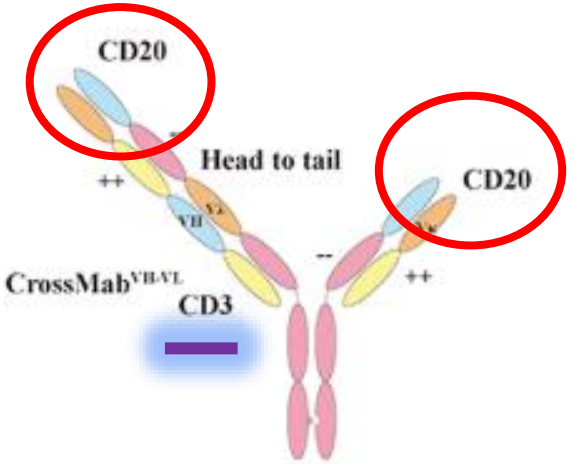


Mosunetuzumab



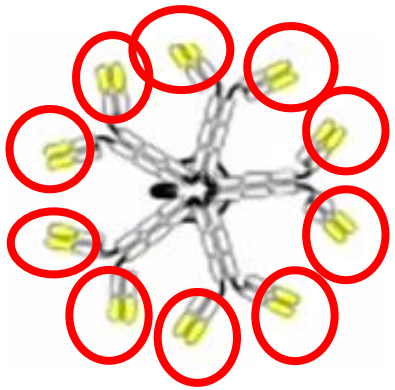
Epcoritamab

2:1 format



Glofitamab

10:1 format



Imvotamab

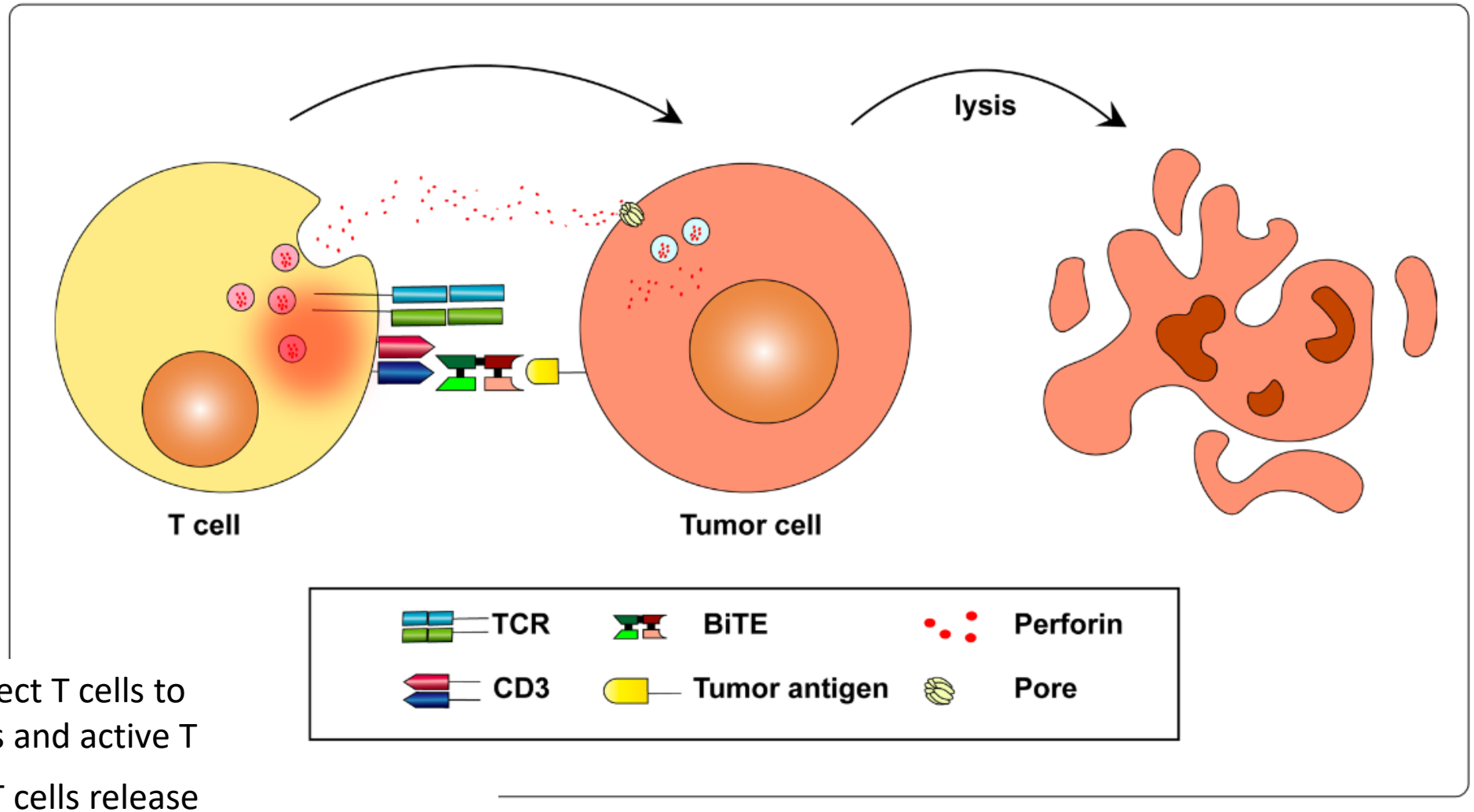
Bacac M, *et al. Clin Cancer Res* 2018; **24**;4785–97

Comparative characteristics of CD20XCD3 BsAb in B NHL

	structure	Target ratio : CD3 ratio	Half-life	Administration	Fc binding	Complement binding	CD3 recognition
Blinatumomab	scFv	1:1	20 min	IV	No	No	CD3δε
Mosunetuzumab	IgG1	1:1	7-21 d	IV / sc	minimal	No	CD3δε
Epcoritamab	IgG4	1:1	7-21 d	sc	minimal	No	CD3ε
Glofitamab	IgG1	2:1	7-21 d	IV	minimal	No	CD3ε
TNB486	IgG4	1:1	7-21 d	IV	minimal	No	CD3δε
Imvotamab	IgM	10:1	3-7 d	IV	Yes	Yes	CD3δε

Mode of action

Tumor cell lysis mediated by the BiTEs



- BiTEs redirect T cells to tumor cells and active T
- Activated T cells release perforin and other granzymes through immunological synapses

Tian et al J Hematol Oncol 2021

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

Phase 2 expansion of epcoritamab study in R/R DLBCL

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

Catherine Thieblemont, et al. J Clin Oncol 2022 & EHA 2022 oral presentation

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.

Catherine Thieblemont, et al. J Clin Oncol 2022

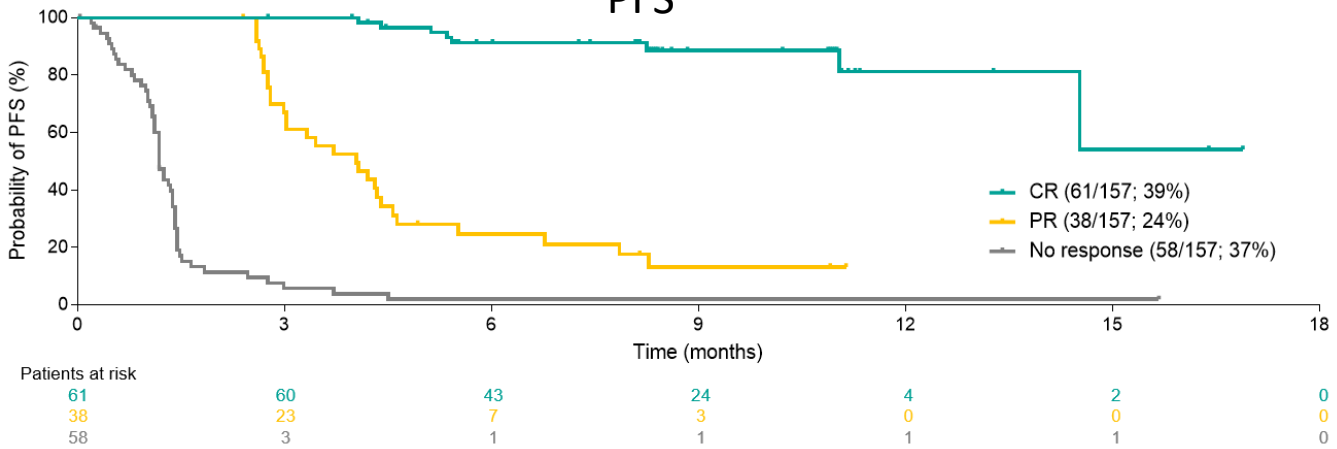
Epcoritamab – expansion cohort
Response rate

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%

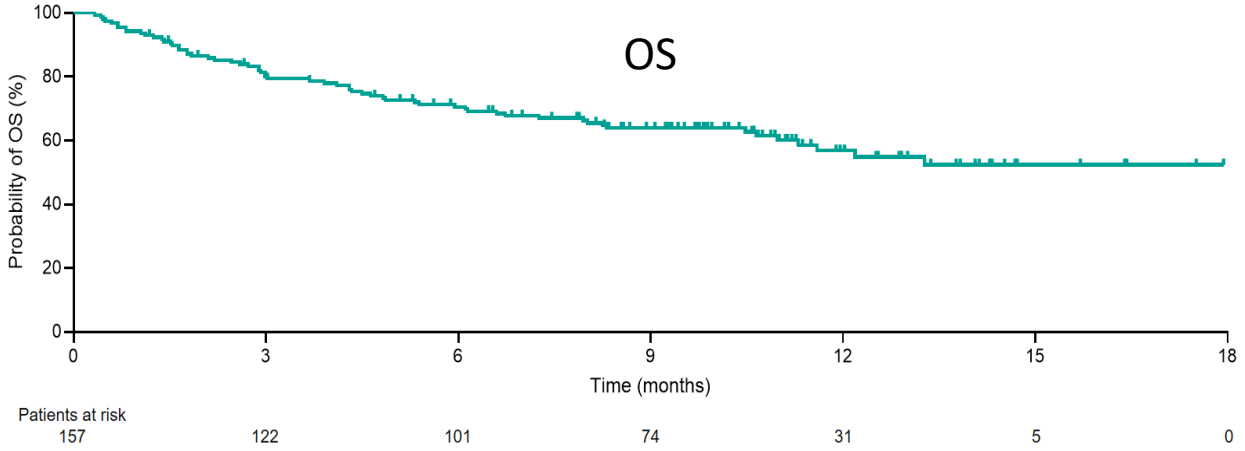
Catherine Thieblemont, et al. J Clin Oncol 2022

PFS



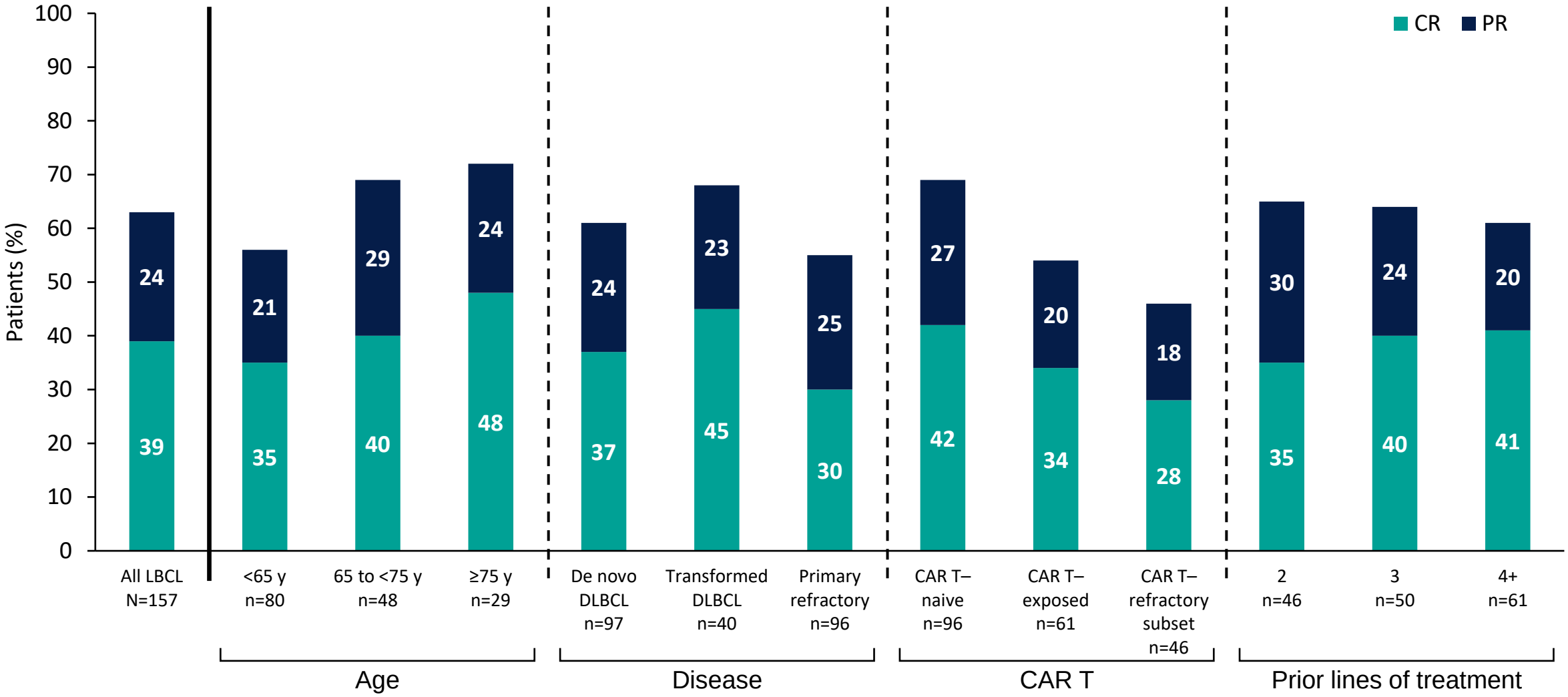
Kaplan–Meier Estimate	
Median PFS for complete responders	**Not reached**
Complete responders remaining in complete response at 9 mo	**89%**
Median PFS, mo (95% CI)	4.4 (3.0–7.9)
PFS at 6 mo, % (95% CI)	43.9 (35.7–51.7)

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)

Deep Responses Consistent Across Key Subgroups



Based on IRC assessment and Lugano criteria.

Thieblemont C, et al. J Clin Oncol 2022

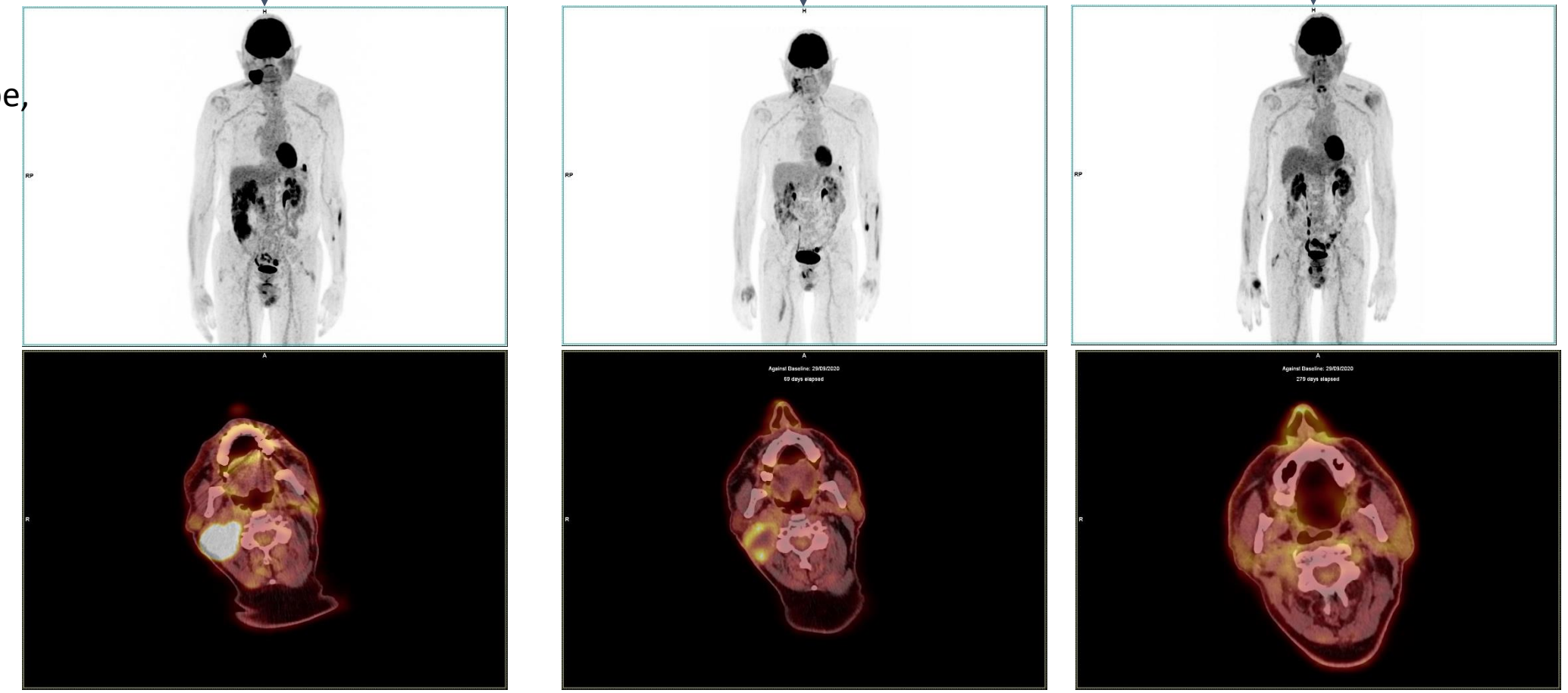
Patient 1. FET

Assessment CR
PR
SD
PD

D1 W6 W12 W18 W24 W36 W48 W60

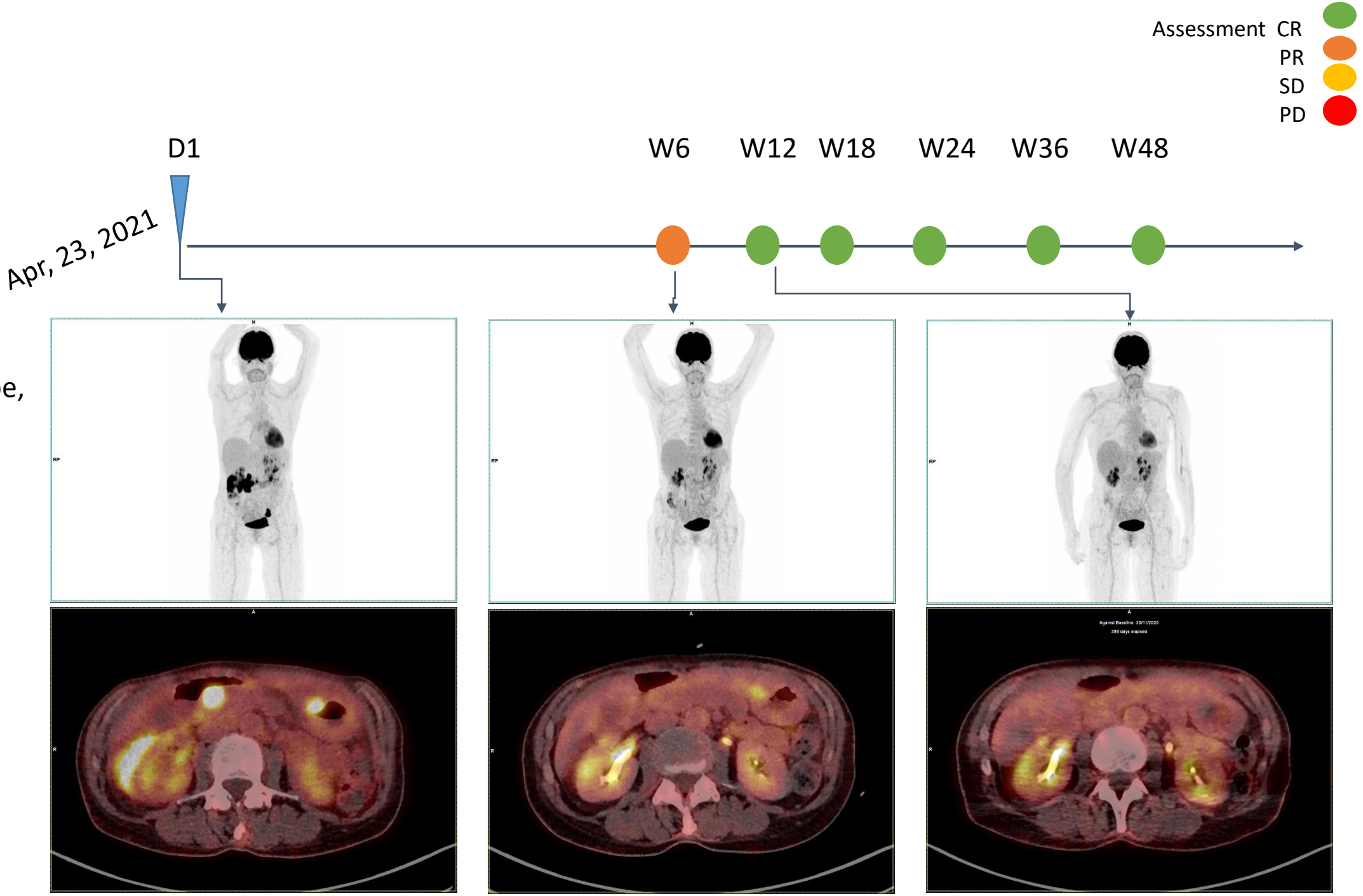
Oct, 29, 2020

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



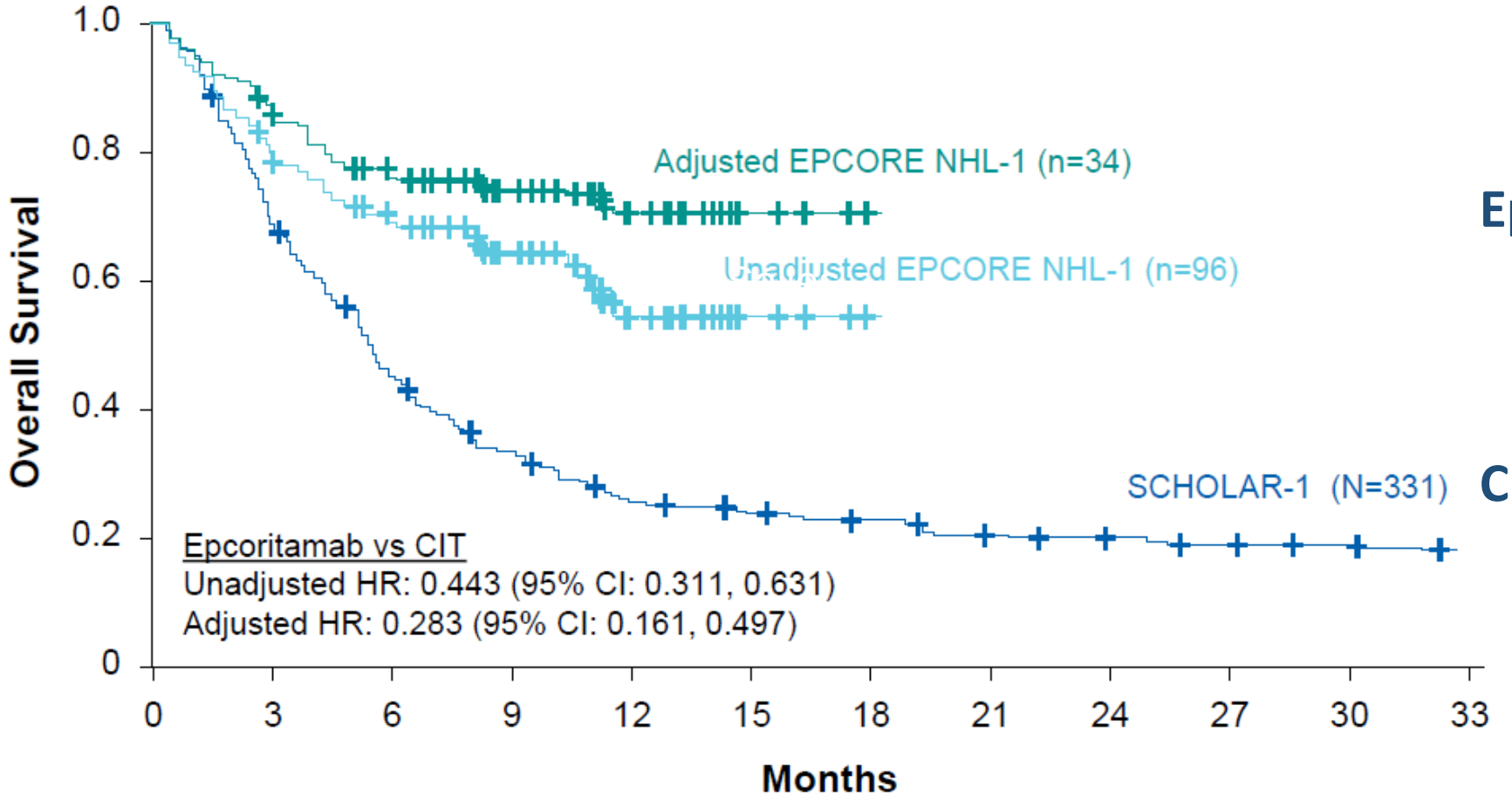
Patient 2. LEF

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



OS: Epcoritamab vs Chemotherapy (historical comparison)

Figure 3. Comparison of OS vs SCHOLAR-1



Epcoritamab

Chemotherapy

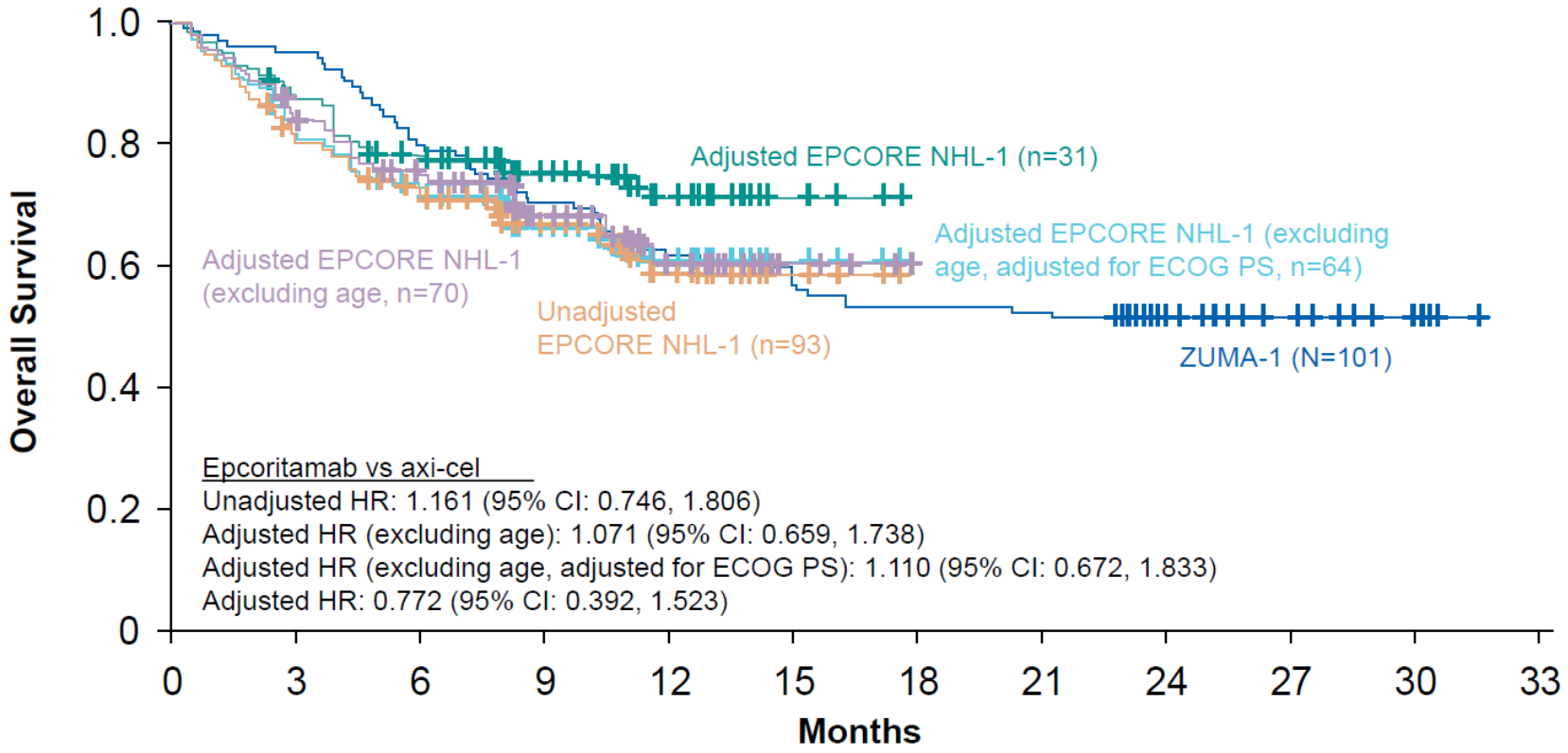
CIT, chemoimmunotherapy; HR, hazard ratio; OS, overall survival.

Salles G et al., *ASH, 2022, Abstr 4912*

OS : epco vs CAR-T (Historical comparison)

Université de Paris

Figure 4. Comparison of OS vs non-ITT ZUMA-1 Study Population



Number at risk												
EPCORE NHL-1	93	74	61	41	21	4	0					
ZUMA-1	101	96	80	70	61	56	53	52	50	25	7	0

Salles G et al., *ASH, 2022, Abstr 4912*

CRS/neurologic AEs with CD3xCD20 Bs Abs

Administration

Ramp-up administration ++++

Cycling, 21 days		C1 D1	C1 D8	C1 D15	C2	C3
Epcoritamab	sc	0.16mg	0.8mg	48mg /24mg	48mg /24mg	48mg /24mg
Mosunetuzumab	IV / sc	1 mg	2 mg	30 mg	30 mg	30 mg
Glofitamab	IV	Obinutuzumab 1000	2.5 mg	10 mg	30 mg	30 mg
Odronextamab	IV	D1,D2 0.2 +0.5mg	D8,D9 4 +20mg	D15,D16 80mg	80mg	80mg

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)**

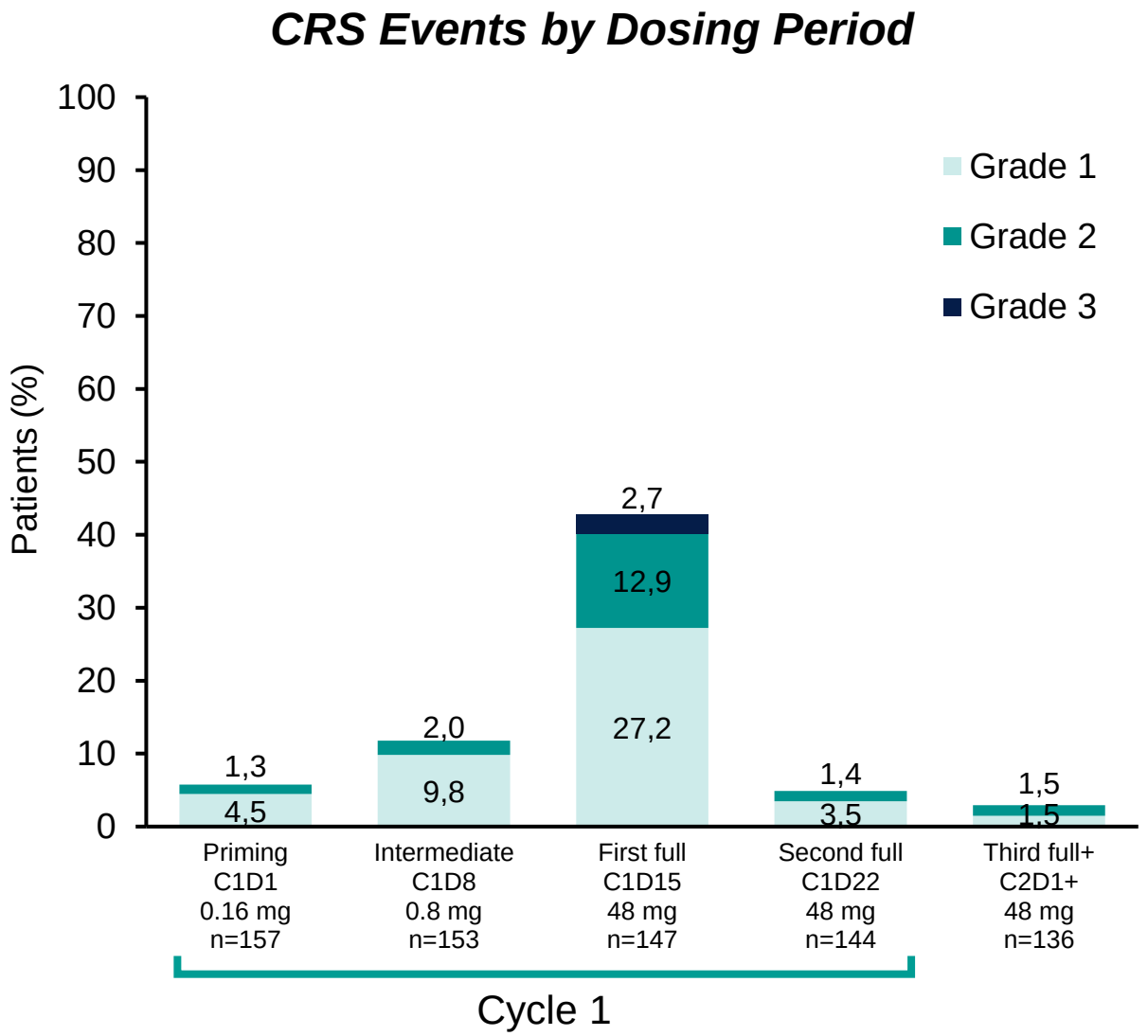
1. Thieblemont C, et al *J Clin Oncol.* 2022:JCO2201725. 2.Dickinson MJ, et al. *N Engl J Med.* 2022;387(24):2220-2231. 3.Budde LE, et al *J Clin Oncol.* 2022;40(5):481-491. 4Kim W-S, et al. *Blood.* 2022;140(Supplement 1):1070-1071.

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.

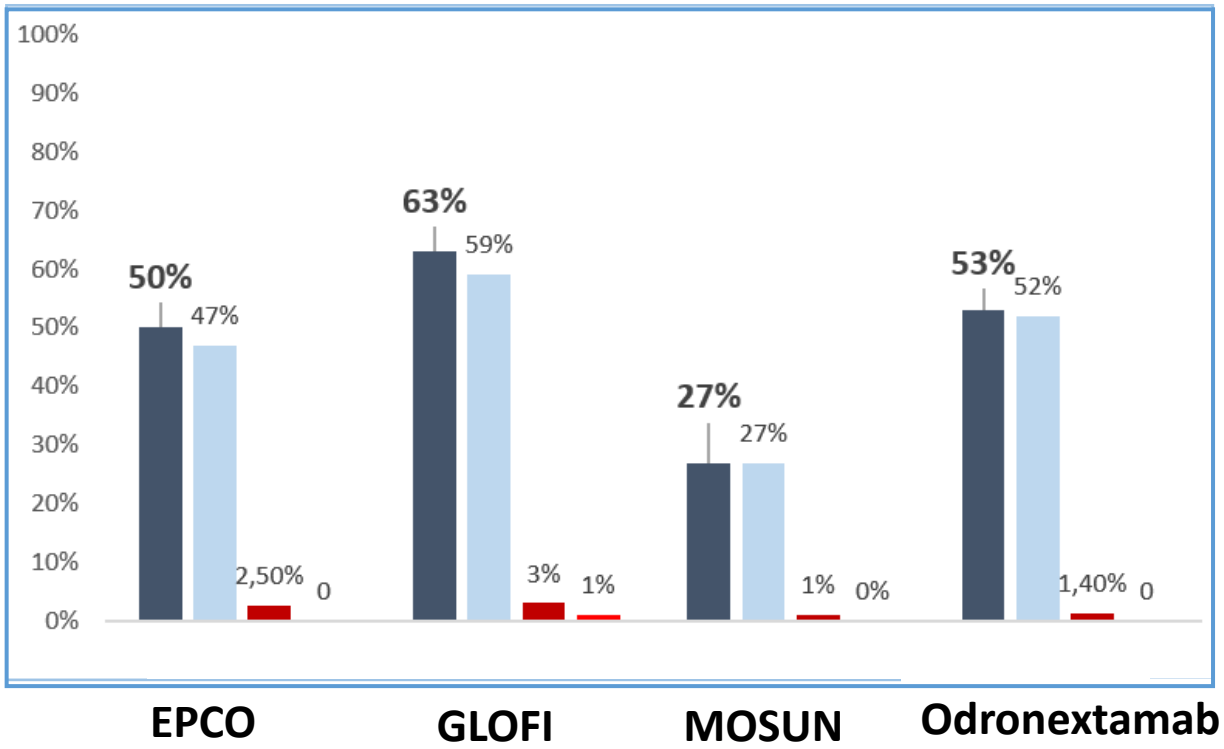
CRS was primarily low grade and predictable: most events occurred following the first full dose



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

Reported incidence

CRS



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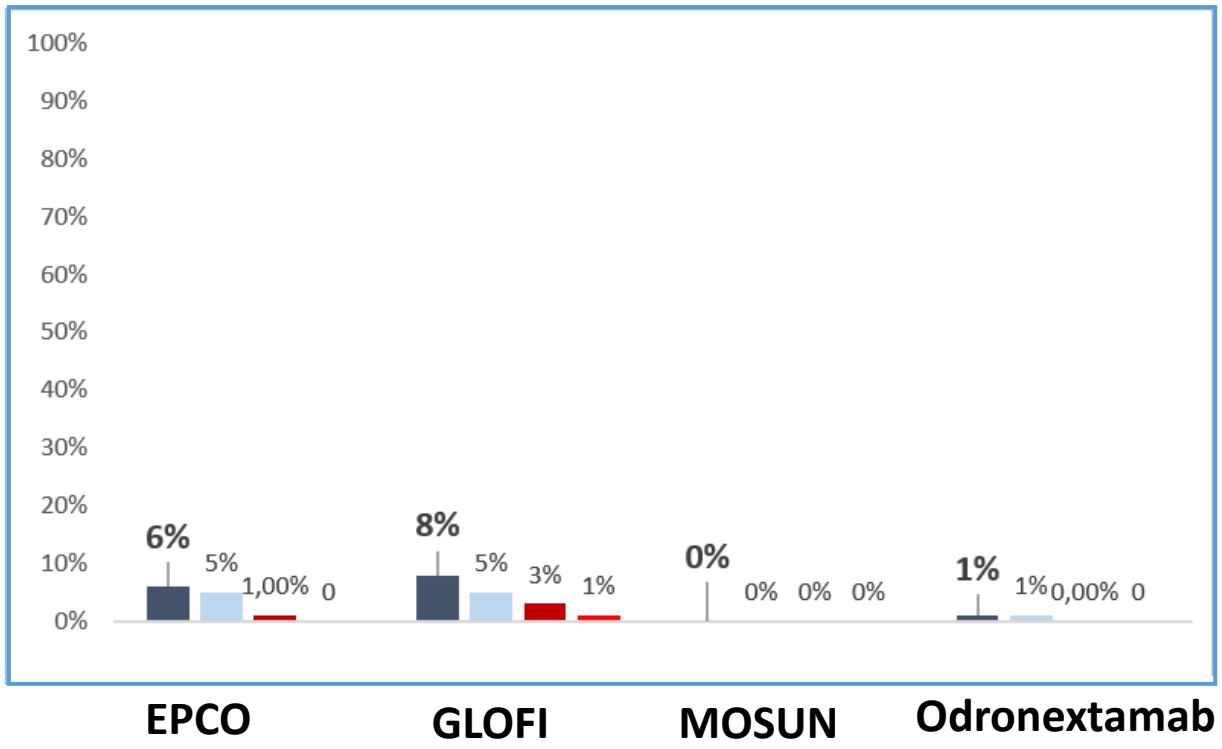
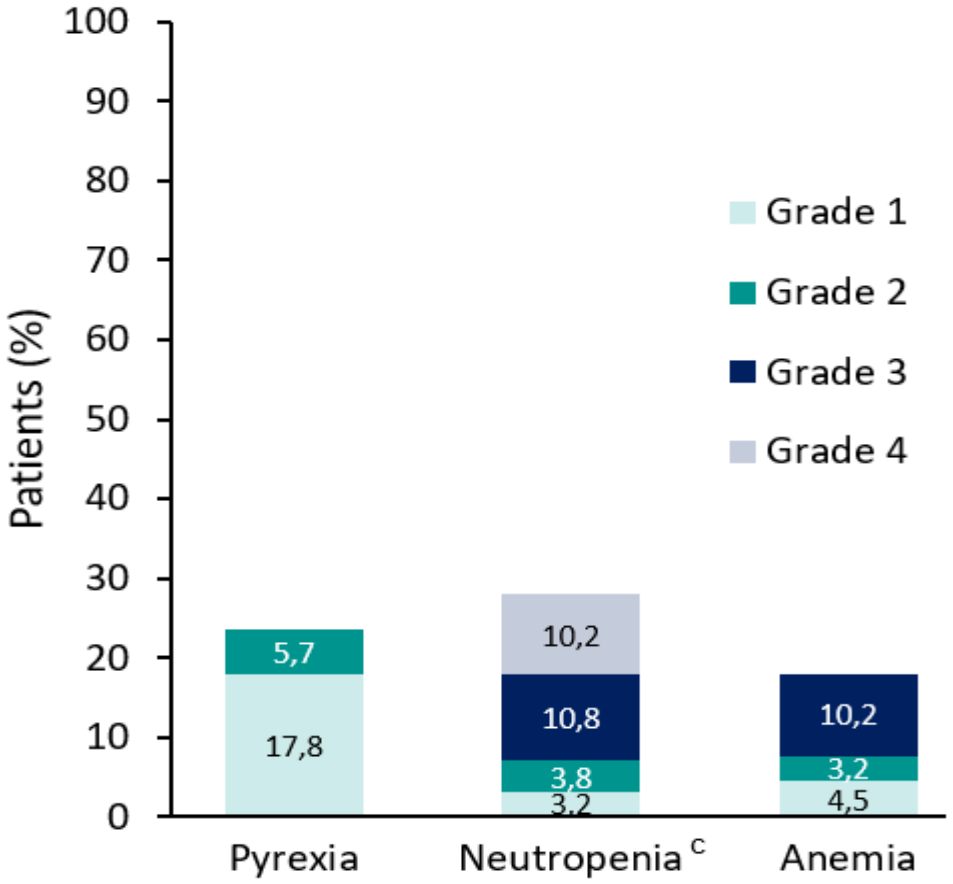


all Grade 1-2 Grade 3 Grade 4-5

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.

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**



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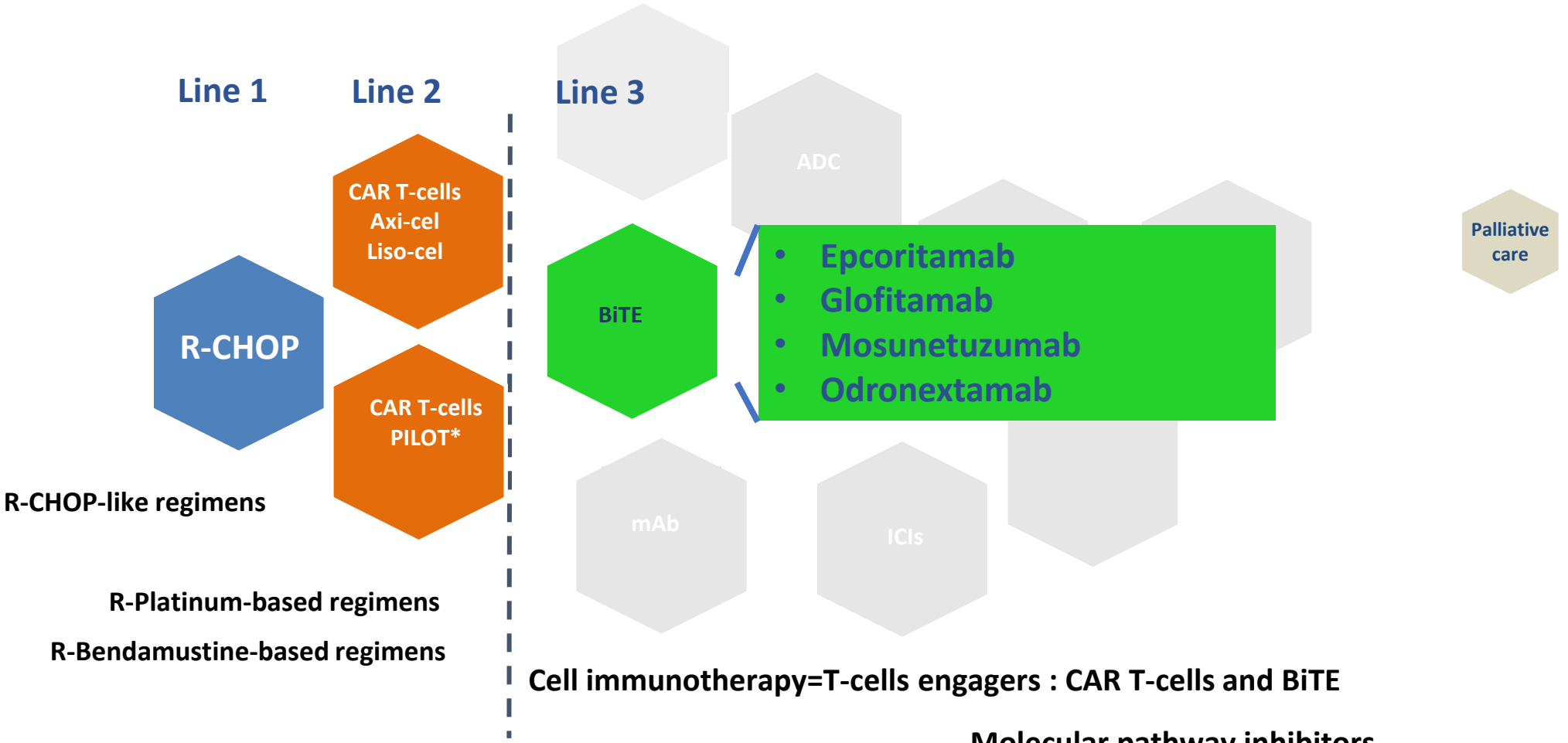
Perspectives

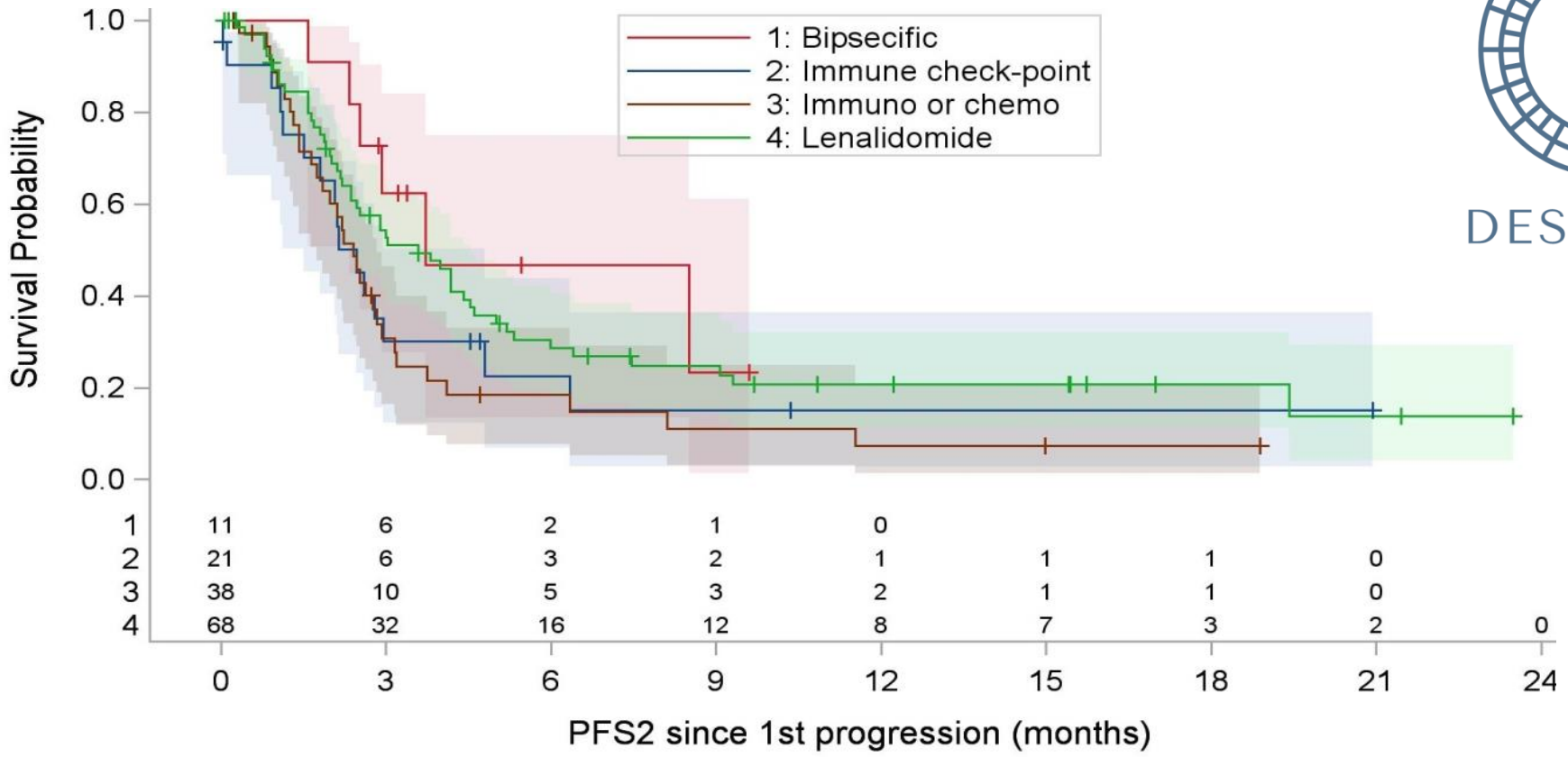
- Combining or sequencing?
- Can we move in first line ?

3rd line treatment



*Sehgal A et al. Lancet Oncol 2022

Relapse after CAR T cells



	No. of Subjects	Event	Censored	Median Survival (95%CL
Bipsecific	11	54.5 % (6)	45.5 % (5)	3.7 (2.3 ; NA)
Immune check-point	21	76.2 % (16)	23.8 % (5)	2.5 (1.5 ; 4.8)
Immuno or chemo	38	81.6 % (31)	18.4 % (7)	2.4 (1.7 ; 2.8)
Lenalidomide	68	72.1 % (49)	27.9 % (19)	3.6 (2.4 ; 4.5)

Di Blasi et al. ASH 2021, Blood 2022

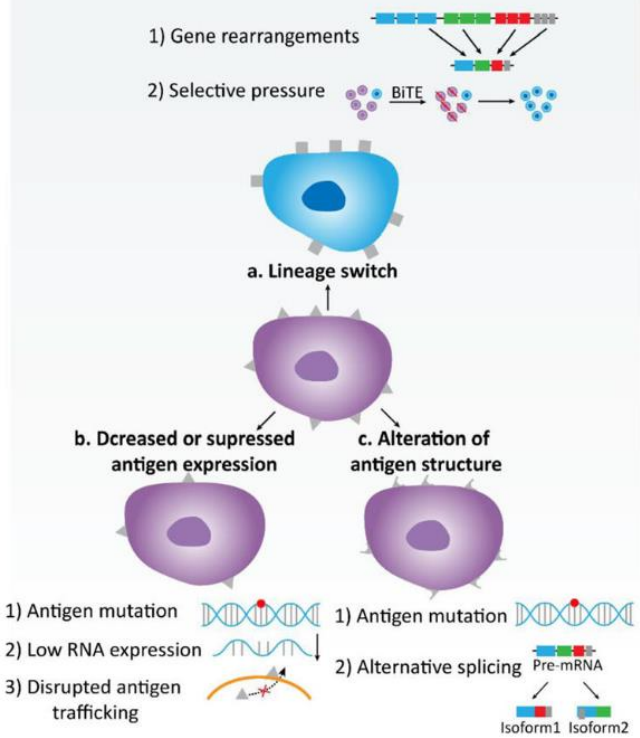
MOSUN	**First line**	**Aggressive NHL**	Mosunetuzumab + CHOP or polatuzumab vedotin- CHP	Untreated NHL	Phase 1b/2	NCT03677141
		Indolent NHL	Mosunetuzumab (SC) + lenalidomide	FL and MZL	Phase 2	NCT04792502
GLOFI	**First line**	**Aggressive NHL**	Glofitamab + R-CHOP or Polatuzumab vedotin- R-CHP	Untreated 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

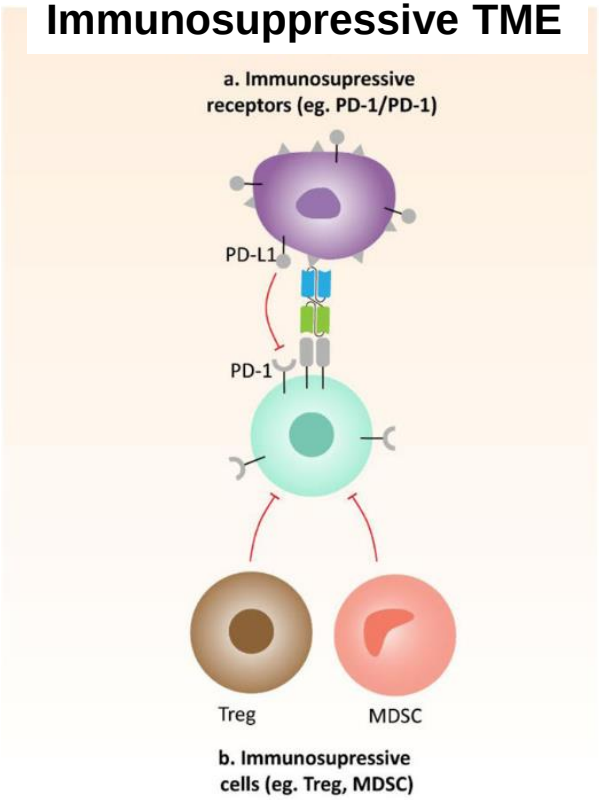
Perspectives

Mechanisms of resistance

Loss of antigen



Immunosuppressive TME



Zhou et al. Biomarker Research2021

Conclusion

- 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 cohort (35-40% with prior CAR-T):
  - 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