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

POLICLINICO DI
SANT'ORSOLA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

Aggressive Lymphoma Workshop

Bologna, Royal Hotel Carlton
May 8-9, 2023

EPCORITAMAB

Dr Pieternella (Elly) Lugtenburg

Erasmus MC Cancer Institute, University Medical Center Rotterdam, NL

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President: **Pier Luigi Zinzani**

Disclosures

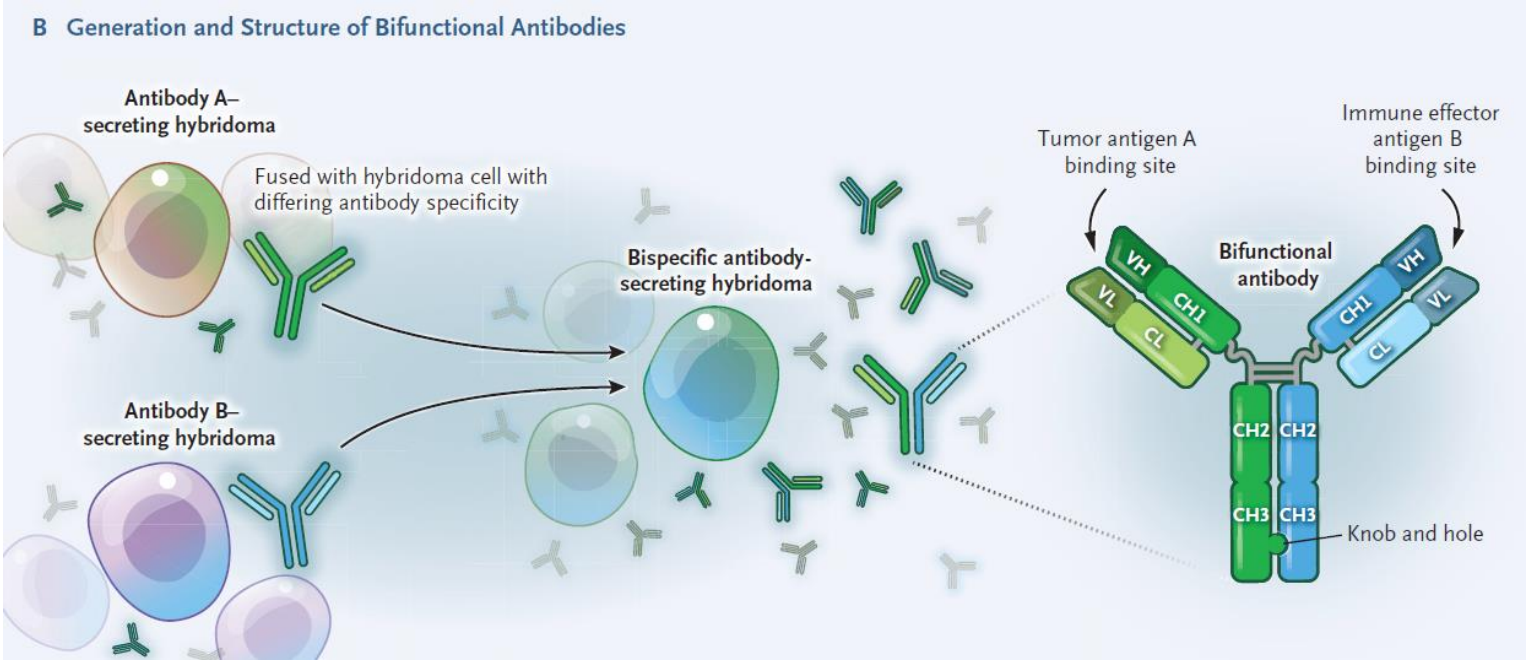
Disclosures of Pieternella Lugtenburg

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda	X						
Servier	X						
Genmab						X	
AbbVie						X	
Celgene						X	
Y-mAbs Therapeutics			X				
Lilly					X		

Epcoritamab

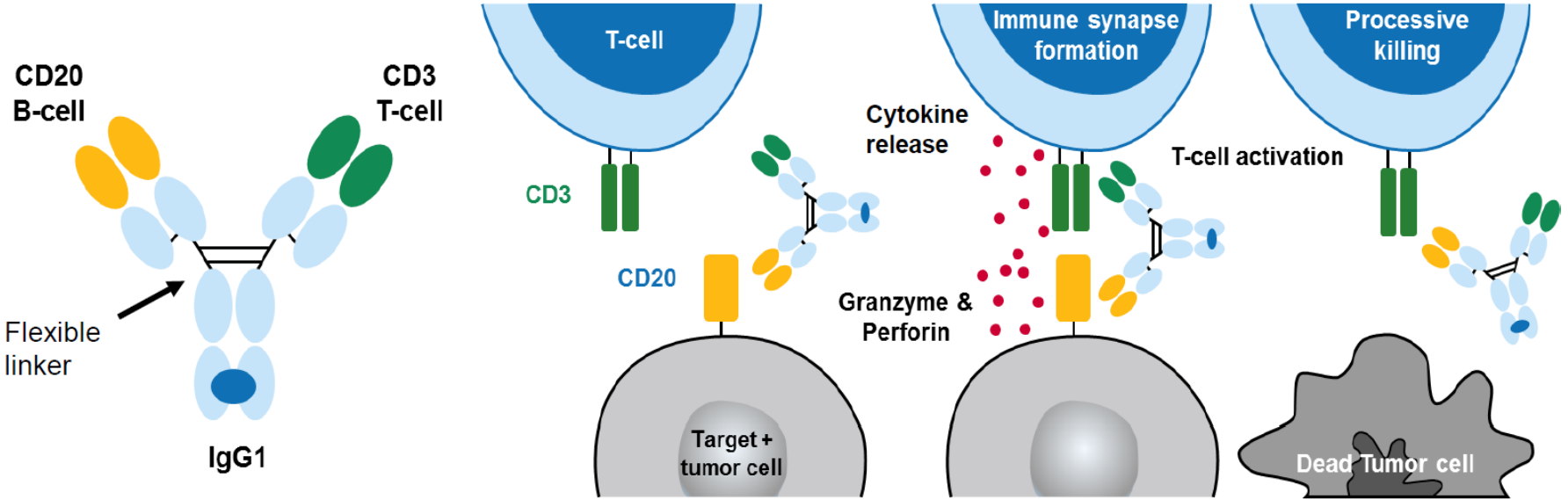
- Introduction bispecific antibodies
- Epcoritamab preclinical data
- Epcoritamab efficacy and safety in LBCL
- Conclusions

Bispecific antibodies



Longo L. N Engl J Med 2022

Mechanism of action T-cell dependent bispecific antibodies

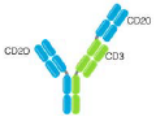
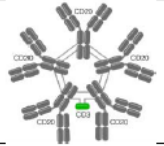


Redirects cytotoxicity of endogenous T cells against malignant B cells by simultaneously binding to CD3 on T cells and a tumor-associated antigen on B cells[1]

Scant data on how they work!

Peer Review ASH 2021

CD3 x CD20 bispecifics for B-NHL

Product name	Schematic depiction	Format	Technology	CD20:CD3 ratio	CD3 clone	CD20 clone	Fc silencing mutations*
Mosunetuzumab[18]		IgG1	Knobs-into-holes (different Fabs)	1:1	UCHT1v9 (CD3δε)	2H7 (type 1 epitope, identical to rituximab)	N297G (No FcγR binding)
Glofitamab[15]		IgG1	Head-to-tail fusion	2:1	SP34-der.(CD3ε)	By-L1(type 2 epitope, identical to obinutuzumab)	IgG1-P329G-LALA (No FcγR binding)
Epcoritamab[16]		IgG1	Controlled Fab-arm exchange	1:1	huCACAO (SP34-der.)(CD3ε)	7D8 (type 1 epitope, shared by ofatumomab)	L234F,L235E,D265A (No FcγR,C1q binding)
Odronexamab[17]		IgG4	Heavy chains with different affinity	1:1	REG1250 (CD3δε)	3B9-10 (type 1 epitope, shared by ofatumomab)	Modified IgG4 (No FcγRIII binding)
Plamotamab[90]		IgG1	Fab-Fc x scFv-Fc	1:1	α-CD3_H1.30 (SP34-der.)(CD3ε)	C2B8_H1_L1 (type 1 epitope, shared by rituximab)	G236R, L328R (No FcγR binding)
IgM 2323[19]		IgM	IgM + modified J chain	10:1	Not reported	Not reported	No

* These Fc silencing mutations do not abolish the binding of BsAb to FcRn

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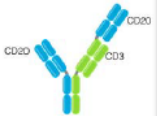
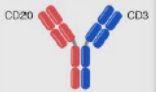
Glofitamab[15]		IgG1	Head-to-tail fusion	2:1	SP34-der.(CD3ε)	By-L1(type 2 epitope, identical to obinutuzumab)	IgG1-P329G-LALA (No FcγR binding)
Epcoritamab[16]		IgG1	Controlled Fab-arm exchange	1:1	huCACAO (SP34-der.)(CD3ε)	7D8 (type 1 epitope, shared by ofatumomab)	L234F,L235E,D265A (No FcγR,C1q binding)
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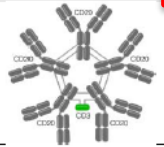
IgM 2323[19]		IgM	IgM + modified J chain	10:1	Not reported	Not reported	No

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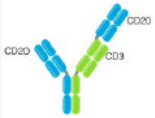
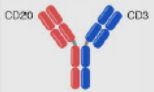
Glofitamab[15]		IgG1	Head-to-tail fusion	2:1	SP34-der.(CD3ε)	By-L1(type 2 epitope, identical to obinutuzumab)	IgG1-P329G-LALA (No FcγR binding)
Epcoritamab[16]		IgG1	Controlled Fab-arm exchange	1:1	huCACAO (SP34-der.)(CD3ε)	7D8 (type 1 epitope, shared by ofatumomab)	L234F,L235E,D265A (No FcγR,C1q binding)
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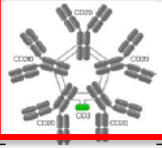
IgM 2323[19]		IgM	IgM + modified J chain	10:1	Not reported	Not reported	No

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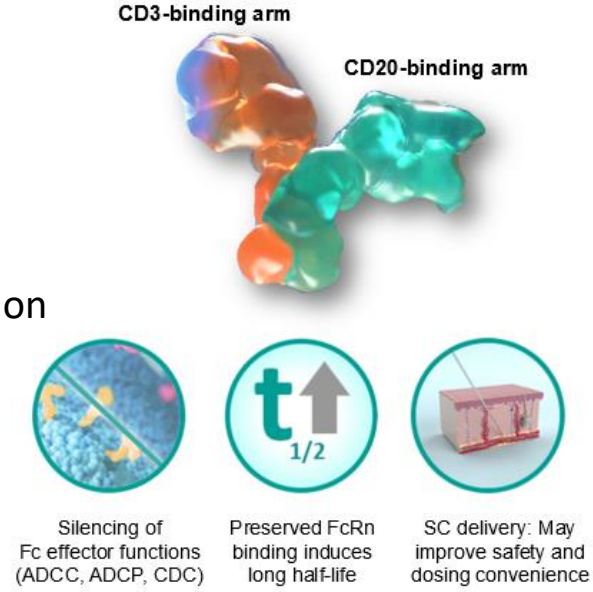
Falchi L, et al. Blood 2022

Epcoritamab

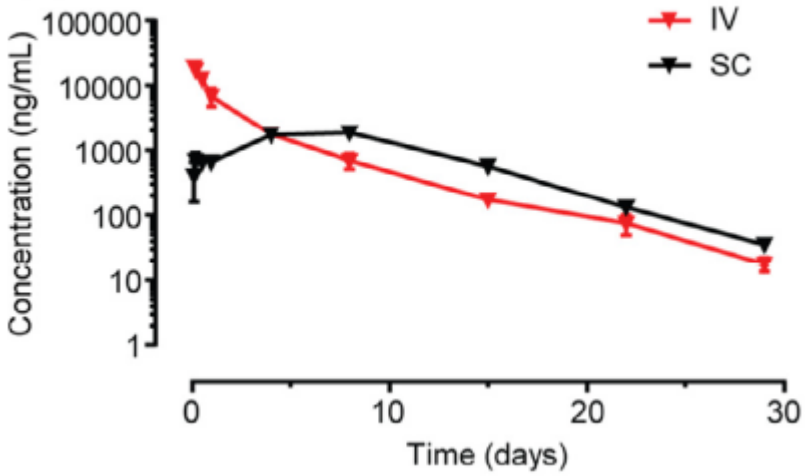
- SC-administered, bispecific CD3xCD20
- retains normal FcRn binding for a long plasma half-life
- Three point mutations were introduced in epcoritamab to ensure:
  - No Fcγ receptor binding to prevent ADCC or ADCP induction
  - No T-cell activation without binding to CD20
  - No C1q binding (no CDC induction)



Chavez et al. Best Prac Res Clin Haematol. 2018; Labrijn et al. PNAS. 2013; Labrijn et al. Nat Protoc. 2014; Mohammed et al. J Blood Med. 2019; Teeling JL et al. Blood. 2004

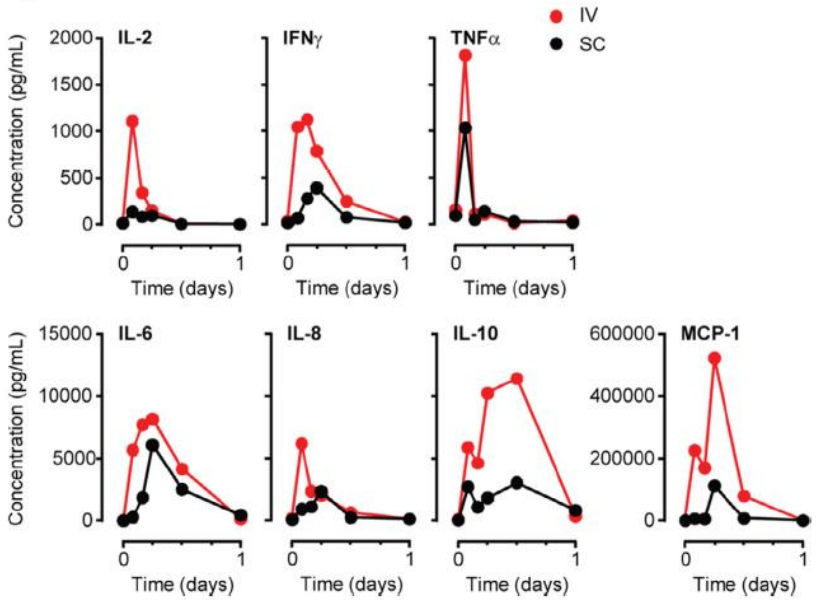
Epcoritamab subcutaneous (monkey)
lower peak and later max concentration, lower peak cytokine levels

E **plasma concentration**



→ **slower peak concentration safer?**

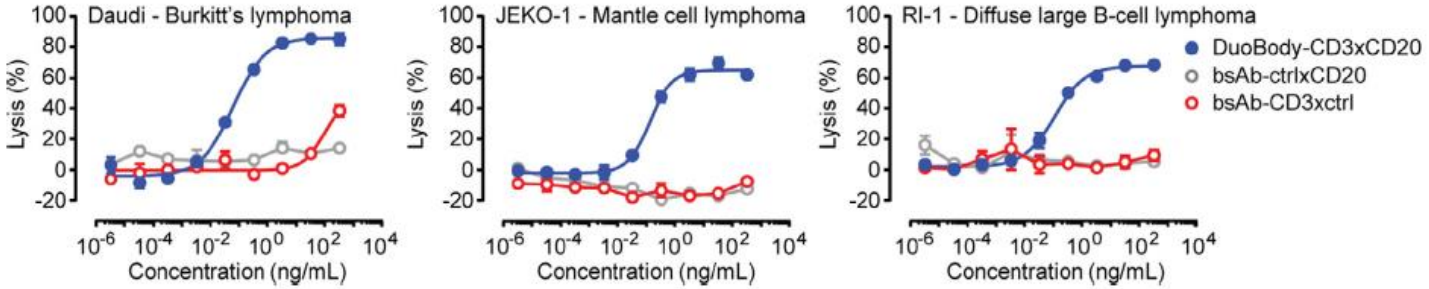
F **cytokines**



Engelberts PJ, et al. EBioMed 2020

Lysis cell-lines regardless of CD20 expression

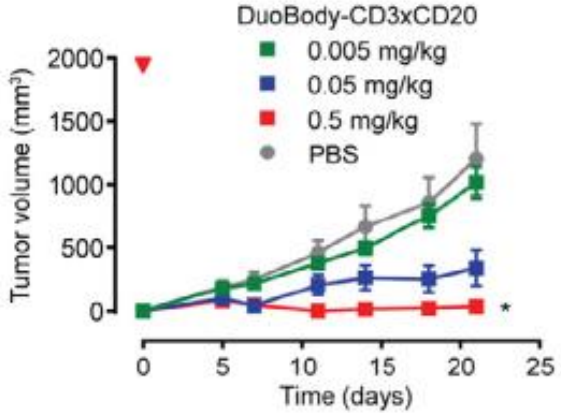
Cell line		CD20-expression level (sABC/cell)			DuoBody-CD3xCD20-induced cytotoxicity (average EC_{50} [SD])		
Name	Lymphoma type	Average (x1,000)	Range (x1,000)	n tests	ng/mL	pM	n donors
OCI-Ly7	GCB	350	209–453	6	0.531 [0.813]	3.540 [5.420]	3
Daudi	BL	331	97–752	11	0.039 [0.022]	0.260 [0.147]	11
SU-DHL-4	GCB	308	101–715	7	0.031 [0.000]	0.207 [0.000]	2
RI-1	ABC	240	150–356	4	0.066 [0.083]	0.440 [0.553]	6
JEKO-1	MCL	233	159–276	3	0.089 [0.033]	0.593 [0.220]	4
WSU-DLCL2	GCB	233	144–330	4	0.116 [0.030]	0.773 [0.200]	4
U-2932	ABC	180	85–241	4	67.604 [114.929]	450.693 [766.193]	4
OCI-Ly18	GCB	166	84–237	4	0.057 [0.042]	0.380 [0.280]	3
RC-K8	ABC	139	78–223	4	0.743 [0.673]	4.953 [4.487]	2
Z-138	MCL	90	53–114	5	0.057 [0.023]	0.380 [0.153]	2
OCI-Ly19	GCB	36	0–62	4	0.181 [0.086]	1.207 [0.573]	2
SU-DHL-8	GCB	33	0–88	8	0.120 [0.105]	0.800 [0.700]	2

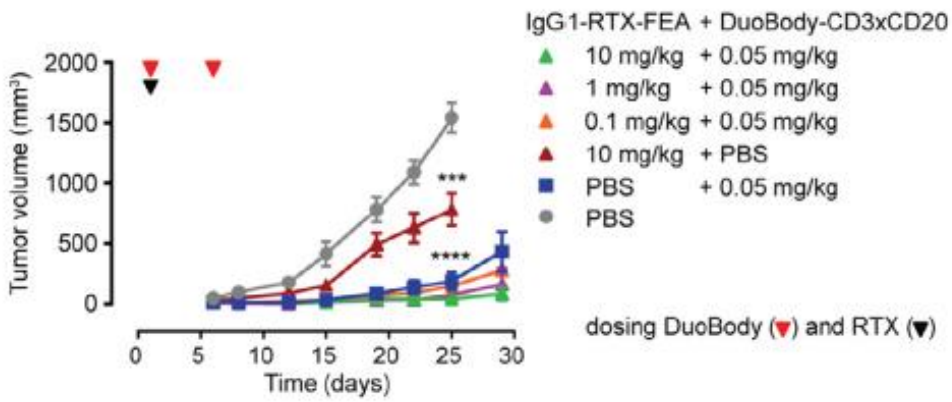


Engelberts PJ, et al. EBioMed 2020

Potency preserved in presence of rituximab

Xenograft models in mice





→ dose-dependent decrease in tumor volume

→ no reduction potency in presence of rituximab

Engelberts PJ, et al. EBioMed 2020

EPCORE NHL-1: Expansion cohort in R/R LBCL

Design

Dose Escalation → **Dose Expansion Data Cutoff: January 31, 2022**
Median follow-up: 10.7 mo

B-NHL:
- ✓ No DLTs
- ✓ MTD not reached
- ✓ RP2D identified
- ✓ Acceptable safety profile
- ✓ Encouraging antitumor activity

Key inclusion criteria:
- R/R CD20+ mature B-cell neoplasm
- ECOG PS 0–2
- Prior treatment with ≥2 prior lines of antineoplastic therapy including ≥1 anti-CD20 mAb
- Measurable disease by CT, MRI, or FDG PET-CT[a]
- Prior CAR T was allowed

Step-up dosing[b]

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

→ Treatment until PD or unacceptable toxicity →

LBCL Cohort N=157
DLBCL, HGBCL, PMBCL, and FL G3B

- Epcoritamab until progression
- Cycle 28 days
- Cycle 1 step-up dosing and corticosteroid CRS prophylaxis
- Epcoritamab was given outpatient except for the first full dose
- No initial debulking treatment was required
- **Primary endpoint:** ORR by IRC
- **Key secondary endpoints:** DOR, TTR, PFS, OS, CR rate and safety/tolerability

Thieblemont C, et al. J Clin Oncol 2023

Highly refractory patient population (patient demographics)

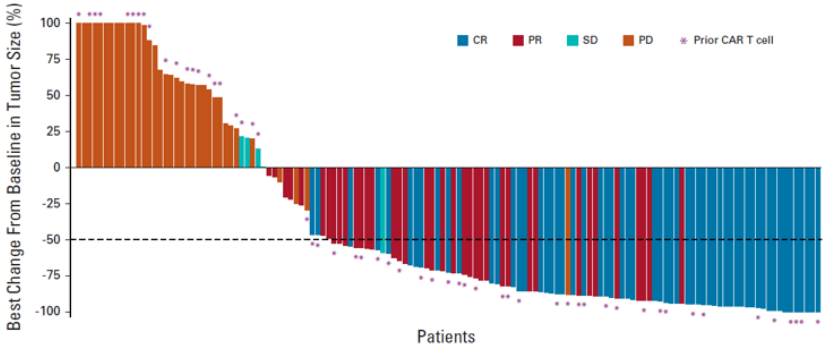
Demographics	LBCL, N=157
Median age (range), y	64 (20–83)
≥75 y, n (%)	29 (18)
ECOG PS, n (%)	
0	74 (47)
1	78 (50)
2	5 (3)
Disease Type, n (%)	**LBCL, N=157**
DLBCL[a]	139 (89)
De novo	97/139 (70)
Transformed	40/139 (29)
DLBCL with DH/TH rearrangements by central FISH[b]	12/88 (14)
HGBCL	9 (6)
PMBCL	4 (3)
FL G3B	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[c] disease, n (%)	96 (61)
Refractory[c] to last systemic therapy, n (%)	130 (83)
Refractory[c] to ≥2 consecutive lines of therapy, n (%)	119 (76)
Prior ASCT, n (%)	31 (20)
Prior CAR T therapy, n (%)	61 (39)
Refractory[c] to CAR T therapy	46/61 (75)

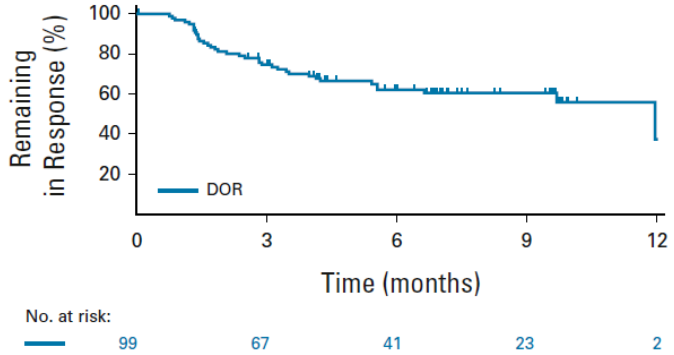
Philips T, et al. ASH 2022, #4251
Thieblemont C, et al. J Clin Oncol 2023

Efficacy (response)

Best Overall Response, n(%)[a]	LBCL N=157
Overall response	99 (63)
CR	61 (39)
PR	38 (24)
Stable disease	5 (3)
Progressive disease	37 (24)
Kaplan–Meier Estimates, mo (range)	
Median time to response	1.4 (1.0–8.4)
Median time to CR	2.7 (1.2–11.1)
Median duration of response (months)	12 (0+ to 15.5+)

Data cutoff: January 31, 2022. [a]Based on IRC assessment and Lugano criteria.





Median FU 10.7 months

- Median DOR among those who achieved CR was NR
- An estimated 89% of CR remained in response at 9 mo

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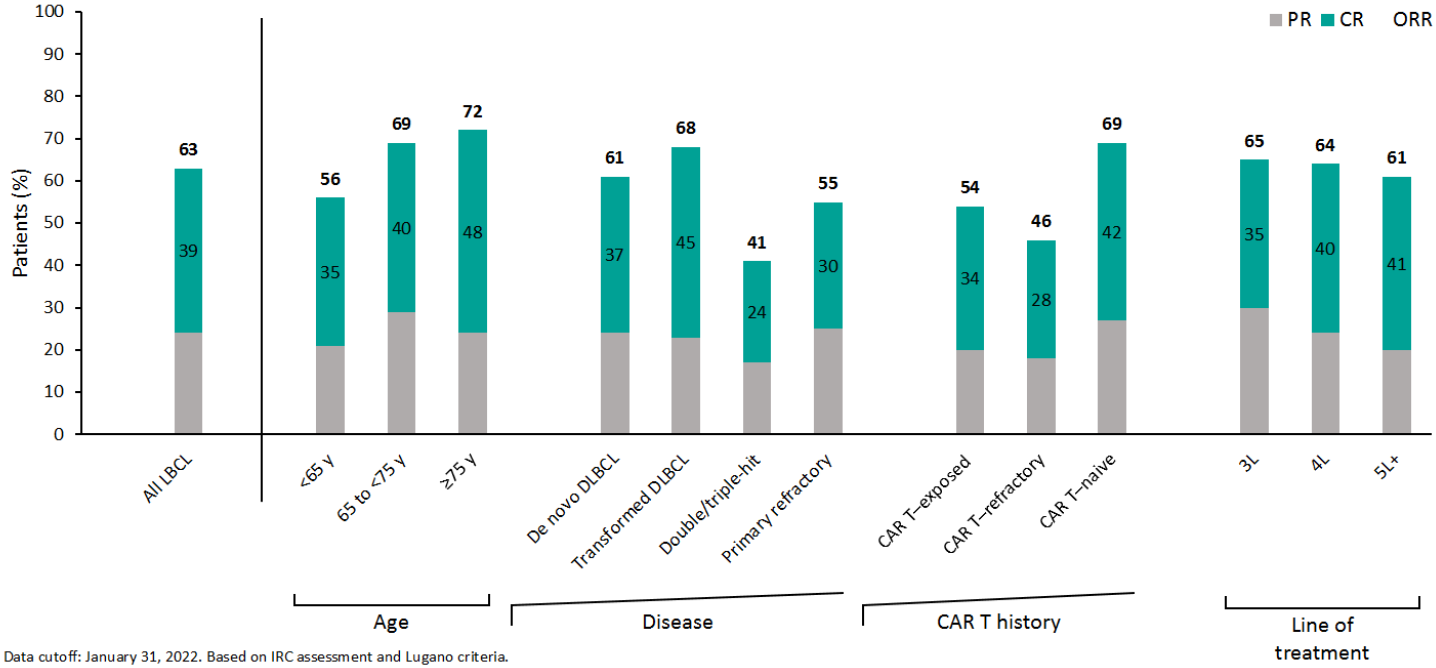
Response in subsets of LBCL patients



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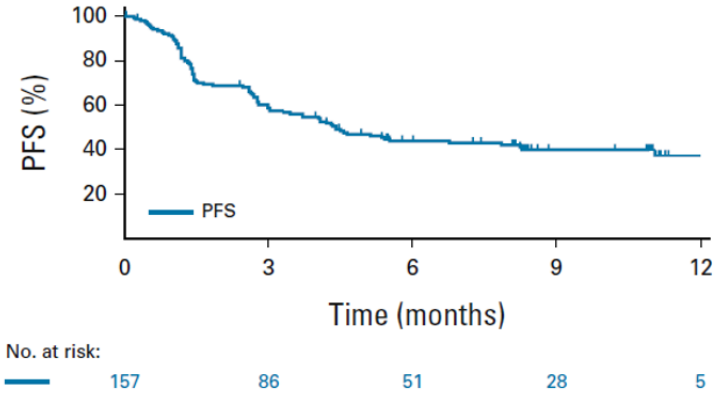
Efficacy: PFS and OS

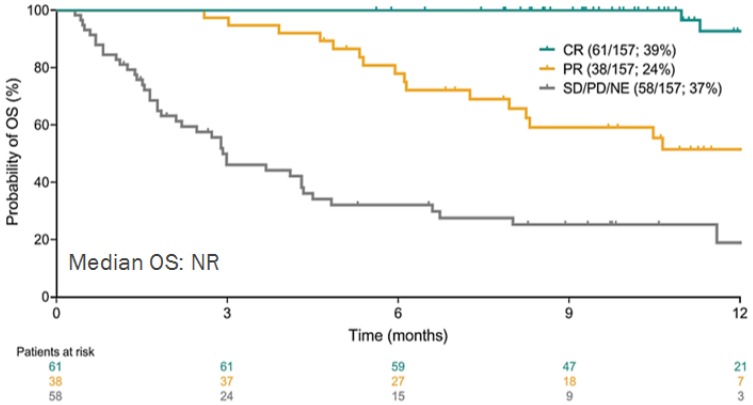
Progression free survival



- median PFS 4.4 m
- 6-months PFS 44%

Median FU 10.7 m

OS by best overall response



- median OS among CR was NR
- Responders OS at 6 m 70.6% and at 9 m 63.9%
- OS non-responders 2.9 m

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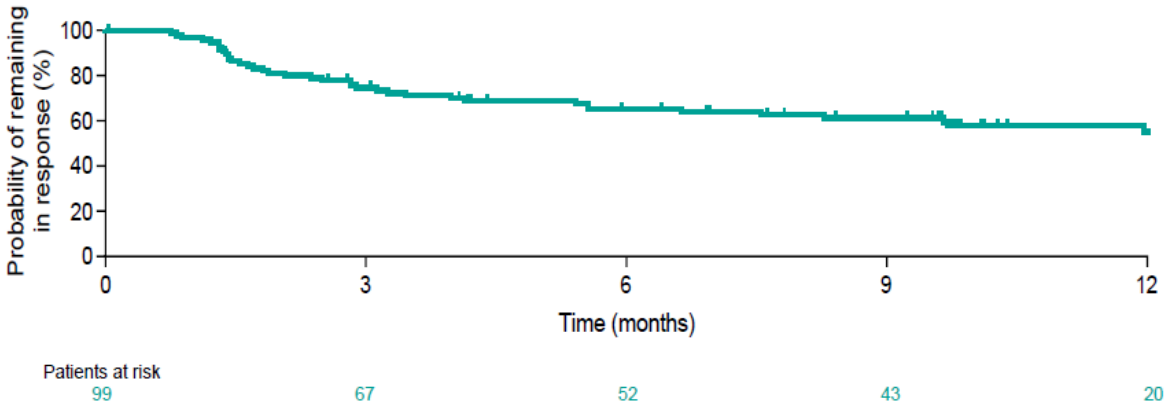
Updated Duration of Response



- As of a more recent data cutoff on June 30, 2022 (median follow-up, 15.7 mo):
  - An estimated 61% and 55% of responders remained in response at 9 and 12 mo, respectively
  - An estimated 89% and 79% of complete responders remained in response at 9 and 12 mo, respectively

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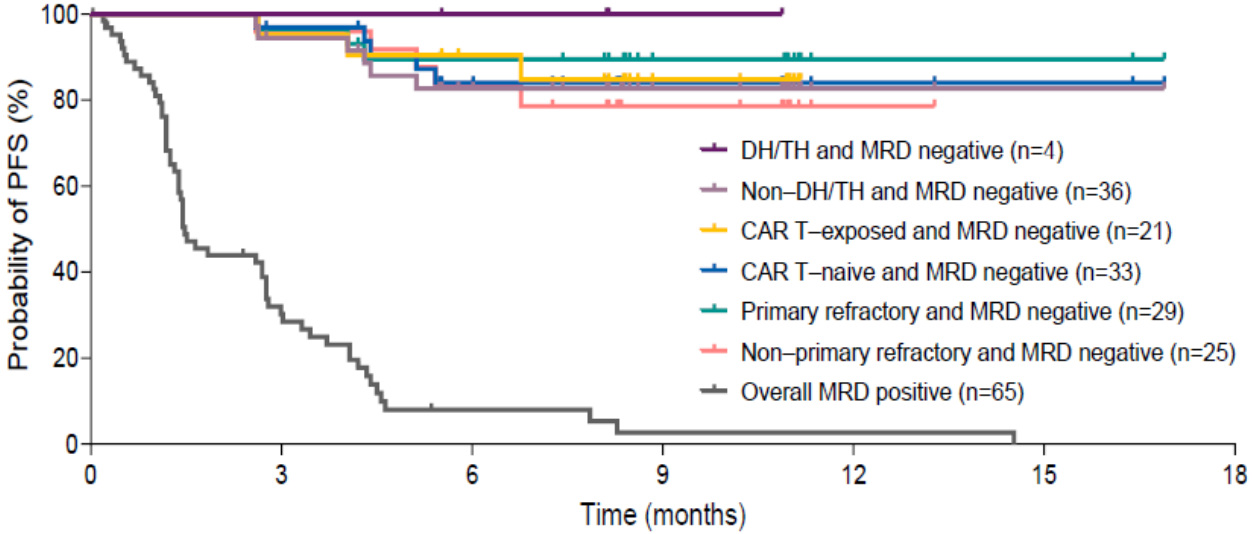
MRD Negativity Was Correlated With Improved PFS



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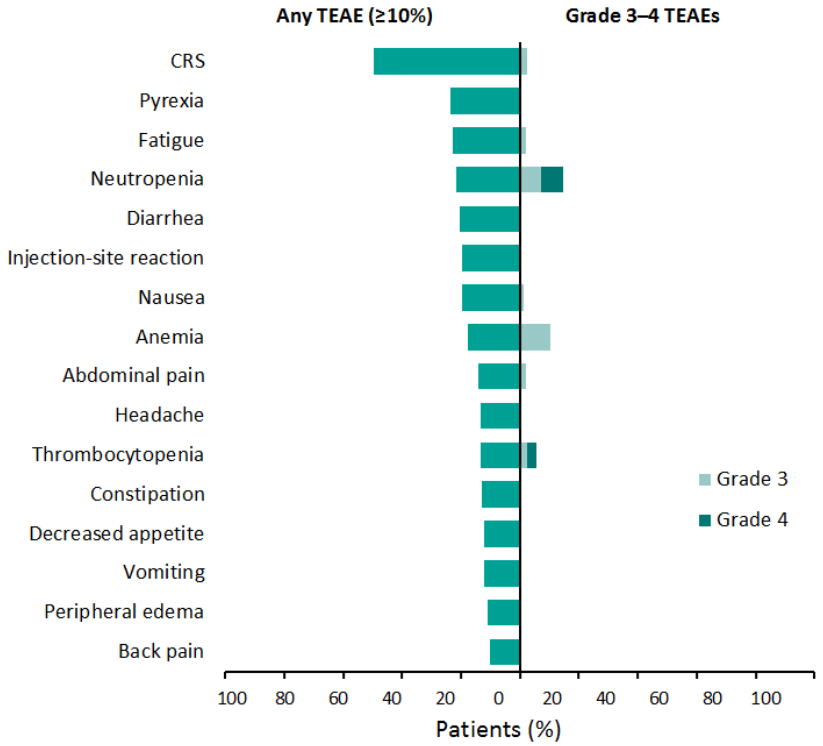
Treatment-Emergent Adverse Events (TEAEs)

Patients, n (%)	LBCL N=157
Any TEAE	156 (99.4)
Related TEAE	130 (82.8)
Grade ≥3 AE	96 (61.1)
Treatment-related	42 (26.8)
Serious AE	89 (56.7)
Treatment-related	55 (35.0)
Grade 5	9 (5.7)
Treatment-related	1 (0.6)

Data cutoff: January 31, 2022.



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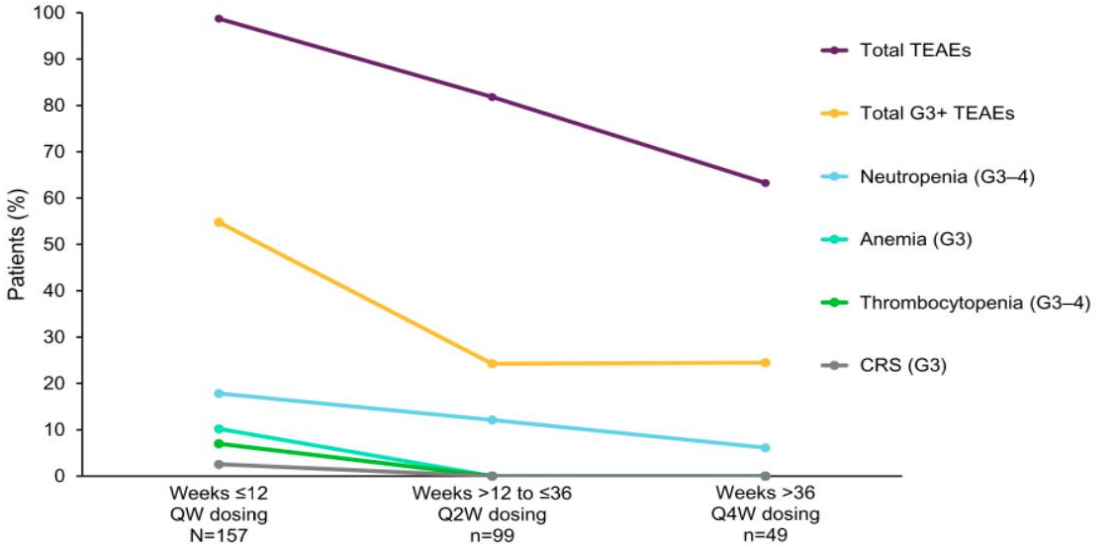
AEs: majority early < 12 weeks



- AEs occurred early in treatment, and incidence of AEs declined after 12 weeks
- Only 1 patient had a related serious TEAE after week 12

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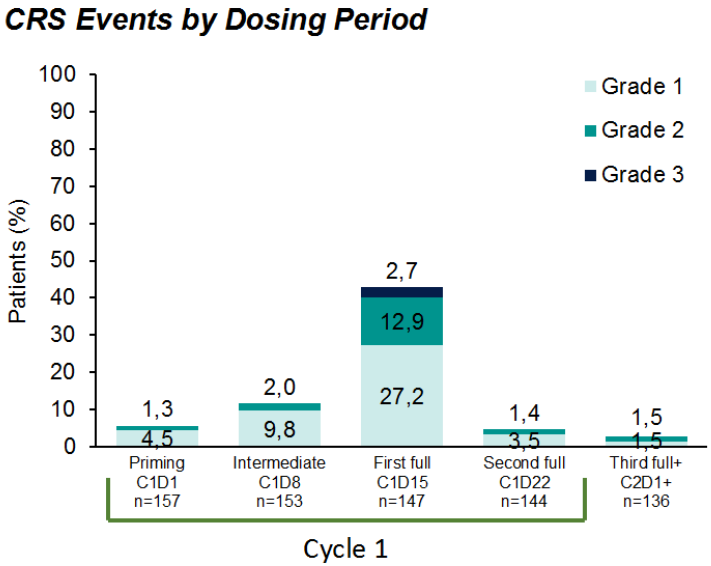
Adverse events: CRS and ICANS

	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 1st full dose, d	0.8 (20h)
Median time to resolution from 1st full dose, d	2 (48h)
CRS treated with tocilizumab, n (%)	22 (14.0)
CRS leading to treatment discontinuation, n (%)	1 (0.6)
CRS resolution, n (%)	77 (98.7)
Leading to treatment discontinuation n (%)	1 (0.6)
ICANS, n (%)	
Grade 1	7 (4.5)
Grade 2	2 (1.3)
Grade 5	1 (0.6)

Data cutoff: January 31, 2022. [a]Graded by Lee et al 2019 criteria

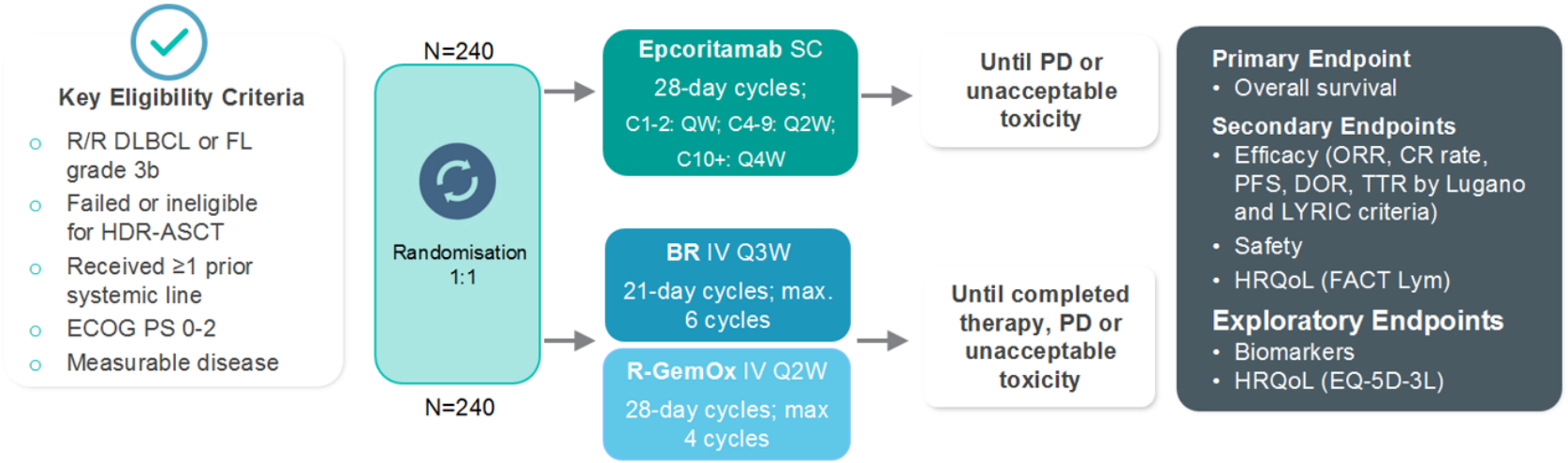


- CRS occurrence was predictable and primarily confined to cycle 1
- Predictable: most CRS occurred after the first full dose with a median time to onset of 20 h
- One patient had a grade 5 ICANS event that was related to epcoritamab

Thieblemont C, et al. J Clin Oncol 2023

Epcoritamab phase 3 rr DLBCL ineligible for curative therapy

A pivotal phase 3, randomized, open-label, multicenter trial to evaluate the efficacy of epcoritamab compared to investigator's choice of chemotherapy in subjects with R/R DLBCL, who have failed or are ineligible for HDT-ASCT.



Epcoritamab ongoing DLBCL studies (some…)

Study	Phase	line	category
Epco +/- R-CHOP	Phase 3	1st line	fit
Epco +/- R-miniCHOP	Phase 3	1st line	unfit
Epco + R-DHAX/C	Phase 1-2	2nd line	transplant eligible
Epco + Gem/Ox	Phase 1-2	≥ 2nd line	transplant ineligible
Epco + lenalidomide; lenalidomide + ibrutinib; CHPola; ibrutinib; cc99282	Phase 1-2	≥ 2nd line	transplant ineligible

Conclusions

- Epcoritamab is a SC, off-the-shelf T-cell–engaging therapy showing powerful single-agent activity in R/R LBCL
- Epcoritamab led to deep and durable responses that correlated with robust PFS and OS
- Subgroup analyses demonstrate high rates of complete response and MRD negativity across standard and poor-prognosis subgroups
- The safety profile was manageable; TEAEs decreased over time
- With longer follow-up, durability of response was reaffirmed; the majority of complete responders remain in response

Thank you!