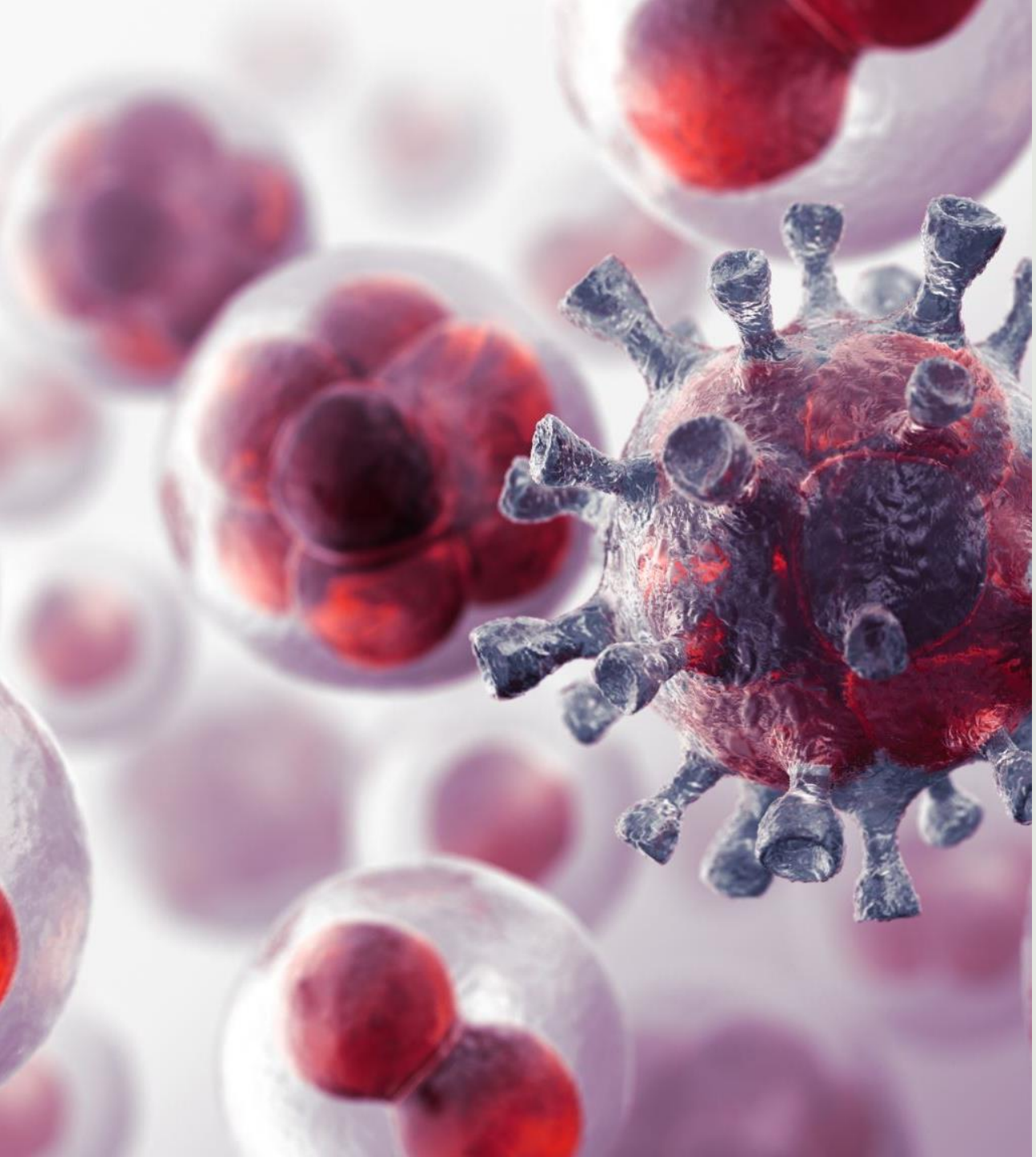

Bispecific Antibodies in Aggressive B cell Lymphomas

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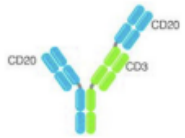
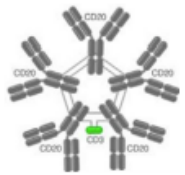
Table 1. Comparative characteristics of CD20XCD3 BsAb currently in development

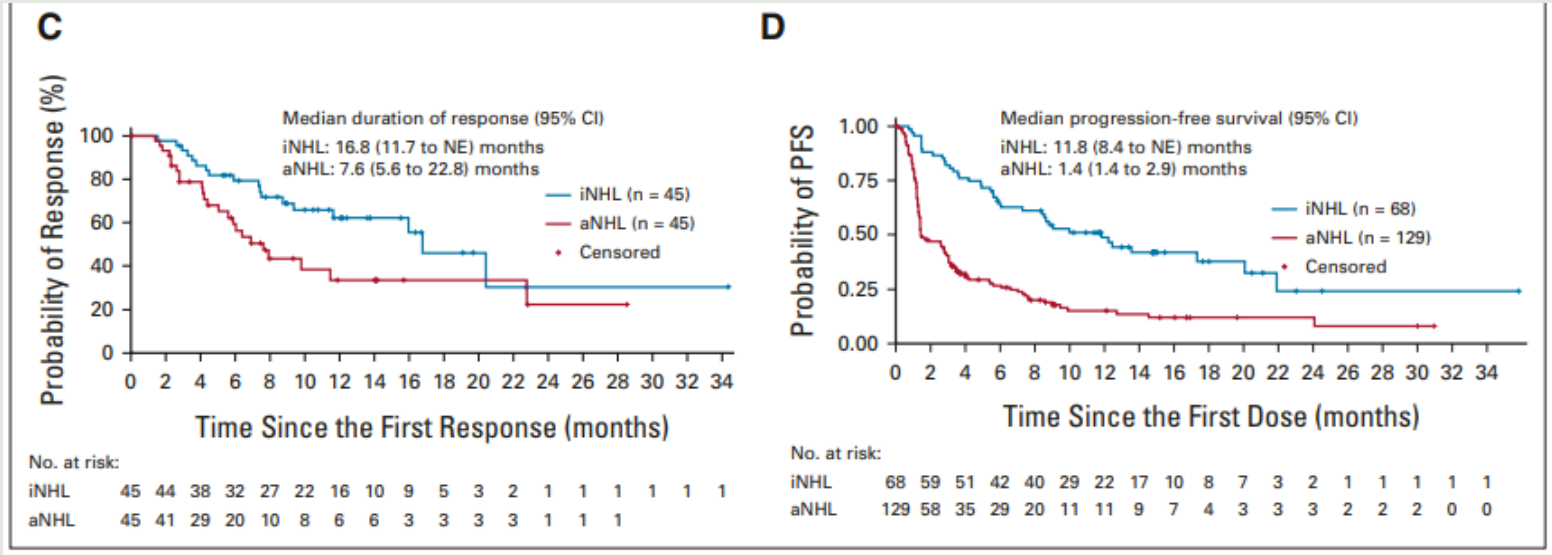
Product name	Schematic depiction	Format	Technology	CD20:CD3 ratio	CD3 clone	CD20 clone	Fc silencing mutations*
Mosunetuzumab[18]		IgG1	Knobs-into-holes (different Fabs)	1:1	UCHT1v9 (CD3δε)	2H7 (type 1 epitope, identical to rituximab)	N297G (no FcγR binding)
Glofitamab[15]		IgG1	Head-to-tail fusion	2:1	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

Falchi L, Vardhana SA, Salles GA. Bispecific antibodies for the treatment of B-cell lymphoma: promises, unknowns, and opportunities. Blood. 2023 Feb 2;141(5):467-480.

Mosunetuzumab

Characteristic	Aggressive NHL[a] (n = 129)
Age, years	
Median	63.0
Range	19-91
Male sex, No. (%)	82 (63.6)
ECOG PS, No. (%)	
0	42 (32.6)
1	86 (66.7)
2	1 (0.8)
Ann Arbor stage at study entry, No. (%)	
No. of evaluable patients[c]	127
Stage I	4 (3.1)
Stage II	15 (11.8)
Stage III	26 (20.5)
Stage IV	82 (64.6)
Prior systemic therapies, No.	
Median	3
Range	1-14
Prior CAR-T therapy, No. (%)	15 (11.6)
Prior autologous stem-cell transplant, No. (%)	44 (34.1)
Refractory to last therapy, No. (%)[d]	106 (82.2)
Refractory to prior anti-CD20 therapy, No. (%)[d]	100 (77.5)

Best Objective Response[a]	Aggressive NHL[b] (n = 129)	Indolent NHL[c] (n = 68)	Post–CAR-T Therapy (n = 19)
ORR, No. (%) [95% CI]	45 (34.9) [26.7 to 43.8]	45 (66.2) [53.7 to 77.2]	7[d] (36.8) [16.3 to 61.6]
Complete response, No. (%) [95% CI]	25 (19.4) [13.0 to 27.3]	33 (48.5) [36.2 to 61.0]	5 (26.3) [9.2 to 51.2]
Partial response, No. (%) [95% CI]	20 (15.5) [9.7 to 22.9]	12 (17.6) [9.5 to 28.8]	2 (10.5) [1.3 to 33.1]
Stable disease, No. (%) [95% CI]	9 (7.0) [3.2 to 12.8]	13 (19.1) [10.6 to 30.5]	0 (0) [0.0 to 17.7]
Progressive disease, No. (%) [95% CI]	70 (54.3) [45.3 to 63.1]	9 (13.2) [6.2 to 23.6]	12 (63.2) [38.4 to 83.7]
Duration of response, median [95% CI], months	7.6 [5.6 to 22.8]	16.8 [11.7 to NE]	Not reported due to small sample size (n = 7)[d]
Duration of response in patients with complete response, median [95% CI], months	22.8 [7.6 to NE]	20.4 [16.0 to NE]	Not reported due to small sample size (n = 5)



Budde LE, Bartlett NL. Single-Agent Mosunetuzumab Shows Durable Complete Responses in Patients With Relapsed or Refractory B-Cell Lymphomas: Phase I Dose-Escalation Study. J Clin Oncol. 2022 Feb 10;40(5):481-491.

Glofitamab

Table 1. Demographic and Clinical Characteristics at Baseline of All 154 Patients Treated at the Phase 2 Dose (Safety Population).*

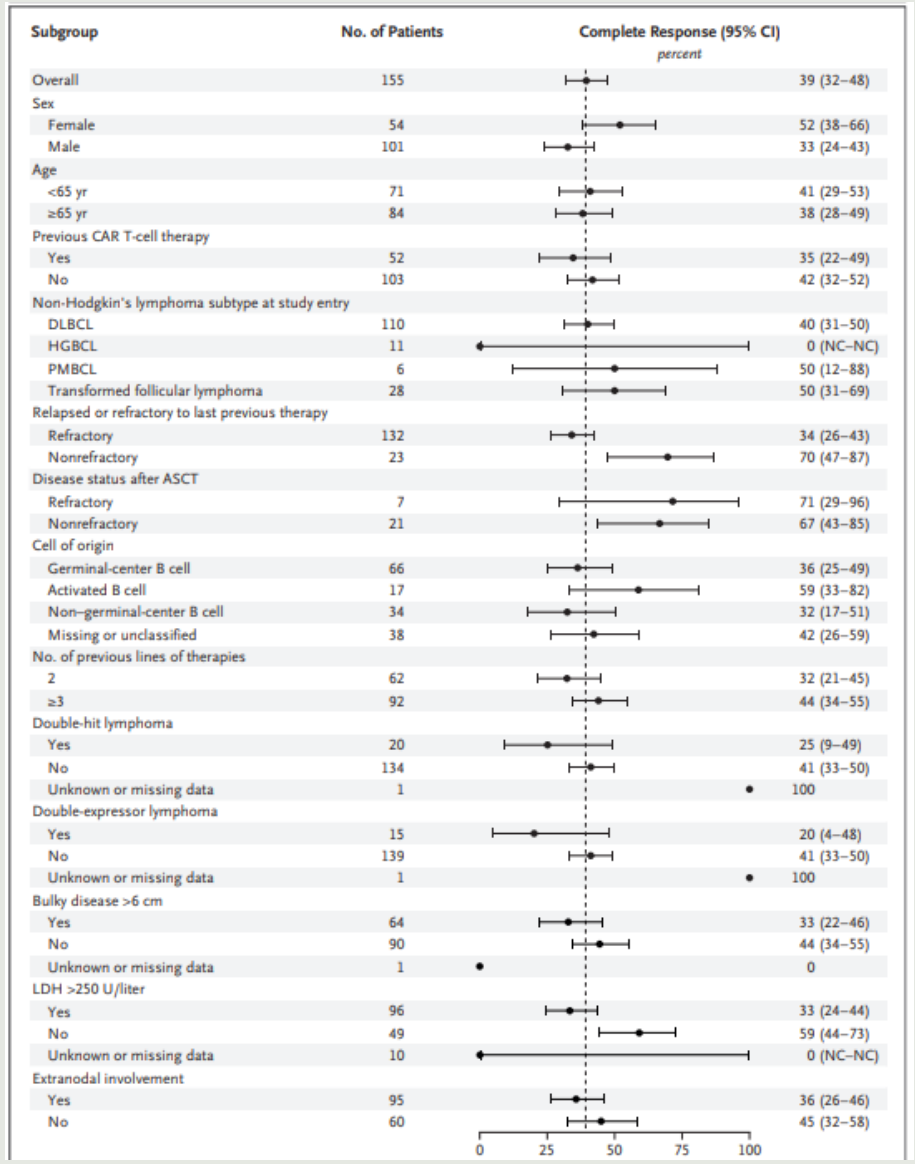
Characteristic	Value
Median age (range) — yr	66 (21–90)
Male sex — no. (%)	100 (65)
ECOG performance-status score — no. (%)†	
0	69 (45)
1	84 (55)
Ann Arbor stage at time of study entry — no. (%)	
I	10 (6)
II	25 (16)
III	31 (20)
IV	85 (55)
Missing data	3 (2)
Non-Hodgkin's lymphoma subtype — no. (%)	
Diffuse 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)
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)

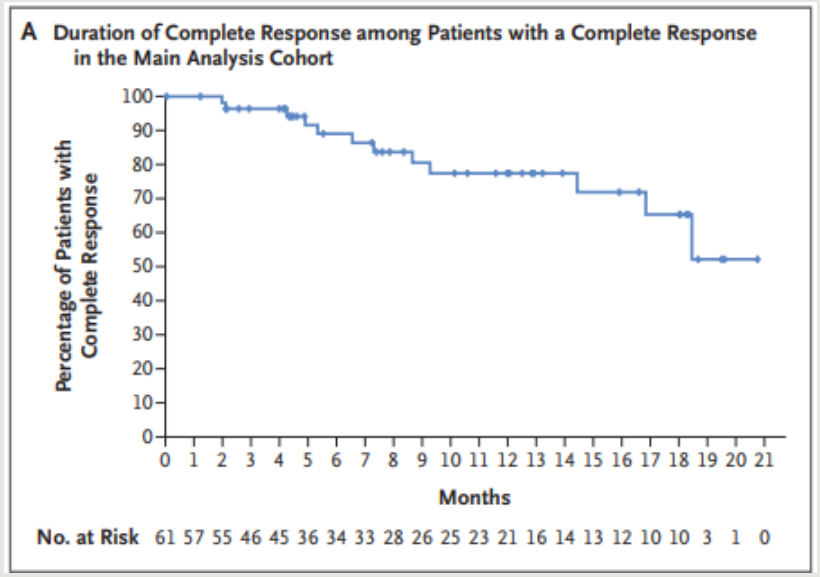
Table 2. Efficacy According to Independent Review Committee and Investigator Assessment (Intention-to-Treat Population).*

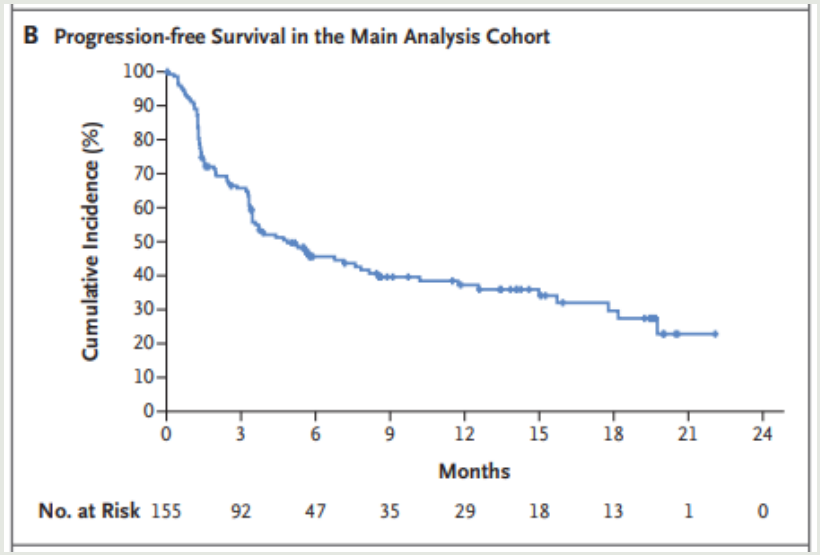
Outcome	Assessment According to Independent Review Committee (N=155)	Assessment According to Investigator (N=155)
Complete response		
No. of patients with response	61	58
Percentage of patients (95% CI)	39 (32–48)	37 (30–46)
Objective response		
No. of patients with response	80	89
Percentage of patients (95% CI)	52 (43–60)	57 (49–65)
Duration of complete response†		
Median (95% CI) — mo	NR (16.8–NR)	19.8 (18.2–NR)
Complete response at 12 mo (95% CI) — %	78 (64–91)	72 (59–86)
Duration of objective response‡		
Median (95% CI) — mo	18.4 (13.7–NR)	10.4 (6.8–NR)
Objective response at 12 mo (95% CI) — %	64 (51–76)	49 (37–61)
Median time to first complete response (range) — days†	42 (31–308)	43 (31–274)
Progression-free survival		
Median (95% CI) — mo	4.9 (3.4–8.1)	3.8 (3.3–5.4)
Alive without progression at 12 mo (95% CI) — %	37 (29–46)	30 (22–38)
Overall survival		
Median (95% CI) — mo	—	11.5 (7.9–15.7)
Alive at 12 mo (95% CI) — %	—	50 (41–58)

Dickinson MJ, Hutchings M. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022 Dec 15;387(24):2220-2231.

Glofitamab







Dickinson MJ, Hutchings M. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022 Dec 15;387(24):2220-2231.

Epcoritamab

	Relapsed or refractory diffuse large B-cell lymphoma (n=46)	Relapsed or refractory follicular lymphoma (n=12)	All patients (n=68)*
Age, years	68 (55–74)	73 (63–76)	68 (57–75)
Sex			
Female	16 (35%)	4 (33%)	23 (34%)
Male	30 (65%)	8 (67%)	45 (66%)
ECOG performance status			
0	23 (50%)	6 (50%)	35 (51%)
1	21 (46%)	4 (33%)	29 (43%)
2	2 (4%)	1 (8%)	3 (4%)
3†	0	1 (8%)†	1 (1%)†
Ann Arbor stage			
I	3 (7%)	0	3 (4%)
II	5 (11%)	4 (33%)	12 (18%)
III	12 (26%)	4 (33%)	16 (24%)
IV	26 (57%)	4 (33%)	37 (54%)
Extranodal disease	29 (63%)	6 (50%)	42 (62%)
Time since diagnosis, months	25·4 (11·0–54·6)	61·5 (34·3–153·1)	29·7 (13·7–66·8)
Time since relapse or progression, months	1·5 (1·1–2·3)	1·6 (1·2–2·6)	1·6 (1·1–2·3)
Number of lines of previous therapy	3·0 (2·0–4·0)	4·5 (2·5–8·0)	3·0 (2·0–4·5)
Previous therapies			
Anti-CD20 monoclonal antibody	46 (100%)	12 (100%)	68 (100%)
Anthracyclines	46 (100%)	9 (75%)	62 (91%)
Alkylating agents	46 (100%)	12 (100%)	67 (99%)
Autologous stem-cell transplantation	7 (15%)	1 (8%)	10 (15%)
CAR-T therapy	5 (11%)	0	6 (9%)
Treatment-refractory patients by therapy			
Last line of systemic therapy	41 (89%)	10 (83%)	58 (85%)
Alkylating agents	40 (87%)	9 (75%)	56 (82%)
Last anti-CD20 monoclonal antibody	41 (89%)	10 (83%)	59 (87%)

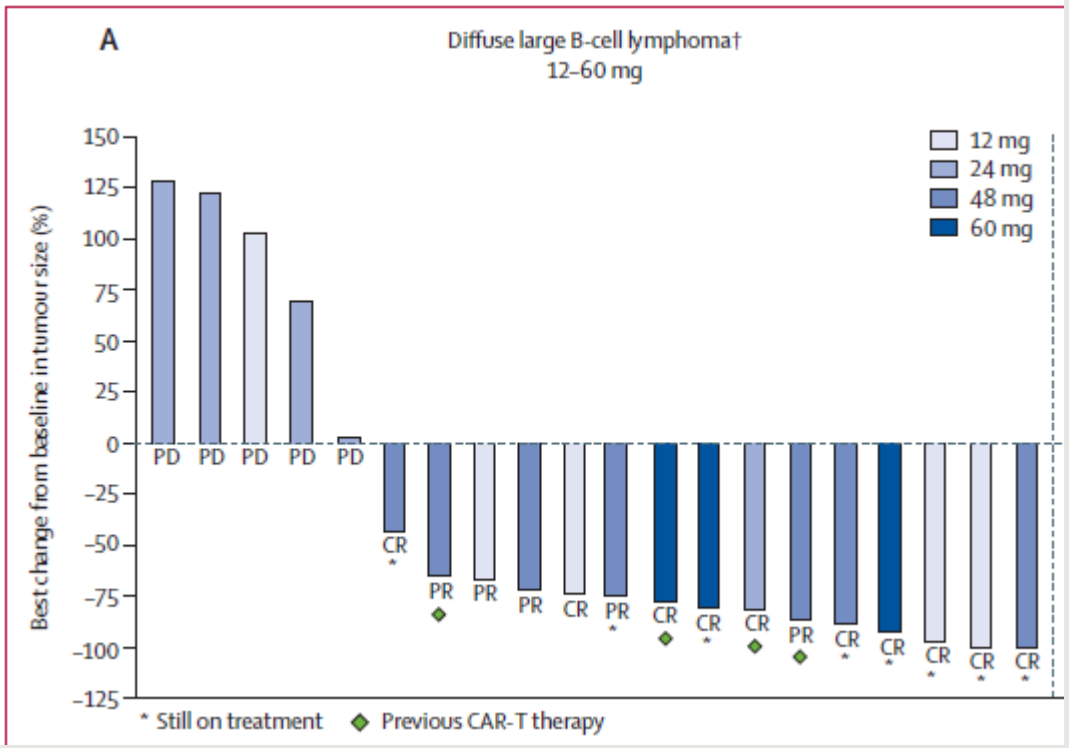
	Relapsed or refractory diffuse large B-cell lymphoma*			Relapsed or refractory follicular lymphoma†		Relapsed or refractory mantle cell lymphoma‡	
	12–60 mg (n=22)	48 mg (n=8)	60 mg (n=3)	0·76–48 mg (n=10)	48 mg (n=1)	0·76–48 mg (n=4)§	48 mg (n=1)
Overall response, n (%, 95% CI)	15 (68%, 45–86)	7 (88%, 47–100)	3 (100%, 29–100)	9 (90%, 55–100)	0 (0, 0–98)	2 (50%, 7–93)	1 (100%, 3–100)
Complete response	10 (45%)	3 (38%)	3 (100%)	5 (50%)	0	1 (25%)	0
Partial response	5 (23%)	4 (50%)	0	4 (40%)	0	1 (25%)	1 (100%)
Stable disease	1 (5%)	0	0	0	0	1 (25%)	0
Progressive disease	5 (23%)	0	0	1 (10%)	1 (100%)	0	0
Time to response, months	1·4 (1·3–2·6)	1·4 (1·3–2·6)	1·3 (1·1–1·4)	1·9 (1·5–3·5)	NA	1·4 (1·3–1·5)	1·3 (1·3–1·3)
Follow-up duration, months	9·3 (8·2–14·8)	8·2 (7·4–9·9)	9·2 (9·2–9·3)	13·6 (10·4–16·5)	6·6 (6·6–6·6)	10·2 (7·7–10·5)	7·7 (7·7–7·7)

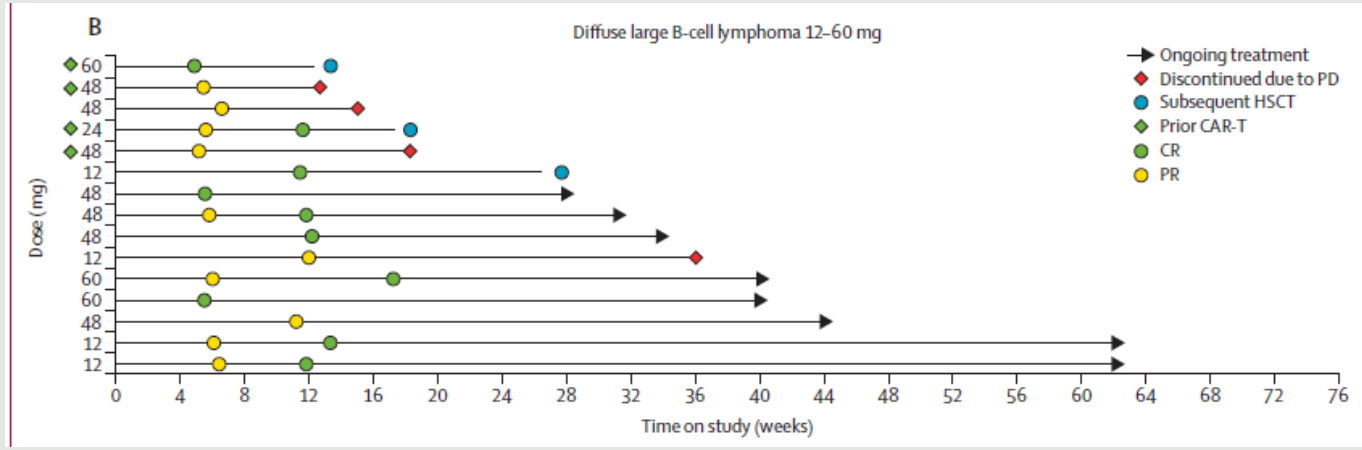
Data are n (%) or median (IQR), unless otherwise stated. Response assessments were based on Lugano classification response criteria[22,23] by investigator assessment. The modified response-evaluable population (defined as patients with at least one post-baseline disease assessment or who died without a post-baseline disease assessment) excluded one patient with relapsed or refractory diffuse large B-cell lymphoma who discontinued before first assessment due to COVID-19 pneumonia and one patient with relapsed or refractory follicular lymphoma who discontinued before first assessment due to coronary artery bypass surgery. Data are not shown for 23 patients with relapsed or refractory diffuse large B-cell lymphoma who received doses of less than 12 mg or for six additional patients with other relapsed or refractory B-cell non-Hodgkin lymphoma histologies. One patient with diffuse large B-cell lymphoma did not receive a full dose of epcoritamab; the patient died of COVID-19 and was not response-evaluable. NA=not applicable. *Includes three patients who received the 60 mg dose before the recommended phase 2 dose was established. †PET scan was not mandatory until a protocol amendment on Nov 4, 2019. ‡Three patients had blastoid or pleomorphic mantle cell lymphoma; one had unknown histology. §Includes one patient who died before response assessment.

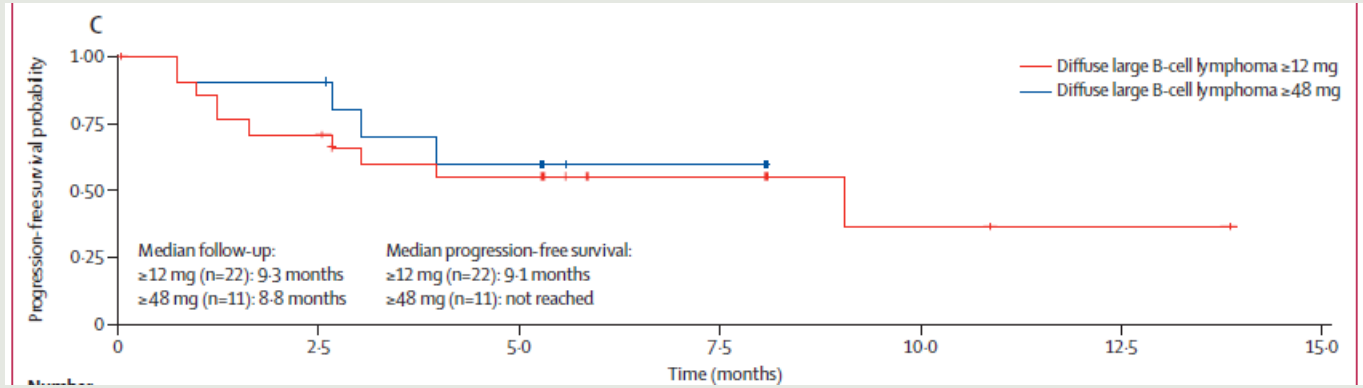
Table 4: **Treatment response by diagnosis in the modified response-evaluable set (n=66)**

Hutchings M, Lugtenburg PJ. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. Lancet. 2021 Sep 25;398(10306):1157-1169.

Epcoritamab







Hutchings M, Lugtenburg PJ. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. Lancet. 2021 Sep 25;398(10306):1157-1169.

Future Directions

Disease	Setting	Modifiers	Trial ID	Report format	Phase	Drug(s)	Histology	N.	Median age, y (range)	Median N. prior therapies (range)	% Prior ASCT/prior CAR-T	ORR (CR), %	DOR, mo	PFS, mo	Follow-up (mo)
aNHL*	First line	R-CHOP candidate	NCT03677141	Abs	I/II	MOSUN-CHOP	DLBCL	40	65 (39-79)	0	NA	82 (79)	NR	NR	NR
			NCT03467373	Abs	I	GLOFIT-R-CHOP	DLBCL	26	68 (26-84)	0	NA	100 (89)	NR	NR	NR
			NCT04663347	Abs	I/II	EPCOR-R-CHOP	DLBCL	24	65 (30-82)	0	NA	100 (73)	nr (1-6.5+)	NR	1.3 (0.2-7.9)
		Older/unfit	NCT03677154	Abs	I/II	MOSUN (IV)	DLBCL	29	82 (67-100)	0	NA	63 (45)	nr (0.2-13+)	NR	5.4 (0.3–16.2)
	≥second line	Transplant eligible	NCT04663347	Abs	I/II	EPCOR-R-DHAX	DLBCL	29	58 (28-75)	1 (1-3)	0/10	100 (86)	NR	NR	5.8 (1.5-11.4)
		Transplant ineligible	NCT04663347	Abs	I/II	EPCOR-GemOx	DLBCL	26	71 (47-87)	2 (1-13)	12/12	92 (60)	NR	NR	9 (1-15)
			NCT02500407	Paper	I/II	MOSUN (IV)	Multiple	116	63 (19-91)	3 (1-14)	34/12	35 (19)	7.6 (5.6-2.8)	1.4 (1.4-2.9)	NR
			NCT02500407	Abs	I/II	MOSUN (SC)	Multiple	50	68 (41-88)†	3.5 (1-9)†	17/42†	29 (18)	NR	NR	4.2 (0.1-7.8)†
			NCT03075696	Abs	I/II	GLOFIT	Multiple	155	66 (21-90)	3 (2-7)	18/33	52 (39)	18.4 (13.7-NE)	4.9 (3.4-8.1)	12.6 (0-22)
			NCT03625037	Paper	I/II	EPCOR	Multiple	157	64 (20-83)	3 (2-11)	20/39	63 (39)	12 (0+-15.5+)	4.4 (3.0-7.9)	NR
			NCT04082936	Abs	I	IgM2323	DLBCL	18	64 (36-84)†	3 (2-9)†	8/20†	31 (25)	nr (2-1.5+)†	NR	7.8 (0.4-23.7)†
			NCT02924402	Abs	I	PLAMO	Multiple	46	61.5 (31-82)†	4 (1-10)†	13/NR†	51 (25)†	NR	NR	NR
			NCT02290951	Paper	I	ODRON	Multiple	85	67 (57-73)†	3 (2-5)†	8/29†	37 (24)	4.4 (2.9-NE); nr (1.6-NE)‡	2 (0.9-5.3)‡	4.2 (1.5-11.5)†
			NCT03671018	Abs	I/II	MOSUN-pola	DLBCL	60	68 (20-83)	3 (1-8)	NR/40	65 (48)	nr (6.3 - NE)	8.9 (3.5-NE)	5.7 (0.7-27.5)
			NCT03533283	Abs	I/II	GLOFIT-pola	Multiple	59	59 (29-82)	2 (1-5)	NR/NR	80 (51)	nr (0.5-23+)	NR	3.7 (1.9-5.3)

Falchi L, Vardhana SA, Salles GA. Bispecific antibodies for the treatment of B-cell lymphoma: promises, unknowns, and opportunities. Blood. 2023 Feb 2;141(5):467-480.