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What is the best timing for bispecific antibody and CAR-T therapy in DLBCL?

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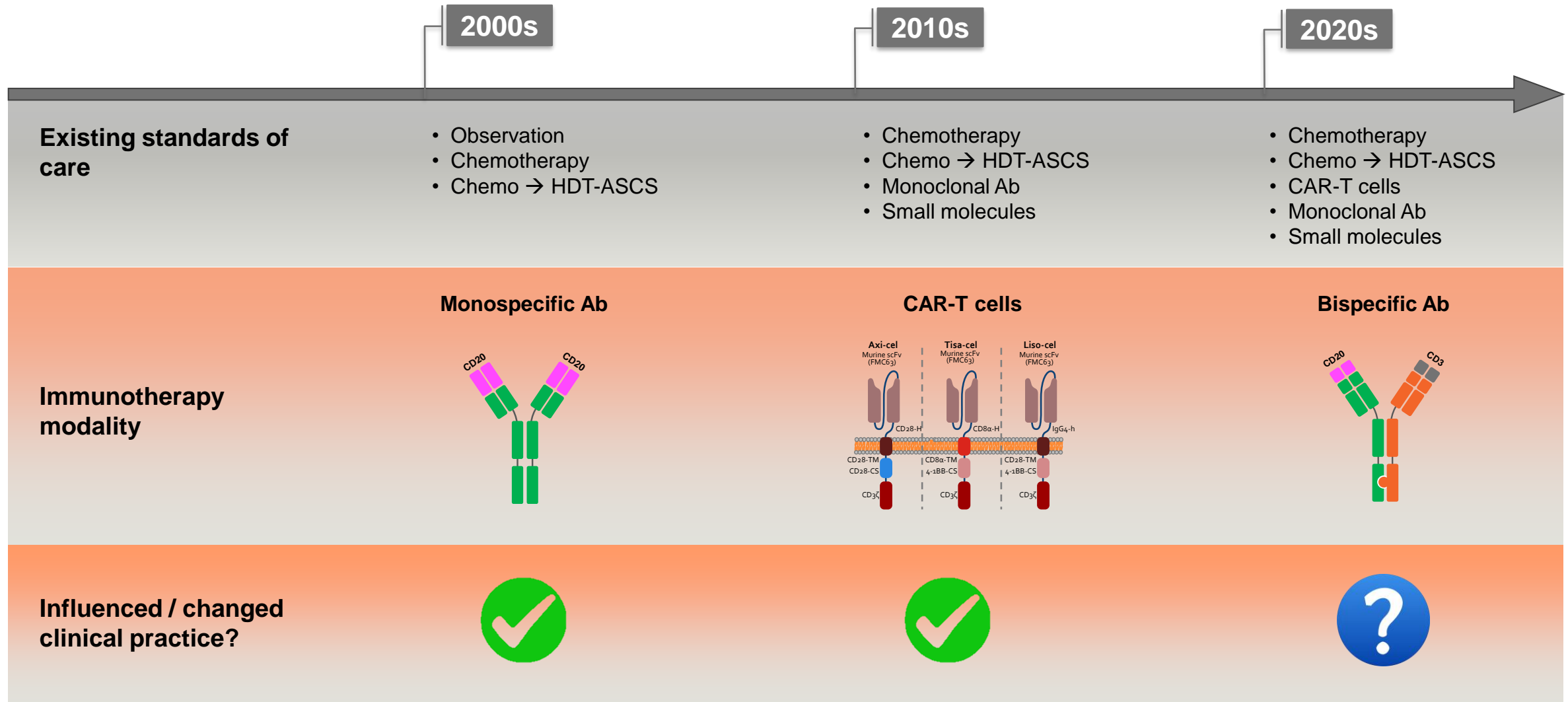
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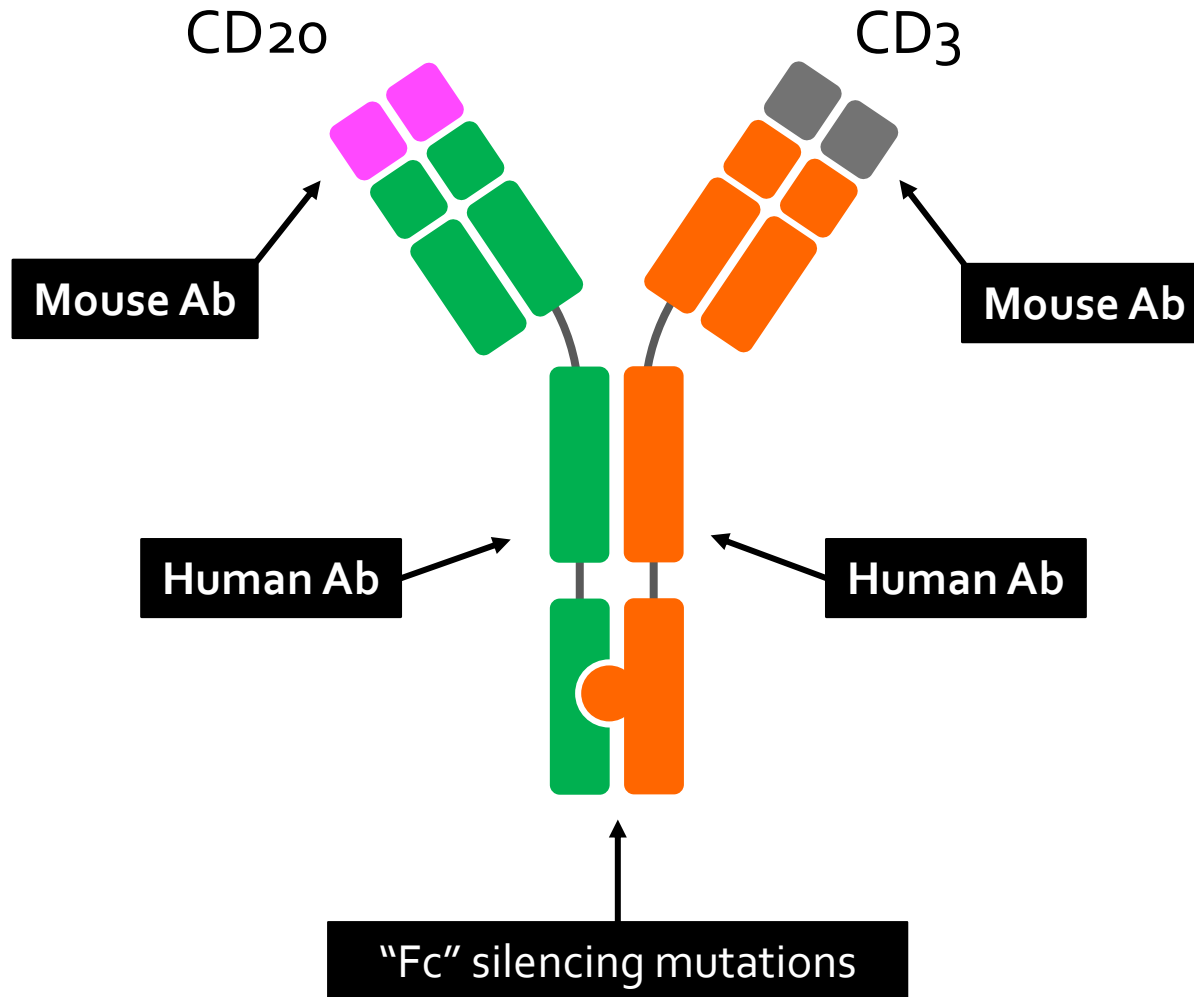
Disclosures for Andrew D. Zelenetz, MD, PhD

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Employee	None
Consultant	BMS/Celgene/JUNO, Genentech/Roche, Gilead/Kite; BeiGene; Pharmacyclics, Jansen, Amgen, Astra-Zeneca, Novartis, MEI Pharma
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Bispecific antibodies: The third “immunotherapy milestone” in B-NHL therapy?

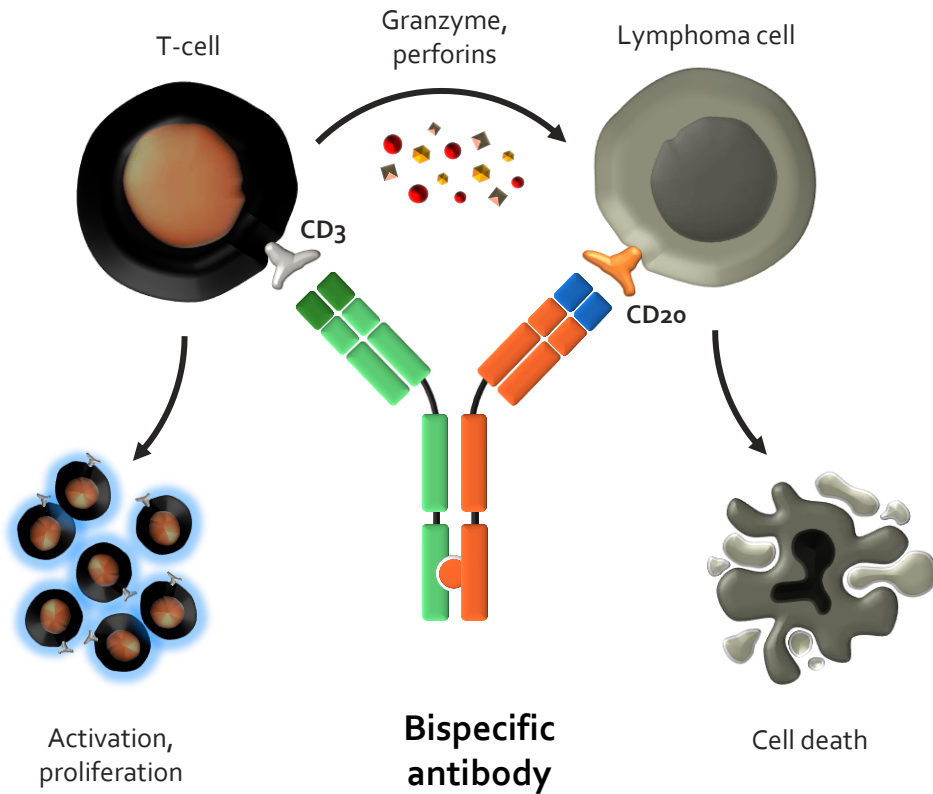


Common structural properties of bispecific antibodies

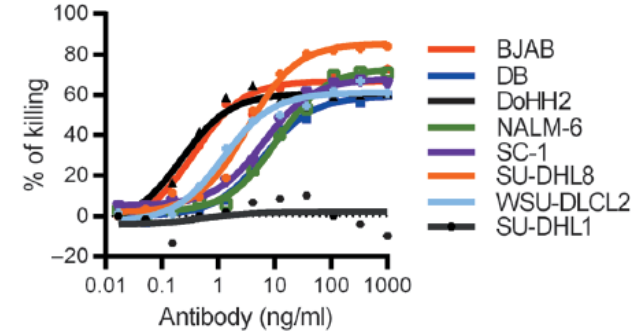


- Bivalent IgG-like, full-length Ab co-targeting **CD20** (B-cells) and **CD3** (pan-T-cell marker)
- Different BsAb target different epitopes on CD20
- **Fc mutations** to avoid ADCC, CDC, or fratricidal killing of anti-tumor T-cells
- Preserved FcRn for prolonged half-life
- Unlike BsAb without Fc domain (eg, BiTEs, DARTs), IgG-like BsAb share **PK properties of MoAb**

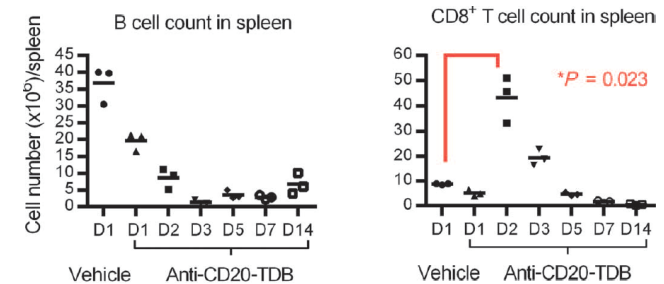
Basic mechanism of action of bispecific antibodies



Activity is target-dependent


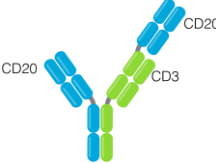





Activity is conditional



Matched time course of tissue B-cell and CD8⁺T-cell numbers after a single dose of mosunetuzumab in huCD20-huCD3 double-transgenic mice.

Overview of CD20xCD3 bispecific antibodies

Product name	Schematic depiction	Format	Technology	CD20:CD3 ratio	CD3 clone	CD20 clone	Fc silencing mutations
Mosunetuzumab		IgG1	Knobs-into-holes (different Fabs)	1:1	UCHT1v9	2H7 (same as rituximab)	Yes
Glofitamab*		IgG1	Head-to-tail fusion	2:1	SP34-der.	By-L1 (same as obinutuzumab)	Yes
Epcoritamab*		IgG1	Controlled Fab-arm exchange	1:1	huCACAO (SP34-der.)	7D8 (shared by ofatumumab)	Yes (prevents FcγR and C1q binding)
Odronextamab		IgG4	Heavy chains with different affinity	1:1	REG1250	3B9-10 (shared by ofatumumab)	Yes
Plamotamab		IgG1	Fab-Fc x scFv-Fc	1:1	α-D3_H1.30 (SP34-der.)	C2B8_H1_L1 (shared by rituximab)	Yes

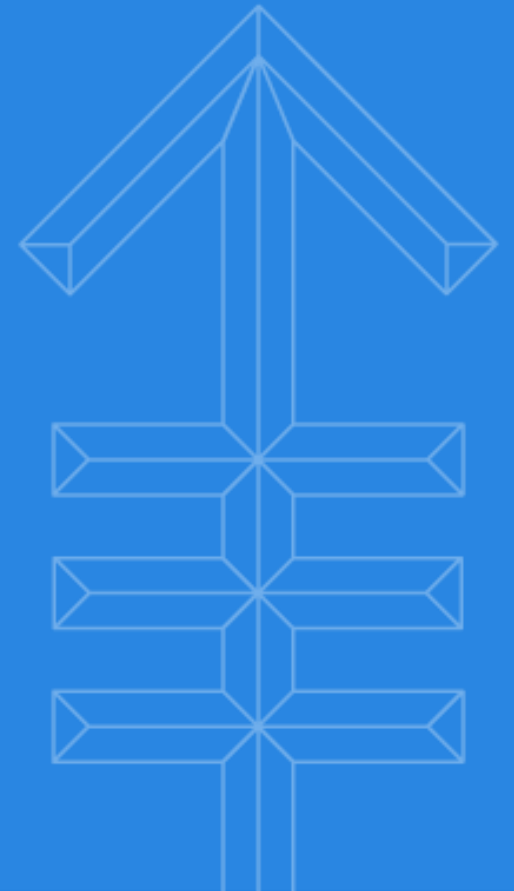
* Approved by the U.S. FDA and other regulatory agencies for the treatment of patients with large B-cell lymphoma



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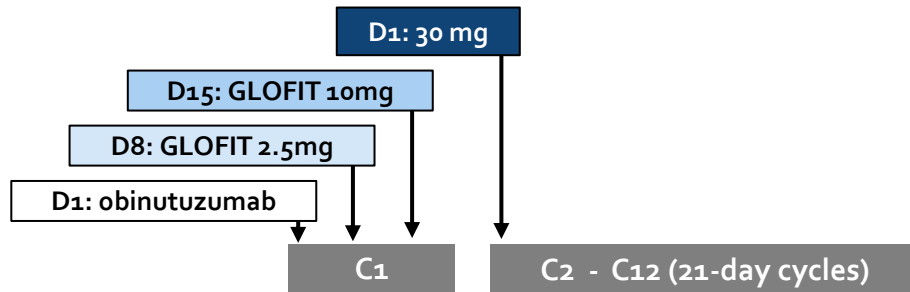
Key Clinical Data

Single-agent CD20xCD3 BsAb



Glofitamab in 3L+ DLBCL: expansion cohort (n=154)

Study Schema



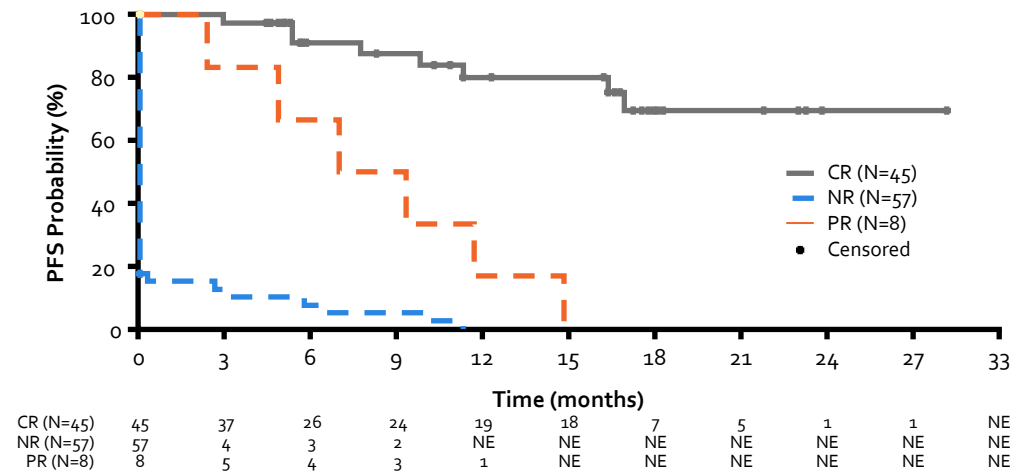
- Premedication: acetaminophen, anti H2, and steroids (dexamethasone preferred).
- Hospitalization on C1D8 (1st GLOFI dose)

Characteristic	N (%)
Median age, years (range)	66.0 (21–90)
NHL subtype	DLBCL 110 (71.4)
	trFL 27 (17.5)
	HGBCL 11 (7.1)
	PMBCL 6 (3.9)
Median no. prior lines, (range)	3 (2–7)
≥3 prior lines	92 (59.7)
Prior CAR-T	51 (33.1)
Refractory to prior CAR-T	46 (29.9)

	IRC (N=155)*
CR, n (%) [95% CI]	62 (40) [32.2–48.2]
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]
Median follow-up, mos (rng)	18.2 (0–33)
Ongoing CRs, n/N (%)	42/62 (68)
Median DoCR, mos (95% CI)	26.9 (18.4–NE)

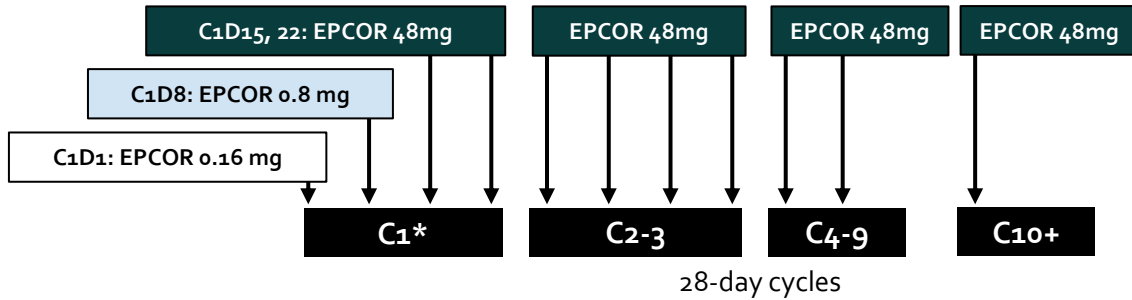
*Intent-to-treat population; CI, confidence interval; NE, not estimable.

Landmark analysis by response at EOT



Epcoritamab in 3L LBCL: Responses and outcomes (n= 157)

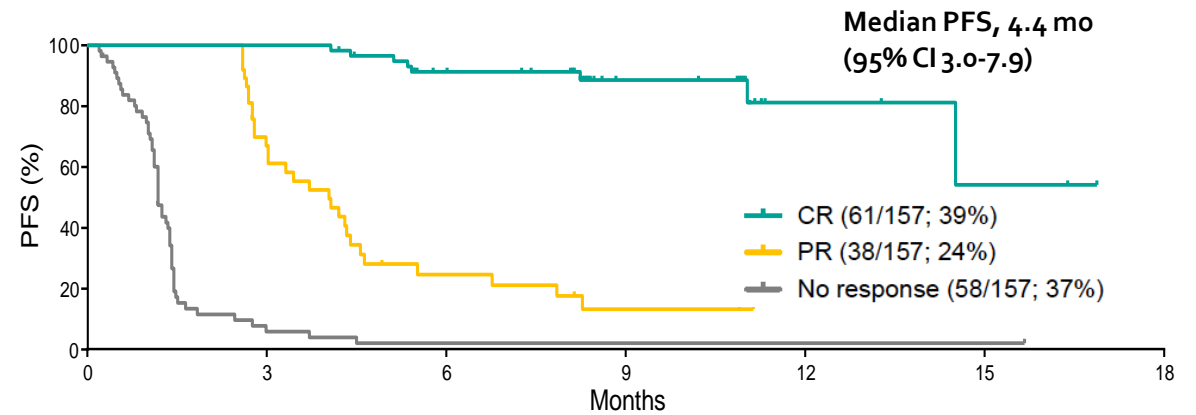
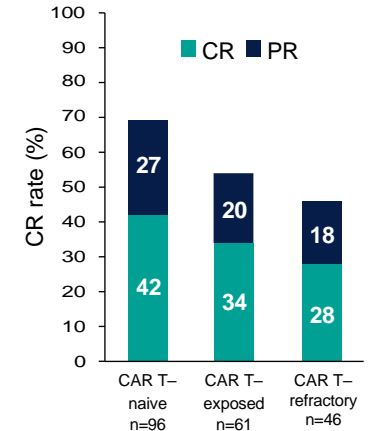
Study Schema



* Premed: acetaminophen, anti H₂, and prednisone x4 days post dose; hospitalization on C1D15.

Characteristic	N=157
Median age (range), y	64 (20–83)
DLBCL	139 (89)
HGBCL	9 (6)
PMBCL	4 (3)
FL Gr3B	5 (3)
Median n. prior lines (range)	3 (2–11)
≥3 Lines of therapy, n (%)	111 (71)
Primary refractory ^b disease, n (%)	96 (61)
Prior CAR T therapy, n (%)	61 (39)

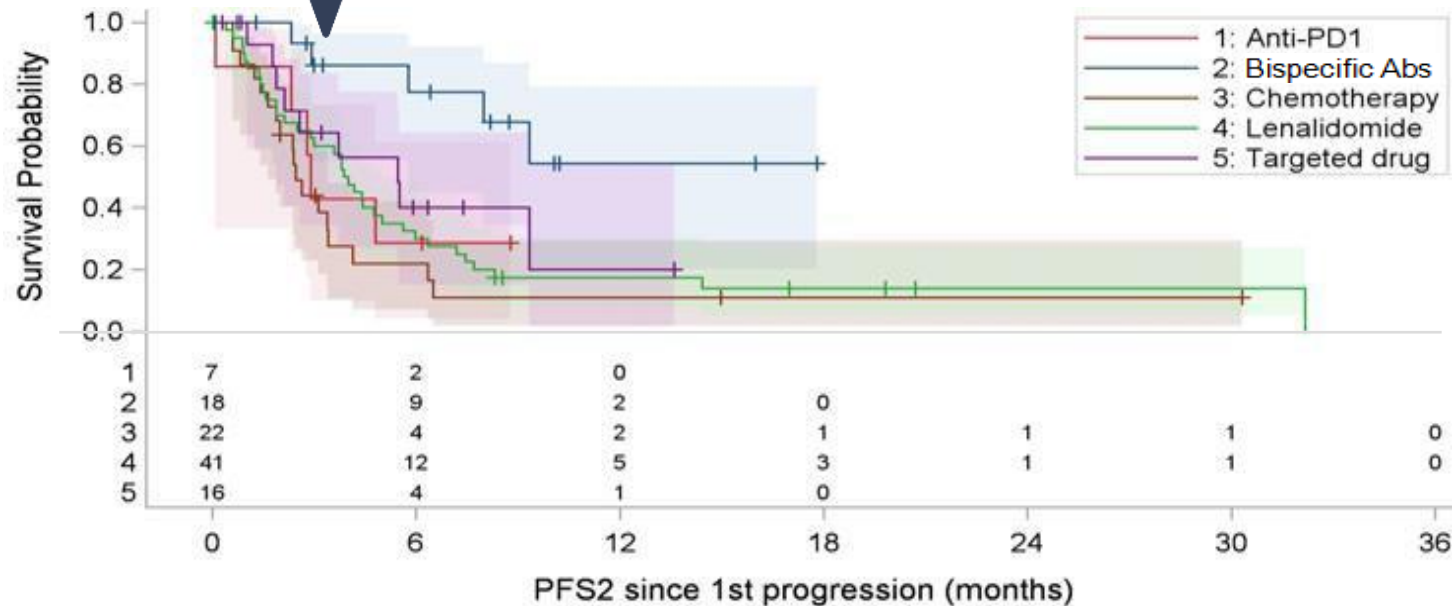
Response	n=157
ORR	99 (63) [95% CI: 55–71]
CR rate	61 (39) [95% CI: 31–47]



Median follow-up = 10.7 months

PFS after CAR-T cell therapy failure by treatment group (DESCAR-T registry)

Bispecific Abs: 6-months PFS 77.5%, HR=0.188 (95% CI, 0.069–0.509), P=0.001



	No. of Subjects	Event	Censored	Median Survival (95%CL)
Anti-PD1	7	71.4 % (5)	28.6 % (2)	2.9 (0.1 ; NA)
Bispecific Abs	18	27.8 % (5)	72.2 % (13)	Not reached (5.8 ; NA)
Chemotherapy	22	81.8 % (18)	18.2 % (4)	2.5 (1.6 ; 3.4)
Lenalidomide	41	85.4 % (35)	14.6 % (6)	3.9 (2.5 ; 5)
Targeted drug *	16	56.3 % (9)	43.8 % (7)	5.5 (1.9 ; NA)

* BTK Inhibitors, MALT-1 inhibitors, anti-CD19, anti-CD38, second CAR T, others.

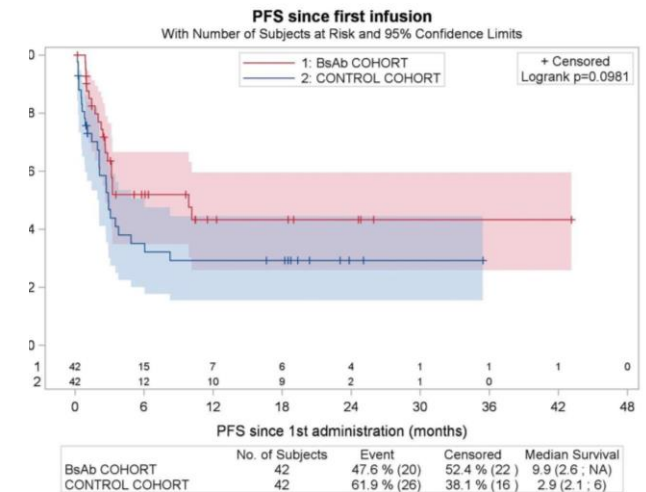
Bispecific antibodies (BsAbs) do not impair response to CAR T cells

- 47 patient with prior BsAb
 - Median time on BsAb 98 days (IQR 56-160)
 - OR 47%, CR 19%
- CAR T-cell therapy after BsAb: axi-cel (n=22, 47%), tisa-cel (n=20, 43%) or liso-cel (n=5, 11%)
 - CRS 79%, grade ≥ 3 6%
 - ICANS 23%, grade ≥ 3 2%
- For comparison to patients without prior BsAb, 42/47 BsAb exposed patients were propensity matched with 42 patients from the DESCART registry
 - Prior BsAb did not impair PFS or OS
 - No differences in toxicities

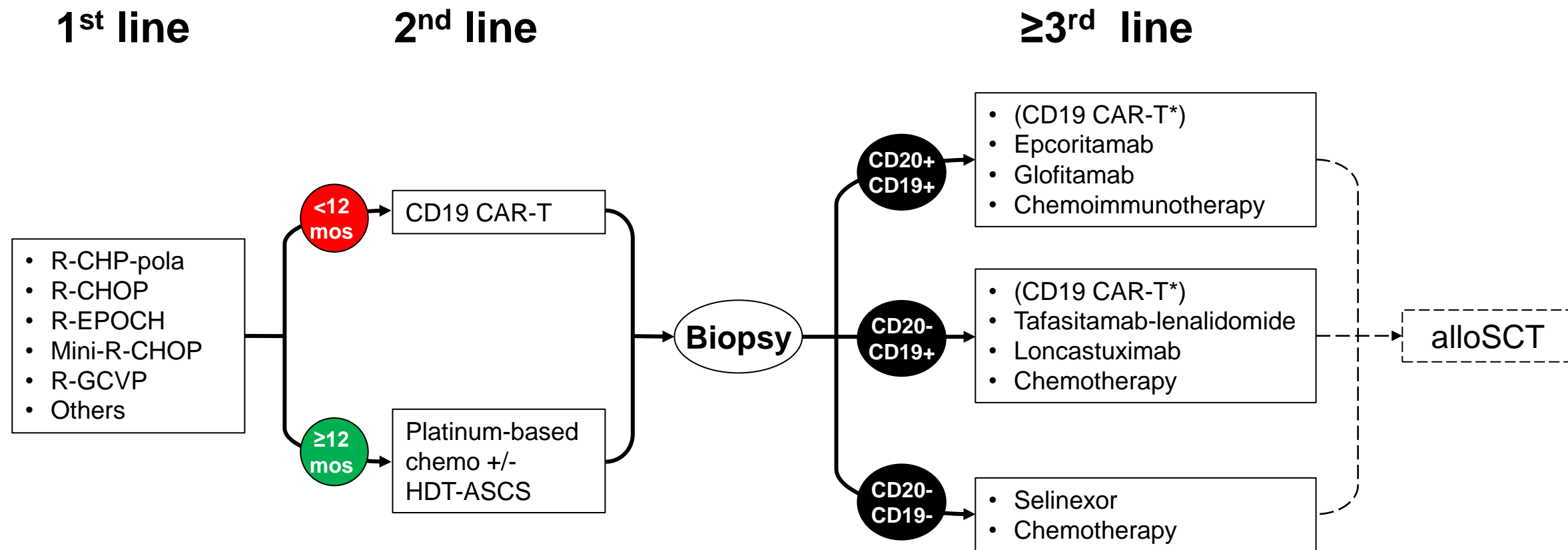
Table.- Baseline characteristics of CAR T-cell recipients according to their previous exposure to bispecific antibody therapy.

Variables	BsAb cohort n=42	Control cohort n=42	SMD
Patient and lymphoma characteristics			
Male gender, n (%)	29 (69)	31 (74)	-0.085
Age, median years (range)	63 (31-82)	67 (21-78)	0.061
Histology, n (%)			
- DLBCL/HGBL	35 (83)	31 (74)	0.196
- PMBL/Transformed	7 (17)	11 (26)	
> 2 prior lines, n (%)	36 (86)	36 (86)	0
Previous SCT, n (%)	8 (19)	7 (17)	-0.05
Bulky disease, n (%)	15 (36)	19 (45)	0.16
CRP > 3mg/dL, n (%)	16 (38)	12 (29)	-0.164
LDH > 2xULN, n (%)***	12 (29)	16 (38)	0.168
ECOG >1, n (%)***	4 (10)	3 (7)	-0.069
CAR-T related characteristics			
Axi-cel, n (%)	22 (52)	20 (48)	-0.078
Months between last prior treatment and CAR-T infusion, median (IQR)	2.7 (2.3-3.8)	2.5 (2.0-3.5)	0.201
Response to bridging, n (%)			
- Responder	8 (19)	5 (12)	-0.159
- Non responder	26 (62)	22 (52)	
- No bridge	5 (12)	11 (26)	
- Not evaluated	3 (7)	4 (10)	
Year of CAR-T infusion ≥ 2020 , n (%)	29 (69)	29 (69)	0

Table_Abbreviations: IQR interquartile range, DLBCL diffuse large B-cell lymphoma, HGBL high grade B-cell lymphoma, PMBL primary mediastinal B-cell lymphoma, SCT stem cell transplant, CRP C-Reactive Protein, LDH Lactate Dehydrogenase, ULN Upper Limit of Normal, ECOG Eastern Cooperative Oncology Group, CAR chimeric antigen receptor.



Proposed R/R DLBCL treatment paradigm



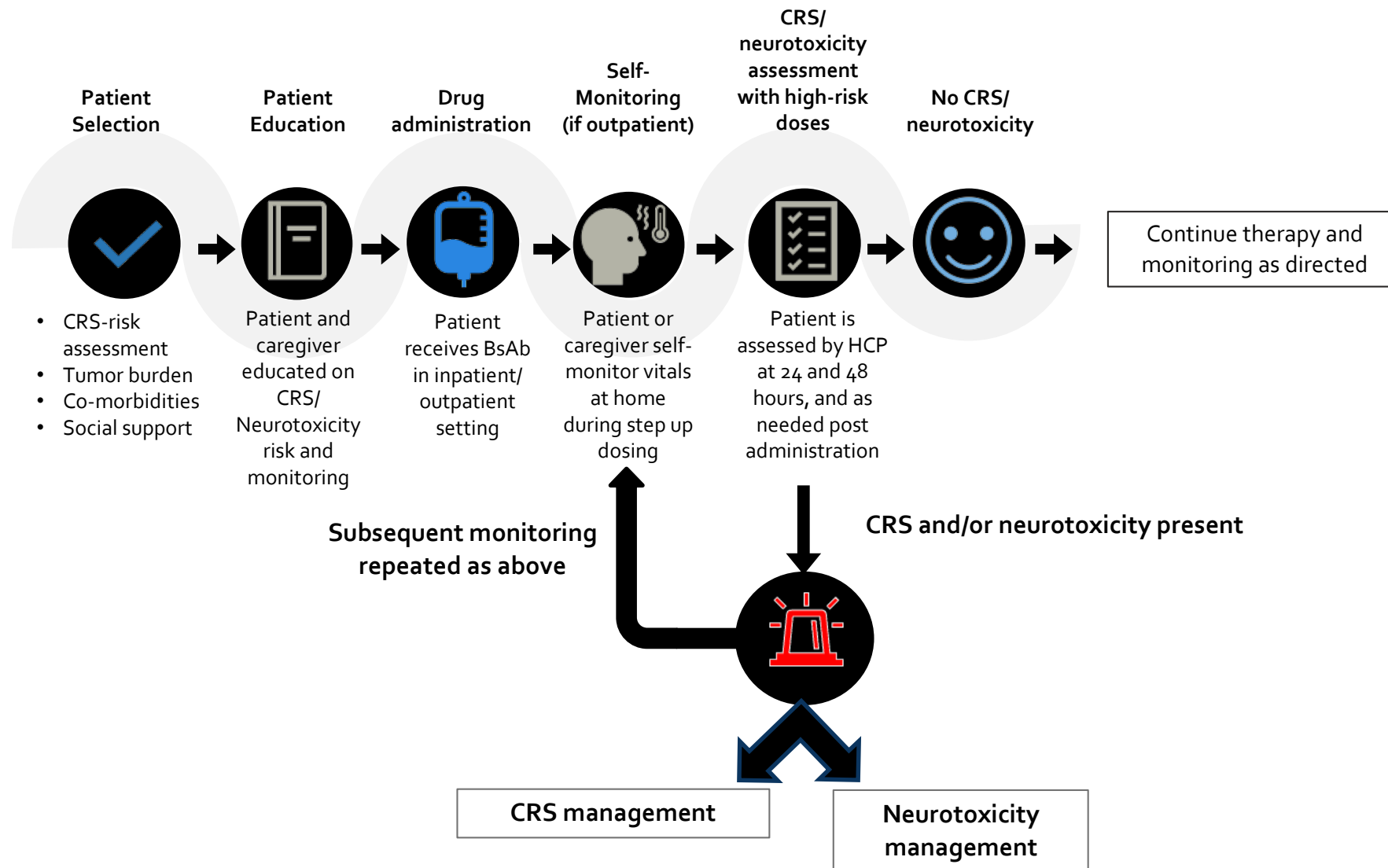
R, rituximab; CH(O)P, cyclophosphamide, doxorubicin, (vincristine), prednisone; EPOCH, etoposide, cyclophosphamide, doxorubicin, (vincristine), prednisone; CAR, chimeric antigen receptor; HDR-ASCS, high-dose therapy with autologous stem cell support; BR, bendamustine, rituximab; alloSCT, allogeneic stem cell transplantation. NOTES: Only drugs / regimens with regulatory approval are listed; clinical trial participation, where available and appropriate, may be offered at each stage of the algorithm; *if not previously used.

CRS mitigation and incidence across CD20xCD3 BsAb Trials*

Drug	N.	Population	Route (target dose)	Mitigation strategies during Cycle 1			% CRS	% toci use
				Step-up dosing	Hospitalization	Other		
Mosunetuzumab	90	FL, R/R	IV (30 mg)	Yes	Optional			8
	39	B-NHL, R/R	SC (45 mg)	Yes	Optional			10
	27	B-NHL, R/R	SC, rapid SUD (45 mg)	Yes	Optional			0
Glofitamab	154	DLBCL, R/R	IV (30 mg)	Yes	Mandatory	Obinutuzumab		32
	29	MCL, R/R	IV (0.6-30 mg)	Yes	Mandatory	Obinutuzumab		24
Epcoritamab	157	LBCL, R/R	SC (48 mg)	Yes	Mandatory	Post-dose steroids		28
Odronextamab	145	B-NHL, R/R	IV (0.5-320 mg)	Yes	Mandatory	Split-dose		5

* This table is not comparative; direct cross-trial comparisons should be avoided.

Consensus recommendations for the management of acute toxicities associated with bispecific antibodies





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Key Clinical Data

**CD20xCD3 BsAb-containing
combinations**



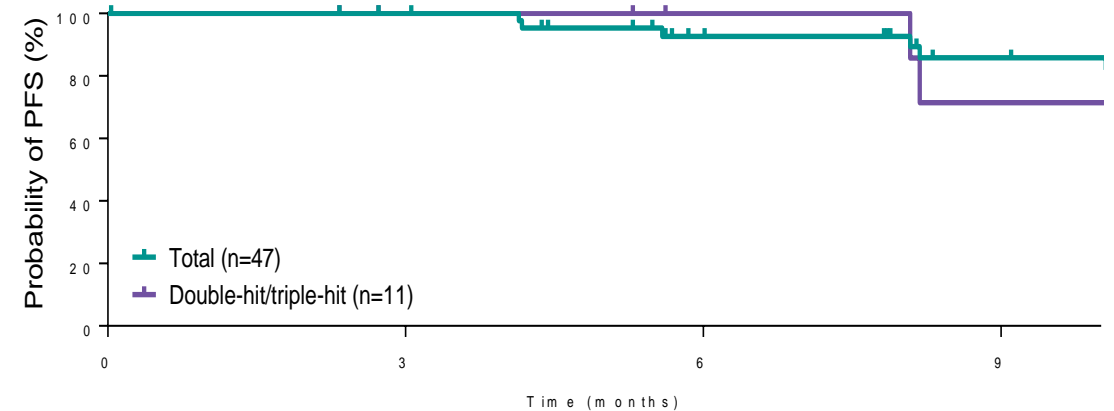
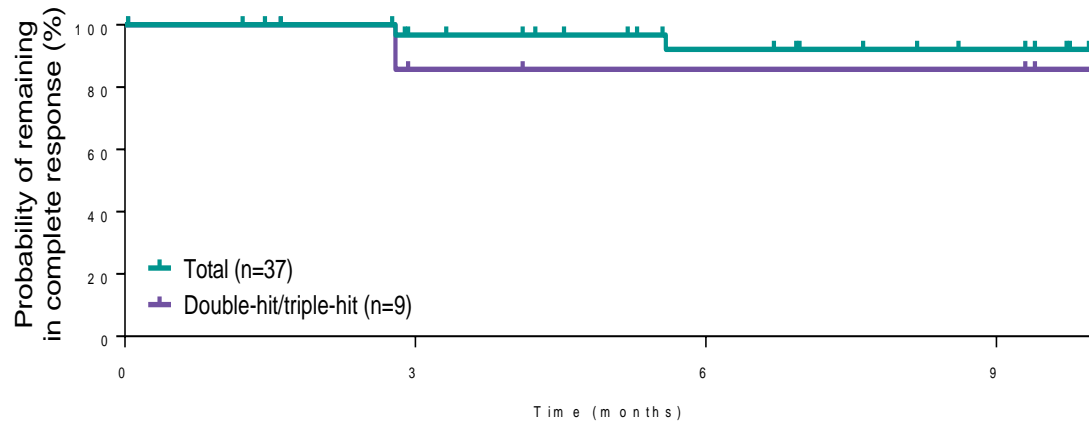
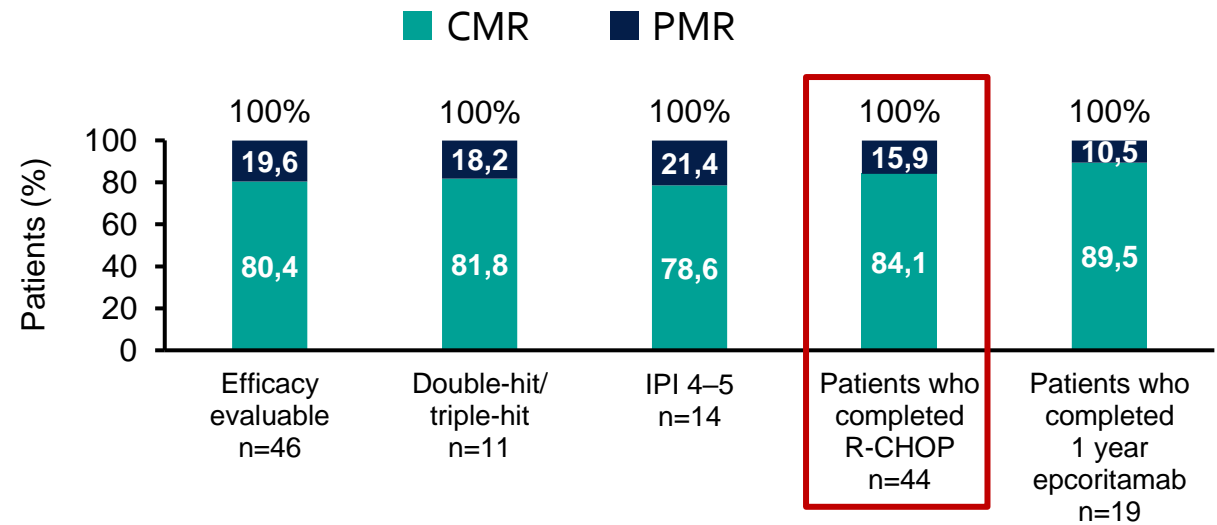
Enhancing the efficacy of BsAbs in R/R DLBCL: Novel-novel doublets

	Descriptor	Mosunetuzumab + polatuzumab (n=98)	Glofitamab + polatuzumab (n=125)	Epcoritamab + lenalidomide (n=35)
Baseline characteristics	Median age (range)	68 (20-98)	67 (23-84)	72 (41-85)
	Median n prior lines (range)	2 (1-8)	2 (1-7)	2 (1-4)
	1 prior line	35.7%	40%	49%
	Prior CAR-T	35.7%	22.4%	23%
Responses	ORR	63.3%	80.2%	71.9%
	CRR	51.0%	59.5%	53.1%
Safety	CRS (G \geq 3)	18.4% (3.1%)	45.9% (0.8%)	69% (11%)
	Neurotoxicity (G \geq 3)	5.1% (2.0%)	3.2% (0)	3% (3%)
	G \geq 3 neutropenia	20.4%	Not reported*	51%
	G5 adverse events	3%	7%	95
Outcomes	Median follow-up	23.9 months	20.4 months	8.2 months
	PFS, months	11.4 (95% CI: 6.2-18.7)	10.4 (95% CI: 7.0-23.5)	Not reported
	DoCR	NR (20.5-NR)	NR (12-month: 72.9%)	NR (95% CI: not reported)

CAR, chimeric antigen receptor; ORR, overall response rate; CRR, complete response rate; G, grade; PFS, progression-free survival; DoCR, duration of complete response; NR, not reached. * The incidence of G \geq 3 neutropenia had been 29.7% in an earlier report (n=111)

Moving BsAb to the 1st line: Epcoritamab + R-CHOP in high-risk DLBCL defined by an IPI ≥ 3

Characteristic	N=47
Median age, y (range)	64 (19–82)
IPI score, n (%)	
3	33 (70)
4–5	14 (30)
<i>MYC/BCL2/BCL6</i> rearrang n (%)	
Double-hit	6 (13)
Triple-hit	5 (11)



Moving BsAb to the 1st line: Glofitamab + R-CHOP in high-risk DLBCL defined by on-treatment ctDNA levels

Key inclusion criteria

- 1L CD20+ LBCL
- ECOG PS 0–2
- IPI 0–5
 - IPI 0 for patients with bulky disease
 - IPI 1–5 for non-US patients
 - IPI 2–5 for patients in the US

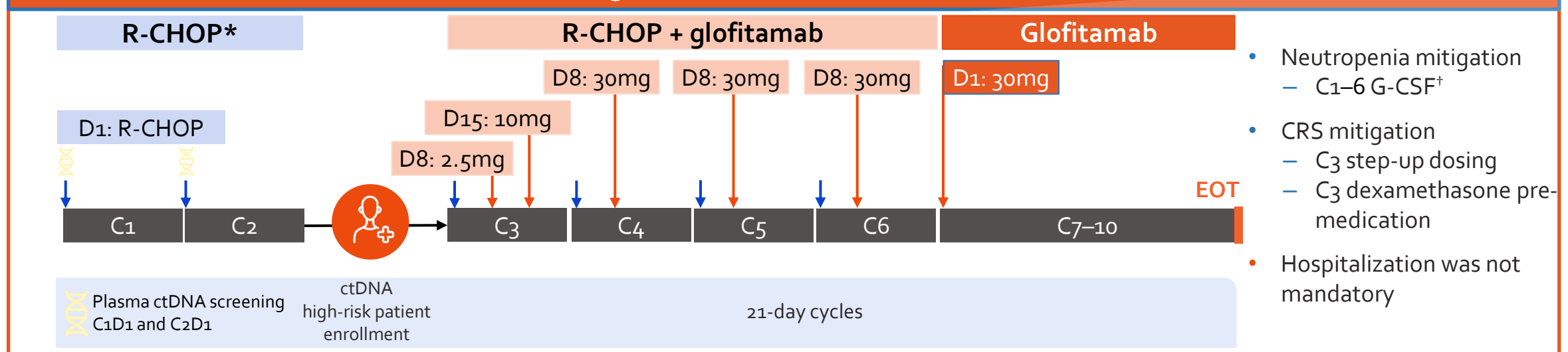
Endpoints

- Primary endpoint is CR at EOT as determined by investigator
- Secondary endpoints include ORR at EOT and safety and tolerability

ctDNA analysis

- ctDNA levels were measured at C1D1 and at C2D1 (AVENIO Oncology Assay for Non-Hodgkin's Lymphoma)¹
- ctDNA high-risk patients: <2-log [100-fold] reduction in ctDNA after one R-CHOP cycle

Dosing and ctDNA assessment schedule



* R-CHOP: IV rituximab 375mg/m², cyclophosphamide 750mg/m², doxorubicin 50mg/m², and vincristine 1.4mg/m² (max. 2mg) on D1, plus oral prednisone 100mg once daily on D1–5. [†] Mandatory.

C, cycle; CR, complete response; CRS, cytokine release syndrome; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; G-CSF, granulocyte-colony stimulating factor; ORR, overall response rate.

Glofitamab + R-CHOP in 1L LBCL at high risk by ctDNA: First results

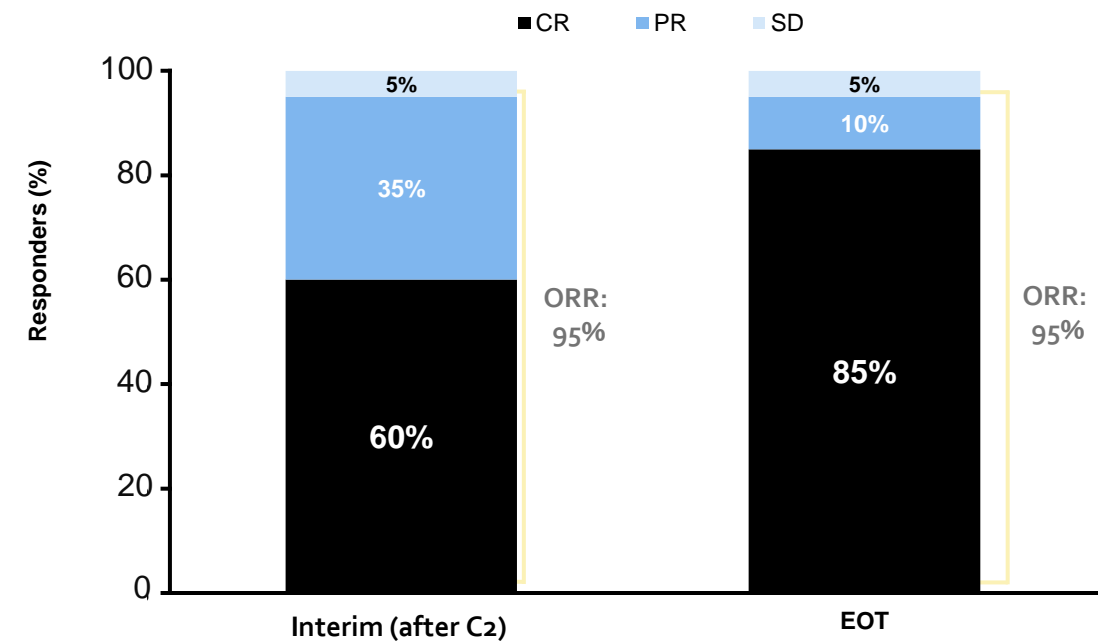
n (%), unless stated	N=29
Median age, years (range)	62.0 (39.0–77.0)
Ann Arbor stage III–IV	23 (79.3)
IPI score 3-5	12 (41.3)
DLBCL category [†]	
DH	2 (6.9)
TH	6 (20.7)
Cell of origin (local)	
GCB	12 (41.4)
ABC [‡]	8 (27.6)
Unclassified	5 (17.2)
Unknown	4 (13.8)

[†] Locally tested.

[‡] Determined by gene expression profiling.

ABC, activated B cell; DH, double-hit; GCB, DLBCL, diffuse large B-cell lymphoma; germinal center B cell; TH, triple-hit.

INV-assessed interim and EOT response rates*



All patients who achieved CR are still in remission



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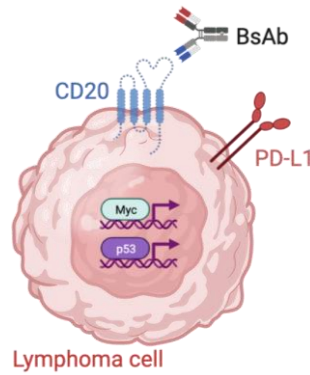
Understanding and Overcoming Resistance to CD20xCD3 BsAbs



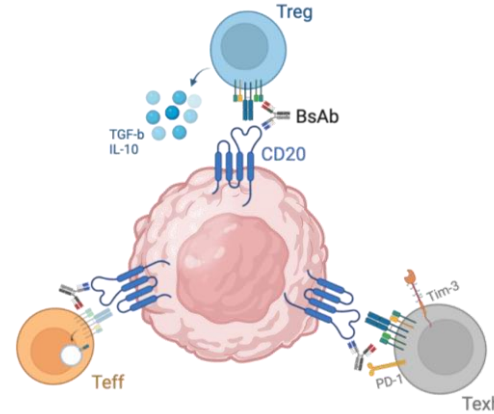
Overcoming resistance to CD20xCD3 bispecific antibodies

Mechanisms of resistance

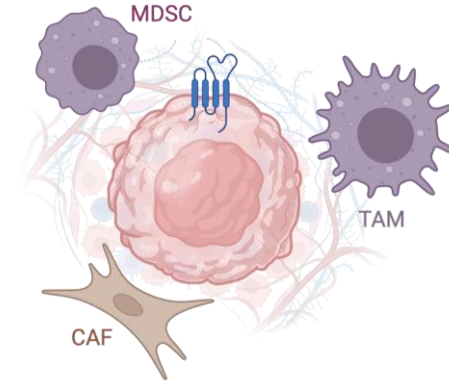
Tumor-intrinsic



T-cell-intrinsic



Tumor- and T-cell-extrinsic



Strategies to overcome resistance

Target different antigens

- BsAb against CD19, CD22, CD79b, ROR1
- Tri- or tetra-specific Ab

Increase T-cell activation / Prevent T-cell exhaustion

- Add immune checkpoint blockers
- Incorporate co-stimulatory BsAb

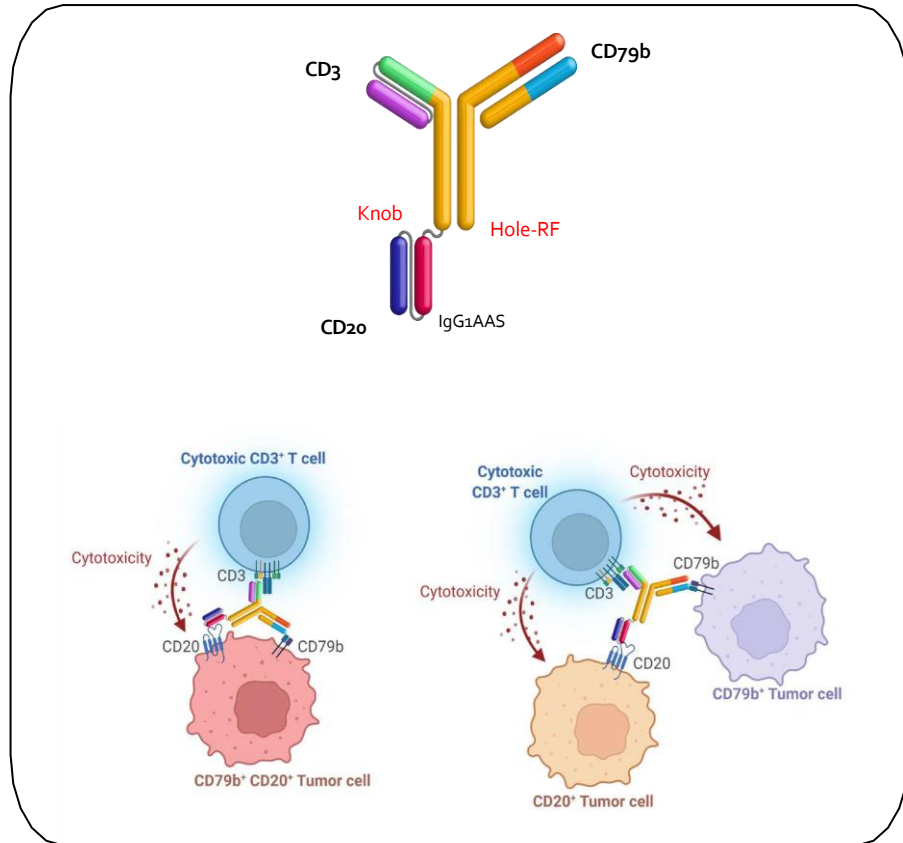
Target the microenvironment

- Lenalidomide; EZH2i; cbl-B-i
- Recruit other immune players**
- Macrophages (CD47); NK cells

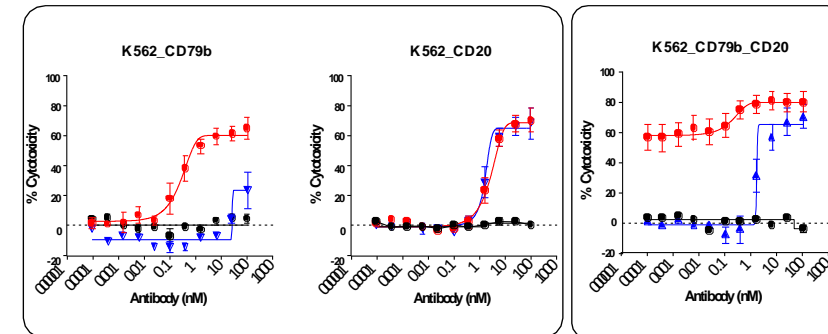


JNJ-80948543: CD79b x CD20 x CD3 trispecific Ab for B-NHL

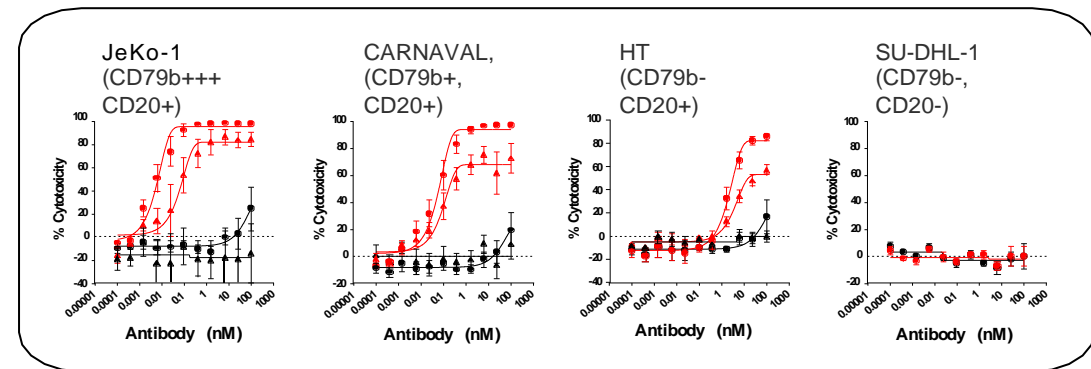
JNJ-80948543: Structure and MoA



Broader antigen targeting (T-cells from healthy donors)

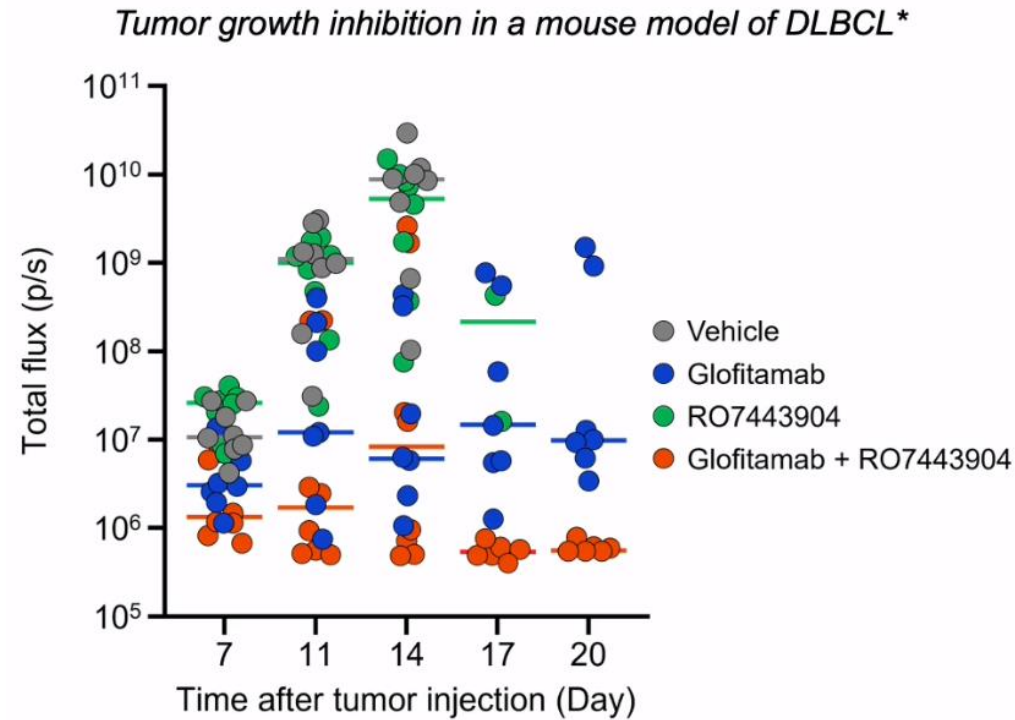


Effect on Tumor Cells Expressing CD79b and/or CD20

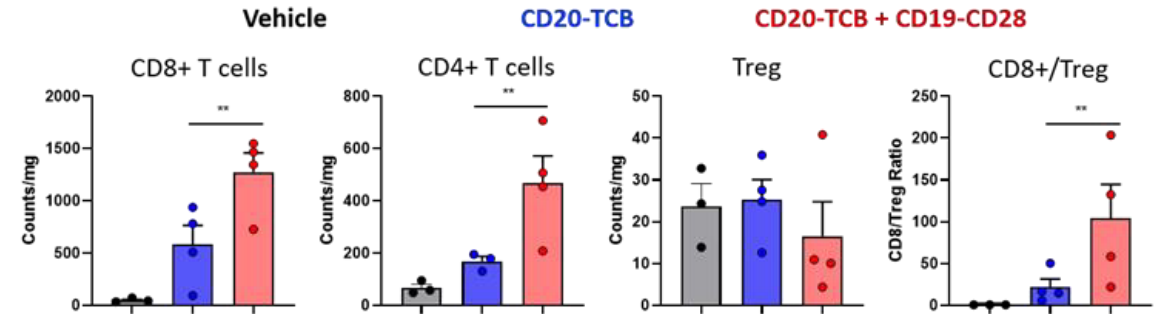


T-cell Redirection Assays; E:T ratio 5:1

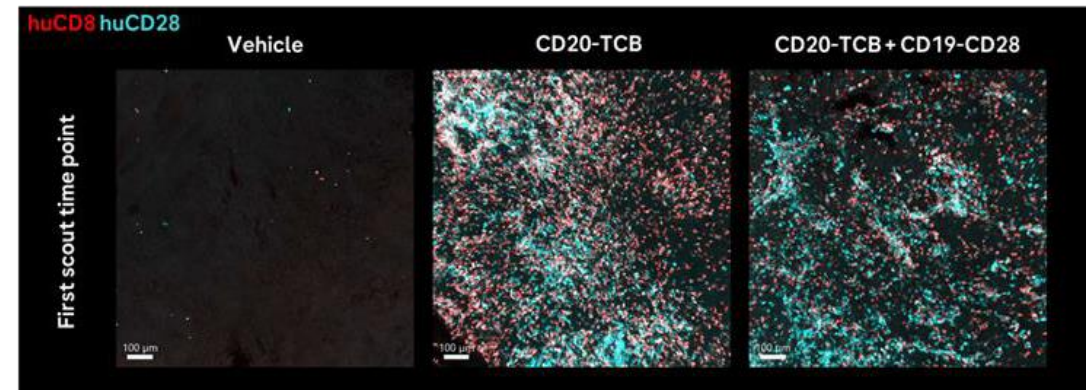
RO7443904 (CD19 x CD28 co-stimulatory Ab) + glofitamab: Preclinical activity



Humanized NSG mice (7-8mice/group) implanted with WSU-DLCL2 Fluc lymphoma cells i.v. and treated once weekly i.v. with glofitamab (0.15mg/kg) or CD19-CD28 (1mg/kg) in monotherapy or with the combination starting on day 3. Tumor growth was recorded with BLI measurement.

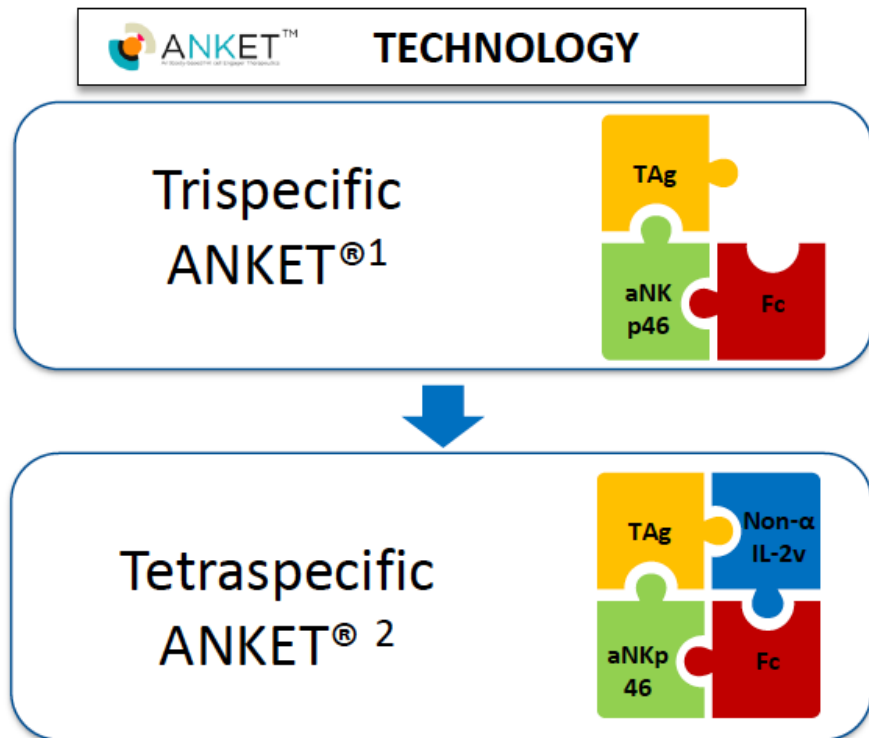


Humanized NSG mice were inoculated s.c. with WSU-DLCL2 lymphoma cells and received obinutuzumab followed by glofitamab (0.15mg/kg) alone or with CD19-CD28 (1mg/kg). Tumors were harvested 8 days later

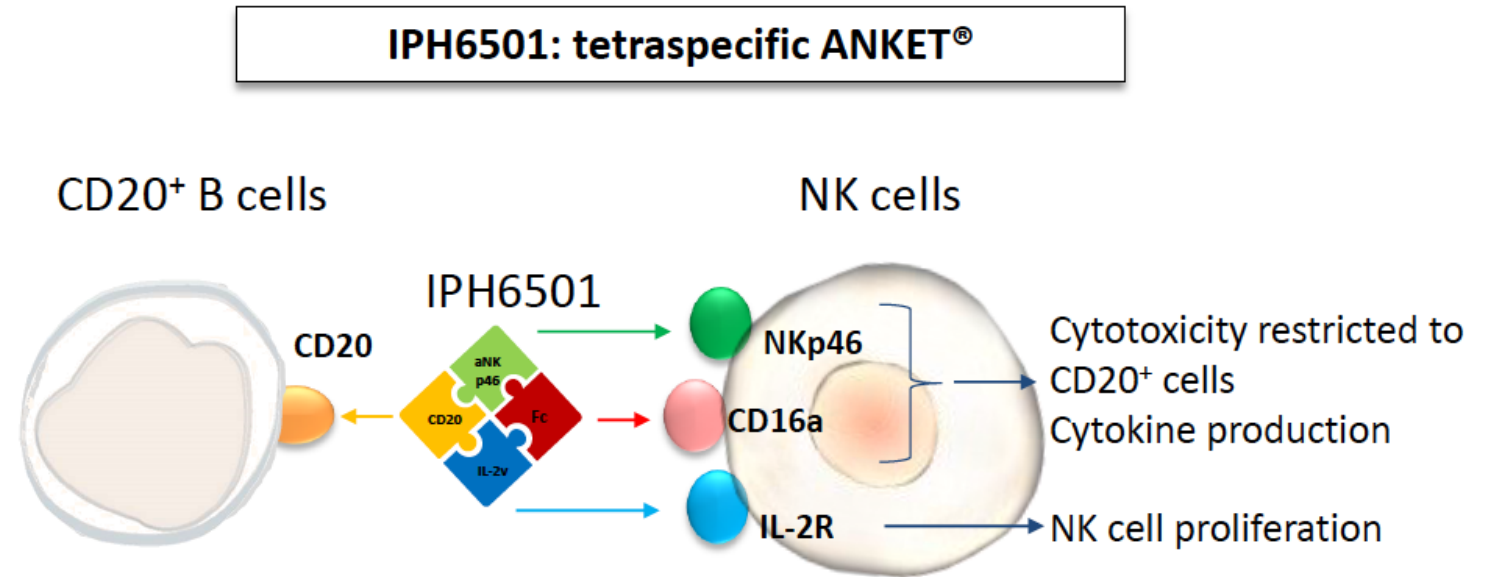


IF in tumors for CD8+CD28+ human T cell frequencies at 6 days after treatment with glofitamab alone or with CD19-CD28(1mg/kg)

IPH6501: First-in-class tetraspecific targeting CD20 developed for the treatment of B-cell malignancies



*IL-2v: IL-2 variant deprived of CD25 (IL-2R α) binding to limit Treg activation and CD25 associated toxicity



IPH6501 is designed to amplify and to redirect NK cell effector functions against CD20⁺ cancer cells

Summary

- **BsAb are a critically important addition in R/R LBCL:**
 - Consistent efficacy results with predictable safety
 - Possible curative potential? Additional follow up needed
 - These data will help inform treatment sequencing in the R/R setting
- **When?**
 - BsAbs are emerging as key 3L option in CD20+ LBCL (optimal sequencing with CAR-T in 3L+?)
 - Ideal role may be as part of 1L therapy
 - To be addressed in ongoing Phase 3 trials
- **How?**
 - CRS mitigating strategies, multidisciplinary management, patient education as pillars of safe implementation of BsAbs in the clinic
 - Fully outpatient administration for selected (low CRS risk) patients
- **Unmet needs:**
 - CD20-negative relapse
 - T-cell exhaustion
 - “Double” CAR-T and BsAb resistant lymphoma

