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Trial watch: bispecific antibodies for the treatment of relapsed or refractory large B-cell lymphoma

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ABSTRACT

Immunotherapy has shaped the treatment approach to diffuse large B-cell lymphoma (DLBCL), with rituximab leading to remarkable improvements in outcomes for both relapsed and treatment-naïve patients. Recently, groundbreaking immunotherapies like chimeric antigen receptor T-cells have entered the treatment arena for relapsed/refractory (R/R) DLBCL and gained regulatory approval in several countries. The concept of harnessing a patient's own T-cells to combat cancer has been further explored through the development of bispecific antibodies (BsAbs), a class of engineered antibody products designed to simultaneously target two different antigens. These novel drugs have demonstrated impressive single-agent activity and manageable toxicity in patients with heavily pretreated B-cell non-Hodgkin lymphoma. In this review, we provide an up-to-date overview of recently completed or ongoing BsAbs trials in patients with R/R DLBCL, including single-agent results, emerging combination data, and novel constructs.

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1. Introduction

Relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) represents a medical challenge, especially for patients affected by primary refractory or early relapsing disease after front-line anthracycline-based chemoimmunotherapy.[1] Platinum-based combinations followed by high-dose therapy and autologous stem cell support (ASCS) have historically constituted the mainstay of second-line therapy, with an estimated 15%–20% cure rate in the rituximab era.[2] Patients not eligible for, or relapsing after two or more treatment lines exhibit poor outcomes, with an overall survival (OS) estimated in months.[1]

While the advent of targeted agents such as polatuzumab vedotin,[3] tafasitamab,[4] and loncastuximab[5] has resulted in incremental benefits for patients with R/R DLBCL, some of the greatest advances in this space have been made with the introduction of T-cell-based immunotherapies, namely chimeric antigen receptor (CAR-) T cells, with mature data showing durable remissions in 30%–40% of patients.[6–8] More recently, two randomized trials have shown the superiority of both axicabtagene ciloleucel and lisocabtagene maraleucel over standard second-line therapy in patients with high-risk R/R DLBCL.[9,10]

Despite significant clinical efficacy, several impediments stand in the way of effective CAR-T cell therapy delivery, including limited access outside large tertiary care centers, complex insurance approval processes, high costs, increased demand *vis-à-vis* limited manufacturing capability, and potentially long product turnaround, among others. Bispecific antibodies (BsAbs) are a novel class of off-the-shelf T-cell redirecting drugs with promising activity in B-cell non-Hodgkin lymphoma and the potential to play a major role in the treatment of R/R DLBCL.

Along the lines of the Trial Watch series,[11–14] here we provide a state-of-the-art overview of BsAb trials for patients with R/R DLBCL, including single-agent and combination data, as well as a look ahead at the future of this field.

2. Structural properties of bispecific antibodies

BsAbs comprise a class of engineered antibody products designed to simultaneously target two different antigens. Various bioengineering technologies have been used for their production, each resulting in constructs with unique structural and pharmacologic properties.[15] Early BsAbs were derived from fragments of monospecific Ab fused together. Such structure requires the administration of these drugs through a continuous intravenous (IV) infusion due to short half-life and rapid clearance from plasma. A major advance has been the introduction of immunoglobulin (Ig)Glike BsAbs, in which the preservation of an Fc region confers longer half-life and allows natural FcRn-mediated recycling processes.[16] The first and most extensively studied method for producing IgG-like BsAbs has been the 'knobs-into-holes' technology, where complementary mutations are introduced within the CH3 domain of each antibody component, thus ensuring consistent pairing of heavy chains.[17] Another approach utilizes the 'knobs-into-holes' or a similar technology to facilitate heterodimerization

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of heavy chains, while addressing light chain mispairing through domain crossover between the antibody's variable and constant regions.[18] Most BsAbs also feature silencing mutations in the Fc region, which abrogate untoward T-cell activation and fratricidal killing through antibody-dependent cellular cytotoxicity (ADCC) and complement fixation (CDC).[18]

BsAbs' cytotoxicity is thought to be driven by intratumoral and peripheral endogenous immune cells recruited by simultaneously targeting tumor and immune effector cell antigens. The so formed immunological synapse triggers T-cell activation and cytotoxic killing in a major histocompatibility complex (MHC)-independent manner.[15] The latter is a key mechanistic feature, as many DLBCL patients frequently exhibit genetic aberrations that abolish expression of MHC class I molecules.[19]

While various B-cell target antigens have been tested (CD19, CD20, CD22, CD37, and CD79b)[20–23] BsAbs against CD3 × CD20 have thus far undergone the most extensive clinical development. Structurally, these agents may possess one or more CD20-binding Fabs in different spatial configurations, conferring different target affinity and *in vitro* potency.[16,24–26] Several CD20 × CD3 BsAbs, including glofitamab, epcoritamab, mosunetuzumab, and odronextamab, have been evaluated in clinical trials (Figure 1) and will be described below.

3. Toxicity overview

The most important adverse events (AEs) associated with BsAb therapy in clinical trials were due to T-cell overactivation. Among these, cytokine release syndrome (CRS) was the most frequent, observed in 15%–80% of patients, depending on the specific agent, route of administration, and dosing regimen used.[27–29] CRS onset occurred primarily during the initial treatment cycle, reflecting target-dependent T-cell activation. Clinically, this syndrome manifested with a range of symptoms, including chills, fever, hypotension, hypoxia, and confusion, usually emerging within the first 2 d post-administration and resolving within 3 d.

Although the term 'immune effector cell – associated neurotoxicity syndrome (ICANS) – like' was coined to characterize the neurological toxicity, prompted by its similarity to the syndrome observed following CAR-T administration (ICANS),[30] its underlying pathogenesis remains less clear. Unlike CAR-T cells,[31] IgG-like BsAbs are not expected to breach the blood–brain barrier and information on the presence of activated T cells or inflammatory cytokines in the cerebrospinal fluid (CSF) of affected patients is scarce. Neurological symptoms included delirium, dysphasia, tremor, lethargy, difficulty concentrating, agitation, aphasia, depressed level of consciousness, encephalopathy, seizures, and cerebral edema.

Various strategies were explored to mitigate T-cell-driven AEs, including step-up dosing during cycle 1,[32,33] slower intravenous infusion,[28,34] and prophylactic corticosteroid administration.[35] Additionally, pretreatment with obinutuzumab was implemented in glofitamab trials based on preclinical evidence suggesting that depleting circulating B cells may attenuate T-cell activation.[24]

Cytopenias were frequently seen following treatment with BsAbs, especially neutropenia (15%–33%) and anemia (19%–38%), primarily of grades 1–2.[36] Their pathogenesis, although poorly understood, is likely multifactorial in nature (e.g. related to disease involvement, prior therapies, and direct BsAb effect). Infectious complications were often linked to neutropenia and B-cell impairment and encompassed febrile

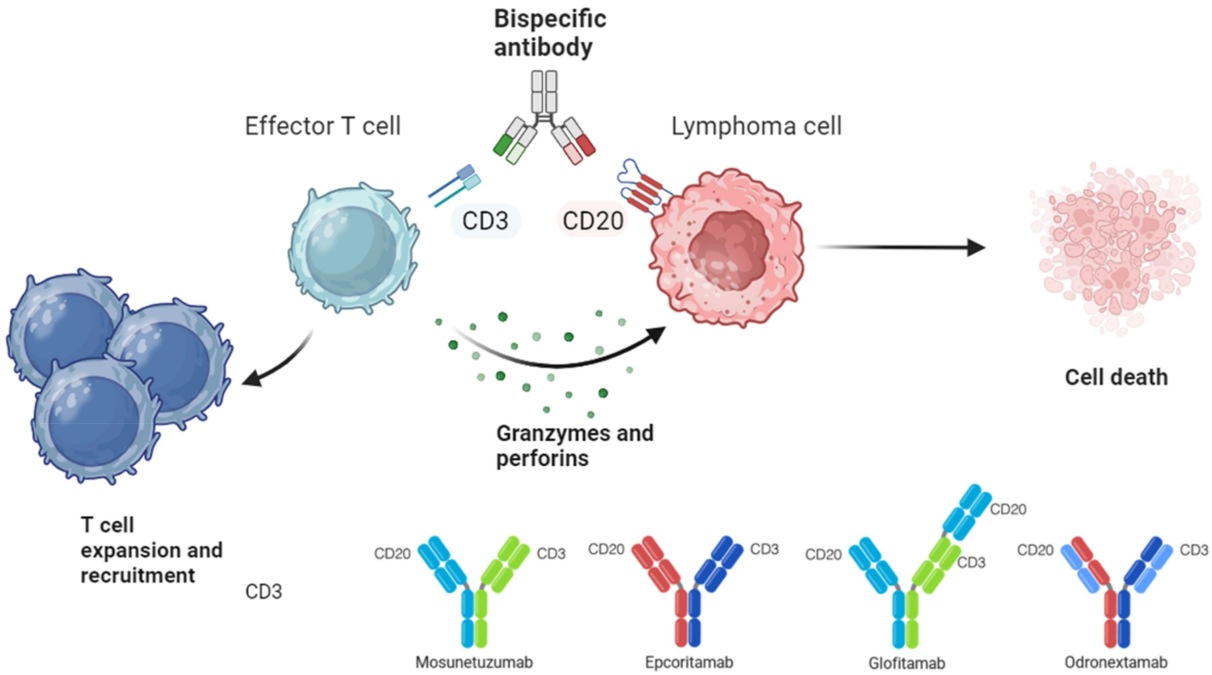

Figure 1. Mechanism of action of antiCD20 and antiCD3 bispecific antibodies. Mosunetuzumab, IgG1 ab with a rituximab-like antiCD20 domain; epcoritamab, IgG1 ab with an ofatumumab-like antiCD20 domain; glofitamab, IgG1 ab with a ratio 2:1 CD20:CD3 and an obinutuzumab-like antiCD20 domain; odronextamab, IgG4 ab with an ofatumumab-like antiCD20 domain.Illustration created with biorender-individual version.

neutropenia (affecting <5% of patients), urinary tract infections, and pneumonia.[27,34,37]

Overall, the safety profile of BsAbs proved to be consistent across trials, with the majority of AEs being manageable and leading to rare treatment interruptions or discontinuations. Consensus recommendations were recently published to aid clinicians in recognizing and managing BsAbrelated toxicities.[38]

4. Single-agent trials

The first T-cell redirecting antibody to show activity in B-cell non-Hodgkin lymphoma (NHL) was blinatumomab, a CD19 × CD3 fusion protein comprised of two single-chain Fragment variable (scFv) moieties. Despite encouraging clinical results,[39] the requirement for multi-week continuous IV administration and the dose-limiting neurologic toxicity hindered further clinical development in lymphoma. In contrast, the more convenient dosing schedule and favorable safety profile seen with CD20 × CD3 IgG-like BsAbs have facilitated their development in this setting.

Mosunetuzumab, the first-in-class anti-CD3 × CD20 BsAb, was evaluated in B-NHL patients in a large phase 1/2 study (NCT02500407)[29] with both fixed and step-up dosing schedules (the latter implemented to mitigate T-cell activation-related toxicities, see below). All patients received the drug IV every 3 weeks for up to eight cycles (for patients achieving a complete response (CR)) or 17 cycles (for those achieving partial response after eight cycles). The recommended phase 2 dose (RP2D) was 30 mg, after two initial 60 mg loading doses. Among 197 patients enrolled in the step-up dosing cohort, 129 with aggressive B-NHL (aNHL) achieved an overall response rate (ORR) and CR rate of 35% and 19%, respectively. Common AEs included CRS (27.4%), neutropenia (28.4%) and hypophosphatemia (23.4%). The most common neurologic AEs reported were headache (17.8%), insomnia (11.2%) and dizziness (10.2%).

An update of the dose expansion DLBCL cohort was recently published[40] (Table 1). Eighty-eight patients received IV mosunetuzumab at the dose of 30 mg, achieving an ORR and CR rate of 40% and 23.9%, respectively. CR rates were consistent among patients with non-germinal center B (non-GCB) DLBCL (28%), transformed FL (tFL, 26%), disease refractory to previous anti-CD20 therapies (21%) and age ≥65 y (29%). Of note, patients with double-hit (DH)/triple-hit (TH) lymphoma ($N = 17$) and those with previous CAR-T therapy failure ($N = 26$) demonstrated lower CR rates of 6% and 12%, respectively. The median progression-free survival (mPFS) was 3.2 months. No new safety signals were recorded and the most common AEs were neutropenia (27.3%) and CRS (26.1%). The latter was mostly of grade 1–2, with only two patients experiencing a grade 3 event. Neurologic AEs occurred in two patients, and both were mild. While the development of mosunetuzumab as a stand-alone therapy for DLBCL has been limited, ongoing clinical trials are evaluating it in the R/R setting as consolidation therapy following ASCS (NCT05412290), CAR-T (NCT04889716), or in the first-line setting following immunochemotherapy (NCT03677154) (Table 3).

Epcoritamab, a subcutaneously administered CD20 × CD3 BsAb produced via controlled Fab arm exchange,[25] was initially studied in a phase 1/2 trial in patients with R/R B-NHL (NCT03625037). The drug was administered with a step-up dosing schedule in cycle 1, then weekly for two cycles, every other week for six cycles and every 28-d cycle thereafter, until progression or unacceptable toxicity.[35] The RP2D was identified as 48 mg and at this dose level the ORR and CR rate of the eight DLBCL patients treated in the dose escalation cohort were 88% and 38%, respectively. Of note, five patients initially achieving a partial response (PR) subsequently converted to a CR. Epcoritamab demonstrated a favorable safety profile, with no treatment-related discontinuations or deaths.

Results from the dose expansion cohort of the trial was recently published.[27] Among 157 patients with R/R DLBCL,

Table 1. BsAb single-agent studies in r/r aNHL patients with published results.

Clinical Trial	Phase	Drug(s)	Histology	Modifiers	N	ORR	CR	mPFS (months)	mDOR (months)	Grade 3–4 CRS	Grade 3–4 ICANS	Grade 3–4 NP	mFU (months)
NCT02500407	I/II	MOSUNETUZUMAB	DLBCL	Dose expansion cohort	88	40%	24%	3.2	7	2.3%	None	21.6%	10.1
NCT03625037	I/II	EPCORITAMAB	DLBCL	Dose expansion cohort	157	63%	39%	4.4	12	2.5%	0.6%	14.6%	10.7
NCT03075696	II	GLOFITAMAB	DLBCL	Dose expansion cohort	155	52%	39%	4.4	18.4	4%	3%	27%	12.6
NCT04657302	I	GLOFITAMAB	DLBCL	Dose expansion cohort	27	67%	52%	8.6	14.4	3.3%	3.3%	30%	15
NCT03888105	II	ODRONEXTAMAB	DLBCL	Dose expansion cohort	127	52%	31%	N/A	10.2	0.7%	None	N/A	26.2
NCT02924402	I	PLAMOTAMAB	DLBCL	Dose escalation cohort	19	47%	26%	N/A	N/A	None	None	16.7%	N/A
NCT04082936	I	IgM-2323	B-NHL	Dose escalation cohort	23	35%	22%	N/A	N/A	3.4%	N/A	N/A	N/A
NCT04594642	I	AZD0486	DLBCL	Dose escalation cohort	5	40%	20%	N/A	N/A	None	7%	15%	3.8
NCT04923048	I/II	GB261	B-NHL	Dose escalation cohort	22	73%	45%	N/A	NR	None	None	14.9%	4.1

Reported abstract data refer to the time of their publication. DLBCL includes DLBCL, not otherwise specified, high-grade B-cell lymphoma, and transformed indolent NHL. Abbreviations: CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; NP, neutropenia; ORR, overall response rate; CR, complete response; mFU, median follow-up; mPFS, median progression-free survival; mDOR, median duration of response; NR, not reached; N/A, not assessed.

ORR and CR rates were 63.1% and 38.9%, respectively, including nine patients who converted their PR into CR after week 36. Epcoritamab exhibited consistent efficacy across high-risk subgroups: CR rates were 30.2% in patients with primary refractory lymphoma ($N = 96$) and 34.4% in those previously exposed to CAR-T therapy ($N = 61$). Median PFS for the entire cohort was 4.4 months, though this was not reached in complete responders. The safety profile aligned with prior reports, with CRS (49.7%) and neutropenia (21.7%) being the most common AEs. Ten patients experienced neurologic toxicity, including one fatal event. Based on these results, in May 2023, the FDA granted accelerated approval to epcoritamab for treatment of adult patients with R/R DLBCL, not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy.[41]

A phase 3 trial of epcoritamab vs. physician's choice in patients with R/R DLBCL ineligible for curative therapy is currently underway (NCT04628494). Finally, a study (NCT05451810) is currently evaluating the feasibility of outpatient subcutaneous administration.

Glofitamab is a peculiar CD20 × CD3 BsAb with two CD20-binding moieties and one CD3-binding site (also called '2:1 format') created by domain crossover and head-to-tail fusion.[28] It was initially studied in a phase 1 trial (NCT03075696) including 171 R/R B-NHL patients, 73 of whom had DLBCL.[28] The CRS mitigating strategy included the step-up dosing and a pretreatment of 1000 mg dose of obinutuzumab. In the study, glofitamab was administered IV every 2 or 3 weeks. For all DLBCL patients, ORR was 41% and CR was 29%. Across the whole cohort, 50% of patients developed CRS, grade 1–2 in 47% and grade 3–4 in only 3%. ICANS-like symptoms were reported in nine patients, with no grade 3–4 events. Grade ≥3 neutropenia occurred in 25% of patients.

The recently published phase 2 expansion cohort (NCT03075696) enrolled 155 patients with R/R DLBCL treated at the target dose of 30 mg for up to 12 3-week cycles.[37] The ORR and CR rates were 52% and 39%, respectively. Complete responses were similar among patients with a history of previous CAR T-cell therapy (35%) and those without (42%).[37] Based on these results, in June 2023, the FDA granted accelerated approval to glofitamab for the treatment of adult patients with R/R DLBCL, not otherwise specified, or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of systemic therapy.[42]

An updated analysis, after a median time on study of 25.8 months, revealed a median duration of CR (DoCR) of 26.9 months among all patients and 22.0 months in those previously treated with CAR-T cell therapy.[43] For patients achieving a CR at the end of treatment (EOT), the 12-month PFS and OS rates were 80% and 90%, respectively. These findings suggest the potential for favorable long-term outcomes with the fixed-duration use of glofitamab in R/R LBCL.[43]

Study NCT04657302 is exploring glofitamab as a single agent in Chinese patients and showed an ORR of 67% and a CR rate of 52% among 27 patients; 8 out of 14 patients in CR had ongoing responses after a median follow-up of 15 months.[44] Finally, a French-led phase 2 study is exploring glofitamab in patients who have relapsed after CAR-T therapy (NCT04703686, currently recruiting), a challenging clinical scenario.

Odronextamab is a fully humanized heterodimeric IgG4-based BsAb that was initially studied (NCT02290951) in a phase 1/2 trial in 145 patients with R/R B-NHL at doses ranging from 0.1 to 320 mg weekly for 9 weeks, then every other week until progression. In DLBCL patients without prior CAR-T therapy ($N = 15$), at 80 mg or higher, odronextamab achieved a 53% CR rate[34] while, in the post-CAR-T setting ($N = 44$) at the RP2D of 160 mg, the CR rate was 30%.[45] Common AEs included CRS (61%), anemia (38%), fatigue (33%), and neutropenia (25%). ICANS-like symptoms were reported in 12% of patients, with 3% exhibiting symptoms of grade ≥3.[34]

To further mitigate the CRS risk, a split step-up dosing approach was explored (NCT03888105). Among 127 evaluable patients, the ORR was 52%, with a CR rate of 31% with no significant differences in activity among selected high-risk subgroups. The toxicity profile was similar to that observed with other CD3 × CD20 BsAbs, including rates of CRS (55%), anemia (43%), and pyrexia (42%). Only one grade 3 CRS and no ICANS-like events were recorded with this optimized step-up regimen. Fourteen patients (10%) discontinued odronextamab due to treatment-related AE.[46]

Study NCT05991388 is exploring odronextamab in pediatric and young adult patients, while an open compassionate use program is available for enrollment (NCT05619367, Table 3).

Plamotamab (a fully humanized CD3 × CD20 BsAb) and imvotamab (IgM-like CD20 × CD3 BsAb) have been evaluated in the phase 1 NCT02924402 and NCT04082936 clinical trials, respectively, where they exhibited early clinical activity without safety signals.[47,48] Their clinical development, however, is less clear at present.

5. Combination trials

Pre-clinical work suggested that the BsAb-mediated T-cell cytotoxicity may be retained with the co-administration of traditional T-cell cytotoxic agents like cyclophosphamide or dexamethasone.[49,50] Furthermore, glofitamab and epcoritamab remained active in combination with anti-CD20 monoclonal antibodies due to partially non-overlapping epitopes, lack of competition for the FcγR, and high activity even at low receptor occupancy rates.[36] These observations sparked interest for BsAb-containing combination studies.

In transplant eligible patients with R/R DLBCL (Table 2), epcoritamab was combined with R-DHAX/C (dexamethasone, high-dose cytarabine, and oxaliplatin/carboplatin) as salvage prior to high-dose therapy (HDT)-ASCS in a phase 1/2 study (NCT04663347, arm 4).[51] Patients who deferred ASCS were allowed to continue the BsAb until progression or unacceptable toxicity. Of 26 response-evaluable patients, 15 proceeded to consolidation, achieving an ORR of 100% and a CR rate of 80%. The remaining 11 who continued epcoritamab without HDT-ASCS had an ORR of 64% and a CR rate of 45%. CRS rate and severity were similar to those seen with single-agent epcoritamab; 21% of patients experienced grade 3 or 4 infections and one patient experienced grade 2 neurological toxicity.

Table 3 outlines ongoing combination trials for epcoritamab (NCT05852717), mosunetuzumab (NCT05464329), and

Table 2. BsAb combination studies in r/r aNHL patients with published results.

Clinical Trial	Phase	Drug(s)	Modifiers	Histology	N	ORR	CR	mPFS (months)	mDOR (months)	G. 3–4 CRS	G. 3–4 ICANS	G. 3–4 NP	mFU (months)
Planned ASCS Consolidation													
NCT04663347	I/II	EPCORITAMAB + R-DHAX/C	Planned ASCS after cycle 3	DLBCL	15	100%	80%	N/A	NR	None	None	N/A	9.2
No ASCS consolidation													
NCT04663347	I/II	EPCORITAMAB + R-DHAX/C	3 cycles of combined therapy. Epcoritamab monotherapy continued until PD or toxicity	DLBCL	11	64%	45%	N/A	NR	None	None	N/A	9.2
NCT04663347	I/II	EPCORITAMAB + GemOx	4 cycles of combined therapy. Epcoritamab monotherapy continued until PD or toxicity	DLBCL	34	91%	59%	N/A	N/A	3%	None	N/A	20.3
NCT05283720	I/II	EPCORITAMAB + LENALIDOMIDE	12 cycles of combined therapy	DLBCL	24	75%	58%	N/A	N/A	8%	3.8%	58%	N/A
NCT03671018	II	MOSUNETUZUMAB + POLATUZUMAB	6 cycles of combined therapy. If CR after C8, mosunetuzumab discontinued. If SD or PR after C8, mosunetuzumab continued up to C17	DLBCL	98	59%	46%	11.4	20.8	3.1%	2%	20.4%	23.9
NCT03533283	I/II	GLOFITAMAB + POLATUZUMAB	6 cycles of combined therapy. Glofitamab continued up to C12	DLBCL	125	80%	59%	10.4	N/A	0.8%	None	N/A	21.6
NCT05335018	II	GLOFITAMAB + LENALIDOMIDE + POSELTINIB	12 cycles of combined therapy	DLBCL	6	100%	50%	N/A	N/A	None	None	33%	N/A

Reported abstract data refer to the time of their publication. DLBCL includes DLBCL, not otherwise specified, high-grade B-cell lymphoma, and transformed indolent NHL. Abbreviations: G., grade; CRS, cytokine release syndrome; ICANS, immune effector cell- associated neurotoxicity syndrome; NP, neutropenia; ASCS, autologous stem cell support; R-DHAX/C, rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin; GemOx, gemcitabine, oxaliplatin; SUD, step-up dosing; Q3W, every 3 weeks; ORR, overall response rate; CR, complete response; SD, stable disease; PR, partial response; PD, progressive disease; mFU, median follow-up; mPFS, median progression-free survival; mDOR, median duration of response; NR, not reached; N/A, not assessed.

Table 3. BsAb studies in R/R aNHL patients without published results.

Clinical Trial	Phase	Drug(s)	Histology	Comments	Primary Endpoints	Key Secondary endpoints	Estimated Enrollment
Planned ASCS Consolidation							
NCT05464329	I	MOSUNETUZUMAB + DHAX/ICE	B-NHL	Planned ASCS after cycle 3	Frequencies and grades of TEAEs	CR rates; PFS and OS	40
NCT05852717	II	EPCORITAMAB + GDP	DLBCL	Planned ASCS after cycle 3	CR rates	ORR; PFS, DOR and OS; feasibility of ASCS or CAR-T cell consolidation	32
NCT05364424	I	GLOFITAMAB + R-ICE	DLBCL	Planned ASCS after cycle 3	ORR	CR rates; PFS, DOR and OS; TEAEs	40
Planned CAR-T Consolidation							
NCT05260957	II	MOSUNETUZUMAB + POLATUZUMAB	B-NHL	Mosunetuzumab + Anti-CD79b ADC; Planned CAR-T therapy after cycle 8	CR rates	ORR; PFS, DOR and OS; CRS and ICANS rates following CAR-T	40
NCT05852717	II	EPCORITAMAB + GDP	DLBCL	Planned CAR-T therapy after cycle 3	CR rates	ORR; PFS, DOR and OS; feasibility of ASCS or CAR-T cell consolidation	32
No Consolidation Planned: Single Agent							
NCT05412290	I	MOSUNETUZUMAB	B-NHL	Administered following ASCS	Frequencies and grades of TEAEs	PFS and OS following ASCS	15
NCT04889716	II	MOSUNETUZUMAB	B-NHL	Administered following CAR-T	CR rates; DLT	PFS, DOR and OS	42
NCT03677154	I/II	MOSUNETUZUMAB	DLBCL	Administered either SC or IV following 1st line therapy	CR rates; ORR; frequencies and grades of TEAEs	PFS, DOR and OS; quality of life	188
NCT05451810	II	EPCORITAMAB	B-NHL	Administered as Outpatient	Frequencies and grades of TEAEs	CR rates; best ORR; PFS, DOR and OS	184
NCT04628494	III	EPCORITAMAB vs chemotherapy	DLBCL	Investigator's choice as control arm, either BR or R-GemOx	OS	CR rates; ORR; PFS, DOR and TTNT; rate and duration of MRD negative status; TEAEs; quality of life	552
NCT04703686	II	GLOFITAMAB	B-NHL	For patients with relapse after CAR-T	OS	CR rates; ORR; PFS, DOR; quality of life	78
NCT05619367		ODRONEXTAMAB	B-NHL	Compassionate use program	N/A	N/A	N/A
NCT05991388	II	ODRONEXTAMAB	B-NHL	For pediatric and young adult patients	CR rates; ORR	PFS, DOR and OS; frequencies and grades of TEAEs	210
No Consolidation Planned: Combinations with Chemotherapeutic Agents							
NCT04313608	I	MOSUNETUZUMAB/GLOFITAMAB + GemOx	DLBCL	8 cycles of combined therapy. Glofitamab monotherapy continued until C12	Frequencies and grades of TEAEs	CR rates; ORR; pharmacokinetics	23
NCT05533775	I/II	GLOFITAMAB + R-ICE	B-NHL	Pediatric and young adult patients	CR rates; frequencies and grades of TEAEs	ORR; PFS, DOR and OS	65
NCT04408638	III	GLOFITAMAB + GemOx vs R-GemOx	DLBCL	8 cycles of combined therapy. Glofitamab monotherapy continued until C12	OS	ORR; PF and DOR; frequencies and grades of TEAEs; quality of life	270
No Consolidation Planned: Combinations with Non-Chemotherapeutic Agents							
NCT04970901	I	MOSUNETUZUMAB/GLOFITAMAB + LONCASTUXIMAB	B-NHL	Mosunetuzumab/Glofitamab + anti-CD19 ADC	Frequencies and grades of TEAEs	CR rates; ORR; PFS, DOR; pharmacokinetics	200
NCT05672251	II	MOSUNETUZUMAB + LONCASTUXIMAB	DLBCL	Mosunetuzumab + anti-CD19 ADC	ORR; Frequencies and grades of TEAEs	CR rates; ORR; PFS, DOR; TEAEs	36
NCT05171647	III	MOSUNETUZUMAB + POLATUZUMAB vs R-GemOx	B-NHL	Mosunetuzumab + anti-CD79b ADC	PFS	CR rates; ORR; DOR and OS; TEAEs; quality of life	222
NCT05315713	I/II	MOSUNETUZUMAB + TIRAGOLUMAB ± ATEZOLIZUMAB	B-NHL	Mosunetuzumab + anti-TIGIT Ab ± anti-PDL1 Ab	Frequencies and grades of TEAEs; ORR	CR rate; PFS, DOR and OS	118
NCT05615636	II	MOSUNETUZUMAB + POLATUZUMAB + TAFASITAMAB + LENALIDOMIDE	DLBCL	Mosunetuzumab + anti-CD79b ADC + anti-CD19 Ab + immune modulator	Best ORR	N/A	36
NCT05169515	I	MOSUNETUZUMAB + CC-220 MOSUNETUZUMAB + CC-99282 GLOFITAMAB + CC-99282	B-NHL	Mosunetuzumab/Glofitamab + cereblon E3 ligase modulator (CELMoD)	Best ORR; DLT; frequencies and grades of TEAEs	Best CR rate; PFS, DOR and OS up to 2 y; serum concentration of CC-220 and CC-99282	121

(*Continued*)

Table 3. (Continued).

Clinical Trial	Phase	Drug(s)	Histology	Comments	Primary Endpoints	Key Secondary endpoints	Estimated Enrollment
NCT05283720[a]	I/II	EPCORITAMAB + immuno-modulating agents	B-NHL	Multi-arm study.	DLT	Best ORR; CR rates; PFS, DOR, OS and TTNT up to 5 y; rate and duration of MRD negative status	394
NCT04077723	I/II	GLOFITITAMAB + RO7227166	B-NHL	Glofitamab + CD19×CD137 BsAb	DLT; TEAEs; CR rates; ORR; PFS, DOR and OS	Pharmacokinetics; quality of life	46
NCT05219513	I	GLOFITAMAB + RO7443904	B-NHL	Glofitamab + CD19×CD28 BsAb	Frequencies and grades of TEAEs	Pharmacokinetics	200
NCT05896163	I/II	GLOFITAMAB + MAPLIRPACEPT	DLBCL	Glofitamab + anti-CD47 Ab	DLT; ORR	CR rates; PFS and DOR; TEAEs	70
NCT02651662	I	ODRONEXTAMAB + CEMIPLIMAB	B-NHL	Odronextamab + anti-PD1 Ab	Frequencies and grades of TEAEs	CR rates; ORR; DOR	62
NCT05685173	I	ODRONEXTAMAB + REGN5837	B-NHL	Odronextamab + CD22×CD28 BsAb	Frequencies and grades of TEAEs	CR rates; ORR; PFS, DOR and OS	91
NCT05328102	II	PLAMOTAMAB + TAFASITAMAB + LENALIDOMIDE vs TAFASITAMAB + LENALIDOMIDE	DLBCL	Study terminated early by the sponsor	frequencies and grades of TEAEs; PFS	N/A	3
Novel Constructs							
NCT05210868	I/II	CM355	B-NHL	CD3×CD20 BsAb	frequencies and grades of TEAEs; ORR	CR rates; ORR; PFS, DOR and OS; pharmacokinetics endpoints	184
NCT05618327	I	JS203	B-NHL	CD3×CD20 BsAb	DLT	CR rates; ORR; PFS, DOR and OS; TEAEs; pharmacokinetics	219
NCT04056975	I	A-319	B-NHL	CD3×CD19 BsAb	Frequencies and grades of TEAEs	Pharmacokinetics endpoints	54
NCT04540796	I	JNJ-75348780	B-NHL	CD3×CD22 BsAb	Frequencies and grades of TEAEs	CR rates; ORR; DOR; pharmacokinetics	148
NCT05424822	I	JNJ-80948543	B-NHL	CD3×CD20×CD79b TsAb	Frequencies and grades of TEAEs	CR rates; ORR; DOR	180
NCT05348889	I	CMG1A46	B-NHL	CD3×CD19×CD20 TsAb	Frequencies and grades of TEAEs	CR rates; ORR; PFS and OS; pharmacokinetics	165
NCT05397496	I	PIT565	B-NHL	CD3×CD2×CD19 TsAb	Frequencies and grades of TEAEs	CR rates; ORR; PFS, DOR; pharmacokinetics	140
NCT05623982	I/II	EMFIZATAMAB	B-NHL	CD3×CD137×PD-L1×CD19 TesAb	Frequencies and grades of TEAEs	CR rates; ORR; PFS, DOR and OS; pharmacokinetics	40
NCT06088654	I/II	IPH6501	B-NHL	NKp46×CD16a×CD122×CD20 TesAb	Frequencies and grades of TEAEs	ORR; DOR and PFS; pharmacokinetics	184

Reported abstract data refer to the time of their publication. DLBCL includes DLBCL, not otherwise specified, high-grade B-cell lymphoma, and transformed indolent NHL.

[a]Epcoritamab investigated in combination with multiple agents across different histologies (DLBCL, FL, MZL). For r/r DLBCL patients, combination therapies encompass lenalidomide, ibrutinib, and CC-99282.

Abbreviations: TEAEs, treatment-emergent adverse events; ADAs, anti-drug antibodies; DLT, dose-limiting toxicity; SC, subcutaneous; IV, intravenous; PFS, progression-free survival; DOR, duration of response; TTNT, time to next treatment; OS, overall survival; ASCS, autologous stem cell support; CAR-T, chimeric antigen receptor T-cell; Cmax, maximum serum concentration; AUC, area under the curve; EORTC, European Organisation for Research and Treatment of Cancer; FACT-Lym, functional assessment of cancer therapy-lymphoma; DHAX, dexamethasone, cytarabine, oxaliplatin; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; GDP, gemcitabine, dexamethasone, cisplatin; R-GemOx, rituximab, gemcitabine, oxaliplatin; BR, bendamustine, rituximab; Ab, antibody; ADC, antibody–drug conjugate; MRD, minimal residual disease; ORR, overall response rate; CR, complete remission; SD, stable disease; PR, partial response; N/A, not assessed; TsAb, trispecific antibody; TesAb, tetraspecific antibody.

glofitamab (NCT05364424) including preplanned HDT-ASCS, with clinical data yet to be reported. CAR-T consolidation is also being explored in the NCT05260957 and NCT05852717 trial following mosunetuzumab and epcoritamab administration, respectively.

Early results of a study exploring epcoritamab in combination with GemOx (gemcitabine and oxaliplatin) in transplant-ineligible patients have been recently reported. In the NCT04663347 trial arm 5, patients received four cycles of GemOx along with concurrent epcoritamab, and subsequently continued epcoritamab until disease progression or unacceptable toxicity. Among 34 evaluable patients, 53% of whom had a primary refractory disease, the ORR was 91%, and the CR rate was 59%. The CR rates were of 57% and 59% among CAR-T exposed and CAR-T naïve patients, respectively. The most common AEs were thrombocytopenia (68%), diarrhea (59%), neutropenia (56%), and CRS (56%). Most CRS events were of low grade (53%) and only one ICANS event of grade 1 was reported.[52]

A phase 1/2 trial (NCT03671018) testing the safety and efficacy of combining mosunetuzumab with polatuzumab in patients with R/R DLBCL was recently reported.[53] Ninety-eight patients received mosunetuzumab according to the single-agent protocol,[40] plus polatuzumab administered on d 1 of cycles 1–6. Fifty-eight patients (59%) had a response, and 45 patients had (46%) a CR. At a median follow-up of 23.9 months, the mPFS was 11.4 months, and the median DoCR was not reached. Among patients who had previously undergone CAR-T therapy ($N = 35$), a CR was achieved in 40%, with a median PFS of 9.6 months. The incidence of CRS was generally low, with 18% of patients experiencing any grade CRS, and 3% experiencing grade ≥3. Additionally, 5% of patients developed neurotoxicity, with 2% experiencing symptoms of grade ≥3.

A separate phase 1b/2 study (NCT03533283) explored glofitamab in association with polatuzumab.[54] Among 125 R/R DLBCL patients treated at the glofitamab target dose of 30 mg, ORR was 80% and CR was 59%. After a median follow-up of 20.4 months, the mPFS and median DoCR were 10.4 and 28.6 months, respectively. CRS was mostly of grade 1–2 (45%), with one CRS-related death. ICANS-like symptoms occurred in four cases (3%), all of grade 1–2.[55]

Other trials are evaluating mosunetuzumab (NCT04313608) and glofitamab (NCT04313608, NCT05533775, and NCT04408638) in conjunction with either GemOx or R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) for transplant-ineligible patients (Table 3).

6. Novel combinations

During the immune synapse formation, T-cell activation and proliferation are amplified by additional interactions with co-stimulatory receptors, such as CD28 and 4-1BB.[56] This notion was leveraged to enhance T-cell-mediated killing and combat T-cell exhaustion during BsAb therapy.[57–59] BsAbs simultaneously targeting B-cell antigens and T-cell co-stimulatory receptors have been developed and are currently in clinical trials, as outlined in Table 3.

RO7227166 is a novel BsAb that simultaneously targets CD19 on B-cells and 4-1BB on T-cells and is currently under investigation in the NCT04077723 phase 1 trial in combination with glofitamab. Preliminary findings comprising 56 efficacy-evaluable subjects indicated an ORR of 67% and a CR rate of 39% in R/R DLBCL, with no new safety signals reported.[60]

A similar antibody, RO7443904, which binds CD19 and CD28, is being studied in combination with glofitamab in another dose escalation trial (NCT05219513). In pre-clinical models, RO7443904 improved glofitamab's anti-tumor effects by increasing intratumoral T-cells without displaying super-agonistic activity or increasing cytokine release.[61]

REGN5837 is a human CD28 × CD22 IgG4-based bispecific antibody that provides a co-stimulatory signal. When combined with odronextamab, REGN5837 improved anti-tumor efficacy and survival in in vivo DLBCL tumor models via enhanced T-cell expansion.[21] This combination is currently being studied in the phase 1 NCT05685173 trial.

Both glofitamab and epcoritamab have been combined with the immunomodulatory agent lenalidomide. A small experience of glofitamab plus lenalidomide and poseltinib, a novel irreversible BTK inhibitor, was recently reported (NCT05335018).[62] In the clinical trial EPCORE NHL-5 (NCT05283720), epcoritamab was administered concurrently with other antineoplastic regimens. When combined with lenalidomide[63] in patients with R/R DLBCL ($N = 24$), the ORR was 75%, with a CR rate of 58%. In this rituximab-free regimen, grade 3+ CRS and ICANS were observed in 8% and 4% of patients, respectively (Table 2), suggesting that the safety of epcoritamab and lenalidomide alone needs further exploration.

Ongoing studies are investigating BsAbs combined with different immune-modulatory agents, including the novel cereblon modulators CC-220 and CC-99282 (NCT05169515); the checkpoint inhibitors tiragolumab (NCT05315713), maplirpacept (NCT05896163), and cemiplimab (NCT02651662); tafasitamab (NCT05615636, NCT05328102); and the monoclonal antibody conjugates loncastuximab (NCT04970901, NCT05672251) and polatuzumab (NCT05171647), as outlined in Table 3.

7. Novel multi-specific antibodies

Given the vast combinatorial possibilities, the landscape of multispecific antibodies is rapidly expanding. Exploring alternative antigen targets beyond CD20, co-targeting two separate tumor-associated antigens, or two separate T-cell receptors, are all avenues under investigation to improve the activity of, and/or overcome resistance to, currently available BsAb.

AZD0486 is a novel anti-CD19 × CD3 BsAb designed to reduce CRS by binding to T-cells with low affinity. In a phase 1 dose escalation study (NCT04594642), among five evaluable R/R DLBCL patients, one achieved PR and one achieved CR.[64] A recent update of the safety data following the introduction of a two-step-up dosing approach revealed a decrease in the incidence of grade 1–2 CRS from 62.5% to 22.2%, and grade 1–2 neurological AEs from 20% to 5.6%. No grade 3 events occurred in either category.[65] GB261 is a CD20 × CD3 BsAb computationally designed to maintain Fc effector function. It also integrates de-tuned CD3 binding to reduce CRS incidence and improve safety features. Early activity was reported in 47

patients treated in the dose-escalation study (NCT04923048), 36 of whom had R/R DLBCL (Table 1).[66] Novel CD3/CD20, CD3/CD19, and CD3/CD22 BsAb constructs are being evaluated in phase 1 studies (NCT05210868, NCT05618327, NCT04056975, and NCT04540796), as outlined in Table 3.

A number of other multispecific antibodies are currently under investigation in phase 1 trials. JNJ-80948543 (CD3 × CD20 × CD79b) and CMG1A46 (CD3 × CD20 × CD19) are trispecific Abs targeting two tumor-associated antigens, currently evaluated in the NCT05424822 and NCT05348889 trial, respectively.[67,68] PIT565 is a CD3 × CD2 × CD19 trispecific Ab investigated in the NCT05397496 trial and designed to provide T-cell activation with both the initial signal (via CD3) and the co-stimulatory signal (via CD2).[69] Emfizatamab is a CD3 × 4-1BB x CD19 × PDL-1 tetraspecific Ab combining a co-stimulatory domain and an immune checkpoint inhibitor target in a single agent, and is currently being explored in the NCT05623982 trial.

Finally, IPH6501 is a tetraspecific molecule designed to engage NK cells through two activating receptors (NKp46 and CD16a/FcγRIIIa) and the stimulatory β chain (CD122) of the interleukin-2 receptor, and simultaneously bind the CD20 antigen expressed on malignant B-cells.[70] This drug is being studied in an ongoing dose-escalation trial in patients with various B-cell lymphoma subtypes (NCT06088654).

8. Conclusions

Since their introduction, CD3 × CD20 BsAbs have represented a breakthrough in the treatment of R/R aNHL, their development has been rapid, and their role in the therapeutic landscape is constantly being re-defined based on emerging data. Response rates are encouraging and the safety profile appears manageable. Clearly, longer follow-up is needed to ascertain durability of responses and curative potential, if any, of these drugs. Moreover, the regulatory approval of glofitamab and epcoritamab will lead to widespread adoption, and real-world efficacy and safety data are likely to inform clinical practice while potentially uncovering previously unidentified challenges.

The promising activity coupled with the unique toxicity profile of BsAbs highlights their combinability. Notably, the lymphoma-killing activity of CD20 × CD3 BsAbs appears unaffected when T-cell cytotoxic agents are co-administered, while concurrent use of immunomodulatory agents that restore the immune synapse may produce synergism with BsAbs. These combinatorial strategies hold promise for improving BsAb efficacy with an acceptable safety profile.

Finally, newer multi-specific Abs, designed to overcome resistance to CD20 × CD3 BsAbs, could improve our understanding of response and resistance, and further refine our approach to this promising therapeutic modality.

Disclosure statement

L.F. has served on advisory boards for ADC Therapeutics, Seagen, AstraZeneca, Ipsen, AbbVie, and Genentech, has consulted for and received Honoraria from Genmab, AbbVie, and Genetech, has consulted for and received research fundings from Genmab, Roche, AbbVie, Genetech, and Innate Pharma, has consulted for EvolveImmune, and has received travel reimbursement from Genmab and AbbVie.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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