REVIEW ARTICLE

New bispecific antibodies in diffuse large B-cell lymphoma

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Abstract

CD20xCD3 T-cell-engaging bispecific antibodies are a highly active new treatment option for patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). Epcoritamab and glofitamab have both been approved in over 30 countries as monotherapy for DLBCL after two prior treatment lines; odronextamab has recent European approval, and mosunetuzumab is active and is being developed as a combination partner. These agents can be safely combined with other immunotherapies and chemotherapy, and single-arm and randomized trial outcomes promise an expanding role for this class of drugs in earlier treatment lines. This review examines the clinical development of the CD20xCD3 bispecific antibodies in DLBCL, how the phase I and II trials inform their current use, and the key distinctions between the agents. We focus on the efficacy and safety of those bispecific antibodies most advanced in development. We also consider emerging understandings of resistance mechanisms. Finally, we review key ongoing trials and combinations and consider the potential future of bispecific antibodies within the sequence of available treatments for DLBCL.

Introduction

The marketing approvals of the CD20xCD3 bispecific antibodies glofitamab, epcoritamab globally, and of odronextamab in Europe for relapsed diffuse large B-cell lymphoma (DLBCL) signal a major shift in the management of this disease. DLBCL has a poor prognosis upon relapse, and cytotoxic chemotherapy is curative in a small fraction of patients. There is a large group of patients for whom CD19-directed, commercially approved chimeric antibody receptor (CAR) T-cell treatments are either unavailable or ineffective. Bispecific antibodies (BsAb) work by binding a B-cell surface antigen, most commonly CD20 on normal and malignant B-cells, and, generally, CD3 on the surface of T cells. The formation of a trimer between the antibody, the target cell and T cells leads to HLA-independent T-cell activation, T-cell expansion and T-cell-mediated target cell death. BsAb are appealing as they are potent in patients whose disease no longer responds to cytotoxic chemotherapy. We review the clinically relevant lessons from the development of the commercially available CD20xCD3 BsAb as treatments for DLBCL, the clinical data resulting in their approvals in relapsed and refractory disease, and the evolving trial landscape that may bring this therapy class into earlier lines of treatments.

Preclinical development

Commonalities and differences

The CD20xCD3 T-cell-engaging BsAb are a significant optimization of the smaller molecule T-cell-engaging drugs that preceded them, such as blinatumomab. Those discussed here have full-length IgG antibody-like formats with a half-life of 6-14 days (Table 1), allowing dosing intervals of a week or more.[1-3] Recombinant antibodies with intact Fc portions are subject to Fc-mediated splenic clearance, tumor-associated antigen-independent activation, and fratricide through destruction of effector T cells mediated by antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicty. Modifications to the Fc region mitigate these concerns and are a feature of all the BsAb discussed here.[1-3]

Epcoritamab, mosunetuzumab and odronextamab all have one CD20 binding site and one CD3 binding site. Glofitamab has two CD20-binding sites, and in preclinical models this structure was more potent than 1:1 formats that were structurally most similar to mosunetuzumab and odronextamab.[4,5] In preclinical models administration of obinutuzumab, which binds the same CD20 epitope as glofitamab, prior to the first dose of glofitamab, resulted in a lower cytokine peak without a reduction in cytotoxic killing.[4] Consequently, and with few exceptions, obinutuzumab is a part of cytokine release mitigation with glofitamab, while it is not used for the various other BsAb.

Pharmacodynamics, pharmacokinetics and route of delivery

Unlike the experience with non-T-cell-engaging antibodies, the relationship between antigen expression and cytotoxicity induced by BsAb is neither linear nor predictable. *In vitro*, similar epcoritamab concentrations induce similar cell death rates across multiple cell lines expressing varying surface density of CD20.[6] This suggests that a minimum level of tumor antigen expression is required but that higher expression is not necessarily correlated with a greater response.[5] Excessive concentrations of BsAb can also have a 'hook effect', with reduced efficacy at high levels of receptor occupancy. In studies of epcoritamab, trimer formation, which is essential for effective cross-linking and T-cell activation, is impaired at high drug concentrations.[7] Therefore, while a minimum threshold of antigen expression appears to be necessary, beyond this the intrinsic biological activity of BsAb appears determined by the unique physiochemical properties of the molecule itself, and in particular the spatial properties of the tumor-associated antigen-binding arm.

When administered intravenously, the time to peak concentration of BsAb is short, occurring within 6 hours of the end of infusion.[1,8] This corresponds to the onset of toxicity such as cytokine release syndrome (CRS), so alternative strategies were explored to modify the peak to reduce the extent of toxicity experienced. For instance, with subcutaneous delivery of epcoritamab in cynomolgous monkey models, peak levels were 7- to 17-fold lower, while the area under the curve was comparable to that following intravenous administration.[6] According to phase I study data, this translated to a peak concentration of epcoritamab using subcutaneous dosing at 2.8 days.[3]

Phase I observations

The early phase studies of BsAb included patients with a spectrum of indolent and aggressive subtypes of relapsed and refractory B-cell non-Hodgkin lymphomas, with subsequent expansion cohorts focusing on patients with specific subtypes of lymphoma. Across the agents, the initial frequency of dosing of the BsAb varied from weekly to monthly, and with each drug, there has been evolution of the schedule during development. The resulting schedules differ in important ways, including the relative proportion of initial doses to the target dose, the number of step-up levels, total corticosteroid exposure and choice, and the duration of treatment (Table 1).

Step-up dosing is universally required

CRS is a dose-dependent and dose-limiting toxicity that, for a given target dose, is most severe at the first exposure.[9,10] CRS is less frequent at second and subsequent exposures to the BsAb, and so step-up dosing reduces the risk of CRS by gradually introducing the BsAb to the patient.[11]

Epcoritamab and odronextamab began phase I studies with pre-determined step-up doses, while mosunetuzumab commenced with fixed dosing before converting to a step-up schedule.[3,8,12] There was more reason to believe that fixed dosing might be deliverable with glofitamab because of obinutuzumab pre-treatment.[13] In the phase I trial of glofitamab, a dose of 600 μg reliably induced clinically meaningful response, and flat dosing up to 25 mg was possible with obinutuzumab pre-treatment, but CRS reliably increased at each dose level and was considered unacceptable at 25 mg. The three-step-up dosing strategy (2.5 mg, 10 mg, 30 mg separated by a week) was ultimately adopted.[1]

From the start of epcoritamab development, which was unique at the time for its subcutaneous method of delivery, the first dose was a "priming" dose of 4 μg leading into the initial evaluated target dose of 12.8 μg. The first clinical response occurred at 120 μg.[14] The recommended phase II dose was supported by a pharmacokinetic/pharmacodynamic model used to forecast optimal trimer formation, which was predicted to occur between 48-96 mg.[3,7] Odronextamab development used a clinical exposure-response analysis to test a number of different step-up doses, beginning with one step-up and ultimately proceeding to dose escalation using split step-up doses (where one dose is split across 2 days) prior to the target dose.[8,15] While efficacy was observed in all dose groups, a significant inflection point in response was observed at a target of 80 mg or higher, which was achieved safely with the additional step-up doses.

While step-up dosing is used for all products, the relative proportion of the first step-up to target dose is variable (Table 1). For glofitamab, the first step-up dose is 8.33% of the target dose, while for epcoritamab it is 0.33% and for odronextamab, 0.44%. Each agent is delivered weekly during the step-up phase, presumably to ensure any CRS has resolved before the next step-up dose, and for convenience. More rapid step-up dosing cannot yet be recommended, but may be feasible in certain contexts. An investigator-initiated trial showed that in patients with a very low burden of disease, a glofitamab regimen com-

Table 1. Characteristics and dosing strategies of some bispecific antibodies.

Agent	Route of administration	Half-life in days, median	Dosing schedule	Cycle length in days	Step-up doses as percentage of target dose, %	Duration of therapy	CRS mitigation: anti-CD20 pre-treatment	CRS mitigation: corticosteroid	Hospitalization recommendations	Visits in first 6 months
Glofitamab	IV	10	*Step-up:* D-7 GPT D1 2.5 mg D8 10 mg *Target*: 30 mg Q3W	21	8.3 33	Fixed: up to 12 cycles	Obinutuzumab 1,000 mg IV D-7	Dexamethasone 20 mg PO/IV for first 3 doses*	First dose	~12
Mosunetuzumab	IV	6-11	*Step-up*: D1 1 mg D8 2 mg D15 60 mg *Target*: D15 60 mg Q3W	21	1.6 3.3	Fixed: up to 17 cycles (8 if CR achieved, 17 if partial response or stable disease)	Nil	Dexamethasone 20 mg PO/IV or methylprednisolone 80 mg for first 4 doses	Nil mandated	~12
Epcoritamab	SC	8.8	*Step-up*: D1 0.16 mg D8 0.80 mg *Target*: 48 mg QW for C1-C3 then Q2W for C4-9, then Q4W C10+	28	0.33 1.7	Indefinite - to progression or intolerance	Nil	Dexamethasone 15 mg or equivalent for 4 days with each of the first 4 doses	First target dose	~18
Odronextamab	IV	14	*Step-up*: D1 0.7 mg D8 4 mg D15 20 mg *Target*: 160 mg QW for C2-4 320 mg Q2W C5+, then Q4W C9+ (if CR)	21	0.4 2.5 12.5	Indefinite - to progression or intolerance	Nil	Dexamethasone 20 mg 1 day prior, on days of dosing, and 1 day after dosing during step-up and first target dose	First 3 doses	~21

*Corticosteroid may be administered on day 1 of cycle 2 if significant cytokine release syndrome is observed during the first cycle. CRS: cytokine release syndrome; IV: intravenous; D: day; GPT: gazyva (obinutuzumab) pre-treatment; QW: weekly; Q2W: every 2 weeks; Q3W: every 3 weeks; Q4W: every 4 weeks; PO: oral; CR: complete response; SC: subcutaneously; C: cycle.

prising step-up dosing on days 1, 3 and 8 had acceptable rates of CRS (grade 1-2 in 13.5%).[16]

Steroid timing and choice are important for optimizing cytokine release syndrome mitigation, and likely affect other toxicities of bispecific antibodies

BsAb require corticosteroid prophylaxis to mitigate CRS. For epcoritamab, steroid premedication was initially a single dose of prednisolone 100 mg on the days of dosing. However, following prohibitive rates of CRS occurring at low doses and before the observation of clinical efficacy, steroid dosing was extended to 4 days.[14] This alteration provided coverage for the later cytokine and drug concentration peaks associated with the subcutaneous route of administration and achievement of a target dose with clinical activity, with acceptable rates of CRS. Due to high rates of grade 4 CRS in initial odronextamab dosing cohorts, optimization of pre-medications led to the use of 20 mg of dexamethasone or equivalent given the day before, the day of and the day following administration of the BsAb.[8]

In addition to supporting the importance of glucocorticoids in CRS mitigation, glofitamab development has highlighted the importance of steroid selection. A cohort of patients within the phase II portion of the NP30179 study had mandated dexamethasone pre-medication as opposed to prior cohorts that allowed investigator choice of methylprednisolone or prednisolone. In a naïve comparison that did not control for patients' characteristics, the all-grade CRS rate was 44% compared to 73% with other preparations, with equivalent response rates observed.[17] Similar findings were made in a 24-patient optimization cohort in the EPCORE NHL-1 study of epcoritamab, in which dexamethasone use resulted in no observed grade 2 or higher CRS and lower median circulating cytokine levels without negative effects on T-cell margination and activation.[18] Dexamethasone has also been recommended in recent guidelines on the management of CRS.[19]

Phase II monotherapy and registration studies

Epcoritamab and glofitamab are currently approved as monotherapy for relapsed and refractory DLBCL after at least two prior lines of therapy in Europe, the USA and other regions. Odronextamab has received approval in Europe,[20] while mosunetuzumab is not being developed as a single agent for use in DLBCL. The phase II trials exploring activity of the approved agents in DLBCL were of similar size, with between 127 and 157 patients, and recruited during the coronavirus 2019 (COVID-19) pandemic, in the calendar years of 2020 to 2022.[21-23]

Indirect comparisons between trials cannot account for potential differences between study populations. However, when reviewing the results of the epcoritamab (EPCORE NHL-1) and glofitamab trials (NP30179) that led to marketing approvals, one is struck by how similar the recruited patient populations and overall efficacy and toxicity outcomes appear to be (Table 2). Despite their independent development and completely different dosing strategies, the results of the two trials reinforce the impressive activity of BsAb as monotherapy in relapsed DLBCL.[3,21,22] Indirect comparisons with the phase II trial of odronextamab, ELM-2, are more challenging as two different treatment dosing strategies were used in that study, and the full data are presently unpublished in peer-reviewed literature.[23-25]

Key common inclusion criteria across these trials were age >18 years, failure of at least two prior lines of treatment, an Eastern Cooperative Oncology Group performance status no higher than 1, and a diagnosis of DLBCL, including patients with transformed disease from follicular lymphoma, primary mediastinal B-cell lymphoma or high-grade B-cell lymphoma with rearrangements of *MYC* and *BCL2*/*BCL6*. Organ function criteria were similar. Both EPCORE-NHL-1 and NP30179 excluded patients with Richter syndrome in the DLBCL expansion arms,[21,22,26] while ELM-2 allowed them, ultimately accounting for 5.5% of the recruited population.[23] Unlike trials of some novel agents in DLBCL that excluded especially refractory and high-risk populations of DLBCL[27] the key trials of CD20xCD3 BsAb are enriched for patients with primary refractory disease, or disease refractory to the immediate prior therapy, accounting for more than 80% of the recruited populations (Table 2). Significantly, patients treated with CAR T cells accounted for more than 30% of patients on the epcoritamab, glofitamab and mosunetuzumab trials.[21,22,26] Importantly, ELM-2 excluded patients previously exposed to CAR T-cell therapy; however, data from the phase I confirm activity in this context.[23]

The delivered regimens are listed in Table 1. Of the three regimens, glofitamab was associated with the fewest visits in the first cycle, and the highest relative first exposure to the drug compared to the target dose. It is unique because of the obinutuzumab pre-treatment and, unlike epcoritamab and odronextamab, glofitamab is given for a fixed course that stops at 12 cycles irrespective of response.[21-23] Two regimens were used for odronextamab, and the final regimen required six infusions in the first 3 weeks, weekly visits until cycle 5, fortnightly to cycle 9, and 4-weekly visits thereafter for responding patients, making it the more demanding among the regimens.[23] Patients were hospitalized for the first three doses of odronextamab to manage CRS risk, while only one hospitalization was required for the first dose of glofitamab (2.5 mg) and for the first target dose of epcoritamab (48 mg).[21,22]

Corticosteroid prophylaxis against CRS was universal, but differed substantially between agents. Epcoritamab required 4 days of prednisolone, 100 mg per dose, until at least the first 4 weeks of exposure (1,600 mg cumulative), while intravenous corticosteroid prophylaxis of 100 mg prednisone, 80 mg of methylprednisone, or 20 mg dexamethasone

was given as a single dose for at least the first 5 weeks of glofitamab treatment (625 mg prednisolone-equivalent cumulatively). Odronextamab therapy requires 20 mg of dexamethasone on dosing days as well as the day prior, and the day following dosing, which, when combined with the split dosing schedule, results in similar cumulative steroid exposure to that when giving treatment with epcoritamab (~1,600 mg).

Efficacy is high, but durable remissions are restricted to those achieving complete response

In general, durable remissions in DLBCL require a complete response to therapy, which is also true with BsAb therapy, and so we find that the complete response rate (CRR) is a useful early indicator of drug activity in DLBCL. The CRR achieved in EPCORE NHL-1 and NP30179 was 40%.[21,22,25,28] The overall response rate (ORR), by contrast, is numerically higher with epcoritamab, owing to a higher rate of partial remissions.

Durable response on an intent-to-treat basis is seemingly restricted to those who achieve a complete response. Most patients who are destined to enjoy a complete remission do so at the first response assessment. Conversion from a partial remission to complete remission occurs in roughly a third of partial responders to glofitamab, odronextamab and epcoritamab, while disease progresses quickly in most of the remaining patients.[21,22,25] In our practice we therefore re-evaluate patients early if a complete response is not achieved at the first response assessment, as progression frequently ensues.

Duration of complete responses

Several landmark analyses since the initial publications assist in an understanding of the longer-term expectations for BsAb, and how clinicians may counsel patients during treatment. Retention of complete remission at the 3-month and end-of-treatment response evaluations positively predicts enduring remission at 12 and 18 months following treatment with glofitamab, and the same is true for epcoritamab.[28-30] After a median follow-up in complete responders of 28.3 months, patients in a complete remission at 3 months on glofitamab had a 24-month survival of 73.4%. Sixty-four percent of patients had neither progressed nor died. In an updated analysis with a median of 37.7 months follow-up, those in complete remission at the end of 12 cycles had a 24-month overall survival of 77%.[28,30] Epcoritamab produced quite similar results. After a median follow-up of 37.1 months, the median duration of complete response was 36.1 months, and 63% of complete responders remained alive at 3 years.[29] For glofitamab and epcoritamab, this ultimately means that the proportion of patients who are in a complete remission at 12 and 18 months are roughly equivalent. This is notable, given that glofitamab is a fixed-course therapy (12 cycles, 8.4 months), while epcoritamab is continued until progression. On the whole, the ELM-2 data are similar to those for the above two trials.[23] The CRR following odronextamab for DLBCL was numerically lower, 31.5%, and the ORR was 52% (Table 2); however, this may be accounted for by differences in patients' characteristics or analysis methods. The estimated 24-month progression-free survival rate in complete responders was 47.2%, which is somewhat lower than the rates achieved by the drugs above. Mosunetuzumab produced a CRR of 24%, overall, and 12% in CAR T-cell-exposed patients (Table 2).[26] It remains an attractive combination partner presently under evaluation in several trials.

Important subgroups

Subgroup analyses across the BsAb pivotal trials have been generally underpowered and, therefore, mostly unrevealing. Patients with relapsed, rather than refractory disease have a substantially higher rate of complete responses, but represent a minority of recruited patients; for example the CRR following glofitamab in patients with relapsed rather than refractory disease was >70%, but these patients only represented 14% of the recruited population.[21] Other factors such as bulk of disease and lactate dehydrogenase level did not change the CRR. Recent data on total metabolic tumor volume determined by positron emission tomography suggest that patients with high burden disease have a poorer progression-free survival following treatment with glofitamab.[30]

Responses in populations exposed to CAR T-cell therapy are surprisingly good. The rates of complete remission after glofitamab (35%) and epcoritamab (34%) were not different from what might be expected of the overall group, but patients tended to have relapsed after CAR T-cell therapy rather than to have had no response at all.[21,22] Data from the phase I trial of odronextamab, ELM-1, showed a 29% CRR in the 44 patients who had received prior CAR T-cell therapy.[31]

Patients who are alive but who are refractory to CAR T-cell therapy frequently have other issues that may prevent selection into a clinical trial, especially persistent cytopenia.[32] While the trials of glofitamab, epcoritamab and odronextamab demonstrate activity in CAR T-cell-treated patients that probably surpasses that of other available options, safety and deliverability in patients with early CAR T-cell failure and associated persistent toxicities are yet to be fully clarified, as is whether the responses are as durable as those seen in patients not exposed to CAR T cells. Investigator-initiated trials and real-world studies may address this question, but with few exceptions prospective trials still exclude patients with progression within 30 days of a CAR T-cell infusion (NCT06414148).[16]

Experience of toxicity from the pivotal phase II studies

Cytokine release syndrome

Rates of CRS observed with BsAb monotherapy are listed in Table 2. CRS and recommendations for its management

have been the subject of recent, useful guidelines.[19] The defining symptom is fever, which can usually be managed with acetaminophen and/or corticosteroids. A critical threshold for admission to hospital is CRS of grade 2 or above, implying the presence of hypotension or hypoxia requiring supplemental oxygen.[33] Overall, the rates of CRS between the BsAb in use for DLBCL are similar (Table 2), although the clinical pattern varies according to the agent, dose, choice of corticosteroid prophylaxis, and disease-related features.[17] Following glofitamab treatment, CRS occurs most frequently with the first 2.5 mg dose, hence admission is currently recommended at that time. With epcoritamab, CRS most commonly occurs with the first target dose, cycle 1 day 15, when hospitalization is recommended.

Avoiding pre-emptive hospitalization is desirable. Well-educated patients with access to out-of-hours medical centers may be managed as outpatients on a case-by-case basis, potentially through the provision of an initial "just-in-case" dose of corticosteroid to take with the onset of a fever, but there are no prospective data supporting such an approach. This strategy is likely to be less feasible in patients with risk factors for CRS, and in those with comorbidities who may poorly tolerate the physiological challenge that it entails. A predictive score for CRS risk after glofitamab therapy was able to reliably predict grade 2 CRS across multiple glofitamab-treated cohorts and used markers of disease burden (lactate dehydrogenase, sum of the product of the diameters on computed tomography, stage), together with age and white cell count.[19,34] A similar three-factor scoring system incorporating prior exposure to CAR T-cell therapy, extranodal disease, and total metabolic tumor volume was able to accurately identify patients at low-risk of grade 2 CRS with epcoritamab.[35] While the sum of the product of the diameters and total metabolic tumor volume may not always be available in routine practice, these scores support the role of risk stratification in managing CRS in patients receiving BsAb for DLBCL.[19,34]

Cytopenia, infection and neurological toxicity

Grade 3/4 neutropenia occurred in 27% and 17.8% of patients following glofitamab and epcoritamab treatment, respectively,[21,22] but rarely led to treatment discontinuation, or to febrile neutropenia. This latter complication can be managed with intermittent doses of granulocyte colony-stimulating factor.

Grade 3/4 thrombocytopenia occurred in 5.7% of patients following epcoritamab, and in 8% following glofitamab, and could be of particular importance in patients who have baseline thrombocytopenia because of the higher risk of bleeding in patients with fever.

Infection is an important side effect of BsAb in lymphoma.[36] Grade 3/4 infection occurred in 15% of patients following glofitamab or epcoritamab, and in each monotherapy trial the most common infection was COVID-19.[21,22] In the recent randomized STARGLO clinical trial, there was an early imbalance of COVID-19-associated deaths in the glofitamab-containing arm, leading to an amendment to mandate treatment discontinuation in patients acquiring COVID-19 on that trial.[37] The field has evolved since the time that trial was conducted, with variants of COVID-19 less likely to cause complications now prevalent, and with the more routine availability of effective vaccines. In our experience BsAb can be judiciously continued in select patients who have acquired COVID-19 during treatment; however, we have observed cases of delayed COVID-19 clearance, COVID-19-associated pneumonitis and organizing pneumonia in patients receiving these agents. A comprehensive evaluation of a patient's competing risks is required before continuing treatment with these agents in symptomatic patients.

As with other B-cell-depleting agents, hypogammaglobulinemia will occur in some patients following BsAb treatment, and replacement may be indicated as primary or secondary prophylaxis against infection. B-cell and immunoglobulin recovery have been best characterized after cessation of mosunetuzumab[38] and glofitamab[39] but are less well characterized with the agents that are given indefinitely. Recovery of B cells and IgM occurred 12-18 months after cessation of glofitamab in the pivotal trial, while rises in IgG were observed 18-24 months after glofitamab cessation. We routinely use antiviral prophylaxis against herpes viral reactivation (valacyclovir), and trimethoprim-sulfamethoxazole to prevent *Pneumocystis jirovecii* pneumonia. There are no data to suggest that one BsAb is more likely to induce infection than another, but physicians should consider a patient's comorbidity, prior therapies and pre-existing immune competence, as well as duration of treatment and cumulative steroid exposure when evaluating that person's risks from acquired infection during treatment.

Neurological toxicity consistent with immune effector cell-associated neurological syndrome occurs in <10% of patients treated with glofitamab, epcoritamab and odronextamab. It needs to be considered in the differential diagnosis of delirium, should such features occur during treatment. In our practice, true immune effector cell-associated neurological syndrome following BsAb treatment has been rare and, except in patients with inexorable disease progression, reversible.

Resistance mechanisms are diverse

Despite the great promise of BsAb, a minority of patients experience complete remission following this treatment. Mechanisms of resistance to BsAb in DLBCL are poorly understood, and developing insights into this area has been complicated by the molecular heterogeneity of DLBCL, differences in the characteristics of patients included on the trials, as well as practical challenges in obtaining sequential biopsies. Defects in host immunity, tumor-intrinsic

Table 2. Efficacy and toxicity of agents in advanced development.

Agent	N of patients	Patient population	N of prior lines, median (range)	Refractory to immediate prior therapy, %	Prior CAR-T, %	ORR/ CRR, %	Median DOR in months	Median DOCR in months	Median PFS/OS in months	CRS rates, %				
										Total	G1	G2	G3	G4
Glofitamab[21,39§]	155*	R/R LBCL	3 (2-7)	86	33	52/39	18.4	29.8	4.9/not reached	63	47	12	3	1
Epcoritamab[22,78§]	157†	R/R LBCL	3 (2-11)	83	39	63/39	12.0	36.1	4.4/not reached	50	32	15	4	0
Odronextamab[23]	127‡	R/R LBCL	2 (2-8)	87	NR	52/32	10.2	17.9	4.4/9.2	53	40	12	2	0
Mosunetuzumab[26]	88	R/R LBCL	3 (2-13)	80	30	42/24	6.9	NE	2.7/11.5	26	21	3	2	0

§Long-term outcomes of glofitamab were determined by an independent review committee, while long-term outcomes of epcoritamab were determined by investigator evaluation. *Included six patients with primary mediastinal B-cell lymphoma (PMBCL); 154 patients received a dose of study treatment. †Included four patients with PMBCL and five patients with follicular lymphoma grade 3B. ‡Included seven patients with Richter syndrome; 141 patients enrolled with 127 patients evaluable for efficacy. CAR-T: chimeric antigen receptor T-cell therapy; ORR: overall response rate; CRR: complete response rate; DOR: duration of response; DOCR: duration of complete response; PFS: progression-free survival; OS: overall survival; CRS: cytokine release syndrome; G: grade; R/R LBCL: relapsed or refractory large B-cell lymphoma; NR: not reported; NE: not estimable.

Table 3. Studies of bispecific antibody combinations in diffuse large B-cell lymphoma with reported results.

Disease setting	Trial ID/Name	Phase	Treatment	Patient population	N of patients	ORR/CRR, %	PFS/OS/DOR	CRS rates, %					Follow-up in months, median
								Total	G1	G2	G3	G4	
First line	NCT03467373[79] NP40126	I/II	Glofit + R-CHOP	Fit IPI 2-5	56	93/84	NR	11	7	4	0	0	17.1
	NCT03467373[80] NP40126	I/II	Glofit + Pola-R-CHP	Fit IPI 1-5	24	100/77	NR	13	13	0	0	0	5.1
	NCT04914741[81,82] COALITION	I/II	Glofit + R-CHOP or Glofit + Pola-R-CHP	Fit, IPI 3-5 or NCCN-IPI 4-8 Age 18-65 years	80	100/98	2-year PFS 86% 2-year OS 92%	22	19	3	0	0	20
	NCT04980222[55]	II	Glofit + R-CHOP	Fit, high-risk by ctDNA IPI 2-5	24	93/80	NR	21	17	4	0	0	NR
	NCT04663347[83] EPCORE NHL-2	I/II	Epcor + R-CHOP	Fit IPI 3-5	47	100/87	2-year PFS 74% 2-year OS 87%	60	45	11	4	0	27.4
	NCT05283720[84] EPCORE NHL-5 (Arm 3)	I/II	Epcor + Pola-R-CHP	Fit IPI 2-5	37	100/89	NR	49	32	16	0	0	7.4
	NCT03677141[85]	I/II	Mosun + R-CHOP	Fit IPI 2-5	40	95/90	2-year PFS 65.4%	60	45	15	0	0	32
	NCT03677154[86]	Ib/II	Mosun ± Pola	Age ≥80 or age 65-79 and unfit	101	80/65	1-year PFS 49.7%	32	21	7	2	0	12.6
	NCT05798156[87,88]	II	Glofit + Pola-R	Unfit Age ≥80 or age 60-79 and unfit IPI 0-5	10	NR	NR	50	50	0	0	0	8
	NCT04663347[89,90] EPCORE-NHL2 (Arm 8)	I/II	Epcor + R-miniCHOP	Unfit Age ≥75 or age 65-74 and unfit	28	89/82	1-year PFS 88% 1-year OS 96%	43	25	29	0	0	9.4

Continued on following page.

Disease setting	Trial ID/Name	Phase	Treatment	Patient population	N of patients	ORR/CRR, %	PFS/OS/DOR	CRS rates, %					Follow up in months, median
								Total	G1	G2	G3	G4	
Second line and beyond	NCT04663347[91] EPCORE NHL-2	I/II	Epcor + R-DHAX/C*	Transplant eligible 2L+	29	76/69	2-year PFS 60% 2-year OS 86%	45	38	7	0	0	27.5
	NCT04663347[59,92] EPCORE NHL-2 (Arm 5)	I/II	Epcor + GemOx	Transplant ineligible 2L+	103	85/61	15-month DOCR 56%	52	28	23	1	0	13.2
	NCT05283720 EPCORE NHL-5	II	Epcor + Lenalidomide Olamide	Transplant eligible and ineligible 2L+	26	75/58	NR	73	65		8	0	NR
	NCT03533283[37] STARGLO	III	Glofit + GemOx *vs.* R-GemOx	Transplant ineligible 2L+	183	68/59	1-year PFS 52% 2-year OS 53%	44	31	11	2	0	20.7
	NCT05364424[93]	I	Glofit + R-ICE†	Transplant or CAR-T eligible 2L	41	78/69	NR	49	29	20	0	0	NR
	NCT04077723[64]	I/II	Glofit + Englumafusp alpha (CD19x4-1BB)	Transplant ineligible 2L+	83	67/57	1-year PFS 46%	55	49	13	1	0	16.2
	NCT05219513[28]	I	Glofit + RO7443904 (CD19xCD28)	Transplant ineligible 2L+	33	64/39	NR	59	36	19	0	4	NR
	NCT03533283[57,94]	I/II	Glofit + Pola	Transplant ineligible 2L+	129	80/62	Median PFS 12 months Median OS 39.2 months	43	27	15	1	0	23.5
	NCT03671018[56]	I/II	Mosun + Pola 2L+	Transplant ineligible 2L+	117	62/50	1-year PFS 46% 1-year OS 66%	17	10	4	3	0	23.9
	NCT05335018[95]	II	Glofitamab + Poseltinib + Lenalidomide	Transplant ineligible Primary refractory or 3L+	28	89/43	6-month PFS 55% 6-month OS 81%	19	14		5		3.6
	NCT03533283[67]	I/II	Glofit + Atezolizumab	Transplant ineligible	31	29/10	NR	42	24	18	0	0	NR

*Autologous stem cell transplant consolidation at investigators' discretion. †Autologous stem cell transplant or chimeric antigen receptor T-cell consolidation at investigators' discretion. ID: identity; ORR: overall response rate; CRR: complete response rate; PFS: progression-free survival; OS: overall survival; DOR: duration of response; CRS: cytokine release syndrome; G: grade; Glofit: glofitamab; R: rituximab; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone; IPI: International Prognostic Index; NR: not reported; Pola: polatuzumab; CHP: cyclophosphamide, doxorubicin, prednisolone; NCCN: National Comprehensive Cancer Network; ctDNA: circulating tumor DNA; Epcor: epcoritamab; Mosun: mosunetuzumab; DHAX/C: dexamethasone, cytarabine, oxaliplatin/carboplatin; 2L: second-line; GemOx: gemcitabine, oxaliplatin; DOCR: duration of complete response; ICE: ifosfamide, carboplatin, etoposide; CAR-T: chimeric antigen receptor T-cell therapy; 3L: third-line.

factors, antigen loss, and microenvironmental changes are all implicated in resistance, and evidence supports contributions from each.

A common feature in biomarker studies has been a positive association between the proportion of CD8$^+$ T cells present in baseline tumor samples and the depth of response. For each of glofitamab, epcoritamab and odronextamab, responders showed a trend towards higher baseline tumor CD8$^+$ T-cell infiltration via a variety of techniques, although nuances appear to be important.[40-42] For instance, a specific increase in an effector-like CD8$^+$ T-cell subset was associated with complete response to glofitamab, as was a naïve phenotype.[42,43] Increased cytotoxic markers were present in circulating CD8$^+$ T cells in patients responding to epcoritamab and glofitamab, both at baseline and in T cells subsequently expanding after BsAb exposure.[40,43] The positive and negative role of other T-cell subsets, in contrast, are less uniformly described; a higher proportion of CD4$^+$ T-regulatory and T-follicular helper type cells within the tumor sample was implicated in reduced response to epcoritamab, which was partly recapitulated with odronextamab (T-regulatory cells only), but was not specifically observed with glofitamab.[40-42] Similarly, the relationship between expression of checkpoint markers and response also appears to be variable, with higher PD-1 expression on T cells being linked to resistance to glofitamab and epcoritamab, but was not demonstrated to be the case with odronextamab.[41,42,44]

Neither the percentage of CD20$^+$ cells nor strength of CD20 expression at the time of first treatment predicts for response, although very few truly CD20$^-$ patients were included in the trials, and we do not recommend using these agents in that circumstance.[41,42,45] Loss of CD20 expression at progression appears to be an important mechanism of tumor resistance. In a retrospective analysis of 42 patients with DLBCL treated with glofitamab at our center, we demonstrated that 63% of patients with pre- and post-treatment samples converted from CD20$^+$ to CD20$^-$, as determined by immunohistochemistry, at progression.[46] Similar findings have been made with epcoritamab and odronextamab,[40,41] and the immunohistochemical evidence is supported by longitudinal molecular analyses demonstrating alterations in genes encoding CD20 in many patients treated with BsAb.[40,41,47,48] As a consequence, newer BsAb targeting additional antigens may show whether clonal escape can be addressed in this way.[49,50]

In addition to these dynamic changes, baseline molecular features typically associated with tumor aggressiveness may also predict for poorer response to BsAb. For instance, both the presence of double-hit translocations and positivity for the dark-zone signature by RNA analysis were associated with shorter progression-free survival with glofitamab monotherapy in the relapsed and refractory setting.[51] However, this may not be the case in all contexts and with all combinations; in newly diagnosed disease, response to epcoritamab in combination with chemotherapy in patients with double-hit large B-cell lympoma appeared roughly equivalent to that in patients with standard-risk disease.[52] Individual genetic aberrations, such as *TP53* mutations and *MYC* dysfunction, are also features associated with resistance to BsAb therapy.[22,53] Despite its ongoing significance in other contexts, cell of origin does not appear predictive of response to any individual agent.[22] However, molecularly sub-classifying tumors according to the LymphGen system suggested poorer outcomes were observed with the *MYD88* and *CD79B* double (MCD) mutation phenotype with both glofitamab and odronextamab monotherapy.[51,53] Taken together, the biomarker studies support the hypothesis that response is associated with more functional, less exhausted T cells favoring a cytotoxic profile, while resistance is characterized by T-cell exhaustion, biological tumor aggressiveness and target-antigen downregulation.

Emerging role of circulating tumor DNA

Evaluation of measurable residual disease using circulating tumor DNA (ctDNA) does not have a routine role in the management of DLBCL, however, it is conceptually appealing to think that measurable residual disease might guide the use of BsAb in DLBCL. Treatment withdrawal, either by protocol design or through response evaluation, may allow adequate B-cell recovery and mitigate the toxicities of B-cell depletion that are emerging as an issue after BsAb.[38] ctDNA levels are closely aligned with tumor load and represent a possible mechanism to simultaneously measure baseline burden and genomic complexity. For instance, patients with higher baseline ctDNA levels had shorter progression-free survival when treated with glofitamab monotherapy, which was positively correlated with high-risk clinical features such as elevated lactate dehydrogenase, bulky disease and high International Prognostic Index.[51] Achievement of measurable residual disease negativity by ctDNA during treatment correlated with improved progression-free survival with all three approved agents.[22,39,53,54] The pace of ctDNA decay may also be an important factor, with patients destined to achieve a complete metabolic response to glofitamab showing a more rapid and sustained decrease in ctDNA at early timepoints.[51] In addition, ctDNA response may augment the interpretation of positron emission tomography imaging assessments; for patients not achieving a complete metabolic response to odronextamab at an interim scan, measurable residual disease negativity by ctDNA appeared useful in predicting improved outcomes compared to those of patients with positive measurable residual disease.[53]

Drawing on these principles of the prognostic significance of ctDNA kinetics more broadly, a number of ongoing trials in newly diagnosed DLBCL are using sub-optimal ctDNA

response to chemoimmunotherapy as a mechanism to identify patients at risk of early progression who may benefit from the addition of a bispecific agent (NCT06050694).[55]

Combination therapy

Combination strategies seek to augment responses and overcome resistance through the addition of active therapeutic partners. Numerous studies including patients with DLBCL exploring various combinations are currently undergoing evaluation in first and later lines of therapy and are summarized in Tables 3 and 4.

Combination with cytotoxic therapy is promising

Polatuzumab vedotin, a CD79b antibody-drug conjugate, has been successfully combined with mosunetuzumab and glofitamab in single-arm phase II studies in relapsed and refractory DLBCL, demonstrating CRR of 50% and 56%, respectively, in patient populations largely analogous to those of the pivotal monotherapy studies.[56,57] Importantly, this apparent increased rate of deep response did not come at the expense of additional toxicity; rates of serious and fatal adverse events were similar, and treatment discontinuation was rare (≤10%). In fact, rates of CRS appeared lower using the combination than with BsAb treatment alone (Tables 2 and 3). The doublet of mosunetuzumab and polatuzumab vedotin is currently being evaluated in the randomized SUNMO clinical trial that pitches the combination against conventional chemotherapy in a transplant-ineligible population (Table 4).[58]

This principle that combination therapy is tolerable and may help to overcome early resistance to bispecific therapy or the combination partner extends beyond 'chemotherapy-light' regimens to include multi-agent cytotoxic therapy in broader populations and earlier treatment lines. A key breakthrough in the management of relapsed DLBCL is the result of STARGLO, a randomized, phase III trial that compares eight 3-weekly cycles of glofitamab with eight cycles of gemcitabine-oxaliplatin (Gem-Ox) to rituximab-gemcitabine-oxaliplatin (R-Gem-Ox), in transplant-ineligible patients with relapsed and refractory DLBCL.[37] A total of 274 patients were randomized 2:1 favoring the experimental arm. Most patients (63%) had received one prior therapy, with 37% exposed to two or more prior lines of treatment. High-risk features, such as refractoriness to the immediate prior therapy (61%), age ≥65 years (63%), and advanced stage disease (71%) were common. Complete responses were seen in 59% of the glofitamab arm, more than double the 25.3% following R-Gem-Ox. With a median follow-up of 20.7 months, this translated into a highly significant improvement of progression-free survival (median 13.8 *vs*. 3.6 months; hazard ratio=0.40 [95% confidence interval: 0.28-0.57]; *P*<0.001) and overall survival (median 25.5 *vs*. 12.9 months; hazard ratio=0.62 [95% confidence interval: 0.43-0.88]; *P*=0.006). At 12 months, a striking 52% of patients receiving glofitamab-Gem-Ox remained alive and in remission. Pre-specified subgroup analyses confirmed a benefit across most important groups, including those defined by age, number of prior lines of therapy, relapsed *versus* refractory status, and cell of origin by immunohistochemistry.

There are some limitations to the STARGLO trial. Firstly, CAR T-cell therapy was not routinely available in many study sites; only 8% had received CAR T cells prior to study entry. Differences in post-protocol therapy might have contributed to a lack of apparent overall survival benefit from the novel combination in the subgroup from the USA and Europe when compared to subjects from Asia and Australia. Since the trial was conducted, CAR T-cell therapy has been approved for high-risk first relapse and is more widely available. Secondly, some have criticized the control arm, as R-Gem-Ox is given on a 2-weekly regimen in some regions. In our experience, 3-weekly R-Gem-Ox is more feasible than the 2-weekly regimen and we would consider it a reasonable standard-of-care comparator, however, this view is not universal and practice may vary by region.

Promising results have been reported in a phase II study of epcoritamab plus Gem-Ox, with ORR and CRR of 85% and 61%, respectively,[59] and numerous other combinations of BsAb with salvage treatments are under investigation in both transplant-eligible and -ineligible populations (Tables 3 and 4). These studies have also highlighted the broad tolerability of combination BsAb and cytotoxic therapy, repeating the theme from polatuzumab vedotin combinations by demonstrating generally lower rates of CRS compared to those expected with bispecific monotherapy. In STARGLO, all-grade CRS was observed in 44% of patients, with grade 3 CRS observed in only 2.3%, compared to 66% and 3%, respectively, with monotherapy.[21,37] This might be due to a reduction in tumor burden resulting from the exposure to chemotherapy. Serious infections were more frequent in the experimental arm (26% *vs*. 12.5%), including a disproportionate number of COVID-19 deaths, resulting in a protocol amendment that required exclusion or cessation of protocol treatment for any patient with recent or new onset COVID-19.[37] Careful evaluation of additional toxicity will be essential in the development of safe and effective combination treatments.

The combination of BsAb and cytotoxic therapy has also been translated to the first-line setting, with a particular focus in patients with high-risk, newly diagnosed DLBCL. In phase I/II combination studies with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone)-like backbone therapy, high rates of complete response have been observed, including in patients with clinically and molecularly poor-risk disease (Table 3).

Table 4. Studies of bispecific antibody combinations in diffuse large B-cell lymphoma without reported results.

Disease setting	Trial ID/Name	Phase	Treatment	Patient population	N of patients planned	Primary endpoint
First line	NCT05800366	II	Glofit + Pola-R-CHP	Fit IPI 2-5	40	CRR (after 8 cycles)
	NCT06050694 GRAIL	II	Pola-R-CHP or Glofit + Pola-R-CHP	Fit Patients with unfavorable response by ctDNA or PET after 2 cycles of treatment receive Glofit	40	Feasibility of ctDNA testing
	NCT06091865[96] OLYMPIA-3	III	Odro + CHOP *vs.* R-CHOP	Fit IPI 2-5	904	PFS
	NCT05578976[97] EPCORE DLBCL-2	III	Epcor + R-CHOP *vs.* R-CHOP	Fit IPI 2-5	900	PFS
	NCT06047080[98] SKYGLO	III	Glofit + Pola-R-CHP *vs.* Pola-R-CHP	Fit IPI 2-5	1,130	PFS
	NCT05660967 EPCORE DLBCL-3	III	Epcor ± Len	Unfit Age ≥80 or age 75-79 and unfit	180	CRR
	NCT06045247	II	Epcor + R-mini-CVP	Unfit Age ≥80 or age <80 and unfit	40	Safety
Second line and beyond	NCT06287398 EPCOR-Sandwich	II	Epcor + R-DHAX + ASCT + Epcor consolidation	Transplant eligible 2L	39	EFS
	NCT05852717[99]	II	Epcor + GDP*	Transplant eligible 2L+	32	CRR (after 3 cycles)
	NCT06213311[100]	II	Glofit + Axi-cel	Transplant eligible 2L refractory or relapse <12 months	40	Safety
	NCT04161248	I	Glofit + R-GDP*	Transplant eligible 2L	18	Safety and RP2D
	NCT05283720 EPCORE NHL-5	II	Epcor + - Len-Ibrutinib (Arm 2) - CC-99282 (Arm 4)	Transplant eligible and ineligible 2L+	394 across all arms	Safety
	NCT05219513[62, 101]	I	Glofit + RO7443904 (CD19xCD28)	Transplant ineligible 2L+	53 (including other B-NHL)	Safety
	NCT05896163[102]	I/II	Glofit + Mapilracept (anti-CD47 antibody)	Transplant ineligible 2L-3L	70	ORR
	NCT05169515	I	Glofit or Mosun + CELMoD (CC-220 or CC-99282)	Transplant ineligible 2L+	121 (including other B-NHL)	ORR
	NCT06458439	II	Epcor before and after CAR-T	CAR-T eligible patients	31	Occurrence of CAR-T infusion
	NCT06414148	II	Epcor ± Len after CAR-T	Post-CAR-T ctDNA MRD positive	40	ORR (at 12 months after CAR-T)
	NCT05685173[103] ATHENA-1	I	Odro + REGN5837 (CD28xCD22)	Transplant ineligible 3L+	91 (including other B-NHL)	Safety
	NCT02651662[66] QLIO-1	I	Odro + Cemiplimab	Transplant ineligible 3L+	62 (including other B-NHL)	Safety
	NCT05315713	I/II	Mosun + Tiragolumab ± Atezolizumab	Transplant ineligible 3L+	118 (terminated after 8 patients)	Safety and ORR
	NCT05615636 2L+	II	Mosun + Pola + Tafasitamab + Len	Transplant ineligible 2L+	36	ORR
	NCT05672251[104]	II	Mosun + Loncastuximab tesirine	3L+	26	Safety and ORR
	NCT05171647[58] SUNMO	III	Mosun + Pola *vs.* R-GemOx	Transplant ineligible 2L+	222	PFS

*Autologous stem cell transplant consolidation at discretion of investigator. ID: identity; Glofit: glofitamab; Pola: polatuzumab; R: rituximab; CHP: cyclophosphamide, doxorubicin, prednisolone; IPI: International Prognostic Index; CRR: complete response rate; ctDNA: circulating tumor DNA; PET: positron emission tomography; Odro: odronextamab; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone; Epcor: epcoritamab; PFS: progression-free survival; Len: lenalidomide; CVP: cyclophosphamide, vincristine, prednisolone; DHAX: dexamethasone, cytarabine, oxaliplatin; ASCT: autologous stem cell transplantation; 2L: second line; EFS: event-free survival; GDP: gemcitabine, dexamethasone, cisplatin; Axi-cel:; axicabtagene ciloleucel; RP2D: recommended phase II dose; B-NHL: B-cell non-Hodgkin lymphoma; ORR: overall response rate; Mosun: mosunetuzumab; 3L: third line; CELMoD: cereblon E3 ligase modulator; CAR-T: chimeric antigen receptor T cells.

Combination with immune-active therapies

As T-cell health and fitness appear to be critical elements in the success of BsAb, numerous strategies utilizing agents capable of augmenting T-cell activity are being explored in phase I/II studies (Tables 3 and 4).

Preclinical work with BsAb and the experience with CAR T-cell development indicate an important role for co-stimulatory signaling in augmenting T-cell fitness and promoting full functionality.[60] In mouse models, potent co-stimulation could be achieved using BsAb targeting 4-1BB or CD28, which were shown to amplify T-cell activity when co-administered with either odronextamab or glofitamab.[61-63] Clinically, this has translated into improved ORR and CRR in early results from phase II studies. For instance, combining the 4-1BBxCD19 fusion protein englumafusp alpha with glofitamab resulted in ORR and CRR of 67% and 57%, respectively, in patients with heavily-treated relapsed and refractory DLBCL, half of whom had previously been exposed to CAR T-cell treatment.[64] Biomarker work supported the hypothesis that co-stimulation could reduce terminal differentiation and T-cell exhaustion.[64] Importantly, despite the augmented activity, CRS rates and grades were similar to those seen with monotherapy.

Combinations with the immunomodulatory agent lenalidomide have also shown promise. In a cohort of 26 patients with relapsed and refractory DLBCL treated with epcoritamab and lenalidomide, the ORR was 75%, with a CRR of 58.3%.[65] In a more heavily pre-treated population, the combination of glofitamab with lenalidomide and the BTK inhibitor poseltinib demonstrated ORR and CRR of 89% and 43%, respectively. Work is ongoing with other immunomodulatory agents including cereblon E3 ligase modulators.

Altering inhibitory checkpoint signaling is an additional mechanism being explored to optimize immunological activity, including through the PD-1/PD-L1 axis, TIGIT and CD47/SIRP-α, but so far, the results are less compelling.[66,67]

Future major trials

STARGLO demonstrated that the potential of chemotherapy combinations needs to be tested further, including in fitter patients who would be considered eligible for autologous transplantation and/or CAR T-cell therapy. Early data from phase II trials suggest that a significantly higher proportion of patients respond to BsAb combination treatment compared to historical expectations with both conventional treatments and BsAb monotherapy (Tables 3 and 4). The SUNMO and EPCORE NHL-5 clinical trials evaluate the doublets of either BsAb and polatuzumab vedotin or lenalidomide against chemotherapy in a transplant-ineligible population in the hope that chemo-light or chemo-free combinations may be tractable in a frailer group of patients.

Each of glofitamab, epcoritamab and odronextamab is being combined with multi-agent chemoimmunotherapy in patients with newly diagnosed International Prognostic Index 2-5 large B-cell lymphoma. The SKYGLO study with glofitamab uses polatuzumab vedotin, rituximab, cyclophosphamide, vincristine and prednisone in the control arm, which has become a standard of care in some jurisdictions for high-risk DLBCL,[68] as the backbone therapy rather than rituximab-CHOP as used in EPCORE DLBCL-2 evaluating epcoritamab and OLYMPIA-3 evaluating odronextamab.

Conclusions: sequencing of bispecific antibodies today, tomorrow, and the future

Long-term follow-up data on BsAb in DLBCL tell a compelling story that, as monotherapy, these drugs offer multi-year remissions to a substantial fraction of patients, and that even against established CAR T-cell therapies, they will be an attractive option for many patients and physicians.[39,69] A patient's circumstances, including those of access, fitness, disease tempo and treatment setting, will drive a physician's choice of one *versus* the other. Constraints of access or manufacturing time and the stresses of referral of patients to distant treatment centers, may mean that the immediacy of BsAb trumps other considerations for some patients.

Where access is a lesser factor, current evidence and guidelines support the use of axicabtagene ciloleucel[70] and lisocabtagene maraleucel[71] as second-line treatment in transplant-eligible patients whose disease relapses within 12 months. Long-term follow up of CAR T-cell therapy goes beyond 5 years, confirming its curative potential. Outcomes may be as good in transplant-ineligible patients[72] but randomized data are lacking for this population, or in those who relapse beyond 12 months. Particularly in those who relapse beyond 12 months, or those with early relapse for whom CAR T-cell therapy is not feasible, the STARGLO trial offers a valuable treatment option. It is glofitamab + Gem-Ox, rather than CAR T-cell therapy that has a randomized trial favoring its use over conventional chemotherapy in those populations.[73] In regions in which conventional chemotherapy has been the only choice, the results of STARGLO are especially persuasive and suggest that the days of conventional chemotherapy alone being an appropriate option for relapsed DLBCL are numbered.

For relapse after CAR T-cell therapy, BsAb are active, but we anticipate lower rates of success in those who are truly refractory to CAR T cells.[74,75] Conversely, we know less about how CAR T cells work in patients whose disease has progressed or been refractory to BsAb treatment.[76] In a retrospective study of 47 BsAb-refractory patients from the DESCAR-T registry who went on to receive CAR T cells, the ORR and CRR to CAR T-cell therapy were consistent

with those of a matched, unexposed population.[77] We need more such data, as more patients will be referred for CAR T-cell therapy in the third line, having been exposed to BsAb in second-, or even first-line treatment.

Looking further into the future, the whole field may change if the results of the randomized trials of BsAb as a first treatment for DLBCL are positive. Little is known about the characteristics of patients whose lymphoma progresses after BsAb plus chemotherapy. Will their disease express CD20? Is re-exposure to a BsAb in the second line a relevant or logical treatment option? While CD19-directed CAR T-cell therapy may be a default option, more data will also be needed to establish whether CAR T cells are effective in that setting, too.

While there are no randomized trials comparing BsAb monotherapy with BsAb combinations, the consistently higher CRR to combinations suggests that in any line of treatment, except for the most frail patients, combinations will be the future. Whether the novel co-stimulatory bispecific agents such as englumafusp alpha, cereblon E3 ligase modulators/immunomodulatory drugs, antibody-drug, or other novel drugs are most effective in BsAb combinations is a pressing question. However, within the limits of what can be gleaned from non-randomized trials, these doublets seem to enhance responses with little toxicity cost. That suggests that BsAb will become a fundamental building block of a long hoped for future of "chemo-free" or "chemo-light" management of DLBCL.

In addition to their appeal as a deliverable combination partner in DLBCL, a key feature of BsAb is their immediate availability and deliverability outside of specialist treatment centers. With this comes the hope and expectation that the regimens currently under evaluation will affect the lives of more patients with DLBCL, and shift survival in this disease globally.

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