REVIEW ARTICLE

Bispecific antibodies in follicular lymphoma

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Abstract

Bispecific antibodies, specifically anti-CD20 T-cell engaging constructs, are poised to alter the treatment paradigm for multiple B-cell malignancies, including follicular lymphoma. Two CD20xCD3 bispecific antibodies, mosunetuzumab and epcoritamab, are now approved in the United States for third-line or later treatment of follicular lymphoma. A third agent, odronextamab, remains under review by regulatory agencies. In pivotal phase II trials, these bispecific antibodies demonstrated overall response rates of approximately 80%, with complete response rates of 60-70%, the majority of which have been durable at 2 years. Important safety signals included risk of infections, neutropenia, and cytokine release syndrome, which occurred in approximately half of patients, but was rarely high grade. Despite similar efficacy and toxicity profiles, key differences exist among agents, primarily relating to treatment duration, route of administration, and prophylactic corticosteroid use. Several ongoing studies are exploring bispecific antibodies in earlier lines of treatment, either as single agents or in combination with other active therapies. This novel class of agents is likely to play a pivotal role in improving outcomes for patients with follicular lymphoma.

Introduction

Bispecific antibodies (BsAb), under investigation for multiple hematologic malignancies, have transformed the treatment of relapsed acute lymphoblastic leukemia, multiple myeloma, diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (FL). These are only one of many new approaches harnessing T cells to fight cancer. Currently approved BsAb for lymphoma simultaneously bind CD20 on B cells and CD3 on endogenous T cells (CD20xCD3) resulting in direct T-cell activation that bypasses the typical interaction between T-cell receptors and major histocompatibility complex proteins required for T-cell activation. Two bispecific CD20xCD3 T-cell engagers, mosunetuzumab and epcoritamab, are approved in the United States for third-line or later treatment of relapsed or refractory (R/R) FL; mosunetuzumab and odronextamab have also been approved in Europe. Broader indications, including earlier lines of therapy in FL, are under active investigation. This review highlights the available efficacy and safety data of BsAb for FL, explores how they are being incorporated into the current treatment landscape, and discusses potential future clinical opportunities in FL.

Bispecific antibody development in lymphoma

The concept of using antibodies recognizing multiple targets, one directed at a chosen target antigen on cancer cells and another towards the T-cell receptor, was first proposed nearly 30 years ago.[1] Current BsAb can largely be divided into two classes: IgG-like subtypes that contain a fragment crystallizable (Fc) region and non-IgG-like fragment-based subtypes without an Fc region but with variable light and heavy chain domains bound by linkers.

Potential advantages of Fc-based BsAb include longer half-lives and the ability to kill cancer cells via effector functions, such as antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity.[2] Nevertheless, suppression of Fc-mediated effector functions can also be advantageous in minimizing off-target toxicity, reducing cytokine release, and improving T-cell infiltration.[3] Fragment-based BsAb, lacking an Fc region, demonstrate improved tissue penetration, but faster renal elimination. For example, the first-in-class BsAb for B-cell malignancies, blinatumomab (CD19xCD3), a small molecule consisting of two single-chain

fragment variable antibodies fused via a short peptide linker, has rapid clearance and a short half-life, necessitating prolonged continuous infusion. Efforts to extend the half-lives of fragment-based BsAb, such as through binding to human serum albumin, have been encouraging.[4] Other elements differentiating BsAb include the number, distribution, and specificity of the fragment antigen-binding (Fab) regions.[5] Additionally, CD3-binding affinity affects the level of T-cell activation, and thus different anti-CD3 clones have been tested and utilized in BsAb development.[6]

The first BsAb investigated for treatment of B-cell malignancies was blinatumomab;[7] however, given the need for prolonged continuous intravenous administration and substantial neurotoxicity in early trials, it was never approved for the treatment of lymphoma. Focus shifted towards CD20xCD3 BsAb with IgG-like structures to address the half-life concerns regarding blinatumomab.[8] There are now three (mosunetuzumab, glofitamab, epcoritamab) approved CD20xCD3 BsAb for lymphoma with a fourth (odronextamab) under review in the United States (Table 1). Mosunetuzumab, a full-length humanized mouse IgG1-based BsAb with near-native antibody architecture,[9] is considered the prototypical first-in-class T-cell engaging BsAb directed against CD3 and CD20. The Fc domain has been modified to prevent FcγR and complement binding. Epcoritamab is a full-length human IgG1 BsAb, generated from a humanized version of mouse anti-human CD3 monoclonal antibody SP34 and human anti-CD20 monoclonal antibody 7D8,[10] using the proprietary DuoBody® technology platform. The Fc domain is silenced via introduction of three mutations, reducing the potential for nonselective T-cell activation. Odronextamab is a first-in-class fully human IgG4 BsAb with a longer half-life, lower immunogenicity, and lower tendency to aggregate.[11] In contrast to other CD20xCD3 BsAb, glofitamab has a unique 2:1 configuration with two CD20 binding regions – the additional CD20-binding region is fused to the CD3-binding region in a head-to-tail manner via a flexible linker.[12] This greater target binding capacity, designed to increase efficacy, likely increases the risk of cytokine release syndrome (CRS). The modified Fc domain in glofitamab does not allow for FcγR or complement binding. Figure 1 shows the structure of various BsAb developed for B-cell non-Hodgkin lymphoma (NHL).

Efficacy of bispecific antibodies in follicular lymphoma

Phase II studies of BsAb in third and later lines of treatment in FL have shown consistent response rates of approximately 80% with 60-70% complete response (CR) rates (Table 2). While follow-up is still limited, the majority of CR appear durable at 2 years[13-15] and limited retreatment data in mosunetuzumab show responses occurring in patients relapsing after a CR.[13] These encouraging data have resulted in BsAb being the favored third-line therapy in FL and has led to the rapid development of clinical trials incorporating BsAb into first- and second-line treatment of FL (*Online Supplementary Table S1*).

Mosunetuzumab

After preclinical studies had demonstrated significant activity of mosunetuzumab in both *in vitro* and *in vivo* lymphoma models,[9] a first-in-human multicenter phase I/Ib dose escalation trial enrolled 238 patients with multiply relapsed B-cell NHL after at least two prior therapies, including 68 with FL, to establish the safety and tolerability of intravenous single-agent mosunetuzumab.[16] Hospitalization for 72 hours was required in all dose escalation cohorts, but was not mandated in the dose expansion cohorts. After testing a fixed dose schedule, cycle (C) 1 step-up dosing, and 11 dose escalation cohorts, C1 step-up dosing was adopted, with the recommended phase II dose (RP2D) schedule set at 1/2/60 mg on days (D) 1, 8, and 15 of C1, followed by 60 mg on C2D1, and 30 mg on D1 of each subsequent 21-day cycle. Patients with a CR discontinued treatment after eight cycles, while those with a partial response or stable disease were allowed to continue treatment for up to 17 cycles.

An international phase II expansion cohort later enrolled 90 patients with R/R FL after two or more prior lines of therapy including an anti-CD20 therapy and an alkylating agent.[17] Patients were heavily pretreated with a median of three prior lines of therapy and more than half (69%) were refractory to the last previous therapy. Fixed-duration mosunetuzumab was given intravenously in 21-day cycles after weekly step-up dosing during C1. The overall response rate (ORR) was 80% with a CR rate (primary endpoint) of 60%. Responses

Table 1. Structure and design of anti-CD20 x anti-CD3 bispecific antibodies.

Agent	Manufacturer	Structure	CD20:CD3 ratio	Anti-CD3 clone	Anti-CD20 clone
Mosunetuzumab	Roche/Genentech	IgG1	1:1	UCHT1v9 (CD3δε)	2H7 (epitope shared with rituximab)
Epcoritamab	AbbVie/Genmab	IgG1	1:1	huCACAO (SP34-der) (CD3ε)	7D8 (epitope shared with ofatumumab)
Odronextamab	Regeneron	IgG4	1:1	REG1250 (CD3δε)	3B9-10 (epitope shared with ofatumumab)
Glofitamab	Roche/Genentech	IgG1	2:1	SP34-der (CD3ε)	By-L1 (epitope shared with obinutuzumab)

Table adapted from Falchi *et al.*[36]

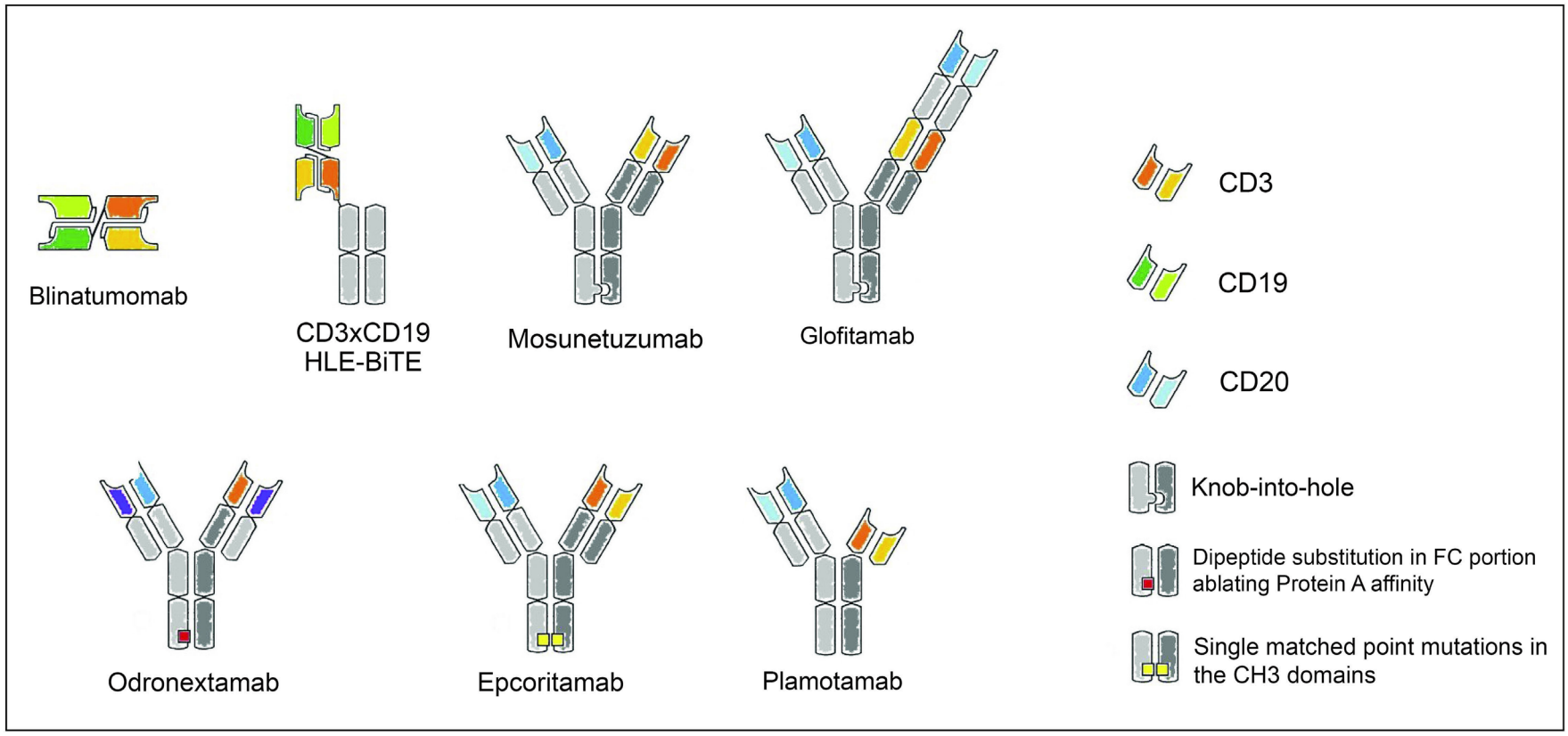

Figure 1. Visual comparison of the structure and design of various bispecific antibodies used for the treatment of B-cell non-Hodgkin lymphoma. Figure reproduced from Lussana F *et al.*, with permission. [38] HLE: half-life extended; BiTE: bispecific T-cell engager; FC: fragment crystallizable region constant; CH3: constant heavy chain 3 region.

Table 2. Efficacy of bispecific antibodies in phase II trials for treatment of patients with relapsed/refractory follicular lymphoma.

Agent	Trial	N of patients	Median follow up in months	Response	Median PFS in months	Median DOR, DoCR in months	Median OS in months
Mosunetuzumab[18]	GO29781 (NCT02500407)	90	37	ORR 80%, CR 60%	24.0	35.9, NR	NR
Epcoritamab[15]	EPCORE NHL-1 (NCT03625037)	128	27	ORR 82%, CR 63%	15.4	NR, NR	NR
Odronextamab[14]	ELM-2 (NCT03888105)	128	20	ORR 80%, CR 73%	20.7	22.6, 25.1	NR
Glofitamab[26]	NP30179 (NCT03075696)	44	13.5	ORR 71%, CR 48%	11.8	10.8	NR

PFS: progression-free survival; DOR: duration of response; DoCR: duration of complete response; OS: overall survival; ORR: overall response rate; CR: complete response; NR: not reported.

were rapid, with a median time to response of 1.4 months and median time to CR of 3.0 months. Responses were seen regardless of age, Follicular Lymphoma International Prognostic Index (FLIPI) score, Ann Arbor stage, number of prior therapies, presence/absence of bulky disease, and whether progression of disease was seen within 24 months (POD24 status) of initial therapy. Follow-up analysis showed that level of CD20 expression and baseline absolute numbers of B cells, T cells, and NK cells also did not influence response.[13] Recently, outcomes after ≥3 years of follow up showed a median progression-free survival of 24 months (43.2% at 36 months) and median overall survival not reached (82.9% at 36 months).[18] The median duration of response was 35.9 months, but was not reached in complete responders. Subgroup analysis confirmed durable remissions in high-risk patients with heavily pretreated R/R FL, age ≥65 years, and POD24. Moreover, measurable residual disease (MRD) analysis at a threshold of $1x10^6$ in patients with CR showed that deep molecular responses occurred quickly. Undetectable MRD was achieved by C4 in most (93%) patients and by all patients by the end of C8.[19] Efforts to identify molecular predictors of response to mosunetuzumab are ongoing. In a small subset of patients in the phase II FL study, whole exome sequencing found similar response rates in patients with mutations in *EZH2*, *TP53*, *BCL2*, *CREBBP*, or *KMT2D*.[20] While initial studies involved intravenous administration, subcutaneous mosunetuzumab has also been evaluated. In a separate cohort of the initial phase I expansion study, subcutaneous mosunetuzumab demonstrated similar single-agent activity compared to the intravenous formulation

in patients with R/R B-cell NHL. In 11 patients with FL, the ORR was 82% (CR rate 64%).[21] High bioavailability (>75%) was also noted. Results of a 90-patient phase II study of subcutaneous mosunetuzumab in R/R FL are pending publication and submission to regulatory authorities to expand the label.

Epcoritamab

Preclinical studies of epcoritamab (DuoBody®-CD3xCD20) demonstrated potent T-cell-mediated cytotoxicity and antitumor activity against malignant B cells *in vitro* and *in vivo*. The *in vitro* potency of epcoritamab was compared to that of four other CD20xCD3 BsAb that were under evaluation, with epcoritamab demonstrating greater T-cell activation and cytotoxicity compared to three of these, and similar potency to the fourth (later identified as glofitamab).[10] Potent activity was also seen against patient-derived DLBCL, FL, and mantle cell lymphoma cell lines.[22] In contrast to the other CD20xCD3 BsAb, epcoritamab was initially developed as a subcutaneous formulation due to delayed and lower peak cytokine levels, potentially reducing the risk of CRS.[10]
The EPCORE NHL-1 trial, a first-in-human multicenter phase I/II study, investigated epcoritamab in patients with R/R B-cell NHL who had received at least two prior lines of therapy (including an anti-CD20 monoclonal antibody and an alkylating agent or lenalidomide).[23] Patients received subcutaneous epcoritamab with step-up dosing during C1. Weekly dosing was given during C1-2, followed by dosing every 2 weeks during C3-6, and then every 4 weeks thereafter until unacceptable toxicity or disease progression. Overall, 68 patients who had received a median of three prior lines of therapy were administered the treatment, and the majority (N=46, 67.6%) had aggressive histologies. Among the patients with FL (N=12), the ORR was 90% (CR, 50%) in patients treated at the RP2D.
In the dose expansion cohorts, 128 patients with R/R FL and a median age of 65 years were enrolled.[15] Patients with high-risk features were represented, including 54% with primary refractory disease. Impressively, the ORR was 82.0% and the CR rate was 62.5%. There were no significant differences in response rates based on age, sex, FLIPI score, or POD24. Modestly lower response rates were observed in patients who had received four or more previous lines of treatment, patients refractory to their last systemic therapy, and those with double refractory disease. With a median follow-up of 17.4 months, the median progression-free survival was 15.4 months, and the median overall survival was not reached. The median time to response was short at 1.4 months. Among patients treated for ten cycles or more, 92% maintained their response at the time of data cutoff. This trial also suggested a role for MRD testing. Rates of progression-free survival were higher among patients with undetectable MRD than in those with MRD. Future efforts to de-escalate or stop treatment based on MRD testing are ongoing.

Odronextamab

ELM-1, a single-arm multicenter phase I dose escalation and dose expansion trial, evaluated intravenous odronextamab in patients with CD20-positive R/R B-cell NHL who had previously received at least one treatment with an anti-CD20 antibody.[24] Patients received step-up split dosing in C1, followed by weekly dosing in C2-4, followed by maintenance therapy given every 2 weeks thereafter until intolerance or disease progression. The primary endpoints of the study were safety and determination of RP2D. Of the 145 patients enrolled, 85 (49%) had DLBCL and 40 (28%) had FL. Patients had received a median of three prior lines of therapy; 82% were refractory to the last line of therapy. Clinical activity was seen across all dose levels and in all NHL subtypes. The ORR and CR rate were 78% and 63%, respectively, in the FL cohort, and 91% and 72%, respectively, in patients who received a dose of 5 mg or higher. The estimated probability of maintaining an ongoing CR at 48 months in patients with FL was 54%.
Subsequently, the pivotal phase II ELM-2 trial enrolled patients with R/R DLBCL and R/R FL.[14] The initial step-up regimen during C1 (1 mg split over D1-2, 20 mg split over D8-9, and the full 80 mg dose on D15) resulted in unacceptable CRS. A modified regimen of 0.7 mg split over D1-2, 4 mg split over D8-9, and 20 mg split over D15-16 essentially eliminated any high-grade CRS. C2 dosing and beyond was 80 mg weekly in C2-4 and every 2 weeks thereafter until intolerance or disease progression. Patients in CR for ≥9 months were allowed to space treatment to every 4 weeks. In the FL cohort, among 128 patients evaluable for efficacy, the ORR was 80% and CR 73%; the probability of maintaining CR for 12 months was 75%. At a median follow-up of 20.1 months, median progression-free survival was 20.7 months, and the median overall survival was not reached. Exploratory analyses looking at the value of detecting circulating tumor DNA have also been conducted. Among 53 FL patients with circulating tumor DNA data available at baseline and following four cycles of treatment, those with undetectable MRD at C4D15 had a significantly longer progression-free survival compared to patients who remained positive (hazard ratio [HR]=0.26, 95% confidence interval [95% CI]: 0.10-0.66).[14] Moreover, among those who achieved a CR according to the findings of interim positron emission tomography/computed tomography scan, a trend for prolonged progression-free survival was observed in those with undetectable MRD (HR=0.29, 95% CI: 0.07-1.1).[25]

Glofitamab

Glofitamab possesses two CD20-binding sites and preclinical studies showed that this BsAb has higher potency than other T-cell redirecting BsAb. One study suggested a 40-fold increase in tumor cell lysis, even in tumors expressing low levels of CD20.[12] After efficacy had been established in animal models, glofitamab was investigated in a first-in-human phase I dose escalation and phase II dose expansion study in

patients with R/R B-cell NHL.[26] All patients received a single dose of obinutuzumab as pretreatment 7 days prior to the first dose of glofitamab in an effort to deplete peripheral and tissue-based B cells and reduce T-cell activation, thus mitigating the risk of CRS. Importantly, this did not appear to decrease the efficacy of the glofitamab.

In the phase I portion, 171 patients were enrolled. They had received a median of three prior lines of therapy and >90% were refractory to a prior line of therapy; 44 (25.7%) of them had FL.[26] The study tested two step-up dosing schedules, and ultimately 2.5/10 mg on C1D1 and C1D8 followed by 30 mg on C2D1 and beyond was selected as the glofitamab RP2D. Patients received a maximum of 12 cycles of glofitamab. While the primary endpoints of this study focused on safety and tolerability, clinical activity was observed at all doses, increasing substantially with dose escalation. In the 44 patients with FL, the ORR was 70.5% (CR, 47.7%) in the overall group and 61.9% (CR, 52.4%) in the 21 patients treated at the RP2D. Glofitamab is approved for R/R large cell lymphoma but plans for development in FL are uncertain, with a single phase II study of glofitamab in frontline treatment of FL ongoing (*Online Supplementary Table S1*).

Safety of bispecific antibodies in follicular lymphoma

Understanding and managing the toxicities of BsAb in FL is a "work in progress" and is confounded by the inclusion of patients with aggressive and indolent histologies in the initial safety trials, potential for unique side effect profiles among the different BsAb products, variable lengths of treatment, conduct of many of the trials during the height of the coronavirus 2019 disease (COVID-19) pandemic, and use of toxicity terms/algorithms developed for chimeric antigen receptor (CAR) T-cell therapy. The bulk of the conversation regarding safety of BsAb in FL should focus on CRS and infection risks, with most other toxicities being less serious or very rare. Across the phase II BsAb trials in FL, CRS was seen in approximately half of patients, although rarely grade ≥3 in severity and with no grade 5 events (Table 3).[13-15] CRS was mitigated in most trials by the use of step-up dosing in C1 and corticosteroid premedication and usually occurred in the first one or two cycles. Neutropenia and infections were common across all products, but more common with agents that were given until progression or intolerance (odronextamab, epcoritamab) than with fixed-duration therapy (mosunetuzumab) (Table 3). Fatal infections, most commonly COVID-related, occurred in the odronextamab and epcoritamab FL trials (Table 4).[14,15] A recent systematic review and meta-analysis of infections in patients with B-cell lymphoma treated with BsAb reported 44% any-grade infections and 20% grade ≥3 infections, and noted highly variable reporting of infection type.[27] Neurotoxicity was uncommon with rare or no serious events in most studies (Table 3). Few patients experienced tumor flare (grade ≥3, less than 3%).[15,17,24,26] Detailed safety data for the phase II studies in FL is described below. Caution should be used when evaluating the attribution of all published BsAb safety data, particularly infections which are nearly uniformly reported as "unrelated" without an accurate method to rule out a contribution from the treatment. It is highly likely that adverse events, other than progressive disease, reported in BsAb studies are at least possibly or probably related to treatment.

Mosunetuzumab

In the 90-patient phase II dose expansion study in R/R FL, the most common adverse events of any grade were CRS (44%), fatigue (37%), and headache (31%).[17] Neutropenia, anemia, and thrombocytopenia occurred in 29%, 13%, and

Table 3. Safety of bispecific antibodies in phase II trials for treatment of patients with relapsed/refractory follicular lymphoma.

Agent	Trial	N of patients	Rate of CRS: any grade (grade ≥3), %	CRS: rates of tocilizumab use, %	Rate of ICANS: any grade (grade ≥3), %	Rate of neutropenia: any grade (grade ≥3), %	Rate of infections: any grade (grade ≥3), %	Treatment discontinuation rate due to adverse events, %
Mosunetuzumab[17]	GO29781 (NCT02500407)	90	44 (2)	8	5 (0)	29 (27)	51 (17)	4
Epcoritamab[15]	EPCORE NHL-1: pivotal cohort	128	66 (2)	24	6 (0)	29 (26)	NA	19
Epcoritamab[15]	EPCORE NHL-1: optimization cohort	86	49 (0)	12	0 (0)	20 (19)	NA	3
Odronextamab[14]	ELM-2 (NCT03888105)	128	56 (4)	17	1 (0)	40 (32)	80 (36)	16
Glofitamab[26]	NP30179 (NCT03075696)	171*	50 (3)	NA	5 (1)	38 (25)	52 (18)	3

*Safety data from a trial not stratified by histology and including all glofitamab cohorts. CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity; NA: not available.

Table 4. Grade 5 (fatal) toxicities in trials of bispecific antibodies.

Agent	Trial	N of patients	Median follow-up in months	N of grade 5 toxicities	N of grade 5 toxicities considered treatment-related	Causes of deaths
Mosunetuzumab[37]	GO29781	90	18.3	8	1	Progressive FL (6), pneumonia (1), pulmonary hemorrhage (1)
Epcoritamab[15]	EPCORE NHL-1	128	17.4	13	0	COVID-19 infection (6), sepsis (1), lymphoma transformation (1), pre-existing MDS (1), interstitial lung disease (1), organizing pneumonia (1), cardiorespiratory failure (1)
Odronextamab[14]	ELM-2	128	20.1	18	4	COVID-19 infection (8), other infection (7), progressive multifocal leukoencephalopathy (1), others not reported (2). Non-COVID-19 infections included pneumonia (3), sepsis (1), systemic mycosis (1), progressive multifocal leukoencephalopathy (1), pseudomonal pneumonia (1), and Escherichia sepsis (1). Treatment-related deaths: pneumonia (1), progressive multifocal leukoencephalopathy (1), Pseudomonal pneumonia (1), and COVID-19 pneumonia + systemic mycosis (1)
Glofitamab	NP30179 (NCT03075696)	171*	13.5	2	0	Gastrointestinal hemorrhage (1), septic shock (1)

*Safety data from a trial not stratified by histology and including all glofitamab cohorts. FL: follicular lymphoma; COVID-19: coronavirus disease 2019; MDS: myelodysplastic syndrome.

10% of patients, respectively. The majority (69%) of patients received growth factor treatment at some point during treatment, although it was not recommended prophylactically. CRS was predominantly low-grade (grade ≥3, 1%), occurred primarily during C1, and most often on D1 and D15; all CRS events resolved with a median duration of 3 days.[17] Common CRS symptoms included fever (98%), hypotension (38%), chills (35%), and headaches (28%). A total of 23% of the patients were admitted to hospital for monitoring and management of CRS. Among patients with CRS, 15% received corticosteroids alone, 8% received tocilizumab alone, and 10% received both corticosteroids and tocilizumab. Neurological events potentially consistent with immune effector cell-associated neurotoxicity syndrome (ICANS) were rare, occurring in 5% of patients, and in all cases were grade 1 or 2. They consisted of confusional state (3%), disturbance in attention (1%), and cognitive disorder (1%).

Grade ≥3 neutropenia occurred in 27% of patients, with no febrile neutropenia. Grade ≥3 serious infections occurred in 14% of patients. Grade ≥3 hypophosphatemia was observed in 17% of patients with no clinical significance. One patient experienced grade 5 (fatal) toxicities not related to progression. Treatment was stopped in four (4%) patients due to toxicities, although these were considered unrelated to mosunetuzumab. Adverse event rates were similar in patients regardless of age and tumor burden.

Epcoritamab

The FL dose expansion cohort of the EPCORE-NHL-1 trial enrolled 128 patients who were treated with a 0.16 mg priming dose on C1D1 and a 0.8 mg intermediate dose on C1D8 followed by 48 mg for all subsequent doses (described as the "pivotal cohort").[15] Patients were hospitalized for 24 hours after the first full dose for monitoring of CRS. An additional 86 patients, the "optimization cohort", received an additional 3 mg intermediate dose on C1D15 in an effort to reduce the incidence and severity of CRS; hospitalization was not required for this cohort. Patients in the pivotal cohort received intravenous prednisolone 100 mg (or equivalent) for 4 days with each C1 dose and the optimization cohort received dexamethasone 15 mg for 4 days with each C1 dose.

In the pivotal cohort, CRS occurred in 66% of patients (40% grade 1, 25% grade 2, and 2% grade 3, with no grade 4-5 cases). In 60% of cases, CRS occurred after the first dose with a median time to onset of 15.3 hours. For management, 24% and 13% of patients received treatment with tocilizumab and corticosteroids, respectively. All cases resolved, and no patients required treatment discontinuation due to CRS. In the optimization cohort, CRS occurred in 49% of patients (40% grade 1 and 9% grade 2); 12% and 13% required tocilizumab and steroids, respectively. ICANS occurred in 6% of patients in the pivotal cohort, all grades 1-2 with a

median onset of 3.5 days and median duration of 2 days. No ICANS occurred in the optimization cohort, perhaps due to the use of dexamethasone instead of prednisolone. Other common toxicities included injection-site reaction (57%), COVID-19 infection (40%), and fatigue (30%). Neutropenia was seen in 28% of patients and, overall, 18% required treatment with growth factor. Febrile neutropenia was rare (3%). Due to adverse events, treatment had to be discontinued in 19% of patients, including 13% for infection. Grade 5 (fatal) adverse events occurred in 13 patients (10.1%); six patients died from COVID-19.

Odronextamab

In the single-arm dose escalation ELM-1 trial, patients received intravenous odronextamab with step-up dosing in C1.[24] Overall, no dose-limiting toxicities were observed, a maximum tolerated dose was not reached, and odronextamab was safely administered up to the maximum dose of 320 mg once per week. The treatment in the phase II ELM-2 study was weekly dosing for 12 weeks (0.7/4/20 mg during C1, 80 mg during C2-4) followed by a maintenance dose of 160 mg every 2 weeks from C5 onwards.[14] Hospitalization was mandated for 24 hours after each infusion during C1 and C2. Results for the 128 patients evaluable for safety in the FL expansion cohort showed that 92.2% of patients experienced treatment-related adverse events, including 64.1% with grade ≥3 adverse events. Twenty (16%) patients had treatment-related adverse events leading to treatment discontinuation. While on study, 18 (14.8%) patients experienced grade 5 (fatal) toxicities, although only four (3.1%) were attributed to odronextamab, all due to infection.

CRS was experienced by over half (56.7%) of patients. Nevertheless, all but one case (1.7%) were grade 1 or 2. CRS occurred after a median of 20 hours, typically lasted 2 days, and resolved with supportive measures (tocilizumab in 17% and corticosteroids in 33% of patients).

Infection while on treatment was extremely common, occurring in nearly 80% of patients. Of these infections, 42.0% were grade 3 or higher. Over one-third (36.7%) of patients developed a COVID-19 infection while on treatment, including eight patients (6.3%) who died from this infection. Several non-COVID fatal infections were also reported.

Management of bispecific antibody toxicities

Recently, an international panel consisting of academic and community physicians, advanced practitioners, registered nurses, and pharmacists convened to provide consensus-based guidelines to help clinicians safely manage BsAb-related toxicities.[28] They highlighted logistical considerations to be in place prior to treatment with BsAb in terms of treatment facility, personnel, patient resources, and patient and caregiver information.

All patients receiving treatment with a BsAb should be educated regarding signs and symptoms of CRS and be able to engage in self-monitoring of vital signs. They should have access to a thermometer, and should also be provided with a prescription for oral dexamethasone to use as needed in the event of CRS after discussion with the treatment team. While most treatment can be delivered in an outpatient setting, depending on geographic distance from the treatment center, hospitalization for 24 hours with the first full dose can be considered. Close collaboration with hospital administrative staff, pharmacy personnel, emergency medicine providers, and inpatient providers is essential to ensure that at least two doses of tocilizumab are available at a nearby hospital. Other providers should be familiar with identification and management of CRS, with Intensive Care Unit-level of care available if needed.

Management of CRS according to severity is highlighted in Table 5. Given very low rates of ICANS-like neurotoxicity, unlike in CD19-directed CAR T-cell therapy, regular neurological assessments and driving restrictions are not required in the vast majority of cases. Regarding cytopenias, growth factor support can be considered for patients who develop neutropenia while on treatment. In the event of active infection, the BsAb should be withheld until the infection clears. Most patients are heavily pretreated and therefore prophylaxis against varicella-zoster virus is recommended. *Pneumocystis jirovecii* pneumonia prophylaxis should be considered for all patients, particularly with epcoritamab and odronextamab, due to frequent steroid use and indefinite treatment.[28] Hypogammaglobulinemia is common and immunoglobulin levels should be monitored and, if low, should be replaced in patients with infections.

Selection of agents

Currently, in the United States, providers have the option to select mosunetuzumab or epcoritamab for third-line or later treatment of R/R FL; odronextamab approval was initially denied by regulatory authorities, but will be readdressed once confirmatory trials have adequate accrual. The European Medicines Agency recently approved odronextamab for treatment of adult patients with FL or DLBCL who have received at least two prior lines of systemic therapy. Efficacy is similar for all agents with high ORR and CR rates (Table 2), and comparable response duration with early follow-up. Toxicities are also relatively comparable (Table 3), with CRS seen in approximately half of patients, but predominantly grades 1-2, transient, and occurring during C1. No specific predictive factors have been associated with a higher risk of developing CRS. Neurotoxicity is rare across all CD20xCD3 BsAb.

Despite similarities in design, unique properties of each agent may help guide treatment selection. Key differences, including treatment duration, route of administration, and protocol for CRS mitigation, are highlighted in Table 6. Mosunetuzumab,

compared to epcoritamab and odronextamab, is currently the only fixed-duration treatment option (eight 21-day cycles in patients achieving CR), which may appeal to patients and providers in terms of convenience, as well as a reduced risk of infection compared to indefinite treatment approaches. In the future, MRD testing for response assessment may affect decisions regarding the duration of treatment, although more data are needed before this strategy can be used in clinical practice.

Apart from treatment duration, another important distinguishing factor between agents is the route of administration. Epcoritamab is administered subcutaneously, and subcutaneous formulations are also under study for both mosunetuzumab and odronextamab. In terms of toxicity profiles, both routes have similar adverse effects, apart from frequent mild injection-site reactions with the subcutaneous administration. Subcutaneous injections are advantageous in terms of reducing cost and resource strain on infusion centers. Finally, dosing schedule (Table 4) should be considered, with much more frequent administration during the first 4-6 cycles with epcoritamab and odronextamab compared to mosunetuzumab.

Use of corticosteroids has short- and long-term toxicities, and thus dosing and duration of corticosteroid prophylaxis should be weighed, as different agents had varying CRS mitigation protocols in their trials. For mosunetuzumab, patients received prophylactic corticosteroids with dexamethasone 20 mg prior to all treatments during C1-C2 (4 doses total, prednisone equivalence of 533.3 mg). In contrast, in the EPCORE-NHL-1 trial of epcoritamab, prednisolone 100 mg was given prior to each treatment during C1 and continued for a total of 4 days (16 doses in total, prednisone equivalence of 1,600 mg). Corticosteroid exposure was also high with odronextamab. In the ELM-1 and ELM-2 trials, patients received prophylactic dexamethasone 20 mg on the day before, the day of, and the day after each treatment during C1 and on C2D1 (15 doses in total, prednisone equivalence of 2,000 mg). While cross-trial comparisons of toxicity are fraught with many limitations, given similar rates of CRS across agents, those minimizing exposure to corticosteroids may be preferred.

A significant difference in grade 5 (fatal) adverse events between mosunetuzumab, epcoritamab, and odronextamab was seen in the key FL trials. These are detailed in Table 4. Specifically, in the EPCORE-NHL-1 trial (N=128), 13 patients experienced grade 5 (fatal) adverse events, six of which were secondary to COVID-19 infection. Close to half (40%) of patients overall were infected by COVID-19.[15] Similarly, in the ELM-2 trial studying odronextamab (N=128), 20 patients (14.8%) experienced grade 5 (fatal) adverse events, eight of which were secondary to COVID-19 infection.[14] These high death rates are in contrast to those in the mosunetuzumab trial (N=90), in which only one treatment-related death due to infection was seen (none due to COVID-19 infection).[17] This is likely in part due to accrual being nearly complete before the onset of the pandemic. Thus, to some extent, adverse events must be considered through the lens of the global pandemic. Real-world safety data of these agents after the pandemic will be useful.

Sequencing and future directions

The aforementioned phase II trials investigated various BsAb for R/R FL after two or more lines of systemic therapy. On-

Table 5. Diagnosis and management of cytokine release syndrome.

Grade and definition	Management
Grade 1: Fever of ≥100.4°F with/without constitutional symptoms requiring symptomatic treatment; no hypotension or hypoxia	Acetaminophen 650-1,000 mg orally If refractory or recurrent fever (<6-8 h) consider dexamethasone 10 mg once Early in-person evaluation (especially in patients with multiple disease risk factors/comorbidities)
Grade 2: Fever of ≥100.4°F with either hypotension not requiring vasopressors and/or hypoxia managed with supplemental low-flow oxygen	Acetaminophen 650-1,000 mg orally, up to 3-4 times daily Dexamethasone 10 mg every 12 h IV fluids and supplemental oxygen as appropriate Tocilizumab if symptoms persist or if clinically unstable
Grade 3: Fever of ≥100.4°F with either hypotension (BP <90/60 or <10 mmHg below, not responsive to fluids) and/or hypoxia requiring high-flow nasal canula, face mask, or Venturi mask)	Inpatient admission (floor *versus* ICU) Acetaminophen 1,000 mg orally, up to 3-4 times daily Dexamethasone 10 mg every 6 h until resolution to grade ≤1, followed by taper Tocilizumab 8 mg/kg IV Consider empiric antibiotics
Grade 4: Fever of ≥100.4°F with life-threatening consequences requiring urgent intervention (e.g., multiple vasopressors, positive pressure respiratory support, mechanical ventilation)	Inpatient admission to the ICU Acetaminophen 1,000 mg orally, up to 3-4 times daily Dexamethasone 20 mg every 6 h until resolution to grade ≤1, followed by taper Tocilizumab 8 mg/kg IV. Consider anakinra or siltuximab if unresponsive to maximal dosing of tocilizumab

Adapted from Crombie JL *et al.*[28] F: Fahrenheit; IV: intravenous; ICU: intensive care unit; BP: blood pressure.

Table 6. Differences in bispecific antibody products based on route of administration, treatment duration, dosing schedules, and premedication regimens.

Agent	Route of administration	Treatment duration	Dosing schedule	Steroid prophylaxis
Mosunetuzumab	Intravenous (approved) Subcutaneous (pending)	Fixed-duration (total of 8 cycles if CR, 17 cycles if PR on interim PET)	21-day cycles: Cycle 1: D1/8/15 Cycles 2-8: D1 Cycles 9-17 (if PR): D1	Dexamethasone 20 mg or MP 80 mg prior to all doses during cycles 1-2
Epcoritamab	Subcutaneous	Indefinite until disease progression or intolerance	28-day cycles: Cycles 1-3: D1/8/15/22 Cycles 4-9: D1/15 Cycles 10+: D1	Prednisolone 100 mg prior to all doses during cycle 1
Odronextamab	Intravenous Subcutaneous	Indefinite until disease progression or intolerance	21-day cycles: Cycle 1: D1/2/8/9/15/16 Cycles 2-4: D1/8/15 Cycles 5+: every 2 weeks	Dexamethasone 20 mg on the day before, of, and after all doses during cycle 1 and for cycle 2 D1 dose
Glofitamab	Intravenous	Fixed-duration (12 total cycles)	21-day cycles: Cycle 1: D1 (obinutuzumab alone)/8/15 Cycle 2+: D1	MP 80 mg prior to each dose

CR: complete response; PR: partial response; PET: positron emission tomography; D: day; MP: methylprednisolone.

going clinical trials are studying the use of BsAb in earlier lines, including in the frontline setting (*Online Supplementary Table S1*). For example, subcutaneous mosunetuzumab monotherapy is currently being studied in an ongoing single-center phase II trial in patients with previously untreated FL or marginal zone lymphoma. A pre-planned interim efficacy analysis in 21 patients revealed a 100% ORR (CR, 83%) and no grade ≥2 CRS was observed.[29] Another small phase II study of subcutaneous mosunetuzumab in previously untreated patients with high tumor-burden FL documented an ORR of 96% and a CR rate of 81% in 26 patients.[30] Moreover, while the pivotal trials investigated monotherapy, a number of ongoing trials are also investigating BsAb in combination with chemoimmunotherapy. Questions remain regarding proper sequencing of the administration of BsAb, specifically relating to CAR T-cell therapy. In 2021, a CD19-directed CAR T-cell product, axicabtagene ciloleucel, was granted accelerated approval by the Food and Drug Administration for treatment of adult patients with R/R FL after two or more prior lines of systemic therapy based on results from the phase II ZUMA-5 trial.[31] More recently, a second CD19-directed CAR T-cell product, lisocabtagene maraleucel, was also approved for adults with R/R FL who have received two or more prior lines of systemic therapy, based on results from the TRANSCEND-FL trial.[32] Notably, neither of the trials reported on prior BsAb exposure and its effect on results. CAR T-cell therapy in large B-cell lymphomas has been demonstrated to have similar efficacy in patients who had or had not been previously exposed to BsAb treatment.[33] For now, we favor use of BsAb, specifically fixed-duration mosunetuzumab, over CAR T-cell therapy in R/R FL given the ease of administration and improved toxicity profile. Major barriers remain in place limiting widespread adoption of CAR T-cell therapy for this indication, including cost, logistical challenges, the potential for significant treatment-related toxicities (CRS, neurotoxicity, prolonged cytopenias), manufacturing time, and resistance mechanisms. Furthermore, emerging data suggest the possibility of an elevated risk of secondary malignancies after CAR T-cell therapy, although further long-term follow-up data are needed.[34,35]

Conclusions

BsAb represent a significant therapeutic advance for FL, with clinical trials suggesting strong efficacy and a manageable safety profile. Efforts are underway to study BsAb in earlier treatment lines and in combination with other agents with which they may possess synergy. Phase III combination trials are ongoing investigating the use of mosunetuzumab, epcoritamab, and odronextamab in patients with FL. Optimization of schedules and treatment duration with evaluation of fixed-duration therapy and retreatment at relapse is needed for all BsAb with FL applications. While the treatment landscape for FL continues to expand, BsAb are likely to remain a cornerstone of treatment with potential applications in first line and beyond.

Disclosures

NLB has served as a consultant for Roche Genentech. IAN has no conflicts of interest to disclose.

Contributions

Both IAN and NLB drafted the manuscript, revised it, and approved the final version.

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