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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 of 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 two 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 (BsAbs), 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 BsAbs 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) follicular lymphoma (FL); mosunetuzumab and odronextamab also have approval in Europe. Broader indications, including earlier lines of therapy in FL, are under active investigation. This review will highlight the available efficacy and safety data of BsAbs for FL, explore how they are being incorporated into the current treatment landscape, and discuss 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 development of BsAbs can largely be divided into two classes: IgG-like subtypes which contain a fragment crystallizable (Fc) region versus 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 BsAbs, 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 BsAbs, such as through binding to human serum albumin, have been encouraging.[4] Other elements differentiating BsAbs 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 treatment of lymphoma. Focus shifted towards CD20xCD3 BsAbs with IgG-like structures to address the half-life concerns of blinatumomab.[8] There are now three (mosunetuzumab, glofitamab, epcoritamab) approved CD20xCD3 BsAbs 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 mAb SP34 and human anti-CD20 mAb 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 BsAbs, 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 higher target binding capacity, designed to increase efficacy, likely increases the risk of cytokine release syndrome. The modified Fc domain in glofitamab does not allow for FcγR or complement binding. Figure 1 shows the structure of various BsAbs developed for B cell non-Hodgkin lymphoma (NHL).

Efficacy of Bispecific Antibodies in Follicular Lymphoma

Phase II studies of BsAbs 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 CRs appear durable at two years.[13-15] and limited retreatment data in mosunetuzumab show responses occurring in patients relapsing after CR.[13] These encouraging data have resulted in BsAbs 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 (Supplementary Table S1).

Mosunetuzumab

After preclinical studies demonstrated significant activity of mosunetuzumab 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 1 step-up dosing, and 11 dose escalation cohorts, cycle 1 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 cycle (C) 1, followed by 60 mg on C2D1, and 30 mg D1 of each subsequent 21-day cycle. Patients with CR discontinued treatment after 8 cycles, while those with partial response (PR) or stable disease (SD) 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 2 or more prior lines of therapy including an anti-CD20 therapy and an alkylating agent.[17] Patients were heavily pretreated with a median of 3 prior lines of therapy and over half (69%) refractory to 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 CR rate (primary endpoint) of 60%. Responses 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, 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 number 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] Median duration of response was 35.9 months, but 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 1 x 10^6 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 initially studied with intravenous administration, subcutaneous mosunetuzumab has also been evaluated. In a separate cohort of the initial phase I expansion, 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*. Epcoritamab potency *in vitro* was compared to four other CD20xCD3 BsAbs 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 BsAbs, it 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 at least 2 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 with a median of 3 prior lines of therapy received treatment, and the majority (n=46, 67.6%) had aggressive histologies. For patients with FL (n=12), ORR was 90% (CR 50%) in patients treated at the R2PD.

In the dose expansion cohorts, 128 patients with R/R FL were enrolled with a median age of 65.[15] Patients with high-risk features were represented, including 54% with primary refractory disease. Impressively, ORR was 82.0% and CR rate 62.5%. There was no significant difference in response rates based on age, sex, FLIPI score, or POD24. Modestly lower response rates were observed in patients with 4 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 PFS was 15.4 months, and the median OS was not reached. Median time to response was rapid at 1.4 months. Among those treated for 10 cycles or more, 92% maintained response at the time of data cutoff. This trial also suggested a role for MRD testing. Among patients with undetectable (u)MRD, rates of progression-free survival were higher compared to patients with MRD. Future efforts to de-escalate or stop treatment based on MRD testing are ongoing.

Odronextamab

ELM-1, a single-arm multi-center 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 endpoint of the study was safety and determination of R2PD. Of the 145 patients enrolled, 85 (49%) had DLBCL and 40 (28%) had FL. Patients had a median of 3 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. In the FL cohort, ORR was 78% and CR 63%, and in patients who received a dose of 5 mg or higher 91% and 72%, respectively. 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 ≥9 months were allowed to space treatment to every 4 weeks. In the FL cohort, of 128 efficacy evaluable patients, 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 PFS was 20.7 months, and median OS was not reached. Exploratory analyses looking at ctDNA detection have also been conducted. Among 53 FL patients with ctDNA data available at baseline and following 4 cycles of treatment, those with uMRD at

C4D15 had a significantly longer PFS compared to patients who remained positive (HR 0.26 [95% CI 0.10–0.66]).[14] Moreover, in those who achieved a complete response on interim PET/CT scan, a trend for prolonged PFS was observed in those with uMRD (HR 0.29 [95% CI 0.07-1.1]).[25]

Glofitamab

As glofitamab possesses two CD20 binding sites, preclinical studies showed higher potency than other T-cell redirecting BsAbs. One study suggested a 40-fold increase in tumor cell lysis, even in tumors expressing low levels of CD20.[12] After efficacy was 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 cytokine release syndrome (CRS). Importantly, this did not appear to decrease the efficacy of the glofitamab.

In the phase I portion, 171 patients were enrolled with a median of 3 prior lines of therapy and >90% refractory to a prior line of therapy; of these, 44 (25.7%) had follicular lymphoma.[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 R2PD. 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 follicular lymphoma, ORR was 70.5% (CR 47.7%) in the overall group and ORR 61.9% (CR 52.4%) in the 21 patients treated at the

R2PD. 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 (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 COVID pandemic, and use of toxicity terms/algorithms developed for CAR-T cell therapy. The bulk of the conversation regarding safety of BsAbs in FL should focus on CRS and infection risks, with most other toxicities being less serious or very rare. Across the phase II BsAbs trials in FL, CRS was seen in approximately half of patients, although rarely grade ≥3 in severity and no grade 5 events (Table 3).[13-15] CRS was mitigated in most trials with the use of step-up dosing in C1 and use of corticosteroid premedication and usually occurred in the first 1-2 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, mostly commonly COVID-related, occurred on 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 BsAbs reported 44% all 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 experience tumor flare (grades ≥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 on 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 cytokine release syndrome (44%), fatigue (37%), and headache (31%).[17] Neutropenia, anemia, and thrombocytopenia occurred in 29%, 13%, and 10% of patients, respectively. The majority (69%) of patients received growth factor treatment at some point during treatment, although was not recommended prophylactically.

CRS was predominantly low-grade (grade ≥3, 1%), occurred primarily during C1, and most often on D1 and 15; 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 patients were admitted to the hospital for monitoring and management of CRS. Among patients with CRS, 15% received corticosteroids alone, 8% received tocilizumab alone, 10% received both corticosteroids and tocilizumab. Neurologic events potentially consistent with immune effector cell-associated neurotoxicity syndrome (ICANS) were rare, occurring in 5% of patients and all grades 1-2. This 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, 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 cytokine release syndrome. An additional 86 patient "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). 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 grade 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 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 18% required treatment with growth factor overall. Febrile neutropenia was rare (3%).Due to adverse events, 19% of patients required treatment discontinuation, including 13% for infection. Grade 5 (fatal) adverse events occurred in 13 patients (10.1%); 6 patients died from COVID-19.

Odronextamab

In the single-arm dose escalation ELM-1 trial, patients received intravenous odronextamab with step-up dosing in cycle 1.[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 phase 2 ELM-2 study prescribed weekly dosing for 12 weeks (0.7/4/20 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 safety-evaluable patients in the FL expansion cohort showed that 92.2% of patients experienced treatment-related adverse events, including 64.1% ≥grade 3. 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 4 (3.1%) were attributed to odronextamab, all due to infection.

CRS was experienced by over half (56.7%) of patients. Nevertheless, all but 1 case (1.7%) were grades 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, 42.0% were grades 3 or higher. Over one-third (36.7%) of patients developed

a COVID-19 infection while on treatment, including 8 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 BsAbs should be educated regarding signs and symptoms of CRS and be able to engage in vital sign self-monitoring. 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 treatment center, hospitalization for 24 hours with the first full dose can be considered. Close collaboration with hospital administrative staff, pharmacy, 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 ICU-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 neurologic 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 held until the infection clears. Most patients are heavily pretreated and therefore prophylaxis against varicella-zoster 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 replaced if low 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 2 prior lines of systemic therapy. Efficacy is similar for all agents with high overall and complete response rates (Table 2), with comparable response duration with early follow-up. Similarly, toxicities are also relatively comparable (Table 3), with CRS seen in approximately half of patients, but predominantly grades 1-2, transient, and occurring during cycle 1. No specific predictive factors have been associated with higher risk of developing CRS. Neurotoxicity is rare across all CD20xCD3 BsAbs.

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 treatment duration decisions, although more data are needed before this can be used in 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 cycles 1-2 (4 doses total, prednisone equivalence of 533.3 mg). In contrast, in the EPCORE-NHL-1 trial for epcoritamab, prednisolone 100 mg was given prior to each treatment during cycle 1 and continued for 4 days total (16 doses total, prednisone equivalence of 1600 mg). Similarly, 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 cycle 1 and on day 1 of cycle 2 (15 doses total, prednisone equivalence of 2000 mg). While cross-trial comparisons for 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, 6 of these being 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, 8 of these being secondary to COVID-19 infection.[14] The high death rates are in contrast to 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 follicular lymphoma after two or more lines of systemic therapy. Ongoing clinical trials are studying the use of BsAb in earlier lines, including in the frontline setting (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. Pre-planned interim efficacy analysis in 21 patients revealed a 100% ORR (83% CR) and no grade ≥2 CRS was observed.[29] Another small phase II study of subcutaneous mosunetuzumab in previously untreated high tumor-burden FL reported ORR 96% and CR 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 BsAbs, specifically relating to CAR T-cell therapy. In 2021, a CD19-directed CAR T-cell product, axicabtagene ciloleucel, was granted accelerated approval by the FDA for treatment of adult patients with R/R FL after 2 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 effect on results. CAR T-cell therapy in large B-cell lymphomas have been demonstrated to have similar efficacy with or without prior BsAb exposure.[33] For now, we favor use of BsAb, specifically fixed-duration mosunetuzumab over CAR T-cell therapy in R/R FL given 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 suggests the possibility of an elevated risk of secondary malignancies after CAR T-cell therapy, although further long-term follow-up data is warranted.[34, 35]

Conclusions

BsAbs represent a significant therapeutic advance for FL, with clinical trials suggesting strong efficacy and a manageable safety profile. Efforts are underway to study BsAbs in earlier treatment lines and in combination with other agents that may possess synergy. Phase III

combination trials are ongoing for use of mosunetuzumab, epcoritamab, and odronextamab in patients with FL. Optimization of schedule and treatment duration with evaluation of fixed duration therapy and retreatment at relapse is needed for all BsAbs with FL applications. While the treatment landscape for follicular lymphoma continues to expand, BsAbs are likely to remain a cornerstone of treatment with potential applications in first line and beyond.

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Table 1. Structure and design of anti-CD20 x anti-CD3 BsAbs. Table adapted from Falchi et al.[36]

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

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

Agent	Trial	N	Median Follow Up (mo)	Response	Median PFS (mo)	Median DOR, DoCR (mo)	Median OS (mo)
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

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

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

Agent	Trial	N	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 in trial not stratified by histology and includes all glofitamab cohorts

CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity; NA: not available

Table 4. Grade 5 (fatal) toxicities on BsAb trials.

Agent	Trial	N	Median follow-up (mo)	Number of grade 5 toxicities	Number 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 in trial not stratified by histology and includes all glofitamab cohorts
FL: follicular lymphoma; MDS: myelodysplastic syndrome

Table 5. Cytokine release syndrome diagnosis and management. Adapted from Crombie JL, et al. [28]

Grade and definition	Management
Grade 1: Fever of ≥100.4°F with/without constitutional symptoms requiring symptomatic treatment; no hypotension or hypoxia	- Acetaminophen 650-1000 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 650-1000 mg orally, up to 3-4 times daily - Dexamethasone 10 mg every 12 hours - 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 mm Hg below, not responsive to fluids) and/or hypoxia requiring high-flow nasal canula, face mask, or venturi mask)	- Inpatient admission (floor versus ICU) - Acetaminophen 1000 mg orally, up to 3-4 daily - Dexamethasone 10 mg every 6 hours until resolution to grade ≤1, followed by taper - Tocilizumab 8 mg/kg intravenously - 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 1000 mg orally, up to 3-4 daily - Dexamethasone 20 mg every 6 hours until resolution to grade ≤1, followed by taper - Tocilizumab 8 mg/kg intravenously. Consider anakinra or siltuximab if unresponsive to maximal dosing of tocilizumab

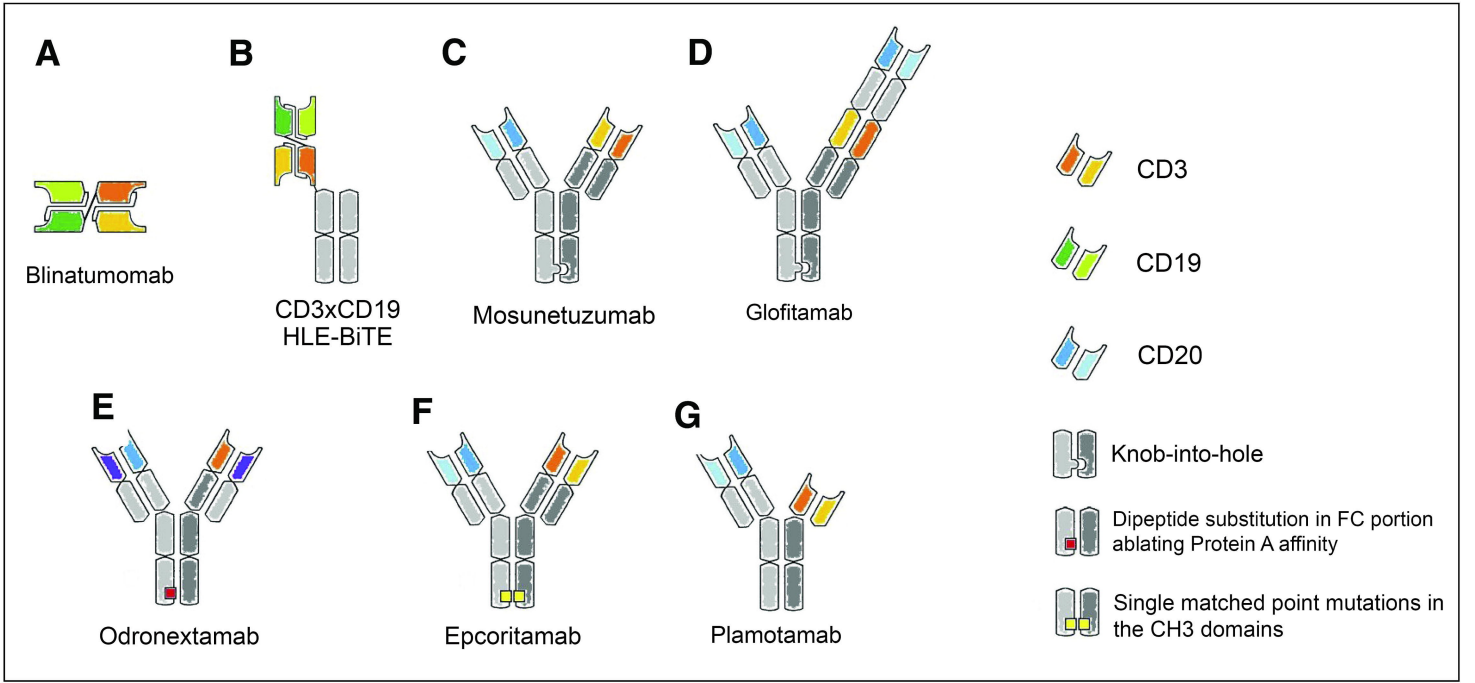
BP: blood pressure; F: Fahrenheit; ICU: intensive care unit; IV: intravenous

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 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 day 1 dose
Glofitamab	Intravenous	Fixed-duration (12 total cycles)	21-day cycles: Cycle 1: D1 (obinutuzmab alone)/8/15 Cycle 2+: D1	MP 80 mg prior to each dose

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

Figure 1. Visual comparison of structure and design of various bispecific antibodies used for treatment of B-cell NHL. Figure obtained from Lussana F, et al. [38]


A
Blinatumomab
B
CD3xCD19
HLE-BiTE
C
Mosunetuzumab
D
Glofitamab
CD3
CD19
CD20
E
Odronextamab
F
Epcoritamab
G
Plamotamab
Knob-into-hole
Dipeptide substitution in FC portion ablating Protein A affinity
Single matched point mutations in the CH3 domains

Supplementary Table S1. Ongoing trials investigating bispecific antibodies in follicular lymphoma.

Treatment	Trial	Phase	Duration of Treatment	Notes
CD3-CD20 Bispecific Antibodies: Frontline Therapy				
Rituximab vs. mosunetuzumab	NCT06337318	III	21-day cycles up to 8 cycles	- Enrolling patients with low tumor burden
Mosunetuzumab vs. investigator choice chemoimmunotherapy	NCT06284122	III	Induction: 28-day cycles up to 12 cycles Maintenance: 8-week cycles up to 9 cycles	- 21-day cycle for cycle 1 - Enrolling patients with FLIPI 2-5
Odronextamab vs. chemoimmunotherapy (R-CHOP, BR, R-CVP)	OLYMPIA-1 (NCT06091254)	III	21-day cycles for 6 cycles, followed by maintenance	
Odronextamab + chemotherapy + maintenance vs. rituximab + chemotherapy +/- maintenance	OLYMPIA-2 (NCT06097364)	III	21-day cycles for 6 cycles, followed by maintenance	
Lenalidomide + epcoritamab	NCT06112847	II	28-day cycles up to 12 cycles	
Tazemetostat + mosunetuzumab	NCT05994235	II	28-day cycles up to 12 cycles	
Epcoritamab + rituximab	NCT05783609	II	28-day cycles up to 9 cycles	- 6-week cycle for cycle 1

Mosunetuzumab + polatuzumab vedotin	NCT05410418	II	21-day cycles up to 8 cycles (if CR) or 17 cycles (if PR/SD after C8)	-
Mosunetuzumab	NCT05389293	II	21-day cycles up to 8 cycles (if CR) or 17 cycles (if PR/SD after C8)	
Mosunetuzumab +/- lenalidomide	BrUOG-401 (NCT04792502)	II	21-day cycles for 4 cycles followed by response assessment. If CR, 4 additional cycles of mosunetuzumab. If PR, 4 additional cycles with addition of lenalidomide. If persistent PR after C8, 4 additional cycles with addition of lenalidomide	- MZL also eligible
Mosunetuzumab +/- polatuzumab vedotin and obinutuzumab	NCT05169658	II	Part A: 21-day cycles up to 8 cycles Part B: 21-day cycles for 6 cycles	- Patients without CR after Part A proceed to Part B (addition of polatuzumab vedotin and Obinutuzumab) - MZL also eligible
Obinutuzumab + glofitamab	NCT05783596	II	21-day cycles up to 12 cycles	- 36-day cycle for cycle 1 - MZL also eligible
CD3-CD20 Bispecific Antibodies: Relapsed/Refractory Disease				
Mosunetuzumab + lenalidomide vs.	CELESTIMO (NCT04712097)	III	28-day cycles up to 12 cycles	

rituximab + lenalidomide				
Epcoritamab + rituximab/lenalidomide (R2)	EPCORE FL-1 (NCT05409066)	III	28-day cycles up to 12 cycles	
Odronextamab + lenalidomide vs. rituximab/lenalidomide (R2)	OLYMPIA-5 (NCT06149286)	III	21-day cycles up to 12 cycles	
Epcoritamab + lenalidomide vs. investigator choice	REFRACT (NCT05848765)	II	28-day cycles up to 12 cycles	- Investigational agents for rounds 2 and 3 not yet selected
Mosunetuzumab	MERLIN (NCT05849857)	II	21-day cycles up to 8 cycles (if CR) or 17 cycles (if PR/SD after C8)	- Enrolling patients with POD24
CD3-CD20 Bispecific Antibodies: Any Line of Treatment				
Mosunetuzumab + lenalidomide	NCT04246086	Ib/II	28-day cycles up to 12 cycles	- 21-day cycle for cycle 1 - Arms testing IV vs SC formulation
Other Bispecific Antibodies: Relapsed/Refractory Disease				
Lenalidomide + blinatumomab	NCT02568553	I	Induction: Blinatumomab D1-56 Consolidation: Blinatumomab D1-7 in 28-day cycles for 6 cycles Maintenance: No blinatumomab	- Enrolling patients with R/R B-cell NHL

C: cycle; CR: complete response; D: day; FLIPI: Follicular Lymphoma; IPI: International Prognostic Index; IV: intravenous; MZL: marginal zone lymphoma; NHL: non-Hodgkin lymphoma; POD24: progression of disease within 24 months; PR: partial response; R/R: relapsed/refractory; SC: subcutaneous; SD: stable disease