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**New bispecific antibodies in diffuse large B-cell lymphoma**

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**Running head.** Bispecific antibodies for DLBCL

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**Abstract**:

The 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 thirty 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 randomised 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, odronextamab in Europe for relapsed diffuse large B-cell lymphoma (DLBCL) signals 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 CAR-T cell treatments are either unavailable or ineffective. Bispecific antibodies 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. BsAbs 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 BsAbs as treatments for DLBCL, the clinical data resulting in their approvals in relapsed and refractory (R/R) 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 BsAbs are a significant optimisation of the smaller molecule T-cell engaging (TCE) 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, tumour-associated antigen (TAA) -independent activation, and fratricide through ADCC/CDC-mediated destruction of effector T-cells. Modifications to the Fc region mitigate these concerns and are a feature of all the BsAbs 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 other BsAbs.

*Pharmacodynamics, pharmacokinetics and route of delivery*

Unlike the experience with non-TCE-antibodies, the relationship between antigen expression and cytotoxicity induced by the BsAbs 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 tumour 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 BsAbs appears determined by the unique physiochemical properties of the molecule itself, and in particular the spatial properties of the TAA-binding arm.

When administered intravenously, the time to peak concentration of BsAbs 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 7-17 fold lower, while the area under the curve was comparable to IV.[6] In phase I study data, this translated to a peak concentration of epcoritamab using SC dosing at 2.8 days.[3]

**Phase I observations**

The early phase studies of BsAbs included patients with a spectrum of indolent and aggressive R/R B-NHL subtypes, with subsequent expansion cohorts focussing on patients with specific subtypes of lymphoma. Across the agents, the initial frequency of dosing of the BsAbs varied from weekly to monthly, and in 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.*

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

Epcoritamab and odronextamab began phase I 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 600mcg reliably induced clinically meaningful response, and flat dosing up to 25mg was possible with obinutuzumab pre-

treatment, but CRS reliably increased at each dose level and was considered unacceptable at 25mg. The 3-step-up dosing strategy (2.5mg, 10mg, 30mg 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 4mcg leading into the initial evaluated target dose of 12.8mcg. The first clinical response occurred at 120mcg.[14] The recommended phase II dose was supported by a PK/PD model used to forecast optimal trimer formation, which was predicted to occur between 48-96mg.[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 two 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 80mg or higher, which was achieved safely with the additional step-up doses.

While step-up dosing is used in 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 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 comprising step-up dosing on days 1, 3 and 8 had acceptable rates of CRS (G1-2 in 13.5%).[16]

*Steroid timing and choice is important for optimising CRS mitigation, and likely impacts other toxicities of the bispecifics*

BsAbs require corticosteroid prophylaxis to mitigate CRS. For epcoritamab, steroid premedication was initially with a single dose of prednisolone 100mg on 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 peak 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 with initial odronextamab dosing cohorts, optimisation of pre-medications led to the use of 20mg of dexamethasone or equivalent starting the day before, the day of and the day following administration.[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 patient characteristics, all grade CRS was 44% vs 73% with other preparations, with equivalent response rates observed.[17] Similar findings have been reported in a 24-patient optimisation cohort in the EPCORE NHL-1 study of epcoritamab, where 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 registrational studies**

Epcoritamab and glofitamab are currently approved as monotherapy for R/R 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 in DLBCL. The phase II trials exploring activity in DLBCL in the approved agents were of a similar size with between 127 and 157 patients, and recruited during the SARS-CoV-2 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 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 BsAbs 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, failure of at least two prior lines of treatment, an ECOG 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 Richter's syndrome in the DLBCL expansion arms,[21, 22, 26] while ELM-2 allowed it, 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 BsAbs 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 1 confirm activity in this context.[23]

The delivered regimens are listed in Table 1. Of the three regimens, glofitamab has 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, it 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 amongst the regimens.[23] Patients were hospitalised for the first three doses of odronextamab to manage CRS risk, while only one hospitalisation was required for the first dose of glofitamab (2.5mg) and for the first target dose of epcoritamab (48mg).[21, 22]

Corticosteroid prophylaxis against CRS was universal, but differed substantially between agents. Epcoritamab required four days of 100mg prednisolone per dose until at least the first four weeks of exposure (1600mg cumulative), while intravenous corticosteroid prophylaxis of 100mg prednisone, 80mg of methylprednisone, or 20mg dexamethasone were given as a single dose for at least the first five weeks of glofitamab treatment (625mg prednisolone-equivalent cumulatively). Odronextamab required 20mg 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 epcoritamab (~1600mg).

*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 CR rate (CRR) to be a useful early indicator of drug activity in DLBCL. The CRR achieved in EPCORE NHL-1 and NP30179 is 40%.[21, 22, 25, 28] The overall response rate, by contrast, is numerically higher with epcoritamab, owing to a higher rate of partial remissions (PR).

Durable response on an intent-to-treat basis is seemingly restricted to those who achieve a CR. Most patients who are destined to enjoy a CR do so at the first response assessment. Conversion from PR to CR occurs in roughly a third of partial responders with glofitamab, odronextamab and epcoritamab, while most of the remaining patients' disease progresses quickly.[21, 22, 25] In our practice, we therefore re-evaluate patients early if a CR is not achieved with 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 of BsAbs, and how clinicians may counsel patients during treatment. Retention of complete remission at the 3-month and end-of-treatment response evaluation positively predicts enduring remission at 12 and 18 months following 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 CR 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 median of 37.7 months follow up, those in a CR 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 CR 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 CR 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 continues until progression. On the whole, the ELM-2 data are similar to the above two trials.[23] The complete remission rate following odronextamab for DLBCL is numerically lower, 31.5%, and the ORR was 52% (Table 2), however this may be accounted for by differences in patient characteristics or analysis methods. The estimated 24-month PFS in complete responders was 47.2%, somewhat lower than achieved by the drugs above. Mosunetuzumab produced a CRR of 24%, overall, and 12% in CAR-T exposed patients (Table 2).[26] It remains an attractive combination partner under ongoing 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 CR, but represent a minority of recruited patients; for example the complete remission rate following glofitamab in patients with relapsed rather than refractory disease is >70%, but these patients only represented 14% of the recruited population.[21] Other factors such as bulk and LDH did not change the complete remission rate. Recent data on total metabolic tumour volume by PET suggest that patients with high burden disease have a poorer progression-free survival following treatment with glofitamab.[30]

Responses in the CAR-T exposed populations are surprisingly good. The rates of complete remission after glofitamab (35%) and epcoritamab (34%) are not different from what might be expected of the overall group, but patients tended to have relapsed after CART rather than had no response at all.[21, 22] Data from the phase I trial of odronextamab, ELM-1, showed a 29% CR-rate in the 44 patients with prior CAR-T.[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-treated patients that probably surpasses other available options, safety and deliverability in patients with early CAR-T failure and associated persistent toxicities is yet to be fully clarified; as is whether the responses are as durable as seen in non-CART-exposed patients. 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 the 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 BsAbs in use for DLBCL are similar (Table 2), however the clinical pattern varies according to the agent, dose, corticosteroid prophylaxis choice,[17] and disease-related features. [17] Following glofitamab, CRS occurs most frequently with the first 2.5mg dose, hence admission is currently recommended at that time. For epcoritamab the CRS most commonly occurs with the first target dose, cycle 1 day 15, when hospitalisation is recommended.

Avoiding pre-emptive hospitalisation is desirable. Well-educated patients with access to out-of-hours medical centres may be managed as an outpatient on a case-by-case basis, potentially through the provision of an initial dose of "just in case" corticosteroid to take with the onset of a fever, but there is no prospective data supporting that approach. This is likely to be less feasible in patients with risk factors for CRS, and in those with comorbidities who may poorly tolerate the physiologic challenge that it entails. A predictive risk score for CRS risk post glofitamab could 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 [SPD] on CT, stage), together with age and white cell count.[19, 34] A similar 3-factor scoring system incorporating prior CAR-T exposure, extranodal disease, and total metabolic tumour volume (TMTV) was able to accurately identify patients at low-risk of grade 2 CRS with epcoritamab.[35] While SPD and TMTV may not always be available in routine practice, these scores support the role of risk stratification in managing CRS in patients receiving BsAbs for DLBCL.[19, 34]

*Cytopenia, infection and neurological toxicity*

Grade 3/4 neutropenia occurs in 27% and 17.8% of patients following glofitamab and epcoritamab, respectively,[21, 22] but rarely leads to treatment discontinuation, or to febrile neutropenia. This 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 due to the higher risk of bleeding in patients with fever.

Infection is an important side effect of BsAbs 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 randomised 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 BsAbs 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 organising pneumonia in patients receiving these agents; a comprehensive evaluation of a patient's competing risks is required before continuing these agents in symptomatic patients.

As with other B-cell-depleting agents, hypogammaglobulinaemia will occur in some patients following BsAbs, and replacement may be indicated as primary or secondary prophylaxis against infection. B-cell and immunoglobulin recovery has been best characterised after cessation of mosunetuzumab[38] and glofitamab [39] but is less well characterised 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 post 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 patient comorbidity, prior therapies and pre-existing immune competence, as well as duration of treatment and cumulative steroid exposure when evaluating a patient's risks from acquired infection during treatment.

Neurological toxicity consistent with immune effector cell associated neurological syndrome (ICANS) 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 ICANS following BsAbs has been rare and, except in patients with inexorable disease progression, reversible.

**Resistance mechanisms are diverse**

Despite their great promise, a minority of patients experience complete remission following BsAb. Mechanisms of resistance to BsAb in DLBCL are poorly understood, and developing insights in this area has been complicated by the molecular heterogeneity of DLBCL, differences in patient characteristics included on the trials, as well as practical challenges in obtaining sequential biopsies. Defects in host immunity, tumour-intrinsic 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 tumour samples and the depth of response. For each of glofitamab, epcoritamab and odronextamab, responders showed a trend towards higher baseline tumour 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 CR with 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, is less uniformly described; a higher proportion of CD4+ T-regulatory and T-follicular helper type cells within the tumour sample was implicated in reduced response to epcoritamab, which was partly recapitulated with odronextamab (Tregs 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 positive cells nor strength of CD20 expression at time of first treatment predicts for response, although very few truly CD20-negative 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 tumour resistance. In a retrospective analysis of 42 patients with DLBCL treated with glofitamab at our centre, we demonstrated that 63% of patients with pre- and post-treatment samples converted from CD20 positive to CD20 negative by immunohistochemistry at progression.[46] Similar findings have been demonstrated with epcoritamab and odronextamab,[40, 41] and the immunohistochemical finding is supported by longitudinal molecular analyses demonstrating alterations in genes encoding CD20 in many patients treated with BsAbs.[40, 41, 47, 48] As a consequence, newer bispecific antibodies targeting additional antigens may address whether clonal escape can be addressed in this way.[49, 50]

In addition to these dynamic changes, baseline molecular features typically associated with tumour aggressiveness may also predict for poorer response to BsAbs. For instance, both the presence of double-hit translocations and positivity for the dark-zone signature by RNA analysis were associated with shorter PFS with glofitamab monotherapy in the R/R setting.[51] However, this may not be the case in all contexts and combinations; in newly diagnosed disease, response to epcoritamab in combination with chemotherapy in patients with DH LBCL appeared roughly equivalent to 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 tumours according to the LymphGen system suggested poorer outcomes were observed with the MCD 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 favouring a cytotoxic profile, while resistance is characterised by T-cell exhaustion, biologic tumour aggressiveness and target-antigen downregulation.

**Emerging role of ct-DNA**

Evaluation of measurable residual disease (MRD) using circulating-tumour DNA (ctDNA) does not have a routine role in the management of DLBCL, however, it is conceptually appealing to think that MRD might guide the use of BsAbs 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 is emerging as an issue after BsAbs.[38]

ctDNA levels are closely aligned with tumour load and represent a possible mechanism to simultaneously measure baseline burden and genomic complexity. Patients with higher baseline ctDNA levels, for instance, had shorter PFS when treated with glofitamab monotherapy, which was positively correlated with high-risk clinical features such as elevated LDH, bulky disease and high IPI.[51]

Achievement of MRD negativity by ctDNA during treatment correlated with improved PFS 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 CMR to glofitamab showing a more rapid and sustained decrease in

ctDNA at early timepoints.[51] In addition, ctDNA response may augment the interpretation of PET imaging assessments; for patients not achieving a CMR to odronextamab at an interim scan, MRD negativity by ctDNA appeared useful in predicting for improved outcomes compared to MRD positive patients.[53]

Drawing upon these principles of the prognostic significance of ctDNA kinetics more broadly, a number of ongoing trials in newly diagnosed DLBCL use 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 summarised in Tables 3 and 4.

*Combination with cytotoxic therapy is promising*

Polatuzumab vedotin, the CD79b antibody drug conjugate, has been successfully combined with mosunetuzumab and glofitamab in single-arm phase II studies in R/R DLBCL, demonstrating CRRs of 50% and 56% respectively in patient populations largely analogous to 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 & 3). The doublet of mosunetuzumab and polatuzumab vedotin is currently being evaluated in the randomised 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, the randomised, phase III, trial that compares 8, 3-weekly cycles of glofitamab with 8 cycles of gemcitabine-oxaliplatin (Gem-Ox) to rituximab-gem-ox, in transplant-ineligible patients with R/R DLBCL. [37] A total of 274 patients were randomised 2:1 favouring the experimental arm. Most patients (63%) had one prior therapy, with 37% exposed to 2 or more prior lines. High-risk features, such as refractoriness to the immediate prior therapy (61%), age >=65 (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 PFS (median 13.8 vs 3.6mo; HR 0.40 (95% CI 0.28-0.57), p<0.001) and OS (median 25.5 vs 12.9mo; HR 0.62 (95% CI 0.43-0.88), p0.006). 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 age, number of prior lines of therapy, relapsed vs refractory status, and cell or origin by IHC.

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 CART-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 criticised the control arm, as R-Gem-Ox is given on a 2-weekly regimen in some regions. In our experience, three-weekly R-Gem-Ox is more feasible than the two-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/CRR of 85%/61%,[59] and numerous other combinations of BsAbs with salvage treatments are under way in both transplant-eligible and ineligible populations (Tables 3 & 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% with monotherapy, respectively.[21, 37] This might be due to a reduction in tumour burden from the chemotherapy exposure. Serious infections were higher 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 infection.[37] Careful evaluation of additional toxicity will be essential in the development of safe and effective combination treatments.

The combination of BsAbs 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-like backbone therapy, high rates of CR have been observed, including in clinically and molecularly poor-risk disease (Table 3).

*Combination with immune-active therapies*

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

Preclinical work with BsAbs and the experience with CAR-T development indicates an important role for co-stimulatory signalling in augmenting T-cell fitness and promoting full functionality.[60] In mouse models, potent co-stimulation could be achieved using BsAbs 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/CRR of 67%/57% in patients with heavily-treated R/R DLBCL, half having prior CAR-T exposure[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 R/R DLBCL treated with epcoritamab and lenalidomide, the ORR was 75%, with 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/CRR of 89%/43%. Work is ongoing with other immunomodulatory agents including CELMoDs.

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

**Future major trials**

STARGLO demonstrated that the potential of chemotherapy combinations needs to be further tested, including in fitter patients who would be considered eligible for autologous transplantation and/or CAR-T therapy. Early data from phase II trials suggests that a significantly higher proportion of patients respond to BsAb combination treatment compared to historical expectations of both conventional treatments and BsAb monotherapy (Tables 3 & 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 patient group.

Each of glofitamab, epcoritamab and odronextamab are being combined with multi-agent chemoimmunotherapy in patients with newly diagnosed IPI 2-5 LBCL. The SKYGLO study with glofitamab uses Pola-R-CHP 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 R-CHOP as used in EPCORE DLBCL-2 evaluating epcoritamab and OLYMPIA-3 evaluating odronextamab).

**Conclusions: sequencing of BsAbs: today, tomorrow, and the future.**

Long-term follow-up data of BsAbs 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, the stresses of referral of patients to distant treatment centres, may mean that the immediacy of BsAbs 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 go beyond 5 years, confirming its curative potential. Outcomes may be as good in the transplant-ineligible[72] but randomised 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 is not feasible, the STARGLO trial offers valuable treatment option. It is glofitamab+Gem-Ox, rather than CAR-T that has a randomised trial favouring its use over conventional chemotherapy in those populations.[73] In regions where conventional chemotherapy has been the only choice, then the results of STARGLO are especially persuasive and suggest the days of conventional chemotherapy alone being an appropriate option for relapsed DLBCL are numbered.

For relapse after CAR-T, the BsAbs are active, but we anticipate lower rates of success in the truly CAR-T refractory.[74, 75] Conversely, we know less about how CAR-T work in patients whose disease has progressed or been refractory to BsAbs treatment.[76] In a retrospective study of 47 BsAb-refractory patients who went on to receive CAR-T from the DESCAR-T registry, the ORR and CRR to CAR-T was consistent with a matched, unexposed population.[77] We need more such data, as more patients will be referred for CAR-T in the third line, having been exposed to BsAbs in the second, or even first.

Looking further into the future, the whole field may change if the results of the randomised trials of BsAbs as a first treatment for DLBCL are positive. Little is known about the characteristics of patients whose lymphoma progresses after bispecific 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 if CAR-T is as effective in that setting, too.

While there are no randomised trials comparing BsAbs monotherapy with BsAb combinations, the consistently higher CR rate in 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, CELMoD/imid, antibody-drug, or other novel drugs offer are most effective in BsAb combinations is a pressing question. However, within the limits of what can be gleaned from non-randomised trials, these doublets seem to enhance responses with little toxicity cost. That suggests that BsAbs 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 the BsAbs is their immediate availability and deliverability outside of specialist treatment centres. With this comes the hope and expectation that the regimens currently under evaluation will impact the lives of more patients with DLBCL, and shift survival in this disease globally.

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*Table 1: Bispecific antibody characteristics and dosing strategies*

| Agent | Route of administration | Half-life (median, days) | Dosing schedule | Cycle length (days) | Step-up doses as percentage of target dose | Duration of therapy | CRS mitigation: anti-CD20 pre-treatment | CRS mitigation: corticosteroid | Hospitalisation recommendations | Visits in first 6 months |
|---|---|---|---|---|---|---|---|---|---|---|
| Glofitamab | IV | 10 | *Step-up:* D-7 GPT D1 2.5mg D8 10mg *Target:* 30mg Q3W | 21 | 8.3%/33% | Fixed - up to 12 cycles | Obinutuzumab 1000mg IV D-7 | Dexamethasone 20mg PO/IV for first 3 doses[±] | First dose | ~12 |
| Mosunetuzumab | IV | 6-11 | *Step-up*: D1 1mg D8 2mg D15 60mg *Target:* D15 60mg Q3W | 21 | 1.6%/3.3% | Fixed – up to 17 cycles (8 if complete response achieved, 17 if partial response or stable disease) | Nil | Dexamethasone 20mg PO/IV or methylprednisolone 80mg for first 4 doses | Nil mandated | ~12 |
| Epcoritamab | SC | 8.8 | *Step-up:* D1 0.16mg D8 0.80mg *Target:* 48mg QW for C1-C3 then Q2W for C4-9, then Q4W C10+ | 28 | 0.33%/1.7% | Indefinite - to progression or intolerance | Nil | Dexamethasone 15mg or equivalent for 4 days with each of the first 4 doses | First target dose | ~18 |
| Odronextamab | IV | 14 | *Step-up:* D1 0.7mg D8 4mg D15 20mg | 21 | 0.4%/2.5%/12.5% | Indefinite - to progression or | Nil | Dexamethasone 20mg 1 day prior, on days of dosing, and one | First 3 doses | ~21 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Target:* 160mg QW for C2-4 320mg Q2W C5+, then Q4W C9+ (if CR) | | | intolerance | | day after dosing during step up and first target dose | | |

CRS, cytokine release syndrome; GPT, gazyva (obinutuzumab) pre-treatment; IV, intravenous; PO, oral
[±] Corticosteroid may be administered on C2D1 if significant CRS is observed during C1

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

| Agent | Number of patients | Patient population | Median prior lines (n, range) | Refractory to immediate prior therapy (%) | Prior CAR-T (%) | Response rates (ORR/CRR) | Median DOR (months) | Median DOCR (months) | Median PFS/OS (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% |

* included 6 patients with PMBCL; 154 patients received a dose of study treatment
† included 4 patients with PMBCL and 5 patients with FL grade 3B
‡ included 7 patients with Richter syndrome; 141 patients enrolled with 127 patient evaluable for efficacy
*** Long term outcomes of glofitamab were reported by independent review committee. Long term outcomes of epcoritamab were reported by investigator evaluation.
DOR, duration of response; PFS, progression free survival; OS, overall survival; CRS, cytokine release syndrome; aNHL, aggressive NHL; NR, not reported; NE, not estimable; R/R LBCL, relapsed or refractory large B-cell lymphoma

*Table 3: Studies of bispecific antibody combinations in DLBCL with reported results*

| Disease setting | Trial ID/Name | Phase | Treatment | Patient population | No. of patients | Response rates ORR/CRR | PFS/OS/DOR | CRS rates | | | | | Follow up (median) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Total | G1 | G2 | G3 | G4 | |
| **First line** | NCT03467373[79] NP40126 | I/II | Glofit + R-CHOP | Fit IPI2-5 | 56 | 93%/84% | NR | 11% | 7% | 4% | 0% | 0% | 17.1mo |
| | NCT03467373[80] NP40126 | I/II | Glofit + Pola-R-CHP | Fit IPI 1-5 | 24 | 100%/77% | NR | 13% | 13% | 0% | 0% | 0% | 5.1mo |
| | NCT04914741[81, 82] COALITION | I/II | Glofit + R-CHOP or Glofit + Pola-R-CHP | Fit, IPI 3-5 or NCCN-IPI 4-8 Ages 18-65yo | 80 | 100%/98% | 2-year PFS 86% 2-year OS 92% | 22% | 19% | 3% | 0% | 0% | 20.7mo |
| | 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% | 27.4mo |
| | 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% | 7.4mo |
| | NCT03677141[85] | I/II | Mosun +R-CHOP | Fit IPI 2-5 | 40 | 95%/90% | 2-year PFS 65.4% | 60% | 45% | 15% | 0% | 0% | 32mo |
| | NCT03677154[86] | Ib/II | Mosun +/- Pola | Unfit Age >=80 or age 65-79 and unfit | 101 | 80%/65% | 1-yr PFS 49.7% | 32% | 21% | 7% | 2% | 0% | 12.6mo |

| Disease setting | Trial ID/Name | Phase | Treatment | Patient population | No. of patients | Response rates ORR/CRR | PFS/OS/DOR | CRS rates | | | | | Follow up (median) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Total | G1 | G2 | G3 | G4 | |
| | 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% | 8mo |
| | 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-yr PFS 88% 1-yr OS 96% | 43% | 25% | 29% | 0% | 0% | 9.4mo |
| **Second line and beyond** | NCT04663347[91] EPCORE NHL-2 | I/II | Epcor + R-DHAX/C* | Transplant eligible 2L+ | 29 | 76%/69% | 2-yr PFS 60% 2-yr OS 86% | 45% | 38% | 7% | 0% | 0% | 27.5mo |
| | NCT04663347[59, 92] EPCORE NHL-2 (Arm 5) | I/II | Epcor + GemOx | Transplant ineligible 2L+ | 103 | 85%/61% | 15-mth DOCR 56% | 52% | 28% | 23% | 1% | 0% | 13.2mo |
| | NCT05283720 EPCORE NHL-5 | II | Epcor + Len | 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-yr PFS 52% 2-yr OS 53% | 44% | 31% | 11% | 2% | 0% | 20.7mo |
| | NCT05364424[93] | I | Glofit + R-ICE† | Transplant or CAR-T eligible 2L | 41 | 78%/69% | NR | 49% | 29% | 20% | 0% | 0% | NR |

| Disease setting | Trial ID/Name | Phase | Treatment | Patient population | No. of patients | Response rates ORR/CRR | PFS/OS/DOR | CRS rates | | | | | Follow up (median) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Total | G1 | G2 | G3 | G4 | |
| | NCT04077723[64] | I/II | Glofit + englumafusp alpha (CD19x4-1BB) | Transplant ineligible 2L+ | 83 | 67%/57% | 1-yr PFS 46% | 55% | 49% | 13% | 1% | 0% | 16.2mo |
| | 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 12mo<br>Median OS 39.2mo | 43% | 27% | 15% | 1% | 0% | 23.5mo |
| | NCT03671018[56] | I/II | Mosun + pola | Transplant ineligible 2L+ | 117 | 62%/50% | 1-yr PFS 46%<br>1-yr OS 66% | 17% | 10% | 4% | 3% | 0% | 23.9mo |
| | NCT05335018[95] | II | Glofitamab + poseltinib + lenalidomide | Transplant ineligible Primary refractory or 3L+ | 28 | 89%/43% | 6-mth PFS 55%<br>6-mth OS 81% | 19% | 14% | | 5% | | 3.6mo |
| | NCT03533283[67] | I/II | Glofit + atezolizumab | Transplant ineligible | 31 | 29%/10% | NR | 42% | 24% | 18% | 0% | 0% | NR |

* autologous stem cell transplant consolidation at investigator discretion. † autologous stem cell transplant or CAR-T consolidation at investigator discretion
Glofit, glofitamab; Epcor, epcoritamab; Mosun, Mosunetuzumab; Odro, odronextamab; Pola, polatuzumab; R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CHP, cyclophosphamide, doxorubicin, prednisolone; IPI, international prognostic index; NR, not reported; mo, months; CRS, cytokine release syndrome; PFS, progression free survival; OS, overall survival; DOR, duration of response; DOCR, duration of complete response; ctDNA, circulating tumour DNA; NCCN-IPI, national comprehensive cancer network international prognostic index; DHAX/C, dexamethasone, cytarabine, oxaliplatin/carboplatin; GemOx, gemcitabine, oxaliplatin

*Table 4: Studies of bispecific antibody combinations in DLBCL without reported results*

| Disease setting | Trial ID/Name | Phase | Treatment | Patient population | No. of patients planned | Primary endpoint |
|---|---|---|---|---|---|---|
| **First line** | NCT05800366 | II | Glofit + Pola-R-CHP | Fit<br>IPI 2-5 | 40 | Complete response rate (after 8 cycles) |
| | NCT06050694<br>GRAIL | II | Pola-R-CHP or Glofit + Pola-R-CHP | Fit<br>Pts with unfavourable response by ctDNA or PET after 2 cycles of treatment receive glofitamab | 40 | Feasibility of ctDNA testing |
| | NCT06091865[96]<br>OLYMPIA-3 | III | Odro + CHOP vs R-CHOP | Fit<br>IPI 2-5 | 904 | Progression free survival |
| | NCT05578976[97]<br>EPCORE DLBCL-2 | III | Epcor + R-CHOP vs R-CHOP | Fit<br>IPI 2-5 | 900 | Progression free survival |
| | NCT06047080[98]<br>SKYGLO | III | Glofit + Pola-R-CHP vs Pola-R-CHP | Fit<br>IPI 2-5 | 1130 | Progression free survival |
| | NCT05660967<br>EPCORE DLBCL-3 | III | Epcor +/- Len | Unfit<br>Age >=80 or age 75-79 and unfit | 180 | Complete response rate |
| | NCT06045247 | II | Epcor + R-mini-CVP | Unfit<br>Age >=80 or <80 and unfit | 40 | Safety |
| **Second line and beyond** | NCT06287398<br>EPCOR-Sandwich | II | Epcor + R-DHAX + ASCT + Epcor consolidation | Transplant eligible<br>2L | 39 | Event free survival |
| | NCT05852717[99] | II | Epcor + GDP* | Transplant eligible<br>2L+ | 32 | Complete response rate (after 3 cycles) |
| | NCT06213311[100] | II | Glofit + axi-cel | Transplant eligible<br>2L refractory or relapse <12mo | 40 | Safety |
| | NCT04161248 | I | Glofit + R-GDP* | Transplant eligible<br>2L | 18 | Safety and RP2D |

| Disease setting | Trial ID/Name | Phase | Treatment | Patient population | No. of patients planned | Primary endpoint |
|---|---|---|---|---|---|---|
| | NCT05283720<br>EPCORE NHL-5 | II | Epcor +<br>- Len-ibrutinib (Arm 2)<br>- CC-99282 (Arm 4) | Transplant eligible and ineligible<br>2L+ | 394 across all arms | Safety |
| | NCT05219513[62, 101] | I | Glofit + RO7443904 (CD19xCD28) | Transplant ineligible<br>2L+ | 53 (including other B-NHL) | Safety |
| | NCT05896163[102] | I/II | Glofit + mapilracept (anti-CD47 antibody) | Transplant ineligible<br>2L-3L | 70 | Overall response rate |
| | NCT05169515 | I | Glofit or Mosun + CELMoDs (CC-220 or CC-99282) | Transplant ineligible<br>2L+ | 121 (including other B-NHL) | Overall response rate |
| | NCT06458439 | II | Epcor before and after CAR-T cells | CAR-T eligible patients | 31 | Occurrence of CAR-T infusion |
| | NCT06414148 | II | Epcor +/- Len after CAR-T | Post CAR-T ctDNA MRD positive | 40 | Overall response rate (at 12 months after CAR-T) |
| | NCT05685173[103]<br>ATHENA-1 | I | Odro + REGN5837 (CD28xCD22) | Transplant ineligible<br>3L+ | 91 (including other B-NHL) | Safety |
| | NCT02651662[66]<br>QLIO-1 | I | Odro + cemiplimab | Transplant ineligible<br>3L+ | 62 (including other B-NHL) | Safety |
| | NCT05315713 | I/II | Mosun + tiragolumab +/- atezolizumab | Transplant ineligible<br>3L+ | 118 (terminated after 8 patients) | Safety and overall response rate |
| | NCT05615636 | II | Mosun + pola + tafasitamab + len | Transplant ineligible<br>2L+ | 36 | Overall response rate |
| | NCT05672251[104] | II | Mosun + loncastuximab tesirine | 3L+ | 26 | Safety and overall response rate |
| | NCT05171647[58]<br>SUNMO | III | Mosun + pola vs R-GemOx | Transplant ineligible<br>2L+ | 222 | Progression free survival |

* autologous stem cell transplant consolidation at discretion of investigator

Glofit, glofitamab; Epcor, epcoritamab; Mosun, Mosunetuzumab; Odro, odronextamab; Pola, polatuzumab; R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CHP, cyclophosphamide, doxorubicin, prednisolone; CVP, cyclophosphamide, vincristine, prednisolone; GDP, gemcitabine, dexamethasone, cisplatin; Axi-cel, Axicabtagene ciloleucel; R-ICE, rituximab ifosphamide, carboplatin, etoposide; Len, lenalidomide; IPI, international prognostic index; NR, not reported; mo, months; PFS, progression free survival; OS, overall survival; DOR, duration of response; DOCR, duration of complete response; ctDNA, circulating tumour DNA; MRD, measurable residual disease; DHAX, dexamethasone, cytarabine, oxaliplatin