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Novel Bispecific T-Cell Engagers for the Treatment of Relapsed B Cell Non-Hodgkin Lymphomas: Current Knowledge and Treatment Considerations

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Abstract: This article provides an overview of the novel treatments focusing on the class of bispecific T cell engagers (BiTEs) for the treatment of diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), the two most prevalent subtypes of B cell non-Hodgkin lymphomas (B-NHL). After a brief outline of these diseases, the difficulties in the management of relapsed or refractory (R/R) disease are highlighted. There are currently 4 main BiTEs showing promise in treating R/R B-NHL—glofitamab, epcoritamab, mosunetuzumab, and odronextamab. Although the rational of their mechanism of action is similar, there are significant differences in their respective clinical trial design, reported outcomes, and the final FDA approvals. Considerations for selecting a specific BiTE therapy, including treatment duration, cost, administration route, adverse effects, and impact on quality of life, are also discussed. Patient preferences and shared decision making should be acknowledged by healthcare providers. Finally, the importance of personalized treatment strategies and ongoing research to optimize outcomes in the evolving landscape of R/R B-NHL therapy cannot be overstated.

Keywords: bispecific, BiTE, glofitamab, epcoritamab, mosunetuzumab, odronextamab

Introduction

B cell non-Hodgkin lymphomas (B-NHL) represent a complex and heterogeneous group of malignancies arising from B-lymphocytes, characterized by clonal proliferation and abnormal differentiation, resulting in the formation of lymphoid tumors. There are many distinct types of B-NHL, as is seen in the WHO classification, with ongoing revisions and evolutions of new entities occurring as novel research efforts shed light on the molecular and genomic landscape of this group of malignancies.[1] Each type exhibits distinct epidemiological, clinical, pathologic, and diagnostic features, with subsequent substantial differences in management considerations and prognosis. Among the different B-NHL subtypes stand out diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) as the most common aggressive and indolent lymphomas, respectively.[2–4]

Diffuse Large B-Cell Lymphoma (DLBCL)

DLBCL, constituting approximately 30–40% of B-NHL cases, is recognized as the most prevalent subtype of B-NHL.[4,5] It typically presents with an aggressive clinical disease, usually as a rapidly growing tumor, manifesting as nodal or extra-nodal masses (ie, involving sites outside lymph nodes and/or spleen).[6,7] Clinical manifestations vary widely, encompassing the so-called 'B-symptoms' (fever, night sweats, weight loss), lymphadenopathy, and/or manifestations arising from extranodal involvement (eg, gastrointestinal bleeding in gastric DLBCL).[8,9] Pathologically, DLBCL is

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characterized by diffuse proliferation of large neoplastic B cells, often expressing CD20 and other B cell antigens.[7] Diagnosis involves a combination of histological examination, immunophenotyping, and molecular studies, with novel techniques such as gene expression profiling heralding future directions for aiding in the identification of distinct subtypes and incorporating targeted therapies.

Epidemiologically, DLBCL is diagnosed typically in older individuals, with a median age of 67 and a slight male predominance (1:1.4).[2] Geographic variations and potential etiological factors, such as infections and immunodeficiency states, contribute to the intricate epidemiology of DLBCL.

Follicular Lymphoma (FL)

FL, comprising approximately 20% of B-NHL cases, may present as a slower-growing indolent disease manifesting as painless lymphadenopathy, bone marrow involvement, and splenomegaly.[3] Alternatively, it may be completely asymptomatic and detected incidentally by laboratory or imaging studies performed for other purposes.[10] Histologically, FL displays a nodular growth pattern, resembling germinal center B cells. Immunophenotyping reveals the expression of CD20+ and CD10+ B cells antigen in a background of follicular dendritic cells, facilitating accurate diagnosis.[11] Molecular analysis, especially the detection of the t(14;18) translocation, further supports diagnostic precision.

The epidemiology of FL reveals a median age at diagnosis of 64, with a slight male preponderance.[3] Unlike DLBCL, FL displays a more indolent course, with some patients experiencing prolonged survival even without any intervention. However, a subset of FL cases may undergo transformation to a more aggressive histology, such as DLBCL, impacting the overall clinical management.[12]

Relapsed or Refractory (R/R) Disease

Frontline therapy for both DLBCL and FL (when needed) typically consists of chemoimmunotherapy, details of which are beyond the scope of this article, with remarkable response rates. Despite this, and the significant advancements in the therapeutic landscape, a considerable number of these patients experience R/R disease. The likelihood of relapse is multifactorial, influenced by disease subtype, stage at diagnosis, and response to initial therapy. Studies indicate that up to 30–40% of DLBCL patients may face R/R disease, underscoring the need for alternative treatment strategies.[7] In contrast, due to the chronic nature of the disease, advanced stage FL is less likely to be curable, and many patients require several lines of treatment, posing challenges in long-term management.[11]

Treatment Strategies for R/R Disease

Managing R/R patients presents a formidable clinical challenge, requiring a nuanced approach. For DLBCL, the standard treatment until recently has been salvage chemotherapy, ideally followed by autologous stem cell transplantation for transplant-eligible patients. However, this approach often results in suboptimal outcomes.[13] Recent advances in the realm of targeted and cellular therapies have given rise to chimeric antigen receptor (CAR) T cell therapy as the treatment of choice in many of these patients. Unfortunately, some of these patients will be unable to receive this therapy owing to rapid disease progression, cost, availability, and poor medical fitness, while others may progress despite being treated.[14]

For R/R follicular lymphoma, after a biopsy to rule out possible transformation, most treatment options consist of different combinations of chemoimmunotherapy with no single treatment choice clearly preferred.[15] CAR T cell therapy has shown promise in this setting as well in third or fourth line of treatment.[16] However, this strategy can be implemented only in dedicated tertiary hospitals, and not in clinics outside of such hospitals. Furthermore, it is not an "off-the-shelf" product, which further precludes its wide scale use.

Recent years have marked the emergence of bispecific T cell engagers (BiTEs) as a novel treatment modality, offering a paradigm shift in the treatment of R/R B-NHL. BiTEs are characterized by their ability to "engage" both T cells and tumor cells, promoting cytotoxic T cell-mediated killing of the latter, thus sparking an interest in expanding the utilization of BiTEs across various B-NHL subtypes.[17]

Overview of Bispecific T Cell Engagers (BiTEs)

Structurally, BiTEs consist of two single-chain variable fragments targeting specific antigens on both T cells and tumor cells, connected by a short linker. The binding of BiTEs to CD3 on T cells and a tumor-specific antigen on B cells facilitates the formation of a cytolytic synapse, leading to targeted T cell activation and subsequent tumor cell lysis.[17,18] Their immune-based mechanism of action, relying on the recruitment and activation of endogenous T cells, distinguishes BiTEs from traditional monoclonal antibodies.

Pharmacologically, some BiTEs exhibit rapid clearance, necessitating continuous infusion or frequent dosing for sustained therapeutic effects (eg, blinatumomab), while others have extended half-lives due to different molecular modifications (eg, altered engineering of the Fc region in glofitamab).[19,20]

Conveniently, BiTEs are "on-shelf" ready to use products, hence they are immediately available in all treatment settings and do not require a complex and sometimes lengthy manufacturing process as in CAR T cell therapy.

The following section will review the 4 main BiTEs currently in clinical use and/or research in R/R B-NHL: glofitamab, epcoritamab, mosunetuzumab and odronextamab.

Glofitamab

Glofitamab, a bispecific monoclonal antibody of the CD20XCD3 class, allows for proximity of the T cells (which express CD3) to the malignant B cells (expressing CD20) while simultaneously inducing T cell activation. This intravenously (IV) administered BiTE is characterized by its unique 2:1 tumor–T-cell binding configuration, boosting efficacy and potency both in vitro and in vivo.[20,21] Additionally, modifications to the Fc portion of this antibody have reduced its affinity to Fcγ receptors and complement component C1q, thus achieving a longer circulatory half-life.

A pivotal Phase 2 study, involving 154 patients with R/R DLBCL who had undergone at least two prior lines of therapy, evaluated the efficacy of glofitamab monotherapy at the phase 2 dose (step-up doses of 2.5 mg and 10 mg, followed by 30 mg on day 1 of cycles 2 through 12) after pretreatment with obinutuzumab, for a fixed duration of 12 cycles total.[22] The study demonstrated a notable complete response (CR) rate of 39%,with responses observed early, at approximately 1.4 months, and displaying durability, as evidenced by 78% of patients maintaining remission at 12 months post-treatment initiation. Treatment discontinuation due to adverse events (AEs) was rare (9% of patients), with cytokine release syndrome (CRS) being the most common AE (63%), typically of low grade (grade 3 CRS in 3% of the patients, and grade 4 in only 1%). Immune cell-associated neurotoxicity syndrome (ICANS) manifested in 8% of the patients, all these events resolved. Neutropenia emerged as the most prevalent higher-grade AE (grade 3 or 4), occurring in over half of the participants. Based on these compelling findings, glofitamab was granted accelerated US Food and Drug Administration (FDA) approval for the treatment of R/R DLBCL following two or more lines of systemic therapy.[23]

Ongoing clinical trials aim to further elucidate the efficacy of glofitamab, both as monotherapy and in combination regimens, across various hematological malignancies, including mantle cell lymphoma (NCT06192888), follicular lymphoma and marginal zone lymphomas (NCT05783596), and Richter syndrome (NCT06186648).

Epcoritamab

Epcoritamab, a subcutaneously (SC) administered bispecific antibody targeting CD3 and CD20, is another novel agent in the treatment landscape of B-NHL. Preclinical studies have showcased epcoritamab's ability to induce potent and selective T-cell-mediated cytotoxic activity against CD20+ malignant B cells.[24] Epcoritamab showed superior potency compared to three other BiTEs with single CD3 and CD20 binding regions, while showing comparable potency as a different BiTE with a single CD3 and two CD20 binding regions. Results were similar with IV and SC administration, and while bioavailability was similar in both routes, plasma cytokine levels were lower in SC administration, which is currently the preferred route.

During dose escalation studies single-agent epcoritamab has exhibited potent antitumor activity across several B-NHL with CR rates up to 50%, while demonstrating an excellent safety profile with fever secondary to CRS being the most common AE.[25] In the Phase I/II EPCORE NHL-1 trial, 157 adults (median age 64 years) with R/R CD20+ large B-cell lymphomas who received at least 2 prior lines of therapy, were treated with SC epcoritamab until progression or

unacceptable toxicity, resulting in an impressive overall response rate (ORR) of 63.1% and a CR rate of 38.9% at a median follow-up of 10.7 months.[26] Response rates were consistent across key subgroups, including those with prior CAR T cell therapy. The median duration of response stood at 12.0 months, with CRS being the most common AE observed (49.7%) also usually of low grade (only 2.5% had grade ≥ 3), and ICANS was seen in 6.4% of patients (all were grade 1–2 except for one fatal event).

With these compelling data, epcoritamab secured its US FDA approval in May 2023 for the treatment of adult patients with R/R DLBCL, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after ≥ 2 lines of systemic therapy.[27]

In the ongoing phase Ib/II EPCORE NHL-2 trial, epcoritamab is being assessed in combination with standard-of-care agents such as RCHOP, bendamustine, and lenalidomide in participants with B-NHL (DLBCL and FL), with interim results showing promise, for example in FL when combined with lenalidomide and rituximab.[28] Preliminary findings following an 8.2-month follow-up from the ongoing phase Ib/IIa NHL-5 trial, wherein epcoritamab was administered concomitantly with lenalidomide for patients with R/R DLBCL, demonstrated profound and sustained therapeutic responses including an ORR of 75%, and a CR rate of 58%.[29] Although these results suggest a potential for epcoritamab to become a cornerstone in earlier lines of treatment, caution should be used when interpreting this data, at least until the complete results are published.

On June 26, 2024, the FDA granted accelerated approval to epcoritamab for adult patients with R/R after ≥ 2 lines of systemic therapy.[30]

Mosunetuzumab

Mosunetuzumab is an IV administered bispecific monoclonal antibody engaging CD20 and CD3 T-cells studied for both aggressive and indolent B-NHL. Its first clinical trial was a Phase I dose-escalation study, which demonstrated better efficacy for indolent B-NHLs as compared with aggressive B-NHLs (ORR of 66.2% vs 34.9%, respectively), with an acceptable safety profile including CRS rates of 27.4% (only 2% had grade ≥ 3 CRS) and neutropenia in 28.4% of patients; ICANS was reported in 5% of patients, none were grade ≥ 3.[31] Building upon this, a phase 2 multicenter trial specifically evaluated its safety and efficacy in 90 R/R FL patients who had received two or more previous therapies.[32] The duration of treatment was fixed – patients with initially achieving CR completed 8 cycles, while patients with a partial response/stable disease continued treatment for up to 17 cycles. Results revealed a notable ORR of 80%, with a CR rate of 60% of patients. Although CRS emerged as the most prevalent AE (44%), it was predominantly grade 1–2 and primarily confined to cycle 1. These findings led to its US FDA approval in December 2022 for patients with R/R FL after 2 or more lines of therapy.[33] Further real-world data corroborated the benefits of mosunetuzumab for this indication.[34]

Results of mosunetuzumab monotherapy patients with R/R DLBCL, however, were somewhat disappointing, with a phase I/II study for such patients showing ORR and CR rates of 42% and 23.9%, respectively, not reaching statistical significance as compared to historical cohorts.[35] Current investigations are exploring combination therapy for mosunetuzumab in this setting. A phase Ib/II study combining mosunetuzumab with polatuzumab vedotin in patients with second line and later R/R DLBCL yielded an ORR of 59.2%, with 45.9% achieving CR.[36] Further trials are underway to evaluate mosunetuzumab's efficacy in diverse settings, including consolidation after autologous stem cell transplantation in R/R aggressive B-NHL (NCT05412290), in the management of refractory/R B-cell acute lymphoblastic leukemia (NCT05961696), and in combination with venetoclax for R/R chronic lymphocytic leukemia (NCT05091424).

Odronextamab

Odronextamab is a hinge-stabilized, fully human IgG4-based, investigational CD20xCD3 bispecific antibody, which is administered IV.

In clinical settings, odronextamab exhibited efficacy, particularly in the phase I trial (ELM-1), where it demonstrated clinical benefit among 145 heavily pretreated patients with CD20+ B-cell malignancies until disease progression or unacceptable toxicity, with an ORR of 51% for the entire cohort (response rate were higher for FL patients).[37] Notably, an expansion cohort within this trial evaluated its efficacy in patients with DLBCL who had experienced disease

progression following CAR T cell therapy (ORR – 33%, CR – 27%). Common grade 3 AEs were cytopenias; CRS was the most frequent serious AE (28%).

These results led to the ongoing pivotal phase 2 trial (ELM-2), which includes patients across five distinct disease-specific cohorts, including DLBCL, FL, mantle cell lymphoma, marginal zone lymphoma (MZL), and other subtypes of B-NHL. Although the final results have yet to be published in their entirety, the published data from the 130 R/R DLBCL patient cohort treated continuously with odronextamab shows a 52% ORR and 31% CR rate.[38] AEs were consistent with the phase I reports; no ICANS events were reported. This drug has not yet been FDA approved.[39]

Considerations in Choosing a Specific BiTE

A comparison between the abovementioned BiTEs can be seen in Table 1. In the complex landscape of R/R B-NHL, choosing the most suitable BiTE therapy requires a thorough consideration of various factors, including disease characteristics, the duration of treatment, cost implications, administration routes, and patient-centric aspects such as AEs and quality of life. Factors such as the patient's overall health, disease stage, and response to previous treatments are also critical for guiding this decision-making process.

Duration of Treatment

One critical consideration in choosing a BiTE for R/R B-NHL is the duration of treatment. While treatment with glofitamab and mosunetuzumab were studied as a fixed duration, in the trials of epcoritamab and odronextamab the treatment was continuous until progression or unacceptable toxicity, although newer trials are exploring an endpoint to these as well. Although the effect of treatment duration on efficacy remains uncertain, it clearly influences both costs and

Table 1 Summary and Comparison of the Current Available Bi-Specific T Cell Engagers for the Treatment of Relapsed/Refractory B-Cell Non-Hodgkin's Lymphoma

	Glofitamab	Epcoritamab	Mosunetuzumab	Odronextamab
Brand name	Columvi	Epkinly	Lunsumio	To be announced
Target antigens	CD3; CD20			
Administration route	IV	SC	SC	IV
Pivotal trial	Dickinson MJ et al 2022[22]	Thieblemont C et al 2023[26]	Budde L et al 2022[31]	Bannerji R et al 2022[36]
Duration of therapy	Fixed - 12 cycles total	Until progression or unacceptable toxicity	Depending on response - 8 cycles at minimum, up to 17 cycles in trial	Until progression or unacceptable toxicity
Efficacy - ORR, CR (%)	ORR - 52%, CR - 39%	ORR - 63%, CR −39%	ORR - 80%, CR - 60%	ORR - 51%, CR - 37%
Rates of CRS (%); grade ≥ 3 (%)	63%; 4%	49.7%; 2.5%	44%; 2%	61%; 7%
Rates of ICANS (%); grade ≥ 3 (%)	8%; 3%	6%; 0.6%	6%; 0%	12%; 3%
Date of FDA approval	June 2023	May 2023 – DLBCL, June 2024 - FL	December 2022	Not yet approved
Approved indication	R/R DLBCL following two or more lines of therapy	R/R DLBCL and FL following two or more lines of therapy	R/R FL following two or more lines of therapy	Still investigational for both R/R FL and R/R DLBCL following two or more lines of therapy

Notes: Duration of therapy, efficacy and rates of CRS and ICANS are derived from the respective pivotal trials.
Abbreviations: CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; FDA, Food and Drug administration; FL, follicular lymphoma; ICANS, immune cell-associated neurotoxicity syndrome; IV, intravenously; ORR, overall response rate; R/R, relapsed or refractory; SC, subcutaneously.

the need for long-term healthcare utilization by patients. New studies of epcoritamab are looking at a fixed duration of treatment. The results of these studies are eagerly awaited. The role of BiTEs as a bridging therapy for patients adequately fit to undergo treatment with CAR T cell therapy or autologous/allogeneic stem cell transplant still requires further research.

Cost Implications

Cost is an inevitable factor in the selection of BiTE therapy, as these treatments are usually involved with substantial economic costs (outside of a clinical trial). The substantial financial burdens include drug acquisition costs, administration fees (outpatient and inpatient), and potential expenses related to managing AEs. As mentioned above, while some BiTEs may offer cost-effectiveness due to shorter treatment durations, others with extended treatment regimens may lead to increased overall expenses. Future comparative cost-effectiveness analyses, factoring in both direct and indirect costs, are needed for hematologists and healthcare policy makers alike in making informed decisions that balance clinical efficacy and financial sustainability.

Administration Route

The administration route is a consideration that directly impacts treatment adherence, patient convenience, and potential AEs. Providers must assess both the practicality and safety of the chosen administration route. SC and IV routes each have distinct advantages and disadvantages. Subcutaneous administration, for instance, may enhance patient compliance and reduce the burden on healthcare facilities. On the other hand, intravenous administration may offer precise control over drug delivery but may necessitate frequent and longer clinic visits. Considering factors such as vascular access, patient preference, and healthcare infrastructure should be performed prior to treatment initiation.

For example, when considering IV or SC administration of rituximab for DLBCL patients, one study found similar efficacy and safety with SC administration (aside for more injection-site reactions); however, patient satisfaction and convenience were substantially better, as were shorter administration time and overall hospital time.[40] Another study reported reduced active healthcare professional (HCP) time and costs.[41] Results of SC administration of daratumumab for patients with multiple myeloma showed similar results in terms of preserved efficacy with lesser costs and HCP time.[42–44]

Patient Considerations

Adverse Events (AEs)

The potential AEs associated with BiTE therapy represent a crucial consideration in the treatment decision-making process. As these therapies involve the activation of T cells to target malignant cells, physicians must be vigilant about immune-related AEs, in this patient population, which is usually heavily pretreated and having accumulated different toxicities from past treatments. CRS and ICANS are common concerns with BiTE therapies and while typically mild, can be severe. In this regard, the risk of CRS was reported to be higher in glofitamab relative to other BiTEs, probably related to its unique construct. Providers must carefully assess the patient's tolerance to potential AEs, considering pre-existing comorbidities, organ function, and performance status, and additional considerations, namely central nervous system involvement of the underlying disease. Monitoring strategies and preemptive interventions should be established to manage and mitigate AEs ensuring the overall safety and well-being of the patient throughout the course of treatment.

Quality of Life (QOL)

To the best of our knowledge, thus far no studies assessing QOL in BiTE therapy have been published. R/R B-NHL patients often face significant physical and emotional challenges, and the chosen of BiTE therapy should aim to strike a balance between disease control and preserving or improving the patient's overall well-being. Factors such as treatment-related fatigue, cognitive impairment, and emotional distress should be carefully evaluated. Past data has shown that engaging in shared decision-making with patients, taking into account their preferences and values when selecting a therapy has been associated with better QOL.[45,46] Quality of life assessments and patient-reported outcomes should be integrated into the treatment monitoring process to ensure a holistic approach to care.

How to Choose a Suitable BiTE: Individualized Selection of Therapy Based on Patient Profiles

At present, the four BiTEs discussed in this review have shown efficacy in the treatment of R/R B-NHL, but the various clinical trials included markedly different indications, patient populations, treatment durations, and outcome measure, making a head-to-head comparison of efficacy impossible. Such analyses will take time as they will likely arise from accumulated experience of real-world data and require tools such as propensity-score matching; nevertheless, they will prove instrumental in delineating the optimal positioning of glofitamab and epcoritamab within the therapeutic armamentarium for R/R DLBCL, with less compelling data for the use of odronextamab and mosunetuzumab in this setting. In the absence of a head-to-head comparison, their selection should be made on an individual basis.

The earliest data accrued for the use of BiTEs in R/R FL has principally been for mosunetuzumab. With notable clinical outcomes and an acceptable safety profile, this treatment is now being integrated into clinical practice. As of June 2024, epcoritamab has also been added to the therapeutic armamentarium.

With data from pivotal studies in hand, an attempt was made to receive FDA approval for odronextamab, attempting to become the first BiTE approved for both R/R FL and DLBCL. However, the FDA opted to defer its approval in March 2024, citing concerns regarding the progress of the Phase 3 confirmatory trial, rather than any issues pertaining to efficacy or safety.[39]

Summary

In the rapidly evolving landscape of relapsed or R/R B-NHL treatment, the treatment with BiTEs is an up-and-coming choice of treatment that requires a refined and comprehensive evaluation by expert hematologists.

With no direct comparison of efficacy, factors such as duration of treatment, cost implications, administration route, and patient considerations, including AEs and QoL, collectively shape the decision-making process. A thorough understanding of the unique features of each BiTE therapy, coupled with a personalized approach to patient care, will enable providers to optimize treatment outcomes while prioritizing the overall well-being of their patients. There is still a vital need for data on patient QoL during and after treatment with these agents. Improvement in patient QoL and satisfaction will ultimately contribute to patient adherence and compliance with the treatment, aspects which should be further studied as well.

As the field continues to advance, ongoing research and clinical experience will contribute to shaping the decision-making framework for selecting the most suitable BiTE therapy in the management of R/R-NHL.

Abbreviations

Adverse event (AE), Bispecific T cell engager (BiTE), B cell non-Hodgkin's lymphoma (B-NHL), Chimeric antigen receptor (CAR), Cytokine release syndrome (CRS), Complete response (CR), Diffuse large B cell lymphoma (DLBCL), Food and Drug administration (FDA), Follicular lymphoma (FL), Healthcare professional (HCP), Immune cell-associated neurotoxicity syndrome (ICANS), Intravenously (IV), Overall response rate (ORR), Quality of life (QoL), Relapsed or refractory (R/R), Subcutaneously (SC).

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