DLBCL Treatment: Emerging Targeted Therapies at EHA 2026

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> Diffuse large B-cell lymphoma (DLBCL) remains a significant clinical challenge, with a substantial proportion of patients experiencing relapse or refractory disease following standard chemoimmunotherapy. The need for novel therapeutic strategies that improve durable response rates and overall survival, particularly in the relapsed/refractory (R/R) setting, is pressing. An expert roundtable at EHA 2026 focused on the evolving landscape of targeted therapies, highlighting their potential to address unmet needs in DLBCL management.

KEY TAKEAWAYS

- The Pivot: The discussion centered on integrating novel targeted agents, including bispecific antibodies and CAR T-cell therapies, into DLBCL treatment algorithms.
- The Data: Specific data points for individual agents were discussed, emphasizing response rates and progression-free survival in R/R DLBCL.
- The Action: Clinicians should evaluate patient eligibility for these advanced therapies, considering their efficacy profiles and toxicity management.

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin lymphoma, with approximately 60-70% of patients achieving long-term remission with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy.1 However, 30-40% of patients experience primary refractory disease or relapse after initial treatment, necessitating alternative therapeutic approaches.1 For these relapsed/refractory (R/R) DLBCL patients, outcomes have historically been poor, with second-line salvage chemotherapy followed by autologous stem cell transplantation (ASCT) offering curative potential for only a subset of eligible patients.2 The discussion at EHA 2026 addressed the critical need for therapies that improve upon these outcomes, particularly for patients ineligible for ASCT or those who relapse post-ASCT.2

Targeted Therapies in Relapsed/Refractory DLBCL

The expert roundtable at EHA 2026 reviewed several classes of targeted therapies demonstrating efficacy in R/R DLBCL. Chimeric antigen receptor (CAR) T-cell therapy has emerged as a significant advance, with three CD19-directed CAR T-cell products (axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel) approved for R/R DLBCL.3 These therapies have shown durable responses in patients who have failed two or more lines of systemic therapy. For instance, in the ZUMA-1 trial, axicabtagene ciloleucel demonstrated an objective response rate (ORR) of 83% and a complete response (CR) rate of 58% in R/R DLBCL patients, with a 5-year overall survival (OS) rate of 42.6%.4 Tisagenlecleucel, in the JULIET study, achieved an ORR of 53.7% and a CR rate of 37.1%, with a 5-year OS of 32.3%.5

Lisocabtagene maraleucel, evaluated in TRANSCEND NHL 001, showed an ORR of 73% and a CR rate of 53%, with a 2-year OS of 51%.6

Bispecific antibodies represent another promising class of agents. These molecules are designed to engage both T-cells and lymphoma cells, facilitating T-cell-mediated cytotoxicity. Mosunetuzumab, a CD20xCD3 bispecific antibody, has demonstrated an ORR of 35% and a CR rate of 17.8% in heavily pretreated R/R DLBCL patients in a phase 1/2 study.7 The median duration of response (DOR) for responders was 22.8 months.7 Glofitamab, another CD20xCD3 bispecific antibody, showed an ORR of 51.6% and a CR rate of 39.4% in R/R DLBCL patients after two or more prior lines of therapy, including those previously treated with CAR T-cell therapy.8 The median DOR was 18.6 months.8 Epcoritamab, a CD3xCD20 bispecific antibody, achieved an ORR of 63% and a CR rate of 39% in a phase 1/2 study of R/R DLBCL patients, with a median DOR of 15.6 months.9

Other emerging targeted therapies discussed included antibody-drug conjugates (ADCs) and small molecule inhibitors. Polatuzumab vedotin, a CD79b-directed ADC, in combination with bendamustine and rituximab (Pola-BR), significantly improved progression-free survival (PFS) compared to BR alone in R/R DLBCL patients ineligible for ASCT.10 The median PFS was 9.5 months for Pola-BR versus 3.7 months for BR, with a hazard ratio (HR) of 0.36 (95% CI, 0.25-0.52; $p < 0.001$).10 Tafasitamab, a CD19-directed antibody, in combination with lenalidomide, demonstrated an ORR of 60% and a CR rate of 40% in R/R DLBCL patients, with a median DOR of 21.6 months.11

Challenges and Future Directions

Despite the advancements, several challenges remain. Patient selection for these advanced therapies is critical, requiring careful consideration of comorbidities, performance status, and prior treatment history.12 The management of treatment-related toxicities, particularly cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) with CAR T-cell therapies and bispecific antibodies, necessitates specialized expertise and infrastructure.13 Access to these therapies also varies, posing a barrier for some patients.12 Future research directions include optimizing sequencing strategies, exploring combination therapies, and identifying biomarkers to predict response and resistance. The integration of these novel agents into earlier lines of therapy, such as first-line treatment for high-risk DLBCL, is also under active investigation.14

CLINICAL IMPLICATIONS

The EHA 2026 roundtable on DLBCL treatment underscores a clear shift in the therapeutic landscape for relapsed/refractory disease. The consistent presentation of high objective response rates and durable remissions with CAR T-cell therapies and bispecific antibodies, even in heavily pretreated populations, means that clinicians can no longer default to salvage chemotherapy alone for eligible patients. The data, while still maturing for some agents, compel a re-evaluation of treatment algorithms, particularly for patients who have failed two or more prior lines of therapy. This is not merely an incremental improvement; it represents a fundamental change in the potential for long-term disease control in a historically challenging patient group. The implications for healthcare systems are substantial. The specialized infrastructure required for CAR T-cell therapy, including apheresis capabilities, inpatient monitoring for CRS and ICANS, and access to tocilizumab, creates a bottleneck in many regions. While bispecific antibodies offer an 'off-the-shelf' alternative, their own toxicity profiles still demand careful management, often in an inpatient setting

initially. Pharmaceutical companies developing these agents, such as Gilead Sciences (axicabtagene ciloleucel), Novartis (tisagenlecleucel), Bristol Myers Squibb (lisocabtagene maraleucel), Genentech/Roche (mosunetuzumab, glofitamab), and AbbVie/Genmab (epcoritamab), must continue to invest in real-world data collection and support for toxicity management education. The cost-effectiveness of these therapies, particularly in the context of their durable benefits, will also be a persistent point of discussion for payers and guideline bodies like NICE and NCCN.

For patients, these advancements offer renewed hope. Where previously a diagnosis of R/R DLBCL often carried a grim prognosis, the availability of therapies with the potential for long-term remission fundamentally alters the conversation. However, the complexity of these treatments, the potential for severe side effects, and the logistical hurdles of access mean that patient education and shared decision-making are more critical than ever. Patients need clear, precise information about the benefits, risks, and practicalities of CAR T-cell therapy versus bispecific antibodies, and how these compare to conventional options. The challenge now lies in ensuring equitable access and optimal delivery of these sophisticated treatments to all eligible patients.

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