DLBCL Treatment Sequencing: EHA 2026 Explores Current Therapies

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> Diffuse large B-cell lymphoma (DLBCL) remains a heterogeneous disease, and despite curative potential, a significant proportion of patients experience relapse or refractory disease following initial therapy. The challenge for clinicians lies in navigating the expanding therapeutic landscape to determine the most effective treatment sequence for individual patients, particularly given the varying efficacy and toxicity profiles of available agents. EHA 2026 provided a focused discussion on current strategies for sequencing established therapies in DLBCL, aiming to clarify optimal pathways for improved patient outcomes.

KEY TAKEAWAYS

- The Pivot: The discussion at EHA 2026 centered on optimizing the sequence of existing DLBCL therapies rather than introducing novel agents.
- The Data: R-CHOP remains the standard first-line therapy, with subsequent lines of treatment dictated by response and eligibility for high-dose chemotherapy and autologous stem cell transplant (ASCT).
- The Action: Clinicians should continue to stratify DLBCL patients based on risk factors and consider early referral for transplant eligibility assessment in appropriate cases.

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin lymphoma, accounting for approximately 30-40% of adult non-Hodgkin lymphoma cases.1 While a substantial proportion of patients are cured with first-line immunochemotherapy, approximately 30-40% experience primary refractory disease or relapse after achieving remission.2 The standard of care for newly diagnosed DLBCL remains R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).3 However, the optimal management of patients who fail R-CHOP, or those with specific high-risk features, necessitates a structured approach to treatment sequencing.

The EHA 2026 session on DLBCL therapeutic pathways addressed the critical need for evidence-based strategies in selecting subsequent lines of therapy. The discussion highlighted that the choice of second-line treatment is primarily influenced by the patient's fitness, the duration of response to R-CHOP, and eligibility for high-dose chemotherapy (HDC) followed by autologous stem cell transplant (ASCT).4 Patients who relapse more than 12 months after R-CHOP are generally considered to have chemosensitive disease and are often candidates for salvage chemotherapy regimens followed by ASCT.5 Common salvage regimens include R-ICE (rituximab, ifosfamide, carboplatin, etoposide), R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin), and R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin).6 A meta-analysis of salvage regimens prior to ASCT showed comparable overall response rates (ORR) ranging from 50% to 70%, with complete response rates (CR) between 25% and 45%.7

Treatment Sequencing in Relapsed/Refractory DLBCL

For patients who are refractory to R-CHOP or relapse within 12 months, the prognosis is generally poorer, and the treatment landscape becomes more complex.8 These patients often have primary refractory disease or early relapse, indicating a more aggressive biology.9 For those ineligible for ASCT due to comorbidities or age, or those who fail ASCT, several options exist, including targeted therapies and cellular therapies. Polatuzumab vedotin in combination with bendamustine and rituximab (Pola-BR) demonstrated a median overall survival (OS) of 12.4 months compared to 4.7 months with BR alone in relapsed/refractory DLBCL (HR=0.42; 95% CI, 0.24-0.73; P=0.002).10 Tafasitamab in combination with lenalidomide (Tafa-Len) showed an ORR of 60% and a CR rate of 40% in patients ineligible for ASCT, with a median duration of response of 21.5 months.11

The advent of CAR T-cell therapy has significantly altered the third-line treatment paradigm for relapsed/refractory DLBCL. Several CAR T-cell products, including axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and lisocabtagene maraleucel (liso-cel), have demonstrated superior outcomes compared to standard salvage chemotherapy in this setting.12 The ZUMA-7 trial, comparing axi-cel to standard of care (SOC) as second-line therapy for early relapsing/refractory DLBCL, reported a median event-free survival (EFS) of 8.3 months for axi-cel versus 2.0 months for SOC (HR=0.40; 95% CI, 0.31-0.51; p<0.001).13 Similarly, the TRANSFORM trial showed a median EFS of 10.1 months for liso-cel versus 2.3 months for SOC (HR=0.34; 95% CI, 0.22-0.52; p<0.0001).14 These data support the earlier integration of CAR T-cell therapy into the treatment sequence for eligible patients.

The EHA 2026 discussion also touched upon emerging data for bispecific antibodies, which offer an off-the-shelf alternative to CAR T-cell therapy, particularly for patients who are ineligible for or fail CAR T-cell therapy. Mosunetuzumab, a CD20xCD3 bispecific antibody, demonstrated an ORR of 35% and a CR rate of 20% in heavily pretreated relapsed/refractory DLBCL patients.15 Glofitamab, another CD20xCD3 bispecific antibody, achieved a CR rate of 39% in a similar patient population.16 These agents are currently being investigated in earlier lines of therapy and may further refine the sequencing algorithm in the future.

The session concluded that while R-CHOP remains the cornerstone, subsequent treatment decisions require careful consideration of patient-specific factors, disease biology, and the evolving evidence base for targeted and cellular therapies. The integration of CAR T-cell therapy into earlier lines for high-risk patients, and the potential role of bispecific antibodies, represent significant advancements that necessitate ongoing refinement of treatment algorithms. Limitations of current data include the lack of head-to-head comparisons between all available second and third-line agents, and the need for further real-world evidence to confirm efficacy and safety in broader patient populations. Future research will likely focus on identifying predictive biomarkers to guide treatment selection and optimize sequencing strategies.

> **CLINICAL IMPLICATIONS**
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> The EHA 2026 discussion on DLBCL treatment sequencing underscores a critical shift in how clinicians must approach relapsed or refractory disease. The era of simply cycling through cytotoxic regimens until futility is over. The robust data supporting CAR T-cell therapy in the second-line setting for early relapsing/refractory patients, as evidenced by ZUMA-7 and TRANSFORM, means that deferring this option is increasingly difficult to justify for eligible patients. This necessitates earlier identification and referral for CAR T-cell assessment, which has significant implications for resource allocation and infrastructure within oncology centers.

> For the pharmaceutical industry, the continued expansion of effective agents, from antibody-drug conjugates like polatuzumab vedotin to bispecific antibodies such as mosunetuzumab and glofitamab, creates a competitive landscape. While these offer valuable options, particularly for patients ineligible for or failing CAR T-cell therapy, the challenge will be to delineate their precise role and optimal sequence. Payers and guideline bodies, including NCCN and ESMO, will need to rapidly integrate these evolving data to ensure access to appropriate therapies without creating unsustainable cost burdens. The current evidence, while compelling for individual agents, still lacks comprehensive head-to-head comparisons across all lines of therapy, leaving some ambiguity in the 'best' sequence.
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> Ultimately, the patient experience is at the forefront. The availability of more effective treatments, even in the relapsed/refractory setting, offers renewed hope. However, the complexity of these pathways, the potential for significant toxicities, and the logistical demands of cellular therapies require thorough patient education and shared decision-making. Clinicians must balance the promise of extended survival with the practicalities of treatment delivery and the potential impact on quality of life. The dry precision of clinical trial data must translate into a nuanced, individualized approach at the bedside, ensuring that the right therapy is delivered at the right time for each patient with DLBCL.

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