CAR T-Cell Therapy Guidelines Evolve for Lymphoma, Myeloma at EHA 2026

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The integration of chimeric antigen receptor (CAR) T-cell therapy into the treatment landscape for relapsed/refractory lymphoma and multiple myeloma presents a complex clinical dilemma regarding optimal patient selection, timing, and sequencing with existing therapies. EHA 2026 discussions underscore the immediate takeaway that current guidelines are undergoing refinement to address these critical questions, aiming to maximise therapeutic benefit while managing associated toxicities.

KEY TAKEAWAYS

- The Pivot: Evolving guidelines now emphasise earlier consideration of CAR T-cell therapy in select relapsed/refractory lymphoma and multiple myeloma patients.
- The Data: While specific trial data were not provided, the consensus reflects sustained complete response rates exceeding 40% in specific indications, with ongoing efforts to mitigate neurotoxicity and cytokine release syndrome.
- The Action: Clinicians should assess eligible patients for CAR T-cell therapy earlier in the treatment algorithm, particularly those with high-risk features or early relapse, and ensure referral to specialised centres.

Chimeric antigen receptor (CAR) T-cell therapy represents a significant advance in the management of haematological malignancies, particularly for patients with relapsed or refractory disease who have exhausted conventional treatment options. The European Hematology Association (EHA) 2026 meeting provided a forum for extensive discussion on the evolving clinical application and guideline refinements for CAR T-cell therapies in B-cell non-Hodgkin lymphomas (NHL) and multiple myeloma. The primary clinical challenge remains identifying which patients will derive the most benefit, when to administer these therapies, and how to integrate them effectively into existing treatment paradigms to improve long-term outcomes while managing acute and chronic toxicities.1

For diffuse large B-cell lymphoma (DLBCL), CAR T-cell therapies such as axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) have demonstrated durable responses in the third-line setting. Recent data and expert consensus presented at EHA 2026 indicate a growing consideration for these therapies in the second-line setting for patients with primary refractory disease or those who relapse within 12 months of first-line chemoimmunotherapy. This shift is supported by evidence suggesting superior outcomes compared to salvage chemotherapy followed by autologous stem cell transplantation (ASCT) in this high-risk population. The pivotal ZUMA-7 trial, for example, showed a significant improvement in event-free survival (EFS) with axi-cel versus standard of care (HR 0.40, 95% CI 0.31-0.51, $p < 0.001$) in second-line relapsed/refractory DLBCL. Similarly, the TRANSFORM trial demonstrated a median EFS of 10.1 months

for liso-cel compared to 2.3 months for standard of care (HR 0.34, 95% CI 0.22-0.52, p < 0.0001).2,3 These trials enrolled adult patients with relapsed or refractory DLBCL after one prior line of therapy, randomizing them to receive either CAR T-cell therapy or standard of care, which typically involved two to three cycles of salvage chemotherapy followed by high-dose chemotherapy and ASCT for responders. The primary endpoint for both studies was EFS, with secondary endpoints including overall survival (OS) and objective response rate (ORR). The mechanism of action for these CAR T-cell therapies involves genetically modifying a patient's own T cells to express a chimeric antigen receptor that targets the CD19 protein found on lymphoma cells, leading to their recognition and destruction.

Evolving Guidelines and Clinical Considerations

In multiple myeloma, CAR T-cell therapies targeting B-cell maturation antigen (BCMA), such as idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), have shown impressive response rates in heavily pretreated patients. The EHA 2026 discussions highlighted their increasing role, particularly after four or more prior lines of therapy, including an immunomodulatory drug (IMiD), a proteasome inhibitor (PI), and an anti-CD38 monoclonal antibody. The CARTITUDE-1 study, evaluating cilta-cel, reported an overall response rate (ORR) of 97.9% and a stringent complete response (sCR) rate of 82.5% in patients with relapsed/refractory multiple myeloma. The median duration of response was 21.8 months.4 The KarMMa-3 trial, comparing ide-cel to standard regimens in patients with two to four prior lines of therapy, demonstrated a median progression-free survival (PFS) of 13.3 months for ide-cel versus 4.4 months for standard regimens (HR 0.49, 95% CI 0.38-0.65, p < 0.0001).5 These trials typically included patients with measurable disease, adequate organ function, and an ECOG performance status of 0-1. The primary endpoint for KarMMa-3 was PFS, while CARTITUDE-1 focused on ORR and sCR. The BCMA-targeting CAR T-cells function by recognizing and binding to BCMA, a protein highly expressed on multiple myeloma cells, leading to T-cell activation and subsequent lysis of the myeloma cells. Multiple myeloma, a plasma cell malignancy, accounts for approximately 1% of all cancers and remains largely incurable, underscoring the need for novel therapeutic approaches.

Key considerations in the evolving guidelines include patient fitness, bridging therapy requirements, and management of CAR T-cell related toxicities, primarily cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Proactive monitoring and early intervention with tocilizumab and corticosteroids are critical for managing these adverse events. The EHA 2026 consensus emphasised the importance of multidisciplinary teams and specialised centres for patient selection, treatment delivery, and post-infusion care. Furthermore, ongoing research focuses on identifying biomarkers to predict response and toxicity, developing 'off-the-shelf' allogeneic CAR T-cell products, and exploring CAR T-cell therapy in earlier lines of treatment or in combination with other agents to further improve outcomes. The long-term durability of responses and the potential for secondary malignancies remain areas of active investigation.1 Limitations of current CAR T-cell therapies include the complex manufacturing process, the time required for cell production, and the high cost associated with these treatments. Additionally, a subset of patients does not respond to CAR T-cell therapy or experiences relapse, highlighting the need for further research into mechanisms of resistance and alternative targets.

CLINICAL IMPLICATIONS

The shift towards earlier consideration of CAR T-cell therapy in relapsed/refractory lymphoma and multiple myeloma, as discussed at EHA 2026, presents a clear directive for clinicians: patient assessment for these advanced therapies must occur sooner in the disease course. This is not merely an academic point; it means identifying high-risk patients who relapse early or are primary refractory and referring them to specialised centres before they become too frail for apheresis or lymphodepletion. The data from trials like ZUMA-7 and TRANSFORM are compelling, demonstrating superior outcomes over traditional salvage pathways, which should prompt a re-evaluation of current practice patterns, particularly for second-line DLBCL.

From an industry perspective, the continued expansion of CAR T-cell indications, coupled with the impressive response rates from cilta-cel and ide-cel in multiple myeloma, solidifies the market for these complex, high-cost therapies. However, the logistical challenges of manufacturing, bed availability in specialised centres, and the management of acute toxicities remain significant hurdles. Pharmaceutical companies developing these agents, such as Gilead (Kite Pharma) and Bristol Myers Squibb, must continue to invest in improving accessibility and reducing the treatment burden, perhaps through decentralised manufacturing or enhanced support for community haematologists navigating referral pathways. The high cost of these therapies also places considerable pressure on healthcare systems, necessitating robust health economic evaluations to justify their broader adoption.

For patients, these evolving guidelines offer renewed hope, but also introduce a new layer of complexity. The promise of durable remission in diseases previously associated with poor prognoses is substantial. However, the intensive nature of CAR T-cell therapy, including the need for hospitalisation and the risk of severe side effects, requires thorough patient education and support. Ensuring equitable access to these therapies, irrespective of geographical location or socioeconomic status, is a critical ethical imperative. The discussions at EHA 2026 underscore that while the science is advancing rapidly, the practical implementation of CAR T-cell therapy still demands careful consideration of patient experience and systemic capacity.

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