

Liso-Cel Delivers Durable OS Benefit in R/R LBCL, Redefining Treatment

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Relapsed or refractory large B-cell lymphoma (R/R LBCL) remains a formidable challenge, particularly for patients whose disease progresses after initial chemoimmunotherapy. For years, the standard approach for these patients involved salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant (ASCT), a regimen fraught with toxicity and often limited by patient fitness.

But a substantial proportion of patients either fail to respond to salvage therapy or are deemed ineligible for transplant, leaving them with few effective options and a dismal prognosis. This unmet need has driven the development of novel therapies, with CAR T-cell therapies emerging as a transformative, albeit complex, treatment modality.

KEY TAKEAWAYS

- **The Pivot:** Liso-cel demonstrated a statistically significant and clinically meaningful overall survival benefit in second-line R/R LBCL, shifting the treatment paradigm.
- **The Data:** Liso-cel cut the risk of death by 27% (HR 0.73; 95% CI, 0.57-0.93; P=.0116) compared to standard of care.
- **The Action:** Clinicians should consider liso-cel as a preferred second-line option for eligible patients with R/R LBCL, particularly those who are transplant-ineligible or have high-risk features.

Large B-cell lymphoma is the most common aggressive non-Hodgkin lymphoma, affecting tens of thousands across Europe annually. While frontline R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) cures approximately 60-70% of patients, the remaining 30-40% will experience relapse or refractory disease. For these patients, the prognosis has historically been poor, with median overall survival (OS) often measured in months rather than years. The traditional second-line approach, involving platinum-based salvage chemotherapy followed by consolidative ASCT, is curative for only a minority, and many patients cannot tolerate or do not respond to this intensive regimen. The need for more effective and tolerable therapies for this high-risk population has been acute, driving significant research into cellular immunotherapies.¹

Lisocabtagene maraleucel (liso-cel), a CD19-directed chimeric antigen receptor (CAR) T-cell therapy, entered the therapeutic landscape with the promise of deep and durable responses in heavily pretreated R/R LBCL. Unlike traditional chemotherapy, liso-cel involves collecting a patient's own T-cells, genetically modifying them to express a CAR that targets the CD19 protein found on lymphoma cells, expanding these modified cells, and then reinfusing them into the patient. This highly personalized approach leverages the patient's immune system to specifically attack cancer cells. The

therapy is administered as a single infusion following lymphodepleting chemotherapy, which helps to create a more favorable environment for CAR T-cell expansion and persistence.²

What the trial actually measured

The TRANSFORM trial, a pivotal Phase III study, directly compared liso-cel to standard of care (SOC) in adults with R/R LBCL after one prior line of therapy. The trial enrolled 184 patients across multiple international sites, randomizing them 1:1 to receive either liso-cel or SOC. Patients in the SOC arm received two or three cycles of platinum-based salvage chemotherapy, followed by high-dose chemotherapy and ASCT for responders. Patients in the liso-cel arm received a single infusion of liso-cel after lymphodepleting chemotherapy. The primary endpoint was event-free survival (EFS), defined as the time from randomization to the first occurrence of progressive disease, relapse, or death from any cause. Secondary endpoints included objective response rate (ORR), complete response (CR) rate, progression-free survival (PFS), and overall survival (OS).³

Initial results from TRANSFORM, published in 2022, showed a dramatic improvement in EFS with liso-cel. The median EFS was 10.1 months for liso-cel compared to 2.3 months for SOC (HR 0.34; 95% CI, 0.22-0.52; $P < .0001$). This represented a 66% reduction in the risk of an event. The ORR was also significantly higher with liso-cel, reaching 86% (95% CI, 78-92) versus 48% (95% CI, 38-59) for SOC. The CR rate was 74% (95% CI, 64-82) with liso-cel, compared to 46% (95% CI, 36-57) with SOC. These early data established liso-cel as a highly effective therapy in this setting, but the question of long-term overall survival benefit remained.³

The most recent update, with a median follow-up of 24.3 months, provided the definitive answer on overall survival. Liso-cel significantly extended OS compared to SOC, cutting the risk of death by 27% (HR 0.73; 95% CI, 0.57-0.93; $P = .0116$). The median OS was not reached in the liso-cel arm, indicating that more than half of the patients were still alive at the time of analysis, while the median OS in the SOC arm was 16.7 months (95% CI, 12.8-23.7). This represents a substantial and clinically meaningful improvement for a patient population with historically poor outcomes. The 24-month OS rate was 59.9% (95% CI, 49.9-68.6) for liso-cel versus 46.9% (95% CI, 36.6-56.6) for SOC.⁴ But the OS benefit was not uniform across all subgroups. Patients with high-risk features, such as a high International Prognostic Index (IPI) score at relapse or refractory disease, appeared to derive particular benefit. For patients with primary refractory disease, the HR for OS was 0.66 (95% CI, 0.46-0.95), suggesting an even greater proportional benefit. This is critical, as primary refractory disease represents one of the most challenging subsets of LBCL. The trial was not powered to detect differences in all subgroups, and that gap matters for precise patient selection. Still, the consistent trend across various risk groups supports the broad applicability of liso-cel in this second-line setting.⁴

Safety data from TRANSFORM showed that cytokine release syndrome (CRS) and neurologic events (NEs), known toxicities of CAR T-cell therapy, were generally manageable. Grade 3 or higher CRS occurred in 4% of liso-cel patients, and Grade 3 or higher NEs occurred in 7%. These rates are consistent with previous studies of liso-cel and are generally lower than those observed with some other CAR T-cell products. The median time to onset of CRS was 5 days, and for NEs, 8 days, allowing for proactive management. The open-label design is the obvious caveat for patient-reported outcomes and some subjective assessments, but the hard endpoints like OS are less susceptible to such bias.³

The comparison to SOC in TRANSFORM is particularly relevant because it included ASCT, which is considered the gold standard for eligible patients. The fact that liso-cel outperformed this intensive regimen, even with its potential for long-term support management of / may help patients with, underscores the potency of CAR T-cell therapy. The trial

design allowed for crossover from the SOC arm to receive liso-cel upon progression, which could potentially dilute the observed OS benefit. Despite this, a significant OS advantage was still demonstrated, suggesting the true benefit of early liso-cel intervention might be even greater. The proportion of patients who crossed over was 20% (18 of 92 patients), which is not insignificant.⁴

The median duration of response (DOR) for liso-cel was not reached, further highlighting the durability of responses. In contrast, the median DOR for SOC was 6.8 months. This sustained disease control translates directly into improved quality of life and reduced need for subsequent lines of therapy, which often come with diminishing returns and increased toxicity. The long-term follow-up also provided reassurance regarding the persistence of CAR T-cells and the sustained remission in a substantial proportion of patients.⁴

The economic implications of CAR T-cell therapy are substantial, with high upfront costs. However, the potential for long-term remission and reduced need for subsequent, often ineffective, treatments could offset some of these costs over time. The improved OS also has significant societal value, allowing patients to live longer, healthier lives. The logistical complexities of CAR T-cell therapy, including apheresis, manufacturing time, and specialized inpatient care, remain a challenge for broader implementation, particularly in smaller centers. This is not a simple outpatient infusion.⁵

Liso-cel was tested only in patients with R/R LBCL after one prior line of therapy. Whether benefits extend to patients with earlier relapse, or those with more heavily pretreated disease, remains unclear from this specific trial. Other CAR T-cell therapies have shown efficacy in later lines, but the TRANSFORM data specifically addresses the second-line setting. The trial's exclusion criteria, typical for CAR T-cell studies, meant that patients with significant comorbidities or active infections were not included, which might limit the generalizability to a broader real-world population. Clinicians must carefully assess patient fitness and comorbidities when considering liso-cel.³

The sustained OS benefit observed with liso-cel in TRANSFORM marks a definitive shift in the treatment algorithm for R/R LBCL. It provides robust evidence that CAR T-cell therapy should be considered a standard second-line option, particularly for patients who are not ideal candidates for ASCT or those with high-risk disease features. The next trial needs to show how liso-cel compares head-to-head with other CAR T-cell products in this space, and whether sequential or combination strategies can further improve outcomes without undue toxicity.⁴

For a comprehensive understanding of current approaches in haematological malignancies and cellular therapies, readers may consult the Oxford Handbook of Clinical Haematology.

CLINICAL IMPLICATIONS

The TRANSFORM data on liso-cel's overall survival benefit is not merely incremental; it redefines the standard of care for second-line relapsed/refractory large B-cell lymphoma. For European GPs and specialists, this means a clear, evidence-based pathway for patients who previously faced a grim prognosis and limited effective options after failing first-line therapy. The median OS not being reached in the liso-cel arm speaks volumes about the durability of this therapy.

This outcome puts pressure on health systems to ensure timely access to CAR T-cell therapy. The logistical hurdles of apheresis, manufacturing, and specialized care are real, but the clinical benefit is now undeniable. Delaying access to an effective therapy like liso-cel, especially for patients with high-risk features, is no longer justifiable given these survival data.

But the cost remains a significant barrier. While the long-term survival benefit may reduce the need for subsequent, often futile, lines of therapy, the upfront investment is substantial. Payers will need to reconcile this with the clear clinical advantage, potentially through value-based agreements or innovative reimbursement models. This is not a cheap drug, but it is an effective one.

Clinicians must also become adept at identifying eligible patients early and managing the unique toxicities of CAR T-cell therapy. The relatively low rates of severe CRS and neurotoxicity with liso-cel are reassuring, but vigilance and specialized expertise remain paramount. This is a complex treatment, not a simple pill, and requires a dedicated multidisciplinary team.

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