

Allogeneic Cell Therapy for EBV+ PTLD: EHA 2026 Insights

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Epstein-Barr virus-positive post-transplant lymphoproliferative disease (EBV+ PTLD) remains a significant complication following solid organ or haematopoietic stem cell transplantation, carrying substantial morbidity and mortality. The challenge lies in balancing effective viral control and tumour eradication with the risks of immunosuppression and graft-versus-host disease. Allogeneic cell therapy offers a targeted approach, leveraging donor immunity against EBV-infected cells.

KEY TAKEAWAYS

- ° The Pivot: Allogeneic cell therapy provides a specific, immune-mediated strategy for EBV+ PTLD.
- ° The Data: Clinical trials demonstrate objective response rates (ORR) ranging from 60% to 80% in refractory EBV+ PTLD.
- ° The Action: Clinicians should consider allogeneic EBV-specific T-cell therapy for patients with EBV+ PTLD, particularly those refractory to rituximab or chemotherapy.

Epstein-Barr virus (EBV) infection is a common trigger for post-transplant lymphoproliferative disease (PTLD), a heterogeneous group of lymphoid proliferations that can occur after solid organ transplantation (SOT) or haematopoietic stem cell transplantation (HSCT).¹ EBV+ PTLD represents a serious complication, with incidence varying based on transplant type, immunosuppression regimen, and recipient EBV serostatus.² Untreated, it can progress rapidly, leading to organ dysfunction and death.³ Current management strategies include reduction of immunosuppression (RIS), rituximab, and chemotherapy.⁴ However, a substantial proportion of patients are refractory to these standard treatments, necessitating alternative therapeutic approaches.⁵ The EHA 2026 presentation on allogeneic cell therapy for EBV+ PTLD focused on the evolving role of adoptive cellular immunotherapies in this challenging clinical setting. The incidence of PTLD is higher in pediatric transplant recipients and in those receiving T-cell depleting agents. The risk is also elevated in patients who are EBV seronegative at the time of transplant and subsequently acquire primary EBV infection. Early diagnosis, often through monitoring of EBV viral load, is crucial for timely intervention and improved outcomes. Despite advances in conventional treatments, a significant unmet need persists for patients with refractory or relapsed EBV+ PTLD, particularly those with aggressive forms of the disease or those unable to tolerate further chemotherapy.

What the study did

The discussion at EHA 2026 highlighted data from multiple clinical trials investigating allogeneic EBV-specific T-cell (EBV-CTL) therapies. These trials typically enrolled patients with biopsy-proven EBV+ PTLD, often those who had

failed initial therapies such as rituximab or multi-agent chemotherapy.⁶ The EBV-CTLs were generated from healthy EBV-seropositive donors, often the original transplant donor, or from third-party donors.⁷ The manufacturing process involves stimulating donor peripheral blood mononuclear cells with EBV antigens to expand EBV-specific T-cells, which are then infused into the patient.⁸ This ex vivo expansion aims to generate a potent and specific T-cell product capable of recognizing and eliminating EBV-infected B cells and PTLD lesions. The mechanism of action relies on the cytotoxic activity of these T-cells against cells expressing latent EBV antigens, thereby restoring immune surveillance against the virus. The primary endpoints in these studies generally included objective response rate (ORR), complete response (CR) rate, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety, particularly the incidence of graft-versus-host disease (GvHD).⁹ Patient populations included both adult and pediatric recipients, with varying types of solid organ transplants (e.g., kidney, liver, heart, lung) and hematopoietic stem cell transplants (e.g., allogeneic, autologous).

Pooled data from several studies indicated that allogeneic EBV-CTL therapy achieved an ORR ranging from 60% to 80% in patients with refractory EBV+ PTLD.¹⁰ Complete responses were observed in approximately 40% to 60% of treated patients.¹¹ The median duration of response was frequently reported to be durable, extending beyond 12 months in many responders.¹² For instance, one meta-analysis presented at the meeting showed a 2-year OS rate of 55% (95% CI, 48%-62%) in patients receiving EBV-CTLs, compared to historical controls with significantly lower survival rates following failure of conventional therapies.¹³ The safety profile was generally favourable, with GvHD occurring in a minority of patients, typically less than 10%, and often manageable.¹⁴ The risk of GvHD was particularly low when using partially HLA-matched or third-party donor cells, or when cells were selected for specific EBV antigens.¹⁵ Cytokine release syndrome (CRS) was also observed but was generally mild to moderate and resolved with supportive care.¹⁶ The efficacy appeared to be consistent across both SOT and HSCT recipients, although the specific challenges of immunosuppression management differed between these populations.¹⁷

Limitations of the presented data include the relatively small sample sizes of individual trials and the heterogeneity in patient populations, prior treatments, and EBV-CTL manufacturing protocols.¹⁸ Most studies were single-arm, phase I/II trials, lacking direct head-to-head comparisons with other therapeutic modalities.¹⁹ The optimal timing for EBV-CTL administration, the ideal cell dose, and the need for concomitant immunosuppression adjustment remain areas requiring further investigation. Furthermore, the long-term immunological effects and potential for late toxicities require continued monitoring. Future research directions include optimising EBV-CTL manufacturing, exploring combination therapies, and identifying biomarkers to predict response and toxicity.²⁰ The development of 'off-the-shelf' universal EBV-CTL products from third-party donors is also an area of active investigation to overcome the logistical challenges of patient-specific cell generation.²¹ This approach aims to provide readily available treatment options, reducing the time from diagnosis to therapy, which is critical in rapidly progressing diseases like PTLD.

CLINICAL IMPLICATIONS

The EHA 2026 discussion on allogeneic EBV-specific T-cell therapy for EBV+ PTLD underscores a critical shift in managing this post-transplant complication. For too long, clinicians have navigated a difficult path with rituximab and chemotherapy, often encountering refractory disease with limited options. The consistent objective response rates of 60% to 80% with EBV-CTLs, even in heavily pre-treated patients, provide a

compelling argument for their earlier consideration, particularly for those who fail initial rituximab monotherapy. This is not merely an incremental improvement; it represents a targeted, immune-mediated approach that addresses the underlying viral pathology, rather than broadly cytotoxic treatments.

The relatively low incidence of graft-versus-host disease (GvHD) with EBV-CTLs, often below 10%, is a significant advantage over unselected donor lymphocyte infusions. This safety profile, combined with durable responses, suggests that these therapies could reduce the long-term morbidity associated with aggressive chemotherapy regimens. However, the logistical complexities of generating patient-specific or donor-specific EBV-CTLs remain a hurdle. The industry must focus on developing more accessible, 'off-the-shelf' products. Companies like Atara Biotherapeutics, with their allogeneic EBV-CTL product tab-cel, are at the forefront of this effort, and their progress will be instrumental in broadening access beyond specialist centres.

For patients, the prospect of a targeted therapy that offers durable remission without the severe toxicities of conventional chemotherapy is transformative. It moves beyond simply managing symptoms to addressing the root cause of the disease. While the evidence base is still largely from phase I/II trials, the consistent efficacy signals warrant a re-evaluation of current treatment algorithms. Guideline bodies, such as the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), should integrate these data into updated recommendations, providing clear guidance on the optimal timing and patient selection for allogeneic EBV-CTL therapy. The anticipation for these therapies is now transitioning into a clear call for action in clinical practice.

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