REPORT AT A GLANCE: EPSTEIN-BARR VIRUS POSITIVE POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE

Intervention	Comparator	Evidence Rating	Annual WAC	Health-Benefit Price Benchmark
tabelecleucel (Pierre Fabre)	Usual care	"A" High certainty of substantial net health benefit	N/A	$143,900 to $273,700 per year

"EBV+ PTLD is a rare and often fatal cancer associated with solid organ transplant and stem cell transplant. Unfortunately, approximately half of EBV+ PTLD cases do not respond to initial treatment or relapse, resulting in a poor prognosis. The limited evidence on tabelecleucel suggests that it provides important clinical benefits in patients with relapsed refractory EBV+ PTLD, extending survival for patients who otherwise do not usually survive beyond a few weeks to months, with few harms."

– ICER's Vice President of Research Foluso Agboola, MBBS, MPH

THEMES AND RECOMMENDATIONS

- Manufacturers should develop and maintain robust patient assistance programs for treatments such as tabelecleucel, as the high cost of such treatments can lead to decreased access.
- Manufacturers should endeavor to include less frequent HLA types in tabelecleucel banks, paying particular attention to historically underrepresented minorities. The banks should aim to include enough HLA types to cover at least 95% of the population.
- All payers, particularly state Medicaid programs, should ensure that their referral networks are adequate for timely access to testing for EBV+ PTLD and treatment with tabelecleucel.
- The manufacturer and funding agencies should support research to investigate broader uses for tabelecleucel, including the optimal place in therapy for EBV+ PTLD.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) is a rare and often fatal cancer that is associated with solid organ transplant (SOT) and allogeneic hematopoietic stem cell transplant (HSCT). The incidence of EBV+ PTLD varies based on transplant type, between 1-30% for solid organ transplants and around 3% for HSCT. EBV+ PTLD can present with or without symptoms, with generalized symptoms such malaise and fatigue, weight loss and swollen lymph nodes; patients may also have symptoms related to the organs affected by disease. Survival after diagnosis depends on the extent of the disease but is estimated to be between 40-60% overall at five years. Diagnosis with PTLD results in almost three times higher post-transplant costs compared with those not diagnosed with PTLD.

Current treatment of EBV+ PTLD includes reduction of immunosuppression, which restores T-cell function and, in non-aggressive disease, may be sufficient to control the disease. Treatment with rituximab without or without chemotherapy can be effective for CD20+ disease, with approximately 50-60% of patients responding to initial therapy. In those patients who responded, three year overall survival is reported to be up to 75% in SOT patients and up to 50% in HSCT patients. Unfortunately, approximately half of EBV+ PTLD cases are refractory to initial treatment and/or relapsed; in such cases, additional treatment options are limited and survival is poor, with a median overall survival of around three weeks for HSCT patients, and four months for SOT patients.

EBV+ PTLD has a tremendous impact on the physical, emotional, and social functioning of affected persons. Because people have already experienced serious illness and rigorous medical treatment peri-transplant, the development of EBV+ PTLD can be a shock, as people may have expected to regain health after transplant. Pain and physical fatigue may limit activities of daily living and may also affect the ability to work or go to school. The side effects of treatments such as rituximab and chemotherapy can be severe and affect quality of life. Both persons with EBV+ PTLD and their caregivers described a large caregiving burden, particularly during pharmacologic treatment. Because of the specialized nature of the care required for transplant patients, patients reported having to deal with insurance coverage barriers, particularly if they needed to seek care outside of their network, and patient groups were concerned that given the severity of EBV+ PTLD, delays in care could have severe consequences.

Tabelecleucel (tab-cel®, Ebvallo® in Europe) is an allogeneic, off-the-shelf, T-cell immunotherapy that targets and eliminates EBV-infected cells. The cells are polyclonal EBV-specific T-cells derived from healthy donors that are selected based on shared human leukocyte antigens (HLA) restriction and partially matched HLA profile. Tabelecleucel is administered intravenously for three doses per cycle for a minimum of two cycles, and can be administered for additional cycles with different HLA restrictions if there is not a complete response to the initial cycles. The manufacturer filed a Biologics License Application (BLA) with the US Food and Drug Administration on May 20, 2024, for patients with EBV+ PTLD who have received at least one prior therapy.

The primary trial of tabelecleucel (ALLELE) was single-arm. The trial enrolled 43 participants with a history of HSCT (n=14) or SOT (n=29) with relapsed or refractory EBV+ PTLD. There was an overall response

Clinical Analyses

rate of 51%, with a median duration of response of 23 months in the trial. One-year survival was 61.1% for the entire cohort (70.1% for the HSCT recipients and 56.2% for the SOT recipients), with a median overall survival of 18.4 months. In comparison, retrospective evidence estimated a median overall survival of 0.7 months for HSCT recipients and 4.1 months for SOT recipients on usual care. There were few harms noted in ALLELE, with only four patients judged to have treatment-related serious adverse events. Of note, there was one case of acute graft-versus-host disease (GvHD) but thought not to be related to tabelecleucel treatment; there were also cases noted in the expanded access program (EAP), possibly related to treatment. Given that outcomes reported from the ALLELE trial and EAP are from 2 years of follow-up or less, longer-term (i.e., 5 year survival) data are needed to confirm the durability of the benefits and the relative lack of severe harm from the treatment. Additional subgroup data are also needed to determine if there is potential effect modification by transplant type.

However, without treatment, relapsed/refractory EBV+ PTLD has a poor prognosis. Treatment with tabelecleucel appears to induce complete or partial response in at least half of patients, extending survival for patients who otherwise usually die in weeks to months, with few harms. Thus, we have a high certainty of substantial net health benefit (A) for tabelecleucel compared with usual care.

Economic Analyses

LONG-TERM COST EFFECTIVENESS

In cost-effectiveness analyses, tabelecleucel results in higher QALYs, evLYs, and life years gained over a lifetime horizon. Based on a placeholder price of $287,500 per 35-day treatment cycle, the incremental cost-effectiveness of tabelecleucel was approximately $183,449 per QALY gained and $156,668 per evLY gained. However, tabelecleucel cost-effectiveness findings should be viewed as an optimistic estimate given the limited clinical evidence available. The actual cost-effectiveness of tabelecleucel will be dependent on its price and the survival benefit of treatment. Our analysis suggests that tabelecleucel would meet commonly used cost-effective thresholds if priced between $143,900 to $273,700 per treatment cycle.

Economic Analyses

POTENTIAL BUDGET IMPACT

At tabelecleucel's placeholder price per 35-day treatment cycle of $287,500, all patients eligible for treatment with tabelecleucel in the overall population could be treated over the span of five years without crossing the ICER potential budget impact threshold of $735 million per year

Public Meeting Deliberations

VOTING RESULTS

ICER assessed, and the independent appraisal committee voted on the evidence for people with relapsed/refractory EBV+ PTLD, who have received at least one prior therapy:

- All panelists (13-0) found that current evidence is **adequate** to demonstrate a net health benefit for tabelecleucel when compared to usual care.

Panel members also weighed potential benefits and disadvantages beyond the direct health effects and weighed special ethical priorities. Voting highlighted the following as particularly important for payers and other policymakers to note:

- There is substantial unmet need despite currently available treatments.
- The treatment is likely to produce substantial improvement in caregivers' quality of life.
- The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

Tabelecleucel has not yet been approved by the FDA for EBV+ PTLD, and the manufacturers have not announced a US price for the therapy if approved. ICER has calculated a health benefit price benchmark (HBPB) to be between $143,900 to $273,700 per treatment cycle.

- Consistent with ICER's process, because there was no firm estimate of a potential launch price during the public meeting, the panel did not take a vote on the treatment's long-term value for money.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent, non-profit research institute that conducts evidence-based reviews of health care interventions, including prescription drugs, other treatments, and diagnostic tests. In collaboration with patients, clinical experts, and other key stakeholders, ICER analyzes the available evidence on the benefits and risks of these interventions to measure their value and suggest fair prices. ICER also regularly reports on the barriers to care for patients and recommends solutions to ensure fair access to prescription drugs. For more information about ICER, please visit www.icer.org.