Tabelecleucel for Epstein-Barr Virus Positive Post-Transplant Lymphoproliferative Disease: Effectiveness and Value

Revised Background and Scope

May 30, 2024

Background

Post-transplant lymphoproliferative disease (PTLD) is a rare, serious, often fatal complication of solid organ transplant (SOT) and allogeneic hematopoietic stem cell transplant (HCST), with only several hundred cases per year reported in the US (United States)[1]. The majority of cases of PTLD are associated with the acquisition or reactivation of Epstein-Barr virus (EBV) post-transplant due to immunosuppression (also called EBV+ PTLD). The majority of EBV+ PTLD are due to proliferation of B-cells.[2] The incidence of EBV+ PTLD is estimated to be between less than 1% to over 30% for SOT, with patients having transplants requiring higher levels of immunosuppression (e.g., heart, lung, multi-organ, intestinal) at higher risk than patients having kidney or liver transplants.[3] For patients undergoing HSCT, the overall incidence is estimated to be around 3%, higher in transplants involving unrelated donors (4-10%) compared with matched, related donors (1-3%).[3] There is also higher risk in patients < 10 or > 60 years old, underwent T-cell depletion therapy, or received anti-T-cell therapy.[2,4] EBV+ PTLD most commonly occurs in the first year after transplant, though it can occur later[2], and results in almost three times higher post-transplant costs compared with those not diagnosed with PTLD[5].

EBV+ PTLD can present with or without symptoms. Generalized symptoms include malaise and fatigue, decreased appetite, unintended weight loss, night sweats, fever, and swollen lymph nodes.[2] Organ-specific symptoms may also occur if disease occurs outside of lymph nodes, most commonly in the gastrointestinal tract, pulmonary system, and central nervous system.[6] Rarely, the disease can present with a fulminant course, marked by multi-organ failure and tumor lysis syndrome.[3] Physical exam and imaging tests can detect lesions, but diagnosis must be confirmed through biopsy of lesions and when indicated, bone marrow biopsy to determine whether the bone marrow is affected. There is heterogeneity in the presentation and clinical course of EBV+ PTLD based on the histology; monomorphic diffuse large B-cell lymphoma is the most common subtype. Survival

after diagnosis depends on the extent of the disease but is estimated to be between 40-60% overall at five years.[7]

Current treatment of EBV+ PTLD depends on site, morphology, and extent of disease. First-line therapy includes reduction of immunosuppression, which restores T-cell function and, in non-aggressive disease, may be sufficient to control the disease.[2] However, reduction of immunosuppression increases the risk of organ rejection or graft-versus-host disease. For solitary or limited disease, surgery or radiation therapy may be employed. If pharmacologic therapy is necessary for patients with CD20+ EBV+ PTLD, treatment with rituximab is effective and can lead to a complete response in up to 20% of cases.[2] However, if a complete response is not achieved with rituximab monotherapy, further treatment with chemotherapy or chemoimmunotherapy is recommended. Unfortunately, approximately half of EBV+ PTLD cases are refractory to currently available treatments and/or relapses; in such cases, additional treatment options are limited, and survival is poor, with a median overall survival of around three weeks for HSCT patients[1], and four months for SOT patients[8].

Tabelecleucel is an off-the-shelf, allogeneic, T-cell immunotherapy that targets and eliminates EBV-infected cells. The cells are polyclonal EBV-specific T-cells derived from healthy EBV-seropositive donors that are selected based on shared HLA restriction and partially matched HLA profile.[9] Tabelecleucel is administered intravenously, initially for three doses on days one, eight, and 15, and can be administered for additional cycles with different HLA restriction if there is no response to the initial cycle. Tabelecleucel was approved in the European Union in 2022 (as Ebvallo) for patients with relapsed or refractory EBV+ PTLD who have received at least one prior therapy. 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 (including chemotherapy for ST patients).[10]

Stakeholder Input

This revised scoping document was developed with input from diverse stakeholders, and incorporates feedback gathered during preliminary calls with those stakeholders and open input submissions from the public. Based on feedback on the draft scope, we have highlighted the heterogeneity of EBV+ PTLD and revised our list of outcomes. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of tabelecleucel.

While EBV+ PTLD is a rare disease, with only a few hundred cases diagnosed in the US each year, it can have a tremendous impact on the physical, emotional, and social functioning of affected persons. Patients have already experienced serious illness and rigorous medical treatment regimens peri-transplant, and the development of EBV+ PTLD can be a shock, as patients 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. Depression and isolation have also been described by persons with EBV+ PTLD, particularly if treatment takes place far from their home and support system. Additionally, people who were diagnosed with EBV+ PTLD described persistent anxiety, specifically the fear that the cancer could return. Finally, social isolation is common, in part because persons with PTLD may avoid public places due to immunosuppression.

Patient groups expressed concern that due to the severity of refractory or relapsed EBV+ PTLD and lack of current treatment options, any delays in care due to the need for prior authorization may be deadly and should be minimized to the extent possible to facilitate timely access to new treatments. Additionally, patient groups were concerned about the potential cost of any new treatments, as orphan drugs are often expensive and thus may not be affordable for the patients who need treatment.

Report Aim

This project will evaluate the health and economic outcomes of tabelecleucel for EBV+ PTLD. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence, such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Applicable Framework Adaptations

We propose to assess tabelecleucel under an adaptation of the ICER Value Framework for treatments of serious, ultra-rare conditions because we believe they meet the following criteria:

- The eligible patient populations for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.
- There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals.

We do not currently believe that tabelecleucel should be considered under an adaptation of the ICER Value Framework for treatments of high-impact "single and short-term therapies" (SSTs). Our preliminary review of the current state of the evidence and conversations with several clinical experts indicate that while tabelecleucel appears to provide clinical benefit for patients with relapsed or refractory EBV+ PTLD who have received at least one prior therapy, its curative potential is currently unknown. However, the final decision on whether the therapy meets the criteria for an SST will be included in the model analysis plan, following a formal systematic literature review of the current state of evidence and additional input from the manufacturer and other stakeholders.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; observational studies and case series will be considered for inclusion as well, given the limited evidence base for tabelecleucel for EBV+PTLD. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for this review is people with Epstein-Barr virus-positive post-transplant lymphoproliferative disease (EBV+ PTLD), who have received at least one prior therapy.

Data permitting, we intend to assess evidence on treatment for EBV+ PTLD for groups stratified by:

- Transplant type (hematopoietic stem-cell transplant vs. solid organ transplant)
- Prior systemic therapy for SOT group (e.g., rituximab with/without chemotherapy)
- Sociodemographic factors (e.g., sex, age, race, ethnicity)

Interventions

The intervention of interest will be:

- Tabelecleucel (Pierre Fabre Laboratories, Atara Biotherapeutics)

Comparators

Data permitting, we intend to compare tabelecleucel to usual care, which may include pharmacologic or nonpharmacologic treatment options.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Quality of Life
    - Mortality
    - Disease progression
    - Degree of immunosuppression
    - Sustained remission
    - Duration of response
    - Avoidance of chemotherapy
    - Adverse events, including:
        - Treatment-related mortality
        - Organ rejection
        - Graft versus host disease
        - Relapse of prior disease for HSCT patients
        - Any serious adverse event (e.g., cytokine release syndrome, tumor flare, febrile neutropenia, sepsis)
        - Any adverse event leading to treatment discontinuation
- Other Outcomes
    - Progression-free survival
    - Response rate (e.g., complete, partial)
    - EBV-specific cytotoxic T-lymphocyte (CTL) precursors
    - EBV-DNA viral load

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered.

Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities*
There is substantial unmet need despite currently available treatments.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on July 26th, 2024. This scoping document provides early thoughts about the general approach.

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of tabelecleucel relative to usual care. Analyses will be conducted from the health care system perspective and the modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Patient and caregiver productivity impacts and other indirect costs will be considered in a separate modified societal perspective analysis. If direct data are lacking on patient and/or caregiver productivity, we will implement a method to capture the potential impacts of tabelecleucel on productivity (patient and/or caregiver). The modified societal perspective analysis will be considered as a co-base case when direct data on indirect costs are available, the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater

than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained.

The target population will consist of people with EBV+ PTLD that is relapsed or refractory to rituximab and/or chemotherapy in those who had an SOT or relapsed or refractory to rituximab in those who had an HSCT. Due to differences in the underlying risk of death between patients who had an SOT versus patients who had an HSCT, we anticipate modeling the cost-effectiveness of tabelecleucel in each population separately and then weighting the costs and health outcomes accordingly. The model will consist of health states that track survival and death. A cohort of patients will transition between states during predetermined cycles of one month over a lifetime time horizon, modeling patients from treatment initiation until death.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between the intervention and comparator. Treatment effectiveness will be estimated using best available evidence.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. Health outcomes will be evaluated in terms of life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to treatment acquisition, treatment administration, treatment monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. Results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, and cost per life-year gained.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework).

These services are ones that would not be directly affected by tabelecleucel (e.g., hospitalizations, chemotherapy), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of EBV+ PTLD beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

References

1. Socie G, Barba P, Barlev A, et al. Outcomes for patients with EBV-positive PTLD post-allogeneic HCT after failure of rituximab-containing therapy. *Bone Marrow Transplant*. Jan 2024;59(1):52-58. doi:10.1038/s41409-023-02127-9
2. Allen UD, Preiksaitis JK. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. Sep 2019;33(9):e13652. doi:10.1111/ctr.13652
3. Dierickx D, Habermann TM. Post-Transplantation Lymphoproliferative Disorders in Adults. *N Engl J Med*. Feb 8 2018;378(6):549-562. doi:10.1056/NEJMra1702693
4. Yamada M, L'Huillier AG, Green M. A Focused Review of Epstein-Barr Virus Infections and PTLD in Pediatric Transplant Recipients: Guidance From the IPTA and ECIL Guidelines. *J Pediatric Infect Dis Soc*. Feb 28 2024;13(Supplement_1):S31-S38. doi:10.1093/jpids/piad097
5. Hart A, Ahn YS, Watson C, et al. Cost burden of post-transplant lymphoproliferative disease following kidney transplants in Medicare-eligible patients by survival status. *J Med Econ*. Jan-Dec 2021;24(1):620-627. doi:10.1080/13696998.2021.1915793
6. Abbas F, El Kossi M, Shaheen IS, Sharma A, Halawa A. Post-transplantation lymphoproliferative disorders: Current concepts and future therapeutic approaches. *World J Transplant*. Feb 28 2020;10(2):29-46. doi:10.5500/wjt.v10.i2.29
7. Nijland ML, Kersten MJ, Pals ST, Bemelman FJ, Ten Berge IJ. Epstein-Barr Virus-Positive Posttransplant Lymphoproliferative Disease After Solid Organ Transplantation: Pathogenesis, Clinical Manifestations, Diagnosis, and Management. *Transplant Direct*. Jan 2016;2(1):e48. doi:10.1097/TXD.0000000000000557
8. Dharnidharka VR, Thirumalai D, Jaeger U, et al. P1107: Clinical outcomes of solid organ transplant patients with EBV+ PTLD who fail rituximab plus chemotherapy: a multinational, retrospective chart review study. *Hemasphere*. 2022;6(Suppl):997-998.
9. Mahadeo KM, Baiocchi R, Beitinjaneh A, et al. Tabelecleucel for allogeneic haematopoietic stem-cell or solid organ transplant recipients with Epstein-Barr virus-positive post-transplant lymphoproliferative disease after failure of rituximab or rituximab and chemotherapy (ALLELE): a phase 3, multicentre, open-label trial. *Lancet Oncol*. Mar 2024;25(3):376-387. doi:10.1016/S1470-2045(23)00649-6
10. Atara Biotherapeutics Submits Tabelecleucel (tab-cel) Biologics License Application For Treatment Of Epstein-Barr Virus Positive Post-Transplant Lymphoproliferative Disease With U.S. FDA. May 20, 2024, 2024. https://investors.atarabio.com/news-events/press-releases/detail/348/atara-biotherapeutics-submits-tabelecleucel-tab-cel