



American Society for
Transplantation and Cellular Therapy

Ms. Becca Piltch
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Institute for Clinical and Economic Review
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May 22, 2024

Dear Program Manager Pitch and ICER Reviewers,

We appreciate the opportunity to provide feedback on the draft scope for the ICER assessment of tabelecleucel in EBV+ PTLD. We commend ICER for recognizing the serious and often fatal nature of this rare disease and for applying the "ICER Value Framework for treatments of serious, ultra-rare conditions."

We offer the following points for consideration to ensure the assessment accurately reflects the complexities of EBV+ PTLD and tabelecleucel's potential value:

1. **PTLD Heterogeneity:** We urge ICER to explicitly account for the diverse morphologies of PTLD, including Hodgkin-like, plasmacytoma-like, and multiple myeloma-like forms. This is crucial, as these subtypes have varying treatment responses and should not be uniformly compared to rituximab.
2. **Evidence Base:** We acknowledge the limitations of randomized controlled trials in rare diseases. Given the paucity of prospective studies in EBV+ PTLD, we strongly recommend including high-quality prospective studies and case series in the evidence review to provide a comprehensive understanding of comparator arm effectiveness.
3. **Primary CNS PTLD:** The scope should clarify whether primary CNS PTLD will be included or excluded. This is important, as treatment considerations and outcomes can differ for this specific subtype.
4. **DLBCL-like PTLD:** We agree that the comparator therapies should reflect the current standard of care for DLBCL-like PTLD, which often involves upfront combination chemoimmunotherapy and potentially autologous stem cell transplant or CAR-T therapy in the relapsed/refractory setting. The assessment should acknowledge the potential lack of sufficient published outcomes data for these approaches in the context of PTLD.
5. **Patient-Important Outcomes:** We would encourage ICER to exclude Response Rate as a patient-important outcome if it has not been demonstrated to be predictive of improvements in progression, delay of subsequent therapy, survival, or quality of life in this setting.
6. **Adverse Events:** We recommend including relapse of prior disease as an adverse event for HSCT patients, as this is a clinically relevant outcome.
7. **Economic Model:** We suggest exploring the use of a microsimulation model if sufficient longitudinal quality-of-life data is available, as it may better capture the lifetime costs and benefits of tabelecleucel compared to a Markov model.
8. **Post-Tabelecleusal Therapies:** Including at least one line of post-tabelecleucel (and comparator) therapy in the model could capture the potential benefits of delaying



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9. subsequent therapies. The appropriateness of crossover between arms should be carefully considered if this model design is adopted.
10. **Willingness-to-Pay Threshold:** Given the rarity of EBV+ PTLD, the limited treatment options and the potential for a small, but meaningful, incremental QALY improvement, we believe a willingness-to-pay threshold of \$200,000/QALY or higher is more appropriate than standard thresholds.
11. **Benefits Beyond Health:** We agree with the assessment of the "Benefits Beyond Health and Special Ethical Priorities" category, as there is a significant unmet need in EBV+ PTLD, and no apparent disparity in prevalence among racial or ethnic groups. The impact on caregiver QOL or return-to-work remains unclear.

We trust that these considerations will enhance the rigor and relevance of ICER's assessment of temozolamide for EBV+ PTLD. We remain committed to collaborating with ICER to ensure patients with this rare and challenging disease have access to safe and effective therapies. If ICER has any questions regarding these comments, please contact Drs. Corey Cutler (corey_cutler@dfci.harvard.edu), Amar Kelkar (AmarH_Kelkar@DFCI.HARVARD.EDU), and Andreas Klein (Andreas.Klein@tuftsmedicine.org)

Sincerely,

A handwritten signature in black ink, appearing to read "CC".

Corey Cutler, MD MPH FRCP(C)
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Pierre Fabre Pharmaceuticals (PFP) Response to the Draft Scoping Document for the Assessment of Tabelecleucel for EBV+ PTLD

PFP provides comments on the draft scoping document prepared by ICER for its assessment of tabelecleucel for Epstein-Barr Virus Positive Post-Transplant Lymphoproliferative Disease (EBV+ PTLD). ICER has summarized the disease state appropriately. Our comments focus on the applicable frameworks proposed by ICER, limitations to currently available management options for EBV+PTLD, and the importance of engaging stakeholders with experience treating and living with this ultra-rare disease.

As ICER acknowledges, EBV+ PTLD is an ultra-rare, acute, and often deadly hematologic malignancy that occurs after transplantation when patient's T-cell immune responses are compromised by immunosuppression. It can impact children or adults who have undergone solid organ transplant (SOT) or hematopoietic cell transplant (HCT) and there are no Food and Drug Administration-approved treatments available. Patients who are refractory to the currently available standard of care (SOC) options or with relapsed disease have limited treatment options and a substantially worse prognosis, with a very limited survival (a median overall survival of around three weeks for HCT patients and four months for SOT patients).^{1,2,3,4,5,6} This is clearly a community with great need, so we encourage ICER to incorporate input from patients, caregivers, and providers with direct experience in this disease.

Below are some initial comments from PFP related to the draft scoping document:

Applicable Framework Adaptations

Tabelecleucel should be assessed under an adaptation of the ICER Value Framework for treatments of high-impact “single and short-term therapies” (SSTs) as well as the ICER Value Framework for treatments of serious, ultra-rare conditions.

We agree with ICER that tabelecleucel should be evaluated under the ICER Value Framework for treatments of serious, ultra-rare conditions. In addition, we believe tabelecleucel also meets the criteria to be evaluated under the ICER Value Framework for SSTs.

- As seen in the ALLELE clinical trial, tabelecleucel is delivered through a short-term course of treatment and it shows clinically meaningful outcomes, including response rate associated with durable responses, prolonged survival, and a favorable safety profile in a patient population with very poor prognosis and high mortality.⁷
 - One treatment cycle for tabelecleucel is 5 weeks. In the ALLELE trial, patients received a median of 2 cycles, with a median treatment duration of 2.1 months overall. Each cycle consisted of 3 doses of tabelecleucel administered on day 1, 8, and 15, followed by an observation period.⁷
 - Tabelecleucel has demonstrated high-impact health gains from short-term treatment. Results from the ALLELE trial demonstrated a significant response rate associated with overall survival. Fifty-one percent of the overall participants had an objective response and an estimated 1-year overall survival of 61.1%. Responses

to tabelecleucel were durable, with median duration of responses of 23 months in overall population.⁷ Median time to response was 1 month in the overall population and 63% of patients experienced clinical benefits.⁷

Comparators

No appropriate comparators to tabelecleucel exist in the R/R EBV+ PTLD population following SOT and HCT.

In the draft scoping doc, ICER acknowledged that it would look at data to compare tabelecleucel to current SOC; we want to emphasize there are limited comparators for the R/R population.

First-line SOC for EBV+ PTLD include reduction in immunosuppression, rituximab, and chemotherapy;^{2,8} however, reported response rates to SOC have been variable and a substantial proportion of patients did not respond to SOC.^{9,10,11}

- Fifty percent of HCT patients treated with rituximab did not respond, and 33% of SOT patients treated with rituximab did not respond to initial rounds of treatment.^{9,10,11} Data for the use of chemotherapy in EBV+ PTLD are limited.⁸
- Guidelines for PTLD in patients with SOT recommend extrapolating treatments from R/R DLBCL in immunocompetent patients; however, there is little evidence for the effectiveness of this in PTLD.² Retrospective studies of salvage chemotherapy for PTLD in HCT patients after rituximab failure have found limited response and high mortality.^{12,13}
- The safety concerns raised with the use of chemotherapy in PTLD patients are well documented in the literature and toxicity has remained a major concern due to the immunosuppressed state of the patients.²⁰

Given the limited options available for treatment of R/R EBV+ PTLD, in many cases treatment consists of palliative care, which is not aimed at treating the disease.¹⁴

- Such palliative care likely includes palliative chemotherapy regimens, steroids, and management of symptoms, pain, and infections, as well as radiotherapy for a small number of patients.
- Historical data show median OS is 0.7 months in HCT recipients with EBV+ PTLD for whom rituximab (R) ± chemotherapy (CT) failed and 4.1 months in SOT recipients with EBV+ PTLD for whom R+CT failed,^{4,19} indicating an unmet and urgent need for clinically tested, safe and effective therapies for this ultra-rare disease with no approved PTLD therapeutic options.¹

A proportion of patients with R/R EBV+ PTLD will likely receive a chemotherapy regimen following failure of first-line treatment as salvage chemotherapy. Chemotherapy in advanced lines is only used as a short-term palliative treatment in the absence of any approved alternative option. Conversely, tabelecleucel has demonstrated in the clinical setting durable response and meaningful overall survival outcomes and may potentially be adopted by the treating physicians as a therapy used with curative intent for R/R EBV+ PTLD patients.



Clinicians and patients may agree to attempt chemotherapy despite the low expected response rates and the substantial short- and long-term toxicity associated with these chemotherapy regimens due to limited and untested treatment options, as otherwise the patients will likely die of their EBV+ PTLD. Toxicity has been reported as a major concern with chemotherapy in both SOT and HCT patients, with high treatment-related mortality (13-50% reported) and treatment-related toxicities, as well as short- and long-term adverse events experienced in both adult and pediatric populations.²¹ Tabelecleucel has a favorable safety profile in this at-risk and ultra-rare patient population as it has demonstrated a well-tolerated safety profile in the clinical setting and there have been no cases reporting adverse reactions similar to the safety concerns observed with other adoptive T-cell therapies.

Therefore, there is a clear and high unmet need in this patient population for a treatment option like tabelecleucel that has demonstrated in the clinical setting that it effectively targets PTLD tumors without causing organ toxicity or further immune suppression.¹⁶

Outcomes

We encourage ICER to continue to solicit stakeholder input throughout the assessment process. Given the rarity of the disease, EBV+ PTLD experts can offer valuable insights on clinical outcomes of importance.

- We encourage ICER to continue to engage with EBV+ PTLD experts to understand the important nuances of the post-transplant patient population for this ultra-rare disease and prioritize the clinical outcomes of greatest importance to patients including overall survival, response rate, durable response, treatment-related mortality, and overall tolerability.
- The treatment of lymphoproliferative disorders in immunocompromised transplant recipients differs from the management of these disorders in immunocompetent patients.¹⁸
- Clinical management of PTLD has unique challenges as treatment must be balanced with the risk of graft rejection, graft versus host disease, and opportunistic infections.¹⁵ The primary goal of treatment is to eradicate PTLD while also preserving the graft and its function.^{15,17} PTLD can jeopardize the graft and compromise the hope of ever resolving a long-term, very severe primary health condition.
- Input from patients and caregivers is essential to ensure that their priorities, needs, and concerns about access to care are addressed.

Significant unmet medical need exists in the R/R EBV+ PTLD population since the estimated mortality is above one-third of diagnosed patients.⁸ Tabelecleucel has demonstrated its effectiveness in the clinical setting as an innovative, targeted and personalized treatment, which represents a potentially transformative treatment advancement with a well-tolerated and favorable safety profile for patients with R/R EBV+ PTLD, for whom there are no approved therapies.



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