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New ways to care

Pierre Fabre Pharmaceuticals (PFP) Response to the Draft Evidence Report for the Assessment of Tabelecleucel for Relapsed or Refractory EBV+ PTLD

Pierre Fabre Pharmaceuticals appreciates the opportunity to respond to ICER's Draft Evidence Report for tabelecleucel for relapsed or refractory (R/R) Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD); we thank ICER for thoughtfully considering feedback from clinical experts, patients, manufacturers, and other stakeholders during this assessment process.

We acknowledge and appreciate that ICER incorporated many of our recommendations and evidence-based feedback about model assumptions, data inputs and methodological approaches in the Draft Evidence Report.

We agree with the following findings in ICER's Draft Evidence Report:

- A high unmet need is associated with R/R EBV+ PTLD due to limitations of current disease management options, poor survival, and the devastating impact of R/R EBV+ PTLD on patients and caregivers.[1]
    - Patients have limited treatment options and are faced with very poor survival (roughly 3 weeks to 4 months).
    - It imposes tremendous impact on physical, emotional and social functioning as well as a high-cost burden with more than three-fold higher post-transplant costs compared with patients who do not have PTLD.
    - Side effects/adverse outcomes of current management options, such as organ/graft failure, can be severe and affect patient health-related quality of life.

- "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."[1]
    - Tabelecleucel demonstrated a response rate of 51% with median duration of response of 23 months and median overall survival of 18.4 months. This compares with median overall survival of 0.7 months for hematopoietic stem cell transplant (HSCT) and 4.1 months for solid organ transplant (SOT) in the real-world setting.[2]
    - Very few harms were noted in the Phase 3 ALLELE clinical trial of tabelecleucel compared with severe side effects associated with current treatment options.[2]

We are also pleased that ICER recognizes that tabelecleucel is a treatment that offers a substantial opportunity to improve patient access due to its formulation as an off-the-shelf, cytotoxic T-cell therapy and its flexible site of administration given it can be administered in an outpatient setting.

- Due to very poor survival, rapid access to treatment is critical to offer patients the best opportunity for survival. Tabelecleucel, as an off-the-shelf T-cell immunotherapy, offers an opportunity to treat more patients in a timely manner.

While ICER has described tabelecleucel as a donor-derived T-cell therapy in the Draft Evidence Report, we request ICER accurately describe tabelecleucel as an allogeneic, off-the shelf, T-cell therapy, as it appears in the literature.

We ask ICER to further consider these additional important aspects prior to the Final Evidence Report:

1. **The modified societal perspective should be included as a co-base case instead of a sensitivity analysis since patient community input substantiates the significant impact of EBV+ PTLD on caregivers and society.**

   ICER stated that it could not conduct a co-base case analysis reflecting the modified societal perspective because there was "no direct data available to inform the analysis" despite vocal feedback from the patient community regarding the significant impact of EBV+ PTLD on caregivers and society. However, as part of Section 5. Benefits Beyond Health and Special Ethical Priorities, ICER acknowledges: "An effective treatment for EBV+ PTLD could produce substantial improvement in caregivers' quality of life since patients could return to their prior level of functioning and decrease caregiver burden."

   As such, we request that ICER consider the modified societal perspective as a co-base case analysis versus a sensitivity analysis, to reflect the robust input from the EBV+ PTLD community.

2. **The eligible population estimate should be decreased based on publicly available data, and the budget impact estimates adjusted accordingly.**

   In ICER's *Revised Scoping Document* published on May 30, 2024, ICER correctly points out: "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)." This estimate of a few hundred cases in the US is well supported in the published literature. However, ICER's *Draft Evidence Report* [1] includes a budget impact analysis with estimates of 13,319 eligible patients (inclusive of SOT and HSCT) in the US over five years.

   Based on epidemiologic data derived from the published literature and appropriately weighted for transplant type, the subset of EBV+ PTLD patients (inclusive of SOT and HSCT) in the US who are refractory to first line treatment with rituximab/chemotherapy is approximately 319 patients per year, a number substantially smaller than ICER's estimate. Please see below for our calculation estimates with sources.

   We assume that there will be approximately 62,500 annual transplant patients in total (SOT 52,818; HCT 9,829). We began with the 2023 transplant incidence rates for SOT

and HCT and grew them annually on a compound annual growth rate (CAGR) based on past annual transplant data from 2016-2023 for each organ (kidney, liver, heart, lung, pancreas, intestine, multi-organ) and for allogeneic HCT.[3,4] From 2026 onward, the transplant incidence was grown at the same rate as the US population yearly growth, 0.51%, based on UN population data.[5] Transplant incidence was further split based on adults vs. children for each organ type/HCT.[6-13]

Because EBV+ PTLD incidences vary greatly depending on organ type/HCT and age group (see Table 1 below), we first applied PTLD incidence rates for each organ type/HCT for adult and children rates (SOT blended average 3.2%, dependent on organ type and age group; HCT blended average 3.0%, dependent on age group), gathered across multiple studies.[7-12,14-29] EBV+ incidence was then applied (SOT average 66.5%, dependent on organ type and age group; HCT 95.0%).[18,30-39] First line treatment rates of rituximab +/- chemotherapy were applied at a flat rate of 75% across all groups, based on published literature.[17,22,40-49]

Patients eligible for tabelecleucel therapy are relapsed/refractory to the above mentioned first lines of therapy. According to literature, 30% of these patients are refractory to rituximab +/- chemotherapy.[14-16,30,36,50-57] Little literature exists specifically for relapsed patients; therefore, refractory rates were assumed to be relapsed/refractory in the calculations. These inputs yield an estimated 1,594 patients over five years or approximately 319 patients with relapsed/refractory EBV+ PTLD per year.

Table 1. PTLD and EBV+ incidences, by transplant type and age group[7-12,14-29]

Transplant type	PTLD incidence	EBV+ incidence
HCT	Adults: 2% Children: 4%	Adults: 95% Children: 95%
Kidney	Adults: 1.5% Children: 10.1%	Adults: 55% Children: 90%
Liver	Adults: 3% Children: 4%	Adults: 80% Children: 90%
Heart	Adults: 6% Children:15%	Adults: 50% Children: 90%
Lung	Adults: 5% Children: 15%	Adults: 80% Children: 90%
Multi-organ	Adults: 12.5% Children: 25%	Adults: 79% Children: 90%
Pancreas	Adults: 9% Children: 9%	Adults: 50% Children: 90%
Intestine	Adults: 10% Children: 10%	Adults: 60% Children: 90%

Note: Incidence rates were gathered for each transplant type and age group across multiple sources of literature to determine the appropriate incidence rate to use in calculations. These rates were applied over the respective transplant type and age groups.

Therefore, the estimate for eligible patients in ICER's budget impact analysis should be revised from 13,319 eligible patients to 1,594 eligible patients over five years (equating to approximately 319 patients per year in the US). A lower budget impact typically correlates with broader patient access to an important new treatment option, which is particularly important in this situation given there are currently no FDA-approved treatments for this ultra-rare disease with poor prognosis and high mortality rates.

We ask that ICER lower the estimate of eligible patients and associated budget impact for tabelecleucel to 1,594 eligible patients over five years based on these public sources and calculations.

3. **ICER should incorporate available long-term efficacy data from the tabelecleucel expanded access protocol into its assessment to more accurately reflect the impact of tabelecleucel on longer-term outcomes.**

   ICER expressed uncertainty about the long-term durability of response for tabelecleucel based on the data from the ALLELE study. However, there are recently published longer-term data from the expanded access protocol that can be used to assess the longer-term benefits of tabelecleucel.[58] While these data represent a smaller cohort than studied in the phase 3 ALLELE study, they provide important insights that reinforce the longer-term safety and efficacy of tabelecleucel for patients with R/R EBV+ PTLD.
   - The estimated one- and two-year overall survival (OS) rates were both 70.0% (95% confidence interval [CI], 46.5-84.7) overall, both 61.5% (95% CI, 30.8-81.8) in HCT, and both 81.5% (95% CI, 43.5-95.1) in SOT (median follow-up: 8.2, 2.8, and 22.5 months, respectively). Patients responding to tabelecleucel had higher one- and two-year OS rates (94.1%) than nonresponders (0%).[58]

   We request that ICER incorporate this published longer-term efficacy data into its assessment.

4. **The costs and quality of life impacts associated with organ/graft rejection among patients with EBV+ PTLD who are treated with chemotherapy should be accounted for in the cost-effectiveness analysis, particularly given that organ/graft rejection due to reduction of immunosuppression is a major adverse outcome in chemotherapy patients, leading to devastating transplant failure with substantial cost and QALY implications.**

   There were no cases of organ/graft rejection attributable to tabelecleucel therapy reported in the ALLELE study. However, Socie et al. reported that 1-3% of patients in a real-world comparator arm experience organ/graft rejection.[59] Graft failure is associated with substantial costs and quality of life impacts. For example, Sussell et al. reported that for the average kidney transplant patient, graft failure would impose additional medical costs

of $78 079 (95% confidence interval [CI] $41 074, $112 409) and a loss of 1.66 QALYs (95% CI 1.15, 2.18).[60]

We request that ICER incorporate the above-mentioned cost and consequences of organ/graft failure for the usual care arm to accurately reflect the costs and consequences of organ/graft failure due to reduction of immunosuppression among chemotherapy patients with EBV+ PTLD.

Again, we appreciate all the actions ICER has taken to solicit and incorporate stakeholder input to date.

We trust that including the modified societal perspective will better capture the significant impact of EBV+ PTLD, not only on patients, but also on caregivers and society. In addition, adjusting the estimated size of the target population to align with published incidence estimates and the intended use of tabelecleucel is important to accurately estimate budget impact. Furthermore, incorporating longer-term safety and efficacy data from the published expanded access protocol can reduce uncertainty with estimating longer-term durability associated with tabelecleucel. Finally, the costs and consequences of organ/graft failure due to reduction of immunosuppression among EBV+ PTLD patients receiving chemotherapy impose a substantial burden on patients. These costs and quality of life impacts should be appropriately considered in the usual care arm of the cost-effectiveness model.

Tabelecleucel, as an innovative and targeted investigational medicine, represents a potentially transformative and valuable treatment advancement for patients with EBV+ PTLD who currently face poor prognosis and high mortality and for whom there are no approved therapies. Timely access to treatment is critical for these patients to offer an opportunity for survival, which underscores the importance of removing barriers that could hinder patient access to timely treatment.

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PIPC Partnership to Improve Patient Care

October 8, 2024

Sarah K. Emond, MPP
President and Chief Executive Officer
Institute for Clinical and Economic Review
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Dear Ms. Emond,

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) assessment of tabelcleucel for Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV +PTLD).

ICER acknowledges the severe toll EBV+PTLD takes on both patients and caregivers and the reality that current treatments can come with a host of side effects that further impact quality of life. PIPC encourages ICER to take the following comments into consideration.

Caregiver impact should be included in the model.

ICER chooses not to include caregiver costs in the model, despite acknowledging in the opening of the report that caregiver burden is high given the severity of disease and the side effects of currently available treatments. The literature supports this assertion that caregiver burden for PTLD is substantial.[1] The modified societal perspective ICER employs uses a proxy version of caregiver cost, while neglecting to incorporate caregiver quality-of-life. PIPC asserts that ICER should be incorporating both directs costs and caregiver quality of life and that both should be included in ICER's base case model.

ICER's model does not reflect the reported results in the trial data it has chosen to use.

The ICER model assumes that the survival benefit for tabelecleucel is the same for patients with hematopoietic stem cell transplantation (HCST) and solid organ transplant (SOT). However, the evidence the report relies on clearly states that the survival benefit is different. The ALLELE RCT reports Median survival was 18.4 months in all patients and 16.4 months in SOT, which suggests survival would be higher in HSCT.

ICER should adhere to the rates of utilization in the trial data it has chosen to use instead of extrapolating its own assumption about dosing. The ICER report states that all patients given tabelecleucel are assumed to receive 3 cycles of treatment. The source of the efficacy data suggests all patients that received at least 1 cycle of tabelecleucel - with a maximum of 3 - were included in the trial results.[1] despite this data, the ICER model assumes *all* patients received all 3

[1] Deng LX, Sharma A, Gedallovich SM, Tandon P, Hansen L, Lai JC. Caregiver burden in adult solid organ transplantation. Transplantation. 2023 Jul 1;107(7):1482-91.

cycles. The dosing in the model should reflect the source of the efficacy data.[1,4] If the mean/median dosage for those patients treated was between 1 and 3 cycles, then the costs should reflect that, as the efficacy data reflects the actual, not preferred, rate of utilization/dosing. We urge ICER to revisit the model to reflect the actual level of utilization that generated the efficacy results from the RCT, not a hypothetical treatment regimen.

ICER's oversimplification risks distorting the actual costs of the treatment being evaluated versus that of usual care.

In the description of the ICER model the report states that they assume that '*after treatment failure with tabelecleucel (or usual care) there is only one subsequent treatment.*' It is not reasonable to apply this rule equally with respect to subsequent treatment costs for patients who remain alive after successful treatment with tablecleucel and usual care.

The basic assumption is not accurate based on the literature suggesting that only a fraction of patients undergo subsequent treatments upon treatment failure in usual care.[2] [3] This assumption is contrary to the goal of assessing the treatment's clinical efficacy. The reason cost of treatment will accrue more rapidly for patients being treated with tabelecleucel is that a much higher proportion of patients being treated remain alive at each timepoint throughout the time horizon of the model than those in the usual care arm. The goal should be to keep patients alive for longer, so a modeling construct should not work against that goal.

ICER Continues to Use the Discriminatory QALY and the Similar Measure evLYG.

Multiple studies have shown that cost-effectiveness models using the quality-adjusted life year (QALY) discriminate against patients with chronic conditions, [4] and people with disabilities.[5] There is widespread recognition that the use of the QALY is discriminatory, reflected in laws that bar its use in government decision-making. The National Council on Disability (NCD), an independent federal agency advising Congress and the administration on disability policy, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments.[6] The recent nondiscrimination regulations governing Section 504 of the

[2] Socié G, Barba P, Barlev A, Sanz J, García-Cadenas I, Chevallier P, Fagioli F, Guzman-Becerra N, Kumar D, Ljungman P, Pigneux A. Outcomes for patients with EBV-positive PTLD post-allogeneic HCT after failure of rituximab-containing therapy. Bone marrow transplantation. 2024 Jan;59(1):52-8.
[3] Dharnidharka V, Thirumalai D, Jaeger U, Zhao W, Dierickx D, Xun P, Minga P, Sawas A, Sadetsky N, Chauvet P, Sundaram E. Clinical outcomes of solid organ transplant patients with Epstein-Barr virus-driven (EBV+) post-transplant lymphoproliferative disorder (PTLD) who fail rituximab plus chemotherapy: a multinational, retrospective chart review study. Blood. 2021 Nov 23;138:2528.
[4] Paulden M. Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable?. Expert review of pharmacoeconomics & outcomes research. 2017 May 4;17(3):239-42.
[5] Nord E, Pinto JL, Richardson J, Menzel P, Ubel P. Incorporating societal concerns for fairness in numerical valuations of health programmes. Health economics. 1999 Feb;8(1):25-39.
[6] https://www.ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf

Rehabilitation Act also bar the use of discriminatory measures such as QALYs in decisions impacting access to care among entities receiving federal financial assistance.

We share the concerns of NCD about the equal value of life year gained (evLYG), a similar measure created by ICER to supplement the QALY. The evLYG is a simplistic fix attempting to address criticism that the QALY devalues life years lived with a disability, yet it fails to account for oversimplified measures of quality-of-life gains in expected life years and it does not account for any health improvements in extended life years. Like the QALY, the evLYG relies on average estimates based on generic survey data and obscures important differences in patients' clinical needs and preferences, particularly those with complex diseases and from underrepresented communities.[7] It assumes that people value life year gains more than quality of life improvements, giving a lower value to health interventions for patient populations that have a lower life expectancy or fewer life years gained from treatment, which may include people with disabilities, underlying chronic conditions, older adults, and certain communities of color.[8] With the evLYG and the QALY, ICER promotes two compromised and flawed measures of health gain. Deciding which to choose is confusing and inconsistent.

ICER continues to assume a linear relationship between severity of disease and utility increments. This is an outdated approach to cost-effectiveness analysis.

As PIPC has included in past ICER comments, the field of cost-effectiveness analysis is evolving. If ICER seeks to provide credible assessments, it is imperative that its methods also evolve. There has been a widespread questioning of several of the assumptions that cost utility analysis is built on.[9] This argument has been most prominent with respect to the reliance on the assumption that every unit of health gain – measured here in health-related quality of life - is equal in value.[10] In other words, a single unit of health generates the same utility whether that health is accrued to someone who is suffering considerable disease burden, or to someone who is suffering minimal disease burden.[11] In fact, several health technology assessment systems in Europe have backed away from direct use of strict cost-per-QALY estimates for this very reason,

[7] DiStefano MJ, Zemplenyi A, Anderson KE, Mendola ND, Nair KV, McQueen RB. Alternative approaches to measuring value: an update on innovative methods in the context of the United States Medicare drug price negotiation program. Expert Rev Pharmacoecon Outcomes Res. 2024 Feb;24(2):171-180. doi: 10.1080/14737167.2023.2283584. Epub 2024 Jan 25. PMID: 37961908.
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[11] MacKillop E, Sheard S. Quantifying life: understanding the history of quality-adjusted life-years (QALYs). Social Science & Medicine. 2018 Aug 1;211:359-66.

and incorporate the role of severity adjacent to the results to make a more context-relevant models.[12,13]

A system of evaluation that treats therapeutic innovations in these disease spaces as of similar relative value for unit of health gain in less severe conditions - and for patients who have minimal disease burden - is thought by many to be inherently unfair and skewed in the wrong direction. This has obvious relevance to patients with EBV+PTSLD as the health utility value of non-responder states is below 0.4 – which is severe disease.[14]

Conclusion

ICER's assessments continue to rely on flawed metrics and dated constructs of cost-effectiveness. PIPC urges ICER to engage directly with patients and people with disabilities and amend its modeling choices to ensure their needs are met.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

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