Tabelecleucel for Epstein-Barr Virus Positive Post-Transplant Lymphoproliferative Disease: Final Policy Recommendations

December 16, 2024

Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the November 14, 2024 New England CEPAC public meeting on the use of tabelecleucel for the treatment of Epstein-Barr Virus Positive Post-Transplant Lymphoproliferative Disease. At the meeting, ICER presented the findings of its revised report on these treatments and the New England CEPAC voting council deliberated on key questions related to their comparative clinical effectiveness, potential other benefits and contextual considerations, and long-term value for money at current prices. Following the votes, ICER convened a Policy Roundtable of two patient experts, two clinical experts, and two payers to discuss how best to apply the evidence and votes to real-world practice and policy. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

A recording of the conversation can be accessed here, and a recording of the voting portion of the meeting can be accessed here. More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's report on these treatments, which includes the same policy recommendations, can be found here.

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, Special Advisor to ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Health Equity

Recommendation 1

All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with relapsed/refractory EBV+ PTLD are introduced in a way that will help reduce health inequities.

There are no data suggesting racial and ethnic differences in EBV+ PTLD prevalence. However, because the use of tabelecleucel requires partial HLA matching, less representation of some racial and ethnic groups in cell banks may reduce the chances of those groups having access to HLA-matched treatment options like tabelecleucel.

The anticipated high price for tabelecleucel may create additional substantial cost sharing burdens for patients, especially if they are outside of a benefit year in which they have already hit their out-of-pocket maximum. Furthermore, because tabelecleucel is a new and specialized therapy, it is most likely to be administered initially through transplant centers. Patients who have barriers to transportation and/or to the time needed for additional visits to their transplant center may experience challenges in accessing tabelecleucel unless providers and payers make special accommodations. All these additional concerns may lead to greater disparities in access and outcomes for patients with fewer resources.

To address these concerns:

<u>Manufacturers should take the following actions:</u>

- Manufacturers should set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments.
- Manufacturers should establish robust patient assistance programs to help those with financial barriers to access treatment.
- 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. Establishment of country and/or region-specific banks may be the most effective way to accomplish this goal.
- During the initial phase of tabelecleucel distribution, manufacturers should join all other relevant stakeholders (e.g., payers, healthcare systems, clinicians, patients) in discussions to ensure equitable, timely, and safe access to treatment. This is particularly important when new paradigms of treatment are involved, as is the case with tabelecleucel. Failure to meaningfully participate in multistakeholder meetings goes against the tenets of corporate responsibility to provide high quality, accessible, equitable care to patients.

<u>Payers should take the following actions:</u>

- Payers should consider wraparound coverage including transportation and housing to ensure equal access to diagnosis and treatment. Distance to transplant centers may affect clinical outcomes, and thus geographical and income constraints should not undermine the tenets of fair access to which all patients have a fundamental right.

- 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.

Clinical specialty societies should take the following actions:

- Facilitate research and education to help clinicians and transplant centers better identify and more quickly diagnose EBV+ PTLD and initiate appropriate care.
- Educate non-transplant specialists, including primary care physicians, about the diagnosis of EBV+ PTLD to help facilitate more rapid diagnosis of the disease and referral back to transplant centers for treatment.

Patient groups should take the following actions:

- Educate post-transplant patients about the signs and symptoms of EBV+ PTLD to help facilitate earlier presentation to care for diagnosis and access to treatment.

Payers

Recommendation 1

Payers and healthcare systems should proactively settle all the details of coverage and payment agreements for tabelecluecel treatment to avoid potentially deadly delays due to the process of negotiating single-case agreements.

The rarity of EBV+ PTLD and the specialized nature of treatment with tabelecleucel may lead to some centers needing to negotiate single-case agreements with out-of-network payers. Given the high mortality rates of patients with untreated relapsed/refractory EBV+ PTLD and the rapidity with which death can occur, delays in care from the need to negotiate single-case agreements could be deadly. Thus, it is imperative that centers who wish to offer treatment with tabelecleucel to their patients take steps to come to an agreement about payment with all potentially relevant payers such that, if needed, an agreement is already in place or can be rapidly executed.

Recommendation 2

Payers should execute the process of prior authorization with great speed and consistency to ensure that patients receive treatment in an expedited fashion.

Since tabelecleucel is likely to be administered (at least initially) by transplant centers, payers could consider gold carding transplant centers of excellence to expedite the initiation of tabelecleucel. Additionally, given the time sensitivity of treatment, payers should consider all tabelecleucel requests as expedited with a turnaround time of 48-72 hours, and if situations arise where peer-to-peer conversations are necessary, payers should ensure that those conversations happen in an expedited fashion. Payers should also ensure that their policies align with clinical trial and NCCN criteria and could consider generating a flag for expedited consideration for tabelecleucel requests to help with streamlining care.

Coverage Criteria: General

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy: https://icer.org/wpcontent/uploads/2020/11/Cornerstones-of-Fair-Drug-Coverage-_-September-28-2020.pdf

Drug-Specific Coverage Criteria: Tabelecleucel

The likely high price of tabelecleucel will lead payers to develop prior authorization criteria and consider other limits on utilization. None of these limits, however, should undermine the tenets of fair access to which all patients have a fundamental right. To explore the appropriate application of evidence to coverage policy, and to reflect the views of patient experts and clinicians on specific ways that payers might appropriately use coverage policy to manage resources prudently, we present the following perspectives on specific elements of cost sharing and coverage criteria for tabelecleucel.

Coverage Criteria

- **Age:** Age criteria are likely to follow the clinical trial criteria and will be expected to cover both children and adults.

- **Clinical Eligibility**: Payers will follow the FDA label but may consider applying elements of the pivotal clinical trial eligibility criteria should the FDA label be framed broadly. The Phase III ALLELE trial included patients with relapsed/refractory EBV+ PTLD who have had at least one prior therapy. However, clinical experts advised that some patients will have contraindications to first-line therapy (e.g., severe liver or renal dysfunction) or will rapidly worsen before completing first-line therapy and payers may receive clinically appropriate requests to approve tabelecleucel prior to completion of first-line therapy or instead of first-line therapy.

- The clinical trial eligibility criteria required that patients have an ECOG performance status ≤3 to be eligible for tabelecleucel treatment. However, clinical experts argued that this criterion is not clinically relevant given the benign side effect profile of tabelecleucel and the fact that ECOG status can change rapidly.

- **Exclusion Criteria**:

  - Given the lack of other effective therapies for relapsed/refractory EBV+ PTLD and the benign side effect profile of tabelecleucel, clinical experts felt that tabelecleucel could be safely given to many patients who would not meet the specific exclusion criteria in the pivotal trial. Thus, payers should be aware that they may receive clinically appropriate requests to administer tabelecleucel to patients with untreated CNS disease or who need for vasopressor or ventilatory support. As evidence evolves, payers should rapidly update clinical eligibility criteria to align with evidence and clinical practice guideline updates.

Dose: Payers will likely follow the clinical trial criteria of a minimum of 2 cycles if a patient responds to the initial treatment cycle, and a maximum of 4 cycles per patient, including allowing HLA restriction switches, in patients with partial or no response to treatment. However, given the lack of other effective treatment options for patients with relapsed/refractory EBV+ PTLD, clinical experts advised that they felt it could be appropriate to request coverage for additional cycles or, in some cases, a new treatment course for a later recurrence of the disease.

Manufacturers

Recommendation 1

Manufacturers should set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. With tabelecleucel, the manufacturer should make real the long-held promise of off-the-shelf therapies being more affordable than current cellular therapies (e.g., CAR-T) and calculate the launch price of tabelecleucel accordingly.

Drug prices that are set well beyond the cost-effective range cause not only financial toxicity for patients and families using the treatments, but also contribute to general health care cost growth that pushes families out of the insurance pool, and that causes others to ration their own care in ways that can be harmful.

Manufacturers should therefore price novel treatments in accordance with the demonstrated benefits to patients. In the case of tabelecleucel, its status as an off-the-shelf therapy, rather than a therapy that requires intensive individualized manufacturing, should be reflected in the launch price – that is, the savings generated by the manufacturing and administration processes should be passed on to the consumer. This would allow more patients access, generating additional data on the real-world effectiveness of novel treatments that could be used in future assessment updates.

Recommendation 2

Although EBV+ PTLD is a rare disease, tabelecleucel is being tested in other EBV-related diseases. If the eligible patient population expands, the manufacturer should consider reducing the price under the premise that treatments with larger eligible populations should have a lower price.

While the population for EBV+ PTLD is small (with an estimate of approximately 150 patients per year in the US eligible for treatment), the mechanism of tabelecleucel is applicable to other EBV-related diseases, and tabelecleucel is currently being tested in those populations. If tabelecleucel is found to be effective in other EBV-related diseases and the population eligible for treatment continues to expand, the manufacturer should consider lowering the price, as a higher price would no longer be needed to support the research and development costs associated with developing a drug to treat an ultra-rare disease.

Recommendation 3

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.

For treatments such as tabelecleucel, whose cost will likely be in the hundreds of thousands of dollars, financial toxicity for patients is of great concern, particularly in the post-transplant population who already have high medical costs due to the need for ongoing monitoring and immunosuppression. For such treatments, patient assistance programs are an important cornerstone of maintaining access. Furthermore, for a rare disease such as EBV+ PTLD, increased access will provide additional data about treatment outcomes, including effectiveness and adverse events.

Recommendation 4

Manufacturers should seek to standardize communication portals to facilitate the efficient and timely transfer of the clinical information necessary to treat patients with tabelecleucel and other future new therapies.

Clinical experts advised that for therapies such as tabelecluecel that require information such as HLA typing, the administrative burden is high due to each manufacturer having separate portals with varying formats. Thus, the complexity involved to input the relevant information before an order can be processed can cause delays in care as well increased need for staff resources to manage portal requests. Manufacturers of new therapies that require additional information (e.g., HLA typing) should look to harmonize their portal questions and information with existing portals to help decrease the administrative burden and potentially decrease delays in care.

Clinicians and Clinical Societies

Recommendation 1

Clinical specialty societies should deliver more education about both EBV+ PTLD and the availability of new treatments like tabelecleucel. Such education is critical to ensuring that clinicians can recognize and diagnose EBV+ PTLD quickly and refer appropriately to transplant centers for treatment, which may improve clinical outcomes.

The number of transplants – both organ transplants and HSCT – in the US has been increasing over time. As the number of transplant survivors increase and return back to community-based care, recognition of EBV+ PTLD outside of transplant centers is increasingly important in ensuring timely care, given the potential for rapid decline with the disease. Additionally, patients with EBV+ PTLD expressed frustration that clinicians did not always know about cutting edge treatments, and thus, the burden was on patients and caregivers to seek out novel therapies like tabelecleucel. It is one of the responsibilities of clinical specialty societies to help educate their members both about the diagnosis of EBV+ PTLD and about new and emerging treatment options. Doing so may improve clinical outcomes, particularly for underserved populations that may face barriers to diagnosis and treatment.

Researchers/Regulators

Recommendation 1

The manufacturer and funding agencies should support research to investigate broader uses for tabelecleucel, including the optimal place in therapy for EBV+ PTLD.

Current first-line treatment for EBV+ PTLD includes reduction in immunsuppresion and rituximab with or without chemotherapy. Both rituximab and chemotherapy have significant risks and toxicities. If longer-term data demonstrate that tabelecleucel provides durable remission in a substantial number of patients with low toxicity, funding agencies, and the manufacturer should support and encourage research to determine if tabelecleucel could be used as first-line therapy for EBV+ PTLD. Additionally, given that around half of patients treated with tabelecleucel did not have a

response to treatment, research should also focus on identifying characteristics, including biomarkers, that may predict treatment response. Doing so will improve treatment efficiency (i.e. delivery of the right treatment to the right patient) and also encourage research into new treatments for EBV+ PTLD patients who do not or would not respond to tabelecleucel. Finally, manufacturers and researchers should be encouraged to collect real-world data on tabelecleucel outcomes, particularly on treatment outcomes, to help push treatment parameters beyond the strict criteria associated with clinical trials.

Recommendation 2

Researchers should develop outcome measures to more accurately characterize caregiver burden for this condition.

EBV+ PTLD is a serious complication post-transplant, and we heard from patients and caregivers that the severity of the illness and rigors of treatment place a substantial burden on caregivers, particularly in the pediatric population. However, that burden is difficult to quantify without validated measures. Research to characterize caregiver burden, develop new condition-specific measures or validate existing measures such as the Zarit Caregiver Burden Interview[1] is needed to understand the impact of the disease on the caregiver and help quantify the value of new therapies. Researchers could follow the example of the work on caregiver burden that has been done in Alzheimer's Disease.

References

1. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist*. 1980;20(6):649-655.

Appendix

Appendix Tables one through three contain conflict of interest (COI) disclosures for all participants at the November 14th, 2024 Public meeting of New England CEPAC.

Appendix Table 1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Foluso Agboola, MBBS, MPH, Vice President of Research, ICER	**Sarah K. Emond, MPP**, President and Chief Executive Officer, ICER
Grace Ham, MSc, Senior Program and Events Coordinator, ICER	**Woojung Lee, PharmD, PhD**, Associate Director of Health Economics and Decision Modeling, ICER
Grace Lin, MD, Medical Director for Health Technology Assessment, ICER	**Avery McKenna, BS**, Associate Research Lead, ICER
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*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Appendix Table 2. New England CEPAC Panel Member Participants and COI Disclosures

Participating Members of New England CEPAC*	
Austin Frakt, PhD, Associate Director, Partnered Evidence-Based Policy Resource Center, VA Boston Healthcare System and Harvard TH Chan School of Public Health	**George Goshua, MD, MSc**, Assistant Professor of Medicine (Hematology-Oncology), Yale
Rebecca Kirch, EVP, Policy and Programs, National Patient Advocate Foundation	**Stephen Kogut, PhD**, Professor, University of Rhode Island
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Aaron Mitchell, MD, MPH, Assistant Attending, Memorial Sloan Kettering Cancer Center	**Brian P. O'Sullivan, MD**, Professor of Pediatrics, Geisel School of Medicine at Dartmouth
Jo Porter, MPH, Chief Strategy Officer, NH Center for Justice and Equity	**Joseph Ross, MD, MHS**, Professor of Medicine and Public Health, Yale University
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Jason Wasfy, MD, MPhil, Associate Professor, Harvard Medical School	

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Appendix Table 3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Upton Allen, O.Ont., CD, MBBS, MSc, FAAP, FRCPC, Hon FRCP (UK), FIDSA, Professor, Department of Paediatrics and Institute of Health Policy Management and Evaluation, University of Toronto	No conflicts to disclose.
Joseph A. Kopec, Patient Advocate	No conflicts to disclose.
Sarah Nikiforow MD, PhD, Technical Director Immune Effector Cell Program, Dana-Farber Cancer Institute	Dr. Sarah Nikiforow served as a PI at Dana-Farber Cancer Center for Tabelecleucel on Atara Biotherapeutics studies (CTL 201, CTL 901, CTL 302, CTL 301, CTL 205), but she did not accept any salary support or payment for serving as PI.
Melissa Pozotrigo, PharmD, BCOP, Senior Clinical Oncology Pharmacist, Oncohealth	Dr. Pozotrigo is a full-time employee at Oncohealth.
Emily Tsiao, PharmD, BCPS, Medical Policies Clinical Pharmacist, Premera Blue Cross	Dr. Tsiao is a full-time employee at Premera Blue Cross.
Douglas Worthen, Patient Advocate	No conflicts to disclose.