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

Draft Evidence Report

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Prepared for

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Grace A. Lin served as the lead author of the report. Avery McKenna led the systematic review and authorship of the comparative clinical effectiveness section of the report with assistance from Finn Raymond. Woojung Lee led the development of the cost-effectiveness model and authored the corresponding sections of the report in collaboration with Marina Richardson. Marina Richardson also conducted the analysis for the budget impact model with the assistance of Yasmine Kayali. Foluso Agboola provided methodologic guidance on the clinical and economic evaluations. We would like to thank Becca Piltch, Grace Ham, and Anna Geiger for their contributions to this report.

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In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:

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Dr. Susan Prockop holds intellectual property rights related to the use of third party viral specific T-cells licensed to Atara Biotherapeutics, with all of her rights assigned to Memorial Sloan Kettering Cancer Center. Dr. Susan Prockop receives support for the conduct of clinical trials through Boston Children's Hospital from AlloVir, Atara, and Jasper, honoraria from Pierre Fabre and Regeneron, consulting services from Ensoma, Century Therapeutics, HEOR and VOR Biopharma, and DSMB from Stanford University and NYBC.

None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of this draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from who we requested input from, or who have submitted public comments so far, please visit: https://icer.org/wp-content/uploads/2024/09/ICER_EBV-PTLD_Key-Stakeholder-List_For-Publication_091224.pdf

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List of Acronyms and Abbreviations Used in this Report

5PS	5-point scale
AHRQ	Agency for Healthcare Research and Quality
AE	Adverse event
AID	Acquired immunodeficiency
BLA	Biologics License Application
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CNS	Central nervous system
CT	Computed tomography
CTL	Cytotoxic T lymphocyte
CTLp	Cytotoxic T lymphocyte precursors
CR	Complete response
EAP	Expanded access program
EBV	Epstein-Barr virus
EBV+	Epstein-Barr virus positive
EBV+LMS	Epstein-Barr virus+ associated leiomyosarcoma
EBV+LPD	Epstein-Barr virus associated lymphoproliferative disease
EBV+NPC	Epstein-Barr virus+ associated nasopharyngeal carcinoma
EBV+ PTLD	Epstein-Barr virus+ post-transplant lymphoproliferative disease
ECOG	Eastern Cooperative Oncology Group
EU	European Union
evLYs	Equal value of life years gained
FDG	Fluorodeoxyglucose
GI	Gastrointestinal
GVHD	Graft-versus-host disease
HCT	Hematopoietic cell transplant
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigens
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplantation
IORA	Independent oncologic response adjudication
IV	Intravenous
IQR	Interquartile range
Kg	Kilogram
KPS	Karnofsky Performance Scale
LDH	Lactate dehydrogenase
LDi	Longest diameter
N	Number
NA	Not applicable
NE	Not evaluable
NIH	National Institutes for Health
NOS	Not otherwise specified
NR	Not reported
ORR	Objective response rate

OS	Overall survival
PET	Positron emission tomography
PID	Primary immunodeficiency
PD	Progressive disease
PPD	Product of the perpendicular diameters
PR	Partial response
PTLD	Post-transplant lymphoproliferative disease
QALY	Quality-adjusted life year
R/R	Relapsed/refractory
Ref	Reference
SAE	Serious adverse event
SD	Stable disease
SDi	Short diameter
SMR	Standardized mortality ratio
SMRW	Standardized mortality ratio weighting
SPD	Sum of the product of the diameters
SPU	Single patient utilization
SOT	Solid organ transplant
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TR	Treatment related
US	United States
%	Percent

Executive Summary

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 (HCST). The incidence of EBV+ PTLD varies based on transplant type, between 1-30% for solid organ transplants and around 3% for HSCT.[1] 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.[2] Survival after diagnosis depends on the extent of the disease but is estimated to be between 40-60% overall at five years.[3] Diagnosis with PTLD results in almost three times higher post-transplant costs compared with those not diagnosed with PTLD.[4]

Current treatment of EBV+ PTLD includes reduction of immunosuppression as first-line therapy, which restores T-cell function and, in non-aggressive disease, may be sufficient to control the disease.[2] Treatment with rituximab without or without chemotherapy can be effective for CD20+ disease, with approximately 50-60% of patients responding to initial therapy.[5] In those patients who responded, 3 year overall survival is reported to be up to 75% in SOT patients and up to 50% in HSCT patients.[6,7] 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 3 weeks for HSCT patients, and four months for SOT patients.[5,8]

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 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 donors that are selected based on shared human leukocyte antigens (HLA) restriction and partially matched HLA profile.[5] 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.[9]

The primary trial of tabelecleucel (ALLELE) was single-arm.[5] 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 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 ALLELE was relatively short-term, longer-term 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.

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Relapsed/Refractory EBV+ PTLD		
Tabelecleucel	Usual care	A

Based on available clinical evidence, we also developed a de novo lifetime decision analytic model of tabelecleucel compared with usual care in patients with relapsed/refractory EBV+ PTLD. We assumed that the overall survival benefit of tabelecleucel is the same for patients who had HSCT and SOT. Based on a placeholder price of $287,500 per 35-day treatment cycle and assuming a single price for the entire population, 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.

1. Background

Post-transplant lymphoproliferative disease (PTLD) is a rare, serious, often fatal cancer. It is a complication of solid organ transplant (SOT) and allogeneic hematopoietic stem cell transplant (HCST), with only an estimated few hundred cases per year reported in the United States (US).[7] The majority of cases of PTLD are associated with the acquisition or reactivation of Epstein-Barr virus (EBV) post-transplant, which is referred to as EBV+ PTLD. Due to the immunosuppression required to prevent organ rejection for SOT or graft versus host disease (GVHD) for HSCT , there is a lack of the ability of the patient's T-cells to control EBV+ cells, resulting in the unchecked proliferation of B-cells and transformation into PTLD.[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) being at higher risk than patients having kidney or liver transplants.[1] Patients who were EBV-negative at the time of transplant were also at higher risk of developing PTLD.[2] 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%).[1] There is also a higher risk for EBV-negative recipients, <10 or >60 years old, underwent T-cell depletion therapy, the degree of human leukocyte antigen (HLA) mismatch, and severity of GVHD.[10,11] EBV+ PTLD most commonly occurs in the first year after transplant, though it can occur later, and results in almost three times higher post-transplant costs compared with those not diagnosed with PTLD.[2,4]

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 the disease occurs outside of lymph nodes, most commonly in the gastrointestinal tract, pulmonary system, and central nervous system.[12] Rarely, the disease can present with a fulminant course, marked by multi-organ failure and tumor lysis syndrome.[1] Diagnosis is based on a combination of EBV viral load, physical exam and imaging tests to detect lesions and tissue biopsy. 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 and response to first line therapy but is estimated to be between 40-60% overall at five years.[3]

Current treatment of EBV+ PTLD depends on site, morphology, and extent of disease. Clinical practice guidelines recommend the reduction of immunosuppression as first-line therapy, 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 reduction of immunosuppression is not sufficient and pharmacologic therapy is necessary, treatment with rituximab is effective for CD20+ disease, with approximately 50-60% of patients responding to initial

therapy.[5] However, in high risk patients or if a complete response is not achieved with rituximab monotherapy, further treatment is required. In SOT patients, chemotherapy is recommended. A range of regimens are used with the most common being cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Unfortunately, HSCT recipients are often not considered candidates for multiagent chemotherapy since it is poorly tolerated. Overall, approximately half of EBV+ PTLD cases are refractory to currently available treatments and/or relapse; 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 4 months for SOT patients.[5,8]

Tabelecleucel (tab-cel®) 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 from a bank of lines based on recognition of EBV targets through a shared HLA and partially matched HLA profile.[5] Tabelecleucel administered on days one, eight, and 15 of each 35-day cycle. The total number of cycles is determined by the response to treatment, which is assessed on day 28 of each cycle. Patients who do not have a complete response to the initial cycles can be administered additional cycles with up to two (for SOT) or four (for HSCT) different HLA restrictions.[5,13] 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.[13] The manufacturer filed a Biologics License Application (BLA) with the US Food and Drug Administration (FDA) on May 20, 2024, for patients with EBV+ PTLD who have received at least one prior therapy (which may include chemotherapy for SOT patients).[9]

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
tabelecleucel	Donor-derived polyclonal EBV-specific T-cell immunotherapy	Intravenous	2 x 10^6 cells/kg on days 1, 8, and 15 of a 35 day cycle

EBV: Epstein-Barr virus; kg: kilogram

2. Patient and Caregiver Perspectives

This report was developed with input from diverse stakeholders, including patients, caregivers of patients, clinicians, researchers, and the manufacturer of the agent of focus in this review (see Supplement for further details). It incorporates feedback gathered during calls with stakeholders and open input submissions from the public. 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 treatments.

While EBV+ PTLD is a rare disease, with only a few hundred cases diagnosed in the US each year, it 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 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. The side effects of treatments such as rituximab and chemotherapy can also be severe and affect quality of life.

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.

Both persons with EBV+ PTLD and their caregivers described a large caregiving burden, both physically and mentally. For example, caregivers noted that it was a full-time job to ensure that their partners or children got the right care, particularly since the disease is rare. Additionally, parents described the difficulty of seeing their children ill and in pain, and worried about their child's future quality of life. Caregivers also conveyed the fear of not knowing if their partner or child would survive. Siblings are also affected, often carrying worry about their ill sibling.

Persons with EBV+ PTLD described side effects from treatment of their disease. Side effects from chemotherapy were particularly debilitating, and persons with EBV+ PTLD expressed wishes that future treatments would mean that they could potentially avoid chemotherapy and its unpleasant side effects.

Patient groups expressed concern that due to the severity of refractory/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, 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. Clinical experts also described that, particularly for the pediatric age group, cancer centers are usually at large academic centers and patients may have to travel long distances for treatment. They expressed optimism that a product such as tabelecleucel, which can be administered in the outpatient setting, could broaden access to treatment.

Patient groups were concerned about the potential cost of new treatments, as orphan drugs are often expensive and thus may not be affordable for the patients who need treatment. Finally, patients expressed frustration that information about new and emerging treatments were limited, and that they often had to do their own research to find new treatments, since their doctors may not discuss new treatments with them.

Health Equity Considerations

There are not known to be racial and ethnic differences in the prevalence of EBV+ PTLD in the US, although there are inequities in referral for transplant, time to transplant, transplant rates, and HLA matches based on race/ethnicity.[14] Women and people with lower socioeconomic status are also known to have different access to solid organ transplants.[14] Since PTLD is a post-transplant disease and usually requires treatment from specialists, access to diagnosis and treatment may be more difficult for persons living in rural areas and those with lower socioeconomic status. Additionally, cytotoxic T-cell therapies are typically offered only at select, specialized centers. A donor-derived, off-the-shelf cytotoxic T-cell therapy that can be administered in an outpatient setting would have the potential to improve access to treatment as well as the speed of treatment, both of which are important for a condition like relapsed/refractory EBV+ PTLD that has a high mortality rate within a short time frame.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review assessing the evidence of tabelecleucel for the treatment of Epstein-Barr Virus Positive Post Transplant Lymphoproliferative Disease (EBV+ PTLD) are outlined in Supplement Section D1.

Scope of Review

We reviewed the clinical effectiveness of tabelecleucel compared to current usual care, which includes both pharmacologic and nonpharmacologic treatments (e.g., reduction in immunosuppression). We sought evidence on patient important outcomes, including mortality, quality of life, disease progression, duration of response, avoidance of chemotherapy, and adverse events such as organ rejection, graft-versus-host-disease (GvHD), and any serious adverse events of interest (i.e., cytokine release syndrome, tumor flare, sepsis). The full scope of the review is detailed in Supplement Section D1.

Evidence Base

Evidence informing our review of tabelecleucel for EBV+ PTLD was derived from three references, from one pivotal Phase III trial (ALLELE) and one expanded access study (EBV-CTL-201) in the United States.[5,15,16] This evidence was supplemented by data from two single center Phase II trials, two ongoing expanded access programs in Europe and an assessment report from the European Medicines Agency (EMA) from the approval of tabelecleucel in Europe.[13,16-18] Table 3.1 outlines the study design and population of the key trials.

As the available evidence for tabelecleucel is from single-arm trials, we also included three additional studies to inform our comparison of usual care: one post-hoc comparative analysis of the ALLELE trial versus an external control arm and two retrospective chart reviews.[7,8,19]

Detailed study design and baseline characteristics for the included studies are reported in Supplement Tables D3.1-6.

Table 3.1 Overview of Trials of Tabelecleucel and Usual Care[5,7,8,13,15-19]

Study	N	Study Design	Population
Pivotal Trial of Tabelecleucel			
ALLELE ATA129-EBV-302 NCT03394365	43	Phase III single-arm open label study	SOT or HSCT recipients with R/R EBV+ PTLD after rituximab ± chemotherapy
Other Trials of Tabelecleucel			
U.S. EAP* EBV-CTL-201 NCT02822495	26	Single-arm Expanded Access Program in the U.S.	SOT or HSCT recipients with R/R EBV+ PTLD with no alternative therapeutic options
EU EAP* ATA129-EAP-901	24	Single-arm Expanded Access Program in Europe	SOT or HSCT recipients with R/R EBV+ PTLD who are not eligible for clinical trial enrollment
EU EAP – SPU* ATA129-SPU	48	Individual Patient Expanded Access Program in Europe	SOT or HSCT recipients with EBV+ PTLD who are not eligible for clinical trial or other EAP enrollment
Phase I/II* 11-130 & 95-024 NCT01498484 and NCT00002663	46	One Phase I/II Single-arm & One Phase II Single arm trial with pooled data	SOT or HSCT recipients with R/R EBV+ PTLD after rituximab ± chemotherapy
Usual Care			
Dharnidharka 2021	86	Retrospective chart review	SOT recipients with R/R EBV+ PTLD after rituximab and chemotherapy
Socie 2024	81	Retrospective chart review	HSCT recipients with R/R EBV+ PTLD after rituximab ± chemotherapy
Barlev 2024	114	Comparative analysis of a subset of ALLELE participants (n=30) and a retrospective chart review (RS002) (n=84)	SOT or HSCT recipients with relapsed/refractory EBV+ PTLD following rituximab ± chemotherapy

EAP: expanded access program, EBV+: Epstein-barr virus positive, EU: European, HSCT: hematopoietic stem cell transplant, PTLD: post-transplant lymphoproliferative disease, R/R: relapsed/refractory, SOT: solid organ transplant, SPU: single patient utilization, U.S.: United States

*Studies enrolled a broader population (EBV-lymphoproliferative disorders and associated malignancies) but the N's in the table above refer to the R/R EBV+ PTLD population of the included studies for this review.

Tabelecleucel

Pivotal Trial

ALLELE was the pivotal Phase III trial which evaluated the efficacy and safety of tabelecleucel for the treatment of relapsed or refractory EBV+ PTLD following solid organ transplant (SOT) or hematopoietic stem-cell transplant (HSCT).[5]

Participants were eligible to enroll in the trial if they had EBV+ PTLD confirmed by biopsy, the disease was relapsed or refractory after treatment with rituximab alone for HSCT patients or rituximab with or without chemotherapy for SOT patients, and there was availability of partially

HLA-matched and HLA-restricted tabelecleucel for the participant. Additionally, the participant had to have adequate organ function, remission of underlying primary disease, and measurable systemic disease using the Lugano Classification response criteria. Participants were excluded if they presented with Burkitt lymphoma, classical Hodgkin lymphoma, or any T cell lymphoma, untreated central nervous system (CNS) PTLD or currently receiving CNS-direct chemotherapy, or suspected grade 2 or greater graft-versus-host-disease (GvHD).

All participants received three doses of tabelecleucel ($2x10^6$ cells per kg) intravenously on days 1, 8, and 15 of a 35-day cycle. Participants were able to use another T-cell line that had a different human leukocyte antigen (HLA) restriction if response was not observed; there was a maximum of four HLA restrictions for HSCT and two for SOT allowed. A median of 2 cycles (interquartile range [IQR]: 1-3) of tabelecleucel was given to SOT recipients and 3 cycles (IQR: 2-4) for HSCT recipients. The median treatment duration was 2.1 months (IQR: 0.5-3.9) overall. The primary endpoint was the response rate, defined in detail in the clinical benefit section below. Table 3.2 contains baseline characteristics for participants in the ALLELE trial. The trial enrolled 29 SOT recipients (including ten kidney, six heart, five lung, one liver, and seven multivisceral transplants) and 14 HSCT recipients. The median age of participants was 49 years old (IQR: 22 – 65), participants were predominantly white (84%) and male (56%). Diffuse large B-cell lymphoma was the disease morphology for 67% participants and 77% had extranodal disease. The median time from PTLD diagnosis to tabelecleucel treatment was 4.0 months (IQR: 2.2-8.6).

Expanded Access Programs (EAP)

Three EAPs – two in Europe, one in the U.S. - were designed to give patients with EBV+ diseases who were not eligible for enrollment in clinical trials access to tabelecleucel.[13,15,18]

EBV-CTL-201 enrolled 26 participants with EBV+ PTLD (14 HSCT, 12 SOT) from 10 U.S. sites.[15] Participants were eligible for treatment if there were no alternative treatment options and they had an ECOG performance status score <4. The participants enrolled in EBV-CTL-201 had a median age of 36 years old, were predominantly white (69%), and male and female participants were evenly enrolled. The majority of participants had diffused large B-cell lymphoma (46%), with four of these participants having extranodal disease. The median time from transplant to PTLD diagnosis was five months (range: 1 – 276), and from diagnosis to first tabelecleucel dose was 2.3 months (range: 0.2 – 67.6). The limited available data on the other two EAPs (ATA129-EAP-901 and ATA129-SPU) in Europe are described in Supplement Sections D2 and D3.

Table 3.2. Baseline Characteristics of ALLELE Trial

Trial		ALLELE
Arms		**All**
N		**43**
Median Age, years (IQR)		48.5 (21.9–65.4)
Sex, n (%)	**Male**	24 (56)
	Female	19 (44)
Race, n (%)	**White**	36 (84)
Disease morphology and histology, n (%)	**Diffuse large B-cell lymphoma**	29 (67)
	Other*	14 (32.6)
Extranodal disease at screening, n (%)		33 (77)
Number of previous lines of systemic treatment		1 (1–2)
Time from initial EBV-positive diagnosis to first dose of tabelecleucel, months		4.0 (2.2–8.6)

EBV: Epstein-barr virus, IQR: interquartile range, n: number, PTLD: post-transplant lymphoproliferative disease
*Other disease morphologies and histologies include PTLD not otherwise specified (NOS), plasmablastic lymphoma, monomorphic PTLD, polymorphic PTLD, plasmacytoma or marginal zone lymphoma, florid follicular hyperplasia.

Baseline Characteristics stratified by transplant type are reported in Supplement Tables D3.2-3.

Evaluation of Clinical Trial Diversity

We did not rate the demographic diversity (race/ethnicity, sex, age) of the participants in the ALLELE trial using the ICER-developed Clinical trial Diversity Rating (CDR) Tool for this review due to a lack of prevalence estimates stratified by demographic categories for this rare condition.[20] Instead, the demographic diversity of the ALLELE trial is described qualitatively in Supplement D1.

Usual Care: Natural History

We did not identify any prospective studies evaluating usual care in relapsed/refractory EBV+ PTLD after treatment with rituximab with or without chemotherapy. Described below are three retrospective chart reviews we identified to inform our comparison of usual care.[7,8,19] The key outcome of the studies was overall survival. Baseline characteristics are described in Table 3.3 below.

Dharnidharka 2021 was an abstract describing a retrospective chart review of 86 SOT participants with EBV+ PTLD who had received rituximab and chemotherapy from January 2000 to December 2018, from 29 centers in Europe and North America, and were refractory or relapsed after treatment.[8]

Socie 2024 was a multicenter retrospective chart review that evaluated 81 HSCT participants who had relapsed/refractory EBV+ PTLD after rituximab with or without chemotherapy, from 22 centers

in Europe and North America.[7] The inclusion and exclusion criteria mirrored those in the ALLELE trial.

Barlev 2024 was a comparative analysis of a subset of participants from the ALLELE trial (N=30) and a retrospective cohort of similar patients from study RS002 (N=84), 36 of which were HSCT recipients and 48 were SOT recipients. The rationale for not including the 13 patients from the overall ALLELE dataset is not described in this publication. In the retrospective cohort, data was collected from 29 centers in Europe and North America between January 2000 and December 2018.[19]

Additional details on study design and baseline characteristics of these retrospective natural history studies can be found in Supplement Tables D3.5-6**.**

Table 3.3. Natural History Baseline Characteristics[7,8,19]

	Dharnidharka 2021	Socie 2024	Barlev 2024
N	**86**	**81**	**84**
Median age at diagnosis, range	43 (1 – 78)	49 (2 – 75)	44* (IQR: 26.4 – 58.6)
Median time from transplant to PTLD onset, range	1.7 Years (0.1 – 27.9)	3 months (0.8 – 100.8)	6.5 months† (IQR: 3.0 – 79.2)
Diffuse large B-cell lymphoma, %	67.4	56.8	NR

IQR: interquartile range, N: number, NR: not reported, PTLD: post-transplant lymphoproliferative disease
*Median age at first dose of PTLD treatment
†Median time from transplant to PTLD diagnosis

3.2. Results

Clinical Benefits

To contextualize the evidence for tabelecleucel, we describe the evidence on usual care first, and subsequently, describe the clinical benefits of tabelecleucel.

Usual Care

Socie 2024 was a retrospective observational study on the natural history cohort of 81 HSCT recipients with relapsed/refractory EBV+ PTLD. The study showed that median overall survival for HSCT recipients with relapsed/refractory EBV+ PTLD after treatment with rituximab with or without chemotherapy is 0.7 months (95%CI: 0.3 – 1.0).[7] Only 36 of 81 (44.4%) participants received next-line therapy after rituximab. Thirty-two participants (of the 36) received chemotherapy-containing regimens; of those, four had a durable response of more than six months. Two of those four participants subsequently relapsed again after treatment.[7]

For SOT recipients, data were drawn from Dharnidharka 2021, the retrospective study of 86 patients identified for this population.[8] The study reported a median overall survival of 4.1 months (95%CI: 1.9 – 8.5) for SOT recipients.[8] There were no data on response to therapy in SOT recipients with relapsed/refractory EBV+ PTLD.

Survival curves for each population can be found in Supplement Section D2.

Tabelecleucel

Key trial results of the pivotal Phase III ALLELE trial and the U.S. EAP are summarized below. Additional evidence on tabelecleucel can be found in Supplement Section D3.

Response

The primary endpoint of the ALLELE trial was objective response rate (ORR). The ORR includes participants with complete response or partial response based on the Lugano Classification with Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) modification (see Supplement Table A1.1. for response definitions).[21] Participants who had no response, stable disease, or progressive disease were judged to be non-responders.

About half of the participants in the ALLELE trial (22 of 43 participants) had an ORR (HSCT: 50%, SOT: 52%).[5] The median time to response was one month (IQR: 1 – 2.1), and the median duration of response was 23 months (95%CI: 6.8 – not estimable (NE)). Of the 22 responders, 12 had a response duration greater than six months. Of note, seven of all participants were deemed not evaluable for response: three died, one withdrew, two were newly enrolled, and one was determined to be not evaluable for unspecified reasons.

Although similar rates of ORR were observed in both HSCT and SOT participants, higher rates of complete response were observed for HSCT recipients compared to SOT (HSCT: 43%, SOT: 21%). Table 3.5 below presents data on response by transplant type.

In the U.S. EAP, 17 out of 26 participants had an ORR (65.4%; 95%CI: 44.3 – 82.8), with a higher rate in the SOT recipients (83.3%) vs. HSCT recipients (50%).[15] The median time to response was one month (range: 0.6 – 7.1). Additional data is presented in Supplement Table D3.8.

Table 3.4. Response Outcomes of ALLELE Trial

Trial	ALLELE		
Outcome	**HSCT**	**SOT**	**Overall**
Median follow up, months (IQR)	14.1 (5.7-23.9)	6 (1.8-18.4)	11 (2.6-19.8)
Overall response rate, n (%)	7 (50)	15 (52)	22 (51)
Complete Response, n (%)	6 (43)	6 (21)	12 (28)
Partial Response, n (%)	1 (7)	9 (31)	10 (23)
Stable Disease, n (%)	3 (21)	2 (7)	5 (12)
Progressive Disease, n (%)	2 (14)	7 (24)	9 (21)
Not evaluable, n (%)	2 (14)	5 (17)	7 (16)
Median time to response, months (IQR)	1 (1-1)	1.1 (1-3)	1 (1-2.1)

HSCT: hematopoietic stem cell transplant, IQR: interquartile range, n: number, SOT: solid organ transplant

Overall Survival (OS)

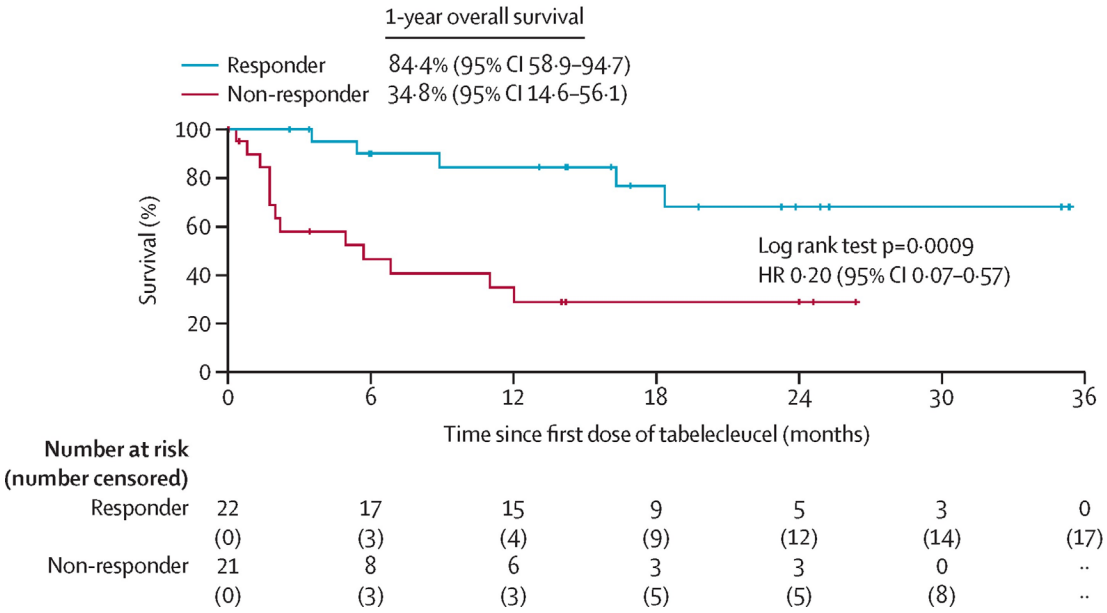
The estimated one-year survival rate in the ALLELE trial was 61.1% in the overall cohort (Median OS: 18.4 months [95% CI: 1-26.2 months), 70.1% for HSCT recipients (Median OS: not reached), and 56.2% for SOT recipients (Median OS: 16.4 months).[5] Figures 3.1-3.3 below show survival stratified by response status for the overall, HSCT, and SOT cohorts. Responders had longer survival than non-responders.

A comparative analysis by Barlev 2024 reported on the overall survival benefit of tabelecleucel in a subset of participants from the ALLELE trial compared to usual care using a retrospective cohort of 84 participants with relapsed/refractory EBV+ PTLD. Using standardized mortality ratio weighting, a greater survival benefit was observed with tabelecleucel than usual care (HR: 0.37; 95%CI 0.2 – 0.71; p=0.003).[19] Unadjusted survival data and additional outcomes are reported in Supplement Table D3.11.

In the U.S. EAP, the estimated survival rate at both one- and two- years was 70% (95%CI:46.5 – 84.7) for all participants. A higher overall survival rate was observed for SOT recipients (81.5%) compared to HSCT recipients (61.5%) in this cohort. Median overall survival was not evaluable.[15]

Qualitatively, participants with relapsed/refractory EBV+ PTLD who were treated with tabelecleucel appear to have prolonged survival compared with these retrospective natural history cohorts.

Figure 3.1. Kaplan-Meier Survival Curve by Response Status for Overall Cohort in ALLELE trial



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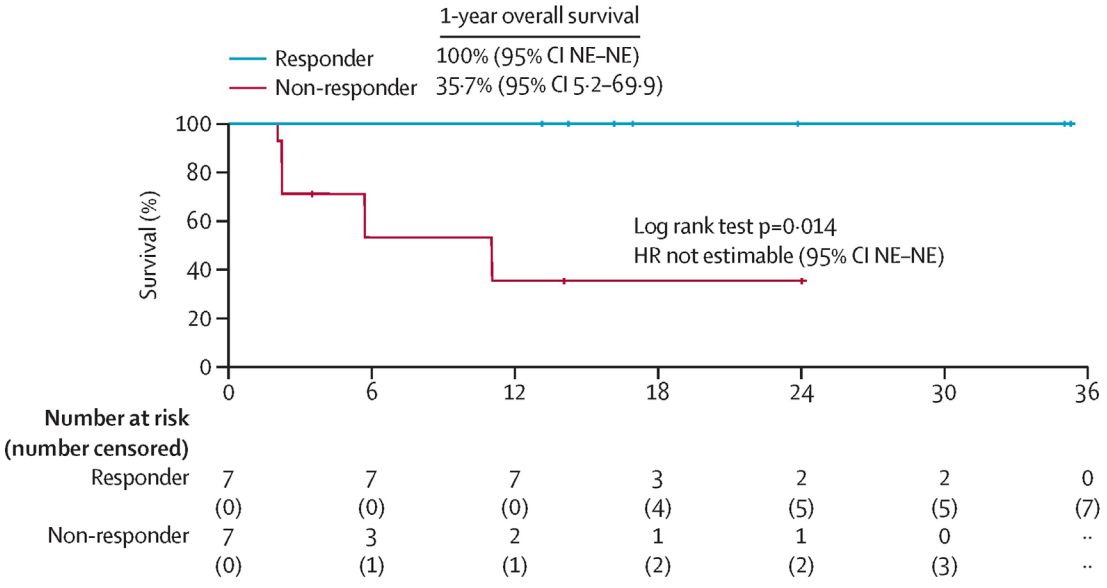
CI: Confidence interval, HR: Hazard ratio

Figure 3.2. Kaplan-Meier Survival Curve by Response Status for HSCT Cohort in ALLELE trial



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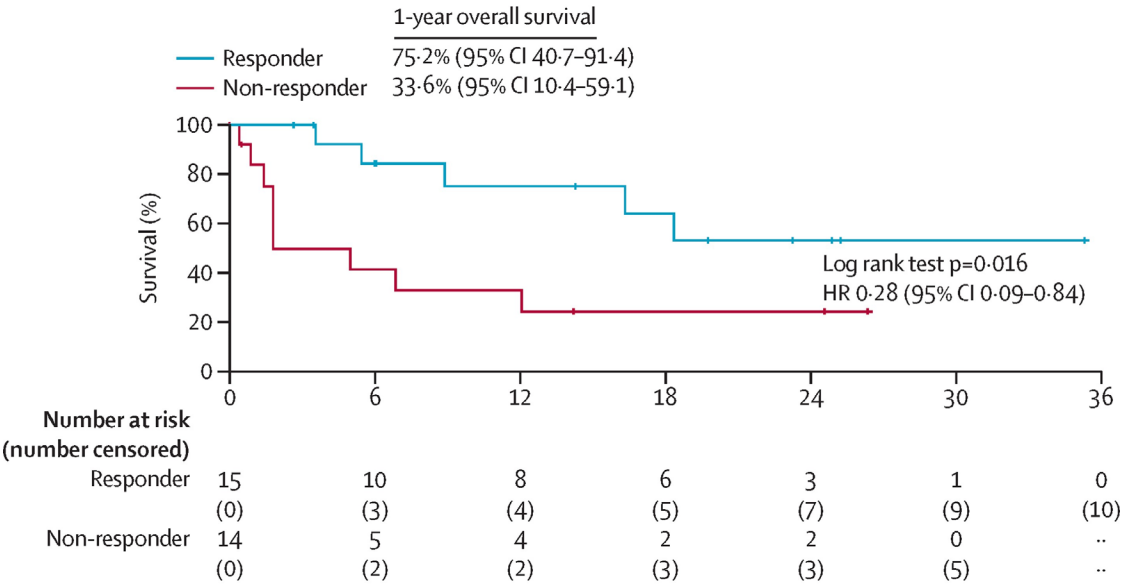
rituximab and chemotherapy (ALLELE): a phase 3, multicentre, open-label trial, Page 382., Copyright (2024), with permission from Elsevier.
CI: confidence interval, HR: hazard ratio, HSCT: hematopoietic stem cell transplant, NE: not estimable

Figure 3.3. Kaplan-Meier Survival Curve by Response Status for SOT Cohort in ALLELE trial



CI: confidence interval, HR: hazard ratio, SOT: solid organ transplant
Reprinted from The Lancet, Vol. 25. 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, Page 382., Copyright (2024), with permission from Elsevier.

Subsequent Treatment

Subsequent treatment after tabelecleucel was given to 14 participants in the ALLELE trial, three of which were responders and 11 were non-responders. Of the 14 participants, eight received chemotherapy or immunotherapy, four received rituximab, one received radiotherapy, rituximab, and cell therapy, and one received a combination of chemotherapy/immunotherapy, radiotherapy, and rituximab.[5] See Supplement Table D3.7. for details.

Quality of Life

We sought evidence on quality of life for participants receiving tabelecleucel but none of the identified trials measured quality of life outcomes.

Harms

Disease progression, pyrexia, diarrhea, fatigue, and nausea were the most commonly reported adverse events (AEs) in the ALLELE trial. Treatment-emergent serious adverse events (SAE) were reported in 23 (53%) participants, four of which were considered treatment-related**.** No treatment-related SAE led to treatment discontinuation. Similar patterns were observed in the other trials (see Supplement Section D2). There was one case of acute graft-versus-host-disease (GvHD) in a HSCT participant; this case was judged by investigators to be non-serious and unrelated to tabelecleucel.[5] Of note, four events of acute GvHD in three participants were reported in the U.S. Expanded Access Program.[15] Three of the events reported in two patients (one patient with grade 4 liver and gastrointestinal GvHD, one patient with grade 3 maculopapular rash) were considered by investigators to be possibly related to tabelecleucel. There was also one report of acute GvHD in the skin in the Phase II trials.[22] Other patient important harms, including tumor flare, cytokine release syndrome, and organ rejection were not observed in the ALLELE trial or other tabelecleucel studies.[5,13,15,18,22]

In total, 18 patients (41.9%) and seven patients (26.9%) died during the ALLELE trial and U.S. EAP, respectively, with the majority due to progressive disease. No deaths were considered to be related to tabelecleucel. Additional safety information on tabelecleucel from the ALLELE trial and the other trials and the safety data reported in the European Medicines Agency Report is described in Supplement Section D2 & Table D3.12-14.

Subgroup Analyses and Heterogeneity

The clinical trials of tabelecleucel attempted to evaluate subgroups of interest. Results based on the transplant type have been described in the body of the evidence. There did not appear to be evidence of effect modification observed for objective response rate and overall survival stratified by key sociodemographic factors (i.e., age, sex, race/ethnicity).[5,15] However, these data are from a small sample size and should be interpreted with caution. Additional subgroup findings, including data on patients with EBV+ PTLD with CNS involvement, are described in Supplement Section D2. and Supplement Tables D3.15-27.

Uncertainty and Controversies

The currently available data demonstrates that treatment of relapsed or refractory EBV+ PTLD with tabelecleucel results in extended survival in both HSCT and SOT patients, when compared with natural history, with few harms. Due to the difficulty and ethics of conducting randomized trials for ultra-rare diseases, tabelecleucel was only tested in a single-arm Phase 3 trial and in expanded access programs, which are subject to bias. For example, there may be differences in the populations in the treated population and the natural history arm that are not accounted for. This could affect estimates of the difference in treatment effect. However, there appears to be large

treatment effect from tabelecleucel on overall survival (median survival of 18 months compared with 1-4 months in the natural history cohort), and a comparative study using propensity scoring to match ALLELE trial participants with natural history cohort patients shows consistent results, increasing our confidence in the treatment effect.

The long-term durability of tabelecleucel treatment has not yet been established, with few patients followed out to 5 years, a typical milestone for cancer patients. Additionally, it is not clear how generalizable the data from the ALLELE study are, since the small sample size and short duration of the trial may obscure differences in treatment effect by transplant type. Although current data from the ALLELE study shows similar overall and complete response rates between the HSCT and SOT groups, the HSCT group had a higher one-year overall survival rate. This may, in part, be due to the heterogeneity of the SOT group, as the underlying survival rate of that group also depends on the type of transplant. More data are needed to establish the long-term effect of tabelecleucel and understand whether there may be clinically important differences in subgroup treatment effect. Finally, more studies are needed to determine whether tabelecleucel courses can be repeated if patients respond and further relapse, or if it may be used earlier in the disease course as first-line therapy.

Overall, serious adverse events were few. Notably, there was one case of acute GvHD reported in the trial and four cases in the U.S. EAP, some of which were likely related to tabelecleucel treatment. More experience with tabelecleucel is needed to gauge the overall risk of GvHD for HSCT patients. Longer term data on safety are also needed to confirm the relative lack of severe side effects from tabelecleucel treatment, especially compared with standard chemotherapy.

Appropriately, for a disease that shortens lifespan considerably, overall response rate and overall survival were the key endpoints in the clinical trial. However, we heard from patients and clinical experts that avoidance of chemotherapy is a desirable outcome given the potentially debilitating side effects of standard chemotherapy. There was very little information about subsequent therapy in the trial and EAP data; future studies for EBV+ PTLD treatments should consider measuring this as a patient-important outcome. Additionally, quality of life measures were not collected during the study and thus it is not clear what impact treatment with tabelecleucel may have had on quality of life for the patient, particularly in patients who did not have a complete response to treatment.

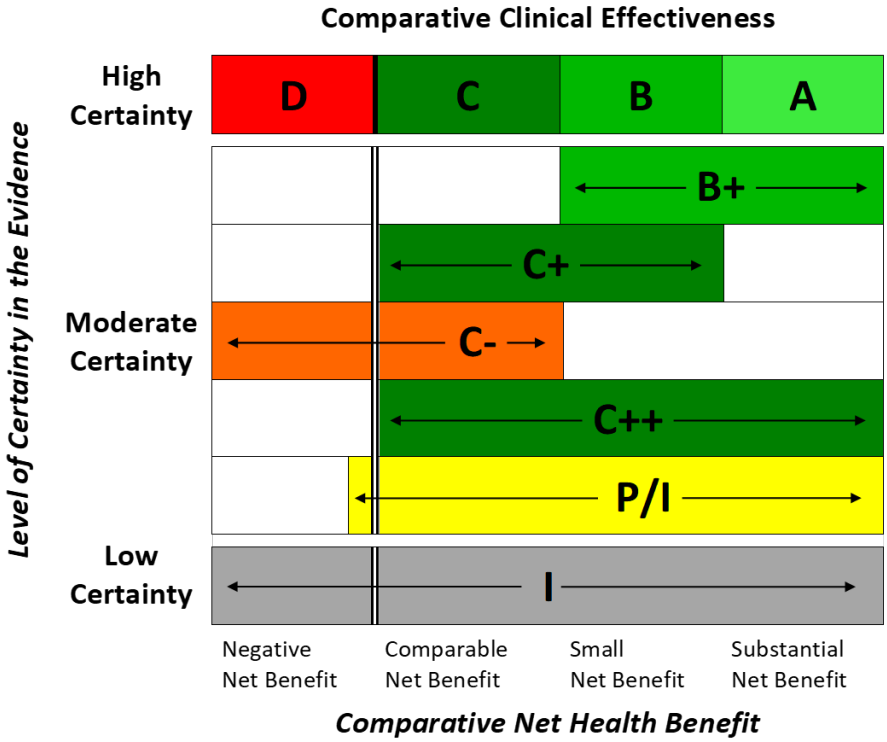
If approved by the FDA, tabelecleucel would be the first commercially available, allogeneic, EBV-specific, off-the-shelf T-cell therapy. Current autologous T-cell therapies (e.g., CAR-T) require a relatively lengthy lead time for treatment (usually weeks) due to the manufacturing process and no such process for EBV-specific T-cells is currently FDA approved. Because relapsed/refractory EBV+ PTLD can be rapidly fatal, the ability to treat within days as long as appropriate cell lines are available could be an advantage over current therapies. In addition, tabelecleucel can be administered in any setting where infusion can be done, which could broaden access to patients

who live in rural areas or far from academic cancer centers, where this type of treatment usually takes place.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" *– Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

EBV+ PTLD is a severe, often fatal complication of HSCT or SOT. While a proportion of EBV+ PTLD patients respond to the reduction in immunosuppression or initial rituximab with or without chemotherapy, approximately half of patients relapse or are refractory to first-line treatments.

Most often, relapsed/refractory disease is treated with additional chemotherapy, which has substantial toxicities. Survival of relapsed or refractory disease is poor, with a median survival of less than one month for HSCT patients and around four months for SOT patients. Thus, there is a great need for an effective therapy for relapsed/refractory EBV+ PTLD.

While data on the effectiveness of tabelecleucel are drawn mainly from one single-arm Phase III trial of 43 patients with relapsed/refractory EBV+ PTLD following HSCT or SOT and EAPs, tabelecleucel appears to extend survival compared with a natural history cohort, without severe adverse events. Additionally, more than one-quarter of patients had a complete response to treatment, and more than half of responders had a duration of response of six months or more. However, data on whether there was any effect modification by transplant type or demographics were sparse. There were also no quality of life data collected during the study, which may be particularly important to understand for patients who did not have a complete response to therapy. Although tabelecleucel treatment appears to have few serious harms, there were four cases of acute GvHD reported between the clinical trial and EAP; this requires attention in follow-up studies. Finally, the long-term durability of response is uncertain, as the median follow-up time in the trial was 11 months.

Without treatment, relapsed/refractory EBV+ PTLD has a poor prognosis, and there is limited efficacy of treatments beyond first-line rituximab and chemotherapy. Treatment with tabelecleucel appears to induce partial or complete remission in a substantial proportion of patients, extending survival for patients who otherwise usually die in weeks to months. Additionally, the safety profile is reassuring, particularly with respect to severe adverse events. Thus, despite data limitations, given the magnitude of benefits of tabelecleucel and few reported harms, we have a high certainty of **substantial net health benefit (A)** compared with usual care.

Table 3.5. Evidence Ratings

Treatment	Comparator	Evidence Rating
Relapsed/Refractory EBV+ PTLD		
Tabelecleucel	Usual Care	A

4. Long-Term Cost Effectiveness

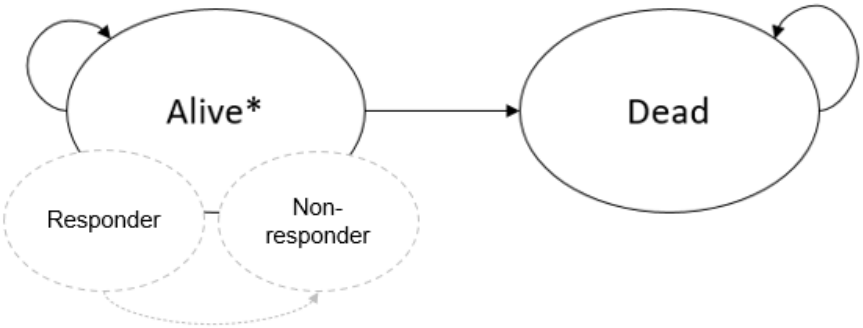
4.1. Methods Overview

The primary aim of this analysis was to estimate the cost-effectiveness of tabelecleucel compared to usual care for EBV+ PTLD over a lifetime time horizon. We developed a *de novo* decision analytic model for this evaluation, informed by the ALLELE trial and other key studies.[5,7,8,19] The model focused on a hypothetical cohort of patients with EBV+ PTLD being treated with tabelecleucel or usual care entering the model. The target population consists of individuals with EBV+ PTLD that are relapsed or refractory to rituximab with or without chemotherapy among those who had a solid organ transplant (SOT), as well as those relapsed or refractory to rituximab after a hematopoietic stem-cell transplant (HSCT). Due to potential differences in the underlying risk of death and treatment efficacy between patients who had an SOT versus patients who had an HSCT, we modeled the cost-effectiveness of tabelecleucel in each population separately and presented results for both the overall and individual (SOT and HSCT) populations. The primary analysis is based on the overall population, weighted by the proportions of patients having received SOT and HSCT in the ALLELE trial.

The model has two health states, 'alive' and 'dead' (Figure 4.1). Parametric survival analysis is used to estimate mortality (i.e., transitions from the 'alive' to the 'dead' health state). The model cycle length is one month, based on the frequency of survival reporting in the clinical data. A cohort of patients transition between states during predetermined cycles, modeling patients from treatment initiation until death. Within the alive health state, response status is tracked. Patients remain in the model until they die. All patients can transition to the 'dead' health state due to all-cause or disease-specific mortality from the 'alive' health state.

Analyses were conducted from the health sector perspective as a base case (i.e., focus on direct medical care costs only) and the modified societal perspective as a scenario analysis. The modified societal perspective was not considered as a co-base case due to a lack of direct data to inform the analysis. Costs and outcomes are discounted at 3% per year. Our analysis follows the approach outlined in ICER's Reference Case, and additional details can be found in the Supplement. The model was developed in Microsoft Excel.

Figure 4.1. Model Structure



*Within the alive health state, response status (i.e., responder, non-responder) is tracked. Patients are assigned as responders or non-responders at the start of cycle two of the model based on the median time to response observed in the ALLELE study. In subsequent model cycles, a proportion of patients move from responder to non-responder based on data from the ALLELE study.

4.2. Key Model Assumptions and Inputs

Key Model Assumptions

Our model includes several assumptions, as stated in Table 4.1.

Table 4.1. Key Model Assumptions

Assumption	Rationale
Response is defined as complete or partial response. Non-response is defined as stable or progressive disease.	Data on more granular classifications are not available for the comparator and for other response-stratified model inputs.
Modeling patients receive either tabelecleucel or usual care as an initial treatment. Patients may receive cycles of tabelecleucel, each consisting of three administrations on days 1, 8, and 15 of a 35-day cycle (hereafter will be referred to as 35-day treatment cycle so as not to be confused with model cycle). Following the initial treatment for both tabelecleucel and the comparator, one additional subsequent treatment was modeled for a proportion of those alive.	Due to the severity of the condition, subsequent treatment is likely. Subsequent treatment was frequently reported in the ALLELE study.

Assumption	Rationale
The subsequent treatment only impacts cost and is assumed to be equivalent in cost to the comparator basket of treatments for patients with relapsed/refractory disease.	The impact of the subsequent treatment on survival will have already been accounted for in the survival curves.
No treatment discontinuation (besides death) is modeled for either the intervention or comparator.	Due to the short course of treatment and the severity of the condition, stakeholders suggested patients would rarely discontinue treatment. All patients in the ALLELE study received the full dose of tabelecleucel without interruption.
Mortality and quality of life for patients surviving 5 years from the initiation of treatment will reflect a post-transplant population. These patients will subsequently be assumed to incur similar health care costs as the general US population.	The 5-year survival rate is a common milestone used to indicate a favorable disease prognosis and a potential cure in oncology, and aligns with the last follow-up time point in the ALLELE study. Patients who reach this milestone are expected to have decreased mortality compared to those who still experience EBV+ PTLD as well as an improved quality of life and lower health care costs. Evidence suggests that long-term mortality is higher in post-transplant patients compared to the general population and that the utility values are slightly lower than the general population. There is a lack of evidence on costs beyond 5 years for these same patients.
The overall survival benefit of tabelecleucel compared to usual care is the same for patients who had a solid organ transplant and a hematopoietic stem-cell transplant.	There is a lack of data on the survival benefit of tabelecleucel separately for patients who had a solid organ transplant and a hematopoietic stem-cell transplant.
The costs of CHOP regimen are used as a proxy for the costs of chemotherapy in the comparator arm.	There is significant variability in the types of chemotherapy regimens used within this population, but there is insufficient data to precisely narrow down the specific regimens used. Therefore, the average costs of chemotherapy will be assumed to be similar to the costs of CHOP regimen, given that CHOP is a commonly used regimen for EBV+ PTLD.

CHOP: cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone, EBV+ PTLD: Epstein-Barr Virus Positive Post-Transplant Lymphoproliferative Disease

Key Model Inputs

Key model inputs are shown in Table 4.2.

Clinical Inputs

Tabelecleucel survival benefit (HR 0.37, 95% CI 0.20 to 0.71) was applied to parametric survival curves fit to overall survival Kaplan-Meier curves from the comparator evidence, separately for the

SOT and HSCT populations. All individuals alive after five years were assumed to experience mortality equivalent to transplant patients following SOT or HSCT using the standardized mortality ratios (SMR) shown in Table 4.2 and applied to US general population mortality.

All patients started the model as a non-responder to their previous line therapy (i.e., rituximab with or without chemotherapy). At one month (the start of cycle two of the model) a percentage of patients transitioned to being a responder based on the ALLELE study.[5] After the initial response assessment at one month, patients can move from being a responder to being a non-responder. The mortality of responders was lower by a factor of 0.20 (95% CI 0.07, 0.57) compared to non-responders based on the ALLELE study.

Health State Utility Inputs

The utilities for a responder and non-responder were based on utility estimates for disease-free survival, and progressive disease, respectively, for a population with diffuse large B-cell lymphoma.[23] A disutility was applied to account for the quality of life impacts associated with chemotherapy treatment. After five years, utilities reflect the health state utilities for the transplant patients.[24,25]

Economic Inputs

A price is not yet known for tabelecleucel in the US, so we used a placeholder price based on the mid-point of the range estimated by IPD Analytics.[26] The assumed cost was for one 35-day treatment cycle consisting of three treatment administrations (infusions). Comparator cost and subsequent therapy costs were informed by rituximab with or without chemotherapy. The "CHOP" regimen (i.e., cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone) was used to calculate the cost of chemotherapy.[27] Costs of adverse events for chemotherapy were applied to account for additional healthcare costs to treat these events. Other health care costs, outside of drug costs, were estimated from a post-transplant population with lymphoproliferative disease following kidney transplant. It was assumed that patients who remain alive after five years will incur similar healthcare costs as the general US population.[28] Full details on model inputs can be found in the Supplement.

Table 4.2. Key Model Inputs

Characteristic	SOT Population	HSCT Population	Source
Demographics			
Mean Age, years	44.4 years	51.9 years	Mahadeo et al., 2024[5]
Female, %	45%	43%	Mahadeo et al., 2024[5]
Mortality			
Overall Survival with Usual Care (0-5 years)	Fitted parametric curves	Fitted parametric curves	Kaplan-Meier curves, digitized (SOT Population: Figure 1 from Dharnidharka et al., 2021[8];

Characteristic	SOT Population	HSCT Population	Source
			HSCT Population: Figure 1 from Socié et al., 2024[7])
Tabelecleucel Overall Survival Benefit, HR (95% CI) (0-5 years)	0.37 (0.20, 0.71)	0.37 (0.20, 0.71)	Barlev et al., 2024[19]
Baseline Overall Survival (5+ years)	US General Population	US General Population	Acturial life table 2019 [29]
SMR Post-transplant (5+ years)	3.08 (3.05, 3.11)	5.80 (5.30, 6.30)	SOT Population: Volesky-Avellaneda et al., 2024 [30] HSCT Population: Bhatia et a;., 2021 [31]
Response			
Responders at One Month with Usual Care, %	13.5%	13%	Socié et al., 2024[7] and Mahadeo et al., 2024[5]
Responders at One Month with Tabelecleucel, %	52%	50%	Mahadeo et al., 2024[5]
Difference in Overall Survival Between Responders vs. Non-Responders, HR (95% CI)	0.2 (0.07, 0.57)	0.2 (0.07, 0.57)	Mahadeo et al., 2024[5]
Utilities			
Responder (0-5 years)	0.83 (0.66, 1)	0.83 (0.66, 1)	Best et al., 2005[23]
Non-Responder (0-5 years)	0.39 (0.31, 0.47)	0.39 (0.31, 0.47)	Best et al., 2005[23]
All patients alive (5+ years)	0.83	0.83	Li et al., 2017, Forsythe et al., 2018[24,25]
Drug Costs			
Tabelecleucel	$287,500 per 35-day treatment cycle ($95,833 per admin)		Placeholder price; IPD Analytics[26]
Usual Care*	$5,773 per month	$8,248 per month	ASP Pricing File, July 2024, and REDBOOK 2024
Administration Costs (for all IV administered drugs)	$134 per administration		HCPCS: 96413 [32]
Other Health Care Costs			
Cost per Month for Those Alive (0-5 years)	$7,268		Hart et al., 2021[4]
Added One-Time Cost at Death (0-5 years)	$203,338		Hart et al., 2021[4]

CI: confidence interval, HSCT: hematopoietic stem-cell transplant, SMR: standardized mortality ratio, SOT: solid organ transplant.

*Costs for granulocyte-colony stimulating factor (G-CSF) are included.

4.3. Results

Base-Case Results

The discounted drug costs, total costs, quality-adjusted life years (QALYs), equal-value life years (evLYs), and life years for tabelecleucel compared to usual care are presented for the overall population in Table 4.3. Results were weighted according to the proportions of SOT (67%) and HSCT (33%) populations observed in the ALLELE trial. Please refer to Supplement Section E3 for the results of the SOT and HSCT populations reported separately.

In the overall population, tabelecleucel had higher QALYs and evLYs and life years gained over a lifetime horizon. Total costs were higher with tabelecleucel compared to usual care, driven by drug costs. Table 4.4 presents the incremental cost-effectiveness ratios estimated based on the clinical and cost outcomes shown in Table 4.3.

Table 4.3. Base-Case Results for Tabelecleucel Compared to Usual Care for the Full Population

Treatment	Drug Cost	Total Cost	QALYs	evLYs	Life Years
Tabelecleucel*	$578,600	$985,680	5.72	6.35	8.04
Usual Care	$14,899	$314,614	2.06	2.06	3.08

evLYs: equal value of life years gained, QALY: quality-adjusted life year
*Based on placeholder price

Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case for the Full Population

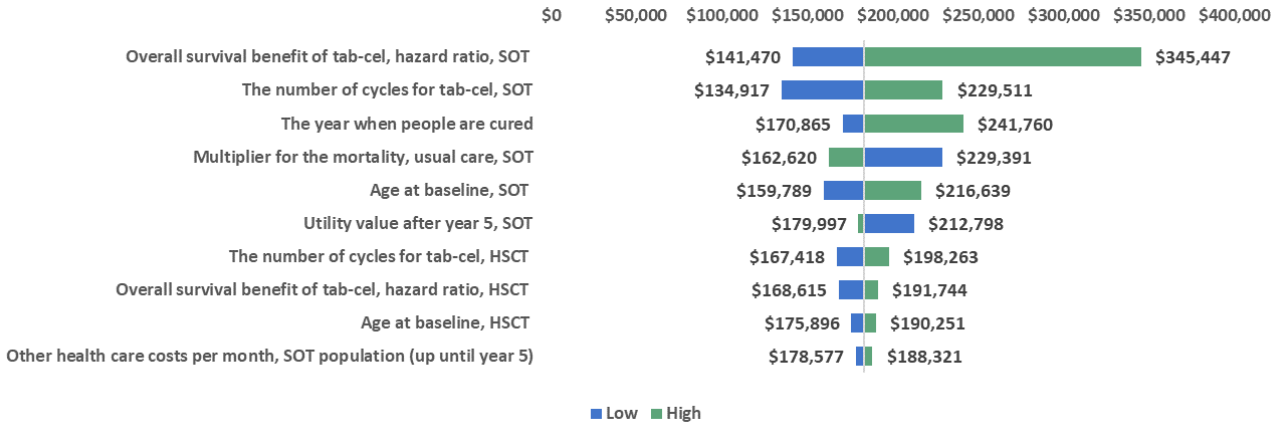
Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained
Tabelecleucel*	**Usual Care**	$183,449	$156,668	$135,255

evLYs: equal value of life years gained, QALY: quality-adjusted life year
*Based on placeholder price

Sensitivity Analyses

Figure 4.2 reports the inputs with the most influence on the incremental cost-effectiveness ratio per QALY. The parameters with the greatest influence on the cost-effectiveness of tabelecleucel were the overall survival benefit of tabelecleucel, with a lower survival benefit leading to a higher incremental cost-effectiveness ratio. Other influential model parameters included the average number of 35-day treatment cycles of tabelecleucel received by patients in the SOT population, the threshold year at which patients are assumed to be cured, and the baseline survival estimates for usual care in the SOT population. Please refer to Supplement Section E4 for the lower and upper inputs for each parameter.

Figure 4.2. Tornado Diagram



tab-cel: tabelecleucel, SOT: solid organ transplantation, HSCT: haematopoietic stem cell transplantation
*Using a placeholder price for tabelecleucel

Tables 4.5 and 4.6 present the probability of tabelecleucel being cost-effective at common thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY and evLY gained, respectively. At the placeholder price for tabelecleucel (i.e., $287,500 per 35-day treatment cycle), 29.2% and 50.7% of the 1,000 iterations within the probabilistic sensitivity analysis resulted in incremental cost-effectiveness ratios beneath $150,000 per QALY and evLY gained, respectively. Please refer to Supplement Section E4 for the mean and 95% credible intervals for model outcomes.

Table 4.5. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Tabelecleucel versus Usual Care

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Tabelecleucel*	0.0%	2.5%	29.2%	64.4%

QALY: quality-adjusted life year
*Based on placeholder price

Table 4.6. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results: Tabelecleucel versus Usual Care

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Tabelecleucel*	0.0%	6.7%	50.7%	81.6%

evLYs: equal value of life years gained
*Based on placeholder price

Scenario Analyses

We conducted several scenario analyses to examine the uncertainty and potential variation in the findings. Table 4.7 reports the incremental cost-effectiveness ratios for the base-case and the following five scenario analyses: (a) scenario 1: modified societal perspective informed by ICER's indirect approach to estimating non-health care sector costs (i.e., patient and caregiver productivity impacts net of consumption costs), (b) scenario 2: alternative response assumption scenario where the probability of moving from response to non-response is assumed to be 0% after six months, (c) scenario 3: alternative survival benefit assumption scenario where the unadjusted overall survival benefit of tabelecleucel is used, (d) scenario 4: alternative survival extrapolation assumption scenario where the flattening of the survival curves was not modeled, (e) scenario 5: a scenario where unrelated medical costs were excluded. In scenario 5, unrelated medical costs were excluded only for those who were alive in and after year 5, as it was not possible to disaggregate the total healthcare costs incurred up to year 5 into related and unrelated medical costs.

The modified societal perspective remained as a scenario analysis because there was no direct data available to inform the analysis, precluding it from being a co-base case as per ICER's Reference Case. The incremental cost-effectiveness ratio was lower with the modified societal perspective compared to the health care sector perspective base case, primarily due to the patient productivity gain during added years of life with tabelecleucel over usual care. Please refer to the Supplement for disaggregated results.

Table 4.7. Scenario Analysis Results

Treatment	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Base-Case Results	$183,449	$156,668	$135,255
Scenario Analysis 1: Modified Societal Perspective (estimated by an indirect approach)**	$88,252	$75,368	$65,067
Scenario Analysis 2: Alternative Response Assumption (No Transition from Response to Non-response after Month 6)	$172,289	$154,860	$135,257
Scenario Analysis 3: Alternative Survival Benefit Assumption (Unadjusted Survival Benefit)	$188,028	$160,933	$139,201
Scenario Analysis 4: Alternative Survival Extrapolation Assumption (No Flattening of the Survival Curves)	$202,700	$172,723	$148,955
Scenario Analysis 5:	$172,958	$147,708	$127,520

Excluding Unrelated Medical Costs			

QALY: quality-adjusted life year, evLY: equal value of life year

*Based on placeholder price

**The modified societal perspective analysis was conducted using the indirect approach for estimating non-health care sector costs (i.e., patient and caregiver productivity impacts net of consumption costs).

Additional scenario analysis findings can be found in Section E5 of the Supplement.

Threshold Analyses

Tables 4.8 and 4.9 report the threshold prices at $50,000, $100,000, $150,000, and $200,000 per QALY and evLY gained, respectively.

Table 4.8. QALY-Based Threshold Analysis Results

	Placeholder Price per 35-day Treatment Cycle*	Price Per Cycle to Achieve $50,000 per QALY Gained	Price Per Cycle to Achieve $100,000 per QALY Gained	Price Per Cycle to Achieve $150,000 per QALY Gained	Price Per Cycle to Achieve $200,000 per QALY Gained
Tabelecleucel	$287,500	$58,667	$144,405	$230,143	$315,880

QALY: quality-adjusted life year

*One 35-day treatment cycle consists of 3 administrations

Table 4.9. evLY-Based Threshold Analysis Results

	Placeholder Price per 35-day Treatment Cycle*	Price Per Cycle to Achieve $50,000 per evLY Gained	Price Per Cycle to Achieve $100,000 per evLY Gained	Price Per Cycle to Achieve $150,000 per evLY Gained	Price Per Cycle to Achieve $200,000 per evLY Gained
Tabelecleucel	$287,500	$73,323	$173,718	$274,112	$374,506

evLYs: equal value of life years gained

*One 35-day treatment cycle consists of 3 administrations

Model Validation

Model validation followed standard practices in the field. We conducted stress testing with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs. Model validation was also conducted in terms of comparisons of model findings to the available clinical trial evidence.

Prior Economic Models

We searched the literature to identify models that were similar to our analysis, however, no relevant prior economic models were identified.

Uncertainty and Controversies

We acknowledge that there is a high level of heterogeneity in disease progression and treatment responses depending on the morphologies of PTLD or the types of transplants a patient has received. However, the currently available clinical and economic data are not sufficiently stratified to fully simulate this heterogeneity. We attempted to address the heterogeneity by modeling patients with EBV+ PTLD following SOT and HSCT separately, based on the clinical evidence presented in the ALLELE trial and other literature, and suggestions from clinical experts. Due to the lack of population-specific data for key model parameters, such as the survival benefit of tabelecleucel, there remains a high level of uncertainty in the results for individual populations. Notably, based on our assessment of the clinical validity of the survival estimates compared to those reported in the ALLELE trial, we suspect that our model overestimates the survival benefit for SOT and underestimates it for HSCT (we did not have stratified data available to estimate survival benefit separately). Therefore, our primary analysis was based on a weighting of results according to the proportions of patients with a SOT and HSCT in the ALLELE trial. We recognize that the proportion of patients with EBV+ PTLD following an SOT compared to an HSCT in the ALLELE study may not reflect what is seen in the real world. However, we believe this was the most reliable estimate for the weighing since the survival benefit was derived from the ALLELE trial. For full transparency, the results for individual populations are reported in the supplement, but these results should be interpreted with caution because they do not reflect the likelihood of population-specific treatment effects.

Furthermore, since the ALLELE study was a single-arm clinical trial, adjusted clinical benefits of tabelecleucel in terms of overall survival and response compared to usual care were not available in the trial. Therefore, the adjusted survival benefit of tabelecleucel was derived from an observational comparative study that includes a subset of the ALLELE study population. For response rates, unadjusted estimates were obtained separately from the trial and observational studies for tabelecleucel and usual care, respectively. Additionally, long-term efficacy data for tabelecleucel are not available from the ALLELE study, introducing significant uncertainty regarding the durability of the treatment effect. To address this uncertainty, we conducted scenario analyses with varying treatment effects of tabelecleucel and its durability.

The composition of usual care is another area of uncertainty. Usual care for EBV+ PTLD is not standardized, and there are limited options for patients who relapse or are refractory to existing therapies. Therefore, defining comparators for tabelecleucel was challenging, which made it

difficult to estimate their duration of use and costs. Based on stakeholder comments and input from clinical experts, we assumed that most patients would receive rituximab with or without chemotherapy, with the composition varying depending on whether patients had received an SOT or HSCT. We also assumed that the costs of chemotherapy could be approximated using the cost of CHOP, as it is a commonly used chemotherapy regimen. However, we acknowledge that some patients may receive different agents with significantly varying costs. To account for this variability, we widely varied the costs of comparators in the sensitivity analysis.

The modeled population was restricted to the patient population consistent with the ALLELE trial population (i.e., individuals with EBV+ PTLD who have received at least one prior therapy), as there is no current signal for a potential FDA label expansion in the US. The economic evaluation results and suggested price benchmark may differ for other patient populations if a label expansion occurs.

Finally, we found no other economic models for the same disease area in the public literature or from other health technology assessment organizations. Therefore, we were unable to validate our model inputs and results against existing models. However, our model was validated and calibrated based on clinical trial data to the extent possible.

4.4 Summary and Comment

The cost-effectiveness analyses suggest that tabelecleucel is associated with a substantial increase in life years, QALYs, and evLYs, and results in higher intervention and non-intervention costs. At a placeholder price of $287,500 per 35-day treatment cycle, the incremental cost-effectiveness ratio of tabelecleucel slightly exceeded the upper end of the acceptable range. Therefore, achieving cost-effectiveness may be possible with a modest discount on the price of tabelecleucel. However, there is substantial uncertainty in this conclusion, as the cost-effectiveness of tabelecleucel is largely dependent on assumptions regarding the duration and durability of the expected survival benefit of treatment.

5. 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 was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

Table 5.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There is substantial unmet need despite currently available treatments.	Although a rare disease, there are currently limited treatment options for patients with relapsed or refractory EBV+ PTLD, and patients usually survive for only weeks to months without treatment. Thus, an effective treatment option for this population would meet a substantial unmet need. To inform unmet need as a benefit beyond health, the results for the evLY and QALY absolute and proportional shortfalls have been reported below. evLY shortfalls: • Absolute shortfall: 26.35 • Proportional shortfall: 89.46% QALY shortfalls: • Absolute shortfall: 25.15 • Proportional shortfall: 89.01% The absolute and proportional shortfalls represent the total and proportional health units of remaining quality adjusted life expectancy, respectively, that would be lost due to un- or under-treated illness. Note that the shortfalls were calculated using the results of the cost-effectiveness analysis that weighted the results by the proportion of patients with SOT and HSCT in the ALLELE trial (67% SOT; 33% HSCT). Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews.

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.	N/A
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.	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.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.	Tabelecleucel is the first commercially available off-the-shelf T-cell therapy. Because the cells are donor-derived, the treatment is able to be delivered more quickly than other cytotoxic T-cell therapies, and has the potential to be delivered in both the inpatient and outpatient setting. Thus, tabelecleucel could broaden access to EBV+ PTLD treatment outside of the specialized academic medical centers where many patients now need to travel to for treatment.

ICER did not calculate the Health Improvement Distribution Index (HIDI) because reliable prevalence estimates for the EBV+ PTLD population were not available.

6. Health Benefit Price Benchmarks

ICER does not provide health benefit price benchmarks as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmarks that will be presented in the next version of this Report.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

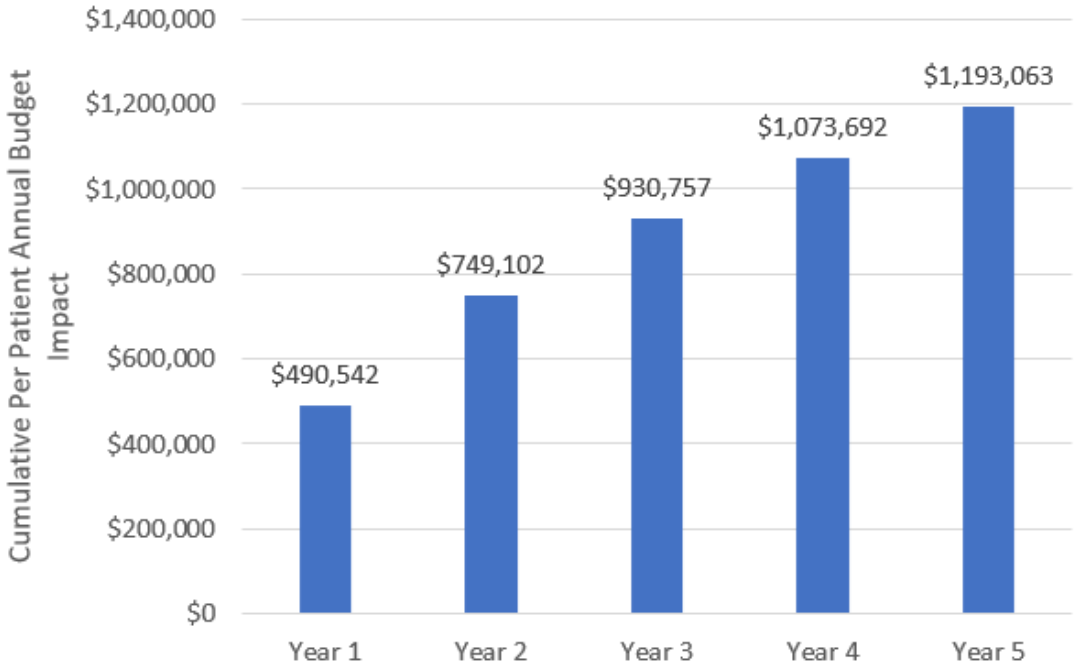
Results from the cost-effectiveness model were used to estimate the potential total budgetary impact of tabelecleucel for patients with EBV+ PTLD. Potential budget impact is defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. We used a placeholder price of $287,500 per cycle and the three threshold prices (at $50,000, $100,000, and $150,000 per evLYG) for tabelecleucel in our estimate of budget impact.

In order to calculate our eligible patient population, we used subpopulation-specific inputs (e.g., incidence of SOT and HSCT); however, in line with the cost-effectiveness analysis, our overall potential budget impact estimates remain representative of the overall population of patients with EBV+ PTLD in the US. Our results are not intended to provide budget impact estimates separately for SOT and HSCT populations, given the uncertainties in the data reported in the cost-effectiveness analysis. This potential budget impact analysis included the estimated number of individuals in the US who would be eligible with tabelecleucel. To estimate the size of the potential candidate population, we used inputs for the incidence of EBV+ PTLD among both SOT (10.5%) and allogeneic HSCT (1.7%) recipients.[7,33,34] We applied these incidence estimates to the number of SOTs and HSCTs that occur each year in the US, approximately 49,187 and 9,299, respectively, to estimate the number of patients who develop EBV+ PTLD post-transplant per year.[35,36] In line with the population of interest for tabelecleucel, we further narrowed the eligible population to patients who have received at least one prior therapy. According to a multicenter, retrospective review, 50% of EBV+ PTLD patients are relapsed or refractory to first-line rituximab therapy, so we used this estimate as a proxy to determine the number of patients who have received at least one prior therapy.[7] Applying these sources resulted in estimates of 13,319 eligible patients in the US over five years. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years or 2,664 patients per year.

7.2. Results

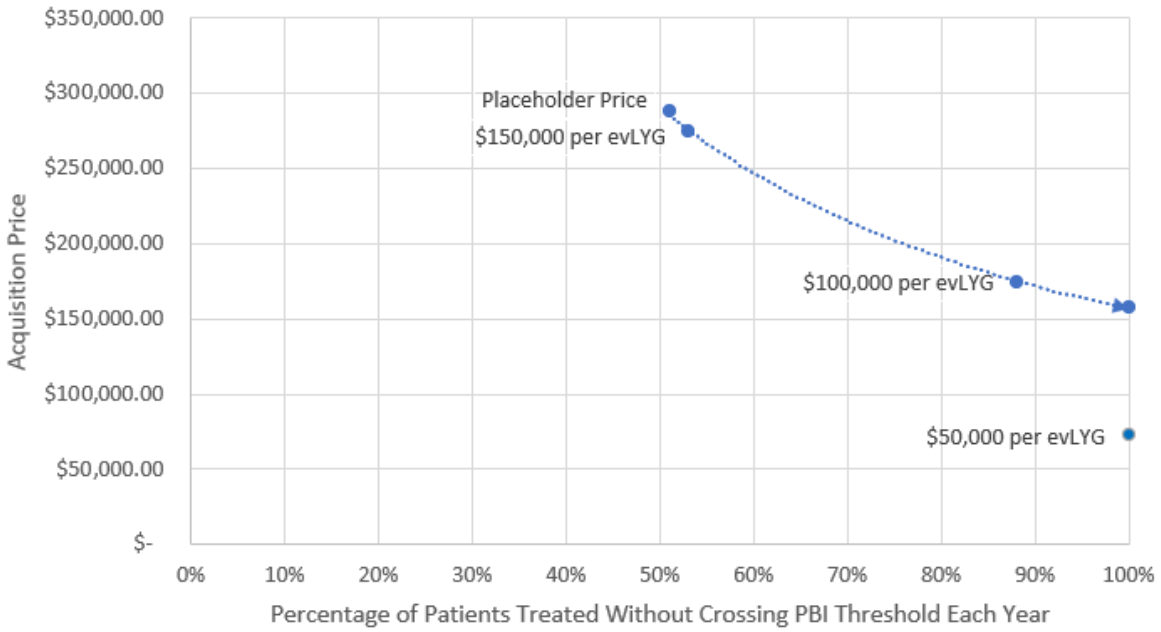
Figure 7.1 illustrates the cumulative annual per patient treated potential budget impact for tabelecleucel compared to usual care for the weighted patient population. At tabelecleucel placeholder price per 35-day treatment cycle of $287,500, the average annual budget impact per patient was $490,542 in year one, with cumulative net annual costs increasing to $1,193,063 in year five.

Figure 7.1. Cumulative Per Patient Annual Budget Impact for Tabelecleucel Compared to Usual Care (for the Overall Population) using a Placeholder Price for Tabelecleucel



Results showed that compared to usual care, 51% of 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. At prices to reach $50,000, $100,000, and $150,000 per evLYG ($73,300, $173,700, and $274,100 respectively), 100%, 87%, and 53% of eligible patients could be treated over five years (Figure 7.2).

Figure 7.2. Percentage of Eligible Patients Treated Without Reaching the Potential Budget Impact Threshold at Placeholder and Threshold Prices



PBI: potential budget impact

References

1. 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
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. 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
4. 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
5. 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. *The Lancet Oncology*. 2024-01-01 2024;25(3)doi:10.1016/s1470-2045(23)00649-6
6. Trappe RU, Dierickx D, Zimmermann H, et al. Response to Rituximab Induction Is a Predictive Marker in B-Cell Post-Transplant Lymphoproliferative Disorder and Allows Successful Stratification Into Rituximab or R-CHOP Consolidation in an International, Prospective, Multicenter Phase II Trial. *J Clin Oncol*. Feb 10 2017;35(5):536-543. doi:10.1200/JCO.2016.69.3564
7. 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 transplantation*. 2024-01-01 2024;59(1)doi:10.1038/s41409-023-02127-9
8. Dharnidharka V, Thirumalai D, Jaeger U, et al. 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*. 2021-01-01 2021;138(SUPPL 1)doi:10.1182/blood-2021-147307
9. 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
10. 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

11. Al-Mansour Z, Nelson BP, Evens AM. Post-transplant lymphoproliferative disease (PTLD): risk factors, diagnosis, and current treatment strategies. *Curr Hematol Malig Rep*. Sep 2013;8(3):173-83. doi:10.1007/s11899-013-0162-5
12. 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
13. European Medicines Agency. Ebvallo: Product Overview. https://www.ema.europa.eu/en/medicines/human/EPAR/ebvallo
14. Kizer KW, English RA, Hackmann M, eds. *Realizing the Promise of Equity in the Organ Transplantation System*. National Academy of Sciences; 2022.
15. Nikiforow S, Whangbo JS, Reshef R, et al. Tabelecleucel for EBV+ PTLD following allogeneic HCT or SOT in a multicenter expanded access protocol. *Blood advances*. 2024-01-01 2024;doi:10.1182/bloodadvances.2023011626
16. Aftab B, Munson D, Rasor K, et al. Correlation of circulating epsteinbarr virus-targeted cytotoxic t lymphocyte precursors (EBV-CTLp) and clinical response following tabelecleucel (tab-cel) infusion in patients with EBV-driven disease. *Hematol Oncol*. 2019-01-01 2019;37doi:10.1002/hon.186_2631
17. Prockop S, Doubrovina E, Suser S, et al. Off-the-shelf EBV-specific T cell immunotherapy for rituximab-refractory EBV-associated lymphoma following transplantation. *The Journal of clinical investigation*. 2020-01-01 2020;130(2)doi:10.1172/jci121127
18. Trappe RU, Choquet S, Clark A, et al. Effectiveness and safety outcomes in patients with EBV+ PTLD treated with allogeneic EBV-specific T-cell immunotherapy (tabelecleucel) under an expanded access program (EAP) in Europe. *Oncol Res Treat*. 2024-01-01 2024;47doi:10.1159/000535363
19. Barlev A, Zimmermann H, Guzman-Becerra N, et al. Comparative analysis of tabelecleucel and current treatment in patients with Epstein-Barr virus-positive post-transplant lymphoproliferative disease following hematopoietic cell transplant or solid organ transplant. *Journal of medical economics*. 2024-01-01 2024;27(1)doi:10.1080/13696998.2024.2354150
20. Agboola FW, AC. A Framework for Evaluating the Diversity of Clinical Trials. *Journal of Clinical Epidemiology*. 2024:111299.
21. Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. *Blood*. Nov 24 2016;128(21):2489-2496. doi:10.1182/blood-2016-05-718528
22. Prockop S, Doubrovina E, Feng A, et al. Long term outcomes of tabelecleucel (allogeneic third-party ebv-targeted cytotoxic t lymphocytes) for rituximab-refractory post-transplant EBV+ lymphomas: A single center experience. *HemaSphere*. 2018-01-01 2018;2doi:10.1097/hs9.0000000000000060
23. Best JH, Hornberger J, Proctor SJ, Omnes LF, Jost F. Cost-effectiveness analysis of rituximab combined with chop for treatment of diffuse large B-cell lymphoma. *Value in health : the*

journal of the International Society for Pharmacoeconomics and Outcomes Research. Jul-Aug 2005;8(4):462-70. doi:10.1111/j.1524-4733.2005.00037.x
24. Li B, Cairns JA, Draper H, et al. Estimating health-state utility values in kidney transplant recipients and waiting-list patients using the EQ-5D-5L. *Value in Health*. 2017;20(7):976-984.
25. Forsythe A, Brandt PS, Dolph M, Patel S, Rabe APJ, Tremblay G. Systematic review of health state utility values for acute myeloid leukemia. *ClinicoEconomics and Outcomes Research*. 2018:83-92.
26. IPD Analytics. Payer & Provider Insights. Accessed August, 2025. https://www.ipdanalytics.com
27. Trappe R, Oertel S, Leblond V, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. *Lancet Oncol*. Feb 2012;13(2):196-206. doi:10.1016/s1470-2045(11)70300-x
28. Jiao B, Basu A. Catalog of age-and medical condition—specific healthcare costs in the United States to inform future costs calculations in cost-effectiveness analysis. *Value in Health*. 2021;24(7):957-965.
29. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. Dec 1982;5(6):649-55.
30. Volesky-Avellaneda KD, Wang JH, Pfeiffer RM, et al. Leading causes of death among adult solid organ transplant recipients in the United States, 1999 to 2019. *medRxiv*. 2024:2024.06.07.24308602.
31. Bhatia S, Dai C, Landier W, et al. Trends in late mortality and life expectancy after allogeneic blood or marrow transplantation over 4 decades: a blood or marrow transplant survivor study report. *JAMA oncology*. 2021;7(11):1626-1634.
32. Centers for Medicare & Medicaid Services. Physician Fee Schedule. Accessed June 21, 2024. https://www.cms.gov/medicare/physician-fee-schedule/search?Y=0&T=4&HT=0&CT=3&H1=96413&M=5
33. Dierickx D, Tousseyn T, Sagaert X, et al. Single-center analysis of biopsy-confirmed posttransplant lymphoproliferative disorder: incidence, clinicopathological characteristics and prognostic factors. *Leuk Lymphoma*. Nov 2013;54(11):2433-40. doi:10.3109/10428194.2013.780655
34. US Department of Health and Human Services Health Resources and Services Administration. OPTN/SRTR 2022 Annual Data Report. 2022;
35. Phelan R, Chen M, Bupp C, et al. Updated Trends in Hematopoietic Cell Transplantation in the United States with an Additional Focus on Adolescent and Young Adult Transplantation Activity and Outcomes. *Transplant Cell Ther*. Jul 2022;28(7):409.e1-409.e10. doi:10.1016/j.jtct.2022.04.012
36. US Department of Health and Human Services Health Resources and Services Administration. OPTN/SRTR 2022 Annual Data Report: Deceased Organ Donation. 2022;

37. Lansky SB, List MA, Lansky LL, Ritter-Sterr C, Miller DR. The measurement of performance in childhood cancer patients. *Cancer*. Oct 1 1987;60(7):1651-6. doi:10.1002/1097-0142(19871001)60:7<1651::aid-cncr2820600738>3.0.co;2-j
38. Montes de Jesus F, Dierickx D, Vergote V, et al. Prognostic superiority of International Prognostic Index over [(18)F]FDG PET/CT volumetric parameters in post-transplant lymphoproliferative disorder. *EJNMMI Res*. Mar 18 2021;11(1):29. doi:10.1186/s13550-021-00769-8
39. Ottersen T, Førde R, Kakad M, et al. A new proposal for priority setting in Norway: Open and fair. *Health Policy*. Mar 2016;120(3):246-51. doi:10.1016/j.healthpol.2016.01.012
40. van de Wetering EJ, Stolk EA, van Exel NJ, Brouwer WB. Balancing equity and efficiency in the Dutch basic benefits package using the principle of proportional shortfall. *Eur J Health Econ*. Feb 2013;14(1):107-15. doi:10.1007/s10198-011-0346-7
41. Stolk EA, van Donselaar G, Brouwer WB, Busschbach JJ. Reconciliation of economic concerns and health policy: illustration of an equity adjustment procedure using proportional shortfall. *Pharmacoeconomics*. 2004;22(17):1097-107. doi:10.2165/00019053-200422170-00001
42. Version 1.2024. NCCN Guidelines for B-Cell Lymphomas. Version 1.2024. (2024).
43. Styczynski J, van der Velden W, Fox CP, et al. Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines. *Haematologica*. Jul 2016;101(7):803-11. doi:10.3324/haematol.2016.144428
44. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med*. Mar 1 1997;126(5):376-80.
45. Higgins J, Thomas, J, Chandler, J, Cumpston, M, Li, T, Page, MJ, Welch, VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). https://training.cochrane.org/handbook/current
46. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. Mar 29 2021;372:n71. doi:10.1136/bmj.n71
47. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. Updated January 31, 2020. https://icer.org/evidence-rating-matrix/
48. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care*. Jun 2010;48(6 Suppl):S145-52. doi:10.1097/MLR.0b013e3181d9913b
49. Compagno F, Basso S, Panigari A, et al. Management of PTLD After Hematopoietic Stem Cell Transplantation: Immunological Perspectives. *Front Immunol*. 2020;11:567020. doi:10.3389/fimmu.2020.567020
50. Baiocchi R, Choquet S, Ghosh M, et al. Clinical Experience of Tabelecleucel in Epstein–Barr Virus-Positive Post-Transplant Lymphoproliferative Disease (EBV+ PTLD) Involving the Central Nervous System. *Transplant Cell Ther*. 2024-01-01 2024;30(2)doi:10.1016/j.jtct.2023.12.495

51. Prockop S, Shen RR, Guzman-Becerra N, et al. Epstein-Barr virus-specific cytotoxic T lymphocyte precursors (EBV-CTLp) after tabelecleucel correlates with response & survival in rituximab relapsing or refractory EBV posttransplant lymphoproliferative disease (PTLD). *Cytotherapy*. 2020-01-01 2020;22(5)doi:10.1016/j.jcyt.2020.03.265
52. Liu JY, Zhang JM, Zhan HS, Sun LY, Wei L. EBV-specific cytotoxic T lymphocytes for refractory EBV-associated post-transplant lymphoproliferative disorder in solid organ transplant recipients: a systematic review. *Transpl Int*. Dec 2021;34(12):2483-2493. doi:10.1111/tri.14107
53. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama*. Sep 13 2016;316(10):1093-103. doi:10.1001/jama.2016.12195
54. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Aug 2019;22(8):931-941. doi:10.1016/j.jval.2019.02.009
55. Liu FF, Bartlett M, Craigie S. A Systematic Literature Review of Health-Related Quality of Life Outcomes and Associated Utility Values in Relapsed and/or Refractory Large B Cell Lymphoma. *PharmacoEconomics-Open*. 2024;8(2):171-190.
56. Zimmermann H, Koenecke C, Dreyling MH, et al. Modified risk-stratified sequential treatment (subcutaneous rituximab with or without chemotherapy) in B-cell Post-transplant lymphoproliferative disorder (PTLD) after Solid organ transplantation (SOT): the prospective multicentre phase II PTLD-2 trial. *Leukemia*. 2022;36(10):2468-2478.
57. Spindler TJ, Ruiz F, Jehng T, et al. Exploring the Impact of Humoral Immunogenicity with Tabelecleucel for the Treatment of EBV+ PTLD Following HCT and SOT. *Blood*. 2022-01-01 2022;140doi:10.1182/blood-2022-157673
58. Weycker D, Li X, Barron R, et al. Importance of risk factors for febrile neutropenia among patients receiving chemotherapy regimens not classified as high-risk in guidelines for myeloid growth factor use. *Journal of the National Comprehensive Cancer Network*. 2015;13(8):979-986.
59. Li S, Liu J, Guo H, et al. Trends in Neutropenia-Related Hospitalization in Older Patients with Non-Hodgkin Lymphoma (NHL) Receiving Myelosuppressive Chemotherapy in the United States: 1995-2015. *Blood*. 2018;132:2308.
60. Centers for Medicare & Medicaid Services. July 2024 ASP Pricing File. Accessed June 24, 2024. https://www.cms.gov/medicare/payment/part-b-drugs/asp-pricing-files
61. Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. *PLoS One*. Jan 28 2010;5(1):e8933. doi:10.1371/journal.pone.0008933
62. IPD Analytics. Budget Impact. Accessed June 25, 2024. https://www.ipdanalytics.com

63. Jiao B, Basu A. Associating Health-Related Quality-of-Life Score with Time Uses to Inform Productivity Measures in Cost-Effectiveness Analysis. *Pharmacoeconomics*. Sep 2023;41(9):1065-1077. doi:10.1007/s40273-023-01246-x
64. Rowen D, Dixon S, Hernández-Alava M, Mukuria C. Estimating informal care inputs associated with EQ-5D for use in economic evaluation. *Eur J Health Econ*. Jul 2016;17(6):733-44. doi:10.1007/s10198-015-0718-5
65. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. https://icer.org/our-approach/methods-process/value-assessment-framework/
66. Pearson SD. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Mar 2018;21(3):258-265. doi:10.1016/j.jval.2017.12.017

Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Epstein-Barr Virus Positive Post Transplant Lymphoproliferative Disease (EBV+ PTLD): EBV+ PTLD is a rare and life-threatening disease that occurs in patients following either allogeneic hematopoietic stem-cell transplant or solid organ transplant when the recipient's ability to maintain T-cell control of Epstein-Barr Virus infection is compromised.[1]

Clinical Response Classifications

Table A1.1 Response Definitions based on the Lugano Classification with LYRIC Modification[21]

Outcome	Definition
Complete response (CR)	PET-CT: score 1, 2, or 3 with or without a residual mass on 5PS CT: target nodes/nodal masses must regress to ≤1.5 cm in LDi
Partial response (PR)	PET-CT: score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size. CT: ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive disease (PD)	PET-CT: score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment. CT: an individual node/lesion must be abnormal with: LDi >1.5 cm and increase by ≥50% from PPD nadir and an increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by ≥2 cm from baseline. New or recurrent splenomegaly New or clear progression of preexisting non measured lesions Regrowth of previously resolved lesions A new node >1.5 cm in any axis or a new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma AND/OR new or recurrent involvement of the bone marrow

5PS: 5-point scale, CT: computed tomography, FDG: fluorodeoxyglucose, LDi: longest diameter, PET: positron emission tomography, PPD: product of the perpendicular diameters, SDi: short diameter, SPD: sum of the product of the diameters

Outcome Definitions

Objective Response Rate: The number of patients that had a complete response or partial response.[5]

Best overall response: The best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation.[5]

Duration of response: The time from the date of initial response until progression after the last response or death due to any cause. Only deaths within 90 days after the last valid disease evaluation were counted as events. For patients without an event of death or disease progression, duration of response was censored at the last disease evaluation date. If a patient was off study and the last disease assessment was not evaluable, the last evaluable disease evaluation date was used. If a patient was still on study and the last disease assessment was not evaluable, the last disease evaluation date was used.[5]

Overall survival: The time from the first dose to the date of death from any cause. Patients who were lost to follow-up or were still alive by the data cutoff date were censored on the last known-to-be-alive date up to the data cutoff date.[5]

Time to response: Time from the date of the first dose to the date of the first partial or complete response. Calculated only for patients who had complete response or partial response with up to 2 different HLA restrictions.[5]

Time to best response: The time from the date of the first dose to the date of the first best overall response.[5]

Diagnostic Definitions

Lansky Score: An assessment for patients <16 years old that uses parent description of child's activity to track ability and response to treatment. It is a useful tool to use over time to track disease progression.[37]

Eastern Cooperative Oncology Group (ECOG) Performance Status Scale: A scale which describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.). It is typically used to conduct clinical trials for the treatment of cancer. A score of 2 indicates an individual is ambulatory and capable of all selfcare but unable to carry out any work activities and are up and mobile for more than 50% of waking hours.[29]

Post-transplant Lymphoproliferative Disease-adapted Prognostic Index: An index used to predict overall survival for patients aged ≥16 years. Univariate and multivariate analyses on the effect of patient's age at diagnosis of PTLD, time from transplantation to PTLD, EBV association of PTLD,

stage of disease, LDH at diagnosis, and the ECOG performance status are undertaken using the Cox proportional-hazards test and Cox regression analysis.[38]

Other Relevant Definitions

Absolute and Proportional Shortfalls: Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[39] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[40,41] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

Health Improvement Distribution Index (HIDI): The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4%=2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above 1 suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. The HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

A2. Potential Cost-Saving Measures in EBV+ PTLD

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 headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for EBV+ PTLD (e.g., hospitalization, 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. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with EBV+ PTLD that could be reduced, eliminated, or made more efficient. No suggestions were received.

A3. Research, Development, and Manufacturing Costs

We asked for information on this topic from the manufacturer but did not receive any input on research, development, and manufacturing costs for this patient population.

A4. Patient Input on Clinical Trial Design

We asked for information on this topic from the manufacturer but did not receive any input on clinical trial design for this patient population.

B. Patient Perspectives: Supplemental Information

B1. Methods

We spoke with and received feedback from patients, caregivers, clinical experts, and the manufacturer of the product throughout the review. We spoke with two patients diagnosed with EBV+ PTLD after solid organ transplants, as well as two caregivers of a child who underwent a transplant and was monitored for EBV+ PTLD post-transplant. We also spoke with several clinicians with expertise in treating EBV+ PTLD, including one pediatric physician specializing in infectious diseases, three adult hematologist/oncologists, and three pediatric hematologist/oncologists. All clinicians had experience with the development or use of cytotoxic T-cell (CTL) therapies.

C. Clinical Guidelines

National Comprehensive Cancer Network (NCCN) Guidelines for B-Cell Lymphomas. Version 1.2024.[42]

The NCCN Guidelines for B-Cell Lymphomas recommends confirmation of diagnosis of PTLD through biopsy with adequate immunophenotyping (e.g., cell surface marker analysis) as well as EBV-specific testing (testing for latent membrane protein and/or in-situ hybridization testing). PTLD subtypes are outlined as nondestructive lesions / hyperplasia, monomorphic PTLD, polymorphic PTLD, and Classical Hodgkin Lymphoma (CHL) type PTLD. First-line therapy for all subtypes is reduction in immunosuppression if possible, followed by rituximab alone or with chemoimmunotherapy. For localized disease, radiation therapy or surgery is recommended where possible. After first-line therapy, if a partial response or progressive disease is observed, additional combinations of rituximab and chemotherapy or EBV-specific cytotoxic T-cell (CTL) therapy are recommended. The recommended dosing of rituximab is 375 mg/m2 weekly for four weeks and recommended concurrent chemotherapy regimen is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

American Society of Transplantation Infectious Diseases Community of Practice Guidelines[2]

The American Society of Transplantation Infectious Diseases Community of Practice Guidelines outline management of EBV+ PTLD after solid organ transplantation. The guidelines highlight risk factors for developing PTLD in SOT recipients such as primary EBV infection, type of organ transplanted, duration of immunosuppression and age. For diagnostic testing, the guidelines recommend identifying patient EBV serostatus, testing EBV viral load, and conducting an examination of tissue. After there is a confirmed PTLD diagnosis, it is recommended to assess the clinical staging of the disease (i.e., identifying presence of symptoms, location of lesions, presence of CNS involvement). The recommended treatment pathway for patients with PTLD is to begin with reduced immunosuppression in patients with early and late B-cell PTLD followed by rituximab monotherapy and then, if a patient is able to tolerate it, chemotherapy is recommended. These guidelines highlight evidence for the use of EBV-specific CTLs in patients with PTLD but does not include a formal recommendation.

European Conference on Infections in Leukemia (ECIL-6)[43]

The European Conference on Infections in Leukemia (ECIL-6) guidelines provide recommendations for the management of EBV+ PTLD after hematopoietic stem cell transplant (HSCT). For the prevention of EBV disease, the guidelines recommend that patients be tested for EBV antibodies prior to transplant. EBV DNAemia should also be monitored after the transplant. Risk factors for developing PTLD pre-transplant include T-cell depletion and EBV serology donor/recipient mismatch and for post-transplant, risk factors include GvHD requiring immunosuppressive treatment and high EBV viral load. When diagnosing EBV+ PTLD, it is recommended that clinicians conduct a physical evaluation, PET/CT scans, tissue biopsy, and evaluate EBV viral load using a PCR. Once diagnosed, the recommended treatment for EBV+ PTLD is rituximab monotherapy. Second-line treatment recommendations are either cellular therapy or additional rituximab combined with chemotherapy.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

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 o 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.

Table D1.1 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.

Section and Topic	Item #	Checklist Item
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.

Section and Topic	Item #	Checklist Item
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for Epstein-Barr virus-positive post-transplant lymphoproliferative disease followed established best research methods.[44,45] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[46] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews.

Table D1.2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

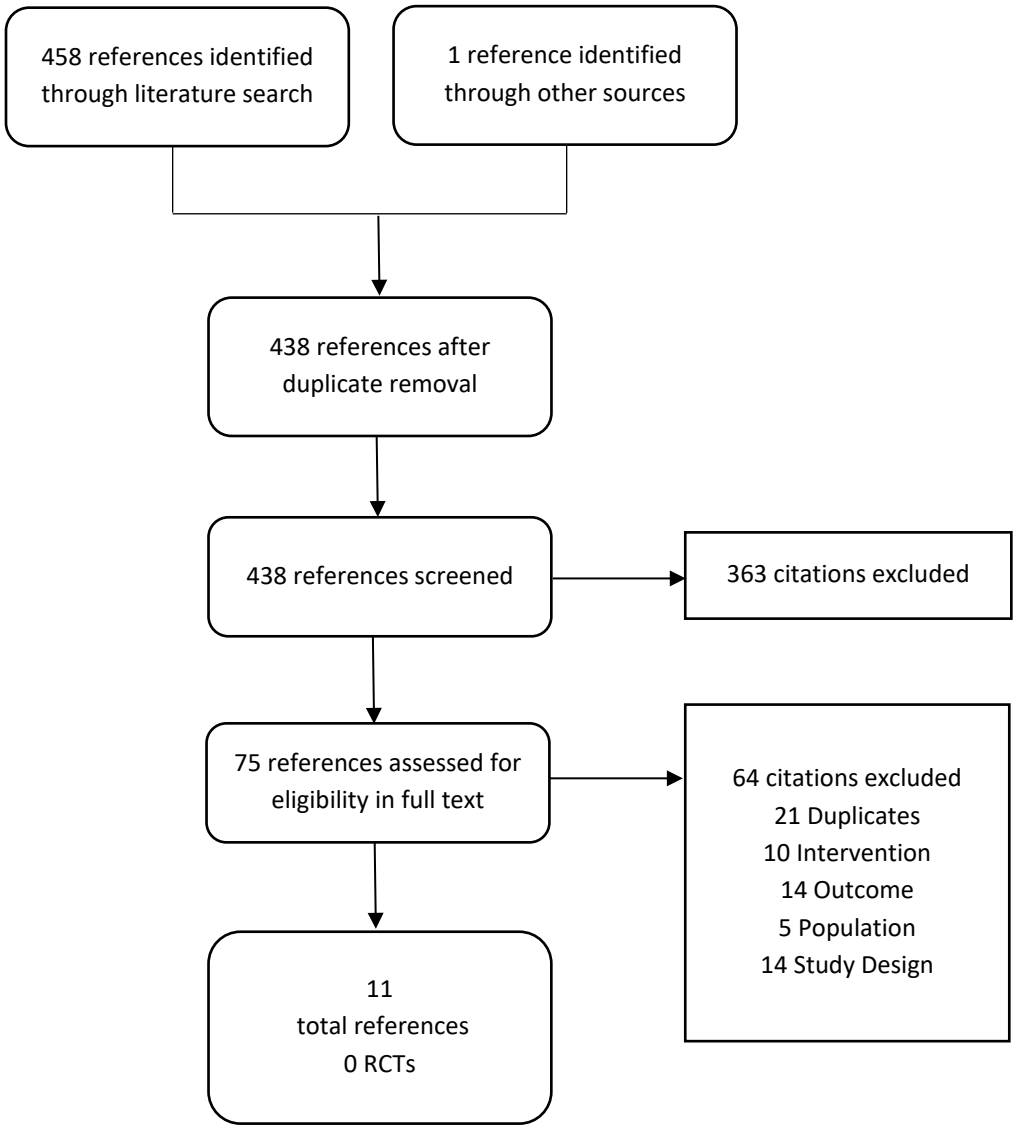
#	Search Terms
1	('epstein barr virus positive post-transplant lymphoproliferative disease' or 'Epstein-Barr virus-associated post-transplant lymphoproliferative disorder*' or 'EBV+ PTLD' or 'EBV PTLD' or 'EBV-positive PTLD' or 'EBV-associated PTLD' or 'EBV-positive post-transplant lymphoproliferative disease' or 'post-transplant lymphoproliferative disease' or 'PTLD' or 'EBV-positive' or 'EBV+' or 'epstein barr virus positive' or ('EBV+' and 'PTLD')).ti,ab.
2	('tabelecleucel' or 'tablecleucel' or 'tab-cel' or 'tab cel' or 'Ebvallo' or 'EBV CTL*' or 'EBV Targeted T-Cell*' or 'Cytotoxic T Lymphocytes Activated Against Epstein-Barr Virus' or 'EBV-CTL*' or 'Allogeneic T-cell ATA129' or 'ata 129' or 'ata129' or 'EBV-cytotoxic t lymphocyte*' or 'Epstein-Barr virus-cytotoxic T lymphocytes').ti,ab.
3	('epstein barr virus positive post-transplant lymphoproliferative disease' or 'Epstein-Barr virus-associated post-transplant lymphoproliferative disorder*' or 'EBV+ PTLD' or 'EBV PTLD' or 'EBV-positive PTLD' or 'EBV-associated PTLD' or 'EBV-positive post-transplant lymphoproliferative disease' or ('EBV+' and 'PTLD')).ti,ab.
4	('natural history' or 'observational' or 'case report' or 'case series' or 'real-world').ti,ab.
5	(1 and 2) or (3 and 4)
6	(animals not (humans and animals)).sh.
7	5 NOT 6

#	Search Terms
8	(addresses or autobiography or bibliography or biography or comment or congresses or consensus development conference or dictionary or directory or duplicate publication or editorial or encyclopedia or festschrift or guideline or interactive tutorial).pt.
9	7 NOT 8
10	limit 9 to English language
11	remove duplicates from 10

Table D1.3. Search Strategy of EMBASE SEARCH

#	Search Terms
1	'epstein barr virus positive post-transplant lymphoproliferative disease':ti,ab OR 'epstein-barr virus-associated post-transplant lymphoproliferative disorder*':ti,ab OR 'EBV+ PTLD':ti,ab OR 'ebv ptld':ti,ab OR 'ebv-positive ptld':ti,ab OR 'ebv-associated ptld':ti,ab OR 'ebv-positive post-transplant lymphoproliferative disease':ti,ab OR 'post-transplant lymphoproliferative disease':ti,ab OR 'ptld':ti,ab OR 'post-transplant lymphoproliferative disorder':ti,ab OR 'epstein barr virus positive':ti,ab OR 'ebv+':ti,ab OR 'ebv-positive':ti,ab
2	'tabelecleucel':ti,ab OR 'tablecleucel':ti,ab OR 'tab-cel':ti,ab OR 'tab cel':ti,ab OR 'ebvallo':ti,ab OR 'ebv ctl*':ti,ab OR 'ebv targeted t-cell*':ti,ab OR 'cytotoxic t lymphocytes activated against epstein-barr virus':ti,ab OR 'ebv-ctl*':ti,ab OR 'allogeneic t-cell' OR 'ata129':ti,ab OR 'ata 129':ti,ab OR 'ata129':ti,ab OR 'ebv-cytotoxic t lymphocyte*':ti,ab OR 'epstein-barr virus-cytotoxic t lymphocytes':ti,ab
3	'natural history':ti,ab OR 'observational':ti,ab OR 'case series':ti,ab OR 'case report':ti,ab OR 'real-world':ti,ab
4	'epstein barr virus positive post-transplant lymphoproliferative disease':ti,ab OR 'epstein-barr virus-associated post-transplant lymphoproliferative disorder*':ti,ab OR 'EBV+ PTLD':ti,ab OR 'ebv ptld':ti,ab OR 'ebv-positive ptld':ti,ab OR 'ebv-associated ptld':ti,ab OR 'ebv-positive post-transplant lymphoproliferative disease':ti,ab
5	(#1 AND #2) OR (#3 AND #4)
6	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
7	#5 NOT #6
8	#7 AND [english]/lim
9	#8 AND [medline]/lim
10	#8 NOT #9
11	#10 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
12	#10 NOT #11

Figure D1.1. PRISMA flow Chart Showing Results of Literature Search for Tabelecleucel for EBV+ PTLD



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, MN); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

Data Extraction

Data were extracted into Microsoft Word and Microsoft Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Quality Assessment

Due to the single-arm study design of the trials evaluated, we did not examine conduct a quality assessment for the included studies in this review.

Evaluation of Clinical Trial Diversity

We sought to evaluate the demographic diversity of clinical trials using the ICER-developed Clinical Trial Diversity rating (CDR) Tool.[20] However, the lack of prevalence estimates for this rare condition precluded the evaluation. As described in our VAF, trials of rare diseases with no reliable disease specific prevalence estimate will not be rated on clinical trial diversity. Instead, a qualitative description of the demographic characteristics of participants in the clinical trial will be presented. The demographic information for the pivotal trial of tabelecleucel (ALLELE) is described below.

The ALLELE trial enrolled patients with a median age of 48.5 years old (IQR: 21.9 – 65.4).[5] An analysis of response by age presented in an EMA assessment report cites there were 12 patients over the age of 65.[13] There was similar enrollment of male (56%) and female (44%) patients. Patients were predominantly white (84%). There were few Black (2%), Asian (5%), and Native Hawaiian or Pacific Islander (2%) patients enrolled (see Supplement Table D3.2).

Information on the Clinical Trial Diversity Rating (CDR) Tool can be found on our website: https://icer.org/news-insights/journal-articles/a-framework-for-evaluating-the-diversity-of-clinical-trials/

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[47,48]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for tabelecleucel using ClinicalTrials.gov. Search terms included "tabelecleucel," "EBV-CTL," and "ATA-129." We did not identify any studies for tabelecleucel that would have met our inclusion criteria for which no findings have been published within two years.

Data Synthesis and Statistical Analyses

Data on key outcomes of the main tabelecleucel trials were summarized in the Evidence Tables below (see Section D3) and synthesized in the body of the report. We assessed feasibility of quantitative synthesis and ultimately did not conduct any pairwise meta-analyses due to the study design of the trials (single-arm) and study population differences. Therefore, the data for each trial is described separately in the main report.

D2. Additional Clinical Evidence

Additional Methods

Evidence Base

Expanded Access Programs

ATA129-EAP-901 is an expanded access program that includes patients with EBV+ diseases unable to join clinical trials for tabelecleucel. At the time of this review, data on 24 participants were available from an abstract presented at an Oncology Research and Treatment conference (Trappe et al. 2024).[18]

ATA129-SPU is an individual patient expanded access program in Europe that is evaluating response to treatment. It is enrolling those with EBV+ diseases who were unable to enroll in either the clinical trials or expanded access programs. At the time of this review, the minimal data available for this program were reported in an EMA assessment report.[13]

Phase II Trials

Two Phase II trials (NCT01498484 and NCT00002663) were initiated to evaluate the efficacy and safety of Epstein-Barr virus cytotoxic T lymphocytes (EBV-CTLs) for the treatment of EBV-induced lymphomas or EBV-associated malignancies.

Efficacy and safety data on a subset of 46 transplant recipients (33 HSCT, 13 SOT) participants with relapsed or refractory EBV+ PTLD who received tabelecleucel from 2005 to 2015 were combined in a single publication (Prockop et. al 2020).[17]

Additional Results

Response

ALLELE

Overall response rate (ORR) was calculated using complete or partial response data in participants who had less than two HLA restrictions. Participants who required treatment with more than two different HLA restrictions were excluded from the ORR calculation. A first restriction switch was reported in 17 of the 43 participants.[5] The main publication does not reference any participants with more than two restriction switches. A European Medical Agency (EMA) assessment report states that two participants had three HLA restrictions. Of the two participants, one had a clinical benefit after their third switch.[13]

Phase II Trials

Of the 46 participants enrolled across the two-phase II trials, 29 had a response to treatment. Similar to the ALLELE trial, higher rates of complete response were observed in HSCT recipients than SOT recipients (58% versus 15%) while the opposite was observed for partial response (9% for HSCT versus 39% in SOT). Median time to response was not reported.[17]

EU Expanded Access Programs

In the ATA129-EAP-901 Expanded Access Program, 16 of the 24 participants (66.7%) experienced a response to treatment, with half being complete responses and half being partial responses.[18]

As of July 2021, the objective response rate for the 48 participants with EBV+ PTLD in the ATA129-SPU EAP was 43.8%, 26.3% for the 19 HSCT recipients, and 55.2% for SOT recipients.[13]

Survival

Phase II Trials

Estimated two-year overall survival was 57% for HSCT recipients and 54% for SOT recipients. Median overall survival was not reported.

We also identified survival data for a slightly larger dataset (N=49) enrolling patients from 2005 to 2018 presented in a poster (Prockop et al. 2018).[22] The estimated three-year OS was 55% for HSCT recipients and 43% for SOT recipients. The median overall survival for non-responders was 1.7 months for HSCT and 1.2 months for SOT. This data was not reported for responders.[22]

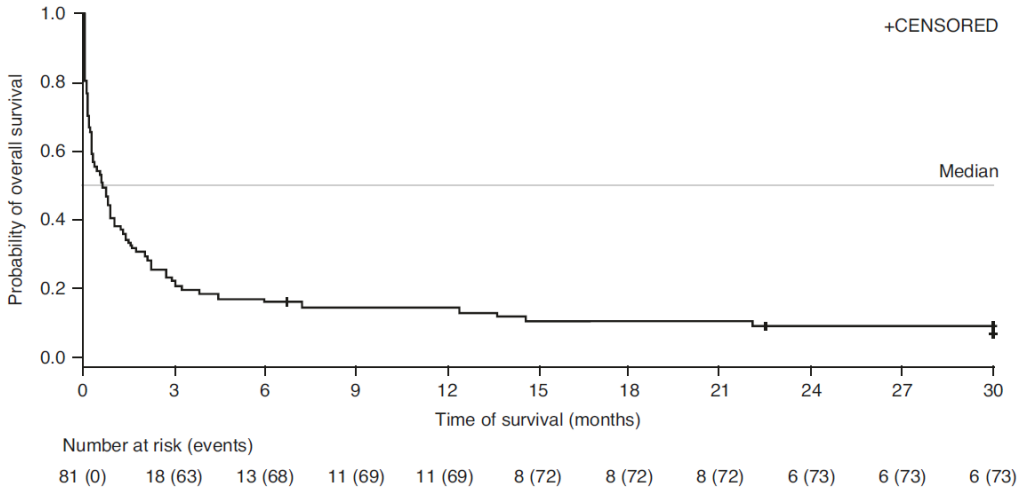
EU EAP

The European Expanded Access Program ATA129-EAP-901 reports survival estimates for 24 participants. Estimated one-year overall survival was 87.5% for HSCT recipients, 66.5% for SOT, and 73.7% overall. Survival stratified by response status was not available.[18]

Usual Care

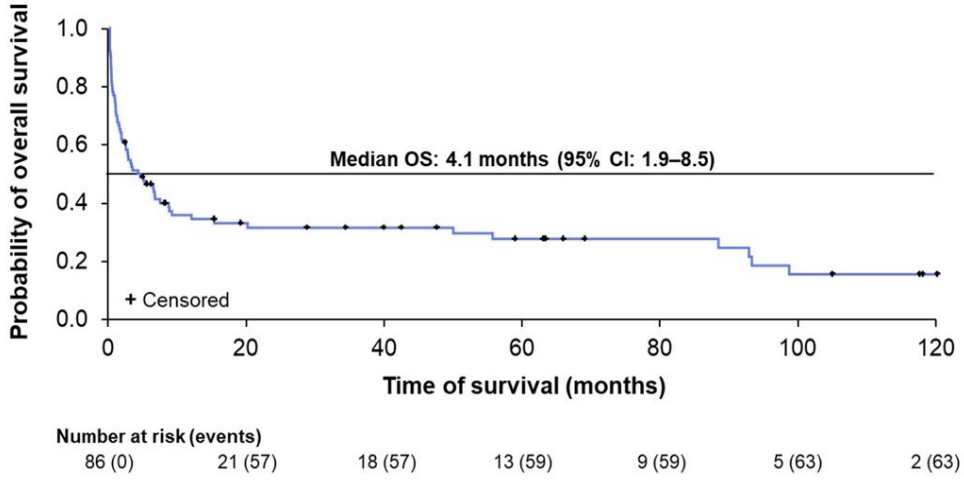
Figures D2.1 and D2.2 below display the overall survival from natural history cohorts of HSCT and SOT recipients who have relapsed/refractory EBV+ PTLD. Figures D2.1 and D2.2 below display the overall survival from natural history cohorts of HSCT and SOT recipients who have relapsed/refractory EBV+ PTLD.

Figure D2.1. Kaplan Meier Overall Survival Curve for HSCT Recipients with Relapsed/Refractory EBV+ PTLD[8]



Citation: Dharnidharka V, Thirumalai D, Jaeger U, Zhao W, Dierickx D, Xun P, Minga P, Sawas A, Sadetsky N, Chauvet P, Sundaram E, Barlev A, Zimmerman H, Trappe RU. 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:S3(1920-1921).

Figure D2.2. Kaplan Meier Overall Survival Curve for SOT Recipients with Relapsed/Refractory EBV+ PTLD[7]



Citation: Socie G, Barba P, Barlev A, Sanz J, Garcia-Cadenas I, Chevallier P, Fagioli F, Guzman-Becerra N, Kumar D, Ljungman P, Pigneux A, Sadetsky N, San Segundo LY, Shadman M, Storek J, Thirumalai D, Xing B, Mohty M. Outcomes for patients with EBV-positive PTLD post-allogeneic HCT after failure of rituximab-containing therapy. Bone Marrow Transplantation, 2024;59(52-58).

EBV Biomarkers

Exploratory data evaluating the connection between disease response and EBV-CTL and EBV-DNA levels were presented in the ALLELE trial. There was no significant correlation between response and post-tabelecleucel infusion peak fold change in EBV-CTL. However, there was significantly lower post-infusion EBV+DNA nadir compared to baseline in those who responded to tabelecleucel (p=0.0005).[5]

Additional Harms

Commonly Reported Adverse Events

In the ALLELE trial, commonly reported adverse events (≥20%) were disease progression, pyrexia, diarrhea, fatigue, and nausea.[5] Additional adverse events observed in the U.S. EAP were cough, hyponatremia, pneumonia, white blood cell count decrease, and increased aspartate aminotransferase.[15] Incidence of specific adverse events can be found in Supplement Tables D3.12-14.

In the ALLELE trial, commonly reported adverse events (≥20%) were disease progression, pyrexia, diarrhea, fatigue, and nausea.[5] Additional adverse events observed in the U.S. EAP were cough, hyponatremia, pneumonia, white blood cell count decrease, and increased aspartate aminotransferase.[15] Incidence of specific adverse events can be found in Supplement Tables D3.12-14.

Mortality

There were 18 deaths reported in the ALLELE trial: five were due to fatal treatment-emergent adverse events (TEAE) felt not to be related to tabelecleucel (three had disease progression, one had respiratory failure, and one had multiple organ dysfunction), six were due to disease progression which didn't meet the criteria for a TEAE, two were due to non-TEAEs, and five occurred after study completion.[5]

In the U.S. EAP, 7 deaths were reported, and 19 participants were censored based on the last date they were known to be alive. Of the seven patients who died, five deaths were from fatal TEAEs (three had disease progression, one had cardiac arrest, one had multiple organ dysfunction syndrome) and two from non-TEAEs. All deaths were judged by investigators to not be related to tabelecleucel treatment.[15]

Across the Phase II trials, eight of the 31 responders died. None of the deaths were a result of progression or PTLD relapse but were related to relapse of primary disease, infection, myocardial infarction, etc. Of the non-responders, the majority (n=13) died due to PTLD progression.[22]

Serious Adverse Events

Treatment emergent serious adverse events (TESAEs) were reported in 23 (53%) of participants in the ALLELE trial and four participants had TESAEs which were considered treatment-related. There were two events of pyrexia and one event each of rash, hypotension, hypoxia, and diarrhea; none of which led to treatment discontinuation.[5]

Treatment emergent serious adverse events (TESAEs) were reported in 23 (53%) of participants in the ALLELE trial and four participants had TESAEs which were considered treatment-related. There were two events of pyrexia and one event each of rash, hypotension, hypoxia, and diarrhea; none of which led to treatment discontinuation.[5]

In the U.S. Expanded Access Program, TESAEs were reported in 17 (65.4%) participants, with five events being fatal; none of the fatal events were considered to be treatment related. Treatment-related serious adverse events were reported in three participants, but none led to treatment discontinuation.[15]

In the U.S. Expanded Access Program, TESAEs were reported in 17 (65.4%) participants, with five events being fatal; none of the fatal events were considered to be treatment related. Treatment-related serious adverse events were reported in three participants, but none led to treatment discontinuation.[15]

In the Phase II publication, TESAEs were not reported.[17] In an abstract with a slightly larger cohort with longer follow-up, 28.6% of participants in the HSCT cohort and 50% in the SOT cohort reported a TESAE. There were two cases that were considered by investigators to be possibly related to tabelecleucel: one case of decreased lymphocyte count in a HSCT patient and one case of acidosis in a SOT patient.[22]

In the EU EAP (ATA129-EAP-901) there were 7 (29.2%) TEAEs including 1 (4.2%) SOT patient who had a TESAE of liver transplant rejection (grade 2) and 2 (8.3%) HSCT patients had non-serious TEAEs of chronic graft-versus-host disease (grade 1 and 2). There was 1 (4.2%) fatal TESAE of disease progression.[18]

Additional data on serious adverse events are in Supplement Table D3.12-13.

Discontinuation

All-cause discontinuation was reported in 24 (55.8%) participants in the ALLELE trial. The majority were due to death (28%), followed by withdrawal by patient (13.9%), lost to follow-up (4.7%), and other (9.3%).[5] Similar rates of discontinuation were observed in the U.S. Expanded Access Program (see Supplement Table D3.8).[15]

All-cause discontinuation was reported in 24 (55.8%) participants in the ALLELE trial. The majority were due to death (28%), followed by withdrawal by patient (13.9%), lost to follow-up (4.7%), and other (9.3%).[5] Similar rates of discontinuation were observed in the U.S. Expanded Access Program (see Supplement Table D3.8).[15]

Tabelecleucel Safety Data from EMA Assessment Report

The dataset included 340 participants who received tabelecleucel, including people who received tabelecleucel for EBV+ diseases outside the scope of our review.[13]

Fatal treatment-emergent serious adverse events were reported in 71 participants, and most were due to disease progression and death. All but one fatal TESAEs were judged to be unrelated to tabelecleucel treatment. One participant had two grade 5 events which investigators considered to be possibly related to treatment.

Safety data on adverse events of special interest were also reported. There was a small rate (1.2%) of infusion related reactions across the clinical program. Graft-versus-host-disease was reported in 14 participants, and three events were considered to be related to tabelecleucel by investigators. Two participants with non-PTLD EBV+ lymphoma experienced grade 1 events of cytokine release syndrome but were not considered to be treatment related. Tumor flare reaction was reported in four participants with three cases determined to be related to treatment. The overall incidence of SOT rejection was 4.3%, and all events besides one (grade 1 TESAE) were not considered to be related to tabelecleucel.

Development of anti-HLA antibodies

Two methods of assessing immunogenicity with tabelecleucel were conducted for participants in the ALLELE trial. Of the participants tested, no immunogenicity associated with tabelecleucel was observed. One out of nine participants tested using the pan anti-HLA antibody method developed anti-HLA antibodies, but no treatment-emergent serious adverse events were observed. Four of the 21 participants tested using the single-antigen bead approach had detection of anti-HLA antibodies. One of which had prior anti-HLA antibodies that did not increase post treatment and three were not related the organ transplant or tabelecleucel.[5] These data were not reported for other trials of tabelecleucel.

Additional Subgroup Analyses and Heterogeneity

ALLELE

Within the SOT cohort, one-year survival was significantly greater for responders compared to non-responders for those who had prior treatment with rituximab and chemotherapy (HR: 0.18; 95%CI:

0.03, 0.94; p=0.023). A significant difference by response was not observed for participants who had prior treatment with rituximab only.

Phase II

The phase II publication (Prockop et al. 2020) reports on response stratified by additional subgroups of interest. However, these data are from trials of very small sample size and should be interpreted with caution. Subgroups differences were not observed for age and were not reported for sex or race/ethnicity. Results with significant differences are described below.[17]

Participants who had prior treatment with rituximab only had higher response rates (80%) versus those treated with rituximab + other treatment (45%) [p=0.03] in the overall and HSCT cohorts but not the SOT group. Significant differences in response were observed by extranodal (51.6%) versus no extranodal disease (92.9%) for the overall population as well as the SOT population (p<0.01), but not the HSCT subgroup. Lastly, significant differences in response by number of disease sites (more than 3 sites=16.7, less than 3=85.7; p=0.03) were observed for SOT recipients, but not for overall or HSCT cohorts. (See Supplement Table D3.25)

Subpopulation of Interest: EBV+ PTLD with Central Nervous System (CNS) Involvement

Those with EBV+ PTLD with CNS involvement have been reported to have worse outcomes and higher unmet need due to difficulty in treatments passing the blood-brain barrier.[49] There was no data provided for participants with CNS involvement in the ALLELE trial. Participants who had untreated CNS PTLD or who were actively receiving CNS-directed chemotherapy or radiotherapy were not included in the study.[5] In two participants in the EAP with relapsed/refractory EBV+ PTLD with CNS involvement had a response to tabelecleucel, one with a complete response and one with a partial response.[15] In the Phase II trial, 11 participants had CNS involvement and five achieved a complete response and four had durable partial remission.[22] Those with EBV+ PTLD with CNS involvement have been reported to have worse outcomes and higher unmet need due to difficulty in treatments passing the blood-brain barrier.[49] There was no data provided for participants with CNS involvement in the ALLELE trial. Participants who had untreated CNS PTLD or who were actively receiving CNS-directed chemotherapy or radiotherapy were not included in the study.[5] In two participants in the EAP with relapsed/refractory EBV+ PTLD with CNS involvement had a response to tabelecleucel, one with a complete response and one with a partial response.[15] In the Phase II trial, 11 participants had CNS involvement and five achieved a complete response and four had durable partial remission.[22]

A conference abstract (Baiocchi 2024) pooled data on 18 participants from four studies evaluating tabelecleucel in participants with relapsed/refractory or treatment naïve EBV+ PTLD with CNS involvement. A conference abstract (Baiocchi 2024) pooled data on 18 participants from four studies evaluating tabelecleucel in participants with relapsed/refractory or treatment naïve EBV+

PTLD with CNS involvement.[50] Objective response rate was reported in 77.8% of participants with a median time to response of 1.8 months (range: 0.7 – 6.4).[50] Objective response rate was reported in 77.8% of participants with a median time to response of 1.8 months (range: 0.7 – 6.4). The one and two-year overall survival rate was 70.6 (95%CI: 43 – 86.6) and 54.9 (95%CI: 27.1 – 75.9), respectively. Responders had similar survival rates at one and two years while non-responders had survival rates of 0% at both time points.

D3. Evidence Tables

Table D3.1. Study Design Table[5,7,8,15,17-19]

NCT/Trial	Study Design	Inclusion/Exclusion	Key Outcomes
Phase III			
NCT03394365 (ATA129-EBV-302) **ALLELE**	Phase III, interventional, non-randomized, parallel assignment, open label study N=43 <u>Population</u> EBV+ PTLD in the setting of SOT or HSCT <u>Duration</u> 5 years of follow-up* <u>Arm</u> IV tab-cel in 35 day cycles, participants receive doses of 2×10^6 cells/kg on days 1, 8, and 15 with up to 2 different HLA restrictions (SOT cohort) or up to 4 different HLA restrictions (HSCT cohort)	**Inclusion** -Prior SOT of kidney, liver, heart, lung, pancreas, small bowel, or any combination of these; or prior allogeneic HSCT -Treatment failure of rituximab or rituximab plus any concurrent or sequentially administered chemotherapy regimen -ECOG performance status ≤3 for subjects aged ≥16 years; Lansky score ≥20 for subjects <16 years -For HSCT cohort only: If allogeneic HSCT was performed as treatment for an acute lymphoid or myeloid malignancy, the underlying primary disease for which the subject underwent transplant must be in morphologic remission -Adequate organ function **Exclusion** -Burkitt lymphoma, classical Hodgkin lymphoma, or any T cell lymphoma -For HSCT cohort: active adenovirus viremia -Treatment with EBV-CTLs or chimeric antigen receptor T cells directed against B cells within 8 weeks of enrollment, or unselected donor lymphocyte infusion within 8 weeks of enrollment (HSCT cohort only)	**Primary endpoint:** -Objective response rate

Phase II / Expanded Access			
NCT/Trial	**Study Design**	**Inclusion/Exclusion**	**Key Outcomes**
NCT02822495 (EBV-CTL-201) **Expanded Access Protocol for Providing Tabelecleucel to Patients With Epstein-Barr Virus-Associated Viremia or Malignancies for Whom There Are No Appropriate Alternative Therapies**	Multi-center, single-arm, open-label expanded access study N=26 <u>Population</u> Participants with EBV-associated diseases and malignancies for whom there are no other appropriate therapeutic options <u>Arm</u> IV tab-cel at a dose of 2 × 106 cells/kg	**Inclusion** -Any of the following diagnoses of EBV+ malignancies or disease: -EBV+ PTLD following allogeneic HSCT -EBV+ PTLD following SOT -EBV viremia and known or suspected immunodeficiency -EBV+ LPD that has developed in the setting of an AID -EBV+ LPD that has developed in the setting of a known or suspected PID -EBV+ LMS -EBV+ NPC -Relapsed or refractory disease **Exclusion** -Current diagnosis of Burkitt's lymphoma, classical Hodgkin's lymphoma, or any T-cell lymphoma -Antithymocyte globulin, alemtuzumab, or similar anti-T-cell antibody therapy, or T-cell immunotherapy ≤4 weeks	**Primary endpoints:** -Objective response rate -Overall survival
ATA129-EAP-901	Expanded access program in patients with EBV+ diseases, who are not eligible for treatment in other Atara clinical development studies. <u>Arm</u> IV tab-cel at a dose of 2 × 106 cells/kg		**Not reported**
ATA-129-SPU	Individual Patient Expanded Access for individual patients with EBV+ diseases, including EBV+ PTLD, who cannot be enrolled in Atara clinical studies or other EAP protocols <u>Arm</u> IV tab-cel at a dose of 2 × 106 cells/kg		**No prespecified efficacy assessments**

NCT/Trial	Study Design	Inclusion/Exclusion	Key Outcomes
NCT01498484 **(Study 11-130)** **A Phase II Study of The Therapeutic Effects Of EBV Immune T-Lymphocytes Derived From A Normal HLA-Compatible Or Partially-Matched Third-Party Donor in the Treatment of EBV Lymphoproliferative Disorders and EBV-Associated Malignancies**	Phase II, non-randomized, open label study N=87 <u>Population</u> Participants with EBV Lymphoproliferative Disorders and EBV-Associated Malignancies <u>Arm</u> IV tab-cel at a dose of 1 or 2 × 106 cells/kg	**Inclusion** -KPS or Lansky score ≥20 -A life expectancy of at least 6 weeks -Patients developing EBV lymphomas or lymphoproliferative disorders following an HSCT or SOT -Patients with AIDS developing EBV lymphomas or lymphoproliferative diseases as a consequence of the profound acquired immunodeficiency induced by HIV -Patients who develop other EBV-associated malignancies without pre-existing immune deficiency -Relapse/refractory to rituximab or rituximab and chemotherapy for SOT and HSCT cohorts **Exclusion** -Patients with active (grade 2-4) acute GVHD, chronic GVHD or an overt autoimmune disease	**Primary endpoint:** -Objective response rate

Phase I/II			
NCT/Trial	**Study Design**	**Inclusion/Exclusion**	**Key Outcomes**
NCT00002663 (Study 95-024) **An Evaluation of the Toxicity and Therapeutic Effects of EBV-Immune T-Lymphocytes Derived From a Normal HLA-Compatible or Haplotype-Matched Donor in the Treatment of EBV-Associated Lymphoproliferative Diseases or Malignancies and Patients With Detectable Circulating Levels of EBV DNA Who Are at High Risk for EBV-Associated Lymphoproliferative Diseases**	Phase I/II, non-randomized, open label study N=58 <u>Population</u> Participants with detectable circulating levels of EBV DNA who are at high risk for EBV-associated lymphoproliferative diseases <u>Arm</u> IV tab-cel at a dose of 1 or 2 × 106 cells/kg	**Inclusion** -Patients developing or at risk for EBV lymphomas or lymphoproliferative disorders following an allogeneic marrow transplant or allogeneic organ transplant -Patients with AIDS developing EBV lymphomas or lymphoproliferative diseases as a consequence of the profound acquired immunodeficiency induced by HIV -Patients who develop EBV lymphomas or lymphoproliferative diseases as a consequence of profound immunodeficiencies associated with a congenital immune deficit or acquired as a sequela of anti-neoplastic or immunosuppressive therapy -Patients who develop other EBV-associated malignancies without pre-existing immune deficiency, including: EBV+ Hodgkin's and Non- Hodgkin's disease, EBV+ nasopharyngeal carcinoma, EBV+ hemophagocytic lymphohistiocytosis, or EBV+ leiomyosarcoma **Exclusion** -Unlikely to survive the 6-8 weeks required for in vitro generation and expansion of the EBV-specific T cells to be used for therapy and the subsequent 3 weeks	**Primary endpoint:** -Objective response rate
Observational Studies			
Dharnidharka 2021 **Clinical Outcomes of Solid Organ Transplant Patients with EBV+ PTLD Who Fail Rituximab Plus Chemotherapy: A Multinational, Retrospective Chart Review Study**	Multinational, multicenter, retrospective chart review N=86 <u>Population</u> Patients with EBV+ PTLD following SOT who received rituximab plus chemotherapy and were refractory or relapsed at any point after therapy	**Inclusion** Patients with EBV+ PTLD following SOT who received rituximab or rituximab plus chemotherapy between January 2000 and December 2018 and were refractory or relapsed at any point after therapy **Exclusion** NR	**Key Endpoints** Survival Mortality

NCT/Trial	Study Design	Inclusion/Exclusion	Key Outcomes
Socie 2024 **Outcomes for patients with EBV-positive PTLD post-allogeneic HCT after failure of rituximab-containing therapy**	Multicenter, non-interventional, retrospective chart review N=81 <u>Population</u> allogeneic HSCT recipients with R/R EBV+ PTLD following rituximab ± chemotherapy failure	**Inclusion** HSCT recipients who were diagnosed with R/R EBV+ PTLD following rituximab ± chemotherapy failure, of any age, and with data records available **Exclusion** Had received cytotoxic T-lymphocytes, donor lymphocyte infusion, or had specific PTLD histology of Burkitt, Hodgkin, or T-cell lymphoma.	**Key Endpoints** Overall Survival
Barlev 2024 **Comparative analysis of tab-cel and current treatment in patients with Epstein-Barr virus positive post-transplant lymphoproliferative disease following hematopoietic cell transplant or solid organ transplant**	Comparative analysis using data from ALLELE study and a descriptive, multinational, multicenter retrospective chart review (RS002) RS002 N= 84 ALLELE N=30 <u>Population</u> patients with EBV+ PTLD following HSCT after failure of rituximab or following SOT after failure of rituximab plus chemotherapy	**Inclusion for ALLELE** See above **Inclusion for RS002** Patients with EBV+ PTLD following HSCT after failure of rituximab or following SOT after failure of rituximab plus chemotherapy **Exclusion for ALLELE** See above **Exclusion for RS002** NR	**Key Endpoints** Overall Survival

Source: www.ClinicalTrials.gov

AID: Acquired immunodeficiency, CTL: Cytotoxic T lymphocyte, EBV+LMS: Epstein-Barr virus+ associated leiomyosarcoma, EBV+LPD: Epstein-Barr virus associated lymphoproliferative disease , EBV+NPC: Epstein-Barr virus+ associated nasopharyngeal carcinoma, EBV+ PTLD: Epstein-Barr virus+ post-transplant lymphoproliferative disease, ECOG: Eastern Cooperative Oncology Group, GVHD: Graft-versus-host disease, HCT: Hematopoietic cell transplant, HIV: Human immunodeficiency virus, HLA: Human leukocyte antigens, HSCT: Hematopoietic stem cell transplantation, IV: Intravenous, kg: kilogram, KPS: Karnofsky Performance Scale, N: number, NR: not reported, PID: Primary immunodeficiency, R/R: relapsed/refractory, SOT: Solid organ transplant, %: percent

*Current data form the ALLELE trial is from 2 years of follow-up

Table D3.2. ALLELE Baseline Characteristics[5,13]

Trial		ALLELE		
Arms		**HSCT**	**SOT**	**All**
N		**14**	**29**	**43**
Age, median years (IQR)		51.9 (21.9–65.1)	44.4 (23.8–67.0)	48.5 (21.9–65.4)
Sex, n (%)	**Male**	8 (57%)	16 (55%)	24 (56%)
	Female	6 (43%)	13 (45%)	19 (44%)
Race, n (%)	**Asian**	1 (7%)	1 (3%)	2 (5%)
	Black or African American	0	1 (3%)	1 (2%)
	Native Hawaiian or Other Pacific Islander	0	1 (3%)	1 (2%)
	White	12 (86%)	24 (83%)	36 (84%)
	Other	1 (7%)	2 (7%)	3 (7%)
ECOG score (age ≥16 years), median (IQR)		1.0 (0–1.0)	1.0 (0–2.0)	1.0 (0–2.0)
ECOG ≥2 (age ≥16 years)*, median (IQR)		3 (23%)	8 (30%)	11 (28%)
Lansky score (age <16 years), median (IQR)		90 (n=1)	40, 90 (n=2)	40, 90, 90 (n=3)
Elevated LDH (age ≥16 years), n (%)		11 (84.6)	19 (70.4)	30 (75)
Post-transplant lymphoproliferative disease-adapted prognostic index (age ≥16 years)*, n (%)	**Low**	1 (8%)	2 (7%)	3 (8%)
	Intermediate	6 (46%)	13 (48%)	19 (48%)
	High	6 (46%)	11 (41%)	17 (43%)
	Unknown	0	1 (4%)	1 (3%)
Disease morphology and histology, n (%)	**Diffuse large B-cell lymphoma**	10 (71%)	19 (66%)	29 (67%)
	Plasmablastic lymphoma	1 (7%)	2 (7%)	3 (7%)
	Other†	3 (21%)	8 (28%)	11 (26%)
Transplant organ type, n (%)	**Kidney**	NA	10 (34%)	NA
	Heart	NA	6 (21%)	NA
	Lung	NA	5 (17%)	NA
	Liver	NA	1 (3%)	NA
	Multivisceral	NA	7 (24%)	NA
Extranodal disease at screening, n (%)		9 (64%)	24 (83%)	33 (77%)

Trial	ALLELE		
Arms	**HSCT**	**SOT**	**All**
N	**14**	**29**	**43**
Number of previous lines of systemic treatment, median (IQR)	1 (1–1)	1 (1–2)	1 (1–2)
Previous rituximab monotherapy‡§, n (%)	14 (100%)	23 (79%)	37 (86%)
Previous chemotherapy in combination with rituximab§, n (%)	1 (7%)	13 (45%)	14 (33%)
Previous immunotherapy (other than rituximab), n (%)	1 (7%)	1 (3%)	2 (5%)
Previous immunotherapy in combination with chemotherapy, n (%)	1 (7%)	0	1 (2%)
Previous immunotherapy alone, n (%)	0	1 (3%)	1 (2%)
Time from transplant to diagnosis, median (IQR)	4.3 months (3.2–7.8)	1.1 years (0.6–8.6)	NA
Time from initial EBV-positive diagnosis to first dose of tabelecleucel, months (IQR)	1.2 (0.8–3.0)	6.6 (3.5–13.0)	4.0 (2.2–8.6)
Time from enrolment to first dose of tabelecleucel, days (IQR)	7.0 (5.0–9.0)	8.0 (5.0–9.0)	7.0 (5.0–9.0)

HSCT: Hematopoietic stem cell transplantation, ECOG: Eastern Cooperative Oncology Group, IQR: Interquartile range, LDH: Lactate dehydrogenase, N: number, NA: not applicable, SOT: Solid organ transplant, %: percent

*There were 13 patients in the hematopoietic stem-cell transplant group, 27 in the solid organ transplant group, and 40 overall with available data.

†Other included variations of diagnoses including monomorphic post-transplant lymphoproliferative disease, polymorphic post-transplant lymphoproliferative disease, plasmacytoma or marginal zone lymphoma, florid follicular hyperplasia, and post-transplant lymphoproliferative disease not otherwise specified.

‡Administered as monotherapy.

§Not mutually exclusive.

Table D3.3. EAPs Baseline Characteristics[15]

Trial		U.S. EAP (NCT02822495)		
Arms		**HSCT**	**SOT**	**All**
N		**14**	**12**	**26**
Median age, years (range)		46.0 (2-74)	27.5 (7-66)	36.0 (2-74)
Age category, n (%)	**<16 years**	2 (14.3)	4 (33.3)	6 (23.1)
	≥16 years	12 (85.7)	8 (66.7)	20 (76.9)
Male, n (%)		7 (50.0)	6 (50.0)	13 (50.0)
Ethnicity, n (%)	**Hispanic/Latino**	1 (7.1)	2 (16.7)	3 (11.5)
	Not Hispanic/Latino	11 (78.6)	8 (66.7)	19 (17.3)
	Not given	2 (14.3)	2 (16.7)	4 (15.4)
Race, n (%)	**White**	10 (71.4)	8 (66.7)	18 (69.2)
	Black	1 (7.1)	0	1 (3.8)
	Asian	2 (14.3)	1 (8.3)	3 (11.5)
	Other/unknowns	1 (7.1)	3 (25.0)	4 (15.4)
Disease risk parameters, n (%)	**Age of ≥60 years**	2 (16.7)	1 (12.5)	3 (15.0)
	ECOG Performance score of ≥2	6 (50.0)	3 (37.5)	9 (45.0)
	Elevated serum LDH	7 (58.3)	4 (50.0)	11 (55.0)
Risk score*‡	**High**	3 (25.0)	2 (25.0)	5 (25.0)
	Intermediate	8 (66.7)	4 (50.0)	12 (60.0)
	Low	1 (8.3)	2 (25.0)	3 (15.0)
Disease morphology/histology, n (%)§	**Diffuse large B-cell lymphoma**	4 (28.6)	8 (66.7)	12 (46.2)
	PTLD NOS	6 (42.9)	0	6 (23.1)
	Polymorphic PTLD	2 (14.3)	1 (8.3)	3 (11.5)
	Hodgkin lymphoma	0	1 (8.3)	1 (3.8)
	Infectious mononucleosis–like PTLD	0	1 (8.3)	1 (3.8)
	Monomorphic B-cell PTLD	0	1 (8.3)	1 (3.8)
	Lymphoproliferative disorder NOS	NR	NR	1 (3.8)
Transplanted organ, n (%)	**Kidney**	NA	6 (50.0)	NA
	Heart	NA	2 (16.7)	NA
	Lung	NA	2 (16.7)	NA
	Intestine	NA	2 (16.7)	NA

Trial		U.S. EAP (NCT02822495)		
Arms		**HSCT**	**SOT**	**All**
N		**14**	**12**	**26**
Median time from transplant to diagnosis of EBV+ PTLD, months (range)		4.4 (1.4-198.4)	7.2 (2.1-275.9)	5.1 (1.4-275.9)
Median time from transplant to first dose of tab-cel, months (range)		6.4 (2.3-202.2)	20.5 (2.3-281.3)	9.3 (2.3-281.3)
Median time from initial EBV-related disease diagnosis to first tab-cel dose, months (range)		1.4 (0.2-8.2)	5.0 (0.2-67.6)	2.3 (0.2-67.6)
Baseline CNS PTLD involvement, n (%)#		1 (7.1)	1 (8.3)	2 (7.7)
Baseline extranodal PTLD (including bone marrow), n (%)¤		1 (7.1)	3 (25.0)	4 (15.4)
Prior rituximab therapy, n (%)**		14 (100)	11 (91.7)	25 (96.2)
Prior chemotherapy, n (%)		1 (7.1)	7 (58.3)	8 (30.8)
Median number of lines of prior systemic therapies (range)		1.0 (1-3)	1.5 (1-3)	1.0 (1-3)
Use of immunosuppressive medications at start of tabelecleucel, n (%)		1 (7.1)	11 (91.7)	12 (46.2)
Median of average cells administered per dose (×106 cells per kg) (range)		1.98 (1.6-2.0)	1.98 (1.6-2.0)	1.98 (1.6-2.0)
Median duration of tabelecleucel treatment, months (range)		1.3 (0.03-3.1)	2.5 (1.2-10.4)	1.8 (0.03-10.4)
Median no. of tabelecleucel doses received (range)		4.0 (1-9)	7.0 (4-27)	6.0 (1-27)
Median no. of tabelecleucel cycles received (range)		2.0 (1-4)	2.5 (2-9)	2.0 (1-9)
Number of tab-cel lots received, n (%)	**1**	14 (100)	8 (66.7)	22 (84.6)
	2	0	3 (25.0)	3 (11.5)
	3	0	0	0
	4	0	1 (8.3)	1 (3.8)

No baseline characteristics are available for ATA-129-SPU

CNS: Central nervous system, EAP: Expanded access program, EBV: Epstein-Barr virus, EBV+ PTLD: Epstein-Barr virus+ post-transplant lymphoproliferative disease, ECOG: Eastern Cooperative Oncology Group, HSCT: Hematopoietic stem cell transplantation, kg: kilogram, LDH: Lactate dehydrogenase, n: number, NOS: not otherwise specified, PTLD: Post-transplant lymphoproliferative disease, SOT: Solid organ transplant, %: percent

*For patients aged >16 years.

†For patients aged ≤16 years.

‡Scored using PTLD–adapted prognostic index.

§Disease morphology/histology was collected for 25 of 26 patients.

#Baseline CNS disease was not officially evaluated by imaging because of low clinical suspicion in 21 of 26 patients.

¤Baseline extranodal disease was missing in 1 patient and not evaluable in 2 patients.

**Administered as a monotherapy; however, patients may have received other prior treatments for PTLD.

Table D3.4. Phase II Baseline Characteristics[17]

Trial		Pooled NCT00002663 + NCT01498484 Pooled	
Arms		**HSCT**	**SOT**
N		**33**	**13**
Average age, year		23.7	19.1
Male, n (%)		15 (45.5)	6 (46.2)
Disease Sites, n (%)	**≥3 sites**	20 (60.6)	6 (46.2)
	1-2 sites with extranodal	7/13, (53.8)	6/7 (85.7)
Disease Morphology/histology, n (%)	**Diffuse large B-cell lymphoma**	24 / 30 (80)	8 (62)
	Monomorphic B-cell PTLD	24/30 (80)	8/13 (61.5)
	Monoclonal	12/14 (85.7)	0/7 (0)
	Donor origin	16/21 (28.6)	5/9 (55.6)
Transplanted Organ, n (%)	**Kidney**	NA	*5 (38.5)*
	Heart	NA	*3 (23.1)*
	Lung	NA	*1 (7.7)*
	Intestine	NA	*1 (7.7)*
	Liver	NA	*2 (15.4)*
	Heart/liver	NA	*1 (7.7)*
	Heart/lung	NA	*0 (0)*
Median Time	**From transplant to diagnosis of EBV+ PTLD, days (range)**	90 (28-1545)	1106 (194-5320)
	From initial EBV-related disease diagnosis to first tab-cel dose, days (range)	34 (6-169)	160 (21-448)
Baseline CNS PTLD Involvement, n (%)		*5 (15.2)*	*6 (46.2)*
Baseline Extranodal PTLD (including bone marrow), n (%)		*25 (75.8)*	*7 (53.8)*
Prior Rituximab Therapy, n (%)		*33 (100)*	*0*
Prior Chemotherapy, n (%)		*7 (21)*	*11 (84)*
Prior GvHD or Rejection, n (%)		18 (54.5)	9 (69.2)

CNS: Central nervous system, GVHD: Graft-versus-host disease, HSCT: Hematopoietic stem cell transplantation, N: number, NA: not applicable, PTLD: Post-transplant lymphoproliferative disease, SOT: Solid organ transplant, %: percent
Italicized data has been calculated from individual patient data

Table D3.5. Observational Studies Baseline Characteristics[7,8]

Trial		Chart Review: SOT	Chart Review: HSCT
		Dharnidharka 2021	Socie 2024
N		**86**	**81**
Sex, n (%)	**Male**	NR	49 (60.5)
	Female	NR	32 (39.5)
Age	**Median age at PTLD diagnosis, years (range)**	43 (1-78)	49 (2-75)
Response Status to Initial Treatment, n (%)	**Refractory**	65 (75.6)	NR
	Relapsed	21 (24.4)	NR
PTLD Histological Subtypes, n (%)	**Monomorphic**	66 (76.7)	52 (64.2)
	Polymorphic	18 (20.9)	18 (22.2)
	Early Lesions	2 (2.3)	2 (2.5)
	Diffuse large B-cell lymphoma	58 (67.4)	46 (56.8)
	Unknown	NR	9 (11.1)
PTLD Stage	**Stage I/II**	NR	8 (9.8)
	Stage III	NR	17 (21.0)
	Stage IV	NR	46 (56.8)
	Unknown	NR	10 (12.3)
Extranodal Sites of PTLD	**Yes**	NR	56 (69.1)
	No	NR	24 (29.6)
	Unknown	NR	1 (1.2)
CD20 Marker at Diagnosis, n (%)	**Positive**	NR	52 (64.2)
	Negative	NR	15 (18.5)
	Unknown	NR	14 (17.3)
Secondary CNS involvement, n (%)		NR	7 (8.6)
Median time from transplant to PTLD onset, years (range)		1.7 (0.1 - 27.9)	3 months (0.8 - 100.8)

Trial	Chart Review: SOT	Chart Review: HSCT
	Dharnidharka 2021	Socie 2024
N	**86**	**81**
Median time from PTLD diagnosis to first dose of treatment, months (range)	NR	0.1 (0.0 - 3.1)
Median follow up time from date of PTLD diagnosis, months	12.9	NR

CNS: Central nervous system, HSCT: Hematopoietic stem cell transplantation, N: number, NR: not reported, PTLD: Post-transplant lymphoproliferative disease, SOT: Solid organ transplant, %: percent

Table D3.6. Comparative Analysis Baseline Characteristics[19]

Trial		Comparative Analysis: SOT & HSCT	
		Barlev 2024	
		Study RS002	ALLELE
N		**84**	**30**
Sex, n (%)	**Male**	57 (69.7)	15 (50.0)
	Female	27 (32.1)	15 (50.0)
Median age at first dose of PTLD treatment (IQR)		44.1 (26.4, 58.6)	41.8 (24.0, 65.1)
Response Status to Initial Treatment, n (%)	**Responder (CR + PR)**	24 (28.6)	10 (33.3)
	Non-responder (SD + PD)	60 (71.4)	19 (63.3)
	Unknown	0	1 (3.3)
Number of prior therapies, n (%)	**1**	55 (65.5)	16 (53.3)
	≥2	29 (34.5)	14 (46.7)
Extranodal sites of PTLD	**Yes**	56 (66.7)	22 (73.3)
Early PTLD onset, n (%)*		44 (52.4)	12 (40.0)
Median time from transplant to PTLD diagnosis (IQR), months		6.5 (3.0, 79.2)	7.4 (3.8, 66.9)
Median time from PTLD diagnosis to R/R date (IQR), months		3.1 (0.8, 8.2)	2.0 (0.9, 3.6)
Median time from PTLD diagnosis to first dose of treatment (IQR), months		3.6 (1.1, 9.6)	3.6 (2.0, 13.0)

CR: Complete response, HSCT: Hematopoietic stem cell transplantation, IQR: Interquartile range, N: number, PD: Progressive disease, PR: Partial response, PTLD: Post-transplant lymphoproliferative disease, R/R: relapsed/refractory, SD: Stable disease, SOT: Solid organ transplant, %: percent

*Defined according to the time from transplant to PTLD diagnosis: early onset was defined as <100 days for HCT patients and <2 years for SOT patients.

Table D3.7. ALLELE Efficacy[5,13]

Trial		ALLELE		
Arms		**HSCT**	**SOT**	**All**
N		**14**	**29**	**43**
Objective response, n (%; 95% CI)		7 (50; 23-77)	15 (52; 33-71)	22 (51; 36-67)
Best overall response, n (%)	**Complete response**	6 (43)	6 (21)	12 (28)
	Partial response	1 (7)	9 (31)	10 (23)
	Stable disease	3 (21)	2 (7)	5 (12)
	Progressive disease	2 (14)	7 (24)	9 (21)
	Not evaluable	2 (14)	5 (17)	7 (16)*
Clinical benefit seen, n (%)		10 (71)	17 (59)	27 (63)
Median follow up, months (IQR)		14.1 (5.7-23.9)	6 (1.8-18.4)	11 (2.6-19.8)
Estimated 1-year overall survival, % (95% CI)		70.1 (38·5–87·6)	56.2 (34.6-73.2)	61.1 (43.7-74.5)
Estimated median overall survival, months (95% CI)		Not reached (5.7-NE)	16.4 (5-NE)	18.4 (6.9-NE)
Response outcomes	**Median time to response, months (IQR)**	1 (1-1)	1.1 (1-3)	1 (1-2.1)
	Median follow-up time after achieving first response, months (IQR)	15.9 (8-23)	2.3 (1.2-14.9)	7 (1.6-15.9)
	Median duration of response, months (95% CI)	23 (15.9-NE)	15.2 (1.2-NE)	23 (6.8-NE)
	Duration of response >6 months, n / N (%)†	6 / 12 (50)	6 / 12 (50)	12 / 22 (55)
	Duration of CR >6 months, n / N (%)	4 / 6 (66.7)	5 / 6 (83.3)	9 / 12 (75)‡
Dosage outcomes	**Clinical benefit seen, n (%)**	10 (71)	17 (59)	27 (63)
	First restriction switch, n (%)	NR	NR	17 (43)
	Median number of doses, n (IQR)	9 (6-12)	6 (3-9)	6 (3-12)
	Median number of cycles, n (IQR)	3 (2-4)	2 (1-3)	2 (1-4)
	Median treatment duration, months (IQR)	2.8 (1.9-4.3)	1.9 (0.5-3.4)	2.1 (0.5-3.9)
Subsequent treatment	**Any, n (%)**	11 (84.6)	3 (10.3)	14 (32.6)
	Chemotherapy or immunotherapy, n (%)	*7 (50)*	1 (3.4)	8 (18.6)
	Rituximab, n (%)	*3 (21.4)*	1 (3.4)	4 (9.3)
	Radiotherapy, rituximab, and cell therapy, n (%)	*0*	1 (3.4)	1 (2.3)
	Chemotherapy or immunotherapy, radiotherapy, and rituximab, n (%)	*1 (7.1)*	*0*	1 (2.3)

Italicized data has been digitized or calculated

CI: Confidence interval, CR: complete response, HSCT: Hematopoietic stem cell transplantation, IQR: Interquartile range, n: number, NR: Not reported, SOT: Solid organ transplant, %: percent

*Of the patients who were not evaluable for response, three had no independent oncological response adjudication assessment because of death, one had no assessment because of withdrawal from the trial, two were newly enrolled in the trial, and one was assessed as not evaluable.

†Of the remaining ten responders (one in HSCT and nine in SOT), four in the SOT group died. Six patients were alive: four in the SOT group had less than 6 months of follow-up; one in the SOT group had partial response when lost to follow-up; and one in the HSCT group had investigator-assessed progressive disease and discontinued treatment.

‡Of whom 4 / 9 (44.4) had subsequent progression of disease

Table D3.8. EAP Efficacy[15,18]

Trial		U.S. EAP (NCT02822495)			EU EAP (ATA129-EAP-901)		
Arms		**HSCT**	**SOT**	**All**	**HSCT**	**SOT**	**All**
N		**14**	**12**	**26**	**NR**	**NR**	**24**
Objective response rate, % (95% CI)		50% (23 - 77)	83.3% (51.6-97.9)	65.4% (44.3-82.8)	NR	NR	NR
Responders, n (%)		7 (50.0)	10 (83.3)	17 (65.4)	NR	NR	16 (66.7)
Best overall response, n (%)	**Complete response**	4 (28.6)	6 (50)	10 (38.5)	NR	NR	8 (33)
	Partial response	3 (21.4)	4 (33.3)	7 (26.9)	NR	NR	8 (33)
	Stable disease	2 (14.3)	1 (8.3)	3 (11.5)	NR	NR	NR
	Progressive disease	4 (28.6)	1 (8.3)	5 (19.2)	NR	NR	NR
	Not evaluable	1 (7.1)	0	1 (3.8)	NR	NR	NR
Median time to response, months (range)		NR	NR	1 (0.6-7.1)	NR	NR	1 (0.8-2.2)
Estimated 6-month OS, % (95% CI)		61.5 (30.8-81.8)	91.7 (53.9-98.8)	75.8 (53.8-88.3)	NR	NR	NR
Estimated 1-year OS, % (95% CI)		61.5 (30.8-81.8)	81.5 (43.5-95.1)	70 (46.5-84.7)	87.5	66.5	73.7 (47.3, 88.3)
Estimated 2-year OS, % (95% CI)		61.5 (30.8-81.8)	81.5 (43.5-95.1)	70 (46.5-84.7)	NR	NR	NR
Estimated 3-year OS, % (95% CI)		NR	NR	NR	NR	NR	NR
Median follow-up, months (range)*		2.8 (1-25.3)	22.5 (2.6-26.2)	8.2 (1-26.2)	9.9 (2.4–13.9)	6.0 (0.7–18.0)	NR
Median OS, months		NE	NE	NE	NR	NR	NR
Status	**Death, n (%)**	5 (35.7)	2 (16.7)	7 (26.9)†	NR	NR	NR
	Censored, n (%)	9 (64.3)	10 (83.3)	19 (73.1)	NR	NR	NR
Censored before 12 months, n (%)		5 (35.7)	2 (16.7)	7 (26.9)	NR	NR	NR
Discontinued study, n (%)		NR	NR	17 *(65)*	NR	NR	NR
Reason for study discontinuation, n (%)	**Death**	NR	NR	7 *(26.9)*	NR	NR	NR
	Lost to follow-up	NR	NR	2 *(7.7)*	NR	NR	NR
	Withdrawal of consent	NR	NR	2 *(7.7)*	NR	NR	NR
	Other‡	NR	NR	6 *(23)*	NR	NR	NR

Trial		U.S. EAP (NCT02822495)			EU EAP (ATA129-EAP-901)		
Arms		**HSCT**	**SOT**	**All**	**HSCT**	**SOT**	**All**
N		**14**	**12**	**26**	**NR**	**NR**	**24**
Reason for treatment discontinuation, n (%)	**Death caused by disease progression**	3 (21.4)	1 (8.3)	4 (15.4)	NR	NR	NR
	Required subsequent EBV therapy§	2 (14.3)	1 (8.1)	3 (11.5)	NR	NR	NR
	Received maximum available tabelecleucel cell	1 (7.1)	1 (8.3)	2 (7.7)	NR	NR	NR
	Physician decision	1 (7.1)	1 (8.3)	2 (7.7)	NR	NR	NR
	Patient preference	2 (14.3)	1 (8.3)	3 (11.5)	NR	NR	NR
	Other#	1 (7.1)	0	1 (3.8)	NR	NR	NR
Response to first cycle of EBV-CTLs, n (%)		NR	NR	12 / 17 (71)	NR	NR	NR

Italicized data has been digitized or calculated

CI: Confidence interval, CTL: Cytotoxic T lymphocyte, EAP: Expanded access program, EBV: Epstein-Barr virus, HSCT: Hematopoietic stem cell transplantation, N: number, NR: Not reported, OS: Overall survival, SOT: Solid organ transplant, %: percent

*Of 14 HCT recipients, 9 had OS follow-up of <4.5 months because of either death (n=5) or study discontinuation (n=4). Of the remaining 5 patients, 3 survived up to the 2-year study completion and 2 were censored between 8 and 13 months, with 1 exiting the study 5 months after treatment discontinuation because of start of subsequent therapy and 1 achieving maximal response. Maximum follow-up for the HCT cohort was 25.3 months, enabling the computation of OS rate estimates up to 24 months, including 95% CIs.

†None were treatment-related per investigator assessment

‡Removed from study by sponsor because of concurrent cytotoxic T-lymphocyte treatment with different agent for cytomegalovirus disease (n = 1); primary disease relapse (n=1); patient noncompliance with follow-up appointments (n=1); patient exiting study 5 months after treatment discontinuation because of start of subsequent therapy (n=1); patient enrolling on different protocol (n=1); and physician decision (n=1).

§Subsequent EBV therapies included immunotherapy, chemotherapy, or radiotherapy.

#Initiation of non-protocol CTL treatment for cytomegalovirus disease.

Table D3.9. Phase II Efficacy[17]

Trial		Pooled NCT00002663 + NCT01498484	
Arms		**HSCT**	**SOT**
N		**33**	**13**
Responders, n (%)		22 (68)	7 (54)
Best overall response, n (%)*	**Complete response**	19 (57.6)	2 (15.4)
	Partial response	3 (9.1)	5 (38.5)
	Stable disease	1 (3)	1 (7.7)
	Progressive disease	9 (27.3)	5 (38.5)
Estimated 2-year OS, % (95% CI)		57 (NR)	54 (NR)
Death, n (%)		9	
Response to first cycle of EBV-CTLs, n (%)	**Complete response**	8 (24.2)	1 (7.7)
	Partial response	7 (21)	2 (15.4)
	Stable disease	5 (15.2)	5 (38.5)
	Progressive disease	12 (36.4)	4 (30.8)
	Not evaluable	NR	NR

CI: Confidence interval, CTL: Cytotoxic T lymphocyte, EBV: Epstein-Barr virus,
HSCT: Hematopoietic stem cell transplantation, N: number, NR: Not reported, OS: Overall survival,
SOT: Solid organ transplant, %: percent
*One subject in HSCT was not evaluable due to relapse of the primary disease for which the subject was transplanted.

Table D3.10. Observational Studies Efficacy[7,8]

Trial				SOT	HSCT
				Dharnidharka 2021	Socie 2024
N				86	81
Treatment after PTLD diagnosis, n (%)			Rituximab Monotherapy	0 (0)	68 (84.0)
			Rituximab with Chemotherapy	86 (100)*	13 (16.0)
Median doses for rituximab alone (range)				NR	2 (1 - 9)
Patients Receiving next-line therapy, n / N (%)			Any	NR	36 / 81 (44.4)
			Chemotherapy-containing regimen	NR	32 / 36 (88.9)
			Achieve durable response >6 months	NR	4 / 36 (11.1)
			Relapsed	NR	2 / 4 (50.0)
Median follow up post R/R to rituximab-containing therapy, months (range)				NR	0.7 (0.03-107.1)
Survival	Median OS (95%CI), months		Unadjusted	4.1 (1.9 - 8.5)	0.7 (0.3 - 1.0)
	OS Rate	3 months	N at risk (events)	NR	18 (63)
			% (95% CI)	NR	22.2 (13.9 - 31.8)
		6 months	N at risk (events)	NR	13 (68)
			% (95% CI)	NR	16.0 (9.1 - 24.8)
		12 months	N at risk (events)	NR	11 (69)
			% (95% CI)	NR	14.7 (8.0 - 23.3)
		24 months	N at risk (events)	NR	6 (73)
			% (95% CI)	NR	9.4 (4.2 - 17.0)
	Survival in those who received next-line therapy		Median (range) follow-up, months	NR	2.0 (0.1 - 107.1)†
			Median OS (95%CI) from start date of next line	NR	2.0 (1.1 - 5.5)†

Trial			SOT	HSCT
			Dharnidharka 2021	Socie 2024
N			**86**	**81**
Mortality	**Total deaths, n (%)**		63 (73.3)	74 (91.4)
	Cause of Death	**PTLD**	41 (65.1)	41 (56.8)
		GvHD	NR	10 (13.5)
		TR-mortality	10 (15.9)	8 (10.8)
		Sepsis infection	NR	5 (6.8)
		Relapses primary disease leading to HCT	NR	3 (4.1)
		Organ rejection / failure	2 (3.2)	3 (4.1)
		Unknown	3 (4.8)	2 (2.7)
		Graft failure	NR	1 (1.4)
		Other	7 (11.1)	0 (0)

CI: Confidence interval, GVHD: Graft-versus-host disease, HSCT: Hematopoietic stem cell transplantation, N: number, NR: Not reported, OS: Overall survival, PTLD: Post-transplant lymphoproliferative disease, R/R: relapsed/refractory, SOT: Solid organ transplant, TR: treatment-related, %: percent

*57% received chemotherapy after rituximab and 43% received rituximab and chemotherapy at the same time

†N=36

Table D3.11. Comparative Analysis Efficacy[50]

Trial				Comparative Analysis: SOT & HSCT	
				Barlev 2024	
				Study RS002	ALLELE
N				**84**	**30**
Survival	**Median OS (95%CI), months**		**Unadjusted**	5.4 (2.5, 12.4)	NE (11.0, NE)
			SMRW adjusted	3.3 (2.0, 8.0)	NE (11.0, NE)
	Overall Survival, SMRW Adjusted*	**6 months**	**Number at risk**	9.4	17
			Survival Probability	*0.36*	*0.7*
		12 months	**Number at risk**	6.7	16
			Survival Probability	*0.29*	*0.62*
		24 months	**Number at risk**	5	5
			Survival Probability	*0.26*	*0.56*
		36 months	**Number at risk**	3.1	0
			Survival Probability	*0.25*	*0.56*
	OS benefit of tab-cel, HR (95% CI); p-value		**Unadjusted**	0.47 (0.25, 0.88); 0.018	
			SMRW adjusted	0.37 (0.2, 0.71); 0.003	
Mortality	**Total deaths, n (%)**			58 (69.0)	11 (36.7)
	Censored, n (%)			26 (31.0)	19 (63.3)

Italicized data has been digitized or calculated

CI: Confidence interval, HR: Hazard ratio, HSCT: Hematopoietic stem cell transplantation, N: number, NE: Not evaluable,

OS: Overall survival, SMRW: Standardized mortality ratio weighting, SOT: Solid organ transplant, %: percent

*From first dose of tab-cel in ALLELE & date of next line of systemic therapy in RS002

Table D3.12. ALLELE Harms[5,13]

Trial		ALLELE		
Arms		**HSCT**	**SOT**	**All**
N		**14**	**29**	**43**
Serious TEAEs of grade 3 or worse, n (%)		8 (57)	15 (52)	23 (53)
TESAEs, n (%)	**Total**	NR	NR	23 (53.5)
	Disease progression	NR	NR	8 (18.6)
	Sepsis	NR	NR	5 (11.6)
	Acute kidney injury	NR	NR	3 (7)
	Pneumonia	NR	NR	3 (7)
	Respiratory failure	NR	NR	3 (7)
	Vomiting	NR	NR	3 (7)
	Atrial flutter	NR	NR	2 (4.7)
	Dehydration	NR	NR	2 (4.7)
	Delirium	NR	NR	2 (4.7)
	Fatigue	NR	NR	2 (4.7)
	Febrile neutropenia	NR	NR	2 (4.7)
	Hypoxia	NR	NR	2 (4.7)
	Influenza	NR	NR	2 (4.7)
	Nausea	NR	NR	2 (4.7)
	Pyrexia	NR	NR	2 (4.7)
Treatment-related SAEs, n (%)		NR	NR	4 (9.3)*
Treatment-related SAEs, n (%)	**Pyrexia**	NR	NR	2 (4.7)
	Erythematous rash	NR	NR	1 (2.3)
	Hypotension	NR	NR	1 (2.3)
	Hypoxia	NR	NR	1 (2.3)
	Diarrhea	NR	NR	1 (2.3)
Death, n (%)		4 (29)	14 (48)	18 (41.9)
Fatal TEAEs, n (%)		1 (7)	4 (14)	5 (12)
Chronic graft versus host disease, n (%)		1 (7)	0	1 (2.3)

Trial		ALLELE		
Arms		**HSCT**	**SOT**	**All**
N		**14**	**29**	**43**
Tumor flare, n (%)		0	0	0
Commonly reported AEs, n (%)	**Disease progression**	5 (36)	16 (55)	21 (49)
	Pyrexia	5 (36)	8 (28)	13 (30)
	Diarrhea	4 (29)	8 (28)	12 (28)
	Fatigue	4 (29)	5 (17)	9 (21)
	Nausea	4 (29)	5 (17)	9 (21)
Reason for discontinuation, n (%)	**All cause**	6 (43.0)	18 (62.1)	24 (55.8)
	Withdrawal by patient	1 (7)	5 (17)	6 (13.9)
	Lost to follow-up	0	2 (6.9)	2 (4.7)
	Death	3 (21.4)	9 (31)	12 (28)
	Other	2 (14.3)	2 (6.9)	4 (9.3)

AE: Adverse event, HSCT: Hematopoietic stem cell transplantation, N: number, NR: Not reported, SAE: Serious adverse event, SOT: Solid organ transplant, TEAE: Treatment-emergent adverse event, TESAE: Treatment-emergent serious adverse event, %: percent

*The maximum grade was grade 1 in two (5%), grade 3 in one (2%), and grade 4 in one (2%).

†The remaining patients (death not including fatal TEAEs), including three (21%) of 14 in the HSCT group and ten (34%) of 29 in the SOT group, died of other causes that did not meet the criteria for a treatment-emergent adverse event, including disease progression in six patients and non-treatment emergent adverse events in two patients, and five patients who died after the end of the study with missing data.

‡Disease progression in three patients and respiratory failure and multiple organ dysfunction syndrome occurring in a single patient each; none of the fatal treatment-emergent serious adverse events were reported as related to tabelecleucel.

§Reported as non-serious and unrelated to tabelecleucel by the investigators.

Table D3.13. U.S. EAP Harms[15]

Trial		NCT02822495		
Arms		**HSCT**	**SOT**	**All**
N		**14**	**12**	**26**
Median follow-up time, months (range)		2.8 (1.0-25.3)†	22.5 (2.6-26.2)	8.2 (1.0-26.2)
Acute GVHD, events		4 (28.6)	0	4 (28.6)*
Tumor Flare, n (%)		0 (0)	0 (0)	0 (0)
Cytokine Release Syndrome, n (%)		0 (0)	0 (0)	0 (0)
Organ Rejection, n (%)		NA	0 (0)	0 (0)
Treatment Emergent Adverse Events, n (%)	**All TEAEs**	14 (100)	12 (100)	26 (100)
	Grade ≥3 TEAEs	12 (85.7)	7 (58.3)	19 (73.1)
	TEAEs leading to study discontinuation	4 (28.6)	4 (33.3)	8 (30.8)
TEAEs >20%, n (%)	**Diarrhea**	NR	NR	9 (34.6)
	Pyrexia	NR	NR	9 (34.6)
	Aspartate aminotransferase increased	NR	NR	8 (30.8)
	Cough	NR	NR	8 (30.8)
	Hyponatremia	NR	NR	8 (30.8)
	Fatigue	NR	NR	8 (30.8)
	White blood cell count decrease	NR	NR	7 (26.9)
	Pneumonia	NR	NR	6 (23.1)
	Disease progression	NR	NR	6 (23.1)

Trial		NCT02822495		
Arms		HSCT	SOT	All
N		14	12	26
Treatment Related TEAEs, n (%)	All TR-TEAEs	4 (28.6)	5 (41.7)	9 (34.6)
	Grade ≥3 TR-TEAEs	2 (14.3)	2 (16.7)	4 (15.4)
	TR-TEAEs leading to study discontinuation	0	1 (8.3)	1 (3.8)
	Abdominal pain†	0 (0)	4 (33.3)	4 (15.4)
	Abdominal distension	0 (0)	1 (8.3)	1 (3.8)
	Anemia	0 (0)	1 (8.3)	1 (3.8)
	Colitis	0 (0)	1 (8.3)	1 (3.8)
	Dizziness	1 (7.1)	0 (0)	1 (3.8)
	Fatigue	0 (0)	1 (8.3)	1 (3.8)
	Febrile neutropenia	0 (0)	1 (8.3)	1 (3.8)
	General physical health deterioration	1 (7.1)	0 (0)	1 (3.8)
	GVHD in gastrointestinal tract	1 (7.1)	0 (0)	1 (3.8)
	GVHD in liver	1 (7.1)	0 (0)	1 (3.8)
	Hypocalcemia	0 (0)	1 (8.3)	1 (3.8)
	Hyponatremia	0 (0)	1 (8.3)	1 (3.8)
	Pneumonitis	0 (0)	1 (8.3)	1 (3.8)
	Pyrexia	0 (0)	1 (8.3)	1 (3.8)
	Rash maculo-papular	1 (7.1)	0 (0)	1 (3.8)
	Tumor pain	0 (0)	1 (8.3)	1 (3.8)
	White blood cell count increased	0 (0)	1 (8.3)	1 (3.8)
TESAEs, n (%)	All TESAEs	9 (64.3)	8 (66.7)	17 (65.4)
	Grade ≥3 TESAEs	9 (64.3)	7 (58.3)	16 (61.5)
	Fatal TESAEs	4 (28.6)	1 (8.3)	5 (19.2)‡
Treatment Related TESAEs, n (%)	All TR-TESAEs	1 (7.1)	2 (16.7)	3 (11.5)
	Grade ≥3 TR-TESAEs	1 (7.1)	2 (16.7)	3 (11.5)
	Fatal TR-TESAEs	0 (0)	0 (0)	0 (0)

Trial		NCT02822495		
Arms		**HSCT**	**SOT**	**All**
N		**14**	**12**	**26**
Treatment Related TESAEs, n (%)	**Abdominal Pain**	NR	NR	1 (3.8)
	Colitis	NR	NR	1 (3.8)
	Acute GvHD of the GI	NR	NR	1 (3.8)
	Acute GvHD of the Liver	NR	NR	1 (3.8)
	Pneumonitis	NR	NR	1 (3.8)

GI: gastrointestinal, GVHD: Graft-versus-host disease, HSCT: Hematopoietic stem cell transplantation, N: number, NR: Not reported, SOT: Solid organ transplant, TEAE: Treatment-emergent adverse event, TESAE: Treatment-emergent serious adverse event, TR: Treatment related, %: percent

*Three events deemed possibly related to tab-cel but there were confounding factors.

†Includes abdominal pain, abdominal discomfort, and abdominal pain lower.

‡Three of 5 deaths were due to disease progression (1 in a pediatric patient); 1 was due to cardiac arrest, and 1 was due to multiple organ dysfunction syndrome. Deaths due to other causes (e.g., other than fatal TESAEs) occurred in 2 additional patients (1 with diffuse alveolar hemorrhage and hypoxic respiratory failure, and 1 with disease progression).

Table D3.14. Phase II Harms[17]

Trial	Pooled NCT00002663 + NCT01498484
Arms	**All**
N	**46**
Acute GVHD, events, n (%)	1 (2.1)
Tumor Flare, n (%)	NR
Cytokine Release Syndrome, n (%)	0 (0)
Organ Rejection, n (%)	0 (0)
Febrile neutropenia, n (%)	0 (0)

GVHD: Graft-versus-host disease, N: number, NR: Not reported, %: percent

Table D3.15. ALLELE Responders versus Non-Responders Subgroup[5]

Arms	HSCT		SOT		All	
Response Type	**Responder**	**Non-Responder**	**Responder**	**Non-Responder**	**Responder**	**Non-Responder**
N	**7**	**7**	**15**	**14**	**22**	**21**
Estimated 1-year overall survival, % (95% CI)	100	35.7 (5.2-69.9)	75.2 (40.7-91.4)	33.6 (10.4-59.1)	84.4 (58.9-94.7)	34.8 (14.6-56.1)
Estimated median overall survival, months (95% CI)	Not reached	11 (2-NE)	Not reached (9-NE)	5 (0.9-NE)	Not reached (16.4-NE)	5.7 (1.8-NE)
Median overall survival, months, HR (95% CI; p value)	NE (NE; 0.014)		0.28 (0.09-0.84; 0.016)		0.2 (0.07-0.57; 0.0009)	

CI: Confidence interval, HR: Hazard ratio, HSCT: Hematopoietic stem cell transplantation, N: number, NE: Not evaluable, SOT: Solid organ transplant, %: percent

Table D3.16. ALLELE Age Subgroups[13]

Age		<18 Years	≥18 Years	<65 Years	≥65 Years
N		**6**	**37**	**31**	**12**
Best Overall Response, n (%)	**Complete response**	2 (33.3)	10 (27)	10 (32.3)	2 (16.7)
	Partial response	2 (33.3)	8 (21.6)	7 (22.6)	3 (25)
	Stable disease	0	5 (13.5)	4 (12.9)	1 (8.3)
	Progressive disease	2 (33.3)	7 (18.9)	5 (16.1)	4 (33.3)
	Not evaluable	0	7 (18.9)	5 (16.1)	2 (16.7)
Responder, n (%; 95% CI)		4 (66.7; 22.3, 95.7)	18 (48.6; 31.9, 65.6)	17 (54.8; 36, 72.7)	5 (41.7; 15.2, 72.3)

CI: Confidence interval, N: number, %: percent

Table D3.17. ALLELE SOT Subgroups[5]

Arms	SOT 1 (Prior rituximab Therapy)		SOT 2 (Prior rituximab + Chemotherapy)	
	Responder	**Non-Responder**	**Responder**	**Non-Responder**
N	**6**	**7**	**9**	**7**
1-year OS, % (95% CI)	62.5 (14.2, 89.3)	33.3 (4.6, 67.6)	85.7 (33.4, 97.9)	34.3 (4.8, 68.5)
HR (95% CI)	0.46 (0.10, 2.10)		0.18 (0.03, 0.94)	
P value	0.32		0.023	

CI: Confidence interval, HR: Hazard ratio, N: number, OS: Overall survival, SOT: Solid organ transplant, %: percent

Table D3.18. ALLELE Subgroup Objective Response Rate[5]

Subgroup		N	Objective Response Rate, % (95% CI)
Overall		22/43	51.2 (35.5, 66.7)
Age	**<median**	13/21	61.9 (38.4, 81.9)
	≥median	9/22	40.9 (20.7, 63.6)
Age	**<18 years**	4/6	66.7 (22.3, 95.7)
	≥18 years	18/37	48.6 (31.9, 65.6)
Sex	**Male**	11/24	45.8 (25.6, 67.2)
	Female	11/19	57.9 (33.5, 79.7)
Race	**Other**	6/7	85.7 (42.1, 99.6)
	White	16/36	44.4 (27.9, 61.9)
Ethnicity	**Hispanic/Latino or Unknown**	3/8	37.5 (8.5, 75.5)
	Not Hispanic/Not Latino	19/35	54.3 (36.6, 71.2)
Region	**Asia Pacific + Europe**	5/7	71.4 (29, 96.3)
	North America	17/36	47.2 (30.4, 64.5)
ECOG Performance score (age ≥16)	**<2**	13/28	46.4 (27.5, 66.1)
	≥ 2	7/11	63.6 (30.8, 89.1)
	Missing	0/1	0 (0, 97.5)
PTLD-adapted prognostic score (age ≥16	**Low risk**	2/3	66.7 (9.4, 99.2)
	Intermediate risk	11/19	57.9 (33.5, 79.7)
	High risk	7/17	41.2 (18.4, 67.1)
	Unknown	0/1	0 (0, 97.5)
Extranodal disease at screening	**No**	4/10	40 (12.2, 73.8)
	Yes	18/33	54.5 (36.4, 71.9)
Number of lines of prior systemic therapies	**1**	15/29	51.7 (32.5, 70.6)
	>1	7/14	50 (23, 77)
Responder per investigator	**Yes**	NR	NR
	No	NR	NR
Responder per IORA	**Yes**	NR	NR
	No	NR	NR

CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, IORA: Independent oncologic response adjudication, N: number, NR: Not reported, PTLD: Post-transplant lymphoproliferative disease, %: percent

Table D3.19. ALLELE Subgroup Overall Survival[5]

Trial		ALLELE	
Subgroup		**N**	**Overall Survival, HR (95% CI; P value)**
Overall		NR	NR
Age	**<median**	21	Ref
	≥median	22	0·92 (0·37, 2·33; 0·86)
Age	**<18 years**	6	Ref
	≥18 years	37	0·6 (0·2–1·83; 0·37)
Sex	**Male**	24	Ref
	Female	19	1·02 (0·4–2·6; 0·96)
Race	**Other**	7	Ref
	White	36	3·79 (0·5–28·5; 0·20)
Ethnicity	**Hispanic/Latino or Unknown**	8	Ref
	Not Hispanic/Not Latino	35	1·22 (0·35–4·23; 0·75)
Region	**Asia Pacific + Europe**	7	Ref
	North America	36	0·88 (0·25–3·05; 0·84)
ECOG Performance score (age ≥16)	**<2**	28	Ref
	≥ 2	11	1·86 (0·68–5·14; 0·23)
	Missing	1	4·92 (0·59–40·93; 0·14)
PTLD-adapted prognostic score (age ≥16	**Low risk**	3	Ref
	Intermediate risk	19	1·13 (0·14–9·22; 0·91)
	High risk	17	1·63 (0·2–13·08; 0·64)
	Unknown	1	5·28 (0·32–88·06; 0·25)
Extranodal disease at screening	**No**	10	Ref
	Yes	33	1·71 (0·5–5·93; 0·40)
Number of lines of prior systemic therapies	**1**	29	Ref
	>1	14	1·24 (0·48–3·19; 0·66)

Trial		ALLELE	
Subgroup		**N**	**Overall Survival, HR (95% CI; P value)**
Responder per investigator	**Yes**	17	Ref
	No	26	8·87 (2·03–38·8; 0·0037)
Responder per IORA	**Yes**	22	Ref
	No	21	4·94 (1·75–14; 0·0026)

CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, IORA: Independent oncologic response adjudication, N: number, NR: Not reported, PTLD: Post-transplant lymphoproliferative disease, Ref: Reference, %: percent

Table D3.20. U.S. EAP Subgroup Objective Response Rate[15]

Trial			NCT02822495	
Transplant type	**Subgroup**		**Responders, n/N (%)**	**Objective Response Rate, % (95% CI)**
HSCT	**Sex**	Male	3/7 (42.9)	42.9 (9.9, 81.6)
		Female	4/7 (57.1)	57.1 (18.4, 90.1)
	Race	White	6/10 (60)	60.0 (26.2, 87.8)
		Other	1/4 (25)	25.0 (0.6, 80.6)
	Ethnicity	Hispanic/Latino	0/1 (0)	0.0 (0.0, 97.5)
		Not Hispanic/Latino	6/11 (54.5)	54.5 (23.4, 83.3)
		Missing	1/2 (50)	50.0 (1.3, 98.7)
	Age group	<16	1/2 (50)	50.0 (1.3, 98.7)
		≥16	6/12 (50)	50.0 (21.1, 78.9)
SOT	**Sex**	Male	4/6 (66.7)	66.7 (22.3, 95.7)
		Female	6/6 (100)	100 (54.1, 100)
	Race	White	6/8 (75)	75.0 (34.9, 96.8)
		Other	4/4 (100)	100 (39.8, 100)
	Ethnicity	Hispanic/Latino	2/2 (100)	100 (15.8, 100)
		Not Hispanic/Latino	6/8 (75)	75.0 (34.9, 96.8)
		Missing	2/2 (100)	100 (15.8, 100)
	Age group	<16	4/4 (100)	100 (39.8, 100)
		≥16	6/8 (75)	75.0 (34.9, 96.8)

CI: Confidence interval, HSCT: Hematopoietic stem cell transplantation, N: number, SOT: Solid organ transplant, %: percent

Table D3.21. U.S. EAP EBV-CTLp Levels[16]

Trial	NCT02822495	
Subgroup	**Responders (n=6)**	**Non-Responders (n=4)**
Median increase in circulating CTLp between baseline and day 34, fold change (range)	5.8 (0.8-133)	-0.3 (1.2-0.02)
Patients showing an increase in EBV-CTLp at day 34 of >3.8-fold, n (%)	5 (83)	NA

CTLp: Cytotoxic T lymphocyte precursors, EAP: Expanded access program, N: number, NA: Not applicable, %: percent

Table D3.22. U.S. EAP Responder Subgroup[15]

Trial	NCT02822495	
Subgroup	**All Participants**	
	Responder	**Non-Responder**
N (%)	17 (65.4)	9 (34.6)
Median OS, months (range)	Not reached	2.4 (1.2-8.2)
1-year OS rate	94.1 (65-99.1)	0%
2-year OS rate (95% CI)	94.1 (65-99.1)	0%

CI: Confidence interval, EAP: Expanded access program, N: number, OS: Overall survival, %: percent

Table D3.23. Pooled U.S. EAP and Phase II Pooled Responder Subgroup (NCT02822495, NCT00002663, NCT01498484)

Arms	Response Type		n/N, (%)	ORR, n (%)	Median OS, Months (Range)	1-Year OS Rate	2-year OS Rate (95% CI)	Median Follow-Up, Months (Range)
HSCT	**All**		50 (100)	31 (65)	NR	NR	NR	NR
	CR		24 / 50 (48)	NR	NR	86.7 (64.2, 95.5)	81.6 (57.9, 92.7)	28.2 (1.4, 88.9)
	PR		7 / 50 (14)	NR	NR	85.7 (33.4, 97.9)	85.7 (33.4, 97.9)	25.3 (5.1, 52.4)
SOT	**All SOT EBV+ PTLD**	**CR**	8 / 26 (47.1)	NR	NR	100%	100%	24.5 (6-45.4)
		PR	9 /26 (52.9)	NR	NR	100%	87.5 (38.7, 98.1)	26.2 (5.4,115)
	SOT 1	**CR**	4 / 7 (66.7)	NR	NR	100%	100%	22.8 (12.9,25.7)
		PR	2 / 7 (33.3)	NR	NR	100%	100%	38.4 (26.2,50.7)
	SOT 2	**CR**	4 / 19 (36.4)	NR	NR	100%	100%	25.1 (6.0,45.4)
		PR	7 / 19 (63.6)	NR	NR	100%	83.3 (27.3,97.5)	24.6 (5.4,115)
All	**All**		76	NR	54.6 (14.8-115)	65.8 (53.6, 75.5)	57.8 (45.4, 68.5)	14.8 (0.4 - 115)
	Responders		48 (63)	48 (63)	NR	91.3 (78.4, 96.6)	86.2 (71.7, 93.6)	NR
	CR		32 (42)	NR	NR	90.1 (72.2, 96.7)	86.2 (67, 94.6)	25.4 (1.4-88.9)
	PR		16 (21)	NR	NR	93.8 (63.2, 99.1)	86.5 (55.8, 96.5)	25.8 (5.1-115)

CI: Confidence interval, CR: Complete response, EAP: Expanded access program, EBV+ PTLD: Epstein-Barr virus positive post-transplant lymphoproliferative disease, HSCT: Hematopoietic stem cell transplantation, N: number, NR: Not reported, ORR: Objective response rate, OS: Overall survival, PR: Partial response, SOT: Solid organ transplant, %: percent

Table D3.24. Pooled U.S. EAP and Phase II Pooled EBV+CNS PTLD Subgroup[50]

Trial		NCT02822495, NCT00002663, NCT01498484, NCT04554914*
N		**18**
Median number of lines of prior therapy (range)		1 (0-5)
ORR, n (%; 95% CI)		14 (77.8%; 95% CI: 52.4, 93.6)
Best overall response, n (%)	**CR**	7 (38.9)
	PR	7 (38.9)
	SD	1 (5.6)
	PD	3 (16.7)
Median time to response, months (range)		1.8 (0.7-6.4)
Median duration of response, months (95% CI)		NE (0.5-NE)
1-year OS rate, % (95% CI)		70.6 (43-86.6)
2-year OS rate, % (95% CI)		54.9 (27.1-75.9)
Responders, %	**1-year OS**	85.7
	2-year OS	66.7
Non responders, %	**1-year OS**	0
	2-year OS	0
Median follow up, months (range)		14.8 (1.4-55.4)

CI: Confidence interval, CNS: Central nervous system, CR: Complete response, EAP: Expanded access program, n: number, ORR: Objective response rate, OS: Overall survival, PD: Progressive disease, PR: Partial response, PTLD: Post-transplant lymphoproliferative disease, SD: Stable disease, %: percent

*NCT00002663: n=10, NCT01498484: n=2, NCT02822495: n=2, NCT04554914: n=4

Table D3.25. Phase II Additional Responder Subgroups[17]

Pooled NCT00002663 + NCT01498484				
Transplant Type	**Subgroup**		**Responders, n/N (%)**	**P Value**
All	**Prior treatment**	**Rituximab only**	20/25 (80)	0.03
		Rituximab + other	9/20 (45)	
	Age	**≥50**	10/15 (66.7)	0.99
		<50	19/30 (63.3)	
	Sites of disease	**≥3 sites**	13/25 (52)	0.067
		<3 sites	16/20 (80)	
		CNS	9/11 (81.8)	0.28
		No CNS	20/34 (58.8)	
		Extranodal	16/31 (51.6)	<0.01
		No extranodal	13/14 (92.9)	
	GvHD	**Prior GvHD/rejection**	16/27 (59.3)	0.53
		No prior GvHD/rejection	13/18 (72.2)	
	Systemic steroids	**Yes**	11/19 (57.9)	0.53
		No	18/26 (69.2)	
	HLA matches	**1-3**	12/19 (63.2)	0.99
		4-6	17/26 (65.4)	

Pooled NCT00002663 + NCT01498484				
Transplant Type	**Subgroup**		**Responders, n/N (%)**	**P Value**
HCT	**Prior treatment**	**Rituximab only**	19/24 (79.2)	0.07
		Rituximab + other	3/8 (37.5)	
	Age	**≥50**	8/13 (61.5)	0.7
		<50	14/19 (73.7)	
	Sites of disease	**≥3 sites**	12/19 (63.2)	0.47
		<3 sites	10/13 (76.9)	
		CNS	4/5 (80)	0.99
		No CNS	18/27 (66.7)	
		Extranodal	15/24 (62.5)	0.38
		No extranodal	7/8 (87.5)	
	GvHD	**Prior GvHD/rejection**	11/18 (61.1)	0.26
		No prior GvHD/rejection	11/14 (78.6)	
	Systemic steroids	**Yes**	9/14 (64.3)	0.71
		No	13/18 (72.2)	
	HLA matches	**1-3**	10/15 (66.7)	0.99
		4-6	12/17 (70.6)	

Pooled NCT00002663 + NCT01498484				
Transplant Type	**Subgroup**		**Responders, n/N (%)**	**P Value**
SOT	**Prior treatment**	**Rituximab only**	1/1 (100)	0.47
		Rituximab + other	6/12 (50)	
	Age	**≥50**	2/2 (100)	0.46
		<50	5/11 (45.5)	
	Sites of disease	**≥3 sites**	1/6 (16.7)	0.03
		<3 sites	6/7 (85.7)	
		CNS	5/6 (83.3)	0.1
		No CNS	2/7 (28.6)	
		Extranodal	1/7 (14.3)	<0.01
		No extranodal	6/6 (100)	
	GvHD	**Prior GvHD/rejection**	5/9 (55.6)	0.99
		No prior GvHD/rejection	2/4 (50)	
	Systemic steroids	**Yes**	2/5 (40)	0.59
		No	5/8 (62.5)	
	HLA matches	**1-3**	2/4 (50)	0.99
		4-6	5/9 (55.6)	

CNS: Central nervous system, GVHD: Graft-versus-host disease HLA: Human leukocyte antigens, HSCT: Hematopoietic stem cell transplantation, n: number, SOT: Solid organ transplant %: percent

Table D3.26. Phase II Responders by HLA Restrictions[17]

Trial		NCT00002663 + NCT01498484		
Subgroup	**Number of HLA restrictions**	**N**	**CR + PR**	**%**
Response to first cycle by number of shared HLA restriction	1 Allele restriction	31	11	35.4
	>1 Allele restriction	13	7	53.8
Ultimate response by number of shared HLA restrictions	1 Allele restriction	31	21	68
	>1 Allele restriction	14	8	57

CR: Complete response, HLA: Human leukocyte antigens, n: number, PR: Partial response, %: percent

Table D3.27. Phase II Response by EBV-CTLp Levels Subgroup[51]

Trial	NCT00002663 + NCT01498484	
Subgroup	**Lowest EBV-CTLp quartile**	**Upper 3 EBV-CTLp quartiles**
N	**11**	**31**
Exhibited a clinical response, n (%)	3 (27.3)	25 (80.6)
CRs, n (%)	2 (18.2)	18 (58.1)
PRs, n (%)	1 (9.1)	7 (22.6)
1 yr OS, % (95% CI)	18.2 (2.9-44.2)	83.9 (65.5-92.9)
2 yr OS, % (95% CI)	18.2 (2.9-44.2)	66.1 (45.9-80.2)
OS, HR (95% CI; p value)	0.168 (0.067-0.425; <0.001)	

CI: Confidence interval, CR: Complete response, CTLp: Cytotoxic T lymphocyte precursors, EAP: Expanded access program, EBV: Epstein-Barr virus, HR: Hazard ratio, n: number,

OS: Overall survival, PR: Partial response, %: percent

Table D3.28. Observational HSCT Subgroups[7]

Subgroup		N	Hazard Ratio (95% CI)	P-value
Age at initial PTLD diagnosis	**<60 years (low risk)**	69	Ref	Ref
	≥60 years (high risk)	12	1.22 (0.59–2.51)	0.5943
Sex	**Male**	49	Ref	Ref
	Female	32	1.10 (0.61–1.99)	0.7566
Elevated baseline LDH (≥250U/L)	**No**	11	Ref	Ref
	Yes	60	2.51 (0.93–6.82)	0.0706
	Missing	10	2.56 (0.75–8.76)	0.1329
Region	**North America**	24	Ref	Ref
	Europe	57	0.99 (0.45–2.21)	0.9852
PTLD stage at initial diagnosis	**Stage 1 or 2**	8	Ref	Ref
	Stage 3 or 4	63	0.86 (0.34–2.19)	0.7563
	Missing	10	0.69 (0.21–2.26)	0.5414
PTLD histology at initial diagnosis	**All other types**	29	Ref	Ref
	Monomorphic	52	0.72 (0.42–1.23)	0.2322
Time from HCT procedure to initial PTLD diagnosis		81	0.99 (0.96–1.02)	0.5952
PTLD onset	**Late**	37	Ref	Ref
	Early	44	2.33 (1.25–4.37)	0.0081
Extranodal sites of PTLD	**No or unknown**	25	Ref	Ref
	Yes	56	1.00 (0.52–1.92)	0.9986
Pre-emptive use of rituximab for PTLD	**No or unknown**	64	Ref	Ref
	Yes	17	0.85 (0.41–1.75)	0.6551
Response to initial therapy	**Responders**	15	Ref	Ref
	Non-responders	66	3.74 (1.81–7.70)	0.0004
Total number of systemic treatments	**1**	43	Ref	Ref
	2	29	0.41 (0.07–2.55)	0.3409
	3	9	0.36 (0.05–2.75)	0.3237
Received next line of therapy	**No**	45	Ref	Ref
	Yes	36	0.53 (0.09–3.18)	0.4832

Subgroup		N	Hazard Ratio (95% CI)	P-value
ECOG / Karnofsky/ Lansky score	**<2/≥70/≥70 (low risk)**	13	Ref	Ref
	≥2/<70/<70 (high risk)	34	1.57 (0.70–3.51)	0.2755
	Missing	34	0.72 (0.31–1.70)	0.4519

CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, HCT: Hematopoietic cell transplant,
LDH: Lactate dehydrogenase, n: number, PTLD: Post-transplant lymphoproliferative disease, Ref: Reference,
U/L: units per liter, %: percent

D4. Ongoing Studies

Table D4.1. Ongoing Studies

NCT/Trial	Study Design	Inclusion/Exclusion	Key Outcomes
NCT04554914 **EBVision**	Phase II, open-label, single-arm, multicohort study N=228 (expected) <u>Population</u> Participants with EBV associated diseases <u>Duration</u> 24 months <u>Arm</u> IV infusion of tabelecleucel 2 × 10^6 T-cells/kg on Days 1, 8, and 15	**Inclusion** -ECOG performance status ≤3 for participants aged ≥16 years; Lansky score ≥20 for participants from <16 years -R/R or newly diagnosed for whom the standard first-line therapy is inappropriate -Participants with R/R disease must have had at least one prior line of systemic therapy -Participant may have systemic disease, systemic and CNS disease, or CNS disease **Exclusion** -Suspected or confirmed Grade ≥2 GvHD per the CIBMTR consensus grading system or extensive chronic GvHD per NIH consensus criteria	**Primary endpoint:** -Objective response rate

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

CIBMTR: Center for International Blood and Marrow Transplant Research, CNS: Central nervous system, GVHD: Graft-versus-host disease, ECOG: Eastern Cooperative Oncology Group, IV: intravenous, N: number, NIH: National Institutes of Health, R/R: relapsed/refractory

D5. Previous Systematic Reviews and Technology Assessments

We identified one previously conducted systematic literature review and no health technology assessments. The systematic literature review is briefly summarized below.

Liu JY, Zhang JM, Zhan HS, Sun LY, Wei L. EBV-specific cytotoxic T lymphocytes for refractory EBV-associated post-transplant lymphoproliferative disorder in solid organ transplant recipients: a systematic review. *Transpl Int*. 2021;34(12):2483-2493.[52]

This systematic review aimed to evaluate clinical studies involving Epstein-Barr virus-cytotoxic T lymphocytes (EBV-CTLs) for treating Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) and to discuss their application in refractory PTLD cases among solid organ transplant (SOT) recipients. Numerous studies have demonstrated the safety and effectiveness of EBV-CTLs for treating PTLD after hematopoietic stem cell transplant (HSCT). However, research on its use in SOT recipients is limited. A search was conducted in four databases for both randomized and non-randomized studies, including case reports and case series, focusing on EBV-CTL infusion for EBV-positive PTLD in SOT recipients of any age. The search yielded 1,250 potential citations, of which 11 studies were included—comprising of one cohort study, three case reports, and seven case series. Prior to EBV-CTL therapy, all patients had been treated with various conventional therapies, including reduction of immunosuppression, rituximab, chemotherapy, antivirals, surgery, radiotherapy, or anti-interleukin-6 agents, with poor efficacy reported. The EBV-CTLs administered included both autologous and HLA-matched third-party types. Among 76 participants, 36 achieved complete remission, 14 achieved partial remission, 19 had stable disease, and 7 experienced disease progression, resulting in an overall response rate of 66%. The most common adverse effects were digestive symptoms, such as nausea and vomiting. Despite the limited number of relevant studies, the review found EBV-CTL therapy to be both reliable and effective. GVHD is known to be a major risk associated with this therapy; however, only one case of GVHD was reported among the studies reviewed, indicating that the therapy was generally safe for SOT recipients. A limitation of the review was that most included studies were case reports or case series, and only a few enrolled enough patients for statistical conclusions. Additionally, significant variability in treatment schedules, cell transfer numbers, and confounding factors such as concurrent radiotherapy and chemotherapy prevented the formation of homogeneous patient groups for statistical analysis.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	X	Time seeking medical care*
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	Patient and caregiver labor market earnings lost*
	Cost of unpaid lost productivity due to illness	NA	X	Patient unpaid productivity*
	Cost of uncompensated household production	NA	X	Patient household production*
Consumption	Future consumption unrelated to health	NA	X	Patient consumption*
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[53]

*Analysis based on ICER's indirect "non-zero" approach. Please see ICER's reference case for further information

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[54]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The target population consists of people with EBV+ PTLD that are relapsed or refractory to rituximab and/or chemotherapy in those who had a solid organ transplant (SOT) or relapsed or refractory to rituximab in those who had a hematopoietic stem-cell transplant (HSCT). Due to differences in the underlying risk of death between patients who had an SOT versus patients who had an HSCT, we modeled the cost-effectiveness of tabelecleucel in each population separately and presented results for both combined and individual populations. Table E1.2 reports the baseline population characteristics for each population.

Table E1.2. Baseline Population Characteristics, by Population

Characteristic	SOT Population	HSCT Population
Mean Age, years	44.4 years	51.9 years
Female, %	45%	43%
Source	Mahadeo et al., 2024[5]	Mahadeo et al., 2024[5]

HSCT: hematopoietic stem-cell transplant, SOT: solid organ transplant

Treatment Strategies

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The intervention of interest will be tabelecleucel (Pierre Fabre Laboratories, Atara Biotherapeutics). The comparator will be usual care, which is assumed to include rituximab with or without chemotherapy.

E2. Model Inputs and Assumptions

Our model included several assumptions stated in Table E2.1.

Table E2.1. Key Model Assumptions

Assumption	Rationale
Response is defined as complete or partial response. Non-response is defined as stable or progressive disease.	Data on more granular classifications are not available for the comparator and for other response-stratified model inputs.
Modeling patients receive either tabelecleucel or usual care as an initial treatment. Patients may receive cycles of tabelecleucel, each consisting of three administrations (hereafter will be referred to as 35-day treatment cycle so as not to be confused with model cycle). Following the initial treatment for both tabelecleucel and the comparator, one additional subsequent treatment was modeled for a proportion of those alive.	Due to the severity of the condition, subsequent treatment is likely. Subsequent treatment was frequently reported in the ALLELE study.
The subsequent treatment only impacts cost and is assumed to be equivalent in cost to the comparator basket of treatments for patients with relapsed/refractory disease.	The impact of the subsequent treatment on survival will have already been accounted for in the survival curves.
No treatment discontinuation (besides death) is modeled for either the intervention or comparator.	Due to the short course of treatment and severity of the condition, stakeholders suggested patients would rarely discontinue treatment. All patients in the ALLELE study received the full dose of tabelecleucel without interruption.
Mortality and quality of life for patients surviving 5 years from the initiation of treatment will reflect a post-transplant population. These patients will subsequently be assumed to incur similar health care costs as the general US population.	The 5-year survival rate is a common milestone used to indicate a favorable disease prognosis and a potential cure in oncology and aligns with the last follow-up time point in the ALLELE study. Patients who reach this milestone are expected to have decreased mortality compared to those who still experience EBV+ PTLD as well as an improved quality of life and lower health care costs. Evidence suggests that long-term mortality is higher in post-transplant patients compared to the general population and that the utility values are slightly lower than the general population. There is a lack of evidence on costs beyond 5 years for these same patients.

Assumption	Rationale
The overall survival benefit of tabelecleucel compared to usual care is the same for patients who had a solid organ transplant and a hematopoietic stem-cell transplant.	There is a lack of data on the survival benefit of tabelecleucel separately for patients who had a solid organ transplant and a hematopoietic stem-cell transplant.
The costs of CHOP regimen are used as a proxy for the costs of chemotherapy in the comparator arm.	There is significant variability in the types of chemotherapy regimens used within this population, but there is insufficient data to precisely narrow down the specific regimens used. Therefore, the average costs of chemotherapy will be assumed to be similar to the costs of CHOP regimen, given that CHOP is a commonly used regimen for EBV+ PTLD.

CHOP: cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone, EBV+ PTLD: Epstein-Barr Virus Positive Post-Transplant Lymphoproliferative Disease

Model Inputs

Clinical Inputs

Key clinical inputs include mortality risk, probability of response, treatment discontinuation, and adverse events.

Mortality

Base-case survival for the comparator is derived from parametric fits to the overall survival Kaplan-Meier curves from the comparator evidence. Kaplan-Meier curves from the evidence were digitized using the algorithm by Guyot and colleagues to impute patient-level time-to-event data. We extracted data points from the digitized copies of published survival curves, then used the extracted values, the number of surviving patients at each time interval, and maximum likelihood functions to estimate the underlying individual patient data and extrapolate the values beyond the study follow-up period. The model curves that were considered included the distributional forms Weibull, exponential, log-normal, log-logistic, and Gompertz. The base-case parametric function was chosen based on the model fit using Akaike information criterion (AIC) values and visual comparison. Transition probabilities from the alive to dead health state were derived on a monthly basis using the survival function with the best model fit.

In the overall survival curves for both the SOT and HSCT populations, we observed a flattening of the curves, indicating that a fraction of patients survive for a long time. When standard parametric curve-fitting did not account for this flattening, we selected a time point where the flattening began and fitted separate parametric curves using a piecewise approach to account for the change in slope. To address the potential uncertainty regarding the flat tail of the curves, we conducted a scenario analysis with an alternative parametric assumption that there is no flattening of the curves. Table E2.2 reports the evidence that was used to inform the base-case survival for the comparator and the curve-fitting parameters used for the base-case analysis.

Table E2.2. Survival Evidence for the Comparator

Population	Period (month)*	Distribution	Parameters	Source
SOT Population	0-60	Lognormal	Intercept=1.61 Scale=3.14	Figure 1 from Dharnidharka et al., 2021[8]
HSCT Population	0-2	Lognormal	Intercept=-0.37 Scale=1.50	Figure 1 from Socié et al., 2024[7]
	3-60	Exponential	Rate=3	Figure 1 from Socié et al., 2024[7]

HSCT: hematopoietic stem-cell transplant, SOT: solid organ transplant, N/A: Not applicable
*Mortality after 5 years from the initiation of treatment was assumed to be equivalent to the mortality of the post-transplant population

Base-case survival for the intervention was estimated by applying an overall survival benefit of tabelecleucel to the transition probabilities estimated for the comparator. Table E2.3 reports the overall survival benefit of tabelecleucel that was modeled. Evidence for the tabelecleucel overall survival benefit was sourced from a comparative analysis of tabelecleucel and current treatment. That evidence did not provide a survival benefit separately for the SOT population and HSCT population, and thus, the same survival benefit will be modeled for both populations, although the underlying risk of mortality was different for each population based on the evidence reported in Table E2.2.

Table E2.3. Tabelecleucel Overall Survival Benefit

Survival Benefit	SOT Population	HSCT Population
Overall Survival Benefit	0.37 (0.20, 0.71)	0.37 (0.20, 0.71)
Source	Barlev et al., 2024 [19]	Barlev et al., 2024 [19]

HSCT: hematopoietic stem-cell transplant, SOT: solid organ transplant

For both arms in the model, anyone alive after five years experienced mortality equivalent to transplant patients following SOT or HSCT. Studies found that the standardized mortality ratio is 3.08 (3.05-3.11) for adult organ recipients and 5.80 (5.30-6.30) for adult blood or marrow transplantation recipients, respectively, compared to the US general population.[30,31] Therefore, the general US population mortality was adjusted using these mortality ratios to estimate the mortality after 5 years in the modeled populations.

Probability of Response

Response status was tracked as an event for all patients in the alive health state and impacted the receipt of subsequent treatment and health state utility estimates. Response was defined as complete or partial response. Non-response was defined as stable or progressive disease. All patients started the model as a non-responder to their previous line therapy (i.e., rituximab with or without chemotherapy). At the start of cycle two, response status will be assessed based on the median time to response observed in the ALLELE study.[5] Table E2.4 reports the percent responders

at the start of cycle two for the SOT population. Table E2.5 reports the percent responders at the start of cycle two for the HSCT population.

Table E2.4. Response at One Month, SOT Population

Parameter	Tabelecleucel	Usual Care
Responders	52%	13.5%
Notes	Responders included those with a best overall response of either a complete or partial response.	Response data was not presented in Dharnidharka et al., 2021[8] and thus we applied the relative difference in response observed between usual care and tabelecleucel for HSCT to the response data for tabelecleucel for SOT to estimate the probability of response for SOT under usual care.
Source	Mahadeo et al., 2024[5]	Socié et al., 2024[7] and Mahadeo et al., 2024[5]

HSCT: hematopoietic stem-cell transplant, SOT: solid organ transplant

Table E2.5. Response at One Month, HSCT Population

Parameter	Tabelecleucel	Usual Care
Responders	50%	13%
Notes	Responders included those with a best overall response of either a complete or partial response.	Response data from Socié et al., 2024 was only available for those with >6 months of response after treatment end date; therefore, we adjusted the >6 month response percent reported in Socié et al., 2024 (11.1%) by the relative differential in 1 month response versus >6 month response reported in the ALLELE study.
Source	Mahadeo et al., 2024[5]	Socié et al., 2024[7] and Mahadeo et al., 2024[5]

HSCT: hematopoietic stem-cell transplant

The proportion of the alive population that is a responder varies over time in two ways. First, we acknowledge that responders have a lower likelihood of mortality as compared to non-responders. To model this, we used a hazard ratio of 0.20 (95% confidence interval: 0.07, 0.57) that compares overall survival between responders and non-responders.[5] Second, after the initial response assessment at one month, we modeled patients moving from being a responder to being a non-responder. Using evidence from the ALLELE study suggesting that 52% of the SOT population were responders at one month and 21% of the SOT population were responders at six months, we estimated a one-month probability of becoming a non-responder if previously a responder of 17% for the SOT population.[5] Using evidence from the ALLELE study suggesting that 50% of the HSCT

population were responders at one month and 43% of the HSCT population were responders at six months, we estimated a one-month probability of becoming a non-responder if previously a responder of 3% for the HSCT population.[5] We compared the percent responders at one month and six months calculated in our model to the estimates reported in the ALLELE study to ensure the validity of these estimates.

Discontinuation

No treatment discontinuation (besides death) was modeled for either the intervention or comparator. Due to the short course of treatment and severity of the condition, stakeholders suggested patients are unlikely to discontinue treatment. Further, all patients in the ALLELE study received the full dose of tabelecleucel without interruption.[5]

Adverse Events

Clinical experts did not indicate that tolerability was a major concern with tabelecleucel and most adverse events were not severe in nature. Thus, the model did not include any costs or decrements in quality of life associated with any specific adverse event of tabelecleucel.

Since the health state utility values and healthcare costs were derived from studies of patients receiving usual care, it is assumed that they already include the disutilities and costs associated with adverse events of usual care or chemotherapy (See Table E2.8 and E2.12 for the health state utility values and health costs, respectively). To exclude the impact of adverse events associated with usual care from the tabelecleucel arm, disutilities and costs for these adverse events were subtracted from the utility and cost estimates for tabelecleucel during the treatment period. The disutility of adverse events of usual care was estimated to be 0.15 based on a systematic literature review study of quality of life in relapsed and/or refractory large B cell lymphoma.[55] The costs of adverse events of usual care were estimated based on the frequency of adverse events grade 3 or 4 obtained from a prospective study among PTLD patients who received rituximab with or without CHOP and the one-off treatment costs of each adverse event obtained from the Healthcare Cost and Utilization Project (HCUP) database (Tables E2.6 and E2.7).

Although graft-versus-host disease and organ rejection are adverse events of special interest, they were not modeled because clinical experts have suggested that these events do not have a causal relationship with the comparator, and there is still limited tabelecleucel-specific evidence for these events.

Table E2.6. Grade 3-4 Adverse Events of Usual Care

Parameter*	SOT Population	HSCT Population
Infection	42%	42%
Leukopenia	37%	37%
Anemia	24%	24%
Thrombocytopenia	22%	22%
Acute renal failure	15%	15%
Gastrointestinal hemorrhage	7%	7%
Source	Zimmermann et al., 2022[56]	Zimmermann et al., 2022[56]

*Only adverse events grade 3 or 4 with a frequency >5% were included

Table E2.7. Costs of Grade 3-4 Adverse Events

Parameter*	Costs	Source
Infection	$25,703	HCUP database (DRG: 808)[57]
Leukopenia	$25,703	HCUP database (DRG: 808)[57]
Anemia	$14,602	HCUP database (DRG: 811)[57]
Thrombocytopenia	$19,803	HCUP database (DRG: 813)[57]
Acute renal failure	$13,929	HCUP database (DRG: 682)[57]
Gastrointestinal hemorrhage	$18,186	HCUP database (DRG: 377)[57]

Health State Utilities

Health state utilities were derived from publicly available literature and are reported in Table E2.8. We used consistent health state utility values across treatments evaluated in the model, but utility values will differ by responder status. The utility for a responder was based on a utility estimate for disease-free survival for a population with diffuse large B-cell lymphoma. The utility for a non-responder was based on a utility estimate for progressive disease for a population with diffuse large B-cell lymphoma. After five years, health state utilities will no longer be specific to responder status but will equate the health state utilities for transplant patients following SOT or HSCT, which are 0.827 and 0.826, respectively.[24,25]

Table E2.8. Health State Utilities

Parameter	SOT Population	HSCT Population
Responder	0.83 (0.66, 1)	0.83 (0.66, 1)
Non-Responder	0.39 (0.31, 0.47)	0.39 (0.31, 0.47)
Source	Best et al., 2005[23]	

HSCT: hematopoietic stem-cell transplant, SOT: solid organ transplant

Drug Utilization

The inputs in Table E2.9 were used to model drug utilization for tabelecleucel.

Table E2.9. Tabelecleucel Regimen

Regimen Parameter	SOT Population	HSCT Population	Source
Number of Cycles*	2	3	Mahadeo et al., 2024 [5]
Number of Doses	6	9	
Route of Administration	Intravenous	Intravenous	

HSCT: hematopoietic stem-cell transplant, SOT: solid organ transplant

*Each 35-day treatment cycle assumed to last one model cycle.

The inputs in Table E2.10 were used to model drug utilization for the comparator. In addition to the use of rituximab with or without chemotherapy, it was assumed that 62.7% of patients in the comparator arm received prophylactic granulocyte colony-stimulating factor (G-CSF) to reduce the risk of neutropenia.[58 59]

Table E2.10. Comparator Basket

Regimen Parameter	SOT Population	HSCT Population
Rituximab Monotherapy	0%	84.0%
Rituximab + Chemotherapy	100%	16.0%
Source	Dharnidharka et al., 2021[8]	Socié et al., 2024[7]

HSCT: hematopoietic stem-cell transplant, SOT: solid organ transplant

One subsequent treatment was modeled for a proportion of those alive in both the comparator and intervention arms. The probability of receipt of subsequent treatment was dependent on responder status and was informed by the percentage receiving subsequent treatment in the ALLELE study. In the ALLELE study, 14 patients (33% of all patients) received subsequent treatment, three of which were responders (14% of all responders) and 11 of which were non-responders (52% of all non-responders).[5] Therefore, immediately after the initial course of the intervention and comparator treatment, 14% of all responders that are currently alive and 52% of all non-responders that are currently alive will initiate a subsequent treatment. The subsequent treatment basket was the same as the comparator basket and only impacted the cost as it is assumed that subsequent treatment would already have impacted the survival curves.

Cost Inputs

All costs used in the model were updated to 2023 US dollars.

Drug Costs

ICER's reference case was followed to estimate the drug costs used in the model. Given tabelecleucel is still undergoing FDA review, a price is not yet known for the US, and thus, a placeholder price was used in the economic model. IPD Analytics estimates an average price per treatment course of $275,000 to $300,000.[26] Therefore, we used the mid-point of this range to estimate the price per cycle of tabelecleucel. Because tabelecleucel will be provider administered,

we added a 6% mark-up to this placeholder acquisition cost. This price will be updated when and if the price becomes known.

For approved drugs that are provider administered, the acquisition price was based on the average sales price (ASP) drug pricing file.[60] The price from this file is inclusive of the ASP and the associated mark-up which is typically 6% (or 6% of the originator product if a biosimilar). The mark-up was removed from the price reported in the ASP drug pricing file to isolate the drug acquisition cost and the mark-up (6% of ASP or 6% of the originator product's ASP if a biosimilar) was programmed in a separate input within the model.

For approved drugs that are not provider-administered but have generic equivalents available (i.e., prednisone), we used the median cost generic wholesale acquisition cost (WAC) as the estimate of the net price in alignment with ICER's reference case.

Table E2.11 reports the net price that was used for each drug in the model. To monetize the chemotherapy used by some patients in the comparator and by some patients in subsequent treatment, we used the "CHOP" (i.e. cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone) regimen.[27] We understand the price of this regimen, and the price of other chemotherapy regimens used for this condition, will vary and thus we will vary this cost over a wide range in sensitivity analyses. The average body surface area used to monetize these estimates will be 1.79 m.[2,61]

Table E2.11. Drug Costs

Drug	Regimen per Treatment Cycle	Net Price Prior to Mark-Up	Notes	Source
Tabelecleucel	2×10^6 cells per kg on days 1, 8 and 15	$287,500 per cycle ($95,833 per admin)	Placeholder price informed by mid-point of range estimated by IPD Analytics	IPD Analytics
Rituximab	375 mg/m^2 once a week for 4 weeks	$39.75 per 10mg	Codes J9312 (rituximab), Q5115 (rituximab-abbs), Q5119 (rituximab-pvvr), and Q5123 (rituximab-arrx) after removing mark-up equivalent to 6% of the originator; products were weighted 28% for the originator, and 24% for each biosimilar	ASP Pricing File, July 2024[60] & IPD Analytics[62]

Drug	Regimen per Treatment Cycle	Net Price Prior to Mark-Up	Notes	Source
Cyclophosphamide	750 mg/m^2 on day 1 for four 21-day cycles	$1.04 per 5mg	Code J9075 after removing 6% mark-up	ASP Pricing File, July 2024[60]
Doxorubicin Hydrochloride	50 mg/m^2 on day 1 for four 21-day cycles	$3.08 per 10mg	Code J9000 after removing 6% mark-up	ASP Pricing File, July 2024[60]
Vincristine Sulfate	1.4 mg/m^2 (max of 2mg) on day 1 for four 21-day cycles	$8.01 per mg	Code J9370 after removing 6% mark-up	ASP Pricing File, July 2024[60]
Prednisone	50 mg/m^2 on days 1-5 for four 21-day cycles	$0.33 per 50mg	Median WAC	REDBOOK
Pegfilgrastim (G-CSF)	6 mg once per chemotherapy cycle	$4,175 per 6mg	Median WAC	REDBOOK

ASP: average sales price, WAC: wholesale acquisition cost

Administration Costs

Tabelecleucel, rituximab, cyclophosphamide, doxorubicin hydrochloride, and vincristine sulfate are all intravenously administered and thus were associated with an administration cost of $134 per administration (HCPCS: 96413).[32] Prednisone is orally administered and does not consist of any administration cost. It is possible that the provider-administered treatments may be administered in an inpatient setting. The additional costs associated with the inpatient admission were assumed to be included in the health care costs included elsewhere in the model (see section below titled Other Health Care Costs).

Other Health Care Costs

To estimate the non-drug health care costs, we inflated the medical cost estimates from Hart et al., 2021 to 2023 US dollars, assuming the year of the costs reported in the Hart et al., 2021 study were 2016 US dollars.[4] Using the per patient-year estimate for those alive at 2 years from Table 3 in Hart et al., 2021, we estimated a per-patient month estimate. This per-patient month estimate was applied to all living members cohort during the first five years of the model. Additionally, for those that died within the first five years of the model, an additional cost at death was assigned based on the difference in medical costs between patients that were dead and alive as reported in Table 3 of Hart et al., 2021.[4] Table E2.12 reports the other health care costs that were included in the economic model. Those who remain alive after five years were assumed to have similar healthcare costs as the general US population.[28]

Table E2.12. Other Health Care Costs

Cost Parameter	SOT Population	HSCT Population
Cost per Month for Those Alive	$7,268	$7,268
Added One-Time Cost at Death	$203,338	$203,338
Source	Hart et al., 2021[4]	

HSCT: hematopoietic stem-cell transplant, SOT: solid organ transplant

Productivity Costs

Given that no direct data on the impact of tabelecleucel on patient productivity (formal and informal labor, household production, and time seeking care) and caregiver productivity time are available, an indirect approach to valuing these domains was used. To inform estimates for the indirect approach, we used the published relationship between patient utility scores and US-based patient time use data to derive the anticipated impacts of the treatment on time spent in each activity due to the disease and its management for the patient.[63] Since no parallel relationship between patient utility scores and caregiver time use data exists for the US setting, we assumed that caregiver time spent is proportional to 75% of patient formal labor time lost. This estimate is based on the modeled relationship between caregiver time required and patient time lost according to patient utility scores in the United Kingdom setting.[64,16] Further details on the implementation of this approach are detailed in ICER's Reference Case.

E3. Results

Tables E3.1 and E3.2 reports the base-case results for tabelecleucel as compared to usual care in the SOT and HSCT populations, separately. Please note that the results for individual populations are subject to a high level of uncertainty due to the lack of data to inform key model parameters specific to each population, such as the survival benefit of tabelecleucel. Therefore, the clinical and economic outcomes in each population may be biased, with the magnitude of the bias unknown.

Table E3.1. Base-Case Results for Tabelecleucel as Compared to Usual Care in the SOT and HSCT Populations

Treatment	Drug Cost	Total Cost	QALYs	evLYs	Life Years
SOT Population					
Tabelecleucel*	$538,295	$978,874	7.40	8.17	10.41
Usual Care	$16,548	$346,072	2.93	2.93	4.34
HSCT Population					
Tabelecleucel*	$660,431	$999,498	2.32	2.65	3.22
Usual Care	$11,552	$250,743	0.31	0.31	0.53

evLYs: equal-value life year, HSCT: hematopoietic stem-cell transplant, QALY: quality-adjusted life year, SOT: solid organ transplant

*Based on a placeholder price

Table E3.2. Incremental Cost-Effectiveness Ratios for the Base Case in the SOT and HSCT Populations

Population	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
SOT Population	$141,476	$120,722	$104,122
HSCT Population	$373,675	$320,323	$277,759

evLYs: equal-value life year, HSCT: hematopoietic stem-cell transplant, QALY: quality-adjusted life year, SOT: solid organ transplant

*Based on a placeholder price

E4. Sensitivity Analyses

Table E4.1. Tornado Diagram Inputs and Results for Tabelecleucel versus Usual Care

Parameter	Min Incremental CE Ratio	Max Incremental CE Ratio	Lower Input*	Upper Input*
Overall survival benefit of tab-cel, hazard ratio, SOT	141,469.8	345,447.3	0.20	0.71
The number of cycles for tab-cel, SOT	134,916.9	229,510.7	1	3
The year when people are cured	170,865.2	241,760.1	4	10
Multiplier for the mortality, usual care, SOT	162,619.8	229,391.3	0.80	1.20
Age at baseline, SOT	159,789.0	216,638.5	35.5	53.3
Utility value after year 5, SOT	179,997.2	212,797.9	0.66	0.85
The number of cycles for tab-cel, HSCT	167,418.0	198,263.0	2	4
Overall survival benefit of tab-cel, hazard ratio, HSCT	168,615.3	191,744.4	0.20	0.71
Age at baseline, HSCT	175,896.4	190,250.7	41.5	62.3
Other health care costs per month, SOT population (up until year 5)	178,577.4	188,321.1	5814.4	8721.6

CE: cost-effectiveness, HSCT: hematopoietic stem-cell transplant, SOT: solid organ transplant

*Lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

†The survival estimates for the usual care were varied by varying the probability of death by +/- 20%. We multiplied a random draw following a normal distribution to the transition probabilities.

Table E4.2. Results of Probabilistic Sensitivity Analysis for Tabelecleucel versus Usual Care

	Tabelecleucel	Usual Care	Incremental
Costs	$976,573 ($720,046, $1,243,174)	$312,987 ($260,265, $369,225)	$663,585
QALYs	5.93 (3.37, 8.55)	2.18 (1.28, 3.48)	3.75
evLYs	6.58 (3.99, 9.08)	2.18 (1.28, 3.48)	4.40
Incremental CE Ration per QALY			$176,831
Incremental CE Ratio per evLY			$150,821

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year

Figure E4.1. Cost-Effectiveness Plane for Tabelecleucel versus Usual Care

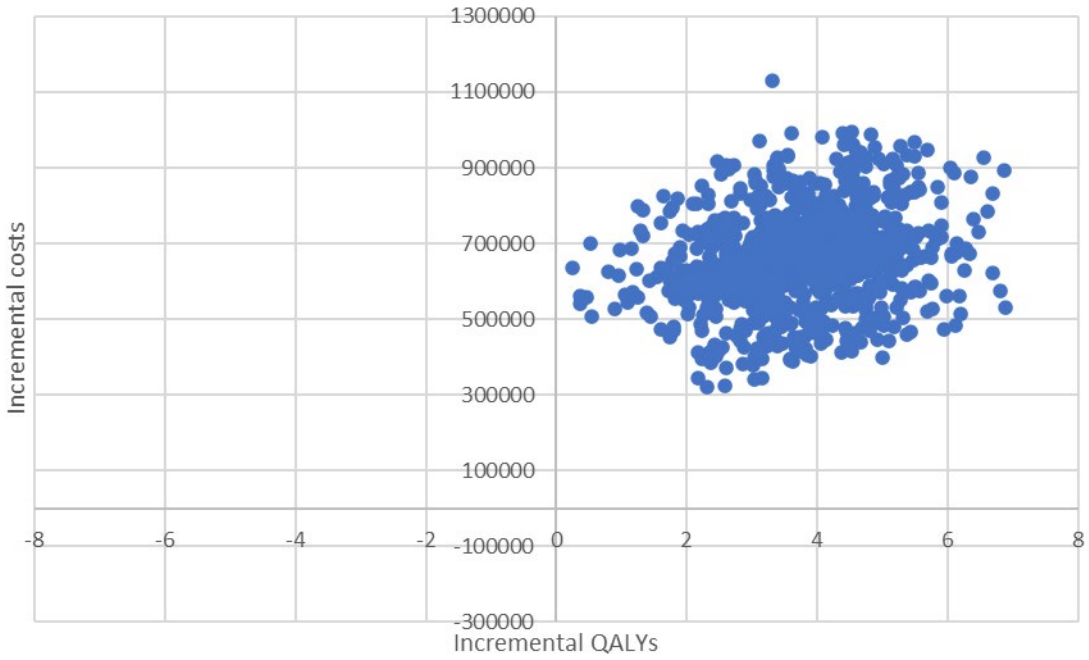
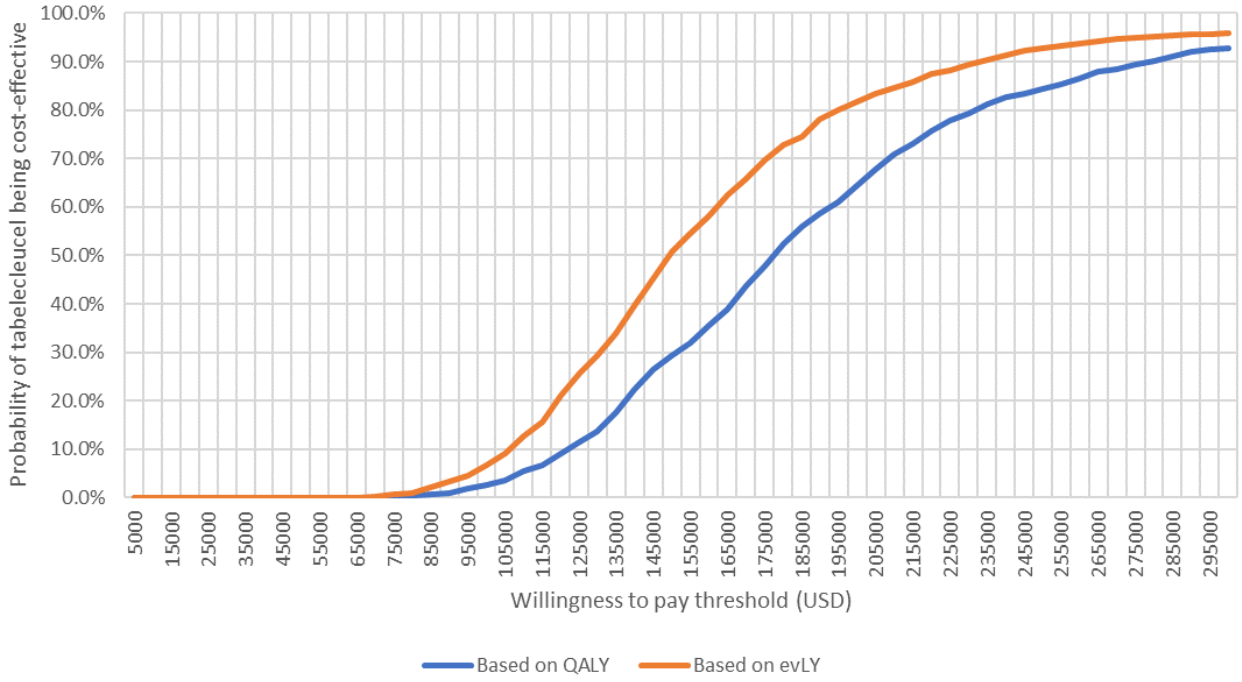


Figure E4.2. Cost-Effectiveness Acceptability Curve for Tabelecleucel versus Usual Care



E5. Scenario Analyses

Scenario Analysis 1: Modified Societal Perspective

Results for the modified societal perspective analysis using the indirect approach for estimating non-health care sector costs (i.e., patient and caregiver productivity impacts net of consumption costs) are presented in Tables E5.1 and E5.2. The incremental total costs of tabelecleucel compared to usual care were lower when using the modified societal perspective, primarily due to an incremental gain in patient productivity during the added years of life, as presented in Table E5.2.

Table E5.1. Model Outcomes for the Modified Societal Perspective Scenario Analysis Using an Indirect Approach for Estimating Non-health Care Sector Costs

Treatment	Total Cost*	QALYs	evLYs	Life Years
Tabelecleucel	$689,857	5.72	6.35	8.04
Usual Care	$357,827	2.06	2.06	3.08

evLYs: equal-value life year, QALY: quality-adjusted life year

*Note: The total cost for tabelecleucel under the modified societal perspective scenario is lower than total cost under a healthcare perspective because the indirect approach for estimating non-healthcare sector costs accounts for productivity gains during life extension – see Table E5.2 below.

Table E5.2. Discounted Non-Health Care Sector Costs for the Modified Societal Perspective Analysis Using an Indirect Approach for Estimating Non-health Care Sector Costs

Treatment	Incremental Patient Productivity (vs. Comparator)	Patient Time Seeking Care	Caregiver Productivity Loss	Patient Consumption Costs*	Total Non-Health Care Sector Costs
Tabelecleucel	$(510,116)	$11,500	$75,705	$205,935	$(295,823)
Usual Care	N/A	$4,931	$38,283	$78,846	$43,214

N/A: Not applicable

Note: Brackets represent a negative value (i.e., cost savings).

*During added life years ($0 patient consumption costs for the comparator)

Scenario Analysis 2: Alternative Response Assumption Scenario (No Transition from Response to Non-response after Month Six)

In this scenario analysis, we assumed that the probability of moving from response to non-response is 0% after six months in both SOT and HSCT populations. Table E5.3 reports the model outcomes for this scenario analysis.

Table E5.3. Model Outcomes for the Alternative Response Assumption Scenario

Treatment	Total Cost	QALYs	evLYs	Life Years
Tabelecleucel	$985,680	6.02	6.46	8.04
Usual Care	$314,602	2.12	2.12	3.08

evLYs: equal-value life year, QALY: quality-adjusted life year

Scenario Analysis 3: Alternative Survival Benefit Assumption (Unadjusted Survival Benefit)

In this scenario analysis, we applied the unadjusted overall survival benefit of tabelecleucel hazard ratio of 0.47. Table E5.4 reports the model outcomes for this scenario analysis.

Table E5.4. Model Outcomes for the Alternative Survival Benefit Assumption Scenario

Treatment	Total Cost	QALYs	evLYs	Life Years
Tabelecleucel	$962,889	5.51	6.09	7.74
Usual Care	$314,614	2.06	2.06	3.08

evLYs: equal-value life year, QALY: quality-adjusted life year

Scenario Analysis 4: Alternative Survival Extrapolation Assumption (No Flattening of the Survival Curves)

We observed that the survival curves for usual care flattened in both the SOT and HSCT populations. In the base-case analysis, this flattening was explicitly modeled for overall survival curves. To account for potential uncertainty in long-term survival in these populations, a scenario analysis was

conducted under an alternative parametric assumption that there is no flattening of the curves. This scenario should be interpreted as a lower bound for survival. Table E5.5 shows the parametric curve parameters and Table E5.6 reports the model outcomes for this scenario analysis.

Table E5.5. Alternative Survival Parameters for the Comparator

Population	Period (month)*	Distribution	Parameters	Source
SOT Population	0-60	Lognormal	Intercept=1.02 Scale=2.55	Figure 1 from Dharnidharka et al., 2021[8]; A standard parametric curve was fitted using the data from months 0 to 60 only, rather than to the entire dataset.
HSCT Population	0-60	Lognormal	Intercept=-0.37 Scale=1.50	Figure 1 from Socié et al., 2024[7] ; A standard parametric curve was fitted instead of using a piece-wise approach.[7]

HSCT: hematopoietic stem-cell transplant, SOT: solid organ transplant

Table E5.6. Model Outcomes for the Scenario Analysis with an Alternative Parametric Assumption

Treatment	Total Cost	QALYs	evLYs	Life Years
Tabelecleucel	$943,664	4.41	4.98	6.22
Usual Care	$283,812	1.16	1.16	1.79

evLYs: equal-value life year, QALY: quality-adjusted life year

Scenario Analysis 5: Excluding Unrelated Medical Costs

In this scenario, unrelated medical costs were excluded from the analysis. Since it was not possible to disaggregate the medical costs incurred up to year 5 from the treatment initiation, only unrelated medical costs after year 5 were excluded. Table E5.7 reports the model outcomes for this scenario analysis.

Table E5.7. Model Outcomes for the Scenario Analysis with Unrelated Medical Costs Excluded

Treatment	Total Cost	QALYs	evLYs	Life Years
Tabelecleucel	$929,377	5.72	6.35	8.04
Usual Care	$296,688	2.06	2.06	3.08

evLYs: equal-value life year, QALY: quality-adjusted life year

E6. Heterogeneity and Subgroups

No subgroup analyses were conducted.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with tabelecleucel.

In order to calculate our eligible patient population, we used subpopulation-specific inputs (e.g., incidence of SOT and HSCT), however, in line with the cost-effectiveness analysis, our overall potential budget impact estimates remain representative of the overall population of patients with EBV+ PTLD in the US. Our results are not intended to provide budget impact estimates separately for SOT and HSCT populations given the uncertainties in the data reported in the cost-effectiveness analysis. The potential budget impact analysis included the estimated number of people in the US who are likely to be eligible for tabelecleucel. To estimate the size of the potential candidate population, we used inputs for the incidence of EBV+ PTLD among both SOT (10.5%) and allogeneic HSCT (1.7%) recipients.[7,33,34] We applied these incidence estimates to the number of SOTs and HSCTs that occur each year in the US, approximately 49,187 and 9,299, respectively, to estimate the number of patients who develop EBV+ PTLD post-transplant per year.[35,36] In line with the population of interest for tabelecleucel, we further narrowed the eligible population to patients who have received at least one prior therapy. According to a multicenter, retrospective review, 50% of EBV+ PTLD patients are relapsed or refractory to first-line rituximab therapy, so we used this estimate as a proxy to determine the number of patients who have received at least one prior therapy.[7] Applying these sources resulted in estimates of 13,319 eligible patients in the US over five years. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 2,664 patients per year.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[65,66] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

The intent of our approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2023-2024, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $735 million per year for new drugs.