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Federal Department of Home Affairs
Federal Office of Public Health FOPH
Health and Accident Insurance Directorate
Section Health Technology Assessment

Health Technology Assessment (HTA)

HTA Report

Title	The CAR T-cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) for the treatment of B-cell acute lymphoblastic leukaemia, diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma
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Technology	Tisagenlecleucel (Kymriah®) Axicabtagene ciloleucel (Yescarta®)
Type of Technology	Medical services
Date	9 July 2024

Conflict of Interest: The authors have no financial, academic, personal or any other conflicts of interest to declare in relation to this project.

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Executive Summary

Background

The chimeric antigen receptor (CAR) T-cell therapies tisagenlecleucel (tisa-cel) and axicabtagene ciloleucel (axi-cel) are provisionally listed in Appendix 1 of the Health Insurance Benefits Ordinance in Switzerland until 31 December 2024 for the third-line treatment of B-cell acute lymphoblastic leukaemia (B-ALL), diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL). This health technology assessment (HTA) evaluates the available evidence regarding the efficacy, effectiveness, safety, costs, cost-effectiveness and budget impact of tisa-cel and axi-cel compared to standard care in these populations. Ethical, legal, social and organisational issues associated with these therapies are also explored.

Methods

A systematic review of clinical studies was conducted in Medline, Embase, the Cochrane Library and the INAHTA HTA database up to 13 April 2023. Systematic reviews, randomised controlled trials (RCTs), non-randomised studies of interventions (NRSI) and single-arm studies were eligible for inclusion. Indirect comparisons between single-arm studies of CAR T-cell therapies and standard care were deemed inappropriate for the clinical evaluation due to the significant risk of confounding. Relevant outcomes were overall survival (OS), progression-free survival (PFS), complete response rate (CRR), overall response rate (ORR), treatment-free interval (TFI), health-related quality of life (HRQoL), treatment discontinuation, and adverse events including B-cell aplasia, cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). The overall certainty of evidence for critical outcomes was assessed using the Grading of Recommendation, Assessment, Development and Evaluations (GRADE) approach. Random-effects meta-analyses were conducted using R.

A systematic review of economic studies was undertaken in the same databases as the clinical evaluation, plus Econlit and the websites of HTA institutes. Data were extracted from retrieved cost and cost-effectiveness studies, and the results described narratively. One study was directly applicable to the HTA context, having been conducted from the perspective of the Swiss healthcare payer. This study was funded by the company (Novartis) who developed Kymriah® (tisa-cel proprietary drug). Additional evaluations were made to assess the cost-effectiveness of axi-cel for patients with relapsed or refractory (r/r) large B-cell lymphoma (LBCL) in the Swiss setting, and to provide comparable evaluations for tisa-cel for patients with r/r B-ALL or DLBCL. The methodology adopted was guided by the existing literature.

Clinical evaluation

It was not feasible to evaluate DLBCL and PMBCL populations separately, therefore studies that included either population were aggregated into a broader 'LBCL' population. For all outcomes reported in single-arm studies, the certainty of evidence was very low, meaning that the true effects are probably different from the estimated effects. The certainty of evidence for NRSIs is noted below. Relative effects were calculated as comparator/CAR T (except where noted).

Tisa-cel for B-ALL

One NRSI and 7 single-arm studies investigated tisa-cel in the B-ALL population. The reported hazard ratio (HR) for OS comparing conventional chemotherapy to tisa-cel at 150 days in patients admitted to intensive care (n=205) reported no evidence of a significant difference (HR 0.89, 95% CI: 0.38 to 2.11; very low certainty evidence). Results from single-arm studies are summarised in the following table:

Outcome (duration)	Result	No of participants (studies)
OS (20 months)	69% (95% CI: 63 to 75; n=76 at risk)	459 (6 observational studies)
PFS	Not reported	Not reported
CRR (28–856 days)	79% (95% CI: 70 to 87)	464 (6 observational studies)
ORR (3–6 months)	68% (95% CI: 60 to 75)	156 (2 observational studies)
CRS (4 days–14 months)	70% (95% CI: 60 to 80)	568 (8 observational studies)
ICANS (6 days–14 months)	26% (95% CI: 12 to 42)	425 (6 observational studies)
B-cell aplasia (24 months)	64% (95% CI: 49 to 78)	196 (4 observational studies)

Axi-cel for LBCL

Two NRSIs and 14 single-arm studies investigated axi-cel in the LBCL population. At 16 months axi-cel reported favourable OS (HR 0.14; 95% CI: 0.05 to 0.38), PFS (HR 0.04; 95% CI: 0.01 to 0.17) and ORR (RR 0.05; 95% CI: 0.00 to 0.77), and no evidence of a statistically significant difference in CRR (RR 0.09; 95% CI: 0.01 to 1.37) compared to no axi-cel (very low certainty evidence). At 24 months, axi-cel reported favourable OS (HR 0.27; 95% CI: 0.0 to 0.38), CRR (RR 0.22; 95% CI: 0.16 to 0.32) and ORR (RR 0.42; 95% CI: 0.35 to 0.50) compared to salvage chemotherapy (moderate certainty evidence). The NRSIs did not report other relevant outcomes. Results from single-arm studies are summarised in the following table:

Outcome	Result	No of participants (studies)
OS (20 months)	53% (95% CI: 49 to 59, n=90 at risk)	654 (6 observational studies)
PFS (20 months)	36% (95% CI: 32 to 40, n=95 at risk)	778 (7 observational studies)
CRR (3–63 months)	52% (95% CI: 43 to 60)	1,061 (11 observational studies)

ORR (1–63 months)	73% (95% CI: 65 to 80)	1,240 (11 observational studies)
CRS (1–60 months)	89% (95% CI: 86 to 91)	1,260 (12 observational studies)
ICANS (1—21 months)	55% (95% CI: 49 to 63)	1,159 (12 observational studies)
B-cell aplasia (12 months)	55% (95% CI: 33 to 76)	22 (2 observational studies)

Tisa-cel for LBCL

One NRSI and 9 single-arm studies investigated tisa-cel in the LBCL population. At 50-90 months, the NRSI reported OS favouring tisa-cel (HR 0.60, 95% CI: 0.44 to 0.77), and no evidence of a statistically significant difference in ORR (RR 1.31, 95% CI: 0.97 to 1.77), compared to standard care (very low certainty evidence). The NRSI did not report other relevant outcomes. Results from single-arm studies are summarised in the following table:

Outcomes	Result	No of participants (studies)
OS (15 months)	44% (95% CI: 39 to 50, n=73 at risk)	529 (5 observational studies)
PFS (15 months)	30% (95% CI: 25 to 36, n=47 at risk)	377 (4 observational studies)
CRR (3–12 months)	37% (95% CI: 33 to 42)	719 (8 observational studies)
ORR (3–12 months)	55% (95% CI: 45 to 65)	803 (8 observational studies)
CRS (1–24 months)	64% (95% CI: 53 to 75)	839 (9 observational studies)
ICANS (1–11 months)	18% (95% CI: 15 to 23)	724 (8 observational studies)
B-cell aplasia (24 months)	1% (95% CI: 0 to 5)	115 (1 observational study)

Economic evaluation

Incremental cost-effectiveness ratios (ICERs) are presented; however, the calculations underpinning these ICERs were based on very low-quality evidence and naïve treatment comparisons. Concerns raised by other HTA bodies in their reviews of company-submitted economic evidence (e.g. lack of comparative safety and efficacy; uncertainty in the extrapolation of OS; majority of quality-adjusted life years [QALYs] gained over the period of extrapolation; applicability of the historical control comparator evidence) are also key concerns with the ICERs presented here (both the existing Swiss values from the literature and the newly generated ICERs). In summary, there is significant uncertainty in the results presented.

Tisa-cel for B-ALL

The existing Swiss evaluation reported a base case ICER of CHF36,419 (Swiss francs) per QALY gained for tisa-cel relative to blinatumomab.[1] In this HTA, an ICER for tisa-cel relative to blinatumomab was generated using updated outcome data for the ELIANA cohort.[2] An ICER of CHF70,634 per QALY gained was estimated. While this comparator aligned with existing

evaluations and HTAs, it failed to capture complexities in the treatment of r/r B-ALL—for example, blinatumomab may be used as a bridge to CAR T-cell therapy. The time horizon and discount rate were shown to be important drivers of the ICER in scenario analysis, highlighting the relative benefit of tisa-cel on long term outcomes as a critical component.

Axi-cel for LBCL

No existing economic evidence on axi-cel for the treatment of r/r LBCL in the Swiss healthcare context was identified. In this HTA, an ICER for axi-cel relative to historical salvage chemotherapy control of CHF88,346 per QALY gained was generated. Concern around the applicability of the historical control to contemporary Swiss practice—due to rituximab-naïve cohorts of the CORAL extension studies (source of OS estimates for the control arm) and given temporary listings of several alternative comparators for r/r DLBCL or PMBCL—is noted. The time horizon and discount rate were again shown to be important drivers of the ICER. The ICER was higher when compared to polatuzumab (in combination with rituximab and bendamustine; POLA-BR) (CHF102,220 per QALY gained).

Tisa-cel for LBCL

The existing Swiss evaluation reported a base case ICER of CHF113,179 per QALY gained for tisa-cel relative to salvage chemotherapy for the management of r/r DLBCL.[1] In this HTA, an ICER for tisa-cel relative to historical salvage chemotherapy control was generated using long-term follow-up data from the JULIET cohort[3] and a similar control group to the existing evaluation (i.e. CORAL extension cohorts). An ICER of CHF129,840 per QALY gained was estimated. Concerns around the applicability of the historical control to contemporary Swiss practice noted above also apply to this comparison. The time horizon and discount rate were again shown to be important drivers of the ICER. The ICER was higher when compared to POLA-BR (CHF157,437 per QALY gained).

Budget Impact

Base case estimates of financial impact for tisa-cel in the management of r/r B-ALL suggest treatment costs of CHF3.4 million and CHF3.8 million in 2023 and 2027, respectively (assuming 6 successfully infused patients in 2023 and 7 in 2027). Accounting for cost offsets for potential comparators, net cost of CHF2.5 million in 2023 was estimated, increasing to CHF2.7 million by 2027.

Base case estimates of financial impact for CAR T-cell therapy in patients with r/r DLBCL or PMBCL are presented at the population level. These estimates suggest treatment costs of CHF37.3 million and CHF60.9 million in 2023 and 2027, respectively (assuming 77 successfully infused patients in

2023 [49 axi-cel; 28 tisa-cel] and 125 in 2027 [80 axi-cel; 45 tisa-cel]). Accounting for cost offsets for potential comparators, net cost of CHF30.0 million isn 2023 was estimated, increasing to CHF49.0 million by 2027.

Ethical, legal, social and organisational issues

Overall, 5 publications addressed organisational issues and 2 addressed ethical issues. Key ethical issues include wait times, issues with patient referrals, and acquiring confirmation of cost coverage prior to treatment. Four key organisational considerations were identified: managing patients' health status between leukapheresis and CAR T-cell therapy infusion; identification, management and treatment of toxicities; ensuring comprehensive education of medical practitioners around CAR T products and processes; the relatively lesser hospital resource use of CAR T (excluding manufacturing) compared to adult stem cell transplant in some settings.

Conclusions

Limited, very low certainty comparative evidence was available to evaluate the relative effectiveness and safety of tisa-cel compared to standard care for the treatment of B-ALL and LBCL. Limited, moderate to very low certainty evidence reported favourable outcomes for axi-cel compared to salvage chemotherapy or no axi-cel, respectively, for effectiveness outcomes; safety data was not reported. Overall, the majority of evidence was single-arm in nature, which is unable to inform research questions regarding relative safety and effectiveness. Given the lack of ongoing comparative studies, the prospect of better evidence in the future is unlikely.

Due to limited comparative evidence comparing CAR T-cell therapies to alternative therapy options, naïve comparisons were relied upon to estimate the incremental benefit of axi-cel and tisa-cel in the economic evaluation, introducing high levels of uncertainty into the results. These comparisons suggest ICERs of approximately CHF70,000 for tisa-cel for r/r B-ALL relative to blinatumomab, and of CHF88,000 for axi-cel in r/r LBCL and CHF130,000 for tisa-cel in r/r DLBCL relative to historical salvage chemotherapy control. It is possible that base case ICERs (LBCL populations) are biased in favour of CAR T-cell therapy due to the reliance on historical control.

In summary, there are important limitations underpinning the ICERs, including limited comparative safety and efficacy evidence, applicability of the comparator evidence to contemporary practice, and uncertainty in the extrapolation of survival outcomes.

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Abbreviations and acronyms

6-MP	mercaptopurine
AE	Adverse event
AIC	Akaike's information criterion
ALL	acute lymphoblastic leukaemia
Auto-SCT	Autologous stem cell transplantation
axi-cel	Axicabtagene ciloleucel
B-ALL	B-cell acute lymphoblastic leukaemia
BIA	budget impact analysis
BIC	Bayesian information criterion
CAD	Canadian Dollar
CADTH	Canadian Agency for Drugs and Technologies in Health
CAR	chimeric antigen receptor
CEAC	cost-effectiveness acceptability curves
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHF	Swiss Franc
CI	confidence interval
CNS	central nervous system
CRR	complete response rate
CRS	cytokine release syndrome
CT	computed tomography
CUA	cost-utility analysis
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
DRG	diagnosis-related group
DSA	deterministic sensitivity analysis
EBMT	European Society for Blood and Marrow Transplantation
EFS	event-free survival
EHA	European Haematology Association
EQ-5D	EuroQol 5-dimension questionnaire
EUR	Euro
FACT-Lym/G	Functional Assessment of Cancer Therapy–Lymphoma/General
FDA	Food and Drug Administration
FOPH	Federal Office of Public Health
GBP	British Pound

GRADE	Grading of Recommendations, Assessment, Development, Evaluations
HGBCL	high-grade B-cell lymphoma
HR	hazard ratio
HRQoL	health-related quality of life
HSUV	health state utility values
HTA	health technology assessment
ICANS	immune effector cell-associated neurotoxicity syndrome
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IgG	immunoglobulin
IHE	Institute of Health Economics
INESSS	Institut National d'Excellence en Santé et en Services Sociaux
IPD	individual patient data
IT	intrathecal
ITT	intention-to-treat
IV	intravenous
IVIG	intravenous immunoglobulin
kg	kilogram
KLV	Krankenpflege-Leistungsverordnung/Health Insurance Benefits Ordinance
KM	Kaplan Meier
LBCL	large B-cell lymphoma
LY	life years
MCID	minimum clinically important difference
MCM	mixture cure models
MRD	measurable residual disease
MRI	magnetic resonance imaging
MTX	methotrexate
NHL	non-Hodgkin lymphoma
NICE	National Institute for Health and Care Excellence
NRSI	non-randomised studies of interventions
ORR	overall response rate
OS	overall survival
PedsQL	paediatric quality of life inventory
PET	positron emission tomography
PFS	progression-free survival
Ph+/-	Philadelphia chromosome positive/negative

PICO	population, intervention, comparator, outcome
PMBCL	primary mediastinal large B-cell lymphoma
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PSM	partitioned survival model
QALY	quality-adjusted life years
QoL	quality of life
r/r	relapse or refractory
RCT	randomised controlled trial
RNA	ribonucleic acid
RoB	risk of bias
ROBINS-I	Risk of Bias in Non-randomised Studies – of Interventions
RR	risk ratio
SAEs	serious adverse events
SBST	Swiss Blood Stem Cell Transplant
SC	subcutaneous
SCT	Stem cell transplantation
SCT	stem cell transplantation
SD	standard deviation
SF-36	short form 36-item health survey
SMR	standard mortality rate
SoC	standard of care
TC/HRBCL	T-cell/histiocyte-rich B-cell lymphoma
TFI	treatment-free interval
tFL	transformed follicular lymphoma
tisa-cel	tisagenlecleucel
TLS	tumour lysis syndrome
tMZL	transformed marginal zone lymphoma
TRAE/TEAE	treatment-related/-emergent adverse event
UK	United Kingdom
US/USA	United States/United States of America
WHO	World Health Organization
WTP	willingness-to-pay

Objective of the HTA report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology, their execution and the results are described. The analytical process is comparative, systematic and transparent, and involves multiple stakeholders. The domains covered in an HTA report include clinical effectiveness and safety; costs, cost-effectiveness and budget impact; and ethical, legal, social and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1 Policy question and context

The chimeric antigen receptor (CAR) T-cell therapies tisagenlecleucel (tisa-cel; Kymriah®) and axicabtagene ciloleucel (axi-cel; Yescarta®) are provisionally listed in Appendix 1 of the Health Insurance Benefits Ordinance and reimbursed by mandatory health insurance until 31 December 2024.[4] The therapies are reimbursed as third-line therapies for patients with refractory or relapsed (r/r) B-cell acute lymphoblastic leukaemia (B-ALL) (Kymriah®), patients with r/r diffuse large B-cell lymphoma (DLBCL) (Kymriah® and Yescarta®) and patients with primary mediastinal B-cell lymphoma (PMBCL) (Yescarta®). To inform future reimbursement decision for these CAR T-cell therapies, the contemporary available evidence is to be re-evaluated.

This HTA report has been produced to evaluate the available evidence regarding the efficacy, effectiveness and safety of tisa-cel and axi-cel compared to standard care. This HTA report also evaluate the costs, cost-effectiveness and budget impact of these CAR T-cell therapies, and explores ethical, legal, social and organisational issues associated with their use.

2 Research question

This HTA report addresses the following research question:

Are the CAR T-cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) clinically effective, safe and cost-effective compared to the current standard of care for the treatment of B-cell acute lymphoblastic leukaemia, diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma?

3 Medical background

3.1 Medical context, disease description and main symptoms

Leukaemia and lymphoma are blood cancers characterised by the abnormal proliferation of cells derived from multipotent haematopoietic stem cells. They can be broadly classified based on the type of affected cells (i.e. precursor or mature cells) and the site in the body that is affected.[5] Those originating in blood-forming tissue such as bone marrow are referred to as leukaemias,[6] while those originating in the lymphatic system are referred to as lymphomas.[5,7] Subtypes of leukaemia and lymphoma can be further differentiated based on morphology, immunophenotype, and cytogenic or molecular analysis.[8,9] As noted in ***Section 1***, there are 3 indications of interest to this project: B-ALL, DLBCL and PMBCL.

3.1.1 B-ALL

B-ALL is a malignancy of precursor B-cells (i.e. lymphoblasts), predominantly originating in the bone marrow. It is defined as an acute disorder due to its rapid progression and the generation of immature cells rather than mature cells.[8] Despite its acute characteristics, B-ALL in children and adults younger than age 25 has a favourable prognosis with current treatments, with projected 5-year survival rates ranging from 80–95% depending on clinical and cytogenic/genetic features.[10]

The symptoms associated with B-ALL arise due to the increasing insufficiency of normal blood cell production, as well as the infiltration of organs with affected cells. Typical symptoms include pale skin and mucous membranes, fatigue, infection, easy bruising or bleeding, bone pain, and constitutional symptoms (e.g. fever, night sweats, weight loss).[11]

Predisposing factors in children include inherited genetic susceptibility, environmental exposure to pesticides, ionising radiation and childhood infections.[12] Predisposing factors in adults are not well understood.[8]

B-ALL is primarily diagnosed in children, with three-quarters of cases diagnosed in those <6 years of age. It occurs more frequently in males than females.[13] Annually, the overall incidence of ALL and lymphoblastic lymphoma in Europe is 1.28 per 100,000 individuals.[14] The age-specific incidence rates of ALL peak in children at 0–14 years (3.59 per 100,000). The incidence reaches a minimum between the ages of 45–54 years (0.53 per 100,000) and then increases with age thereafter (1.45 per 100,000 at 75–99 years).[14] The incidence of ALL is considerably higher in southern Europe compared to other European regions.[14]

3.1.1.1 Subtypes of B-ALL

Primary refractory B-ALL – Primary refractory B-ALL implies that treatment has failed and leukaemic bone marrow, blood or cells at another extramedullary site remain present after 4–6 weeks of induction therapy.[15] In the clinical setting, this is indicated as >1% blasts (i.e. M1 morphology) or measurable residual disease (MRD) ≥1% at the end of induction therapy (i.e. treatment with the intent of putting the disease into remission) or consolidation therapy (i.e. treatment of disease in remission with the intent of preventing relapse).[15]

Relapsed B-ALL – Relapsed B-ALL indicates that cancer has recurred after achieving complete remission. This may occur at any time post-treatment and will only be considered a relapse if it involves the same type of cancer (i.e. B-ALL).[15] The risk of relapse in this patient group is typically associated with age, immunophenotype, leukaemic blast molecular findings, white blood cell count at diagnosis, and response to initial treatment.[15] The response rate to initial treatment is considered the most important factor to predict relapse, with the interval between diagnosis and relapse defined using the following schema: (i) very early: <18 months; (ii) early: 18–36 months (or at the end of chemotherapy); (iii) late: ≥3 years (or after completion of therapy).[15]

3.1.2 DLBCL

DLBCL is a malignancy of mature B-cells originating in the lymphatic system.[9] It is the most common subtype of non-Hodgkin lymphoma (NHL) in adults (i.e. cancer originating in the lymphatic system), accounting for approximately 25% of NHL cases worldwide.[16] DLBCL is an aggressive disease; however, up to 60% of patients can achieve complete remission after first-line therapies.[17] The majority of DLBCL cases—approximately 80%—are defined as 'not otherwise specified' according to the current World Health Organization (WHO) classification of lymphomas and, as such, typically lack defining characteristics and symptoms.[5]

The symptoms associated with DLBCL depend on the sites affected by malignancy. Patients with DLBCL may present with a rapidly growing mass in lymph node sites, commonly the neck, groin or abdomen; however, extra-nodal involvement in other organs is common.[18] In addition to a solid mass, systemic B symptoms (e.g. fever, weight loss, night sweats) are experienced by up to 30% of patients.[19]

Predisposing risk factors for DLBCL include family history of lymphoma, autoimmune disease, human immunodeficiency virus infection, hepatitis C virus seropositivity, high body mass index as a young adult, and occupational exposure to pesticides, fertilizers and alkylating agents.[20,21]

DLBCL is more commonly diagnosed in males (55%) than females, with a median age of diagnosis of 64 years and the incidence steadily increasing with age.[16,22] In Europe, the crude incidence of DLBCL is 3.8 per 100,000 individuals per year.[14] The incidence of DLBCL is significantly lower in eastern (1.79

per 100,000) and northern (0.79 per 100,000) Europe compared to other European regions.[14] According to the EUROCARE-5[23] population-based study conducted across Europe, the age-standardised 5-year relative survival of DLBCL has increased from 42.0% (1997–1999) to 55.4% (2006–2008).[23]

3.1.3 PMBCL

PMBCL is an aggressive, rare subtype of NHL, representing 2–3% of NHL diagnoses.[24] It originates in the anterior superior mediastinum (i.e. the space between the lungs) and, as such, commonly causes cough and airway disruptions, as well as superior vena cava syndrome with corresponding hoarseness, dyspnoea and upper extremity swelling.[25]

The prognosis of PMBCL after first-line therapies is favourable, with a 5-year estimated survival rate of approximately 70–85%.[24] However, the prognosis of patients with refractory disease that does not respond to salvage chemotherapy is poor.[26]

PMBCL is most commonly diagnosed in Caucasian females between the ages of 30–39.[24] To date, only a single population-based study conducted in the United States of America (USA) has estimated the incidence of PMBCL, reporting an annual incidence of 0.4 per million in a United States (US) population.

4 Technology

4.1 Technology description

CAR T-cell therapies use genetically modified, autologous T cells to target and destroy cancer cells.[27] The therapy involves expressing engineered receptors, known as CARs, in a patient's immune cells (i.e. T-cells), to target cancer cells.[28] Two CAR T-cell therapies that are provisionally reimbursed in Switzerland are the focus of this evaluation: tisa-cel (Kymriah®) and axi-cel (Yescarta®).

4.2 Production and administration of CAR T-cell therapies

The process of producing CAR T-cell therapies is presented in ***Figure 1***. The first step is leukapheresis, which involves harvesting the patient's T cells from peripheral blood.[29] In current CAR T-cell therapies, harvested T cells are sent to a specialist/certified laboratory to be genetically modified to express a CAR specific to CD19 B lymphocytes (i.e. cancerous cells).[27] This is accomplished using either viral or non-viral methods.[28] Transduction involves the use of viral vectors to deliver ribonucleic acid (RNA) into the patient's T cells. The RNA is subsequently reverse transcribed and integrated into the T cells' deoxyribonucleic acid (DNA), facilitating receptor expression. Other methods to insert RNA/DNA include chemical transfection, electroporation and the use of nanoparticles.[28,30] After selection of modified cells, the cells are cultured (i.e. grown in expanded numbers) until enough are available for clinical use.[28]

Patients typically receive bridging chemotherapy and/or radiotherapy while the CAR T-cells are being manufactured, in order to slow disease progression in the time between apheresis and CAR T-cell infusion.[31] Prior to infusion with the CAR T-cells, patients typically receive lymphodepleting chemotherapy with fludarabine, cytarabine, cyclophosphamide or bendamustine in different combinations depending on the indication.[32-35] To reduce potential reactions to the CAR T infusion, it is recommended that patients are pre-medicated with paracetamol and/or antihistamines 30–60 minutes prior to infusion.[36,37] Patients receive the CAR T-cells as a one-off IV infusion and are then monitored for adverse events (AEs) in hospital. The dose of CAR T-cells administered depends on the diagnosis (i.e. ALL, DLBCL, PMBCL), patient body weight and the type of therapy (i.e. axi-cel or tisa-cel).[36,37]

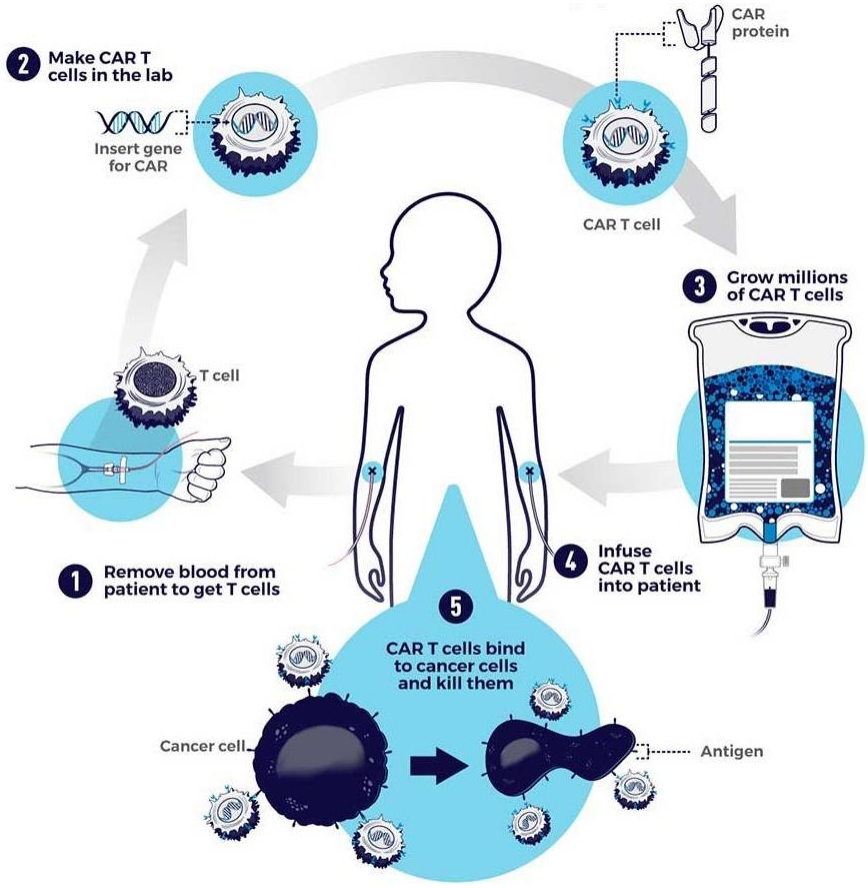


Figure 1 T-cell harvest and CAR T-cell infusion process

Source: National Cancer Institute[38]

4.3 Adverse events

CAR T-cell therapies are associated with a range of potential AEs that vary in severity from mild to life-threatening. One of the most common side effects is cytokine release-syndrome (CRS), which causes acute to subacute fever, flu-like symptoms, hypotension (i.e. low blood pressure) and hypoxia (i.e. reduced blood oxygen concentration). Severe cases of CRS can be life threatening, requiring urgent medical attention.[32-34,39] Another potentially severe side effect is immune effector cell-associated neurotoxicity syndrome (ICANS), which causes neurological symptoms such as cognitive deficits, aphasia (i.e. difficulty communicating and comprehending language) and seizures. In rare cases, it can lead to progressive therapy-refractory fatal cerebral oedema (i.e. brain swelling).[40] Longer-term side effects of CAR T-cell therapies can include cytopenia (i.e. reduced blood cell count) and hypogammaglobulinaemia (i.e. reduced serum immunoglobulin).[40] Other common AEs include, but are not limited to, infections and B-cell aplasia (i.e. reduced B-cell count).[39] Owing to the AEs associated with CAR T-cell therapies, Onkopedia clinical practice guidelines (non-binding) recommend that treatment be reserved for highly specialised centres with extensive experience in managing cellular immunotherapies, including direct access to an intensive care unit (ICU).[39]

4.4 Contraindications

Contraindications to tisa-cel or axi-cel include known hypersensitivity to tisa-cel or axi-cel, or any of their excipients.[32-35]

4.5 Alternative technologies

4.5.1 B-ALL

4.5.1.1 Chemotherapy

Chemotherapy is the cornerstone of treatment for ALL patients. The treatment regimen will typically depend on the phase of treatment and the protocol being followed. Each of the 3 treatment phases—remission induction, consolidation/intensification and maintenance/continuation—call for differing agents to be administered.

Remission induction therapy includes the following agents:

- **Glucocorticoids** – The type, dose and schedule of glucocorticoid (e.g. prednisone, dexamethasone or hydrocortisone) will differ depending on patient age, risk category and chosen protocol.[41] The addition of prophylactic antibiotics (e.g. levofloxacin) may be used to mitigate glucocorticoid-associated AEs.[41]

- **Vincristine** – Vincristine is a vinca alkaloid that acts to prevent mitosis, thereby blocking cancer cell growth.[41] Weekly vincristine is administered during induction therapy via intravenous (IV) injection.[15] The dose is typically capped at 2 mg to reduce the incidence and severity of peripheral neuropathy.[41]
- **Asparaginase** – Asparaginase is frequently used in the treatment of children with ALL, leading to superior outcomes;[41] however, asparaginase has a relatively high risk for AEs, including allergic reaction (i.e. anaphylaxis), coagulopathies (i.e. thrombosis), acute pancreatitis and hepatic toxicities.[41] It is recommended that administration be performed in a setting where such reactions can be managed.[41]
- **Anthracycline** – Weekly administration of an anthracycline (e.g. doxorubicin, epirubicin, idarubicin or liposomal doxorubicin) is typically included in most ALL treatment protocols.[41]

Consolidation/intensification therapy includes the following agents:

- **Cyclophosphamide** – Cyclophosphamide is a nitrogen mustard drug that has an anti-neoplastic effect produced through alkylation.[42] It is given as an IV infusion of 40–50 mg/kg as divided doses across 2–5 days in those with haematologic deficiency, or at 10–15 mg/kg every 7–10 days or 3–5 mg/kg twice weekly.[43]
- **Cytarabine** – Cytarabine (cytosine arabinoside) is an antimetabolic agent that blocks the function of DNA polymerase. It is administered via IV infusion or subcutaneous (SC) injection and dosage may vary.[43]
- **Vincristine** – as above.
- **Asparaginase** – as above.
- **Mercaptopurine** – Mercaptopurine (6-MP) is a purine antagonist that inhibits the phosphoribosyl pyrophosphate amidotransferase enzyme, altering the synthesis and function of DNA and RNA.[44] It is administered once daily as an oral tablet at a dose of 1.5–2.5 mg/kg.[45]
- **IT methotrexate or triple IT therapy** – Intrathecal (IT) methotrexate (MTX) inhibits enzymes that allow nucleotide synthesis (e.g. dihydrofolate reductase, thymidylate synthase).[46] When administered intrathecally (i.e. injected into the spinal canal) it prevents leukaemia from entering the central nervous system via cerebral spinal fluid.[43] Triple IT therapy combines IT MTX, cytarabine and hydrocortisone.[15] Dosage varies depending on age and weight.[47]

Maintenance therapy includes the following agents:

- **6-MP** – As above, administered daily.
- **IT MTX and MTX** – As above. During the maintenance phase, MTX may be administered orally once per week at varying doses; however, it is recommended for patients also to receive IT MTX periodically, as recommended by the treating physician.[43]

- **Vincristine–glucocorticoid pulses** – As above, administered simultaneously via pulse therapy.[41] Pulse therapy dosing allows for continuation of a drug for disease control, given at a high concentration followed by a prolonged dose-free period.[48] Intervals are as recommended by a specific protocol or the treating physician.

4.5.1.2 Allogeneic SCT

Allogenic stem cell transplantation (SCT) is considered to be the only cure for r/r B-ALL.[15] In the treatment pathway, allogenic SCT is used as consolidation therapy in selected patients after their first complete remission.[15] Patients who may be considered for allogenic SCT include those with MRD at end-of-consolidation or induction failure.[15] Patient selection, timing of transplantation and additional features of allogenic SCT are highly individualistic and will differ between institutions.[15] In children and young adults with B-ALL, the preferred graft choice is a human leukocyte antigen (HLA)-matched sibling donor, although a matched unrelated donor may also be used when a sibling donor is unavailable.[15] A partially matched family member or umbilical cord blood may also be considered when an HLA -matched donor is unavailable.[15]

4.5.1.3 Immunotherapy

In children and young adults, immunotherapy may be considered in the setting of r/r B-ALL; it is typically not considered in first-line therapy.[15] Immunotherapy aims to use the patient's immune system to fight cancer, by activating or suppressing substances naturally made by the body or made in a laboratory to target affected cells.[49] The following treatments may be utilised in B-ALL:[41]

- **Blinatumomab** – a bispecific T-cell engager that directs CD3+ effector memory T cells to CD19+ cancer cells.
- **Inotuzamab ozogamicin** – a human monoclonal antibody drug conjugate directed against CD22.

4.5.2 DLBCL

The standard treatment for DLBCL is chemoimmunotherapy utilising R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone)[50] First-line therapy typically consists of 6 cycles of R-CHOP, although this can vary according to clinical presentation.[51] R-CHOP includes the following agents:

- **Rituximab** – an anti-CD20 monoclonal antibody used in the management of lymphoproliferative conditions.[52] Rituximab is administered by IV infusion. Patients should be given acetaminophen and antihistamine before each infusion. Rituximab should be diluted in an infusion bag of either 0.9% sodium chloride or 5% dextrose in water.[52]

- **Cyclophosphamide** – a nitrogen mustard drug that has an anti-neoplastic effect produced through alkylation.[42] As part of the R-CHOP regimen, 750 mg/m^2 of IV cyclophosphamide is administered on day 1 every 3 weeks for 6 cycles.[42]
- **Doxorubicin** – an antibiotic able to intercalate within DNA base pairs, leading to breakage of DNA strands and inhibition of nucleic acid synthesis. Doxorubicin is an IV administration commonly given in 21-day intervals.[53]
- **Vincristine** – a vinca alkaloid that prevents mitosis, blocking cancer cell growth.[41] Weekly vincristine is administered during induction therapy via IV injection.[15] The dose is typically capped at 2 mg to reduce the incidence and severity of peripheral neuropathy.[41]
- **Prednisone** – a synthetic, anti-inflammatory glucocorticoid derived from cortisone. Prednisone decreases inflammation via suppression of the migration of polymorphonuclear leukocytes and reversing increased capillary permeability, and suppresses the immune system.[54] It may be administered orally with food.

Refractory or relapsed DLBCL

Salvage chemotherapy followed by high-dose therapy with autologous SCT is an alternative option for transplant-eligible patients who have chemotherapy-sensitive disease.[50] As induction therapy, patients receive 3 cycles of either R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) or R-ICE (rituximab, ifosfamide, carboplatin, etoposide).[51] The BEAM protocol (carmustine, etoposide, cytarabine, melphalan) is then used as high-dose therapy prior to autologous SCT.[51] For patients who cannot receive high-dose therapy or are ineligible for SCT, palliation is offered.[51]

4.5.3 PMBCL

There is no clear evidence and a lack of published randomised trials to establish a standard therapeutic approach for PMBCL, resulting in no international consensus on an optimal initial chemotherapy regimen.[55] Clinical management decisions are primarily based on extrapolated data from retrospective series or subgroup analyses of trials originally designed for DLBCL (conducted in adult patients) or Burkitt lymphoma (conducted in paediatric patients).[56] Therefore, patients with PMBCL are often treated with the same protocols as those with DLBCL.[51] R-CHOP and DA-EPOCH-R (prednisolone, rituximab, doxorubicin, vincristine, etoposide, cyclophosphamide, filgrastim) are the 2 most commonly used protocols as first-line treatment for PMBCL patients.[51] In clinical studies, patients have also been treated with radiation for residual tumours following first-line therapy.[51]

Refractory or relapsed PMBCL

In r/r PMBCL patients for whom consolidation radiotherapy was not administered during earlier treatment, radiotherapy can be considered if the patient is presenting with residual localised mediastinal

disease that is fluorodeoxyglucose-avid on positron emission tomography – computed tomography (PET–CT). Also, if feasible, a biopsy should be performed to investigate whether recurrent or residual disease is present. There is a lack of evidence regarding the optimal salvage chemotherapy regimen for relapsed PMBCL. Therefore, it appears reasonable that the approach to salvage chemotherapy regimens should be similar to that used in the treatment of relapsed DLBCL.[51,55]

4.6 Regulatory status/provider

In Switzerland, CAR T-cell therapies tisa-cel (Kymriah®) and axi-cel (Yescarta®) are approved by Swissmedic.[34,35] Both Kymriah® and Yescarta® are provisionally listed in Appendix 1 of the Health Insurance Benefits Ordinance (KLV) and are reimbursed by mandatory health insurance until 31 December 2024.[4] The populations eligible for these drugs in Switzerland are outlined in ***Section 5.1.*** Approved dosages for each CAR T-cell therapy are provided in ***Section 4.2***. The coverage conditions of Kymriah® and Yescarta® according to the KLV are as follows:[4]

> *'The therapy includes the treatment complex consisting of autologous T cell collection (apheresis), their ex vivo gene modification and expansion, any lympho-depleting pre-therapies, infusion of CAR-T cells and treatment of any CAR-T-specific side effects. Implementation in the centres approved by "The Joint Accreditation Committee-ISCT & EBMT (JACIE)" for allogeneic and/or autologous stem cell transplantation in accordance with the guidelines of JACIE and the Foundation for the Accreditation of Cellular Therapy (Fact): "FACT-JACIE International Standards for hematopoietic Cellular Therapy Product Collection, Processing and Administration," 6th ed. Dated March 2015, 6.1. ed. Dated February 2017, 7th ed. Dated March 2018, or 8th ed. Dated May 2021. All cases must be recorded in a registry. If therapy is to be provided at a centre that is not recognized in accordance with the above-mentioned requirements, special approval of the insurer must be sought, who will take into account the recommendation of the medical examiner.'*[4]

Reimbursement in other European countries for Kymriah® and Yescarta® is outlined in ***Table 1*** and ***Table 2***.

Table 1 Reimbursement of tisa-cel (Kymriah®) in European countries other than Switzerland

Country	Regulatory status	Reimbursement	Population	Treatment line
France[57,58]	Approved	Reimbursed	DLBCL	Third-line or later therapy
			B-ALL	First-line therapy or later depending on indication
Germany[59]	Approved	Reimbursed	B-ALL	Same indication as current HTA
			DLBCL	Third-line therapy

Country	Regulatory status	Reimbursement	Population	Treatment line
Spain[60]	Approved	Reimbursed	B-ALL	Same indication as current HTA
			DLBCL	Third-line therapy
Denmark[61]	Approved	Not reimbursed	DLBCL ‡	NA
		Reimbursed	B-ALL	Same indication as current HTA
Italy[62]	Approved	Reimbursed	B-ALL	Same indication as current HTA
			DLBCL	Third-line therapy
UK[63]	Approved	Reimbursed	B-ALL	Same indication as current HTA
Austria[64]	Approved	Reimbursed	B-ALL	Same indication as current HTA
			DLBCL	Third-line therapy

Abbreviations:
ALL = acute lymphoblastic lymphoma, **DLBCL** = diffuse large B-cell lymphoma, **NA** = not applicable, **NR** = not reported, **UK** = United Kingdom.
Notes:
‡ On 2 April 2023, the Presidency decided to reassess the recommendation regarding Kymriah for relapsed refractory DLBCL, 3rd line.

Table 2 Reimbursement of axi-cel (Yescarta®) in European countries other than Switzerland

Country*	Regulatory status	Reimbursement	Population	Treatment line
France[65]	Approved	Reimbursed	DLBCL	Third-line therapy
Germany[66]	Approved	Reimbursed	DLBCL	Third-line therapy
			PMBCL	Third-line therapy
Spain[67]	Approved	Reimbursed	DLBCL	Second-line therapy§
			PMBCL	Third-line therapy
Scotland[68]	Approved		DLBCL	Third-line therapy
Denmark[69]	Approved	Not reimbursed	DLBCL‡	NA
Italy[62]	Approved	Reimbursed†	DLBCL	Third-line therapy
			PMBCL	Third-line therapy
UK[70]	Approved	Reimbursed	DLBCL	Third-line therapy
			PMBCL	Third-line therapy
Austria[71]	Approved	Reimbursed	DLBCL	Third-line therapy
			PMBCL	Third-line therapy

Abbreviations:
DLBCL = diffuse large B-cell lymphoma, **NA** = not applicable, **NR** = not reported, **PMBCL** = primary mediastinal B-cell lymphoma, **UK** = United Kingdom.
Notes:
* Countries were chosen at random based on published and retrievable data via targeted searches.
† As of May 2023 this innovative technology has been archived.
‡ As of April 2023 the Presidency decided to reassess the recommendation regarding Yescarta for relapsed refractory DLBCL, 3rd line.
§ Used in the second-line if refractory to first-line immunotherapy, whereas third-line after 2 or more lines of systemic therapy.

5 Population, Intervention, Comparator, Outcome (PICO)

The PICO and study selection criteria for the 3 eligible populations for this HTA are outlined in ***Table 3***, ***Table 4*** and ***Table 5*** and described in ***Sections 5.1*** to ***5.4***.

Table 3 PICO and study selection criteria, population 1

Population	Children and young adults (up to age 25) with refractory B-ALL, or have relapsed B-ALL after stem cell transplantation, or have relapsed B-ALL after 2 or more lines of therapy
Intervention(s)	Tisagenlecleucel (Kymriah®) therapy (i.e. the entire treatment complex of CAR T-cell therapy) *Excluded: stem cell therapy following CAR T-cell therapy*
Comparator	Standard care *Excluded: stem cell therapy following standard care*
Outcome(s)	Overall survival Progression-free survival Complete response rate Overall response rate Treatment-free interval Health-related quality of life [a] Treatment discontinuation [b] Adverse events [c]
Economic outcome(s)	Costs, utilities, Lys, QALYs, cost-effectiveness/cost-utility, ICER, budget impact
Study design	Systematic reviews or HTA reports with or without meta-analyses of primary randomised controlled trials and/or non-randomised studies of interventions. In the absence of existing reviews, primary comparative study designs will be included. In the absence of comparative study designs, single-arm studies relating to the intervention will be included. For the economic literature review, only full economic evaluations will be included.
Limits	Publication date from 1 January 2010 No language limitations applied Sample size at least 10 patients in each treatment arm
Publication type	Peer-reviewed publications with full description of methods and results *Excluded: narrative reviews, letters to the editor, conference abstracts, opinion articles.*

Abbreviations:
B-ALL = B-cell acute lymphocytic leukaemia, **CAR T-cell** = chimeric antigen receptor T-cell, **HTA** = health technology assessment, **ICER** = incremental cost-effectiveness ratio, **LY** = life year, **QALY** = quality-adjusted life year.
Notes:
[a] using any reliable and valid instrument.
[b] defined as production failure, patient died waiting for infusion, patient decided against infusion during pre-infusion therapies.
[c] including cytokine release syndrome, B-cell aplasia, cytopenia, hypogammaglobulinaemia, infection etc.

Table 4 PICO and study selection criteria, population 2

Population	Adults with refractory or relapsed DLBCL (according to WHO classification of haematopoietic and lymphatic neoplasms, 2008) after at least 2 lines of therapy
Intervention(s)*	Tisagenlecleucel (Kymriah®) therapy (i.e. the entire treatment complex of CAR T-cell therapy) Axicabtagene ciloleucel (Yescarta®) therapy (i.e. the entire treatment complex of CAR T-cell therapy) *Excluded: stem cell therapy following CAR T-cell therapy*
Comparator	Standard care *Excluded: stem cell therapy following standard care*
Outcome(s)	Overall survival Progression-free survival Complete response rate Overall response rate Treatment-free interval Health-related quality of life [a] Treatment discontinuation [b] Adverse events [c]
Economic outcome(s)	Costs, utilities, Lys, QALYs, cost-effectiveness/cost-utility, ICER, budget impact
Study design	Systematic reviews or HTA reports with or without meta-analyses of primary randomised controlled trials and/or non-randomised studies of interventions. In the absence of existing reviews, primary comparative study designs will be included. In the absence of comparative study designs, single-arm studies relating to the intervention(s) will be included. For the economic literature review, only full economic evaluations will be included.
Limits	Publication date from 1 January 2010 No language limitations applied Sample size at least 10 patients in each treatment arm
Publication type	Peer-reviewed publications with full description of methods and results *Excluded: narrative reviews, letters to the editor, conference abstracts, opinion articles.*

Abbreviations:
DLBCL = diffuse large B-cell lymphoma, **CAR T-cell** = chimeric antigen receptor T-cell, **HTA** = health technology assessment, **ICER** = incremental cost-effectiveness ratio, **LY** = life year, **QALY** = quality-adjusted life year.
Notes:
* The analysis will evaluate tisagenlecleucel (tisa-cel) and axicabtagene ciloleucel (axi-cel) compared to placebo separately; tisa-cel and axi-cel will not be compared directly or indirectly.
[a] using any reliable and valid instrument.
[b] defined as production failure, patient died waiting for infusion, patient decided against infusion during pre-infusion therapies.
[c] including cytokine release syndrome, B-cell aplasia, cytopenia, hypogammaglobulinaemia, infection etc.

Table 5 PICO and study selection criteria, population 3

Population	Adults with refractory or relapsed PMBCL after at least 2 lines of therapy
Intervention(s)	Axicabtagene ciloleucel (Yescarta®) therapy (i.e. the entire treatment complex of CAR T-cell therapy) *Excluded: stem cell therapy following CAR T-cell therapy*
Comparator	Standard care *Excluded: stem cell therapy following standard care*
Outcome(s)	Overall survival Progression-free survival Complete response rate Overall response rate Treatment-free interval Health-related quality of life [a] Treatment discontinuation [b] Adverse events [c]
Economic outcome(s)	Costs, utilities, Lys, QALYs, cost-effectiveness/cost-utility, ICER, budget impact
Study design	Systematic reviews or HTA reports with or without meta-analyses of primary randomised controlled trials and/or non-randomised studies of interventions. In the absence of existing reviews, primary comparative study designs will be included. In the absence of comparative study designs, single-arm studies relating to the intervention will be included. For the economic literature review, only full economic evaluations will be included.
Limits	Publication date from 1 January 2010 No language limitations applied Sample size at least 10 patients in each treatment arm
Publication type	Peer-reviewed publications with full description of methods and results *Excluded: narrative reviews, letters to the editor, conference abstracts, opinion articles.*

Abbreviations:
CAR T-cell = chimeric antigen receptor T-cell, **HTA** = health technology assessment, **ICER** = incremental cost-effectiveness ratio, **LY** = life year, **PMBCL** = primary mediastinal B-cell lymphoma, **QALY** = quality-adjusted life year.
Notes:
[a] using any reliable and valid instrument.
[b] defined as production failure, patient died waiting for infusion, patient decided against infusion during pre-infusion therapies.
[c] including cytokine release syndrome, B-cell aplasia, cytopenia, hypogammaglobulinaemia, infection etc.

5.1 Population(s)

The 3 eligible populations for this HTA are defined per Appendix 1 of the Health Insurance Benefits Ordinance in Switzerland:[4]

- Children and young adults (up to age 25) with refractory B-ALL, or have relapsed B-ALL after SCT, or have 2 or more lines of therapy (indicated for tisa-cel)
- adults with refractory or relapsed DLBCL (according to WHO classification of haematopoietic and lymphatic neoplasms, 2008) after at least 2 lines of therapy (indicated for tisa-cel or axi-cel)
- adults with refractory or relapsed PMBCL after at least 2 lines of therapy (indicated for axi-cel).

Due to the overlapping nature of the populations in the included studies, evidence for the DLBCL and PMBCL populations have been combined into a single group representing large B-cell lymphoma (LBCL) more broadly. These studies primarily include DLBCL patients, but may also include patients with PMBCL, transformed follicular lymphoma (tFL), T-cell/histiocyte-rich B-cell lymphoma (TC/HRBCL) and/or high-grade B-cell lymphoma (HGBCL).

5.2 Intervention(s)

The eligible interventions for this HTA are limited to 2 of the CAR T-cell therapies provisionally reimbursed in Switzerland: tisa-cel (Kymriah®) and axi-cel (Yescarta®).[4] The evaluation of these therapies considers the entire treatment complex as a whole, that is, inclusive of leukapheresis up to infusion and post-infusion follow-up (see ***Section 7.2.2.2*** for follow-up timepoints). Studies that included systematic follow-up of all patients with SCT following CAR T were excluded as this is patient-specific and not part of a routine CAR T-cell treatment cycle.[72,73]

5.3 Comparator(s)

The population of interest for this HTA specifically requires patients to have r/r disease after at least 2 lines of therapy. In such cases, the treatment options are more limited compared to patients with ALL, DLBCL or PMBCL being treated with first-line therapies. The comparator has been broadly defined as ‘standard care’, the definition of which varies depending on the patient population.

For B-ALL, the choice of comparator depends on the nature of the relapse (greater bone marrow relapse, any bone marrow relapse following SCT, primary treatment refractory etc.), the subtype of the cancer (i.e. Philadelphia chromosome positive or negative [Ph+/Ph-]), prior therapies, comorbidities, and suitability for allogenic SCT.[8,11] Depending on the clinical characteristics of the patients, standard care may include immunotherapy with blinatumomab or inotuzumab, or chemotherapy with a regimen such

as FLAG-IDA (fludarabine, high-dose ara-C, granulocyte colony-stimulating factor and idarubicin) or tyrosine kinase inhibitors (for Ph+ patients).[8,11]

For patients with r/r DLBCL, standard care includes salvage chemotherapy (R-DHAP, R-ICE, R-GEMOX [rituximab, gemcitabine, oxaliplatin] or R-GDP [rituximab, gemcitabine, dexamethasone and cisplatin]) and/or high-dose therapy (BEAM) and autologous SCT.[51,74] Alternatively, patients may receive allogenic SCT, or palliative care to relieve suffering (i.e. care aimed at improving quality of life/relieving suffering of patients and their families).[51,74,75] Patients ineligible for SCT due to age or comorbidity may be treated with R-GEMOX, more intensive regimens (e.g. R-DHAP or R-ICE), or more recently, polatuzumab in combination with rituximab and bendamustine (POLA-BR) or tafasitamab in combination with lenalidomide.[9,51]

For r/r PMBCL, salvage treatments are similar to those for DLBCL and include immunotherapy (pembrolizumab, nivolumab etc.), attempted reinduction with non-cross-resistant agents followed by consolidation with high-dose chemotherapy, and autologous SCT in patients with chemosensitive disease.[76-78]

Both polatuzumab and tafasitamab have temporary listings on the Specialty List for the treatment of r/r DLBCL in patients ineligible for autologous SCT, while pembrolizumab is temporarily listed for treatment of r/r PMBCL after at least 2 lines of therapy.

Additional information regarding relevant comparators to the Swiss context was sought from clinical experts during this HTA. Results of this expert engagement are presented in ***Section 8.2.5***. Important complexities in the treatment pathways for r/r B-ALL, DLBCL and PMBCL were highlighted, as identified comparators—for example, blinatumomab and inotuzumab for r/r B-ALL and polatuzumab in r/r DLBCL—may be used to bridge to CAR T-cell therapy rather than as an alternative treatment option.

5.4 Outcome(s)

The primary purpose of CAR T-cell therapies is to cure (i.e. remove and prevent recurrence of malignant tumours) and improve survival and quality of life of patients with cancer. The outcomes under investigation in this HTA have been chosen to address the intent of the treatment and will be measured at longest follow-up. The following outcomes will be investigated:

Overall survival (OS), defined as the time from randomisation (or study enrolment in the case of non-randomised studies of interventions [NRSI] and single-arm studies) or treatment administration to death of any cause.

Progression-free survival (PFS), defined as the time from randomisation (or study enrolment in the case of NRSIs and single-arm studies) or treatment administration to disease progression, relapse or death from any cause, or to last follow-up.[39,79]

Complete response rate (CRR), also known as complete remission, defined as the disappearance of all signs of cancer. (This does not indicate that the cancer has been cured.)[80,81]

Overall response rate (ORR), defined as the proportion of patients that have a CRR or partial response (PR) to cancer therapy.[81]

Treatment-free interval (TFI), defined as the time from discontinuation of cancer treatment to the start of subsequent treatment (to be considered TFI the cancer progression has to occur after treatment discontinuation.)[82] TFI is used as a surrogate for a state of good health, as it assumes that the patient is clinically stable and not subject to treatment tolerability or toxicity issues.[82]

Health-related quality of life (HRQoL) and disease-specific quality of life (QoL), measured with an established instrument (e.g. Short Form 36-item health survey [SF-36],[83] EuroQol 5-dimension questionnaire [EQ-5D],[84] Paediatric Quality of Life Inventory [PedsQL],[85] Functional Assessment of Cancer Therapy–Lymphoma [FACT–Lym],[86] FACT-General [FACT-G],[87] European Organization for Research and Treatment of Cancer quality of life core questionnaire [EORTC QLQ-C30]).[88] HRQoL is a patient-reported outcome of overall health status measured via the assessment of domains that focus on physical, mental, emotional and social functioning. Other patient-reported outcome measures exist to assess the disease-specific impact of different types of cancer and therapies on QoL.

Treatment discontinuation may be a result of AEs, issues during the manufacturing of CAR T-cells (i.e. production failure, patient died waiting for infusion), or decisions made by the patient or clinician (e.g. patient decided against infusion during pre-infusion therapies).

Adverse events of interest:

Serious adverse events (SAEs), defined as *'an adverse event (AE) that results in death, is life-threatening, leads to hospitalisation (or prolonged existing hospitalisation), results in persistent or significant disability, a birth defect, or any other important medical event that may jeopardise the patient or require medical intervention to prevent any of the outcomes listed above*.'[89] AEs deemed as serious by the study investigators of each trial have been considered relevant to the analysis.

AEs, treatment-related AEs (TRAEs) and treatment-emergent AEs (TEAEs). Irrespective of severity, AEs are defined as any unanticipated medical incident in a patient that has received a treatment, which does not have to be causally related to the treatment administered.[89] AEs or TRAEs/TEAEs identified and deemed relevant by the study investigators of each trial have been

considered appropriate to the analysis. In addition to overall numbers of AEs and SAEs, rates of specific AEs of interest have also been captured in the analysis, including:

Cytokine release syndrome (CRS) is an acute systemic inflammatory syndrome, often associated with CAR T-cell therapy, and characterised by multiple organ dysfunction and fever.[90] CRS identified and deemed relevant by the study investigators of each trial was considered relevant to the analysis.

Immune effector cell-associated neurotoxicity syndrome (ICANS), also referred to as cytokine release encephalopathy syndrome, CAR T encephalopathy or neurotoxicity, is a neuropsychiatric syndrome associated with CAR T-cell therapy.[91] ICANS/neurotoxicity identified and deemed relevant by the study investigators of each trial was considered relevant to the analysis.

B-cell aplasia is characterised by an extremely low B-cell count. It is often associated with CAR T-cell therapy, occurring when anti-CD19 CAR T-cells destroy CD19-expressing B-lymphocytes.[92] **B-cell aplasia duration** is also useful to detect functional CAR persistence. B-cell aplasia event rates and duration identified and deemed relevant by the study investigators of each trial were considered relevant to the analysis.

Cytopenia, defined as the reduction of one or more mature blood cell types in the peripheral blood, is a common occurrence following CAR T-cell therapy.[93] This may include red blood cells (erythrocytes), resulting in anaemia; white blood cells (leukocytes), resulting in leukopenia; or platelets (thrombocytes), resulting in thrombocytopenia.[94] When the levels of all blood cell types are low, this is described as pancytopenia.[93] A type of leukopenia characterised by low levels of neutrophils—(febrile) neutropenia—is also of importance.[94] Cytopenia identified and deemed relevant by the study investigators of each trial was considered relevant to the analysis.

Hypogammaglobulinaemia is characterised by low serum immunoglobulin (IgG) antibody levels.[95] IgG is critical for immune system function to recognise antigens and trigger an immune response to eradicate possible sources of infection.[95] Low IgG requires treatment with intravenous immunoglobulin (IVIG) to relieve clinical symptoms.[95] Therefore, where reported by study investigators, the **usage and administration of IVIG to treat hypogammaglobulinaemia, and events rates of hypogammaglobulinaemia reported directly,** were also relevant outcomes.

Infections. Typically, clinical trials will report infection rates if they fulfill one or more of the following criteria: (1) requires anti-infective treatment, (2) leads to significant disability, hospitalisation or death, (3) need for surgical or other intervention.[96] Serious or opportunistic infections such as viral, bacterial, fungal or parasitic infections identified and deemed relevant by the study investigators of each trial were considered relevant to the analysis.[96]

Tumour lysis syndrome (TLS), is a spontaneous and rare oncological emergency characterised by a group of metabolic disorders, including hyperkalaemia, hyperphosphataemia, hypocalcaemia and hyperuricaemia, typically occurring as a result of various cancer treatments leading to end-organ damage.[97] TLS identified and deemed relevant by the study investigators of each trial were considered appropriate to the analysis.

Secondary malignancies, defined as the occurrence of a new cancer unrelated to the original malignancy, may occur as a result of cancer treatment.[98] Secondary malignancies identified and deemed relevant by the study investigators of each trial were considered appropriate to the analysis.

A **minimum clinically important difference (MCID)** is the smallest difference in a specific outcome measure that would warrant a change in patient management to produce patient-perceived improvement. Other metrics used to determine the smallest change in outcome measurement that translates to a patient feeling better, as well as changes in function, include the minimally important difference, minimally important change and minimal clinically important improvement.[99-101] MCIDs for HRQoL are detailed in ***Appendix F***.

6 HTA key questions

For the evaluation of the technology the following key questions covering central HTA domains, as designated by the EUnetHTA Core Model (clinical effectiveness, safety, costs, cost-effectiveness, budget impact, ethical, legal, social and organisational aspects), are addressed:

1. In children and young adults (up to age 25) with r/r B-ALL after SCT or 2 or more lines of therapy, is tisa-cel safe and efficacious/effective compared to standard care?
2. In adults with r/r DLBCL after at least 2 lines of therapy, are tisa-cel and axi-cel safe and efficacious/effective compared to standard care?
3. In adults with r/r PMBCL after at least 2 lines of therapy, is axi-cel safe and efficacious/effective compared to standard care?
4. In children and young adults (up to age 25) with r/r B-ALL after SCT or 2 or more lines of therapy, is tisa-cel cost-effective compared to standard care?
5. In adult patients with r/r DLBCL after at least 2 lines of therapy, are axi-cel and tisa-cel cost-effective compared to standard care?
6. In adult patients with r/r PMBCL after at least 2 lines of therapy, is axi-cel cost-effective compared to standard care?
7. What is the potential budget impact of continued funding of CAR T-cell therapies for the currently reimbursed populations?
8. Are there ethical, legal, social or organisational issues related to tisa-cel or axi-cel use in Switzerland?

7 Effectiveness, efficacy and safety

Summary statement effectiveness, efficacy and safety

It was not feasible to evaluate DLBCL and PMBCL populations separately, therefore studies that included either population were aggregated into a broader LBCL population. For all outcomes reported in single-arm studies, the certainty of evidence was very low, meaning that the true effects are probably different from the estimated effects. The certainty of evidence for NRSIs is noted below. Relative effects were calculated as comparator/CAR T (except where noted).

One NRSI and 7 single-arm studies investigated **tisa-cel in the B-ALL** population. The reported hazard ratio (HR) for OS comparing conventional chemotherapy to tisa-cel at 150 days in patients admitted to intensive care (n=205) reported no evidence of a statistically significant difference (HR 0.89, 95% CI: 0.38 to 2.11; very low certainty evidence). Results from single-arm studies are summarised in the following table:

Outcome (duration)	Result	Participants (studies)
OS (20 months)	69% (95% CI: 63 to 75; n=76 at risk)	459 (6 observational studies)
PFS	Not reported	Not reported
CRR (28–856 days)	79% (95% CI: 70 to 87)	464 (6 observational studies)
ORR (3–6 months)	68% (95% CI: 60 to 75)	156 (2 observational studies)
CRS (4 days–14 months)	70% (95% CI: 60 to 80)	568 (8 observational studies)
ICANS (6 days—14 months)	26% (95% CI: 12 to 42)	425 (6 observational studies)
B-cell aplasia (24 months)	64% (95% CI: 49 to 78)	196 (4 observational studies)

Two NRSIs and 14 single-arm studies investigated **axi-cel in the LBCL population**. At 16 months axi-cel reported favourable OS (HR 0.14; 95% CI: 0.05 to 0.38), PFS (HR 0.04; 95% CI: 0.01 to 0.17) and ORR (RR 0.05; 95% CI: 0.00 to 0.77), and no evidence of a statistically significant difference in CRR (RR 0.09; 95% CI: 0.01 to 1.37) compared to no axi-cel (very low certainty evidence). At 24 months, axi-cel reported favourable OS (HR 0.27; 95% CI: 0.0 to 0.38), CRR (RR 0.22; 95% CI: 0.16 to 0.32) and ORR (RR 0.42; 95% CI: 0.35 to 0.50) compared to salvage chemotherapy (moderate certainty evidence). The NRSIs did not report other relevant outcomes. Results from single-arm studies are summarised in the following table:

Outcomes	Result	No of participants (studies)
OS (20 months)	53% (95% CI: 49 to 59, n=90 at risk)	654 (6 observational studies)
PFS (20 months)	36% (95% CI: 32 to 40, n=95 at risk)	778 (7 observational studies)
CRR (3–63 months)	52% (95% CI: 43 to 60)	1,061 (11 observational studies)

Outcomes	Result	No of participants (studies)
ORR (1–63 months)	73% (95% CI: 65 to 80)	1,240 (11 observational studies)
CRS (1–60 months)	89% (95% CI: 86 to 91)	1,260 (12 observational studies)
ICANS (–-21 months)	55% (95% CI: 49 to 63)	1,159 (12 observational studies)
B-cell aplasia (12 months)	55% (95% CI: 33 to 76)	22 (2 observational studies)

One NRSI and 9 single-arm studies investigated **tisa-cel in the LBCL population**. At 50-90 months, the NRSI reported OS favouring tisa-cel (HR 0.60, 95% CI: 0.44 to 0.77), and no evidence of a statistically significant difference in ORR (RR 1.31, 95% CI: 0.97 to 1.77), compared to standard care (very low certainty evidence). The NRSI did not report other relevant outcomes. Results from single-arm studies are summarised in the following table:

Outcomes	Result	Participants (studies)
OS (15 months)	44% (95% CI: 39 to 50, n=73 at risk)	529 (5 observational studies)
PFS (15 months)	30% (95% CI: 25 to 36, n=47 at risk)	377 (4 observational studies)
CRR (3–12 months)	37% (95% CI: 33 to 42)	719 (8 observational studies)
ORR (3–12 months)	55% (95% CI: 45 to 65)	803 (8 observational studies)
CRS (1–24 months)	64% (95% CI: 53 to 75)	839 (9 observational studies)
ICANS (1–11 months)	18% (95% CI: 15 to 23)	724 (8 observational studies)
B-cell aplasia (24 months)	1% (95% CI: 0 to 5)	115 (1 observational study)

7.1 Methodology effectiveness, efficacy and safety

The proposed methods were developed with reference to the Cochrane Handbook for Systematic Reviews of Interventions.[102] They have been described in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[103]

7.1.1 Databases and search strategy

A systematic literature search was conducted in 4 databases (Medline, Embase, Cochrane Library, INAHTA HTA database) and websites of HTA agencies up to 13 April 2023. CAR T-cell therapies are novel technologies, therefore only studies from 1 January 2010 onwards were considered.[39] The search strategy includes filters to exclude non-human studies. No other filters were used during the searches. Searches were also conducted in ClinicalTrials.gov and the EU Clinical Trials Register to identify ongoing clinical trials related to tisa-cel or axi-cel in the eligible populations. ***Appendix A*** outlines the search strategy for each database. The results of the search strategy were cross-checked against the studies included in existing published reviews on the topic.[39,104,105]

7.2 Study selection

Results from the literature searches were imported into Rayyan (Rayyan Systems Inc, USA).[106] Rayyan functions similarly to EndNote but allows for easy blinding of reviewers and management of study inclusion conflicts. The search results were screened against the predetermined eligibility criteria (***Section 5***) by 2 reviewers independently. Following the title and abstract screen, all articles deemed potentially relevant were reviewed in full text by each reviewer independently. Conflicts between reviewers on study inclusion were settled via consensus. If consensus could not be reached, a third reviewer decided whether to include or exclude the citation. Reasons for excluding articles at full-text review were documented (***Appendix E***), and the results of the study selection were reported in a PRISMA flow diagram (***Figure 2***).

The entire library of search results was screened by title and abstract by 2 reviewers in full (instead of having each reviewer screen half of the sample), after establishing a high degree of inter-rater reliability.

7.2.1 Assessment of quality of evidence

Assessment of the quality of evidence was performed by one reviewer and checked by a second reviewer. Any differences were settled via consensus. If consensus could not be reached, a third reviewer was consulted. The quality and risk of bias of included evidence was assessed using different tools depending on the research design. NRSIs were evaluated using the Cochrane Risk of Bias in Non-randomised Studies – of Interventions (ROBINS–I) tool.[107] The quality of reporting in single-arm studies was evaluated using the Institute of Health Economics (IHE) quality appraisal checklist.[108]

The overall certainty of evidence for the reported outcomes was appraised using the GRADE approach.[109] Results of the assessments for each domain (i.e. risk of bias, inconsistency, indirectness, imprecision, other considerations) was compiled into an overall evaluation of the certainty of the evidence (i.e. an overall GRADE score), ranging between high, moderate, low and very low. A GRADE summary of findings table was produced for each intervention and population group (i.e. tisa-cel + B-ALL, tisa-cel + LBCL, axi-cel + LBCL). Separate summary of findings tables were produced for each level of evidence (i.e. NRSIs and single-arm studies).

7.2.2 Methodology data extraction, analysis and synthesis of the domains of effectiveness, efficacy and safety

7.2.2.1 Data extraction

One reviewer independently extracted data (on a study-arm level, where applicable) into a standardised template, which was checked against the original study record by a second reviewer. Disagreements were settled by discussion or utilisation of a third independent reviewer. Data of interest included:[110,111]

- study information: study identifier, author, country, year, number of institutions, setting (i.e. hospital, community care etc.), study design, length of follow-up, inclusion/exclusion criteria.
- demographic information: number of enrolled participants, number of participants lost to follow-up, number of treatment cross-overs, age, sex, ethnicity, comorbidities, diagnosis, previous SCT (i.e. autologous or allogeneic), previous lines of therapy (e.g. 2, 3, 4).
- intervention and comparator: type of CAR T-cell therapy, type of lymphodepleting chemotherapy, pre-medication regimen, pre-medication administration route (i.e. oral or IV), dosage, type of comparator (including dosage and regimen), concomitant and prior interventions (including name, dosage and regimen).
- outcomes of interest: intention to treat (ITT) population; number of events; time to event; baseline, final or change from baseline score with standard deviation (SD) in any of the aforementioned outcomes (***Section 5.4***).

For studies reporting outcomes graphically instead of numerically, *WebPlotDigitizer* was used to estimate numerical values.[112]

7.2.2.2 Data synthesis

A de novo meta-analysis was performed for specific outcomes of interest from primary research reports of NRSIs and single-arm studies. This was due to the absence of existing systematic reviews with meta-analyses that matched the predefined inclusion criteria. Meta-analyses were performed using R software (metafor package). Random-effects models using the generic inverse variance method were used as the basis for the primary analysis. Random-effects models were used. Meta-analyses were performed for outcomes reported by at least 2 studies.

Except for HRQoL, all outcomes included in the review are dichotomous. Dichotomous outcomes were reported as a risk ratio (RR) with 95% confidence intervals (CI), time-to-event outcomes were reported as HR with 95% CI or plotted on a Kaplan Meier (KM) survival curve, and HRQoL was reported as mean difference between treatment arms with 95% CIs. Where included studies reported different HRQoL scales, standardised mean differences with 95% CIs were used. Standardised mean differences were interpreted using generic SD units and also re-expressed as the most commonly reported scale of HRQoL included in the analysis. All outcomes were reported at longest follow-up.

Given the limited treatment options for patients with refractory or relapsed ALL, DLBCL or PMBCL after at least 2 lines of therapy, it is impossible to account for the personalised nature of last-line therapies in planned meta-analysis techniques.

7.2.2.3 Meta-analyses of single-arm trials

The synthesis of single-arm trials was conducted for all included outcomes in R. The synthesis of single-arm trials was illustrated using forest plots because it allowed for a visual representation of the reported effect sizes relative to similar studies.

Random-effects models using the generic inverse variance method were used as the basis for the analysis. Meta-analyses were performed for outcomes reported by at least 2 studies.

7.2.2.3.1 Dichotomous outcomes

All but one of the outcomes were dichotomous. The total number of events at the longest follow-up timepoint was extracted and used in the analysis. Results were reported as proportions (reported in text as percentages) with 95% CI.

7.2.2.3.2 Continuous outcomes

The only continuous outcome analysed was HRQoL. The mean change and corresponding SD between baseline and longest follow-up timepoint were extracted and included in the analyses. Results were reported as mean change with 95% CI.

7.2.2.4 Analyses of time-to-event data from single-arm trials

The synthesis of time-to-event (i.e. OS and PFS) data from the single-arm trials was conducted in R studio.

The time-to-event data from the single-arm trials were compared by illustrating the respective KM curves on a single plot. The combined event probability and 95% CI (plot specific average) for context relevant timepoints were also calculated. Statistical comparisons between individual trial KM curves were not performed. This was due to the KM curves being recreated using approximations of timepoints and events extracted from publications, not the original data.

7.2.2.5 Assessment of heterogeneity

Heterogeneity was assessed graphically by the presentation of forest plots. Heterogeneity was assessed statistically using the Chi^2 test ($p < 0.10$ representing significant heterogeneity) and the I^2 statistic for the meta-analysis of dichotomous outcomes, and Tau^2 and I^2 for continuous outcomes. The thresholds for low, moderate, substantial and considerable heterogeneity were as proposed in the Cochrane handbook (I^2 = 0–40% might not be important; 30–60% moderate heterogeneity; 50–90% substantial heterogeneity; 75–100% considerable heterogeneity). Where substantial heterogeneity was evident, the causes were explored through subgroup analysis as described in ***Section 7.2.2.7***.

7.2.2.6 Publication bias

Publication bias was not assessed owing to limited data availability.

7.2.2.7 Subgroup and sensitivity analysis

Subgroup and sensitivity analyses were not conducted owing to limited data availability.

7.2.2.8 Imputation methods for dealing with missing values

Missing SDs were obtained from available means, sample sizes, standard errors and 95% confidence intervals using formulae detailed in the Cochrane Handbook for Systematic Reviews of Interventions (version 6.1). In situations where data were unavailable to calculate SD, it was imputed using the 'impute_SD' function in the R (version 1.4) package 'metagear', following the imputation methods described by Braken 1992.[113-116] Where continuous values needed to be combined, formulae detailed in the Cochrane handbook were used. For studies that reported outcomes graphically, *WebPlotDigitizer* was used to convert graph points into numerical values.[112] Where missing data could not be calculated or imputed through other means, study authors were contacted to obtain primary data.

7.2.2.9 Narrative synthesis

Where fewer than 2 comparative studies reported an outcome, results were tabulated and described narratively in the text. For continuous outcomes, the mean change from baseline or final follow-up score and SD were reported for each study arm, as well as the mean difference and 95% CI comparing the mean effects between groups. For dichotomous outcomes, event rates for each trial arm were reported along with a risk ratio or odds ratio and 95% CI comparing the event rates between groups.

Indirect, naïve comparisons to single-arm studies of comparator interventions were not conducted, owing to the methodological concerns associated with this approach.[102] Therefore, the clinical evaluation of the report focuses on either direct comparative evidence comparing CAR T-cell therapy to a relevant comparator intervention, or single-arm evidence for CAR T-cell therapy.

7.2.2.10 Deviations from the HTA protocol

There were several methodological changes made from the HTA protocol:

1. The entire library of search results was screened by title and abstract by 2 reviewers in full (instead of having each reviewer screen half of the sample), after establishing a high degree of inter-rater reliability. This increased the level of rigour in the study selection process compared to the method proposed in the HTA protocol.
2. Due to the overlapping nature of the populations in the included studies, evidence for the DLBCL and PMBCL populations were combined into a single group representing LBCL more broadly.

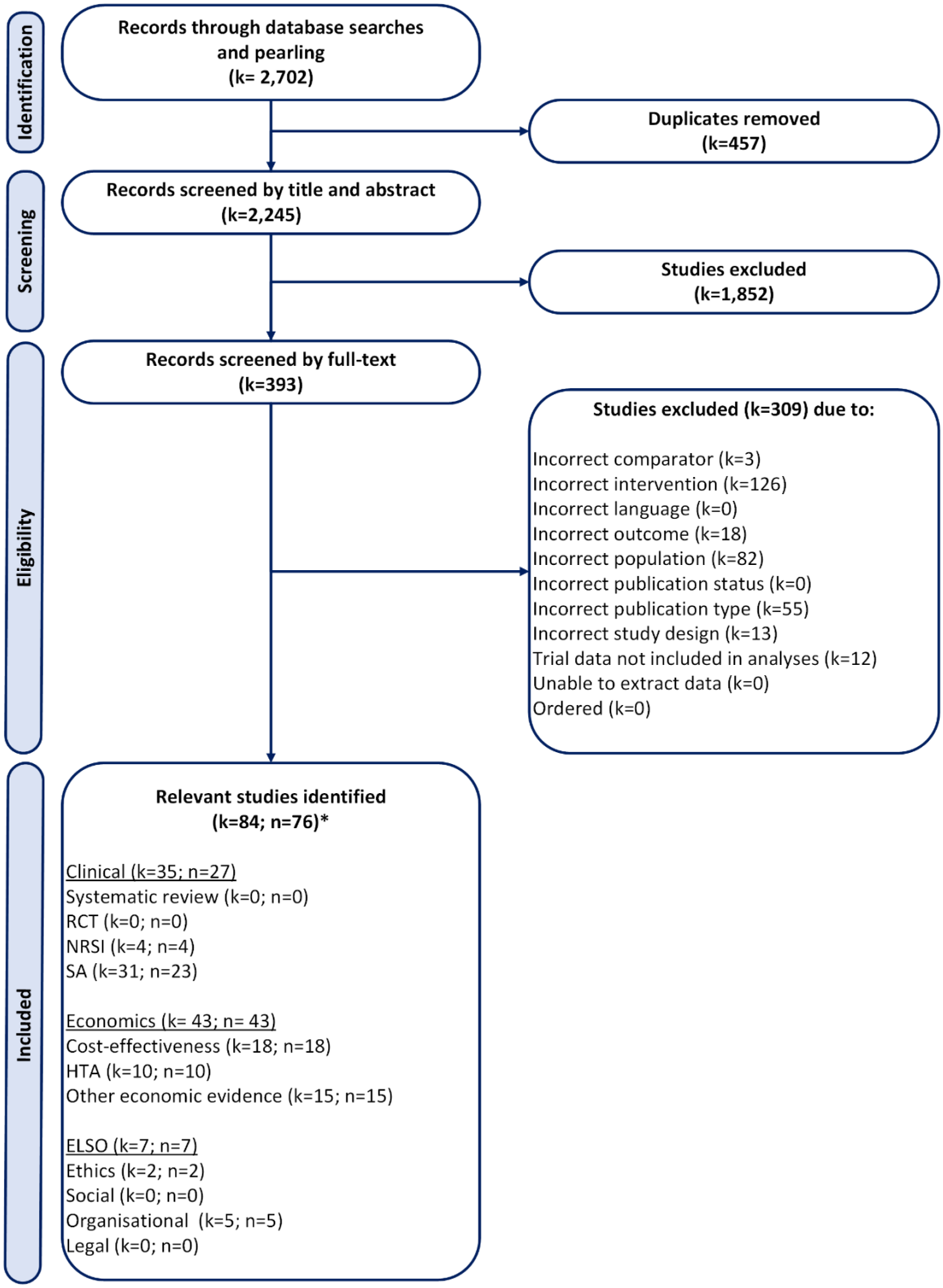
These studies primarily comprised DLBCL patients, but may also include patients with PMBCL, tFL, TC/HRBCL and/or HGBCL. This decision was made in consultation with the Federal Office of Public Health (FOPH) owing to the limited evidence available that strictly met the inclusion criteria defined in the protocol.

3. Publication bias and subgroup analysis was not conducted owing to limited data availability.

7.3 Results effectiveness, efficacy and safety

7.3.1 PRISMA flow diagram

Figure 2 PRISMA flow diagram



Abbreviations:
ELSO = ethical, legal, social organisational domains, **HTA** = health technology assessment, **k** = number of publications, **NRSI** = non-randomised study of intervention, **n** = number of trials, **RCT** = randomised control trial, **SA** = single-arm study.
Notes:
* Total does not equal the sum of all HTA domains as publications can be included in multiple HTA domains.

7.3.2 Study characteristics and quality assessment of included studies

7.3.2.1 Study characteristics

Overall, 27 studies were included in the assessment of clinical effectiveness and safety (full list reported in ***Appendix B***). The characteristics of each included trial are briefly described below per study design, with additional details presented in ***Table 6*** to ***Table 8***.

7.3.2.1.1 Non-randomised studies of interventions

In total, 4 NRSIs were included in the assessment of clinical effectiveness and safety of axi-cel and tisa-cel: one single centre and 3 multicentre (5, 10, 11 sites). All NRSIs were conducted in the USA, with 2 conducted in 10 and 11 countries, respectively (see ***Table 6*** and ***Table 7***). One NRSI compared tisa-cel to conventional chemotherapy for B-ALL, one compared axi-cel to salvage chemotherapy in LBCL, one compared axi-cel to no axi-cel in LBCL, and one compared tisa-cel to rituximab plus chemotherapy, followed by SCT in LBCL.

The sample size in the 4 included NRSIs was 38, 205, 371 and 412, respectively. The median duration of follow-up ranged from 21 days to 15.5 months. Participants were most commonly male, with ages varying across the populations of interest. In the B-ALL population, the age of children/young adults ranged from 3 months to 25 years. In adult patients included in the LBCL populations, age ranges were poorly reported, with the median age between 52.7 and 63 years.

For clinical effectiveness, the most frequently studied outcomes included OS, PFS and ORR. For safety, the most reported outcomes included CRS and ICANS. TFI, HRQoL, SAEs, AEs, TRAEs/TEAEs, B-cell aplasia, B-cell aplasia duration, cytopenia, hypogammaglobulinaemia, IVIG use to treat hypogammaglobulinaemia, infections, TLS and secondary malignancies were not reported.

7.3.2.1.2 Single-arm studies

In total, 23 single-arm studies were included in the assessment of clinical effectiveness and safety of axi-cel and tisa-cel. Of these single-arm studies, 16 were multicentre and 7 were single-centre. The included studies were conducted in various countries; 18 studies included study centres in the USA. One study had a centre in Switzerland.[117]

Seven single-arm studies investigated tisa-cel in B-ALL, 14 investigated axi-cel in LBCL, and 9 investigated tisa-cel in LBCL. All studies investigated the use of a single IV infusion of either axi-cel or tisa-cel; where specified, the median dose administered to study participants is reported as a table note to ***Table 6***, ***Table 7*** and ***Table 8***.

The median sample size was 66 (range 11–298), with 2,783 participants across all single-arm studies. The median duration of follow-up ranged from 1 to 63 months. Participants were most commonly male, with ages varying across the populations of interest. In the B-ALL population, the median age of children/young adults ranged from 0.41 months to 29.2 years. In adult patients included in the DLBCL, PMBCL, LBCL and aggressive-NHL populations, median age was 60 years (median range 56 to 67 years).

For clinical effectiveness, the most frequently studied outcomes included OS, CRR and ORR. For safety, the most reported outcomes included CRS, ICANS and cytopenia. TFI was not reported.

7.3.3 Evidence table: tisa-cel for B-ALL

Table 6 Characteristics of included studies assessing the clinical effectiveness and safety of tisa-cel in patients with B-ALL

Study; Core reference; Associated references	Study design; Country; Number of centres; Funding	Intervention(s); Lymphodepletion type, n (%); Median follow-up (range)	Sample size; Median age (range); Male sex, n (%)	Indication, n (%); Prior lines of therapy	Marrow burden, median (range); CNS status/KMT2A rearrangement, n (%)	Outcomes
NRSI						
Ragoonanan 2022[118]	Retrospective, NRSI USA Multicentre (5 sites) NR	Tisa-cel NR 28 (5–150) days [A]	n=39 13 (1.5–25) years 16 (41)	B-ALL NR	NR NR	OS CRS ICANS Discontinuation
		Conventional chemotherapy NR 21 (1–183) days [A]	n=166 11 (0.3–25) years 111 (66.9)	B-ALL NR	NR NR	
Single-arm						
Dourthe 2021[119]	Prospective, single-arm France Multicentre (2 sites) NR	Tisa-cel Flu/Cy: 51 (100) 15.5 (95% CI: 12.2–17.9) months	n=51 17 (1–29.2) years 31 (60.78)	Primary refractory B-ALL: 6 (11.76) Relapsed B-ALL: 45 (88.24) Median 3 (range 1–6) SCT: 30 (59) Blinatumomab: 17 (33) Inotuzumab: 11 (22)	% BM blasts >50%: 12 (24) MRD $\geqslant 10^{-2}$: 26 (31) KMT2Ar: 7 (14)	OS CRS ICANS B-cell aplasia

Study; Core reference; Associated references	Study design; Country; Number of centres; Funding	Intervention(s); Lymphodepletion type, n (%); Median follow-up (range)	Sample size; Median age (range); Male sex, n (%)	Indication, n (%); Prior lines of therapy	Marrow burden, median (range); CNS status/KMT2A rearrangement, n (%)	Outcomes
ELIANA[120] NCT02435849[2,121]	Prospective, single-arm; phase 2 11 countries [B] Multicentre (25 sites) Novartis	Tisa-cel [C] Flu/Cy: 71 (95) Cytarabine/etoposide: 1 (1) 39 (NR) months	n=75 11 (3–23) years 43 (57)	Primary refractory B-ALL: 6 (8) Chemorefractory/relapsed B-ALL: 69 (92) Median 3 (range 1–8)	Morphological blast count in bone marrow: 74 (5–99) CNS-1: 63 (84) CNS-2: 10 (13) CNS-3: 1 (1) Unknown: 1 (1)	OS CRR ORR HRQoL SAEs AEs TRAEs/TEAEs CRS B-cell aplasia rate + duration Cytopenia Hypogam + IVIG Infection TLS SM Discontinuation
ENSIGN[122] NCT02228096[123]	Prospective, single-arm; phase 2 USA Multicentre (13 sites) Novartis	Tisa-cel [D] NR 60 (NR) months	n=64 Mean 12.4 (SD 5.16) years 30 (46.9)	B-ALL NR	NR NR	OS CRR ORR SAEs AEs CRS B-cell aplasia/duration Cytopenia Hypogam Infection TLS Discontinuation

Study; Core reference; Associated references	Study design; Country; Number of centres; Funding	Intervention(s); Lymphodepletion type, n (%); Median follow-up (range)	Sample size; Median age (range); Male sex, n (%)	Indication, n (%); Prior lines of therapy	Marrow burden, median (range); CNS status/KMT2A rearrangement, n (%)	Outcomes
Ghorashian 2022[117]	Retrospective, single-arm 10 countries [E] Multicentre (15 sites) None	Tisa-cel [F] NR 14 (IQR 9–21) months	n=35 17 months (IQR 14.9–24.6 months) 21 (55)	B-ALL refractory to one or more prior lines: 19 (50) Median 2 (range 2–3)	MRD-negative: 7 (20) MRD-positive: 0–<1%: 5 (14) 1–<5%: 5 (14) 5–<10%: 2 (6) 10–<50%: 9 (26) 50–100%: 7 (20) CNS-positive: 1 (3) KMT2Ar: 29 (76)	OS CRR CRS ICANS B-cell aplasia/duration Cytopenia Hypogam + IVIG Infection Discontinuation
Moskop 2022[124]	Retrospective, single-arm USA Multicentre (15 sites) NR	Tisa-cel [G] Flu/Cy: 14 (100) 231 (44–856) days	n=14 0 (0–9) years NR	Primary refractory B-ALL: 5 (35.7) First relapse: 5 (35.7) Second/greater relapse: 4 (28.6) NR: 8 (57.1) Blinatumomab: 3 (21.4) Inotuzumab: 3 (21.4)	MRD-negative: 5 (35.7) MRD-positive: 7 (50) >M1 marrow (>5% blasts; range: 6-90% blasts): 1 (7.1) Not assessed: 1 (7.1) KMT2Ar: 12 (85.7)	OS CRR CRS ICANS B-cell aplasia duration Discontinuation
Pasquini 2020[125]	Prospective, single-arm USA & Canada Multicentre (73 sites) Funders [H]	Tisa-cel [I] Flu/Cy: 255 (100) 13 (4–28) months	n=255 13.2 (0.41–26.17) years 150 (58.8)	Primary refractory/relapsed B-ALL: 159 (62.3) Complete remission: 95 (37.2) Unknown: 1 (0.5) Median 3 (range 0–15) Blinatumomab: 38 (14.9) Inotuzumab: 27 (10.6)	MRD-negative: 44 (17.3) Prior CNS involvement: 24 (9.4)	OS CRR CRS ICANS Cytopenia Hypogam + IVIG Infection SM Discontinuation

Study; Core reference; Associated references	Study design; Country; Number of centres; Funding	Intervention(s); Lymphodepletion type, n (%); Median follow-up (range)	Sample size; Median age (range); Male sex, n (%)	Indication, n (%); Prior lines of therapy	Marrow burden, median (range); CNS status/KMT2A rearrangement, n (%)	Outcomes
Ravich 2022[126]	Retrospective, single-arm USA Multicentre (2 sites) Funders [J]	Tisa-cel [K] All patients received Flu/Cy with 2 receiving additional agents due to high disease burden 386 (11–1,187) days	n=31 7.9 (0.8–23.6) years 18 (58.1)	Primary refractory B-ALL: 11 (35.5) Relapse 1: 14 (45.2) Relapse 2: 5 (16.1) Relapse 3+: 1 (3.2) Any agent: n=8 (26) Blinatumomab: n=6 (19) Inotuzumab: n=5 (16) CAR T therapy: n=1 (3)	MRD-negative: 3 (9.68) MRD-positive: >0–<5%: 15 (48.39) ⩾5%: 13 (41.93) CNS-3: 1 (3.2) Non-CNS extramedullary disease: 3 (9.7) KMT2Ar: 5 (19.4)	OS CRR TRAEs/TEAEs CRS ICANS B-cell aplasia Discontinuation

Abbreviations:
AEs = adverse events, **B-ALL** = B-cell lymphoblastic leukaemia, **CNS** = central nervous system, **CRR** = complete response rate, **CRS** = cytokine release syndrome, **Flu/Cy** = fludarabine/cyclophosphamide, **HRQoL** = health-related quality of life, **ICANS** = immune effector cell-associated neurotoxicity syndrome, **IQR** = interquartile range, **IVIG** = intravenous immunoglobulin, **KMT2Ar** = KMT2A gene rearrangement, **MRD** = minimal residual disease, **n** = number, **NR** = not reported, **NRSI** = non-randomised studies of interventions, **ORR** = overall response rate, **OS** = overall survival, **SAEs** = serious adverse events, **SCT** = stem cell transplantation, **SD** = standard deviation, **SM** = secondary malignancies, **Tisa-cel** = tisagenlecleucel, **TRAEs/TEAEs** = treatment-related/-emergent adverse events, **USA** = United States of America.
Notes:
[A] Overall hospital length of stay.
[B] 11 countries = North America (USA, Canada), Europe (Austria, Belgium, France, Germany, Italy, Norway, Spain), Asia (Japan), Australia (25 sites).
[C] Patients ≤50 kg = $0.2 \times 10^6 – 5.0 \times 10^6$ CAR-positive T cells/kg patient weight; patients > 50 kg = $0.1 \times 10^8 – 2.5 \times 10^8$ CAR-positive T cells.
[D] Patients ≤50 kg = $0.2\text{-}5 \times 10^6 – 5.0 \times 10^6$ CAR-positive T cells/kg patient weight; patients > 50 kg = $0.1\text{-}2 \times 10^8 – 2.5 \times 10^8$ CAR-positive T cells.
[E] 10 countries = Austria; Belgium; Finland; France; Germany; Israel; Italy; Spain; Switzerland; UK (15 sites).
[F] Median dose: 2.3×10^6 cells/kg patient weight (IQR: 2.0–4.4).
[G] Median dose: 2.29×10^6 cells/kg patient weight (Range: 1.3–4.6).
[H] CIBMTR is supported primarily by Public Health Service grant U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).
[I] Patients ≤50 kg = 2×10^6 CAR-positive T cells/kg patient weight; patients > 50 kg = 0.9×10^8 CAR-positive T cells.
[J] National Institutes of Health (NIH)/National Cancer Institute (NCI) grant P30CA021765, American Society of Transplantation and Cellular Therapy (AT), St. Baldrick's Foundation Scholar Award (CLB), Johns Hopkins Summer Provost's Undergraduate Research Award (JWR), Johns Hopkins Woodrow Wilson Fellowship (JWR), American Lebanese Syrian Associated Charities (ALSAC).
[K] Patients ≤50 kg = median: 2.1 (range: 0.9–4.5) $\times 10^6$ CAR-positive T cells/kg patient weight (n=21); patients > 50 kg = median 1.1 (range: 0.5–1.6) $\times 10^8$ CAR-positive T cells (n=10).

7.3.4 Evidence table: axi-cel for LBCL

Table 7 Characteristics of included studies assessing the clinical effectiveness and safety of axi-cel in patients with LBCL

Study; Core reference; Associated references	Study design; Country; Number of centres; Funding	Intervention(s); Lymphodepletion type, n (%); Median follow-up (range)	Sample size; Median age (range); Male sex, n (%)	Indication, n (%); Prior lines of therapy	Histology, n (%); Stage, n (%)	Outcomes
NRSI						
Mian 2021[127]	Retrospective, NRSI USA Single centre Kite Pharma	Axi-cel 3-day regimen of lymphodepleting chemotherapy 5 (2–16) months	n=27 63 (25–77) years 18 (66.7)	Primary refractory: 7 (25.9) Refractory: 9 (33.3) Relapsed: 11 (40.7) 3 (2–6)	DLBCL: 20 (74.1) PMBCL: 4 (14.8) tFL/other: 3 (11.1) NR	OS PFS CRR ORR Discontinuation
		No axi-cel N/A 5 (2–16) months	n=11 62 (38–76) years 9 (81.8)	Primary refractory: 2 (18.2) Refractory: 1 (9.1) Relapsed: 7 (63.6) 4 (2–6)	DLBCL: 5 (45.5) PMBCL: 0 (0) tFL/other: 5 (45.5) NR	
Neelapu 2021[128]	Retrospective, NRSI (propensity-matched, historical control; ZUMA-1 vs SCHOLAR-1l) USA, Israel, Canada, Australia, Belgium, Czechia, Finland, Germany, Sweden, Switzerland, UK Multicentre Kite, a Gilead Company	Axi-cel Flu/Cy: 81 (100) 2.3 (NR) years	n=81 (survival set) [L] ≥65 years, 23% (NR) 54 (67)	Primary refractory disease: 23 (28) Refractory to second-line or subsequent therapy: 43 (53) Relapse after auto SCT: 16 (20) NR	"Excludes diagnoses other than DLBCL, TFL, PMBCL" Stage III-IV: 68 (84)	OS CRR ORR
		Salvage chemotherapy N/A NR (7.3-14.8) years	n=331 (survival set) [L] ≥65 years, 15% (NR) 225 (68)	Primary refractory: 125 (38) Refractory to second-line or subsequent therapy: 165 (50) Relapse after auto SCT: 71 (21) NR	"Excludes diagnoses other than DLBCL, TFL, PMBCL" Stage III-IV: 80/124 (65)	

Study; Core reference; Associated references	Study design; Country; Number of centres; Funding	Intervention(s); Lymphodepletion type, n (%); Median follow-up (range)	Sample size; Median age (range); Male sex, n (%)	Indication, n (%); Prior lines of therapy	Histology, n (%); Stage, n (%)	Outcomes
Single-arm						
Bachy 2022[129]	Retrospective, single-arm France Multicentre (23) NR	Axi-cel NR 13 (95% CI: 12.1-13.5) months	n=209 62 (20-79) years 121 (57.9)	Relapsed or refractory DLBCL after at least two lines of prior therapy Median 2 (range 2-8)	DLBCL: 165 (78.9) T/HRBCL: 1 (0.5) DLBCL, leg type: 1 (0.5) tFL: 37 (17.7) tMZL: 5 (2.4) Stage I: 18 (8.6) Stage II: 26 (12.4) Stage III: 29 (13.9) Stage IV: 126 (60.3) Missing: 10 (4.8)	OS PFS CRR ORR CRS ICANS Cytopenia
Baird 2021[130]	Retrospective, single-arm USA Single centre Funders [A]	Axi-cel [B] Flu/Cy: 41 (100) 20 (3–28) months	n=41 56 (21–76) years 24 (58.5)	Chemorefractory at apheresis: 38 (92.7) Primary refractory: 19 (46.3) Relapse post-SCT: 8 (19.5) Median 3 (range 2–4)	DLBCL: 26 (63.4) tFL: 12 (29.3) PMBCL: 3 (7.3) Stage I/II: 9 (22) Stage III/IV: 32 (78)	OS PFS CRR ORR CRS ICANS B-cell aplasia rate Hypogam + IVIG Infection Discontinuation
Benoit 2023[131]	Retrospective, single-arm Canada Single centre NR	Axi-cel NR 5 (NR) months	n=15 59 (28–71) years 9 (60)	Refractory disease: 11 (73) 2: 15 (100%) ≥3 prior lines: 0 (0%)	DLBCL: 10 (67) PMBCL: 1 (7) tFL: 4 (27) Stage III/IV at infusion: 12 (80)	CRR ORR CRS ICANS Cytopenia Discontinuation

Study; Core reference; Associated references	Study design; Country; Number of centres; Funding	Intervention(s); Lymphodepletion type, n (%); Median follow-up (range)	Sample size; Median age (range); Male sex, n (%)	Indication, n (%); Prior lines of therapy	Histology, n (%); Stage, n (%)	Outcomes
Bethge 2022[132]	Retrospective, single-arm Germany Multicentre (21 sites) NR	Axi-cel NR 11 (1–29) months	n=173 60 (20–83) years 120 (69)	Refractory at lymphodepletion: 92 (53) ≥3 prior lines: 116 (67%)	DLBCL: 153 (88) PMBCL: 14 (8) tFL/other: 6 (4) NR	CRR ORR CRS ICANS Discontinuation
Gauthier 2022[133]	Retrospective, single-arm USA Multicentre Funders [D]	Axi-cel [E] Flu/Cy: 68 (100) 3 (NR) months	n=68 62 (25–79) years 47 (69)	Relapsed: 33 (49) Secondary refractory: 22 (32) Primary refractory: 13 (19) Median 3 (range 2–9)	DLBCL: 50 (74) Transformed: 14 (21) Other LBCL histologies: 4 (5.9) Burkitt lymphoma: 0 (0) Stage I: 0 (0) Stage II: 11 (17) Stage III: 16 (25) Stage IV: 38 (58) NR: 3	CRR ORR CRS ICANS Infection Discontinuation
Grana 2021[134]	Retrospective, single-arm USA Single centre NR	Axi-cel Lymphodepletion administered (no further details provided) 11 (NR) months	n=37 59 (23–75) years 22 (59.5)	Primary refractory: 19 (51.4) Resistance to 2 consecutive lines of therapy: 18 (48.7) Relapse post-SCT: 12 (32.4) 2 prior lines: 4 (10.8) 3 prior lines: 16 (43.2) 4 prior lines: 9 (24.3) 5 prior lines: 3 (8.1) 6+ prior lines: 5 (13.5)	DLBCL: 22 (59.5) PMBCL: 4 (10.8) HGBCL: 2 (5.4) DLBCL arising from FL: 9 (24.3) Stage I: 0 Stage II: 1 (2.7) Stage II bulky: 1 (2.7) Stage III: 16 (43.2) Stage IV: 14 (37.8) Unknown/missing: 5 (13.5)	CRR CRS ICANS Discontinuation

Study; Core reference; Associated references	Study design; Country; Number of centres; Funding	Intervention(s); Lymphodepletion type, n (%); Median follow-up (range)	Sample size; Median age (range); Male sex, n (%)	Indication, n (%); Prior lines of therapy	Histology, n (%); Stage, n (%)	Outcomes
Melody 2022[135]	Retrospective, single-arm USA Multicentre (3 sites) NR	Axi-cel NR 30 (NR) days	n=97 56 (24–76) years 62 (64)	NR Median 3 (range 2–8)	DLBCL (de novo): 63 (65) DLBCL (transformed): 18 (19) PMBCL: 7 (7) HGBCL: 8 (8) T/HRBCL: 1 (1) NR	CRS ICANS Discontinuation
Panaite 2022[136]	Retrospective, single-arm USA Single centre Innovation in Cancer Informatics fund	Axi-cel NR NR	n=53 63 (25–79) years 36 (68)	Primary refractory: 38 (72) Relapsed: 15 (28) Median 3 (range 2–9)	DLBCL: 41 (77) tFL: 11 (21) PMBCL: 1 (2) NR	ORR CRS ICANS Cytopenia IVIG Infection Discontinuation
Pinnix 2020[137]	Retrospective, single-arm USA Single centre Funders [F]	Axi-cel [G] Flu/Cy: 124 (100) 11 (95% CI: 10–12) months	n=124 60 (18–85) years 92 (74)	NR Median 3 (range 2–11)	DLBCL: 95 (77) tFL: 20 (16) PMBCL: 9 (7) Stage I/II: 18 (15) Stage III/IV: 106 (85)	PFS CRR ORR CRS ICANS Discontinuation
Riedell 2022[138]	Retrospective, single-arm USA Multicentre (8 sites) Funders [C]	Axi-cel Flu/Cy: 155 (99) Ben: 1 (1) None: 0 (0) 12 (NR) months	n=156 59 (IQR 53–67) years 118 (76)	Primary refractory: 63 (40) Refractory to most recent therapy: 47 (30) Relapsed: 46 (29) Median 3 (range 2–10)	DLBCL: 117 (75) tFL: 28 (18) HGBCL: 9 (6) PMBCL: 2 (1) Stage III/IV: 128 (82)	OS PFS CRR ORR CRS ICANS Discontinuation

Study; Core reference; Associated references	Study design; Country; Number of centres; Funding	Intervention(s); Lymphodepletion type, n (%); Median follow-up (range)	Sample size; Median age (range); Male sex, n (%)	Indication, n (%); Prior lines of therapy	Histology, n (%); Stage, n (%)	Outcomes
Sesques 2020[139]	Retrospective, single-arm France Single centre Funder [H]	Axi-cel Flu/Cy: NR (98) Ben: NR (2) 6 (NR) months	n=28 59 (27–72) years 16 (57)	Primary refractory: 19 (68) Refractory to most recent therapy: 26 (93) Number of lines before leukapheresis (≥4): 22 (79)	DLBCL: 17 (61) PMBCL: 3 (11) tFL: 8 (29) Stage III/IV: 20 (74)	OS PFS CRR ORR CRS ICANS
Sim 2019[140]	Retrospective, single-arm USA Multicentre (2 sites) NR	Axi-cel Flu/Cy: 11 (100) 3.3 (1.1–12) months	n=11 NR NR	Primary refractory: 8 (66.67) Relapsed/refractory: 4 (33.33) Median 2 (range 2–5)	DLBCL: 9 (75) tFL: 3 (25) Stage I/II: 4 (33.33) Stage III: 6 (50) Stage III/IV: 2 (16.67)	OS PFS Infection
ZUMA-1[141] NCT02348216[142-144]	Prospective, single-arm USA & Israel Multicentre (22 sites) Funders [I]	Axi-cel [J] Flu/Cy: 111 (100) 63 (NR) months	n=111 58 (23-76) years 68 (67)	Primary refractory disease: 2 (2) Refractory to second-line or subsequent therapy: 78 (77) Relapse after auto SCT: 21 (21) NR	DLBCL: 77 (76) PMBCL: 8 (8) tFL: 16 (16) Stage I/II: 15 (15) Stage III/IV: 86 (85)	OS PFS CRR ORR CRS SM SAE AE Cytopaenia Infection Discontinuation TRAEs/TEAEs CRS ICANS

Study; Core reference; Associated references	Study design; Country; Number of centres; Funding	Intervention(s); Lymphodepletion type, n (%); Median follow-up (range)	Sample size; Median age (range); Male sex, n (%)	Indication, n (%); Prior lines of therapy	Histology, n (%); Stage, n (%)	Outcomes
ZUMA-9[145] NCT03153462	Retrospective, single-arm USA Multicentre (17 sites) Funder[K]	Axi-cel Flu/Cy: 298 (100) 13 (3–21) months	n=298 60 (21–83) years 192 (64)	Primary refractory: 101 (33.9) Refractory to most recent therapy: 125 (42.0) Relapsed: 72 (24.0) Median 3 (range 2–11)	DLBCL: 203 (68.1) PMBCL: 19 (6.4) tFL: 76 (25.5) Stage I/II: 52 (17.6) Stage III/IV: 244 (82.4)	OS PFS CRR ORR CRS ICANS Discontinuation

Abbreviations:
AEs = adverse events, **Axi-cel** = axicabtagene ciloleucel, **Ben** = bendamustine, **CI** = confidence interval, **CRR** = complete response rate, **CRS** = cytokine release syndrome, **DLBCL** = diffuse large B-cell lymphoma, **FL** = follicular lymphoma, **Flu/Cy** = fludarabine/cyclophosphamide, **HGBCL** = high-grade B-cell lymphoma, **Hypogam** = hypogammaglobulinemia, **ICANS** = immune effector cell-associated neurotoxicity syndrome, **IQR** = interquartile range, **IVIG** = intravenous immunoglobulin, **LBCL** = lymphoblastic B-cell leukaemia**, n** = number, **NR** = not reported, **ORR** = overall response rate, **OS** = overall survival, **PFS** = progression-free survival, **PMBCL** = primary mediastinal B-cell lymphoma, **SAEs** = serious adverse events, **SCT** = stem cell transplantation, **SM** = secondary malignancies, **T/HRBCL** = T-cell/histiocyte-rich B-cell lymphoma, **tFL** = transformed follicular lymphoma, **Tisa-cel** = tisagenlecleucel, **TRAEs/TEAEs** = treatment-related/-emergent adverse events, **UK** = United Kingdom, **USA** = United States of America.
Notes:
[A] National Institutes of Health/National Cancer Institute grants 2P01CA049605-29A1 (C.L.M. and D.M.) and 5P30CA124435 (C.L.M.), and by the Virginia and D. K. Ludwig Fund for Cancer Research. C.L.M. is a member of the Parker Institute for Cancer Immunotherapy, which supports the Stanford University Cancer Immunotherapy Program.
[B] Median dose: 2 ×10^6 CAR-positive T cells/kg.
[C] National Cancer Institute/ National Institutes of Health (K23-CA201594), and this work was supported by National Cancer Institute/National Institutes of Health grant P30-CA076292.
[D] National Institutes of Health/National Cancer Institute Cancer Center Support Grant (P30 CA015704-45).
[E] Target dose: 2 × 106 CAR-positive viable T cells/kg.
Maximum dose: 2 × 108 CAR-positive viable T cells.
[F] Supported in part by National Institutes of Health, National Cancer Institute, Cancer Center Support (CORE) grant CA 016672 to the University of Texas MD Anderson Cancer Center.
[G] 2 x 10^6 per kg CAR T-cells
[H] Silvana Novelli received a grant from the FEHH-Fundación CRIS. Editing was funded by the Institut de Recherche sur les Cancers et le Sang, a nonprofit organization.
[I] Kite Pharma, which provided all the study materials, and in part by the Leukemia & Lymphoma Society Therapy Acceleration Program, Moffitt Cancer Center Support Grant P30 CA076292, and MD Anderson Cancer Center Support Grant P30 CA016672. Effort for F.L.L. was in part supported by National Cancer Institute Cancer Clinical Investigator Team Leadership Award P30 CA076292-18S4.
[J] Median dose: 2 × 10^6 CAR-positive T cells/kg (Minimum: 1 × 10^6 CAR-positive T cells/kg).
[K] Moffitt Cancer Center support grant (P30-CA076292), and a National Cancer Institute grant (CA201594).
[L] Numbers of patients reported in various analyses in Neelapu 2021 varied due to propensity matching methods. Actual numbers of patients in each analysis differed from these totals, depending on the propensity-matching method, and data availability. Data reported in this table were for the common support set for survival.

7.3.5 Evidence table: tisa-cel for LBCL

Table 8 Characteristics of included studies assessing the clinical effectiveness and safety of tisa-cel in patients with LBCL

Study; Core reference; Associated references	Study design; Country; Number of centres; Funding	Intervention(s); Lymphodepletion type, n (%); Median follow-up (range)	Sample size; Median age (range); Male sex, n (%)	Indication, n (%); Prior lines of therapy	Histology, n (%); Stage, n (%)	Outcomes
NRSI						
Maziarz 2022[146]	Retrospective, NRSI (propensity-matched, historical control; JULIET vs CORAL) JULIET: 10 countries [c] CORAL: 12 countries (NR) JULIET: Multicentre (27 sites) CORAL: Multicentre (NR) Novartis	Tisa-cel NR 8.3 (NR) months	n=166 Mean 55.8 (±12.9) years 104 (62.7)	Relapsed or refractory DLBCL after at least two lines of prior therapy Median 3 (range 1-8)	DLBCL 1 or II: 42 (26.4) III or IV: 117 (73.6)	OS ORR
		Standard of care (chemotherapy, followed by SCT) NA 4.9 (NR) months	n=205 Mean 52.7 (±11.5) years 130 (63.4)	Relapsed or refractory DLBCL after at least two lines of prior therapy Median 2 (range 2-6)	DLBCL 1 or II: 77 (36.6) III or IV: 128 (62.4)	

Study; Core reference; Associated references	Study design; Country; Number of centres; Funding	Intervention(s); Lymphodepletion type, n (%); Median follow-up (range)	Sample size; Median age (range); Male sex, n (%)	Indication, n (%); Prior lines of therapy	Histology, n (%); Stage, n (%)	Outcomes
Single-arm						
Bachy 2022[129]	Retrospective, single-arm France Multicentre (23) NR	Axi-cel NR 13 (95% CI: 12.1-13.5) months	n=209 64 (20-81) years 126 (60.3)	Relapsed or refractory DLBCL after at least two lines of prior therapy Median 2 (range 2-10)	DLBCL: 166 (79.4) T/HRBCL: 2 (1.0) DLBCL after PCNSL: 1 (0.5) tFL: 33 (15.8) tMZL: 7 (3.3) Stage I: 16 (7.7) Stage II: 22 (10.5) Stage III: 24 (11.5) Stage IV: 140 (67.0) Missing: 7 (3.3)	OS PFS CRR ORR CRS ICANS Cytopenia
Benoit 2023[131]	Retrospective, single-arm Canada Single centre NR	Tisa-cel NR 11.2 (NR) months	n=10 67 (51–80) years 9 (90)	Refractory disease: 4 (40) Median 2 (range 2-4) ≥3 prior lines: 5 (50%)	DLBCL: 6 (60) PMBCL: 0 (0) tFL: 4 (40) Stage III/IV at infusion: 9 (90)	CRR ORR CRS ICANS Cytopenia Discontinuation
Bethge 2022[132]	Retrospective, single-arm Germany Multicentre (21 sites) NR	Tisa-cel NR 11 (1–29) months	n=183 61 (1–-83) years 116 (64)	Refractory at lymphodepletion: 121 (66) ≥3 prior lines: 136 (74%)	DLBCL: 170 (93) PMBCL: 2 (1) tFL/other: 11 (6) NR	CRR ORR CRS ICANS Discontinuation

Study; Core reference; Associated references	Study design; Country; Number of centres; Funding	Intervention(s); Lymphodepletion type, n (%); Median follow-up (range)	Sample size; Median age (range); Male sex, n (%)	Indication, n (%); Prior lines of therapy	Histology, n (%); Stage, n (%)	Outcomes
Gauthier 2022[133]	Retrospective, single-arm USA Multicentre Funders [A]	Tisa-cel [B] Flu/Cy: 31 (100) 3 (NR) months	n=31 64 (23–81) years 21 (68)	Relapsed: 11 (35) Secondary refractory: 16 (52) Primary refractory: 4 (13) Median 3 (range 2–9)	DLBCL: 18 (58) Transformed: 12 (39) Other LBCL histologies: 1 (3) Stage I: 3 (10) Stage II: 4 (13) Stage III: 5 (16) Stage IV: 14 (45) NR: 5 (16)	CRR ORR CRS ICANS Infection Discontinuation
JULIET 2019[147] NCT02445248[3,148]	Prospective, single-arm; phase 2 10 countries [C] Multicentre (27 sites) Novartis	Tisa-cel [D] Flu/Cy: 81 (73) BEN: 22 (20) 40.3 (IQR 37.8–43.8) months	n=111 56 (22–76) years 60 (67)	Relapse after most recent therapy: 50 (45) Refractory DLBCL: 61 (55) 1 prior line: 5 (5%) 2 prior lines: 49 (44%) 3 prior lines: 34 (31%) 4–6 prior lines: 23 (21%)	DLBCL: 88 (79) tFL: 21 (19) Other: 2 (2) Stage I: 8 (7) Stage II: 19 (17) Stage III: 22 (20) Stage IV: 62 (56)	OS PFS ORR HRQoL SAEs TRAEs/TEAEs CRS B-cell aplasia rate Cytopenia Hypogam Infection TLS Discontinuation AE

Study; Core reference; Associated references	Study design; Country; Number of centres; Funding	Intervention(s); Lymphodepletion type, n (%); Median follow-up (range)	Sample size; Median age (range); Male sex, n (%)	Indication, n (%); Prior lines of therapy	Histology, n (%); Stage, n (%)	Outcomes
Pasquini 2020[125]	Prospective, single-arm USA & Canada Multicentre (73 sites) Funders [E]	Tisa-cel [F] Flu/Cy: 141 (91) Ben: 14 (9) 11.9 (3.8–19) months	n=155 65.4 (18–89) years 91 (53.5)	Aggressive NHL – Primary refractory/relapsed: 147 (94.8) Complete remission: 7 (4.5) Unknown: 1 (0.7) Median 4 (range 0–11)	tFL: 42 (27.1) NR	OS CRR CRS ORR ICANS Cytopenia Hypogam + IVIG Infection SMs Discontinuation
Riedell 2022[138]	Retrospective, single-arm USA Multicentre (8 sites) Funders [G]	Tisa-cel Flu/Cy: 41 (49) BEN: 43 (51) None: 1 (1) 13.8 (NR) months	n=84 67 (IQR 61–72) years 44 (52)	Aggressive NHL – Primary refractory: 17 (20) Refractory to most recent therapy: 33 (39) Relapsed: 34 (40) Median 4 (range 2–9)	DLBCL: 71 (85) tFL: 7 (8) HGBCL: 6 (7) PMBCL: 0 (0)s Stage I/II: NR Stage III/IV: 68 (81)	OS PFS CRR ORR CRS ICANS Discontinuation
Sesques 2020[139]	Retrospective, single-arm France Single centre Funder [H]	Tisa-cel Flu/Cy: NR (98) BEN: NR (2) 5.7 (NR) months	n=33 62 (28–75) years 24 (72)	Primary refractory: 19 (58) Refractory to most recent therapy: 29 (88) Number of lines before leukapheresis (≥4): 21 (64%)	DLBCL: 21 (64) PMBCL: 1 (3) tFL: 10 (30) tMZL: 1 (3) Stage III/IV: 26 (81)	OS PFS CRR ORR CRS ICANS

Study; Core reference; Associated references	Study design; Country; Number of centres; Funding	Intervention(s); Lymphodepletion type, n (%); Median follow-up (range)	Sample size; Median age (range); Male sex, n (%)	Indication, n (%); Prior lines of therapy	Histology, n (%); Stage, n (%)	Outcomes
Yagi 2022[149]	Retrospective, single-arm Japan Single centre NR	Tisa-cel Flu/Cy: 19 (90.48) 6.3 (0.4–14.8) months	n=21 57 (32–66) years 14 (66.7)	Relapsed: 4 (19.0) Refractory: 17 (81.0) Primary refractory: 9 (42.9) Refractory to second-line or later therapy: 4 (19.0) Relapsed ≥12 months post-SCT: 4 (9.0) Chemotherapy: 2 prior lines: 5 (23.8%) 3 prior lines: 8 (38.1%) 4-6 prior lines: 12 (57.1%)	DLBCL: 20 (95.2) tFL: 1 (4.8) Stage I/II: 8 (38.1) Stage III/IV: 13 (61.9)	OS PFS CRR CRS ICANS Infection Discontinuation

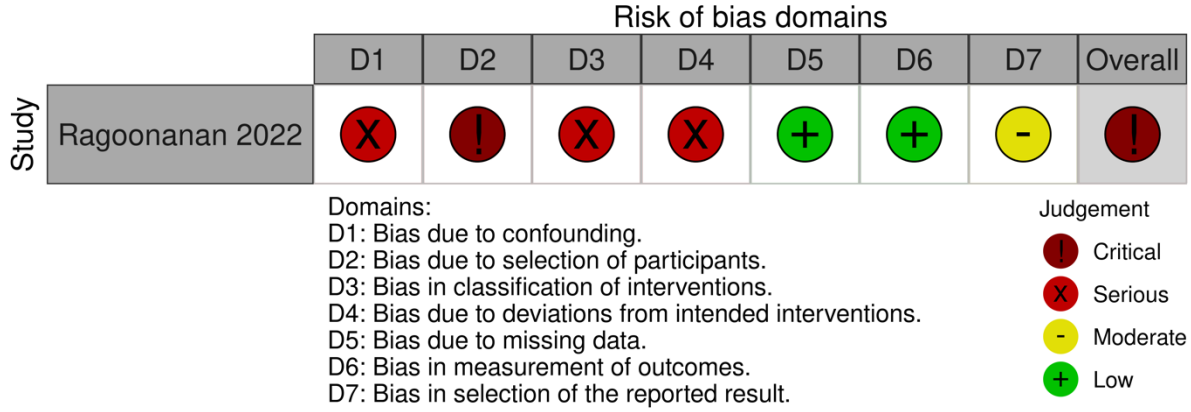
Abbreviations:
AE = adverse events, **Ben** = bendamustine, **CRR** = complete response rate, C**RS** = cytokine release syndrome, **DLBCL** = diffuse large B-cell lymphoma, **Flu/Cy** = fludarabine/cyclophosphamide, **HGBCL** = high-grade B-cell lymphoma, **Hypogam** = hypogammaglobulinemia, **ICANS** = immune effector cell-associated neurotoxicity syndrome, **IQR** = interquartile range, **IVIG** = intravenous immunoglobulin, **LBCL** = lymphoblastic B-cell leukaemia, **n** = number, **NR** = not reported, **ORR** = overall response rate, **OS** = overall survival, **PCNSL** = primary central nervous system lymphoma, **PFS** = progression-free survival, **PMBCL** = primary mediastinal B-cell lymphoma, **SAEs** = serious adverse events, **SCT** = stem cell transplantation, **SM** = secondary malignancy, **tFL** = transformed follicular lymphoma, **T/HRBCL** = T-cell/histocyte-rich B cell lymphoma, **tMZL** = transformed marginal zone lymphoma, **Tisa-cel** = tisagenlecleucel, **TLS** = tumour lysis syndrome, **TRAEs/TEAEs** = treatment-related/-emergent adverse events, **USA** = United States of America.
Notes:
[A] National Institutes of Health/National Cancer Institute Cancer Center Support Grant (P30 CA015704-45).
[B] Median dose: 2.2×10^8 (IQR: 1.4–2.85; Range: 0.31–4).
[C] 10 countries = North America (USA, Canada), Europe (Austria, France, Germany, Italy, the Netherlands, Norway), Australia, and Asia (Japan) (27 sites).
[D] Median dose : 3.0×10^8 CAR-positive viable T cells (Range : 0.1×10^8–6.0×10^8)
[E] The CIBMTR is supported primarily by Public Health Service grant U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).
[F] Median dose: 1.8×10^8 CAR-positive T cells.
[G] Supported in part by a grant from Novartis Pharmaceuticals (to D.L.P.), National Cancer Institute Grant P30 CA008748 (to M.A.P.), and National Center for Advancing Translational Sciences Award UL1-TR002494 (to V.B.).
[H] Silvana Novelli received a grant from the FEHH-Fundación CRIS. Editing was funded by the Institut de Recherche sur les Cancers et le Sang, a nonprofit organization.

7.3.6 Risk of bias

7.3.6.1 Tisa-cel for B-ALL

The risk of bias in the NRSI of tisa-cel for B-ALL is summarised in ***Figure 3***.[118] Ragoonanan 2022[118] was rated as having a critical risk of bias owing to confounding (i.e. confounding factors not controlled for), selection of participants (i.e. patients retrospectively selected based on outcome of ICU admission), classification of interventions (i.e. dosage not reported, 'conventional chemotherapy' not defined) and deviations from intended interventions (i.e. co-interventions varied across groups).[118]

Figure 3 Risk of bias in NRSI of tisa-cel for B-ALL



Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **NRSI** = non-randomised study of interventions.

The risk of bias in the included single-arm studies of tisa-cel for B-ALL is summarised in ***Table 9***. Four studies were rated as having a low risk of bias,[119,120,122,125] and 3 studies a moderate risk of bias.[117,124,126] All studies included patients with varying stages of disease, none of the outcome assessors were blinded to the intervention status, and only one of the studies clearly reported if a consecutive sample of patients was enrolled. Furthermore, studies rated as having a moderate risk of bias were primarily downgraded due to the use of retrospective study designs and failure to define outcomes *a priori*.

Table 9 Risk of bias in single-arm studies of tisa-cel for B-ALL

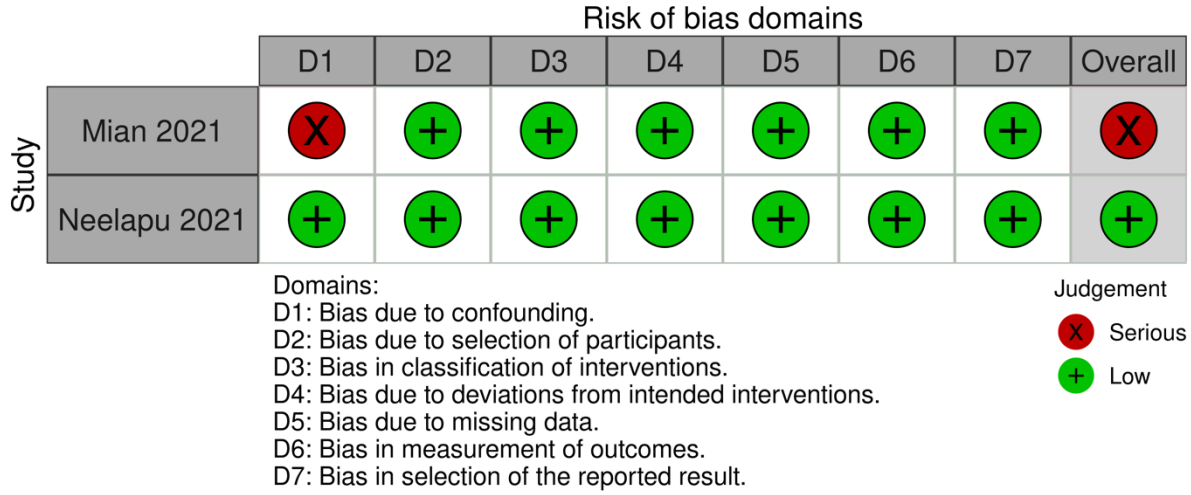
	Dourthe 2021[119]	ELIANA[120]	ENSIGN[122]	Ghorashian 2022[117]	Moskop 2022[124]	Pasquini 2020[125]	Ravich 2022[126]
Study objective							
1. Objective clearly stated?	Y	Y	Y	Y	Y	Y	Y
Study design							
2. Prospective?	Y	Y	Y	N	N	Y	N
3. Multicentre?	Y	Y	Y	Y	Y	Y	Y
4. Consecutive recruitment?	Y	U	U	U	U	U	U
Study population							
5. Were patient characteristics included?	Y	Y	PY	Y	Y	Y	Y
6. Eligibility criteria clearly stated?	Y	Y	Y	Y	Y	Y	Y
7. Patients enrolled with similar disease status?	N	N	N	N	N	N	N
Intervention and co-intervention							
8. Intervention of interest clearly described?	Y	Y	Y	Y	Y	Y	Y
9. Additional interventions clearly described?	Y	Y	Y	Y	Y	Y	Y
Outcome measure							
10. Outcome measures established a priori?	Y	Y	Y	N	N	Y	N
11. Assessors blinded to intervention?	N	N	N	N	N	N	N
12. Outcomes measured with objective methods?	Y	Y	Y	Y	Y	Y	Y
13. Outcomes measured before and after intervention?	Y	Y	Y	Y	Y	Y	Y
Statistical analysis							
14. Statistical tests appropriate?	Y	Y	NI	Y	N	Y	Y
Results and conclusions							
15. Follow-up long enough for important outcomes to occur?	Y	Y	Y	Y	Y	Y	Y
16. Losses to follow-up reported?	Y	Y	Y	Y	Y	Y	Y
17. Random variability estimated in analysis?	Y	Y	Y	Y	Y	Y	Y
18. Adverse events reported?	Y	Y	Y	Y	Y	Y	Y
19. Conclusions supported by results?	Y	Y	Y	Y	Y	Y	Y
Competing interest and sources of support							
20. Competing interests and sources of support disclosed?	Y	Y	Y	Y	N	Y	Y
Overall score	**18/20 (90%)**	**17/20 (85%)**	**16/20 (80%)**	**15/20 (75%)**	**13/20 (65%)**	**17/20 (85%)**	**15/20 (75%)**

Abbreviations:
N = no, **NI** = no information, **P** = partial, **U** = unclear, **Y** = yes.
Notes:
Overall scores allocated by totalling the number of yes answers for the 20 applicable questions, with a corresponding percentage. Score of ≤50% = high level of bias, 51–≤75% = moderate level of bias, 76–100% = low level of bias.

7.3.6.2 Axi-cel for LBCL

The risk of bias in the NRSIs of axi-cel for LBCL is summarised in ***Figure 4***.[127,146] The study by Neelapu 2021 was rated as having a low risk of bias.[128] The study by Mian 2021 was rated as having a serious risk of bias due to confounding not controlled for in the analysis; the risk of confounding was elevated due to baseline imbalances in histology, performance status and stem cell use.[127]

Figure 4 Risk of bias in NRSIs of axi-cel for LBCL



Abbreviations:
LBCL = large B-cell lymphoma, **NRSI** = non-randomised study of interventions.

The risk of bias in the included single-arm studies of axi-cel for LBCL is summarised in ***Table 10***. Overall, 2 studies were rated as having a low risk of bias,[138,141] and 12 a moderate risk of bias.[129-137,139,140] None of the included studies blinded the outcome assessors to the intervention status; most did not define outcomes of interest *a priori* and most included patients with varying stages of disease. Furthermore, studies rated as having a moderate risk of bias were further downgraded primarily due to retrospective study design, unclear reporting of enrolment method (i.e. consecutive or non-consecutive), single-centre study design, and a lack of reporting on dosage of CAR T infusions.

Table 10 Risk of bias in single-arm studies of axi-cel for LBCL

	Baird 2021[130]	Bachy 2022[129]	Benoit 2023[131]	Bethge 2022[132]	Gauthier 2022[133]	Grana 2021[134]	Melody 2022[135]	Panaite 2022[136]	Pinnix 2020[137]	Riedell 2022[138]	Sesques 2020[139]	Sim 2019[140]	ZUMA-9[145]	ZUMA-1[141]
Study objective														
1. Objective clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Study design														
2. Prospective?	N	N	N	N	N	N	N	U	N	N	P	N	N	Y
3. Multicentre?	N	Y	N	Y	Y	N	Y	N	U	Y	N	Y	Y	Y
4. Consecutive recruitment?	Y	U	U	Y	Y	U	U	U	U	Y	U	U	U	U
Study population														
5. Were patient characteristics included?	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	Y
6. Eligibility criteria clearly stated?	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7. Patients enrolled with similar disease status?	N	Y	N	U	N	N	U	U	N	N	N	N	N	N
Intervention and co-intervention														
8. Intervention of interest clearly described?	Y	P	P	P	Y	P	P	P	Y	P	P	P	P	Y

	Baird 2021[130]	Bachy 2022[129]	Benoit 2023[131]	Bethge 2022[132]	Gauthier 2022[133]	Grana 2021[134]	Melody 2022[135]	Panaite 2022[136]	Pinnix 2020[137]	Riedell 2022[138]	Sesques 2020[139]	Sim 2019[140]	ZUMA-9[145]	ZUMA-1[141]
9. Additional interventions clearly described?	Y	N	Y	U	Y	Y	N	P	Y	Y	Y	Y	Y	Y
Outcome measure														
10. Outcome measures established a priori?	N	N	N	N	N	N	N	U	N	N	N	N	N	Y
11. Assessors blinded to intervention?	N	N	N	N	N	N	N	N	N	N	N	N	N	N
12. Outcomes measured with objective methods?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
13. Outcomes measured before and after intervention?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Statistical analysis														
14. Statistical tests appropriate?	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Results and conclusions														
15. Follow-up long enough for important	Y	Y	N	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y

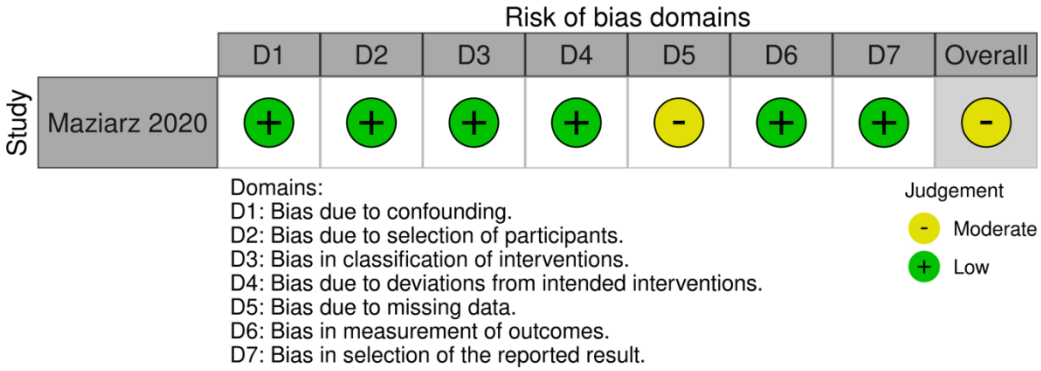
	Baird 2021[130]	Bachy 2022[129]	Benoit 2023[131]	Bethge 2022[132]	Gauthier 2022[133]	Grana 2021[134]	Melody 2022[135]	Panaite 2022[136]	Pinnix 2020[137]	Riedell 2022[138]	Sesques 2020[139]	Sim 2019[140]	ZUMA-9[145]	ZUMA-1[141]
outcomes to occur?														
16. Losses to follow-up reported?	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
17. Random variability estimated in analysis?	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y
18. Adverse events reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
19. Conclusions supported by results?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Competing interest and sources of support														
20. Competing interests and sources of support disclosed?	Y	Y	P	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y
Overall score	**15/20 (75%)**	**15/20 (75%)**	**12/20 (60%)**	**14.5/20 (72.5%)**	**15/20 (75%)**	**13/20 (65%)**	**11/19 (57.9%)**	**13/20 (65%)**	**14/20 (70%)**	**15.5/20 (77.5%)**	**14/20 (70%)**	**14.5/20 (72.5%)**	**14.5/20 (72.5%)**	**17/20 (85%)**

Abbreviations:
N = no, **NA** = not applicable, **P** = partial, **U** = unclear, **Y** = yes.
Notes:
Overall scores allocated by totalling the number of yes answers for the applicable questions, with a corresponding percentage. Score of ≤50% = high level of bias, 51–≤75% = moderate level of bias, 76–100% = low level of bias.

7.3.6.3 Tisa-cel for LBCL

The risk of bias in the NRSI of tisa-cel for LBCL is summarised in ***Figure 5***.[146] The study by Maziarz 2022 was rated as having a moderate risk of bias due to missing data, because the analysis was adjusted using important confounding variables only when data was available for each covariate from ≥80% of patients in both treatment cohorts.[146] Patients that had missing data for important confounders were excluded from the adjusted analysis.

Figure 5 Risk of bias in NRSIs of tisa-cel for LBCL



Abbreviations:
LBCL = large B-cell lymphoma, **NRSI** = non-randomised study of interventions.

The risk of bias in the included single-arm studies of tisa-cel for LBCL is summarised in ***Table 11***. Overall, 3 studies were rated as having a low risk of bias,[125,138,147] and 6 a moderate risk of bias.[132,133,139,149] Almost all studies included patients with varying stages of disease, none of the outcome assessors were blinded to the intervention status, and few studies defined the outcomes of interest *a priori*. Furthermore, studies rated as having a moderate risk of bias were downgraded primarily due to retrospective study design, single-centre study design, and a lack of reporting on dosage of CAR T infusions.[129,132,133,138,139,147,149]

Table 11 Risk of bias in single-arm studies of tisa-cel for LBCL

	Bachy 2022[129]	Gauthier 2022[133]	Riedell 2022[138]	Pasquini 2020[125]	Yagi 2022[149]	Benoit 2023[131]	Bethge 2022[132]	JULIET 2019[147]	Sesques 2020[139]
Study objective									
1. Objective clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Study design									
2. Prospective?	N	N	N	Y	N	N	N	Y	P
3. Multicentre?	Y	Y	Y	Y	N	N	Y	Y	N
4. Consecutive recruitment?	U	Y	Y	U	U	U	Y	U	U
Study population									

	Bachy 2022[129]	Gauthier 2022[133]	Riedell 2022[138]	Pasquini 2020[125]	Yagi 2022[149]	Benoit 2023[131]	Bethge 2022[132]	JULIET 2019[147]	Sesques 2020[139]
5. Were patient characteristics included?	Y	Y	Y	Y	Y	Y	Y	P	Y
6. Eligibility criteria clearly stated?	P	Y	Y	Y	Y	Y	Y	Y	Y
7. Patients enrolled with similar disease status?	Y	N	N	N	N	Y	U	N	N
Intervention and co-intervention									
8. Intervention of interest clearly described?	P	Y	P	Y	P	P	P	Y	P
9. Additional interventions clearly described?	N	Y	Y	Y	Y	Y	U	Y	Y
Outcome measure									
10. Outcome measures established a priori?	N	N	N	Y	N	N	N	Y	N
11. Assessors blinded to intervention?	N	N	N	N	N	N	N	N	N
12. Outcomes measured with objective methods?	Y	Y	Y	Y	Y	Y	Y	Y	Y
13. Outcomes measured before and after intervention?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Statistical analysis									
14. Statistical tests appropriate?	U	Y	Y	Y	Y	Y	Y	Y	Y
Results and conclusions									
15. Follow-up long enough for important outcomes to occur?	Y	U	Y	Y	Y	N	Y	Y	Y
16. Losses to follow-up reported?	Y	Y	Y	Y	Y	N	Y	Y	Y
17. Random variability estimated in analysis?	Y	Y	Y	Y	Y	Y	Y	Y	Y
18. Adverse events reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y
19. Conclusions supported by results?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Competing interest and sources of support									
20. Competing interests and sources of support disclosed?	Y	Y	Y	Y	Y	P	Y	Y	Y
Overall score	**15/20 (75%)**	**15/20 (75%)**	**15.5/20 (77.5%)**	**17/20 (85%)**	**13.5/20 (67.5%)**	**12/20 (60%)**	**14.5/20 (72.5%)**	**16.5/20 (82.5%)**	**14/20 (70%)**

Abbreviations:
N = no, **P** = partial, **U** = unclear, **Y** = yes.
Notes:
Overall scores allocated by totalling the number of yes answers for the 20 applicable questions, with a corresponding percentage. Score of ≤50% = high level of bias, 51–≤75% = moderate level of bias, 76–100% = low level of bias.

7.3.7 Applicability

Applicability refers to the generalisability of the included clinical studies to the Swiss context. This involves comparing patient demographics and clinical characteristics of the included studies to what occurs in Swiss practice. An overview of the demographic and clinical characteristics of patients treated with CAR T-cell therapies in Switzerland between 2019 and 2021 is shown in ***Table 12***.

These data were collected as part of the Swiss Blood Stem Cell Transplant (SBST) registry of patients treated with CAR T-cell therapy and provided to the HTA authors by the FOPH (citation unavailable). Based on these data, the applicability of the included studies was evaluated based on country, age, sex, disease stage (LBCL population only), number of prior therapies, lymphodepleting chemotherapy regimen, and time from slot request to CAR T-cell infusion. Where studies did not adequately report 2 or more of these characteristics, applicability concerns were noted when assessing the overall certainty of evidence using GRADE. Other factors were not evaluated due to limitations in the reporting quality of either the SBST data or the included studies.

Table 12 Characteristics of Swiss patients treated with CAR T-cell therapies (2019–2021)

Characteristic	Axi-cel DLBCL+ r/r PMBCL/3L (%)	Tisa-cel r/r DLBCL/3L (%)	Tisa-cel r/r ALL/3L (%)
Total patients	**50**	**71**	**15**
Sex			
Male	32 (64.0)	44 (62.0)	9 (60.0)
Female	18 (36.0)	27 (38.0)	6 (40.0)
Age			
<10	0 (0.0)	0 (0.0)	2 (13.3)
10–20	0 (0.0)	0 (0.0)	6 (40.0)
20–30	1 (2.0)	1 (1.4)	7 (46.7)
30–40	3 (6.0)	1 (1.4)	0 (0.0)
40–50	3 (6.0)	6 (8.5)	0 (0.0)
50–60	12 (24.0)	8 (11.3)	0 (0.0)
60–70	12 (24.0)	21 (29.6)	0 (0.0)
71–75	11 (22.0)	19 (26.8)	0 (0.0)
76–80	7 (14.0)	14 (19.7)	0 (0.0)
>80	1 (2.0)	1 (1.4)	0 (0.0)
Median	60–70	60–70	10–20
Karnofsky performance status at slot request			
Poor (≤ 80)	21 (42.0)	33 (46.5)	5 (33.3)
Good (>80)	29 (58.0)	38 (53.5)	5 (33.3)
No data	0 (0.0)	0 (0.0)	5 (33.3)
Prior stem cell transplantation			
Total	35 (70.0)	48 (67.6)	10 (66.7)
Allogenic	2 (4.0)	1 (1.4)	5 (33.3)

Characteristic	Axi-cel DLBCL+ r/r PMBCL/3L (%)	Tisa-cel r/r DLBCL/3L (%)	Tisa-cel r/r ALL/3L (%)
Autologous	13 (26.0)	22 (31.0)	0 (0.0)
Number of previous therapies			
2	12 (24.0)	18 (25.4)	7 (46.7)
≥ 3	38 (76.0)	53 (74.6)	8 (53.3)
Histology			
Proportion transformed lymphoma	16 (32.0)	22 (31.0)	NA
Disease stage			
Intermediate	11 (22.0)	25 (35.2)	NA
Advanced	39 (78.0)	46 (64.8)	NA
Bridging therapy *			
Therapy <60 days pre slot request	25 (50.0)	35 (49.3)	9 (60.0)
Therapy <60 days pre CAR T-cell infusion	8 (16.0)	8 (11.3)	4 (26.7)
Lymphodepleting chemotherapy			
Fludarabine/Cyclophosphamide	50 (100.0)	70 (98.6)	15 (100.0)
Cyclophosphamide	0 (0.0)	0 (0.0)	0 (0.0)
Fludarabine/Bendamustine	0 (0.0)	1 (1.4)	0 (0.0)
CAR T infusion timing			
Time between slot request and infusion of CAR T	54 (48-63) days	46 (40-61) days †	46 (40-61) days †

Abbreviations:
Axi-cel = axicabtagene ciloleucel, **BTKi** = Burton's tyrosine kinase inhibitor, **CAR T** = chimeric antigen receptor T, **CNS** = central nervous system, **NA** = not applicable, **NR** = not reported, **r/r DLBCL/3L** = relapsed or refractory diffuse large B-cell lymphoma in the 3rd or higher line of therapy (i.e. at least 2 previous lines of therapy including stem cell transplantation), **r/r PMBCL/3L** = relapsed or refractory primary mediastinal B-cell lymphoma in the 3rd or higher line of therapy (i.e. at least 2 previous lines of therapy including stem cell transplantation), **r/r ALL/3L** = relapsed or refractory paediatric acute lymphoblastic leukaemia c (i.e. at least 2 previous lines of therapy incl. stem cell transplantation), **tisa-cel** = tisagenlecleucel.

Notes:
* Defined as anti-tumour therapy within 60 days prior to CAR T-cell infusion.
† The SBST dataset did not differentiate between indication for tisa-cel infusion. It is assumed that the time between slot request and infusion is the same for the B-ALL and LBCL populations.

7.3.7.1 Tisa-cel for B-ALL

There were no applicability concerns regarding the countries in which studies were conducted. The included studies were predominantly conducted in, or had at least one centre in, North America,[118,120,122,124-126] western Europe,[117,120] and Australia.[120] One study included a study centre in Switzerland.[117]

There were applicability concerns regarding the age of patients treated with CAR T-cell therapy in 2 of the included studies.[117,124] The median age of Swiss patients was between 10 and 20 years. The majority of studies included patients with a median age between 8 and 13 years;[118,120,122,125,126] however, 2 studies included patients with a younger median age (under 1 year[124] and 17 months[117]).

There were no applicability concerns regarding the sex of included patients. The Swiss population included 60% males, compared to 41–59% in the included studies.[117,118,120,122,124-126]

There were no applicability concerns with studies that reported the number of prior therapies given to patients prior to CAR T infusion. In the Swiss population, 47% of patients received at least 2 prior therapies, and 53% received 3 or more. Correspondingly, the included studies reported that the median number of prior therapies was 3 (range 0–15). Two studies did not report how many prior therapies were given.[118,122]

There were no applicability concerns with studies that reported the type of lymphodepleting chemotherapy given to patients. A total of 100% of Swiss patients received lymphodepleting chemotherapy with fludarabine/cyclophosphamide. Three of the included studies did not report the type of lymphodepletion regimen used;[117,118,122] the remaining 4 treated 95–100% of patients with fludarabine/cyclophosphamide.[120,124-126]

There were no applicability concerns with studies that reported the median time from slot request to CAR T infusion. Patients in Switzerland received a CAR T infusion at a median of 46 days (range 40–61) after slot request; patients in the included studies received CAR T at a median of 33 to 45 days after leukapheresis (range 21–105 days).[120,124,125] Four of the included studies did not report the time from leukapheresis to infusion, and this uncertainty is a major concern regarding the applicability of their results.[117,118,122,126]

7.3.7.2 Axi-cel for LBCL

There were no applicability concerns regarding the countries in which studies were conducted. The majority of studies were conducted in the USA,[127-130,133-138,141,145] with a subset conducted in, or having at least one centre in, France,[129,139] Germany,[132] Canada,[131] or Israel.[141] One multi-country study included centres in Switzerland.[128]

There were no applicability concerns regarding the age or sex of patients in the included studies. The median age in Swiss patients was 60–70 years, comprising 64% males. Comparatively, the median age in the included studies ranged from 56–64 years, comprising 57% to 74% males.

There were applicability concerns regarding the disease stage of patients in the included studies. Of Swiss patients treated with axi-cel for LBCL, 78% were at an advanced stage of disease (i.e. stage III/IV). The included studies enrolled between 65% and 85% of patients with stage III/IV disease;[128-131,133,134,138,139,141,145] however, 4 studies did not report disease stage.[127,132,135,136]

There were generally no applicability concerns with studies that reported the number of prior therapies given to patients prior to CAR T infusion. In the Swiss population, most patients (76%) received 3 or more therapies prior to CAR T infusion. In the included studies the median number of prior therapies was 3 (range 2–15).[127,129-136,138,145] One study, ZUMA-1, did not clearly report the number of prior therapies patients received.[128,141]

There were no applicability concerns with studies that reported the type of lymphodepleting chemotherapy given to patients. A total of 100% of Swiss patients received lymphodepleting chemotherapy with fludarabine/cyclophosphamide. Six studies treated 98% to 100% of patients with fludarabine/cyclophosphamide.[128,130,133,138,141,145] The remaining studies did not report the type of lymphodepleting chemotherapy regimen given.

There were applicability concerns regarding the time between leukapheresis and CAR T infusion in the included studies. The median time from slot request to CAR T infusion in Switzerland was 54 days (range 48–63). Patients in the included studies received CAR T infusion sooner, with a median time between leukapheresis and CAR T infusion of 17 to 38 days (range 17–133 days).[127,131-133,137-139,141] Seven studies did not report the time from leukapheresis to CAR T infusion.[128-130,134-136,145]

7.3.7.3 Tisa-cel for LBCL

There were no applicability concerns regarding the countries in which the included studies were conducted. The majority of studies were conducted in, or contained at least one centre in, the USA,[125,133,138,146,147] western Europe,[129,132,139,146,147] Canada,[125,131,146,147] Japan[146,147,149] or Australia.[146,147]

There were no applicability concerns regarding the age of patients in the included studies. The median age of Swiss patients was 60 to 70 years; the median age in the included studies ranged from 51 to 67 years.

There were applicability concerns regarding the sex of enrolled patients in one study.[131] Swiss patients comprised 62% males. The majority of studies included 57–74% males; however, one study included 90% male participants.[131]

There were applicability concerns regarding the disease stage of patients in the included studies. Of Swiss patients treated with tisa-cel for LBCL, 65% were at an advanced stage of disease (i.e. stage III/IV). In comparison, the included studies enrolled between 61% and 90% of patients with stage III/IV disease.[129,131,133,138,139,146,147,149] Two studies did not report disease stage.[125,132]

There were no applicability concerns with studies that reported the number of previous therapies given to patients prior to CAR T infusion. In the Swiss population, most patients (75%) received 3 or more therapies prior to CAR T infusion. In the included studies, the median number of prior therapies was 3 to 4 (range 1–11).[125,129,131-133,138,139,146,147,149]

There were no applicability concerns with studies that reported the type of lymphodepleting chemotherapy given to patients. A total of 99% of Swiss patients received lymphodepleting chemotherapy with fludarabine/cyclophosphamide and 1% received fludarabine/bendamustine. Four of the included studies did not report the type of lymphodepletion regimen used;[129,131,132,146] the remaining studies treated 90% to 100% of patients with fludarabine/cyclophosphamide.[125,133,138,139,147,149]

There were no applicability concerns regarding the time between leukapheresis and CAR T infusion in the majority of included studies. The median time from slot request to CAR T infusion in Switzerland was 46 days (range 40–61). Patients in the included studies received CAR T infusion at a median of 43 days (range 48–526 days).[125,131-133,138,139,147] One study infused patients with tisa-cel a median of 70 days after leukapheresis (range 48–116), which is an applicability concern.[149] Two did not report the length of time between slot request and infusion.[129,146]

7.3.8 Findings: Effectiveness/efficacy and safety

In this section, results are presented by population and drug type, then by study design. The following points apply to data reported in the effectiveness and safety sections:

- All outcomes have been reported at longest follow-up. This follow-up duration may differ within and across studies for the outcomes reported, therefore to provide context, the median follow-up duration reported by each study was included in the summary tables (***Table 13*** to ***Table 16***).
- Where studies were not identified for a specific population, drug type and study design, summary tables were not created.
- GRADE summary of findings tables for OS, PFS, CRR, ORR, CRS, ICANS and B-cell aplasia rates can be found in ***Section 7.3.15*** (***Table 23*** to ***Table 29***).

7.3.9 Effectiveness/efficacy findings: tisa-cel for B-ALL

One NRSI and 7 single-arm studies investigated the effectiveness/efficacy of tisa-cel in the B-ALL population. There was very low certainty evidence for the outcomes included in the GRADE assessment. A high-level summary of the results is as follows:

- The NRSI reported an HR for OS comparing conventional chemotherapy to tisa-cel of 0.89 (95% CI: 0.38 to 2.11) at 150 days in ICU patients, demonstrating no significant difference between groups. The reported OS in the 6 single-arm studies was 69% at 20 months (95% CI: 63 to 75; number at risk: 76).
- The NRSI did not report a CRR. The proportion of patients that experienced a complete response in the 6 single-arm studies was 79% (95% CI: 70 to 87) at 1 to 29 months.
- The NRSI did not report an ORR. The proportion of patients that experienced an overall response in the 2 single-arm studies was 68% (95% CI: 60 to 75) at 3 to 6 months.
- The NRSI did not report HRQoL. HRQoL was reported by one single-arm study at 12 months. The mean change in EQ-5D visual analogue scale was 23.40 (95% CI: 6.92 to 39.88); the mean change in PedsQL was 26.30 (95% CI: 11.94 to 40.66), representing a statistically significant improvement.
- TFI was not reported by the NRSI or single-arm studies.

7.3.9.1 Effectiveness summary tables: tisa-cel for B-ALL

7.3.9.1.1 NRSI

A summary of the NRSI effectiveness evidence for tisa-cel versus standard of care in B-ALL is presented in ***Table 13***.

Table 13 Summary of NRSI effectiveness evidence for tisa-cel vs standard care in B-ALL

Outcome*	Ragoonanan 2022[118]			
	Tisa-cel (n=39)	SoC (conventional chemotherapy) (n=166)	Difference (95% CI)	Summary estimate
Median follow-up, days/months	28 days (range: 5 to 150)	21 days (range: 1 to 183)	NA	NA
Overall survival, probability (95% CI)	NR	NR	HR 0.89 (95% CI: 0.38 to 2.11) †	k=1, n=205 HR 0.89 (95% CI: 0.38 to 2.11)
Overall survival, median months	NR	NR	NR	NR
Progression-free survival, probability (95% CI)	NR	NR	NR	NR
Progression-free survival, median months	NR	NR	NR	NR
Complete response rate, n (%)	NR	NR	NR	NR
Overall response rate, n (%)	NR	NR	NR	NR
Treatment-free interval, median months	NR	NR	NR	NR
HRQoL, mean (SD)	NR	NR	NR	NR
Treatment discontinuation, n	0 (0)	NR	NR	1 NRSI, n=39 Not estimable

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **HR** = hazard ratio, **n** = number, **NA** = not applicable, **NR** = not reported, **NRSI** = non-randomised studies of interventions, **SD** = standard deviation, **SoC** = standard of care, **tisa-cel** = tisagenlecleucel, **HRQoL** = health-related quality of life.
Notes:
* All outcomes reported at longest follow-up.
† Overall survival reflects ICU-admitted patients only; HR obtained from the study authors; Based on the Kaplan-Meier curve in the publication, it is assumed that this HR was calculated as patients alive after standard of care vs CAR T, with HR < 1 favouring CAR T.

7.3.9.1.2 Single-arm

A summary of the single-arm effectiveness evidence for tisa-cel in B-ALL is presented in ***Table 14***.

Table 14 Summary of single-arm effectiveness evidence for tisa-cel in B-ALL

Outcome*	Ghorashian 2022[117]	Ravich 2022[126]	Pasquini 2020[125]	Moskop 2022[124]	ENSIGN 2019[122,123,150]	ELIANA 2018[2,120,121]	Dourthe 2021[119]	Summary estimate
	(n=35)	(n=31)	(n=249)	(n=14)	(n=64)	(n=79)	(n=51)	
Median follow-up, days/months	14 months (IQR: 9 to 21)	386 days (range: 11 to 1187)	13.4 months (range: 3.5 to 27.9)	231 days (range: 44 to 856)	24 months (range: 0.1 to 36.5)	38.8 months (NR)	15.5 (95% CI: 12.2 to 17.9) months	NA
Overall survival, n (%) (95% CI)	29 (84.0) (95% CI: 64.0 to 93.0)	19 (67.4) (95% CI: 7.9 to 81.0)	192 (77.2) (95% CI: 69.8 to 83.1)	10 (71)	NR	50 (62.8) (95% CI: 50.7 to 72.7)	38 (74.0) (95% CI: 57.0 to 85.0)	k=6 , n=459 69% at 20 months (number at risk: 76; 95% CI: 63 to 75)
Overall survival, median months	Not reached (95% CI: not reached)	Not reached (NR)	Not estimable (95% CI: 20.63 to NE)	NR	29.9 months (95% CI: 15.1 to 42.4)	Not reached (NR)	NR	NA
Progression-free survival, probability (%) (95% CI)	NR	NR	NR	NR	NR	NR	NR	NA
Progression-free survival, median months	NR	NR	NR	NR	NR	NR	NR	NA
Complete response rate, n (%)	24/28 (86.0)	25/30 (83.0)	213 (86.0)	7 (50.0)	43 (67.0)	66 (84.0)	NR	k=6, n=464 79% (95% CI: 70 to 87)
Overall response rate, n (%)	NR	NR	NR	NR	45/64 (70.0)	61/92 (66.0)	NR	k=2, n=156 68% (95% CI: 60 to 75)
Treatment-free interval, median months	NR	NR	NR	NR	NR	NR	NR	NR
HRQoL, mean change (95% CI)	NR	NR	NR	NR	NR	26.30 (95% CI: 11.94 to 40.66), p<0.0001, n=14§	NR	k=1 , n=14 mean change 26.30 (95% CI: :

Outcome*	Ghorashian 2022[117]	Ravich 2022[126]	Pasquini 2020[125]	Moskop 2022[124]	ENSIGN 2019[122,123,150]	ELIANA 2018[2,120,121]	Dourthe 2021[119]	Summary estimate
	(n=35)	(n=31)	(n=249)	(n=14)	(n=64)	(n=79)	(n=51)	
								11.94 to 40.66)
						23.40 (95% CI: 6.92 to 39.88), p<0.0001, n=14 ‖	NR	k=1, n=14 mean change 23.40 (95% CI: : 6.92 to 39.88)
Treatment discontinuation, n (%)	3/38 (79.0)	2/33 (61.0)	0/255 (0.0)	2/16 (13.0)	11/75 (15.0)	18/87 (21.0)	NR	k=6 , n=156 6% (95% CI: 1 to 14)

Abbreviations:

B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **IQR** = interquartile range, **n** = number, **NA** = not applicable, **NE** = not estimable, **NR** = not reported, **SA** = single arm, **tisa-cel** = tisagenlecleucel, **HRQoL** = health-related quality of life.

Notes:

* All outcomes reported at longest follow-up

‡ Two participants reported in this study were administered tisa-cel

§ PedsQL overall score

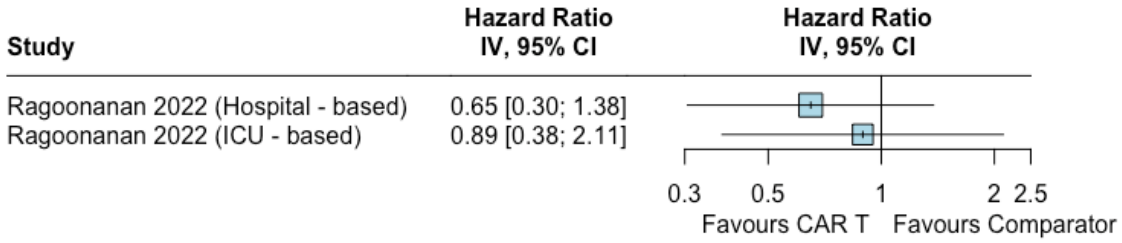
‖ EQ-5D VAS overall score

7.3.9.2 Overall survival (OS)

Overall, one NRSI and 6 single-arm studies reported OS in patients with B-ALL.[2,117-119,124-126]

The NRSI compared tisa-cel to conventional therapy (standard of care [SoC]) in patients admitted to ICU.[118] Separate OS HRs were reported for patients admitted to general hospital and those admitted to ICU (***Figure 6***). These HRs were provided to the HTA authors by the study authors. Based on the KM curves in the publication, it is assumed that these HRs were calculated as SoC versus CAR T, with HR <1 favouring CAR T (i.e. representing worse OS in the SoC group). It is unclear what the 'hospital-based' group represents, as the inclusion criteria for the study required all patients to have been admitted to ICU. It is possible that the study authors included a separate cohort of non-ICU-admitted patients in the hospital-based group, but this could not be verified. Neither of studies reported evidence of a statistically significant difference between the OS of patients that received tisa-cel and those that underwent conventional therapy. Heterogeneity could not be assessed. The overall GRADE certainty of evidence was assessed to be very low.

Figure 6 Overall survival in B-ALL patients receiving tisa-cel (NRSI)



Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **ICU** = intensive care unit, **IV** = inverse variance, **NRSI** = non-randomised studies of interventions, **tisa-cel** = tisagenlecleucel.

The single NRSI and 6 single-arm studies illustrated OS using KM curves (***Figure 7***).[2,117-119,124-126]

The KM curve published in the single NRSI displays a high rate of mortality.[118] Within 4 months of receiving tisa-cel, the probability of survival for B-ALL patients drops below 50%.

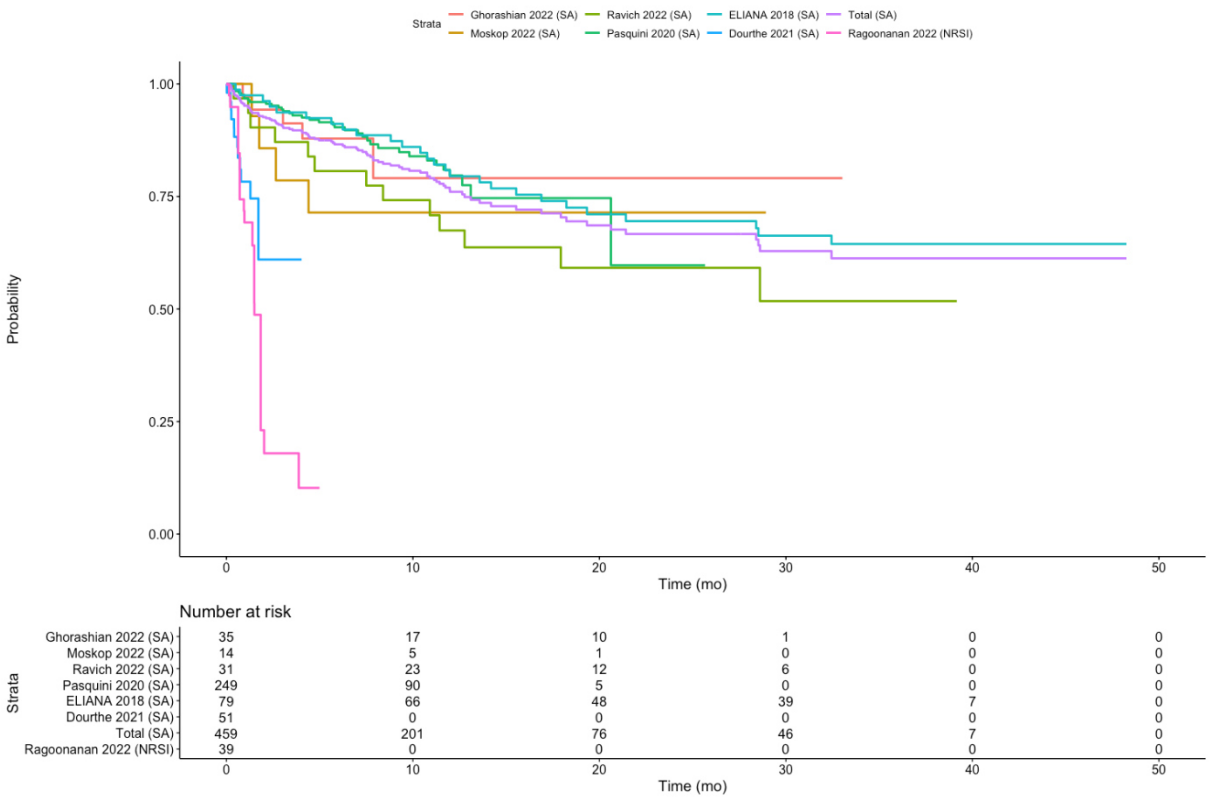
In contrast, the KM curves from the single-arm studies illustrate a stable survival rate for B-ALL patients receiving tisa-cel.[2,117,123-126] Overall 5 curves had similar trends (regardless of sample size) with comparable rates of change. At the 20-month timepoint the combined probability of survival across all curves was 69% (number at risk: 76; 95% CI: 63 to 75). The probability dropped to 65% (number at risk: 46; 95% CI: 57 to 73) at 30 months and 63% (number at risk: 7; 95% CI: 53 to 72) at 40 months.

In line with the NRSI, one KM curve of a single-arm study illustrated a rapidly decreasing survival rate for B-ALL patients receiving tisa-cel.[119] At the 1-month timepoint the probability of survival was 78% (number at risk: 28; 95% CI: 67 to 91). The probability dropped to 61% (number at risk: 7; 95% CI: 44

to 85) at 2 months. The probability of survival does not drop below 61%, plateauing between 2 and 4 months.

It is probable that the OS rate reported in the NRSI was lower than that reported in the single-arm studies because it was a retrospective study of patients that required admission to ICU following CAR T-cell therapy or standard chemotherapy.

Figure 7 Combined overall survival curves in B-ALL patients receiving tisa-cel (NRSI and single-arm)



Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **mo** = months, **NRSI** = non-randomised studies of interventions, **SA** = single-arm studies, **tisa-cel** = tisagenlecleucel.

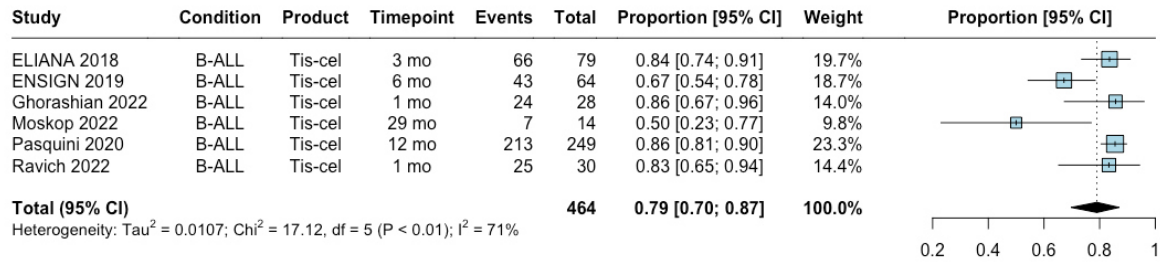
7.3.9.3 Progression-free survival

PFS was not reported in the included NRSI or single-arm studies.

7.3.9.4 Complete response rate

CRR was not reported in the included NRSI. Overall, 6 single-arm studies reported CRR in patients with B-ALL being treated with tisa-cel (***Figure 8***). Between 1–29 months (longest follow-up), 79% (95% CI: 70 to 87) achieved complete response (CR). Substantial heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 8 Complete response rate in B-ALL patients receiving tisa-cel (single-arm)

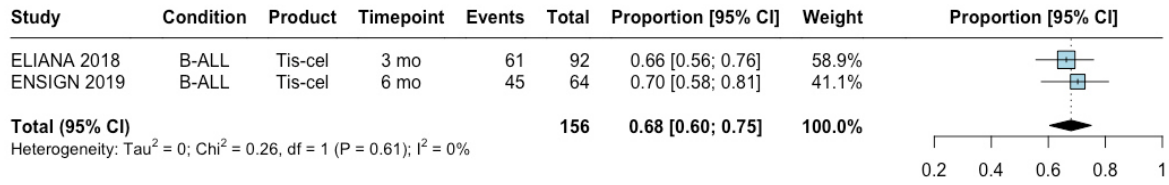


Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **tis-cel** = tisagenlecleucel.

7.3.9.5 Overall response rate

ORR was not reported in the included NRSI. Two single-arm studies reported ORR in patients with B-ALL being treated with tisa-cel (***Figure 9***). Between 3–6 months (longest follow-up), 68% (95% CI: 60 to 75) achieved ORR. Little to no heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 9 Overall response rate in B-ALL patients receiving tisa-cel (single-arm)



Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **tis-cel** = tisagenlecleucel.

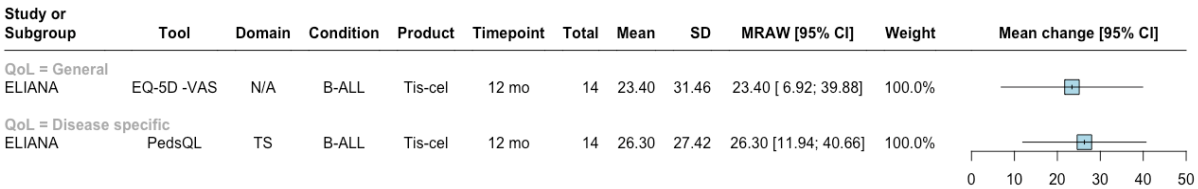
7.3.9.6 Treatment-free interval

TFI was not reported in the included NRSI or single-arm studies.

7.3.9.7 Health-related quality of life

HRQoL was not reported in the included NRSI. One single-arm study reported HRQoL in patients with B-ALL being treated with tisa-cel (***Figure 10***).[121] At 12 months, the mean change from baseline for EQ-5D visual analogue scale and PedsQL total score were both statistically and clinically significant (***Appendix F***). Heterogeneity could not be assessed.

Figure 10 HRQoL in B-ALL patients receiving tisa-cel (single-arm)

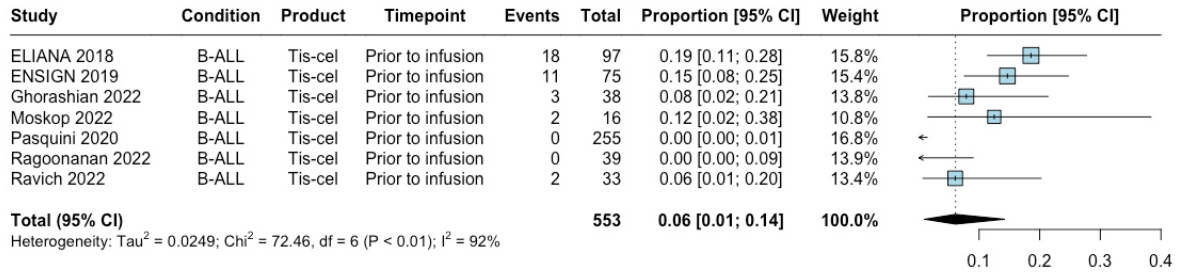


Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **EQ-5D-VAS** = EuroQol 5-dimension questionnaire visual analogue scale, **HRQoL** = health-related quality of life, **mo** = months, **MRAW** = raw, untransformed means, **N/A** = not applicable, **PedsQL** = paediatric quality of life inventory, **SD** = standard deviation, **tis-cel** = tisagenlecleucel, **TS** = total score, **QoL** = quality of life.

7.3.9.8 Treatment discontinuation

One NRSI (only tisa-cel treatment arm included) and 6 single-arm studies reported treatment discontinuation in patients with B-ALL being treated with tisa-cel (***Figure 11***).[2,117,118,122,124-126] Prior to infusion, 6% (95% CI: 1 to 14) discontinued treatment. Considerable heterogeneity was reported.

Figure 11 Treatment discontinuation in B-ALL patients receiving tisa-cel (single-arm)



Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **tis-cel** = tisagenlecleucel.

7.3.10 Safety findings: Tisa-cel for B-ALL

One NRSI and 7 single-arm studies investigated the safety of tisa-cel in the B-ALL population. There was very low certainty evidence for the outcomes included in the GRADE assessment. A high-level summary of the results are as follows:

- For safety, the NRSI only reported CRS and ICANS in the tisa-cel treatment arm, not the conventional chemotherapy arm, therefore these results were included in the analysis of single-arm studies. No other safety outcomes were reported.
- SAEs, AEs and TRAEs were not well reported across the included single-arm studies.
- The proportion of patients that experienced CRS in the 1 NRSI and 7 single-arm studies was 70% (95% CI: 60 to 80) at 4 days to 14 months.
- The proportion of patients that experienced ICANS in the 1 NRSI and 5 single-arm studies was 26% (95% CI: 12 to 42) at 6 days to 14 months.
- The proportion of patients that experienced B-cell aplasia rate in the 4 single-arm studies was 64% (95% CI: 49 to 78) at 24 months. The mean duration of B-cell aplasia was 20.11 months (95% CI: 6.01 to 34.21).

7.3.10.1 Safety summary tables: Tisa-cel for B-ALL

7.3.10.1.1 NRSI

A summary of the NRSI safety evidence for tisa-cel versus SoC in B-ALL is presented in ***Table 15***.

Table 15 Summary of NRSI safety evidence for tisa-cel vs standard of care in B-ALL

Outcome*	**Ragoonanan 2022[118]**			
	Tisa-cel (n=39)	**SoC (conventional chemotherapy) (n=166)**	**Difference (95% CI)**	**Summary estimate**
Median follow-up, days/months	6 days (range: 0 to 43)	1 day (range: 0 to 116)	NA	NA
SAE, any, n (%)	NR	NR	NR	NA
AE, any, n (%)	NR	NR	NR	NA
TRAE/TEAE, any, n (%)	NR	NR	NR	NA
CRS				
any, n (%)	36 (92.3)	NR	NR	See ***Table 16***
Grade ≥3, n (%)	27 (69.2)	NR	NR	See ***Table 16***
ICANS				
Any, n (%)	22 (56.4)	NR	NR	See ***Table 16***
Grade ≥3, n (%)	9 (23.1)	NR	NR	See ***Table 16***
B-cell aplasia, n (%)	NR	NR	NR	NR
Median duration, days/months	NR	NR	NR	NR
Cytopenia, n (%)	NR	NR	NR	NA
Hypogammaglobulinaemia, n (%)	NR	NR	NR	NA
IVIG usage, n (%)	NR	NR	NR	NA
Infections, n (%)	NR	NR	NR	NA
Tumour lysis syndrome, n (%)	NR	NR	NR	NA
Secondary malignancies, n (%)	NR	NR	NR	NA

Abbreviations:
AE = adverse event, **B-ALL** = B-cell acute lymphoblastic leukaemia, **CRS** = cytokine release syndrome, **ICANS** = Immune effector cell-associated neurotoxicity syndrome, **IVIG** = intravenous immunoglobulin, **n** = number, **NA** = not applicable, **NR** = not reported, **NRSI** = non-randomised studies of interventions, **SAE** = serious adverse event, **SoC** = standard of care, **tisa-cel** = tisagenlecleucel, **TRAE/TEAE** = treatment-related/-emergent adverse event.
Notes:
* All outcomes reported at longest follow-up

7.3.10.1.2 Single-arm

A summary of the single-arm safety evidence for tisa-cel in B-ALL is presented in ***Table 16***.

Table 16 Summary of single-arm safety evidence for tisa-cel in B-ALL

Outcome*	Ghorashian 2022[117]	Ravich 2022[126]	Pasquini 2020[125]	Moskop 2022[124]	ENSIGN 2019[122,123,150]	ELIANA 2018[2,120,121]	Dourthe 2021[119]	Summary estimate
	(n=35)	(n=31)	(n=255)	(n=14)	(n=64)	(n=79)	(n=51)	
Median follow-up, days/months	14 months (IQR: 9 to 21)	386 days (range: 11 to 1187)	13.4 months (range: 3.5 to 27.9)	231 days (range: 44 to 856)	24 months (range: 0.1 to 36.5)	38.8 months (NR)	15.5 (95% CI: 12.2 to 17.9) months	NA
SAE, any, n (%)	NR	NR	NR	NR	30 (47.0)	62 (78.0)	NR	k=2, n=143 64% (95% CI: 31 to 90)
AE, any, n (%)	NR	NR	NR	NR	64 (100.0)	74 (94.0)	NR	k=2, n=143 98% (95% CI: 88 to 100)
TRAE/TEAE, any, n (%)	NR	4 (13.0)	NR	NR	NR	71 (95.0)	NR	k=2, n=106 57% (95% CI: 0 to 100)
CRS								
any, n (%)	21 (60.0)	19 (61.0)	140 (55.0)	11 (79.0)	50 (78.0)	61 (77.0)	30 (59.0)	k=8, n=568 70% (95% CI: 60 to 80)
Grade ≥3, n (%)	5 (14.0)	6 (19.0)	41 (16.0)	3 (21.0)	19 (30.0)	38 (48.0)	10 (20.0)	k=8, n=568 29% (95% CI: 17 to 43)
ICANS								
any, n (%)	9 (26.0)	9 (29.0)	69 (27.0)	0 (0.0)	NR	NR	12 (24.0)	k=6 SA, n=425 26% (95% CI: 12 to 42)
Grade ≥3, n (%)	0 (0.0)	3 (10.0)	23 (9.0)	0 (0.0)	NR	NR	4 (8.0)	k=6, n=425 7% (95% CI: 2 to 14)

Outcome*	Ghorashian 2022[117]	Ravich 2022[126]	Pasquini 2020[125]	Moskop 2022[124]	ENSIGN 2019[122,123,150]	ELIANA 2018[2,120,121]	Dourthe 2021[119]	Summary estimate
	(n=35)	(n=31)	(n=255)	(n=14)	(n=64)	(n=79)	(n=51)	
B-cell aplasia, n (%)	25 (71.0)	25 (81.0)	NR	NR	NR	47 (59.0)	23 (45.0)	k=4 , n=196 64% (95% CI: 49 to 78)
Median duration, days/months	24.4 months (95% CI: 7.17 to 41.63)	NR	NR	171 days (range: 28 to 414) or 5.7 months (95% CI: -0.75 to 12.15)	35.5 months (95% CI: 7.81 to 63.19), n=54	27.8 months (95% CI: 8.92 to 46.68), n=50	NR	k=4 , n=153 Mean change: 20.11 (95% CI: 6.01 to 34.21)
Cytopenia, n (%)	15/23 (65.0)	NR	71 (28.0)	NR	NR	33 (42.0)	NR	k=3, n=357 43% (95% CI: 23 to 63)
Hypogammaglobulinaemia, n (%)	27/31 (87.0)	NR	134 (53.0)	NR	33 (52.0)	25 (32.0)	NR	k=4, n=429 56% (95% CI: 33 to 78)
IVIG usage, n (%)	27/31 (87.0)	NR	124 (49.0)	NR	NR	72 (91.0)	NR	k=3, n=365 77% (95% CI: 48 to 97)
Infections, n (%)	10 (29.0)	NR	118 (46.0)	NR	26 (41.0)	34 (43.0)	NR	k=4, n=433 43% (95% CI: 37 to 48)
Tumour lysis syndrome, n (%)	NR	NR	NR	NR	2 (3.0)	4 (5.0)	NR	k=2, n=143 4% (95% CI: 1 to 8)
Secondary malignancies, n (%)	NR	NR	6 (2.0)	NR	NR	1 (1.0)	NR	k=2, n=334 2% (95% CI: 1 to 4)

Abbreviations:

AEs = adverse events, **B-ALL** = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **CRS** = cytokine release syndrome, **ICANS** = Immune effector cell-associated neurotoxicity syndrome, **IVIG** = intravenous immunoglobulin, **n** = number, **NA** = not applicable, **NR** = not reported, **NRSI** = non-randomised studies of interventions, **SA** = single arm, **SAEs** = serious adverse events, **tisa-cel** = tisagenlecleucel, **TRAEs/TEAEs** = treatment-related/-emergent adverse events.

Notes:

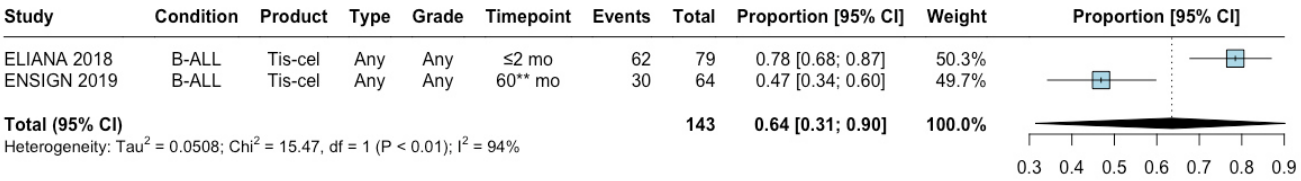
* All outcomes reported at longest follow-up.

‡ Two participants reported in this study were administered tisa-cel.

7.3.10.2 Serious adverse events

SAEs were not reported in the included NRSI. Two single-arm studies reported SAEs in patients with B-ALL being treated with tisa-cel (***Figure 12***). Between ≤2 and 60 months (longest follow-up), 64% (95% CI: 31 to 90) reported SAEs of any grade. Considerable heterogeneity was reported.

Figure 12 Serious adverse events in B-ALL patients receiving tisa-cel (single-arm)

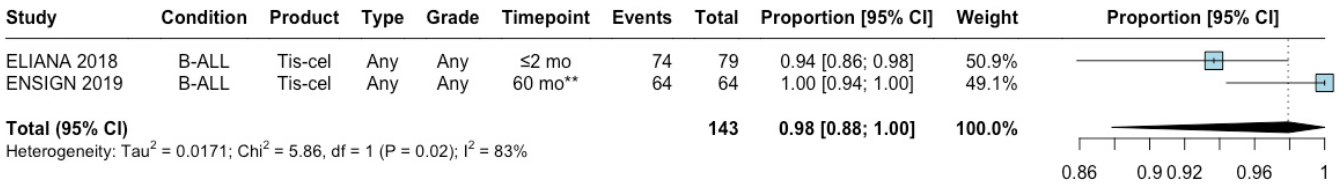


Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **tis-cel** = tisagenlecleucel.
Notes:
** Point of last follow-up.

7.3.10.3 Adverse events

AEs were not reported in the included NRSI. Two single-arm studies reported AEs in patients with B-ALL being treated with tisa-cel (***Figure 13***). Between ≤2 and 60 months (longest follow-up), 98% (95% CI: 88 to 100) reported AEs of any grade. Considerable heterogeneity was reported. Along with any-grade AEs, one study also reported that 68% of participants experienced AE grade ≥3 at ≤2 months.[2]

Figure 13 Adverse events in B-ALL patients receiving tisa-cel (single-arm)

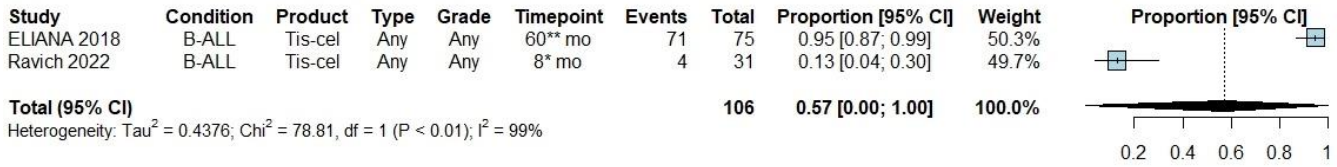


Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **tis-cel** = tisagenlecleucel.
Notes:
** Point of last follow-up.

7.3.10.4 Treatment-related/-emergent adverse events

TRAEs/TEAEs were not reported in the included NRSI. Two single-arm studies reported TRAEs/TEAEs in patients with B-ALL being treated with tisa-cel (***Figure 14***). Between 8 and 60 months (longest follow-up), 57% (95% CI: 0 to 100) reported TRAEs/TEAEs of any grade. Considerable heterogeneity was reported.

Figure 14 Treatment-related/-emergent adverse events in B-ALL patients receiving tisa-cel (single-arm)

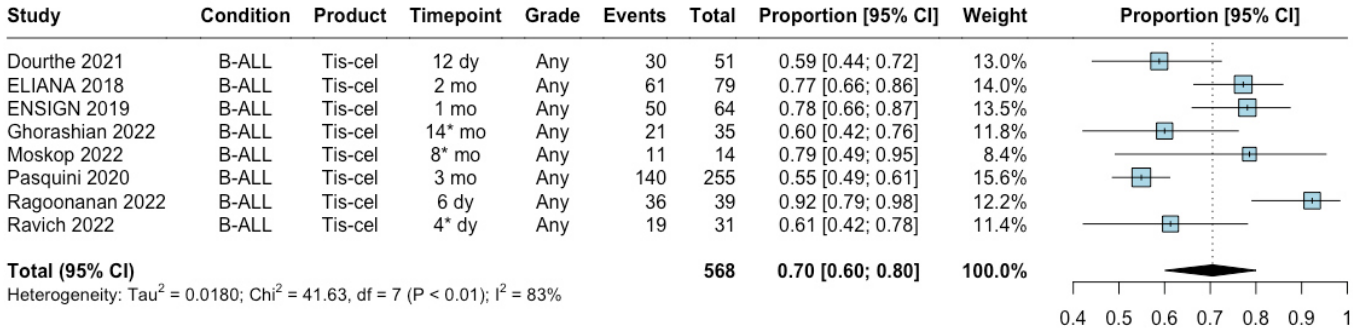


Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **tis-cel** = tisagenlecleucel.
Notes:
* Median timepoint.
** Point of last follow-up.

7.3.10.5 Cytokine release syndrome

Overall, 1 NRSI (which did not report CRS in the comparator arm) and 7 single-arm studies reported CRS of any grade in patients with B-ALL being treated with tisa-cel (***Figure 15***). Between 4 days and 14 months (longest follow-up), 70% (95% CI: 60 to 80) reported CRS of any grade. Considerable heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

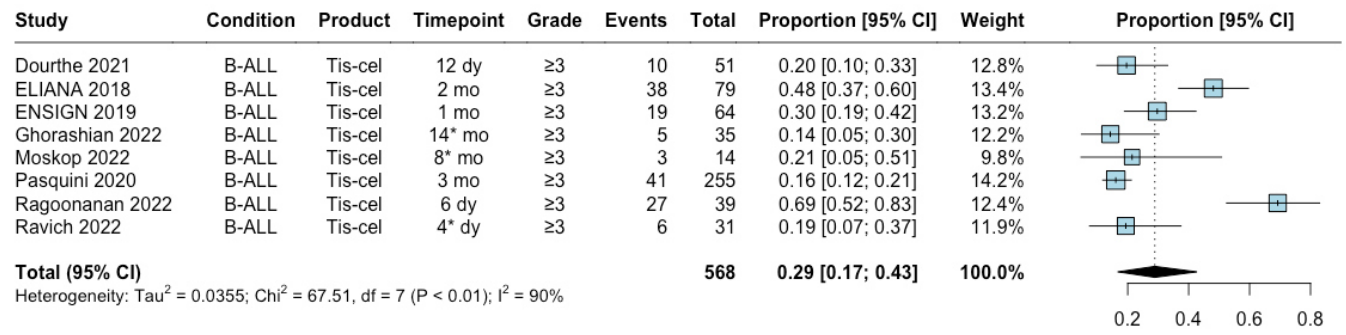
Figure 15 Any-grade cytokine release syndrome in B-ALL patients receiving tisa-cel (NRSI and single-arm combined)



Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **NRSI** = non-randomised studies of interventions, **tis-cel** = tisagenlecleucel.
Notes:
* Median timepoint.

One NRSI (which did not report CRS in the comparator arm) and 7 single-arm studies reported CRS grade ≥3 in patients with B-ALL being treated with tisa-cel (***Figure 16***). Between 4 days and 14 months (longest follow-up), 29% (95% CI: 17 to 43) reported CRS grade ≥3. Considerable heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 16 Grade ≥3 cytokine release syndrome in B-ALL patients receiving tisa-cel (NRSI and single-arm combined)

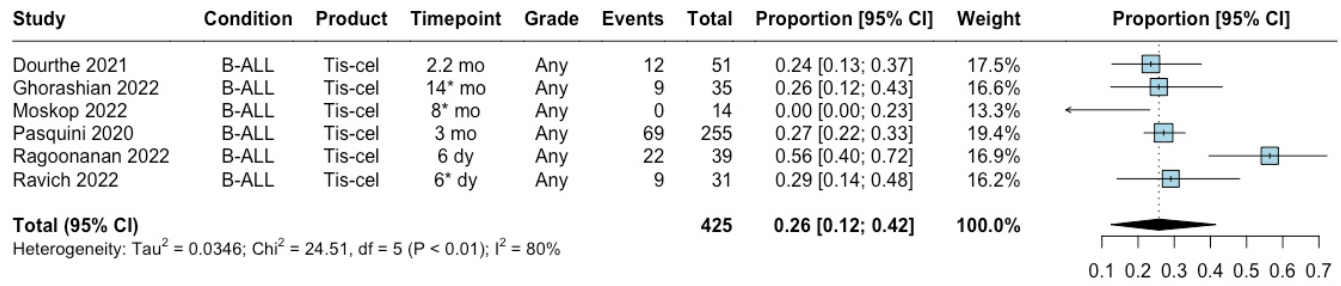


Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **NRSI** = non-randomised studies of interventions, **tis-cel** = tisagenlecleucel.
Notes:
* Median timepoint.

7.3.10.6 Immune effector cell-associated neurotoxicity syndrome

Overall, 1 NRSI (which did not report ICANS in the comparator arm) and 5 single-arm studies reported ICANS of any grade in patients with B-ALL being treated with tisa-cel (***Figure 17***). Between 6 days and 14 months (longest follow-up), 26% (95% CI: 12 to 42) reported ICANS of any grade. Considerable heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

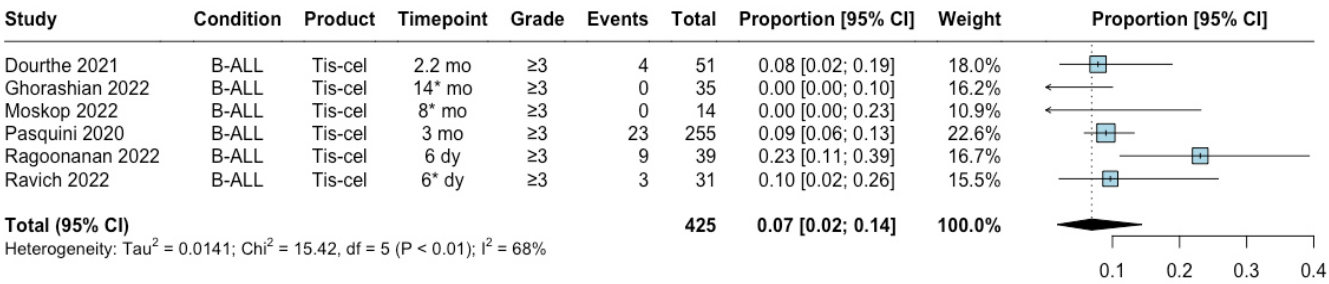
Figure 17 Any-grade immune effector cell-associated neurotoxicity syndrome in B-ALL patients receiving tisa-cel (NRSI and single-arm combined)



Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **NRSI** = non-randomised studies of interventions, **tis-cel** = tisagenlecleucel.
Notes:
* Median timepoint.

One NRSI (which did not report ICANS in the comparator arm) and 5 single-arm studies reported ICANS grade ≥3 in patients with B-ALL being treated with tisa-cel (***Figure 18***). Between 6 days and 14 months (longest follow-up), 7% (95% CI: 2 to 14) reported ICANS grade ≥3. Substantial heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 18 Grade ≥3 immune effector cell-associated neurotoxicity syndrome in B-ALL patients receiving tisa-cel (NRSI and single-arm combined)

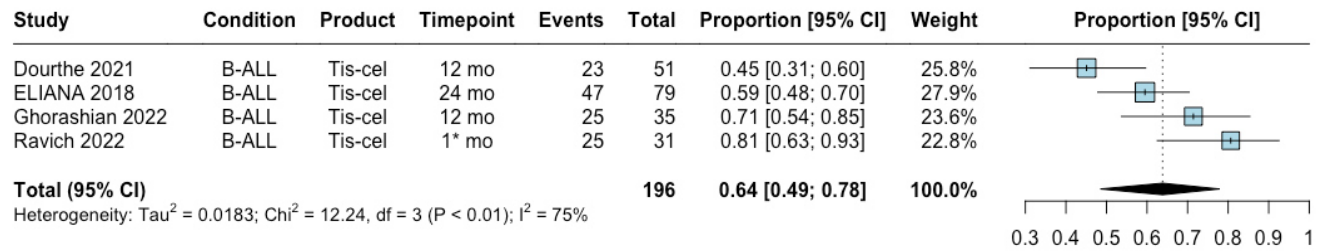


Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **NRSI** = non-randomised studies of interventions, **tis-cel** = tisagenlecleucel.
Notes:
* Median timepoint.

7.3.10.7 B-cell aplasia

B-cell aplasia was not reported in the included NRSI. Four single-arm studies reported B-cell aplasia in patients with B-ALL being treated with tisa-cel (***Figure 19***). Between 1 and 24 months (longest follow-up), 64% (95% CI: 49 to 78) reported B-cell aplasia. Considerable heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 19 B-cell aplasia in B-ALL patients receiving tisa-cel (single-arm)



Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **tis-cel** = tisagenlecleucel.
Notes:
* Median timepoint.

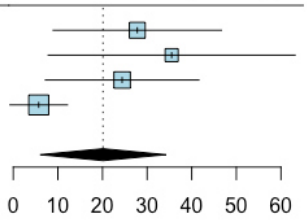
7.3.10.8 B-cell aplasia duration

B-cell aplasia duration was not reported in the included NRSI. Four single-arm studies reported B-cell aplasia in patients with B-ALL being treated with tisa-cel (***Figure 20***). The mean duration of B-cell aplasia was reported to be 20.11 months (95% CI: 6.01 to 34.21). Substantial heterogeneity was reported.

Figure 20 B-cell aplasia duration in B-ALL patients receiving tisa-cel (single-arm)

Study	Condition	Product	Total	Mean	SD	MRAW [95% CI]	Weight
ELIANA 2018	B-ALL	Tis-cel	50	27.80	68.10	27.80 [8.92; 46.68]	23.1%
ENSIGN 2019	B-ALL	Tis-cel	54	35.50	103.80	35.50 [7.81; 63.19]	15.6%
Ghorashian 2022	B-ALL	Tis-cel	35	24.40	52.00	24.40 [7.17; 41.63]	24.8%
Moskop 2022	B-ALL	Tis-cel	14	5.70	12.31	5.70 [-0.75; 12.15]	36.4%
Total (95% CI)			**153**			**20.11 [6.01; 34.21]**	**100.0%**

Heterogeneity: Tau^2 = 131.1516; Chi^2 = 10.97, df = 3 (P = 0.01); I^2 = 73%



Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **MRAW** = raw, untransformed mean, **SD** = standard deviation, **tis-cel** = tisagenlecleucel.

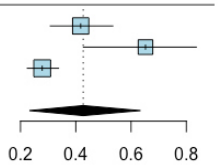
7.3.10.9 Cytopenia

Cytopenia was not reported in the included NRSI. Overall, 3 single-arm studies reported cytopenia in patients with B-ALL being treated with tisa-cel (***Figure 21***). Between 2 and 14 months (longest follow-up), 43% (95% CI: 23 to 63) reported cytopenia of any grade. Considerable heterogeneity was reported.

Figure 21 Cytopenia in B-ALL patients receiving tisa-cel (single-arm)

Study	Condition	Product	Type	Grade	Timepoint	Events	Total	Proportion [95% CI]	Weight
ELIANA 2018	B-ALL	Tis-cel	Cytopenia	Any	2 mo	33	79	0.42 [0.31; 0.53]	34.7%
Ghorashian 2022	B-ALL	Tis-cel	Cytopenia	Any	14* mo	15	23	0.65 [0.43; 0.84]	28.0%
Pasquini 2020	B-ALL	Tis-cel	Cytopenia	Any	3 mo	71	255	0.28 [0.22; 0.34]	37.3%
Total (95% CI)							**357**	**0.43 [0.23; 0.63]**	**100.0%**

Heterogeneity: Tau^2 = 0.0283; Chi^2 = 15.50, df = 2 (P < 0.01); I^2 = 87%



Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **tis-cel** = tisagenlecleucel.
Notes:
* Median timepoint.

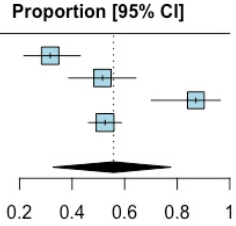
7.3.10.10 Hypogammaglobulinaemia

Hypogammaglobulinaemia was not reported in the included NRSI. Overall, 4 single-arm studies reported hypogammaglobulinaemia in patients with B-ALL being treated with tisa-cel (***Figure 22***).[117,120,122,125] Between 1 and 60 months (longest follow-up), 56% (95% CI: 33 to 78) reported hypogammaglobulinaemia of any grade. Considerable heterogeneity was reported.

Figure 22 Hypogammaglobulinaemia in B-ALL patients receiving tisa-cel (single-arm)

Study	Condition	Product	Timepoint	Grade	Events	Total	Proportion [95% CI]	Weight
ELIANA 2018	B-ALL	Tis-cel	2 mo	Any	25	79	0.32 [0.22; 0.43]	25.3%
ENSIGN 2019	B-ALL	Tis-cel	60** mo	Any	33	64	0.52 [0.39; 0.64]	25.0%
Ghorashian 2022	B-ALL	Tis-cel	14* mo	Any	27	31	0.87 [0.70; 0.96]	23.3%
Pasquini 2020	B-ALL	Tis-cel	1 mo	Any	134	255	0.53 [0.46; 0.59]	26.4%
Total (95% CI)						**429**	**0.56 [0.33; 0.78]**	**100.0%**

Heterogeneity: Tau^2 = 0.0516; Chi^2 = 31.71, df = 3 (P < 0.01); I^2 = 91%

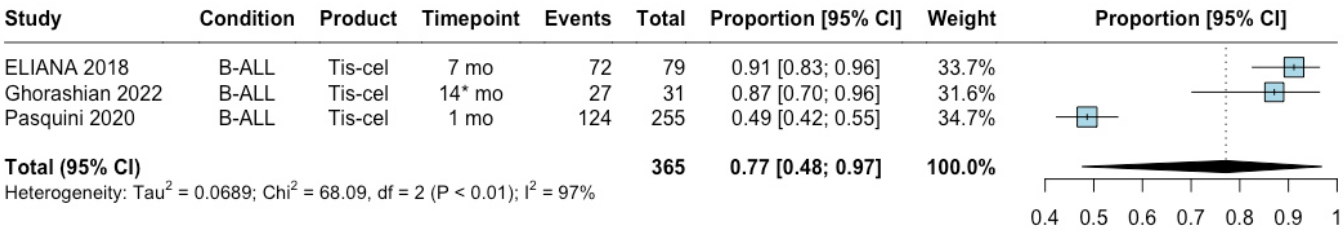


Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **tis-cel** = tisagenlecleucel.
Notes:
* Median timepoint.
** Point of last follow-up.

7.3.10.11 Use/administration of IVIG to treat hypogammaglobulinaemia

Usage or administration of IVIG was not reported in the included NRSI. Overall, 3 single-arm studies reported use/administration of IVIG to treat hypogammaglobulinaemia in patients with B-ALL being treated with tisa-cel (***Figure 23***).[117,120,125] Between 1 and 14 months (longest follow-up), 77% (95% CI: 48 to 97) reported use/administration of IVIG to treat hypogammaglobulinaemia. Considerable heterogeneity was reported.

Figure 23 Use or administration of IVIG to treat hypogammaglobulinaemia in B-ALL patients receiving tisa-cel (single-arm)

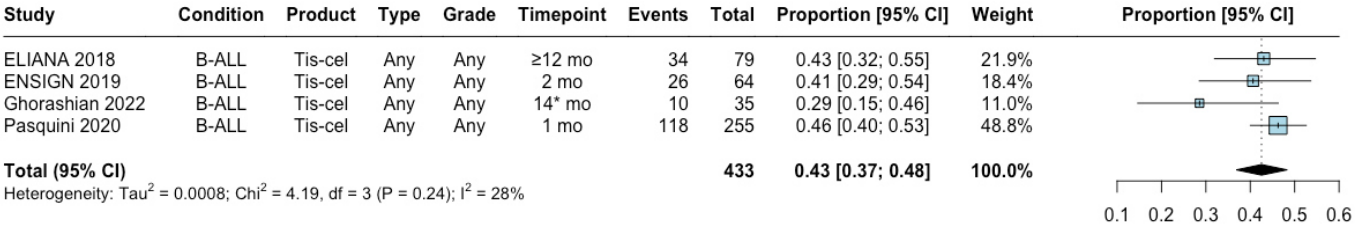


Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **tis-cel** = tisagenlecleucel.
Notes:
* Median timepoint.

7.3.10.12 Infections

Infections were not reported in the included NRSI. Overall, 4 single-arm studies reported infections in patients with B-ALL being treated with tisa-cel (***Figure 24***).[117,120,122,125] Between 1 and 14 months (longest follow-up), 43% (95% CI: 37 to 48) reported infections of any grade. Low heterogeneity was reported.

Figure 24 Infections in B-ALL patients receiving tisa-cel (single-arm)

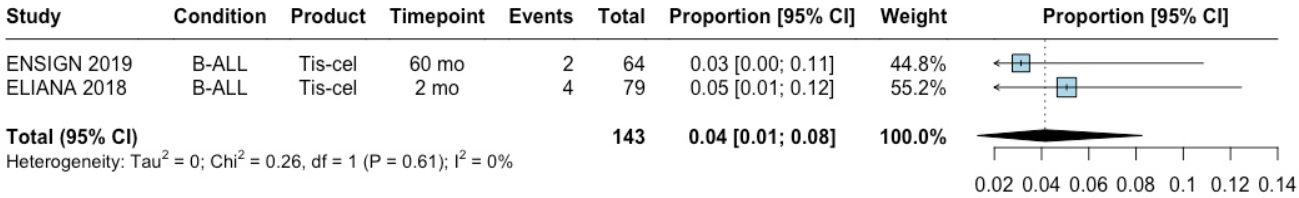


Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **tis-cel** = tisagenlecleucel.
Notes:
* Median timepoint.

7.3.10.13 Tumour lysis syndrome

TLS was not reported in the included NRSI. Overall, 2 single-arm studies reported TLS in patients with B-ALL being treated with tisa-cel (***Figure 25***).[120,122] Between 2 and 60 months (longest follow-up), 4% (95% CI: 1 to 8) reported TLS. Little to no heterogeneity was reported.

Figure 25 Tumour lysis syndrome in B-ALL patients receiving tisa-cel (single-arm)

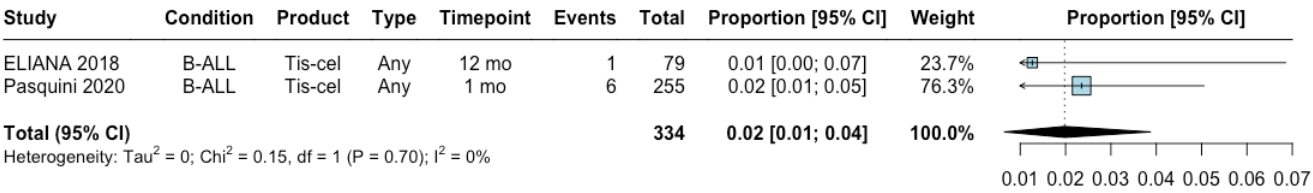


Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **tis-cel** = tisagenlecleucel.

7.3.10.14 Secondary malignancies

Secondary malignancies were not reported in the included NRSI. Overall, 2 single-arm studies reported secondary malignancies in patients with B-ALL being treated with tisa-cel (***Figure 26***).[2,125] Between 1 and 12 months (longest follow-up), 2% (95% CI: 1 to 4) reported secondary malignancies. Little to no heterogeneity was reported.

Figure 26 Secondary malignancies in B-ALL patients receiving tisa-cel (single-arm)



Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **mo** = months, **tis-cel** = tisagenlecleucel.

7.3.11 Effectiveness/efficacy findings: axi-cel for LBCL

Two NRSIs and 14 single-arm studies investigated the effectiveness/efficacy of axi-cel in the LBCL population. There was moderate to very low certainty evidence for the outcomes included in the GRADE assessment. A high-level summary of the results is as follows:

- Two NRSIs reported OS (could not be meta-analysed due to heterogeneity). At longest follow up, both trials reported statistically significant OS in favour of axi-cel. The 6 single-arm studies reported OS of 53% (95% CI: 49 to 59, n=90 at risk) at 20 months.
- One NRSI reported PFS. At 16 months, Mian 2021 reported statistically significant PFS (HR 0.04; 95% CI: 0.01 to 0.17) in favour of axi-cel when compared to no axi-cel. The 7 single-arm studies reported PFS of 36% (95% CI: 32 to 40, n=95 at risk) at 20 months.
- Two NRSIs reported a CRR of 0.22 (95% CI: 0.16 to 0.31) at 16-24 months, favouring axi-cel. The proportion of patients that experienced a complete response in the 11 single-arm studies was 52% (95% CI: 43 to 60) at 3 to 63 months.
- Two NRSIs reported an ORR of 0.23 (95% CI: 0.04 to 1.47) at 16 to 24 months, favouring axi-cel. The proportion of patients that experienced an overall response in the 11 single-arm studies was 73% (95% CI: 65 to 80).
- TFI and HRQoL were not reported in the NRSI or single-arm studies.

7.3.11.1 Effectiveness/efficacy summary tables: Axi-cel for LBCL

7.3.11.1.1 NRSI

A summary of the NRSI effectiveness evidence for axi-cel versus SoC and no axi-cel in LBCL is presented in ***Table 17***.

Table 17 Summary of NRSI effectiveness/efficacy evidence for axi-cel vs salvage chemotherapy or no axi-cel in LBCL

Outcome*	Mian 2021[127]			Neelapu 2021[128]			Summary estimate
	Axi-cel (n=27)	No axi-cel (n=11)	Difference (95% CI)	Axi-cel (n=81)	Salvage chemotherapy (n=331)	Difference (95% CI)	
Median follow-up, days/months	5 months (range: 2 to 16)	5 months (range: 2 to 16)	NA	27.1 months	5.4 months	NA	NA
Overall survival, probability (95% CI) †	NR	NR	HR 0.14 (95% CI: 0.05 to 0.38)	NR	NR	HR 0.27 (95% CI: 0.00 to 0.38)	NA
Overall survival, median months	13 months (95% CI: 7.7 to not reached)	1 month (95% CI: 0.4 to 3.7)	NR	31.0 months (95% CI: 11.5 to not estimable)	5.4 months (95% CI: 4.6 to 6.3)	25.6 months (95% CI: 6.0 to not estimable)	NA
Progression-free survival, probability (95% CI) †	NR	NR	HR 0.04 (95% CI: 0.01 to 0.17)	NR	NR	NR	k=1, n=38 HR 0.04 (95% CI: 0.01 to 0.17)
Progression-free survival, median months	10.5 months (95% CI: 5.7 to not reached)	NR	NR	NR	NR	NR	NA
Complete response rate, n (%)	13 (48.0)	NR	RR 0.09 (95% CI: 0.01 to 1.37)	43/80 (54.0)	41/340 (12.00)	RR: 0.22 (95% CI: 0.16 to 0.32)	k=2, n=458 RR: 0.22 (95% CI: 0.16 to 0.31)
Overall response rate, n (%)	23 (85.0)	0 (0.0)	RR 0.05 (95% CI: 0.00 to 0.77)	66/80 (83.0)	117/340 (34.00)	RR: 0.42 (95% CI: 0.35 to 0.50)	k=2, n=450 RR: 0.23 (95% CI: 0.04 to

Outcome*	Mian 2021[127]			Neelapu 2021[128]			Summary estimate
	Axi-cel (n=27)	No axi-cel (n=11)	Difference (95% CI)	Axi-cel (n=81)	Salvage chemotherapy (n=331)	Difference (95% CI)	
							1.47)
Treatment-free interval, median months	NR	NR	NR	NR	NR	NR	NR
HRQoL, mean (SD)	NR	NR	NR	NR	NR	NR	NR
Treatment discontinuation, n	NA	NA	NA	NA	NA	NA	NR

Abbreviations:
Axi-cel = axicabtagene ciloleucel, **CI** = confidence interval, **HR** = hazard ratio, **LBCL** = large B-cell lymphoma, **n** = number, **NA** = not applicable, **NR** = not reported, **NRSI** = non-randomised studies of interventions, **RR** = risk ratio, **auto-SCT** = autologous stem cell transplant, **SD** = standard deviation, **SoC** = standard of care, **HRQoL** = quality of life.
Notes:
* All outcomes reported at longest follow-up.
** Relative effects calculated as patients alive after standard of care vs CAR T, with HR or RR < 1 favouring CAR T (highlighted in blue font).

7.3.11.1.2 Single-arm

A summary of the single-arm effectiveness evidence for axi-cel in LBCL is presented in ***Table 18***.

Table 18 Summary of single-arm effectiveness/efficacy evidence for axi-cel in LBCL (1 of 2)

Outcome*	Gauthier 2022[133]	NCT03601442[138]	Bachy 2022[129]	Baird 2021[130]	Benoit 2023[131]	Bethge 2022[132]	Grana 2021[134]
	(n=68)	(n=156)	(n=209)	(n=41)	(n=15)	(n=173)	(n=37)
Median follow-up, days/months	3 months (NR)	12.4 months (NR)	13 months (95% CI: 12.1 to 13.5)	19.8 months (range: 3.3 to 27.6)	5.3 months (NR)	11 months (range: 1 to 29)	11 months (NR)
Overall survival, probability (95% CI)	NR	NR	63.5 (95% CI: 55.0 to 70.8)	68.7 (95% CI: 55.2 to 85.4)	NR	NR	NR
Overall survival, median months	NR	NR	NR	Not reached (16.6 to NE)	NR	NR	7.5 months (NR)
Progression-free survival, probability (95% CI)	NR	NR	46.6 (95% CI: 38.5 to 54.3)	63.4 (95% CI: 49.6 to 80.9)	6.3 (42)	60.55 (35)	NR
Progression-free survival, median months	NR	NR	NR	6.1 months (3.1 to NE)	3.2 months (NR)	NR	5.8 months (NR)
Complete response rate, n (%)	36 (53.0)	66/149 (44.0)	126 (60.3)	27 (66.0)	5 (33.0)	73 (42.0)	11 (30.0)

Outcome*	Gauthier 2022[133]	NCT03601442[138]	Bachy 2022[129]	Baird 2021[130]	Benoit 2023[131]	Bethge 2022[132]	Grana 2021[134]
Overall response rate, n (%)	49 (72.0)	77/149 (52.0)	168 (80.4)	36 (88.0)	7 (47.0)	128 (74.0)	NR
Treatment-free interval, median months	NR	NR	NR	NR	NR	NR	NR
HRQoL, mean (SD)	NR	NR	NR	NR	NR	NR	NR
Treatment discontinuation, n	0 (0.0)	12/168 (7.0)	NR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations:
axi-cel = axicabtagene ciloleucel, **CI** = confidence interval, **LBCL** = large B-cell lymphoma, **n** = number, **NA** = not applicable, **NE** = not estimable, **NR** = not reported, **SD** = standard deviation, **HRQoL** = quality of life.
Notes:
* All outcomes reported at longest follow-up.

Table 18b Summary of single-arm effectiveness/efficacy evidence for axi-cel in LBCL (continued, 2 of 2)

Outcome*	Melody 2022[135]	Panaite 2022[136]	Sesques 2020[139]	ZUMA-9 2020[145]	Pinnix 2020[137]	ZUMA-1[141-144,151]	Sim 2019[140]	Summary estimate
	(n=97)	(n=53)	(n=28)	(n=298)	(n=124)	(n=101)	(n=11)	
Median follow-up, days/months	30 days (NR)	NR	5.7 months (NR)	12.9 months (range: 3.2 to 20.7)	11.1 months (95% CI: 9.9 to 12.3)	63.1 months (range: 58.9 to 68.4)	3.3 months (range 1.1 to 12)	NA
Overall survival, n (%; 95% CI)	NR	NR	20 (73.7) (95% CI: 55.9 to 97.0)	187/275 (68.0) (95% CI: 63 to 74)	NR	43 (42.6) (95% CI: 32.8 to 51.9)	9 (87.5) (95% CI: 67.3 to 100)	k=6, n=654 53% (number at risk: 90; 95% CI: 49 to 59) at 20 months
Overall survival, median months	NR	NR	Not reached (95% CI: 4.6 to not reached)	Not reached (95% CI: NR)	21.9 months (NE)	25.8 months (95% CI: 12.8 to NE)	NR	NA
Progression-free survival, n (%; 95% CI)	NR	NR	13 (45.7) (95% CI: 29.3 to 71.3)	129/275 (47) (95% CI: 41 to 53)	46 (37) (95% CI: 26.4 to 44.1)	32 (31.8) (95% CI: 22.9 to 41.1)	11 (100) (95% CI: 0 to 1)	k=7, n=778 36% (number at risk: 95; 95% CI: 32 to 40) at 20 months
Progression-free survival, median months	NR	NR	3.1 months (95% CI: 2.9 to not reached)	8.3 months (95% CI: 6.0 to 15.1)	6.2 months (95% CI: 4.1 to 8.3)	5.9 months (95% CI: 3.3 to 15)	NR	NA
Complete response rate, n (%)	NR	NR	10/25 (40.0)	90/112 (80.0)	60 (48.0)	59 (58.0) 3/7 (43.0)	NR	k=12, n=1,061 52% (95% CI: 43

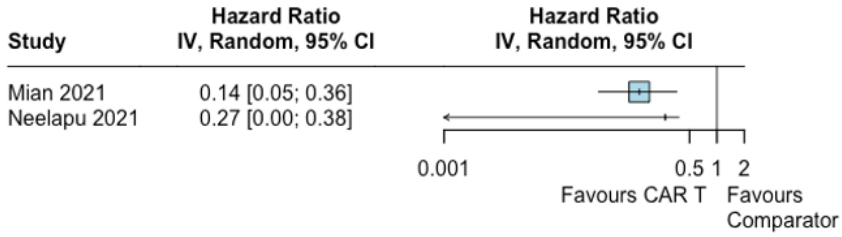
Outcome*	Melody 2022[135]	Panaite 2022[136]	Sesques 2020[139]	ZUMA-9 2020[145]	Pinnix 2020[137]	ZUMA-1[141-144,151]	Sim 2019[140]	Summary estimate
								to 60)
Overall response rate, n (%)	NR	37 (70.0)	12/25 (48.0)	225/275 (82.0)	96 (77.0)	84 (83.0) 5/7 (71.0)	NR	k=11, n=1,240 73% (95% CI: 65 to 80)
Treatment-free interval, median months	NR	NR	NR	NR	NR	NR	NR	NA
HRQoL, mean (SD)	NR	NR	NR	NR	NR	NR	NR	NA
Treatment discontinuation, n	0 (0.0)	0 (0.0)	NR	23 (8.0)	24/148 (16.0)	10/111 (9.0)	NR	k=12, n=1,247 3% (95% CI: 0 to 8)

Abbreviations:
Axi-cel = axicabtagene ciloleucel, **CI** = confidence interval, **LBCL** = large B-cell lymphoma, **n** = number, **NA** = not applicable, **NE** = not estimable, **NR** = not reported, **SD** = standard deviation, **tisa-cel** = tisagenlecleucel, **HRQoL** = health-related quality of life.
Notes:
* All outcomes reported at longest follow-up.

7.3.11.2 Overall survival

Overall, 2 NRSIs reported OS in patients with LBCL when comparing axi-cel to no axi-cel (Mian 2021) or salvage chemotherapy (Neelapu 2021).[127,128] At longest follow up, both studies reported statistically significant OS in favour of axi-cel (***Figure 27***). The overall GRADE certainty of evidence for axi-cel versus standard care was assessed to be very low (Mian 2021) and moderate (Neelapu 2021).

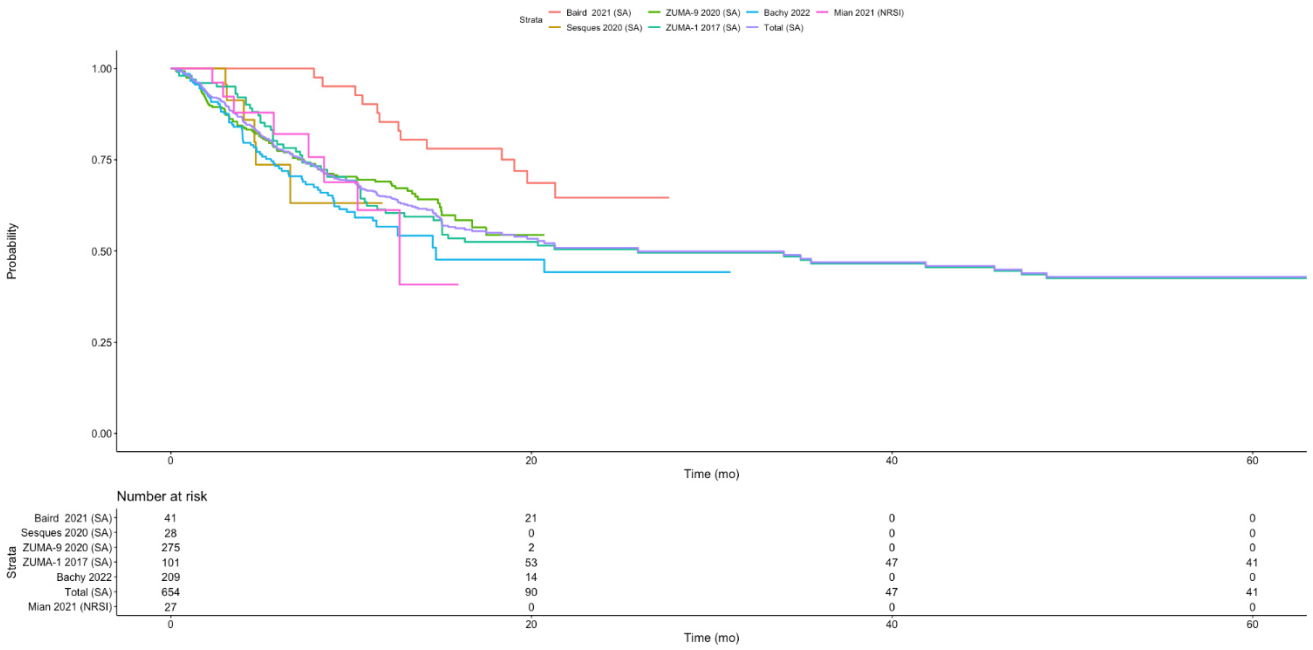
Figure 27 Overall survival in LBCL patients receiving axi-cel (NRSI)



Abbreviations:
Axi-cel = axicabtagene ciloleucel, **CAR T** = chimeric antigen receptor T cell, **CI** = confidence interval, **HR** = hazard ratio, **IV** = inverse variance, **LBCL** = large B-cell lymphoma, **NRSI** = non-randomised studies of interventions.

One NRSI and 6 single-arm studies illustrated OS using KM curves (***Figure 28***).[127,129,130,139,144,145] In the NRSI, survival gradually declined over the follow-up period. Survival was 92% (24 at risk; 95% CI: 83 to 100) at 3 months, 82% (14 at risk; 95% CI: 67 to 100) at 6 months, and 61% (4 at risk; 95% CI: 41 to 91) at 12 months. The single-arm studies illustrated a similar decline in survival for LBCL patients receiving axi-cel.[129,130,139,144,145] Survival was 82% (480 at risk; 95% CI: 79 to 85) at 5 months, 70% (359 at risk; 95% CI: 66 to 73) at 10 months, and 53% (90 at risk; 95% CI: 49 to 59) at 20 months.

Figure 28 Combined overall survival curves in LBCL patients receiving axi-cel (NRSI and single-arm)

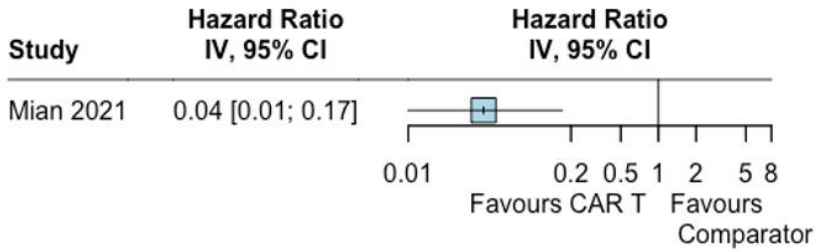


Abbreviations:
axi-cel = axicabtagene ciloleucel, **LBCL** = large B-cell lymphoma, **mo** = months, **NRSI** = non-randomised studies of interventions, **SA** = single-arm studies.

7.3.11.3 Progression-free survival

Overall, one NRSI reported PFS in patients with LBCL when comparing axi-cel to no axi-cel.[127] At 16 months, Mian 2021 reported statistically significant PFS in favour of axi-cel (***Figure 29***). The overall GRADE certainty of evidence for axi-cel versus no axi-cel was assessed to be very low.

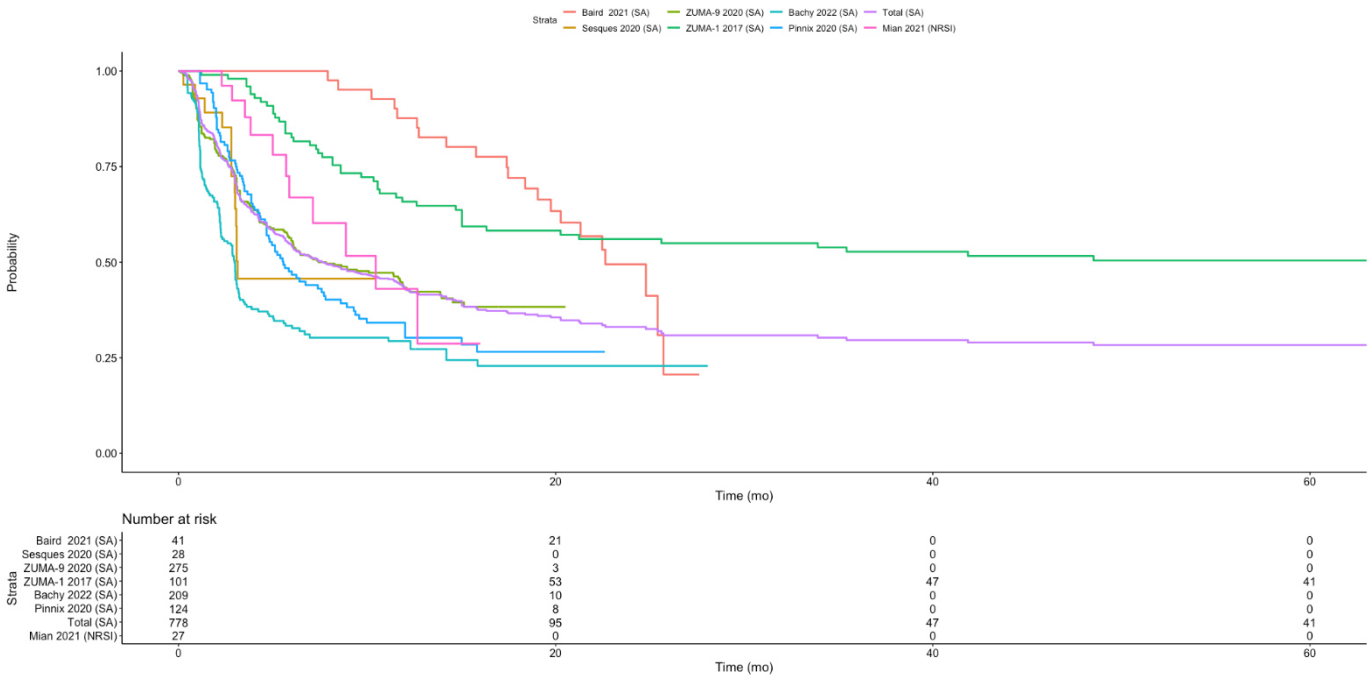
Figure 29 Progression-free survival in LBCL patients receiving axi-cel (NRSI)



Abbreviations:
axi-cel = axicabtagene ciloleucel, **CAR T** = chimeric antigen receptor T cell, **CI** = confidence interval, **HR** = hazard ratio, **IV** = inverse variance, **LBCL** = large B-cell lymphoma, **NRSI** = non-randomised studies of interventions.

One NRSI and 6 single-arm studies illustrated PFS using KM curves (***Figure 30***).[127,129,130,137,139,144,145] Overall PFS was 47% (288 at risk; 95% CI: 43 to 51) at 10 months, and 36% (95 at risk; 95% CI: 32 to 40) at 20 months.

Figure 30 Combined progression-free survival curves in LBCL patients receiving axi-cel (NRSI and single-arm)



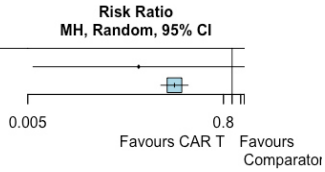
Abbreviations:
axi-cel = axicabtagene ciloleucel, **LBCL** = large B-cell lymphoma, **mo** = months, **NRSI** = non-randomised studies of interventions, **SA** = single-arm studies.

7.3.11.4 Complete response rate

Overall, 2 NRSIs reported CRR in patients with LBCL, comparing axi-cel to no axi-cel (Mian 2021) or salvage chemotherapy (Neelapu 2021).[127,128] At longest follow up, there was no evidence of a statistically significant difference in patients treated with axi-cel compared to no axi-cel; a statistically significant difference favouring axi-cel was observed compared to salvage chemotherapy (***Figure 31***). The overall GRADE certainty of evidence was assessed to be very low for axi-cel versus no axi-cel, and moderate for axi-cel versus salvage chemotherapy.

Figure 31 Complete response rate in LBCL patients receiving axi-cel (NRSI)

Study	Condition	Product	Comparator	Timepoint	Comparator Events	Comparator Total	CAR T Events	CAR T Total	Risk Ratio MH, Random, 95% CI	Weight
Mian 2021	LBCL	Axi-cel	No axi-cel	16 mo	0	11	13	27	0.09 [0.01; 1.37]	1.6%
Neelapu 2021	LBCL	Axi-cel	Salvage chemotherapy	24 mo	41	340	43	80	0.22 [0.16; 0.32]	98.4%



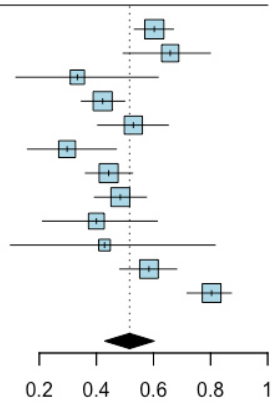
Abbreviations:
axi-cel = axicabtagene ciloleucel, **CAR T** = chimeric antigen receptor T cell, **CI** = confidence interval, **LBCL** = large B-cell lymphoma, **MH** = Mantel-Haenszel, **mo** = months.

Overall, 11 single-arm studies reported CRR in patients with LBCL being treated with axi-cel (***Figure 32***). Between 3 and 63 months (longest follow-up), 52% (95% CI: 43 to 60) achieved CR. Considerable heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 32 Complete response rate in LBCL patients receiving axi-cel (NRSI and single-arm)

Study	Condition	Product	Timepoint	Events	Total	Proportion [95% CI]	Weight
Bachy 2022	DLBCL	Axi-cel	13 mo	126	209	0.60 [0.53; 0.67]	10.1%
Baird 2021	LBCL	Axi-cel	20* mo	27	41	0.66 [0.49; 0.80]	8.1%
Benoit 2023	LBCL	Axi-cel	3 mo	5	15	0.33 [0.12; 0.62]	5.6%
Bethge 2022	LBCL	Axi-cel	11* mo	73	173	0.42 [0.35; 0.50]	10.0%
Gauthier 2022	B-NHL	Axi-cel	3 mo	36	68	0.53 [0.40; 0.65]	9.0%
Grana 2021	LBCL	Axi-cel	11* mo	11	37	0.30 [0.16; 0.47]	7.8%
NCT03601442 2022	B-NHL	Axi-cel	3 mo	66	149	0.44 [0.36; 0.53]	9.9%
Pinnix 2020	LBCL	Axi-cel	11* mo	60	124	0.48 [0.39; 0.58]	9.7%
Sesques 2020	LBCL	Axi-cel	3 mo	10	25	0.40 [0.21; 0.61]	6.9%
ZUMA-1	DLBCL	Axi-cel	12 mo	3	7	0.43 [0.10; 0.82]	3.7%
ZUMA-1	LBCL	Axi-cel	63* mo	59	101	0.58 [0.48; 0.68]	9.5%
ZUMA-9	LBCL	Axi-cel	3 mo	90	112	0.80 [0.72; 0.87]	9.6%
Total (95% CI)					**1061**	**0.52 [0.43; 0.60]**	**100.0%**

Heterogeneity: $Tau^2 = 0.0175$; $Chi^2 = 72.72$, df = 11 ($P < 0.01$); $I^2 = 85\%$

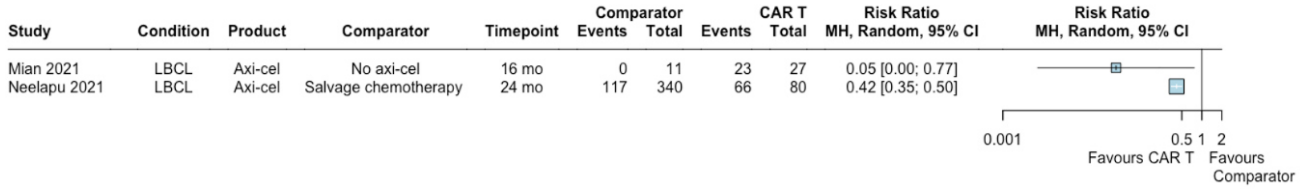


Abbreviations:
axi-cel = axicabtagene ciloleucel, **B-NHL** = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months.
Notes:
* Median timepoint.
** Point of last follow-up.

7.3.11.5 Overall response rate

Two NRSIs reported ORR in patients with LBCL, comparing axi-cel to no axi-cel (Mian 2021) or salvage chemotherapy (Neelapu 2021).[127,128] At longest follow up, a statistically significant difference favouring axi-cel was observed in both studies (***Figure 33***). The overall GRADE certainty of evidence was assessed to be very low for axi-cel versus no axi-cel, and moderate for axi-cel versus salvage chemotherapy.

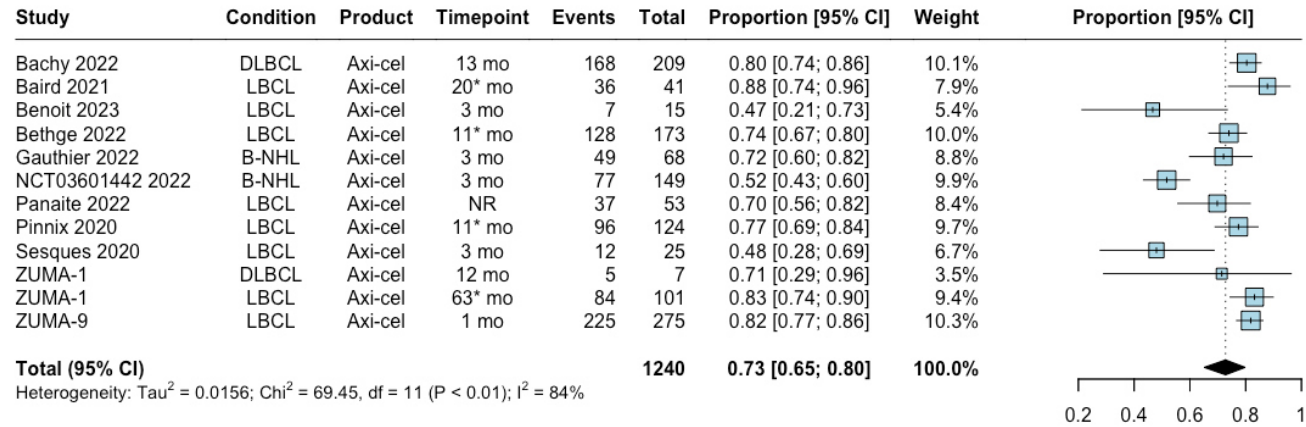
Figure 33 Overall response rate in LBCL patients receiving axi-cel (NRSI)



Abbreviations:
axi-cel = axicabtagene ciloleucel, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **MH** = Mantel-Haenszel, **mo** = months.

Overall, 11 single-arm studies reported ORR in patients with LBCL being treated with axi-cel (***Figure 34***). Between 1 and 63 months (longest follow-up), 73% (95% CI: 65 to 80) achieved OR. Considerable heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 34 Overall response rate in LBCL patients receiving axi-cel (single-arm)



Abbreviations:
axi-cel = axicabtagene ciloleucel, **B-NHL** = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months.
Notes:
* Median timepoint.

7.3.11.6 Treatment-free interval

TFI was not reported in the included NRSI or single-arm studies.

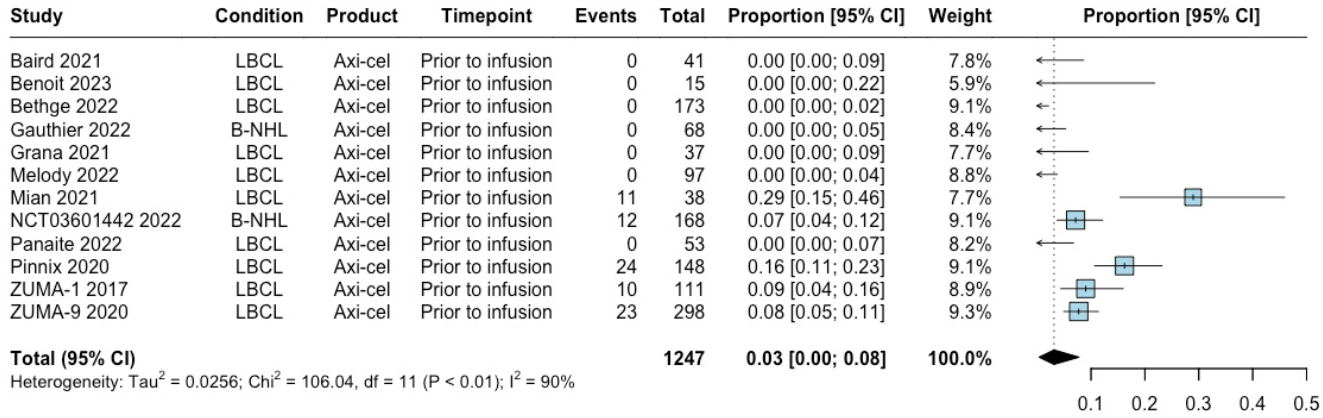
7.3.11.7 Health-related quality of life

HRQoL was not reported in the included NRSI or single-arm studies.

7.3.11.8 Treatment discontinuation

One NRSI (only axi-cel treatment arm included) and 11 single-arm studies reported treatment discontinuation in patients with LBCL being treated with axi-cel (***Figure 35***). The NRSI and single-arm studies were included in the same analysis because only the CAR T treatment arm was relevant for this outcome. Prior to CAR T infusion, 3% (95% CI: 0 to 8) discontinued treatment. Considerable heterogeneity was reported.

Figure 35 Treatment discontinuation in LBCL patients receiving axi-cel (single-arm)



Abbreviations:
axi-cel = axicabtagene ciloleucel, **B-NHL** = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months.

7.3.12 Safety findings: Axi-cel for LBCL

No NRSIs and 14 single-arm studies investigated the safety of axi-cel in the LBCL population. There was very low certainty evidence for the outcomes included in the GRADE assessment. A high-level summary of the results is as follows:

- SAEs, AES, TRAEs and B-cell aplasia rates were not well reported across the single-arm studies.
- The proportion of patients that experienced CRS (any) in the 12 single-arm studies was 89% (95% CI: 86 to 91) at 1 to 60 months.
- The proportion of patients that experienced ICANS (any) in the 12 single-arm studies was 55% (95% CI: 49 to 62) at 1 to 21 months.
- B-cell aplasia duration and TLS were not reported.

7.3.12.1 Safety summary tables: Axi-cel for LBCL

7.3.12.1.1 Single-arm

A summary of the single-arm safety evidence for axi-cel in LBCL is presented in ***Table 16***.

Table 19 Summary of single-arm safety evidence for axi-cel in LBCL (1 of 2)

Outcome*	Gauthier 2022[133]	NCT03601442[138]	Bachy 2022[129]	Baird 2021[130]	Benoit 2023[131]	Bethge 2022[132]	Grana 2021[134]
	(n=68)	(n=156)	(n=209)	(n=41)	(n=15)	(n=173)	(n=37)
Median follow-up, days/months	3 months (NR)	12.4 months (NR)	13 months (95% CI: 12.1 to 13.5)	19.8 months (range: 3.3 to 27.6)	5.3 months (NR)	11 months (range: 1 to 29)	11 months (NR)
SAE, any, n (%)	NR	NR	NR	NR	NR	NR	NR
AE, any, n (%)	NR	NR	NR	NR	NR	NR	NR
TRAE/TEAE, any, n (%)	NR	NR	NR	NR	NR	NR	NR
CRS							
any, n (%)	59 (87.0)	133 (85)	180 (86.1)	37 (90.2)	13 (87.0)	141 (82.0)	36 (97.3)
grade ≥3, n (%)	5 (7.3)	14 (9.0)	11 (5.3)	1 (2.4)	0 (0.0)	18 (10.0)	6 (16.2)
ICANS							
any, n (%)	42 (62.0)	88 (56.0)	102 (48.8)	23 (56.1)	6 (40.0)	76 (44.0)	27 (73.0)
grade ≥3, n (%)	20 (29.4)	60 (38.0)	29 (13.9)	10 (24.4)	2 (13.0)	28 (16.0)	16 (43.2)
B-cell aplasia, n (%)	NR	NR	NR	9/15 (60.0)	NR	NR	NR
median duration, days/months	NR	NR	NR	NR	NR	NR	NR
Cytopenia†, n (%)	NR	NR	71 (34.0)	NR	1 (7.0)‡	NR	NR
Hypogammaglobulinaemia, n (%)	NR	NR	NR	5/17 (29.4)	NR	NR	NR
IVIG usage, n (%)	NR	NR	NR	15 (37.0)	NR	NR	NR
Infections, n (%)	6 (9.0)‡	NR	NR	27 (66.0)	NR	NR	NR
Tumour lysis syndrome, n (%)	NR	NR	NR	NR	NR	NR	NR
Secondary malignancies, n (%)	NR	NR	NR	NR	NR	NR	NR

Table 20b Summary of single-arm safety evidence for axi-cel in LBCL, continued (2 of 2)

Outcome*	Melody 2022[135]	Panaite 2022[136]	Sesques 2020[139]	ZUMA-9 2020[145]	Pinnix 2020[137]	ZUMA-1[141-144,151]	Sim 2019[140]	Summary estimate
	(n=97)	(n=53)	(n=28)	(n=298)	(n=124)	(n=108)	(n=11)	
Median follow-up, days/months	30 days (NR)	NR	5.7 months (NR)	12.9 months (range: 3.2 to 20.7)	11.1 months (95% CI: 9.9 to 12.3)	63.1 months (range: 58.9 to 68.4)	3.3 months (range 1.1 to 12)	NA
SAE, any, n (%)	NR	NR	NR	NR	NR	60 (56)	NR	k=1, n=108 56% (95% CI: 46 to 65)
AE, any, n (%)	NR	NR	NR	NR	NR	108 (100)§	NR	k=1, n=108 100% (95% CI: 97 to 100)
TRAE/TEAE, any, n (%)	NR	NR	NR	NR	NR	77/77 (100) 24/24 (100)	NR	k=1, n=101 100% (95% CI: 98 to 100)
CRS								
any, n (%)	85 (88.0)	45 (85.0)	26 (93.0)	251/275 (91.2)	NR	94/101 (93.0) 6/7 (86.0)	NR	k=12, n=1,260 89% (95% CI: 86 to 91)
grade ≥3, n (%)	2 (2.0)	5 (9.0)	2 (7.0)	19/275 (7.0)	11 (9.0)	11/101 (11.0) 6/7 (86.0)	NR	k=13, n=1,384 7 (95% CI: 5 to 10)
ICANS								
any, n (%)	48 (49.0)	31 (58.0)	9 (32.0)	189/275 (69.0)	NR	6/7 (86.0)	NR	k=12, n=1,159 55% (95% CI: 49 to 62)
grade ≥3, n (%)	23 (24.0)	9 (17.0)	3 (11.0)	85/275 (31.0)	49 (40.0)	NR	NR	k=13, n=1,283 26% (95% CI: 19 to 32)
B-cell aplasia, n (%)	NR	NR	NR	NR	NR	3/7 (43.0)	NR	k=2, n=22 55% (95% CI: 33 to 76)
Median duration, days/months	NR	NR	NR	NR	NR	NR	NR	NA
Cytopenia, n (%)	NR	32 (60.0)‡	NR	NR	NR	59 (55.0)	NR	k=4, n=385 39% (95% CI: 18 to 63)
Hypogammaglobulinaemia, n (%)	NR	NR	NR	NR	NR	3/7 (43.0)	NR	k=2, n=24 33% (95% CI: 14 to 54)
IVIG usage, n (%)	NR	15 (28.0)	NR	NR	NR	NR	NR	k=2, n=94 32% (95% CI: 23 to 42)

Outcome*	Melody 2022[135]	Panaite 2022[136]	Sesques 2020[139]	ZUMA-9 2020[145]	Pinnix 2020[137]	ZUMA-1[141-144,151]	Sim 2019[140]	Summary estimate
Infections, n (%)	NR	40 (75.0)	NR	NR	NR	30 (28.0)‡	1 (9.1)	k=5, n=281 36% (95% CI: 11 to 66)
Tumour lysis syndrome, n (%)	NR	NR	NR	NR	NR	NR	NR	NA
Secondary malignancies, n (%)	NR	NR	NR	NR	NR	5/101 (5.0)	NR	k=1, n=101 5 (95% CI: 2 to 11)

Abbreviations:

Axi-cel = axicabtagene ciloleucel, **AE** = adverse event, **CI** = confidence interval, **CRS** = cytokine release syndrome, **ICANS** = immune effector cell-associated neurotoxicity syndrome, **IVIG** = intravenous immunoglobulin, **k** = number of publications, **LBCL** = large B-cell lymphoma**, n** = number, **NA** = not applicable, **NR** = not reported, **SA** = single arm, **SAE** = serious adverse event, **TRAE/TEAE** = treatment-related/-emergent adverse event.

Notes:

* All outcomes reported at longest follow-up.

‡ Only grade 3-4 reported.

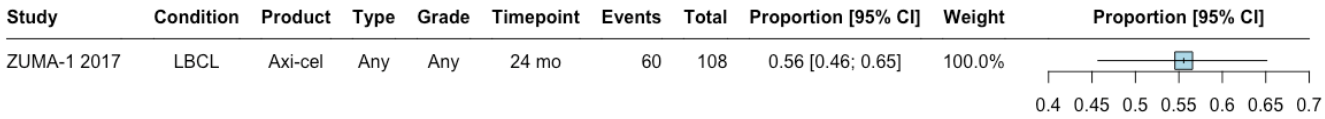
§ 96/101 (95) of these AEs were grade ≥3

† 1 month of follow up.

7.3.12.2 Serious adverse events

SAEs were not reported in the included NRSI. One single-arm study reported SAEs in patients with LBCL being treated with axi-cel (***Figure 36***). At 24 months, 56% (95% CI: 46 to 65) reported SAEs of any grade. Heterogeneity could not be assessed.

Figure 36 Serious adverse events in LBCL patients receiving axi-cel (single-arm)

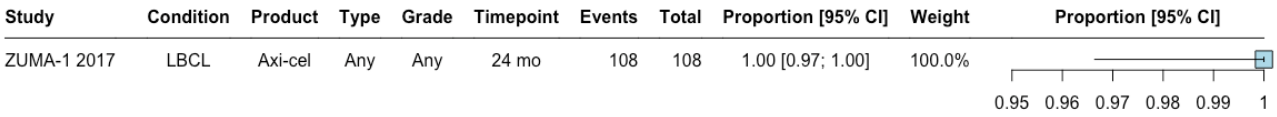


Abbreviations:
axi-cel = axicabtagene ciloleucel, **CI** = confidence interval, **LBCL** = large B-cell lymphoma, **mo** = months.

7.3.12.3 Adverse events

AEs were not reported in the included NRSI. One single-arm study reported AEs in patients with LBCL being treated with axi-cel (***Figure 37***) At 24 months, 100% (95% CI: 97 to 100) reported AEs of any grade. Heterogeneity could not be assessed. Along with any-grade AEs, one study also reported that 95% of participants (96/101) experienced AE grade ≥3 at 20 months.[141]

Figure 37 Adverse events in LBCL patients receiving axi-cel (single-arm)

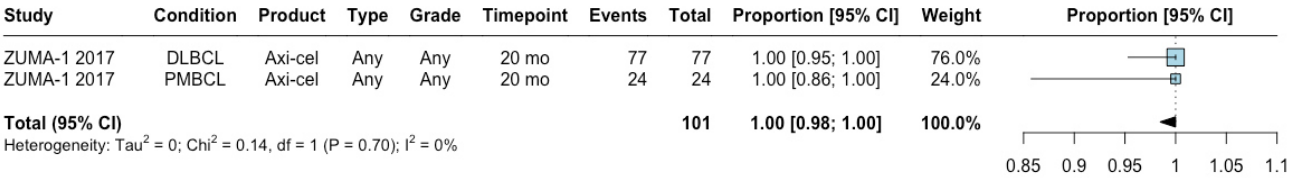


Abbreviations:
axi-cel = axicabtagene ciloleucel, **CI** = confidence interval, **LBCL** = large B-cell lymphoma, **mo** = months.

7.3.12.4 Treatment-related/-emergent adverse events

TRAEs/TEAEs were not reported in the included NRSI. One single-arm study (with 2 population arms) reported TRAEs/TEAEs in patients with LBCL being treated with axi-cel (***Figure 38***). At the longest follow-up, 100% (95% CI: 98 to 100) reported TRAEs/TEAEs of any grade. Little to no heterogeneity was reported.

Figure 38 Treatment-related/-emergent adverse events in LBCL patients receiving axi-cel (single-arm)



Abbreviations:
axi-cel = axicabtagene ciloleucel, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months, **PMBCL** = primary mediastinal B-cell lymphoma.

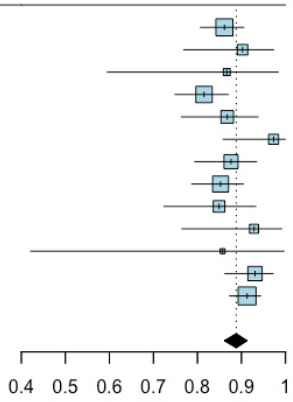
7.3.12.5 Cytokine release syndrome

CRS was not reported in the included NRSI. Overall, 12 single-arm studies reported CRS of any grade in patients with LBCL being treated with axi-cel (***Figure 39***). Between 1 and 60 months (longest follow-up), 89% (95% CI: 86 to 91) reported CRS of any grade. Moderate heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 39 Any-grade cytokine release syndrome in LBCL patients receiving axi-cel (single-arm)

Study	Condition	Product	Timepoint	Grade	Events	Total	Proportion [95% CI]	Weight
Bachy 2022	DLBCL	Axi-cel	13 mo	Any	180	209	0.86 [0.81; 0.91]	13.2%
Baird 2021	LBCL	Axi-cel	20* mo	Any	37	41	0.90 [0.77; 0.97]	5.0%
Benoit 2023	LBCL	Axi-cel	5* mo	Any	13	15	0.87 [0.60; 0.98]	2.2%
Bethge 2022	LBCL	Axi-cel	3 mo	Any	141	173	0.82 [0.75; 0.87]	12.2%
Gauthier 2022	B-NHL	Axi-cel	NR	Any	59	68	0.87 [0.76; 0.94]	7.2%
Grana 2021	LBCL	Axi-cel	6 mo	Any	36	37	0.97 [0.86; 1.00]	4.6%
Melody 2022	LBCL	Axi-cel	1 mo	Any	85	97	0.88 [0.79; 0.93]	9.0%
NCT03601442 2022	B-NHL	Axi-cel	NR	Any	133	156	0.85 [0.79; 0.90]	11.6%
Panaite 2022	LBCL	Axi-cel	NR	Any	45	53	0.85 [0.72; 0.93]	6.1%
Sesques 2020	LBCL	Axi-cel	1 mo	Any	26	28	0.93 [0.76; 0.99]	3.7%
ZUMA-1 2017	DLBCL	Axi-cel	1 mo	Any	6	7	0.86 [0.42; 1.00]	1.1%
ZUMA-1 2017	LBCL	Axi-cel	60 mo	Any	94	101	0.93 [0.86; 0.97]	9.3%
ZUMA-9 2020	LBCL	Axi-cel	21 mo	Any	251	275	0.91 [0.87; 0.94]	14.6%
Total (95% CI)						**1260**	**0.89 [0.86; 0.91]**	**100.0%**

Heterogeneity: $Tau^2 = 0.0018$; $Chi^2 = 18.69$, df = 12 (P = 0.10); $I^2 = 36\%$



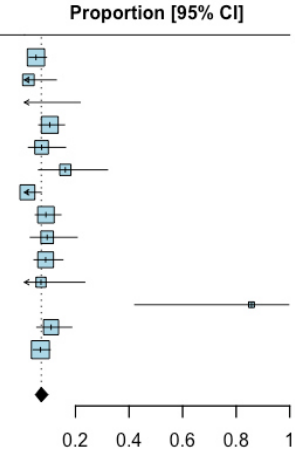
Abbreviations:
axi-cel = axicabtagene ciloleucel, **B-NHL** = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months, **NR** = not reported.
Notes:
* Median timepoint.

Thirteen single-arm studies reported CRS grade ≥3 in patients with LBCL being treated with axi-cel (***Figure 40***). Between 1 and 60 months (longest follow-up), 7% (95% CI: 5 to 10) reported CRS grade ≥3. Moderate heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 40 Cytokine release syndrome ≥3 grade in LBCL patients receiving axi-cel (single-arm combined)

Study	Condition	Product	Timepoint	Grade	Events	Total	Proportion [95% CI]	Weight
Bachy 2022	DLBCL	Axi-cel	13 mo	≥3	11	209	0.05 [0.03; 0.09]	11.2%
Baird 2021	LBCL	Axi-cel	20* mo	≥3	1	41	0.02 [0.00; 0.13]	5.0%
Benoit 2023	LBCL	Axi-cel	5* mo	≥3	0	15	0.00 [0.00; 0.22]	2.3%
Bethge 2022	LBCL	Axi-cel	3 mo	≥3	18	173	0.10 [0.06; 0.16]	10.6%
Gauthier 2022	B-NHL	Axi-cel	NR	≥3	5	68	0.07 [0.02; 0.16]	6.9%
Grana 2021	LBCL	Axi-cel	6 mo	≥3	6	37	0.16 [0.06; 0.32]	4.7%
Melody 2022	LBCL	Axi-cel	1 mo	≥3	2	97	0.02 [0.00; 0.07]	8.3%
NCT03601442 2022	B-NHL	Axi-cel	NR	≥3	14	156	0.09 [0.05; 0.15]	10.2%
Panaite 2022	LBCL	Axi-cel	NR	≥2	5	53	0.09 [0.03; 0.21]	5.9%
Pinnix 2020	LBCL	Axi-cel	11 mo**	≥3	11	124	0.09 [0.05; 0.15]	9.3%
Sesques 2020	LBCL	Axi-cel	1 mo	≥3	2	28	0.07 [0.01; 0.24]	3.8%
ZUMA-1 2017	DLBCL	Axi-cel	1 mo	≥3	6	7	0.86 [0.42; 1.00]	1.2%
ZUMA-1 2017	LBCL	Axi-cel	60 mo	≥3	11	101	0.11 [0.06; 0.19]	8.5%
ZUMA-9 2020	LBCL	Axi-cel	21 mo	≥3	19	275	0.07 [0.04; 0.11]	12.1%
Total (95% CI)						**1384**	**0.07 [0.05; 0.10]**	**100.0%**

Heterogeneity: $Tau^2 = 0.0027$; $Chi^2 = 39.72$, df = 13 (P < 0.01); $I^2 = 67\%$



Abbreviations:
axi-cel = axicabtagene ciloleucel, **B-NHL** = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months, **NR** = not reported.
Notes:
* Median timepoint. ** Point of last follow-up.

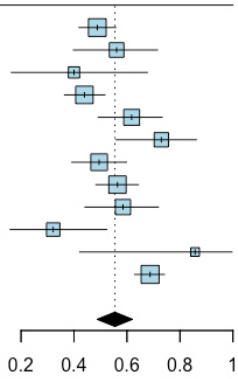
7.3.12.6 Immune effector cell-associated neurotoxicity syndrome

ICANS was not reported in the included NRSI. Overall, 12 single-arm studies reported ICANS of any grade in patients with LBCL being treated with axi-cel (***Figure 41***). Between 1 and 21 months (longest follow-up), 55% (95% CI: 49 to 62) reported ICANS of any grade. Considerable heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 41 Any-grade immune effector cell-associated neurotoxicity syndrome in LBCL patients receiving axi-cel (single-arm)

Study	Condition	Product	Timepoint	Grade	Events	Total	Proportion [95% CI]	Weight
Bachy 2022	DLBCL	Axi-cel	13 mo	Any	102	209	0.49 [0.42; 0.56]	11.2%
Baird 2021	LBCL	Axi-cel	20* mo	Any	23	41	0.56 [0.40; 0.72]	7.6%
Benoit 2023	LBCL	Axi-cel	5* mo	Any	6	15	0.40 [0.16; 0.68]	4.5%
Bethge 2022	LBCL	Axi-cel	3 mo	Any	76	173	0.44 [0.36; 0.52]	10.9%
Gauthier 2022	B-NHL	Axi-cel	NR	Any	42	68	0.62 [0.49; 0.73]	9.0%
Grana 2021	LBCL	Axi-cel	6 mo	Any	27	37	0.73 [0.56; 0.86]	7.3%
Melody 2022	LBCL	Axi-cel	1 mo	Any	48	97	0.49 [0.39; 0.60]	9.9%
NCT03601442 2022	B-NHL	Axi-cel	NR	Any	88	156	0.56 [0.48; 0.64]	10.8%
Panaite 2022	LBCL	Axi-cel	NR	Any	31	53	0.58 [0.44; 0.72]	8.3%
Sesques 2020	LBCL	Axi-cel	1 mo	Any	9	28	0.32 [0.16; 0.52]	6.4%
ZUMA-1 2017	DLBCL	Axi-cel	1 mo	Any	6	7	0.86 [0.42; 1.00]	2.7%
ZUMA-9 2020	LBCL	Axi-cel	21 mo	Any	189	275	0.69 [0.63; 0.74]	11.5%
Total (95% CI)						**1159**	**0.55 [0.49; 0.62]**	**100.0%**

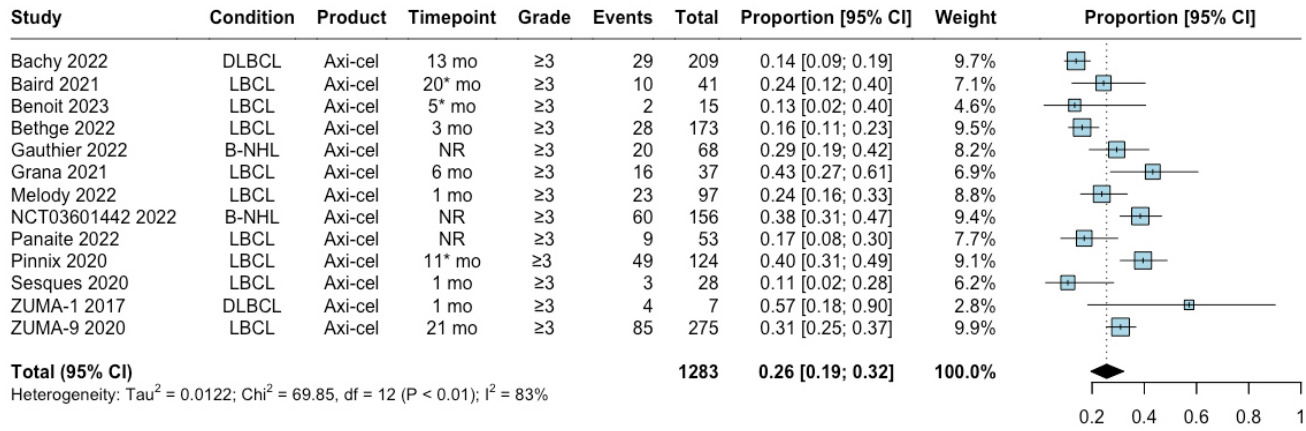
Heterogeneity: $Tau^2 = 0.0089$; $Chi^2 = 50.73$, df = 11 ($P < 0.01$); $I^2 = 78\%$



Abbreviations:
axi-cel = axicabtagene ciloleucel, **B-NHL** = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months, **NR** = not reported.
Notes:
* Median timepoint.

ICANS grade ≥3 was not reported in the included NRSI. Thirteen single-arm studies reported ICANS grade ≥3 in patients with LBCL being treated with axi-cel (***Figure 42***). Between 1 and 21 months (longest follow-up), 26% (95% CI: 19 to 32) reported ICANS grade ≥3. Considerable heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 42 Immune effector cell-associated neurotoxicity syndrome grade ≥3 in LBCL patients receiving axi-cel (single-arm)

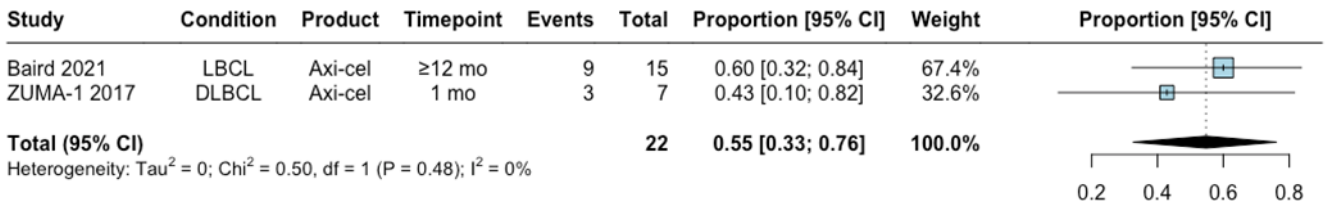


Abbreviations:
axi-cel = axicabtagene ciloleucel, **B-NHL** = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months, **NR** = not reported.
Notes:
* Median timepoint.

7.3.12.7 B-cell aplasia

B-cell aplasia was not reported in the included NRSI. Two single-arm studies reported B-cell aplasia in patients with LBCL being treated with axi-cel (***Figure 43***). From 1 month to ≥12 months, 55% (95% CI: 33 to 76) reported B-cell aplasia. Little to no heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 43 B-cell aplasia in LBCL patients receiving axi-cel (single-arm)



Abbreviations:
axi-cel = axicabtagene ciloleucel, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months.

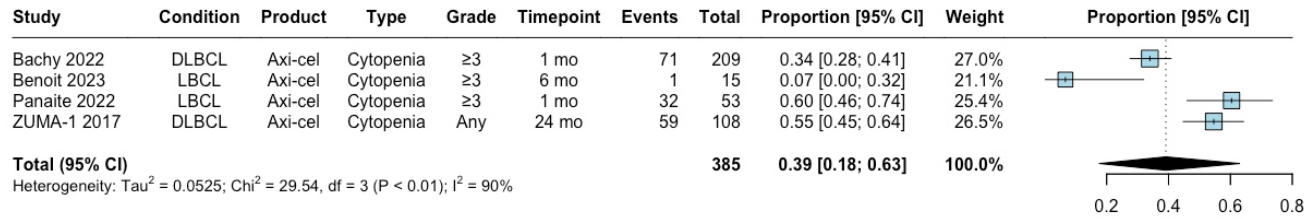
7.3.12.8 B-cell aplasia duration

B-cell aplasia duration was not reported in the included NRSI or the single-arm studies.

7.3.12.9 Cytopenia

Cytopenia was not reported in the included NRSI. Overall, 4 single-arm studies reported cytopenia in patients with LBCL being treated with axi-cel (***Figure 44***). Between 1 and 24 months (longest follow-up), 39% (95% CI: 18 to 63) reported cytopenia of any grade or grade ≥3. Considerable heterogeneity was reported.

Figure 44 Cytopenia in LBCL patients receiving axi-cel (single-arm)

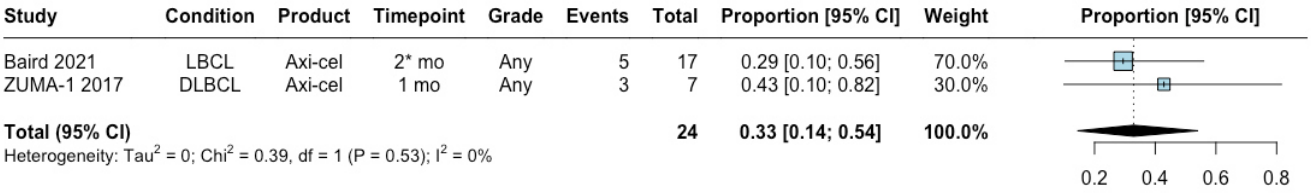


Abbreviations:
axi-cel = axicabtagene ciloleucel, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months.

7.3.12.10 Hypogammaglobulinaemia

Hypogammaglobulinaemia was not reported in the included NRSI. Overall, 2 single-arm studies reported hypogammaglobulinaemia in patients with LBCL being treated with axi-cel (***Figure 45***). Between 1 and 2 months (longest follow-up), 33% (95% CI: 14 to 54) reported hypogammaglobulinaemia of any grade. Little to no heterogeneity was reported.

Figure 45 Hypogammaglobulinaemia in LBCL patients receiving axi-cel (single-arm)

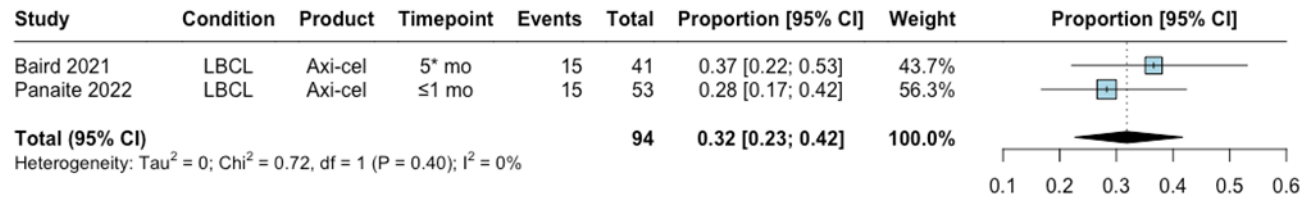


Abbreviations:
axi-cel = axicabtagene ciloleucel, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months.
Notes:
* Median timepoint.

7.3.12.11 Usage/administration of IVIG to treat hypogammaglobulinaemia

Usage/administration of IVIG was not reported in the included NRSI. Overall, 2 single-arm studies reported usage/administration of IVIG to treat hypogammaglobulinaemia in patients with LBCL being treated with axi-cel (***Figure 46***). From ≤1 month to 5 months (longest follow-up), 32% (95% CI: 23 to 42) reported usage/administration of IVIG to treat hypogammaglobulinaemia. Little to no heterogeneity was reported.

Figure 46 Usage/administration of IVIG to treat hypogammaglobulinaemia in LBCL patients receiving axi-cel (single-arm)

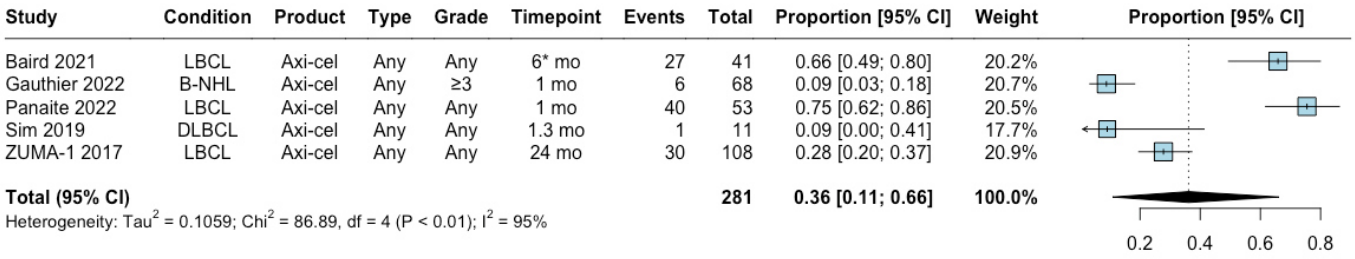


Abbreviations:
axi-cel = axicabtagene ciloleucel, **CI** = confidence interval, **IVIG** = intravenous immunoglobulin, **LBCL** = large B-cell lymphoma, **mo** = months.
Notes:
* Median timepoint.

7.3.12.12 Infections

Infections were not reported in the included NRSI. Overall, 5 single-arm studies reported infections in patients with LBCL being treated with axi-cel (***Figure 47***). Between 1 month and 24 months (longest follow-up), 36% (95% CI: 11 to 66) reported infections of any grade or grade ≥3. Considerable heterogeneity was reported.

Figure 47 Infections in LBCL patients receiving axi-cel (single-arm)



Abbreviations:
axi-cel = axicabtagene ciloleucel, **B-NHL** = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **LBCL** = large B-cell lymphoma, **mo** = months.
Notes:
* Median timepoint.

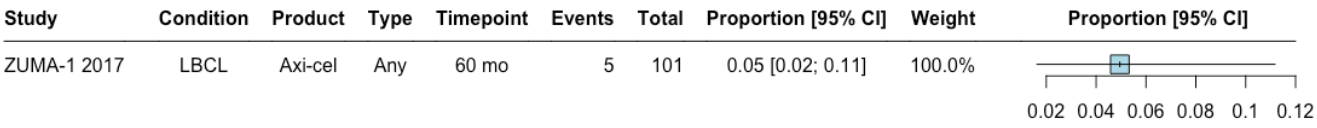
7.3.12.13 Tumour lysis syndrome

TLS was not reported in the included NRSI or single-arm studies.

7.3.12.14 Secondary malignancies

Secondary malignancies were not reported in the included NRSI. One single-arm study reported secondary malignancies in patients with LBCL treated with axi-cel (***Figure 48***). At 60 months (longest follow-up), 5% (95% CI: 0.02 to 0.11) reported secondary malignancies. Heterogeneity could not be assessed.

Figure 48 Secondary malignancies in LBCL patients receiving axi-cel (single-arm)



Abbreviations:
axi-cel = axicabtagene ciloleucel, **CI** = confidence interval, **LBCL** = large B-cell lymphoma, **mo** = months.

7.3.13 Effectiveness/efficacy findings: Tisa-cel for LBCL

One NRSI and 9 single-arm studies investigated the effectiveness/efficacy of tisa-cel in the LBCL population. There was very low certainty evidence for the outcomes included in the GRADE assessment. A high-level summary of the results is as follows:

- The NRSI reported OS (HR 0.60, 95% CI: 0.44 to 0.77) favouring tisa-cel at 50-90 months. The reported OS in 5 single-arm studies was 44% (number at risk: 73; 95% CI: 39 to 50) at 15 months.
- The NRSI did not report PFS. The reported PFS in 4 single-arm studies was 30% (number at risk: 47; 95% CI: 25 to 36) at 15 months.
- The NRSI did not report CRR. The proportion of patients that experienced a complete response in 8 single-arm studies was 37% (95% CI: 33 to 42) at 3 to 12 months.
- The NRSI reported an ORR of 1.31 (95% CI: 0.97 to 1.77), reporting a non-statistically significant difference favouring the comparator. The proportion of patients that experienced an overall response in 8 single-arm studies was 55% (95% CI: 45 to 65) at 3 to 12 months.
- HRQoL was reported by one single-arm study at 18 months. The mean change in FACT-Lym score was 7.8 (95% CI: 3.7 to 11.9); mean change in FACT-G score was 6.01 (95% CI: 3.18 to 8.84); mean change in SF-36 physical health score was 4.3 (95% CI: 0.23 to 8.83); all were statistically and clinically significant favouring tisa-cel. The mean change in SF-36 mental health score was 2.3 (95% CI: 1.89 to 6.49), which was not clinically significant.
- TFI was not reported in the NRSI or single-arm studies.

7.3.13.1 Effectiveness/efficacy summary tables: Tisa-cel for LBCL

7.3.13.1.1 NRSI

Table 20 Summary of NRSI effectiveness evidence for tisa-cel vs SoC in LBCL

Outcome	Maziarz 2022[146]			
	Tisa-cel (n=163)	SoC (n=205)	Difference (95% CI)	Summary estimate
Median follow-up, days/months	8.3 months (NR)	4.9 months (NR)	NA	NA
Overall survival, probability (95% CI)**	8.25 (95% CI: 5.82 to 12.42)	4.86 (95% CI: 3.52 to 6.08)	HR 0.60 (95% CI: 0.44 to 0.77)	k=1, n=368 HR 0.60 (95% CI: 0.44 to 0.77)
Overall survival, median months	NR	NR	NR	NR
Progression-free survival, probability (95% CI)	NR	NR	NR	NR
Progression-free survival, median months	NR	NR	NR	NR
Complete response rate, n (%)	NR	NR	NR	NR
Overall response rate, n (%)	54/143 (38)	59 (29)	RR: 1.31 (95% CI: 0.97 to 1.77)	k=1, n=348 RR:1.31 (95% CI: 0.97 to 1.77)
Treatment-free interval, median months	NR	NR	NR	NR
HRQoL, mean (SD)	NR	NR	NR	NR
Treatment discontinuation, n	NR	NR	NR	NR

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CI** = confidence interval, **HR** = hazard ratio, **n** = number, **NA** = not applicable, **NR** = not reported, **NRSI** = non-randomised studies of interventions, **SD** = standard deviation, **SoC** = standard of care, **tisa-cel** = tisagenlecleucel, **HRQoL** = health-related quality of life.
Notes:
* Relative effects calculated as patients alive after standard of care vs CAR T, with HR < 1 favouring CAR T (highlighted in blue font).

7.3.13.1.2 Single-arm

A summary of the single-arm effectiveness evidence for tisa-cel in LBCL is presented in ***Table 21***.

Table 21 Summary of single-arm effectiveness/efficacy evidence for tisa-cel in LBCL

Outcome*	Bachy 2022[129]	Gauthier 2022[133]	Pasquini 2020[125]	NCT03601442[138]	Yagi 2022[149]	Benoit 2023[131]	Bethge 2022[132]	Sesques 2020[139]	JULIET[3,147,148]	Summary estimate
	(n=209)	(n=31)	(n=155)	(n=84)	(n=21)	(n=10)	(n=183)	(n=33)	(n=115)	
Median follow-up, days/months	13 months (95% CI: 12.1 to 13.5)	3 months (NR)	11.9 months (range: 3.8 to 19)	13.8 months (NR)	6.3 months (range: 0.4 to 14.8)	11.2 months (NR)	11 months (range: 1 to 29)	5.7 months	40.3 months (IQR: 37.8 to 43.8)	NA
Overall survival, probability (95% CI)	102 (48.80) (95% CI: 39.70 to 57.20)	NR	86/152 (56.3) (95% CI: 44.2 to 66.8)	NR	14.53 (69.2) (95% CI: 43.7 to 84.9)	NR	NR	22 (65.7) (95% CI: 48.8 to 85.6)	54 (49) (95% CI: 39 to 59)	k=5, n=529 44% (number at risk: 73; 95% CI: 39 to 50) at 15 months
Progression-free survival, probability (95% CI)	69 (33.20) (95% CI: 25.70 to 40.80)	NR	NR	NR	11 (53.1) (95% CI: 28.3 to 72.7)	NR	NR	15 (44.2) (95% CI: 29.4 to 66.5)	51 (32.9) (95% 24.5 to 44.1)	k=4, n=377 30% (number at risk: 47; 95% CI: 25 to 36) at 15 months
Complete response rate, n (%)	88 (42.10)	10 (32.0)	60/152 (39.5)	29/82 (35.0)	13 (62.0)	1 (10.0)	59 (32.0)	12/31 (39.0)	NR	k=8, n=719 37% (95% CI: 33 to 42)
Overall response rate, n (%)	138 (66.0)	18 (58.0)	93/152 (61.0)	34/82 (41.0)	NR	2 (20.0)	128/173 (74.0)	13/31 (42.0)	61 (53.0)	k=8, n=803 55% (95% CI: 45 to 65)
Treatment-free interval, median months	NR	NR	NR	NR	NR	NR	NR	NR	NR	NA
HRQoL, mean change (SD)										

Outcome*	Bachy 2022[129]	Gauthier 2022[133]	Pasquini 2020[125]	NCT03601442[138]	Yagi 2022[149]	Benoit 2023[131]	Bethge 2022[132]	Sesques 2020[139]	JULIET[3,147,148]	Summary estimate
	(n=209)	(n=31)	(n=155)	(n=84)	(n=21)	(n=10)	(n=183)	(n=33)	(n=115)	
FACT-G TS	NR	NR	NR	NR	NR	NR	NR	NR	6.01 (95% CI: 3.18 to 8.84), n=21	k=1, n=21 Mean change 6.01 (95% CI: 3.18 to 8.84)
FACT-Lym TS	NR	NR	NR	NR	NR	NR	NR	NR	7.80 (95% CI: 3.70 to 11.90), n=21	k=1, n=21 Mean change 7.80 (95% CI: 3.70 to 11.90)
SF-36 physical health TS	NR	NR	NR	NR	NR	NR	NR	NR	4.30 (95% CI: -0.23 to 8.83), n=21	k=1, n=21 Mean change 4.30 (95% CI -0.23 to 8.83)
SF-36 mental health TS	NR	NR	NR	NR	NR	NR	NR	NR	2.30 (95% CI: -1.89 to 6.49), n=21	k=1, n=21 Mean change 2.30 (95% CI -1.89 to 6.49)
Treatment discontinuation, n (%)	NR	0 (0.0)	0 (0.0)	8/92 (9.0)	2/9 (22.0)	0 (0.0)	0 (0.0)	NR	54/165 (33.0)	k=7, n=645 4% (95% CI: 0 to 16)

Abbreviations:

CI = confidence interval, **FACT-G** = Functional Assessment of Cancer Therapy – General, **FACT-Lym** = Functional Assessment of Cancer Therapy – Lymphoma, **HR** = hazard ratio, **IQR** = interquartile range, **LBCL** = large B-cell lymphoma, **n** = number, **NA** = not applicable, **NE** = not estimable, **NR** = not reported, **SD** = standard deviation, **SF-36** = short form 36-item health survey, **tisa-cel** = tisagenlecleucel, **TS** = total score, **HRQoL** = health-related quality of life.

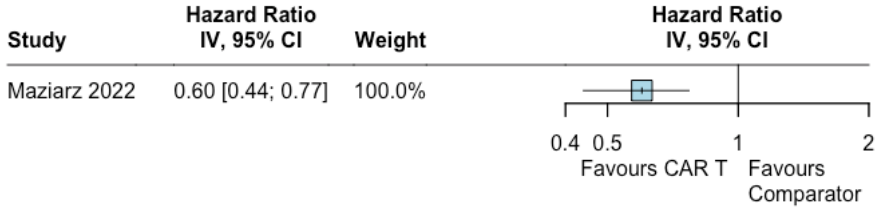
Notes:

* All outcomes reported at longest follow-up.

7.3.13.2 Overall survival

One NRSI reported OS in patients with LBCL treated with tisa-cel, which demonstrated a statistically significant effect favouring tisa-cel (***Figure 49***).[146] The follow-up duration of the analysis was not reported. The overall certainty of the evidence was very low.

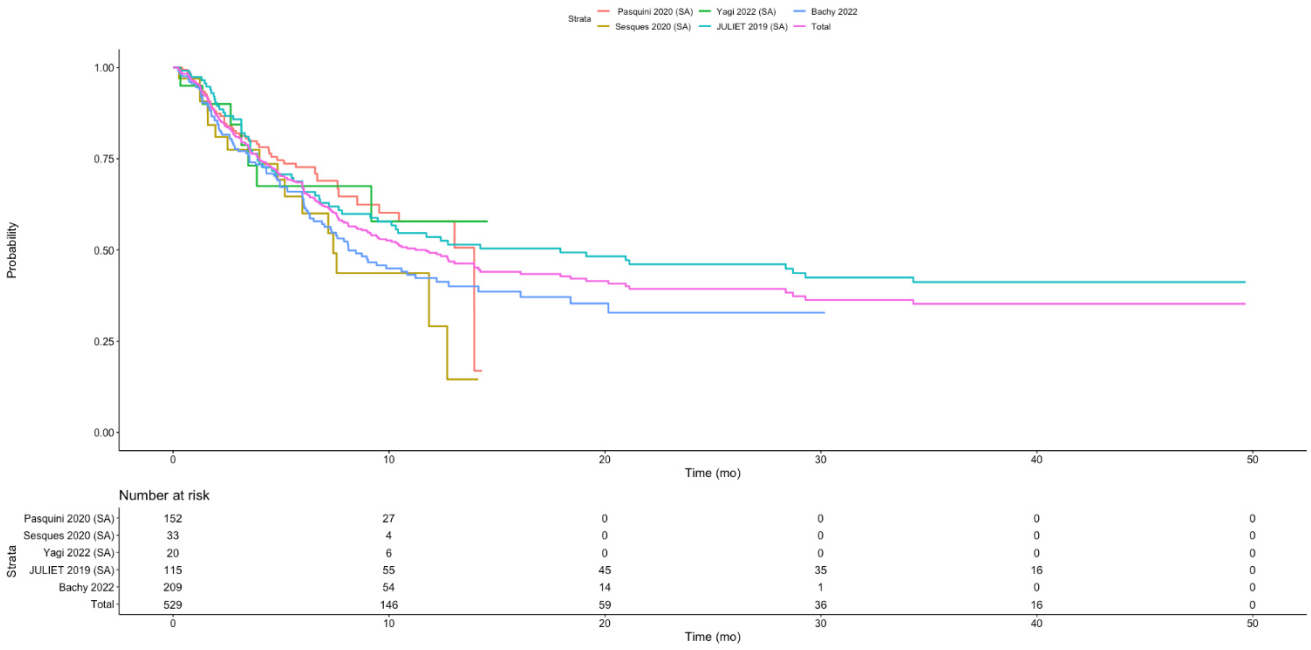
Figure 49 Overall survival curves in LBCL patients receiving tisa-cel (NRSI)



Abbreviations:
CAR T = chimeric antigen receptor T cell, **CI** = confidence interval, **IV** = inverse variance, **LBCL** = large B-cell lymphoma, **NRSI** = non-randomised studies of interventions.

Overall, 5 single-arm studies reported OS in patients with LBCL treated with tisa-cel.[125,129,147,149] KM curves from the single-arm studies illustrate similar survival rates for LBCL patients receiving tisa-cel. All 5 curves had similar trends, regardless of sample size, with comparable rates of change. At the 5-month timepoint the probability of survival across all curves was around 70% (number at risk: 290; 95% CI: 66 to 75). The probability dropped to 53% (number at risk: 146; 95% CI: 48 to 58) at 10 months and 44% (number at risk: 73; 95% CI: 39 to 50) at 15 months. Between 15 and 50 months the probability of survival for the combined single-arm studies plateaued at around 40%.

Figure 50 Overall survival curves in LBCL patients receiving tisa-cel (single-arm only)



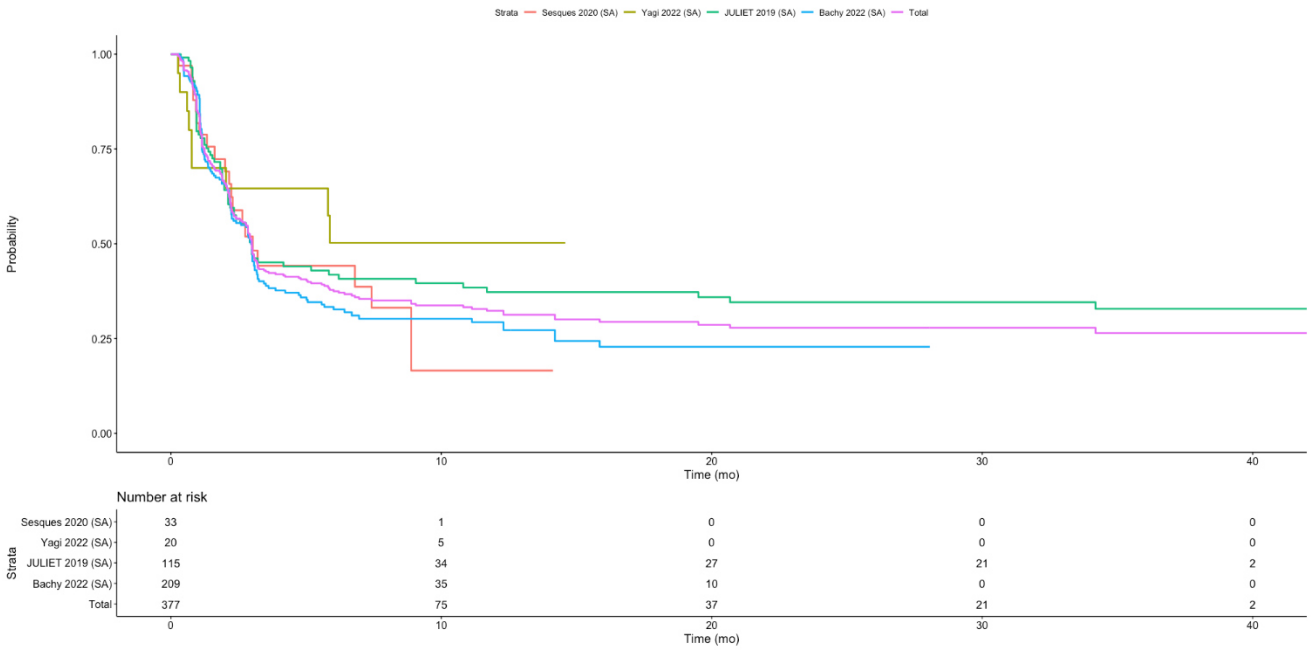
Abbreviations:
LBCL = large B-cell lymphoma, **mo** = months, **SA** = single-arm, **tisa-cel** = tisagenlecleucel.

7.3.13.3 Progression-free survival

Overall, 4 single-arm studies reported PFS in patients with LBCL treated with tisa-cel.[3,129,139,149]

KM curves from the single-arm studies illustrate similar PFS for LBCL patients receiving tisa-cel. All 4 curves had similar trends with comparable rates of change. At the 1-month timepoint the probability of survival across all curves was around 85% (number at risk: 310; 95% CI: 81 to 88). PFS probability dropped to 49% (number at risk: 158; 95% CI: 44 to 54) at 3 months, 41% (number at risk: 118; 95% CI: 36 to 46) at 5 months and 30% (number at risk: 47; 95% CI: 25 to 36) at 15 months. Between 15 and 40 months (longest follow-up) the probability of survival for the combined single-arm studies plateaued at around 30%.

Figure 51 Progression-free survival curves in LBCL patients receiving tisa-cel (single-arm only)

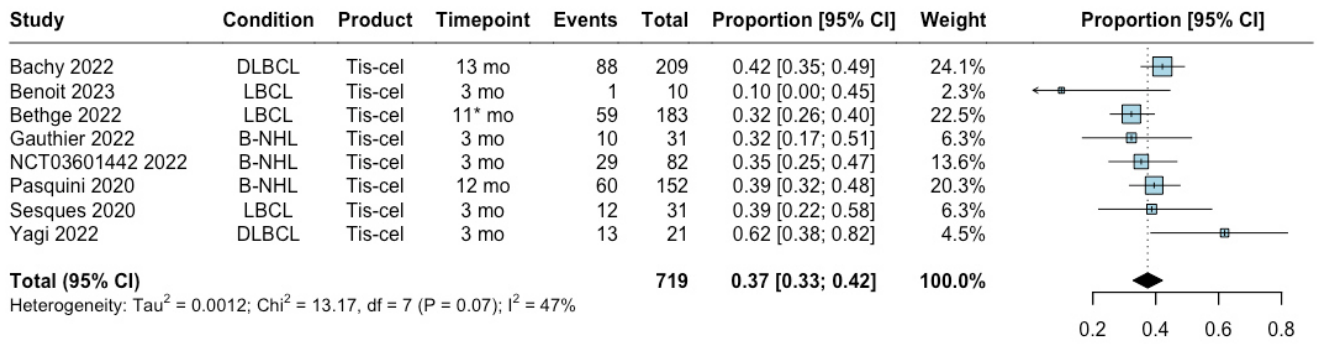


Abbreviations:
LBCL = large B-cell lymphoma, **mo** = months, **SA** = single-arm, **tisa-cel** = tisagenlecleucel.

7.3.13.4 Complete response rate

No NRSIs matching the PICO criteria were identified. Overall, 8 single-arm studies reported CRR in patients with LBCL treated with tisa-cel (***Figure 52***). Between 3 and 13 months (longest follow-up), 37% (95% CI: 33 to 42) achieved a complete response. Moderate heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 52 Complete response rate in LBCL patients receiving tisa-cel (single-arm)

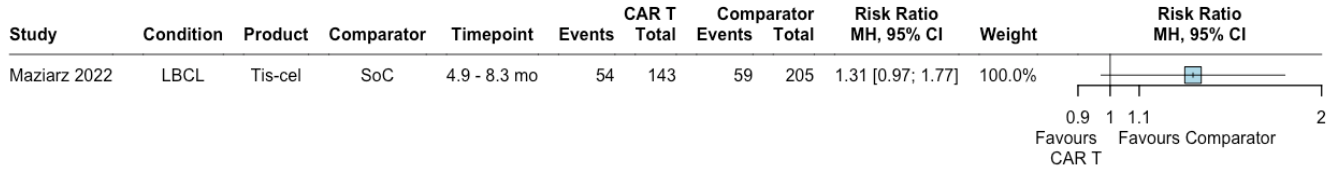


Abbreviations:
B-NHL = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months, **NR** = not reported, **tis-cel** = tisagenlecleucel.
Notes:
* Median timepoint.

7.3.13.5 Overall response rate

One NRSI reported ORR in patients with LBCL when comparing tis-cel to standard care.[152] At longest follow up, the study did not report a statistically significant result (***Figure 53***). The overall GRADE certainty of evidence for tis-cel versus standard care was assessed to be very low.

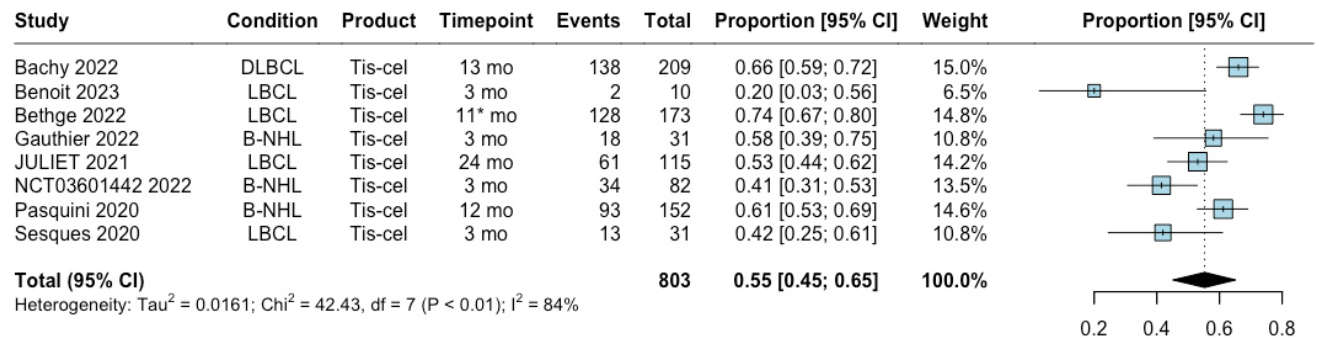
Figure 53 Overall response rate in LBCL patients receiving tis-cel (NRSI)



Abbreviations:
CI = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **MH** = Mantel-Haenszel, **mo** = months, **tis-cel** = tisagenlecleucel.

Overall, 8 single-arm studies reported ORR in patients with LBCL treated with tisa-cel (***Figure 54***).[125,129,131-133,138,139,147] Between 3 and 24 months (longest follow-up), 53% (95% CI: 42 to 64) achieved an overall response. Considerable heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 54 Overall response rate in LBCL patients receiving tisa-cel (single-arm)



Abbreviations:
B-NHL = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **LBCL** = large B-cell lymphoma, **mo** = months, **NR** = not reported, **tis-cel** = tisagenlecleucel.
Notes:
* Median timepoint.

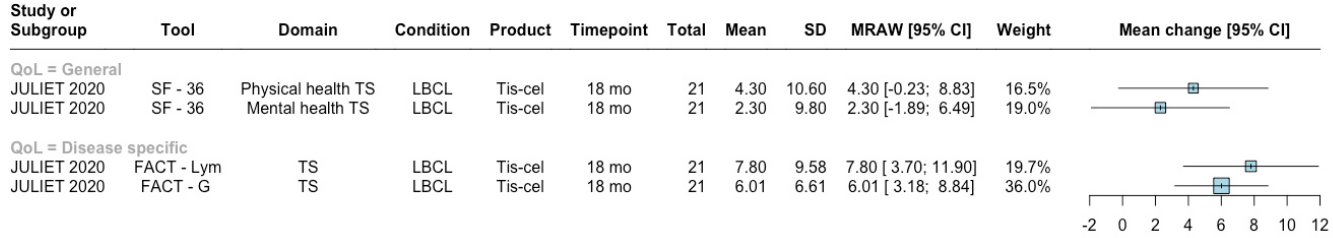
7.3.13.6 Treatment-free interval

TFI was not reported in the included single-arm studies. No NRSIs matching the PICO criteria were identified.

7.3.13.7 Health-related quality of life

No NRSIs matching the PICO criteria were identified. One single-arm study reported HRQoL in patients with LBCL being treated with tisa-cel (***Figure 55***).[148] At 18 months, the mean changes from baseline for FACT-G and FACT-Lym were statistically and clinically significant, with results greater than the MCID lower limit for both measures (***Appendix F***). However, for SF-36 only the physical health component was found to be statistically and clinically significant, with results greater than the MCID for this measure (***Appendix F***).

Figure 55 Health-related quality of life in LBCL patients receiving tisa-cel (single-arm)

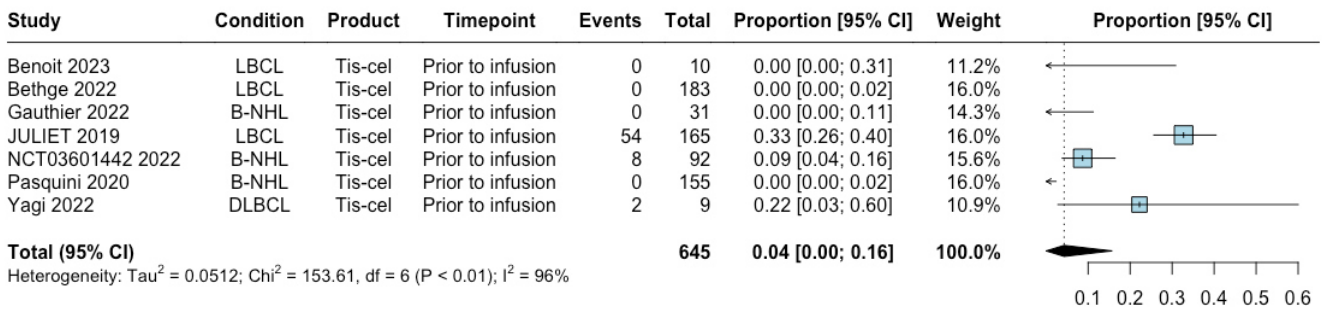


Abbreviations:
CI = confidence interval, **FACT-G** = Functional Assessment of Cancer Therapy – General, **FACT-Lym** = Functional Assessment of Cancer Therapy – Lymphoma, **LBCL** = large B-cell lymphoma, **HRQoL** = health-related quality of life, **mo** = months, **QoL** = quality of life, **SD** = standard deviation, **SF-36** = short form 36-item health survey, **tis-cel** = tisagenlecleucel, **TS** = total score.

7.3.13.8 Treatment discontinuation

No NRSIs matching the PICO criteria were identified. Overall, 7 single-arm studies reported treatment discontinuation in patients with LBCL being treated with tisa-cel (***Figure 56***).[125,131-133,138,149] Prior to infusion, 4% (95% CI: 0.0 to 16.0) discontinued treatment. Considerable heterogeneity was reported.

Figure 56 Treatment discontinuation in LBCL patients receiving tisa-cel (single-arm)



Abbreviations:
B-NHL = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months, **NR** = not reported, **tis-cel** = tisagenlecleucel.

7.3.14 Safety findings: Tisa-cel for LBCL

Nine single-arm studies (no NRSIs) investigated the safety of tisa-cel in the LBCL population. There was very low certainty evidence for the outcomes included in the GRADE assessment. A high-level summary of the results is as follows:

- SAEs, AEs and TRAEs were not well reported across the included single-arm studies.
- The proportion of patients that experienced CRS (any) in the 9 single-arm studies was 64% (95% CI: 53 to 75) at 1 to 24 months.
- The proportion of patients that experienced ICANS (any) in the 8 single-arm studies was 18% (95% CI: 15 to 23) at 1 to 12 months.
- B-cell aplasia rates were not well reported in the included single-arm studies.
- B-cell aplasia duration was not reported in the included single-arm studies.

7.3.14.1 Safety summary tables: Tisa-cel for LBCL

A summary of the single-arm safety evidence for tisa-cel in LBCL is presented in ***Table 22***.

Table 22 Summary of single-arm safety evidence for tisa-cel in LBCL

Outcome*	Bachy 2022[129]	Gauthier 2022[133]	Pasquini 2020[125]	NCT03601442[138]	Yagi 2022[149]	Benoit 2023[131]	Bethge 2022[132]	Sesques 2020[139]	JULIET[3,147,148]	Overall summary estimate
	(n=209)	(n=31)	(n=155)	(n=84)	(n=21)	(n=10)	(n=183)	(n=33)	(n=115)	
Median follow-up, days/months	13 months (95% CI: 12.1 to 13.5)	3 months (NR)	11.9 months (range: 3.8 to 19)	13.8 months (NR)	6.3 months (range: 0.4 to 14.8)	11.2 months (NR)	11 months (range: 1 to 29)	5.7 months	40.3 months (IQR: 37.8 to 43.8)	NA
SAE, any, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	72/111 (65.0)	k=1, n=111 65% (95% CI: 55 to 74)
AE, any, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	115 (100)§	k=1, n=115 100% (95% CI: 97 to 100)
TRAE/TEAE, any, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	99/111 (89.0)	k=1, n=111 89% (95% CI: 82 to 94)
CRS										
any, n (%)	158 (75.6)	22 (71.0)	70 (45.2)	33 (39.0)	18 (85.7)	6 (60.0)	118 (64.0)	26/31 (84.0)	66 (57.0)	k=9, n=839 64% (95% CI: 53 to 75)
grade ≥3, n (%)	19 (9.1)	0 (0.0)	7 (4.5)	1 (1.0)	2 (10.0)	0 (0.0)	24 (13.0)	3/31 (10.0)	26 (23.0)	k=9, n=839 7% (95% CI: 3 to 12)
ICANS										
any, n (%)	46 (22.0)	7 (23.0)	28 (18.1)	9 (11.0)	1 (4.8)	3 (30.0)	40 (22.0)	8/31 (26.0)	NR	k=8, n=724 18% (95% CI: 15 to 23)
grade ≥3, n (%)	6 (2.9)	4 (13.0)	8 (5.1)	1 (1.0)	0 (0.0)	0 (0.0)	12 (7.0)	3/31 (10.0)	NR	k=8, n=724 4% (95% CI: 2 to 6)

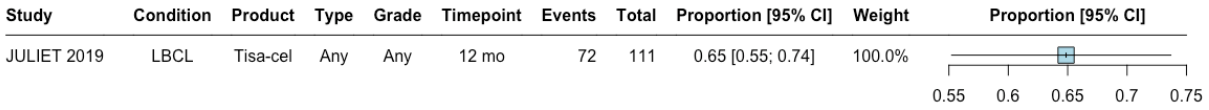
Outcome*	Bachy 2022[129]	Gauthier 2022[133]	Pasquini 2020[125]	NCT03601442[138]	Yagi 2022[149]	Benoit 2023[131]	Bethge 2022[132]	Sesques 2020[139]	JULIET[3,147,148]	Overall summary estimate
B-cell aplasia, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	1 (1.0)	k=1, n=115 1% (95% CI: 0 to 5)
median duration, days/months	NR	NR	NR	NR	NR	NR	NR	NR	NR	NA
Cytopenia, n (%)	26 (12.4)	NR	8 (5.0)	NR	NR	3 (30.0)‡	NR	NR	52/111 (47.0)	k=4, n=485 20% (95% CI: 4 to 43)
Hypogammaglobulinaemia, n (%)	NR	NR	56 (36.0)	NR	NR	NR	NR	NR	10 (9.0)	k=2, n=270 21% (95% CI: 2 to 52)
IVIG usage, n (%)	NR	NR	26 (17.0)	NR	NR	NR	NR	NR	NR	k=1, n=155 17% (95% CI: 11 to 24)
Infections, n (%)	NR	1 (3.0)	39 (25.2)	NR	1 (5.0)	NR	NR	NR	43 (37.0)	k=4, n=322 17% (95% CI: 4 to 35)
Tumour lysis syndrome, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	0/96 (0.0)	k=1, n=96 0%
Secondary malignancies, n (%)	NR	NR	6 (4.0)	NR	NR	NR	NR	NR	NR	k=1, n=155 4% (95% CI: 1 to 8)

Abbreviations:
AE = adverse event, **CI** = confidence interval, **CRS** = cytokine release syndrome, **ICANS** = immune effector cell-associated neurotoxicity syndrome, **IVIG** = intravenous immunoglobulin, **IQR** = interquartile range, **LBCL** = large B-cell lymphoma, **n** = number, **NA** = not applicable, **NR** = not reported, **SAE** = serious adverse event, **tisa-cel** = tisagenlecleucel, **TRAE/TEAE** = treatment-related/-emergent adverse event
Notes:
* All outcomes reported at longest follow-up.
‡ Only grade 3–4 reported.
§ 104/115 (90.5%) of these AEs were grade ≥3.

7.3.14.2 Serious adverse events

No NRSIs matching the PICO criteria were identified. One single-arm study reported SAEs in patients with LBCL being treated with tisa-cel (***Figure 57***).[147] At 12 months, 65% (95% CI: 55 to 74) reported SAEs of any grade. Heterogeneity could not be assessed.

Figure 57 Serious adverse events in LBCL patients receiving tisa-cel (single-arm)

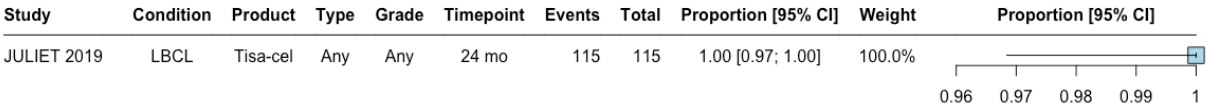


Abbreviations:
CI = confidence interval, **LBCL** = large B-cell lymphoma, **mo** = months, **tisa-cel** = tisagenlecleucel.

7.3.14.3 Adverse events

No NRSIs matching the PICO criteria were identified. One single-arm study reported AEs in patients with LBCL being treated with tisa-cel (***Figure 58***).[3] At 24 months, 100% (95% CI: 97 to 100) reported AEs of any grade. Heterogeneity could not be assessed. Along with any-grade AEs, one study also reported that 90.5% of participants (104/115) experienced AE grade ≥3 at 24 months.[3]

Figure 58 Adverse events in LBCL patients receiving tisa-cel (single-arm)

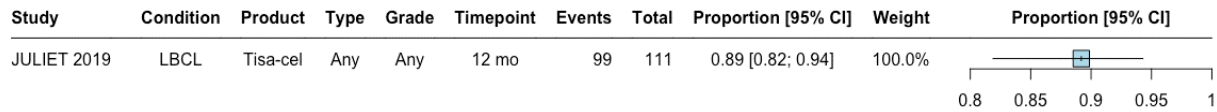


Abbreviations:
CI = confidence interval, **LBCL** = large B-cell lymphoma, **mo** = months, **tisa-cel** = tisagenlecleucel.

7.3.14.4 Treatment-related/-emergent adverse events

No NRSIs matching the PICO criteria were identified. One single-arm study reported TRAEs/TEAEs in patients with LBCL being treated with tisa-cel (***Figure 59***).[147] At 12 months, 89% (95% CI: 82 to 94) reported TRAEs/TEAEs of any grade. Heterogeneity could not be assessed.

Figure 59 Treatment-related/-emergent adverse events in LBCL patients receiving tisa-cel (single-arm)



Abbreviations:
CI = confidence interval, **LBCL** = large B-cell lymphoma, **mo** = months, **tisa-cel** = tisagenlecleucel.

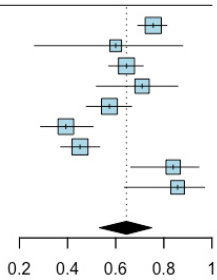
7.3.14.5 Cytokine release syndrome

No NRSIs matching the PICO criteria were identified. Overall, 9 single-arm studies reported CRS of any grade in patients with LBCL being treated with tisa-cel (***Figure 60***).[125,129,131-133,138,139,147,149] Between 1 and 24 months (longest follow-up), 64% (95% CI: 53 to 75) reported CRS of any grade. Considerable heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 60 Any-grade cytokine release syndrome in LBCL patients receiving tisa-cel (single-arm)

Study	Condition	Product	Timepoint	Grade	Events	Total	Proportion [95% CI]	Weight
Bachy 2022	DLBCL	Tis-cel	13 mo	Any	158	209	0.76 [0.69; 0.81]	13.0%
Benoit 2023	LBCL	Tisa-cel	11* mo	Any	6	10	0.60 [0.26; 0.88]	6.8%
Bethge 2022	LBCL	Tisa-cel	≥3 mo	Any	118	183	0.64 [0.57; 0.71]	12.9%
Gauthier 2022	B-NHL	Tisa-cel	NR	Any	22	31	0.71 [0.52; 0.86]	10.2%
JULIET 2019	LBCL	Tisa-cel	24 mo	Any	66	115	0.57 [0.48; 0.67]	12.5%
NCT03601442 2022	B-NHL	Tisa-cel	NR	Any	33	84	0.39 [0.29; 0.51]	12.2%
Pasquini 2020	B-NHL	Tisa-cel	3 mo	Any	70	155	0.45 [0.37; 0.53]	12.8%
Sesques 2020	LBCL	Tisa-cel	1 mo	Any	26	31	0.84 [0.66; 0.95]	10.2%
Yagi 2022	DLBCL	Tisa-cel	6* mo	Any	18	21	0.86 [0.64; 0.97]	9.2%
Total (95% CI)						**839**	**0.64 [0.53; 0.75]**	**100.0%**

Heterogeneity: $Tau^2 = 0.0236$; $Chi^2 = 68.47$, df = 8 (P < 0.01); $I^2 = 88\%$



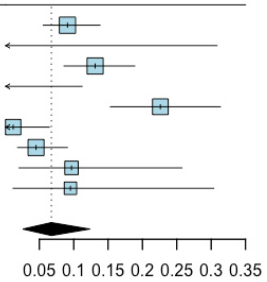
Abbreviations:
B-NHL = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months, **NR** = not reported, **tisa-cel** = tisagenlecleucel.
Notes:
* Median timepoint.

Nine single-arm studies reported CRS grade ≥3 in patients with LBCL being treated with tisa-cel (***Figure 61***).[125,129,131-133,138,139,147,149] Between 1 and 24 months (longest follow-up) 7% (95% CI: 0.03 to 0.12) reported CRS grade ≥3. Considerable heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 61 Cytokine release syndrome grade ≥3 in LBCL patients receiving tisa-cel (single-arm)

Study	Condition	Product	Timepoint	Grade	Events	Total	Proportion [95% CI]	Weight
Bachy 2022	DLBCL	Tis-cel	13 mo	≥3	19	209	0.09 [0.06; 0.14]	14.0%
Benoit 2023	LBCL	Tisa-cel	11* mo	≥3	0	10	0.00 [0.00; 0.31]	5.6%
Bethge 2022	LBCL	Tisa-cel	≥3 mo	≥3	24	183	0.13 [0.09; 0.19]	13.8%
Gauthier 2022	B-NHL	Tisa-cel	NR	≥3	0	31	0.00 [0.00; 0.11]	9.6%
JULIET 2019	LBCL	Tisa-cel	24 mo	≥3	26	115	0.23 [0.15; 0.31]	13.1%
NCT03601442 2022	B-NHL	Tisa-cel	NR	≥3	1	84	0.01 [0.00; 0.06]	12.5%
Pasquini 2020	B-NHL	Tisa-cel	3 mo	≥3	7	155	0.05 [0.02; 0.09]	13.6%
Sesques 2020	LBCL	Tisa-cel	1 mo	≥3	3	31	0.10 [0.02; 0.26]	9.6%
Yagi 2022	DLBCL	Tisa-cel	6* mo	≥3	2	21	0.10 [0.01; 0.30]	8.2%
Total (95% CI)						**839**	**0.07 [0.03; 0.12]**	**100.0%**

Heterogeneity: $Tau^2 = 0.0138$; $Chi^2 = 42.40$, df = 8 (P < 0.01); $I^2 = 81\%$



Abbreviations:
B-NHL = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months, **NR** = not reported, **tisa-cel** = tisagenlecleucel.
Notes:
* Median timepoint.

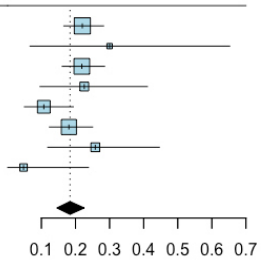
7.3.14.6 Immune effector cell-associated neurotoxicity syndrome

No NRSIs matching the PICO criteria were identified. Overall, 8 single-arm studies reported ICANS (any grade) in patients with LBCL being treated with tisa-cel (***Figure 62***).[125,129,131-133,138,139,149] Between 1 and 12 months (longest follow-up) 18% (95% CI: 15 to 23) reported ICANS of any grade. Moderate heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 62 Any-grade immune effector cell-associated neurotoxicity syndrome in LBCL patients receiving tisa-cel (single-arm)

Study	Condition	Product	Timepoint	Grade	Events	Total	Proportion [95% CI]	Weight
Bachy 2022	DLBCL	Tis-cel	13 mo	Any	46	209	0.22 [0.17; 0.28]	23.0%
Benoit 2023	LBCL	Tisa-cel	11* mo	Any	3	10	0.30 [0.07; 0.65]	2.5%
Bethge 2022	LBCL	Tisa-cel	≥3 mo	Any	40	183	0.22 [0.16; 0.29]	21.7%
Gauthier 2022	B-NHL	Tisa-cel	NR	Any	7	31	0.23 [0.10; 0.41]	6.8%
NCT03601442 2022	B-NHL	Tisa-cel	NR	Any	9	84	0.11 [0.05; 0.19]	14.2%
Pasquini 2020	B-NHL	Tisa-cel	3 mo	Any	28	155	0.18 [0.12; 0.25]	20.1%
Sesques 2020	LBCL	Tisa-cel	1 mo	Any	8	31	0.26 [0.12; 0.45]	6.8%
Yagi 2022	DLBCL	Tisa-cel	6* mo	Any	1	21	0.05 [0.00; 0.24]	4.9%
Total (95% CI)						**724**	**0.18 [0.15; 0.23]**	**100.0%**

Heterogeneity: $Tau^2 = 0.0016$; $Chi^2 = 11.67$, df = 7 (P = 0.11); $I^2 = 40\%$



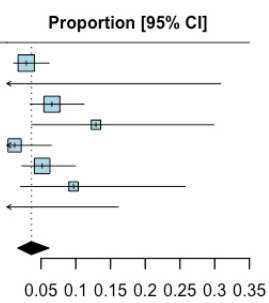
Abbreviations:
B-NHL = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months, **NR** = not reported, **tisa-cel** = tisagenlecleucel.
Notes:
* Median timepoint.

Eight single-arm studies reported ICANS grade ≥3 in patients with LBCL being treated with tisa-cel (***Figure 63***).[125,129,131-133,138,139,149] Between 1 and 13 months (longest follow-up), 4% (95% CI: 2 to 6) reported ICANS grade ≥3. Moderate heterogeneity was reported. The overall GRADE certainty of evidence was assessed to be very low.

Figure 63 Immune effector cell-associated neurotoxicity syndrome grade ≥3 in LBCL patients receiving tisa-cel (single-arm)

Study	Condition	Product	Timepoint	Grade	Events	Total	Proportion [95% CI]	Weight
Bachy 2022	DLBCL	Tis-cel	13 mo	≥3	6	209	0.03 [0.01; 0.06]	22.2%
Benoit 2023	LBCL	Tisa-cel	11* mo	≥3	0	10	0.00 [0.00; 0.31]	2.8%
Bethge 2022	LBCL	Tisa-cel	≥3 mo	≥3	12	183	0.07 [0.03; 0.11]	21.1%
Gauthier 2022	B-NHL	Tisa-cel	NR	≥3	4	31	0.13 [0.04; 0.30]	7.2%
NCT03601442 2022	B-NHL	Tisa-cel	NR	≥3	1	84	0.01 [0.00; 0.06]	14.4%
Pasquini 2020	B-NHL	Tisa-cel	3 mo	≥3	8	155	0.05 [0.02; 0.10]	19.7%
Sesques 2020	LBCL	Tisa-cel	1 mo	≥3	3	31	0.10 [0.02; 0.26]	7.2%
Yagi 2022	DLBCL	Tisa-cel	6* mo	≥3	0	21	0.00 [0.00; 0.16]	5.3%
Total (95% CI)						**724**	**0.04 [0.02; 0.06]**	**100.0%**

Heterogeneity: $Tau^2 = 0.0021$; $Chi^2 = 12.14$, df = 7 (P = 0.10); $I^2 = 42\%$

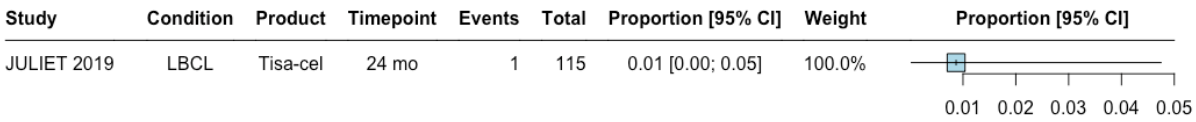


Abbreviations:
B-NHL = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **DLBCL** = diffuse large B-cell lymphoma, **LBCL** = large B-cell lymphoma, **mo** = months, **NR** = not reported, **tisa-cel** = tisagenlecleucel.
Notes:
* Median timepoint.

7.3.14.7 B-cell aplasia

No NRSIs matching the PICO criteria were identified. One single-arm study reported B-cell aplasia in patients with LBCL being treated with tisa-cel (***Figure 64***).[3] At 24 months, 1% (95% CI: 0 to 5) reported B-cell aplasia. Heterogeneity could not be assessed. The overall GRADE certainty of evidence was assessed to be very low.

Figure 64 B-cell aplasia in LBCL patients receiving tisa-cel (single-arm)



Abbreviations:
CI = confidence interval, **LBCL** = large B-cell lymphoma, **mo** = months, **tisa-cel** = tisagenlecleucel.

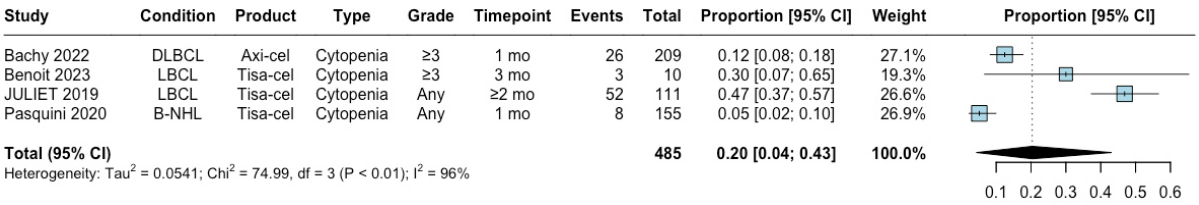
7.3.14.8 B-cell aplasia duration

B-cell aplasia duration was not reported in the included single-arm studies. No NRSIs matching the PICO criteria were identified.

7.3.14.9 Cytopenia

No NRSIs matching the PICO criteria were identified. Overall, 4 single-arm studies reported cytopenia in patients with LBCL being treated with tisa-cel (***Figure 65***).[125,131,147] Between 1 and 3 months (longest follow-up), 20% (95% CI: 4 to 43) reported cytopenia of any grade or grade ≥3. Considerable heterogeneity was reported.

Figure 65 Cytopenia in LBCL patients receiving tisa-cel (single-arm)

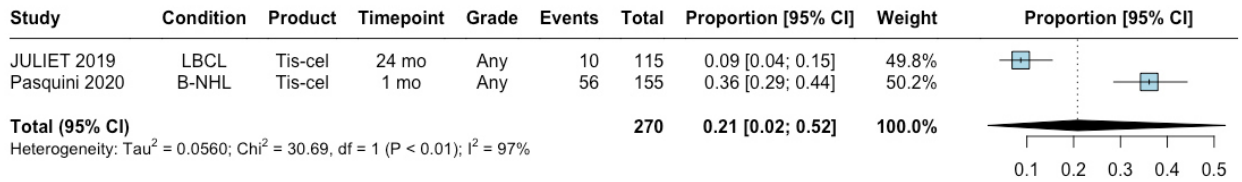


Abbreviations:
B-NHL = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **LBCL** = large B-cell lymphoma, **mo** = months, **tisa-cel** = tisagenlecleucel.

7.3.14.10 Hypogammaglobulinaemia

No NRSIs matching the PICO criteria were identified. Overall, 2 single-arm studies reported hypogammaglobulinaemia in patients with LBCL being treated with tisa-cel (***Figure 66***).[125,147] Between 1 and 24 months (longest follow-up), 21% (95% CI: 2 to 52) reported hypogammaglobulinaemia of any grade. Considerable heterogeneity was reported.

Figure 66 Hypogammaglobulinaemia in LBCL patients receiving tisa-cel (single-arm)

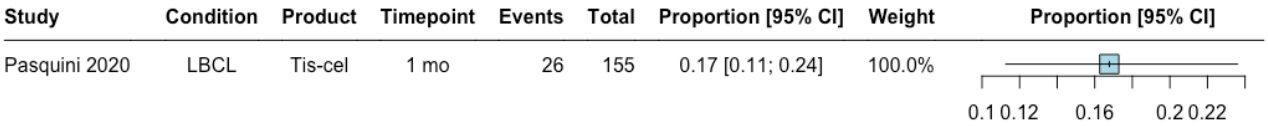


Abbreviations:
B-NHL = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **LBCL** = large B-cell lymphoma, **mo** = months, **tis-cel** = tisagenlecleucel.

7.3.14.11 Usage/administration of IVIG to treat hypogammaglobulinaemia

No NRSIs matching the PICO criteria were identified. One single-arm study reported usage/administration of IVIG to treat hypogammaglobulinaemia in patients with LBCL being treated with tisa-cel (***Figure 67***).[125] At one month (longest follow-up), 17% (95% CI: 11 to 24) reported usage/administration of IVIG to treat hypogammaglobulinaemia. Heterogeneity could not be assessed.

Figure 67 Usage/administration of IVIG to treat hypogammaglobulinaemia in LBCL patients receiving tisa-cel (single-arm)

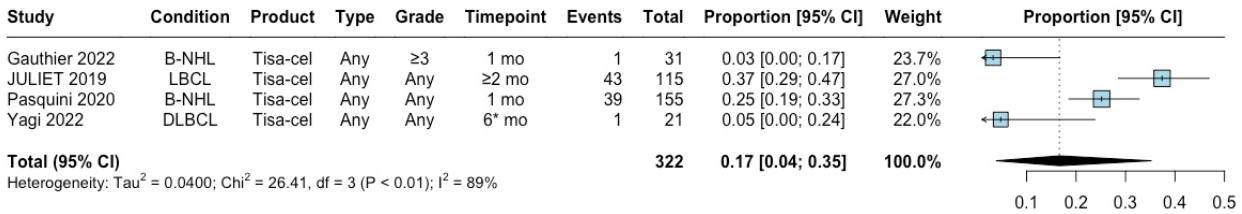


Abbreviations:
B-NHL = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **IVIG** = intravenous immunoglobulin, **LBCL** = large B-cell lymphoma, **mo** = months, **tis-cel** = tisagenlecleucel.

7.3.14.12 Infections

No NRSIs matching the PICO criteria were identified. Overall, 4 single-arm studies reported infections in patients with LBCL being treated with tisa-cel (***Figure 68***).[125,133,147,149] Between 1 and 6 months (longest follow-up), 17% (95% CI: 4 to 35) reported infections of any grade or grade ≥3. Considerable heterogeneity was reported.

Figure 68 Infections in LBCL patients receiving tisa-cel (single-arm)



Abbreviations:
B-NHL = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **LBCL** = large B-cell lymphoma, **mo** = months, **tisa-cel** = tisagenlecleucel.
Notes:
* Median timepoint.

7.3.14.13 Tumour lysis syndrome

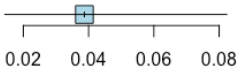
No NRSIs matching the PICO criteria were identified. One single-arm study reported TLS in patients with LBCL being treated with tisa-cel.[147] At ≥2 months, 0% (n=0/96) reported TLS.

7.3.14.14 Secondary malignancies

No NRSIs matching the PICO criteria were identified. One single-arm study reported secondary malignancies in patients with LBCL being treated with tisa-cel (***Figure 69***).[125] At one month (longest follow-up), 4% (95% CI: 1 to 8) reported secondary malignancies. Heterogeneity could not be assessed.

Figure 69 Secondary malignancies in LBCL patients receiving tisa-cel (single-arm)

Study	Condition	Product	Type	Timepoint	Events	Total	Proportion [95% CI]	Weight	Proportion [95% CI]
Pasquini 2020	B-NHL	Tis-cel	Any	1 mo	6	155	0.04 [0.01; 0.08]	100.0%	



Abbreviations:
B-NHL = B-cell non-Hodgkin lymphoma, **CI** = confidence interval, **LBCL** = large B-cell lymphoma, **mo** = months, **tis-cel** = tisagenlecleucel.

7.3.15 GRADE summary of findings tables

The following tables (***Table 23*** to ***Table 29***) summarise the overall strength of evidence supporting the key findings related to the safety and efficacy of CAR T-cell therapies in the eligible populations, separated by level of evidence. NRSI and single-arm studies are summarised in separate summary of findings tables. As per the GRADE approach, only key outcomes are reported in the summary of findings tables for each comparison.[109] These outcomes are reflected in the PICO criteria in ***Section 5***. The certainty of evidence supporting an outcome, as scored according to the GRADE approach, is defined into the following categories:[109]

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty**: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- **Very low certainty**: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Table 23 GRADE summary of findings table: tisa-cel for B-ALL (NRSI)

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI) *	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with tisa-cel	Risk with standard care			
Overall survival assessed at 150 days	570 per 1,000[d]	529 per 1,000 (273 to 832)	**HR 0.89** (0.38 to 2.11)	205 (1 non-randomised study)	⊕◯◯◯ Very low[a,b,c]
Progression-free survival	NR	NR	NR	NR	NR
Complete response rate	NR	NR	NR	NR	NR
Overall response rate	NR	NR	NR	NR	NR
Cytokine release syndrome – any	NR	NR	NR	NR	NR
Cytokine release syndrome – grade ≥3	NR	NR	NR	NR	NR
ICANS – any	NR	NR	NR	NR	NR
ICANS – grade ≥3	NR	NR	NR	NR	NR
B-cell aplasia	NR	NR	NR	NR	NR

Abbreviations:
CAR T = chimeric antigen receptor T-cell, **CI** = confidence interval, **CNS** = central nervous system, **HR** = hazard ratio, **ICANS** = immune effector cell-associated neurotoxicity syndrome**, LBCL** = large B-cell lymphoma, **NR** = not reported, **RoB** = risk of bias, **SCT** = stem cell transplant.

Notes:
a. Critical risk of bias owing to confounding, selection of participants, classification of the interventions, and deviations from intended interventions.
b. Downgraded for indirectness due to lower percentage of males and prior SCT than Swiss practice, and failure to report prior therapies, CNS involvement, lymphodepletion regimen, and time between leukapheresis and CAR T infusion; study includes only patients that were admitted to an intensive care unit.
c. 95% CIs cross line of no effect.
d. Absolute effects estimated from the reported Kaplan-Meier curve at 30 days.
* Relative effects calculated as standard care vs tisa-cel, with HR < 1 favouring CAR T.

Table 24 GRADE summary of findings table: tisa-cel for B-ALL (single-arm studies)

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)
Overall survival (OS) assessed at 20 months	69% (95% CI: 63 to 75) n=76 at risk	459 (6 observational studies)[a]	⊕◯◯◯ Very low[b,c]
Progression-free survival	NR	NR	NR
Complete response rate assessed at longest follow-up (range 28 days to 856 days)	79% (95% CI: 70 to 87)	464 (6 observational studies)	⊕◯◯◯ Very low[d,e,f]
Overall response rate assessed at longest follow-up (range 3 months to 6 months)	68% (95% CI: 60 to 75)	156 (2 observational studies)	⊕◯◯◯ Very low[g,h]
Cytokine release syndrome – any assessed at longest follow-up (range 4 days to 14 months)	70% (95% CI: 60 to 80)	568 (8 observational studies)	⊕◯◯◯ Very low[e,i,j]
Cytokine release syndrome – grade ≥3 assessed at longest follow-up (range 4 days to 14 months)	29% (95% CI: 17 to 43)	568 (8 observational studies)	⊕◯◯◯ Very low[e,i,j]
ICANS – any assessed at longest follow-up (range 6 days to 14 months)	26% (95% CI: 12 to 42)	425 (6 observational studies)	⊕◯◯◯ Very low[e,f,k]
ICANS – grade ≥3 assessed at longest follow-up (range 6 days to 14 months)	7% (95% CI: 2 to 14)	425 (6 observational studies)[l]	⊕◯◯◯ Very low[f,k,m]
B-cell aplasia assessed at 24 months	64% (95% CI: 49 to 78)	196 (4 observational studies)	⊕◯◯◯ Very low[h,m,n,o]

Abbreviations:
CAR T = chimeric antigen receptor T-cell, **CI** = confidence interval, **ICANS** = immune effector cell-associated neurotoxicity syndrome**, LBCL** = large B-cell lymphoma, **NR** = not reported, **RoB** = risk of bias.

Notes:
a. Studies that do not report a percentage omitted.
b. All studies had a moderate RoB.
c. Downgraded for indirectness due to low median age relative to Swiss practice, and poor reporting of prior therapies and time from leukapheresis to CAR T infusion.
d. 4 studies had a moderate RoB, and 2 had a low RoB.
e. I2 = 75% to 100%: considerable heterogeneity.
f. 4 studies had applicability concerns relating to issues such as age, percentage of males, number of prior therapies, type of lymphodepletion, prior stem cell use, and time from slot request to infusion.
g. I2 = 0% to 40%: might not be important.
h. Small sample size (100–199).
i. 1 study had a critical RoB, 4 a moderate RoB, 2 a low RoB.
j. 5 studies had applicability concerns relating to issues such as age, percentage of males, number of prior therapies, type of lymphodepletion, prior stem cell use, and time from slot request to infusion.
k. 1 study had a critical RoB, 3 a moderate RoB, and 1 a low RoB.
l. NRSI safety outcomes combined with single-arm safety outcomes as comparator events numbers not reported.
m. I^2 = 50% to 90%: may represent substantial heterogeneity.
n. 3 studies had a moderate RoB, and 1 a low RoB.
o. 2 studies had applicability concerns relating to issues such as age, number of prior therapies, type of lymphodepletion, prior stem cell use, and time from slot request to infusion.

Table 25 GRADE summary of findings table: axi-cel vs salvage chemotherapy for LBCL (NRSI)

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI) *	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with axi-cel	Risk with salvage chemotherapy			
Overall survival assessed at 24 months	540 per 1,000	189 per 1,000 (0 to 256)	**HR 0.27** (95% CI: 0.0 to 0.38)	412 (1 NRSI)	⊕⊕⊕◯ Moderate[a]
Progression-free survival	NR	NR	NR	NR	NR
Complete response rate follow-up duration NR	538 per 1,000	118 per 1,000 (86 to 172)	**RR 0.22** (95% CI: 0.16 to 0.32)	420 (1 NRSI)	⊕⊕⊕◯ Moderate[a]
Overall response rate follow-up duration NR	830 per 1,000	291 per 1,000 (0 to 415)	**RR 0.42** (95% CI: 0.35 to 0.50)	420 (1 NRSI)	⊕⊕⊕◯ Moderate[a]
Cytokine release syndrome – any	NR	NR	NR	NR	NR
Cytokine release syndrome – grade ≥3	NR	NR	NR	NR	NR
ICANS – any	NR	NR	NR	NR	NR
ICANS – grade ≥3	NR	NR	NR	NR	NR
B-cell aplasia	NR	NR	NR	NR	NR

Abbreviations:
CI = confidence interval, **ICANS** = immune effector cell-associated neurotoxicity syndrome**, LBCL** = large B-cell lymphoma, **NR** = not reported, **NRSI** = non-randomised study of interventions, **RoB** = risk of bias.
Notes:
[a] Downgraded due to indirectness due to inadequate reporting of median age, age range, prior therapies, and time from slot request to infusion.
* Relative effects calculated as no axi-cel versus axi-cel, with lower results favouring axi-cel.

Table 26 GRADE summary of findings table: axi-cel vs no axi-cel for LBCL (NRSI)

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI) *	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with axi-cel	Risk with no axi-cel			
Overall survival assessed at 16 months	375 per 1,000[d]	64 per 1,000 (23 to 164)	**HR 0.14** (0.05 to 0.38)	38 (1 NRSI)	⊕◯◯◯ Very low[a,b,c]
Progression-free survival assessed at 16 months	280 per 1,000[d]	13 per 1,000 (3 to 54)	**HR 0.04** (0.01 to 0.17)	38 (1 NRSI)	⊕◯◯◯ Very low[a,b,c]
Complete response rate assessed at 16 months	480 per 1,000[d]	43 per 1,000 (5 to 658)	**RR 0.09** (0.01 to 1.37)	38 (1 NRSI)	⊕◯◯◯ Very low[a,b,c]
Overall response rate assessed at 16 months	850 per 1,000[d]	43 per 1,000 (0 to 655)	**RR 0.05** (0.00 to 0.77)	38 (1 NRSI)	⊕◯◯◯ Very low[a,b,c]
Cytokine release syndrome – any	NR	NR	NR	NR	NR
Cytokine release syndrome – grade ≥3	NR	NR	NR	NR	NR
ICANS – any	NR	NR	NR	NR	NR
ICANS – grade ≥3	NR	NR	NR	NR	NR
B-cell aplasia	NR	NR	NR	NR	NR

Abbreviations:
CAR T = chimeric antigen receptor T-cell, **CI** = confidence interval, **ICANS** = immune effector cell-associated neurotoxicity syndrome**, LBCL** = large B-cell lymphoma, **NR** = not reported, **NRSI** = non-randomised study of interventions, **RoB** = risk of bias.
Notes:
a. Serious RoB owing to a high risk of confounding.
b. Downgraded for indirectness due to shorter median time between leukapheresis and CAR T infusion than Swiss practice, and lack of reporting of disease stage.
c. Sample size <99.
d. Absolute effects estimated from Kaplan-Meier curves from Mian 2021 at 16 months.
* Relative effects calculated as no axi-cel versus axi-cel, with lower results favouring axi-cel.

Table 27 GRADE summary of findings table: axi-cel for LBCL (single-arm studies)

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)
Overall survival assessed at 20 months	53% (95% CI: 49 to 59) n=90 at risk	654 (6 observational studies)[a]	⊕◯◯◯ Very low[b,c]
Progression-free survival assessed at 20 months	36% (95% CI: 32 to 40) n=95 at risk	778 (7 observational studies)[a]	⊕◯◯◯ Very low[b,c,d]
Complete response rate assessed at longest follow-up (range 3 months to 63 months)	52% (95% CI: 43 to 60)	1,061 (11 observational studies)	⊕◯◯◯ Very low[b,c,e]
Overall response rate assessed at longest follow-up (range 1 months to 63 months)	73% (95% CI: 65 to 80)	1,240 (11 observational studies)	⊕◯◯◯ Very low[b,c,e]
Cytokine release syndrome – any assessed at longest follow-up (range 1 months to 60 months)	89% (95% CI: 86 to 91)	1,260 (12 observational studies)	⊕◯◯◯ Very low[b,c,f,g]
Cytokine release syndrome – grade ≥3 assessed at longest follow-up (range 1 months to 60 months)	7% (95% CI: 5 to 10)	1,384 (13 observational studies)	⊕◯◯◯ Very low[b,c,g,h]
ICANS – any assessed at longest follow-up (range 1 months to 21 months)	55% (95% CI: 49 to 63)	1,159 (12 observational studies)	⊕◯◯◯ Very low[b,c,e]
ICANS – grade ≥3 assessed at longest follow-up (range 1 months to 21 months)	26% (95% CI: 19 to 32)	1,283 (13 observational studies)	⊕◯◯◯ Very low[b,c,e]
B-cell aplasia assessed at longest follow-up (12 months)	55% (95% CI: 33 to 76)	22 (2 observational studies)	⊕◯◯◯ Very low[c,i]

Abbreviations:
CAR T = chimeric antigen receptor T-cell, **CI** = confidence interval, **ICANS** = immune effector cell-associated neurotoxicity syndrome**, LBCL** = large B-cell lymphoma, **RoB** = risk of bias.
Notes:
a. Studies that did not report a probability were omitted.
b. The majority of studies were at moderate or high RoB.
c. All studies either had a shorter median time from leukapheresis to CAR T infusion compared to Swiss practice or did not report the duration.
d. 20-month results varied between 25% and 75%.
e. I^2 = 75% to 100%: considerable heterogeneity.
f. I^2 = 30% to 60%: moderate heterogeneity.
g. Large confidence intervals for several studies.
h. I^2 = 50% to 90%: substantial heterogeneity.
i. Very small sample size (1–99).

Table 28 GRADE summary of findings table: tisa-cel vs standard care for LBCL (NRSI)

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with standard care	Risk with tisa-cel			
Overall survival assessed at 50-90 months	NR	NR	**HR 0.60** (0.44 to 0.77) *	348 (1 NRSI)	⊕◯◯◯ Very low [a,b]
Progression-free survival	NR	NR	NR	NR	NR
Complete response rate	NR	NR	NR	NR	NR
Overall response rate follow-up duration NR	288 per 1,000	377 per 1,000 (279 to 509)	**RR 1.31** (0.97 to 1.77)	348 (1 NRSI)	⊕◯◯◯ Very low [a,b]
Cytokine release syndrome – any	NR	NR	NR	NR	NR
Cytokine release syndrome – grade ≥3	NR	NR	NR	NR	NR
ICANS – any	NR	NR	NR	NR	NR
ICANS – grade ≥3	NR	NR	NR	NR	NR
B-cell aplasia	NR	NR	NR	NR	NR

Abbreviations:
CI = confidence interval, **HR** = hazard ratio, **ICANS** = immune effector cell-associated neurotoxicity syndrome**, LBCL** = large B-cell lymphoma, **NR** = not reported, **NRSI** = non-randomised study of interventions, **RoB** = risk of bias, **RR** = relative risk.
Notes:
[a] Downgraded for risk of bias due to plausible residual confounding.
[b] Downgraded for indirectness due to lack of reporting on age range, lymphodepletion regimens, prior stem cell treatments, and time from slot request to infusion.
* Relative effects calculated as standard care vs tisa-cel, with HR < 1 favouring CAR T.

Table 29 GRADE summary of findings table: tisa-cel for LBCL (single-arm studies)

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)
Overall survival assessed at 15 months	44% (95% CI: 39 to 50) n=73 at risk	529 (5 observational studies)[a]	⊕◯◯◯ Very low[b,c]
Progression-free survival assessed at 15 months	30% (95% CI: 25 to 36) n=47 at risk	377 (4 observational studies)[a]	⊕◯◯◯ Very low[c,d,e]
Complete response rate assessed at longest follow-up (range 3 months to 13 months)	37% (95% CI: 33 to 42)	719 (8 observational studies)	⊕◯◯◯ Very low[c,f,g]
Overall response rate assessed at longest follow-up (range 3 months to 24 months)	55% (95% CI: 45 to 65)	803 (8 observational studies)	⊕◯◯◯ Very low[h,i,j,k]
Cytokine release syndrome – any assessed at longest follow-up (range 1 month to 24 months)	64% (95% CI: 53 to 75)	839 (9 observational studies)	⊕◯◯◯ Very low[i,l,m]
Cytokine release syndrome – grade ≥3 assessed at longest follow-up (range 1 month to 24 months)	7% (95% CI: 3 to 12)	839 (9 observational studies)	⊕◯◯◯ Very low[i,k,l,m]
ICANS – any assessed at longest follow-up (range 1 month to 13 months)	18% (95% CI: 15 to 23)	724 (8 observational studies)	⊕◯◯◯ Very low[f,j,n]
ICANS – grade ≥3 assessed at longest follow-up (range 1 month to 13 months)	4% (95% CI: 2 to 6)	724 (8 observational studies)	⊕◯◯◯ Very low[f,g,j]
B-cell aplasia assessed at 24 months	1% (95% CI: 0 to 5)	115 (1 observational study)	⊕◯◯◯ Very low[o,p,q]

Abbreviations:
CI = confidence interval, **ICANS** = immune effector cell-associated neurotoxicity syndrome**, LBCL** = large B-cell lymphoma, **RoB** = risk of bias.
Notes:
a. Studies that did not report a probability were omitted.
b. 4 studies had a moderate RoB, and 1 a low RoB.
c. The majority of studies enrolled a higher percentage of patients with disease stage III/IV than Swiss practice (or disease stage was not reported); 1 study had a substantially longer median time from slot request to CAR T infusion.
d. All studies had a moderate RoB.
e. Range of survival at 10 months ranged between 50% and <20%.
f. 1 study had a high RoB, 6 a moderate RoB, and 1 a low RoB.
g. I^2 = 30% to 60%: may represent moderate heterogeneity.
h. 1 study had a high RoB, 6 a moderate RoB, and 1 a low RoB.
i. I^2 = 75% to 100%: considerable heterogeneity.
j. The majority of studies enrolled a higher percentage of patients with disease stage III/IV than Swiss practice (or disease stage was not reported), and 1 study included a significantly higher proportion of male patients.
k. Proportions varied, some studies reported events in nearly all participants, whereas others reported events in very few participants.
l. 1 study had a high risk of bias, 7 a moderate risk of bias, and 1 a low risk of bias.
m. The majority of studies enrolled a higher percentage of patients with disease stage III/IV than Swiss practice (or stage not reported), 1 study had substantially longer median time from slot request to CAR T infusion, 1 study included a significantly higher proportion of males.
n. I^2 = 30% to 60%: may represent moderate heterogeneity.
o. This study had a moderate RoB.
p. A higher percentage of patients had disease stage III/IV than Swiss practice.
q. Small sample size (100–199).

8 Costs, cost-effectiveness and budget impact

Summary statement costs, cost-effectiveness and budget impact

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Naïve treatment comparisons were not included in the clinical evidence review; however, they were drawn in the economic evaluations to inform incremental cost-effectiveness ratio (ICER) calculations. This was considered appropriate given uncertainty analyses could be performed to explore the impact of various assumptions on cost-effectiveness outcomes. Nonetheless, while ICERs are presented, the calculations underpinning these ICERs were based on very low-quality evidence, naïve treatment comparisons, and several assumptions. Concerns raised by other HTA bodies in their reviews of company-submitted economic evidence (e.g. lack of comparative safety and efficacy, uncertainty in the extrapolation of OS, majority of QALYs gained over the period of extrapolation, applicability of the comparator evidence) are also key concerns with the ICERs presented here.

One existing economic study—with a high quality of reporting but a conflict of interest—was directly applicable to the HTA context, having been conducted from the perspective of the Swiss healthcare payer. The study assessed the cost-utility of tisa-cel for patients with B-ALL and DLBCL, and reported base case ICERs of CHF36,419 (Swiss francs) (2023 CHF36,277) relative to blinatumomab for B-ALL, and CHF113,179 (2023 CHF112,584) relative to salvage chemotherapy for LBCL.[1] Other economic literature reviewed as part of this HTA highlighted the high cost burden of CAR T products.

Additional de novo evaluations were made to assess the cost-effectiveness of axi-cel for patients with r/r LBCL in the Swiss setting, and to provide comparable evaluations for tisa-cel for patients with r/r B-ALL or DLBCL. The methodology adopted was guided by the existing literature. Survival outcomes were modelled using reconstructed individual patient data (IPD) from the most recently published datasets for each pivotal study, extrapolated over a lifetime horizon. Assessments of cost-effectiveness were made based on naïve treatment comparisons and relied on data for modelled comparators retrieved via pragmatic (not systematic) searches. Estimates of the potential budget impact of tisa-cel and axi-cel for the relevant indications—accounting for cost offsets for comparator therapies that may be substituted—were also made.

For paediatric and young adult patients with r/r B-ALL, de novo modelling suggested an ICER of CHF70,634 per QALY gained for tisa-cel relative to blinatumomab. The lognormal distributions used to extrapolate OS showed survival rates of 37.9% and 6.2% for CAR T-cell therapy and blinatumomab, respectively, after 10 years; 16.2% and 0.7%, respectively, after 40 years; and 9.3% and 0.2%, respectively, after 80 years. While a lifetime horizon is relevant, the long-term consequences of CAR T-

cell therapies are not yet known, so such extrapolations are uncertain. The time horizon and discount rate were shown to be important drivers of the ICER in scenario analysis, with the major impact being on the incremental QALY side of the ICER equation. This highlights the relative benefit of tisa-cel on survival outcomes as a critical component. Moreover, while the selection of comparator aligned with existing evaluations and HTAs, it failed to capture complexities in the treatment of r/r B-ALL, meaning that uncertainty exists around the incremental benefit attributed to CAR T-cell therapy in the calculations.

Base case estimates of financial impact for tisa-cel in the management of r/r B-ALL suggest treatment costs of CHF3.4 million and CHF3.8 million in 2023 and 2027, respectively (assuming 6 successfully infused patients in 2023 and 7 in 2027). Accounting for cost offsets for potential comparators, net cost of CHF2.5 million in 2023 was estimated, increasing to CHF2.7 million by 2027.

Axi-cel showed an ICER of CHF88,346 for r/r LBCL when compared to a historical control (i.e. survival data from CORAL extension studies). The ICER was higher when compared to POLA-BR (CHF102,220). ICERs for tisa-cel for the treatment of r/r DLBCL when compared to historical control or POLA-BR were estimated at CHF129,840 and CHF157,437, respectively. Base case extrapolations for axi-cel and tisa-cel demonstrated survival rates of 33.3% and 22.4% at 80 years of age, respectively, which were optimistic relative to alternate extrapolations. The generalised gamma distribution used in scenario analysis suggested survival rates of 22.7% and 16.7%, respectively. Concerns were also raised over the applicability of the historical control arm to contemporary Swiss practice (due to rituximab-naïve cohorts of the CORAL extension studies). Moreover, several alternative comparators have temporary listings on the Specialty List for r/r DLBCL (tafasitamab [in combination with lenalidomide and subsequent monotherapy]; polatuzumab [in combination with rituximab and bendamustine]) or r/r PMBCL (pembrolizumab). Again, the time horizon and discount rate were shown to be important drivers of the ICER in comparisons with historical controls for both axi-cel and tisa-cel.

Base case estimates of financial impact for CAR T-cell therapy with axi-cel or tisa-cel in patients with r/r DLBCL or PMBCL suggest treatment costs of CHF37.3 million and CHF 60.9 million in 2023 and 2027, respectively (assuming 77 successfully infused patients in 2023 [49 axi-cel; 28 tisa-cel] and 125 in 2027 [80 axi-cel; 45 tisa-cel]). Accounting for cost offsets for potential comparators, net cost of CHF30.0 million in 2023 was estimated, increasing to CHF49.0 million by 2027. These projections may be impacted by a practice shift moving CAR T-cell therapies into the second-line treatment setting (not accounted for in the projections).

8.1 Review of economic literature

8.1.1 Methodology

The systematic literature review of economic evidence and methods for evaluating the costs, cost-effectiveness and budget impact of CAR T-cell therapies in the Swiss context are discussed below.

8.1.1.1 Databases and search strategy

As described in ***Section 7.1.1***, a systematic literature search was conducted in 4 databases (Medline, Embase, the Cochrane Library, INAHTA HTA database) for studies published between 1 January 2010 and 13 April 2023. The websites of HTA agencies were also searched. ***Appendix A*** outlines the search strategy for each database. A single literature review was conducted to capture both clinical and economic literature relating to axi-cel or tisa-cel in the relevant populations.

8.1.1.2 Study selection

The PICO guiding the review of economic studies is described in ***Section 5***. Regarding the outcomes, full economic evaluations (studies that value both costs and benefits of different treatments) were included. Studies reporting costs associated with CAR T-cell therapy (either comparative or single-arm studies) were also considered, as were HTA reports.

An initial search of full economic evaluations was conducted at the protocol phase to inform the planned evaluation methodology (results reported in the ***HTA Protocol***). During the HTA, an updated search of the economic literature was conducted, extended to capture any new publications along with other economic studies (e.g. costing studies). This occurred in parallel with the systematic search for clinical evidence, using the same searches as used to capture clinical evidence.

For axi-cel, studies considering r/r LBCL—a broader population than those defined in the population components of the PICO—were also included. For the costing studies, studies of CAR T-cell therapy in general (i.e. not reporting axi-cel or tisa-cel separately) were considered, given that methods and results are informative and can aid the model inputs. Inclusion was also not strictly limited to CAR T-cell therapy use in the third-line setting for the same reason.

8.1.1.3 Data extraction, analysis and synthesis

Data pertaining to the following domains were extracted from the identified cost-effectiveness analyses: first author, publication year, country, perspective, currency and costing year, target population, intervention(s), comparators(s), analysis method (model type and structure, time horizon and discount rate), source of clinical evidence, quality of life inputs, AEs, conflicts of interest, results (incremental cost, incremental effectiveness, ICER), sensitivity analysis, key drivers and author conclusions.

Data were extracted by one reviewer (DS or MM) and checked by a second (MM or DS). Results of the included cost and cost-effectiveness studies were synthesised narratively. To facilitate comparisons in the narrative review, extracted incremental costs and ICERs were converted into 2023 Swiss francs (CHF) by using annual average foreign exchange rates for the reported costing year (or publication year if costing year was unreported) and inflated to 2023 values (using a healthcare goods-specific consumer price index).[153,154]

8.1.1.4 Assessment of evidence applicability

Each cost-effectiveness analysis was assessed against the applicability checklist items outlined by the National Institute for Health and Care Excellence (NICE).[155] This checklist asks users to consider the applicability of each study in terms of the population studied, interventions included, healthcare system of use, perspective of the analysis, discounting of future costs and outcomes, and the outcome measure used.

Studies were judged to be either directly applicable, partially applicable or not applicable. Judgements were largely based on the alignment of each study with the PICO criteria and the setting in which the evaluation was conducted. Only Swiss-specific evaluations were judged as directly applicable. The applicability of the existing evidence to the evaluation context is described narratively.

8.1.1.5 Assessment of study reporting quality and limitations

When directly applicable evidence was retrieved, the quality of reporting was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist to determine the study's usefulness for decision-makers.[156] Additionally, a full assessment of the study limitations using NICE's study limitations checklist items was also undertaken.[155] Results of the assessments are described narratively.

8.1.2 Results of the literature review

8.1.2.1 Search results

A PRISMA flowchart summarising the overall systematic literature search is available in ***Figure 2*** (***Section 7.3.1***). In brief, 18 cost-effectiveness studies, 10 HTAs with an economic evaluation component and 15 additional economic studies (e.g. costing studies) were identified (***Appendix C***).

Summary tables for the identified cost-effectiveness studies are provided (***Table 30*** to ***Table 32***), followed by a narrative synthesis. Summary tables for the included HTAs and additional economic evidence are provided in ***Appendix G***, along with the results of the applicability assessments, critical appraisal and limitations assessment for the existing Swiss evaluation.

A mock evaluation constructed to inform a review of the NICE approach to appraising regenerative medicines and cell therapy products, which was referenced by several included studies and provides useful information for model conceptualisation and construction, is also described narratively below.

Table 30 Economic summary table: tisa-cel for r/r B-ALL in paediatric and young adult patients

Study ID	Setting; perspective	Currency; costing year	Comparator(s)	Clinical data sources	Methods (model; time horizon; discount rate)	Incremental cost	Incremental effect	Conclusion (Cost effective?)	Potential conflicts/funder
Lin, 2018[157]	United States; healthcare payer	2017 US dollar	Blinatumomab, clofarabine monotherapy or clofarabine combination therapy	Maude 2018, von Stackelberg 2016, Jeha 2006, Hijiya 2009, Locatelli 2009, Miano, 2012	Markov cohort; lifetime; 3.0% p.a.	Difference in mean costs: USD266,000–431,000 (CHF253,929–411,441) [A] vs blinatumomab (reference)	Difference in mean LYs: -2.6 to 12.1 Difference in mean QALYs: -0.61 to 5.17 [A] vs blinatumomab (reference)	Possible, but depends on long-term outcomes, which are uncertain. ICER (vs blinatumomab): USD61,000 (CHF58,232), USD151,000 (CHF144,147), USD184,000 (CHF175,650) or dominated depending on the scenario.	Department of Veterans Affairs (supported in part by an advanced fellowship)
Maria 2020[158]	Spain; Spanish National Health System	2018 Euro	Salvage chemotherapy (FLA-IDA)	ELIANA, ENSIGN and B2101J Von Stackelberg 2011	3-state PSM; lifetime; 3.0% p.a.	EUR28,378 (CHF31,992)	LY: 10.10 QALYs: 8.97	Tisa-cel would represent a cost-effective intervention. ICER: EUR28,819 (CHF32489)	Novartis(funder)
Moradi-Lakeh, 2021[1]	Switzerland; Swiss mandatory health insurance system (societal in sensitivity)	Swiss franc (costing year NR)	Salvage chemotherapy (FLA-IDA), clofarabine combination therapy, or blinatumomab	ELIANA, ENSIGN and B2101J Von Stackelberg 2011, von Stackelberg 2016, Hijiya 2011, Locatelli 2009, Miano 2012	Hybrid decision tree and 3-state PSM; lifetime; 3.5% p.a.	CHF229,550 (2023 CHF228,343), CHF226,344 (2023 CHF225,154) and CHF252,374 (2023 CHF251,047) vs clofarabine combination, blinatumomab and salvage chemotherapy, respectively.	LY: 7.39, 6.89 and 8.86 QALYs: 6.65, 6.22 and 7.90 vs clofarabine, blinatumomab, and salvage chemotherapy, respectively.	Cost-effective using a WTP of CHF100,000 to 150,000 ICER: CHF 34,530 (2023 CHF34,348), CHF 36,419 (2023 CHF36,227), and CHF 31,961 (2023 CHF31,793) vs clofarabine combination therapy, blinatumomab, and salvage chemotherapy	Novartis, Switzerland (funder)

Study ID	Setting; perspective	Currency; costing year	Comparator(s)	Clinical data sources	Methods (model; time horizon; discount rate)	Incremental cost	Incremental effect	Conclusion (Cost effective?)	Potential conflicts/funder
Sarkar, 2019[159]	United States; third-party payer (societal in sensitivity)	2017 US dollar	Clofarabine, etopside and cyclophosphamide	Maude 2018 Hijiya 2011	Microsimulation state-transition model; lifetime; 3.0% p.a.	USD528,200 (CHF504,230)	QALYs: 8.18	Tisa-cel would be considered cost-effective. ICER: USD64,600 (CHF61,668)	National Institutes of Health (funder)
Thielen, 2020[160]	the Netherlands; healthcare payer and societal (as base case)	Euro (costing year NR)	(1) clofarabine, (2) clofarabine, etoposide and cyclophosphamide, or (3) blinatumomab	ELIANA, ENSIGN and B2101J Hijiya 2011, von Stackelberg 2016, Evoltra summary of product characteristics	3-state PSM; lifetime; 4.0% p.a. for costs and 1.5% p.a. for effects	EUR391,876 (CHF416,037), EUR358,759 (CHF380,878), EUR285,420 (CHF303,018) vs clofarabine, clofarabine combination, blinatumomab.	LY: 13.27, 11.55, 10.84; QALYs: 10.77, 9.56, 9.01; vs clofarabine, clofarabine combination, blinatumomab	At a WTP of EUR80,000, tisa-cel is cost-effective. ICER: EUR36,378 (CHF38,621), EUR37,531 (CHF39,845) and EUR31,682 (CHF33,635) vs clofarabine, clofarabine combination, blinatumomab	Novartis (funder)
Wakase, 2021[161]	Japan; healthcare payer (societal in scenario)	2018 Japanese yen	Blinatumomab (base case) or clofarabine combination therapy (sensitivity)	ELIANA, ENSIGN and B2101J (pooled) Von Stackelberg 2016 (BLIN) Hijiya 2011, Locatelli 2009, Miano 2012 (pooled; clofarabine combination)	Hybrid decision tree and 3-state PSM; lifetime, 2.0% p.a.	JPY17,300,081 (CHF149,558) and JPY25,289,867 (CHF218,629) vs blinatumomab, clofarabine combination	LYs: 9.4 and 10.6; QALYs: 8.5, 9.6; vs. blinatumomab; clofarabine combination	Cost-effective ICER: JPY2,035,071 (CHF17,593), JPY2,644,702 (CHF22,863) vs blinatumomab; clofarabine combination	Novartis (funder)

Study ID	Setting; perspective	Currency; costing year	Comparator(s)	Clinical data sources	Methods (model; time horizon; discount rate)	Incremental cost	Incremental effect	Conclusion (Cost effective?)	Potential conflicts/funder
Wang, 2022[162]	Singapore; healthcare payer	Singapore dollar and US dollar (costing year NR)	Blinatumomab or salvage chemotherapy	ELIANA, ENSIGN and B2101J Von Stakelberg 2011, von Stackelberg 2016 (pseudo IPD)	Hybrid decision tree and 3-state PSM; lifetime; 3.0% p.a.	SGD452,317 (CHF312,970) and SGD389,679 (CHF269,629) vs salvage chemotherapy and blinatumomab	LYs: 11.78, 8.70; QALYs: 9.87, 7.50; vs salvage chemotherapy and blinatumomab	Tisa-cel likely to be cost-effective. ICER: SGD45,840 (CHF31,718) and SGD51,978 (CHF35,965) vs salvage chemotherapy and blinatumomab	Novartis Singapore (funder)
Whittington, 2018[163]	United States; healthcare payer	2017 US dollar	Clofarabine monotherapy	B2202, B2205J and B2101J trials (pseudo-IPD) Jeha 2006	Hybrid decision tree and 3-state PSM; lifetime; 3.0% p.a.	USD329,498 (CHF314,545)	LYs: 7.91 QALYs: 7.18	Tisa-cel likely provides gains in survival and seems to be priced in alignment with these benefits. ICER: USD45,871 (CHF43,789)	Institute for Clinical and Economic Review (funder)

Abbreviations:

B-ALL = B-cell acute lymphoblastic leukaemia, **CHF** = Swiss franc, **DLBCL** = diffuse large B-cell lymphoma, **FLA-IDA** = fludarabine, cytarabine and idarubicin, **ICER** = incremental cost-effectiveness ratio, **IPD** = individual patient data, **LY** = life year, **NR** = not reported, **PFS** = progression-free survival, **PSM** = partitioned survival model, **QALY** = quality-adjusted life year, **r/r** = relapsed or refractory, **SCT** = stem cell transplantation, **tisa-cel** = tisagenlecleucel, **WTP** = willingness-to-pay.

Notes:

[A] Results reported as difference in mean outcomes (mean outcomes calculated from 100,000 simulations for each scenario). Base case results reported across 3 scenarios, based on varying assumed percentage of patients with PFS at 5 years. Range captures the variation in results across these scenarios.

Table 31 Economic summary table: axi-cel for r/r LBCL

Study ID	Setting; perspective	Currency; costing year	Comparator(s)	Clinical data sources	Methods (model; time horizon; discount rate)	Incremental cost	Incremental effect	Conclusion (Cost effective?)	Potential conflicts/funder
Population: **r/r DLBCL**									
Li, 2022[164]	China; healthcare system	2020 US dollar	Salvage chemotherapy (R-DHAP)	ZUMA-1 (pseudo-IPD) SCHOLAR-1 (pseudo-IPD)	Hybrid decision tree and 3-state PSM; lifetime; 5.0% p.a.	USD175,380 (CHF163,013)	LY: 3.43 QALYs: 2.61	Not cost-effective at WTP of USD31,120 (CHF28,926). ICER: USD67,250 (CHF62,508)	Grants from National Natural Science Foundation of China and Science and Technology Department of Fujian Province of China
Lin, 2019[165]	United States; healthcare payer	2018 US dollar	Salvage chemoimmunotherapy as bridge to SCT (R-DHAP, R-GDP, R-GEMOX, R-ICE)	ZUMA-1 SCHOLAR-1	Markov cohort; lifetime; 3.0% p.a.	Difference in mean costs: USD469,000–486,000 (CHF447,708–463,936) [A]	Difference in mean LYs: 5.46 to 8.15 Difference in mean QALYs: 2.25 to 3.72 [A]	Possible, but depends on long-term outcomes, which are uncertain. ICER: USD129,000-194,000 [A] (CHF123,143-185,192)	Department of Veterans Affairs

Study ID	Setting; perspective	Currency; costing year	Comparator(s)	Clinical data sources	Methods (model; time horizon; discount rate)	Incremental cost	Incremental effect	Conclusion (Cost effective?)	Potential conflicts/funder
Population: **r/r LBCL**									
Hillis, 2022[166]	Canada; healthcare payer and societal	2021 Canadian dollar	BSC (several chemotherapy options)	ZUMA-1 (IPD) SCHOLAR-1 (IPD)	3-state PSM; lifetime; 1.5% p.a.	Payer: CAD485,693 (CHF352,119) Societal: CAD606,010 (CHF439,347)	LY: 6.19 QALY: 4.57	Axi-cel may be cost-effective. ICER: Payer: CAD106,392 (CHF77,132); Societal: CAD132,747 (CHF96,239)	Gilead Sciences Canada (funder)
Roth, 2018[167]	United States; healthcare payer	2017 US dollar	Salvage chemotherapy (R-DHAP)	ZUMA-1 (IPD) SCHOLAR-1	3-state PSM; lifetime; 3.0% p.a.	USD380,184 (CHF362,931)	LY: 6.90 QALYs: 6.54	Axi-cel is clinically promising and potentially cost-effective. ICER: USD58,146 (CHF55,507)	Kite, a Gilead Company (funder)

Study ID	Setting; perspective	Currency; costing year	Comparator(s)	Clinical data sources	Methods (model; time horizon; discount rate)	Incremental cost	Incremental effect	Conclusion (Cost effective?)	Potential conflicts/funder
Whittington, 2019[168]	United States; public payer and commercial perspectives	NR (assume US dollar, costing year also NR)	Salvage chemotherapy (R-DHAP)	ZUMA-1 (pseudo-IPD) SCHOLAR-1 (pseudo-IPD)	Hybrid decision tree and 3-state PSM; trial based (24 months) and lifetime; 3.0% p.a.	Public payer: USD348,100–403,500 (CHF339,604–393,652) [B] Commercial payer: USD436,500–491,900 (CHF425,847–479,895) [B]	LYs: 1.89 to 5.82 QALYs: 1.52 to 4.90 [B]	Axi-cel associated with positive but uncertain gains in survival. Cost-effective under some long-term survival assumptions. ICER: public payer: USD82,400-230,900 [B] (CHF80,389-225,265) Commercial payer : USD100,400-289,000.[B] (CHF97,950-281,947)	Institute for Clinical and Economic Review provided funding for a prior CAR T review. No additional funding for this article.

Abbreviations:

axi-cel = axicabtagene ciloleucel, **BSC** = best supportive care, **CHF** = Swiss franc, **DLBCL** = diffuse large B-cell lymphoma, **ICER** = incremental cost-effectiveness ratio, **IPD** = individual patient data, **LBCL** = large B-cell lymphoma, **LY** = life year, **NR** = not reported, **PSM** = partitioned survival model, **QALY** = quality-adjusted life year, **R-DHAP** = rituximab, dexamethasone, cisplatin, cytarabine, **R-GDP** = rituximab, gemcitabine, dexamethasone, cisplatin, **R-GEMOX** = rituximab, gemcitabine, oxaliplatin, **R-ICE** = rituximab, ifosfamide, carboplatin, etoposide, **r/r** = relapsed or refractory, **SCT** = stem cell transplantation, **WTP** = willingness-to-pay

Notes:

[A] Results reported as difference in mean outcomes; 100,000 simulations run for each scenario. Base case results reported across 3 scenarios, based on varying assumed percentage of patients with PFS at 5 years. Range captures the variation in results across these scenarios.

[B] Results reported across 5 different scenarios, which considered different extrapolation approaches to model long-term survival outcomes. Range captures the variation in results across these 5 scenarios.

Table 32 Economic summary table: tisa-cel for r/r DLBCL

Study ID	Setting; perspective	Costing year; currency	Comparator(s)	Clinical data sources	Methods (model; time horizon; discount rate)	Incremental cost	Incremental effect	Conclusion (Cost effective?)	Potential conflicts/funder
Cher, 2020[169]	Singapore; healthcare payer	2018 Singapore dollar and US dollar	Salvage chemotherapy (R-ICE or R-DHAP)	JULIET trial (pseudo IPD) CORAL-1 extension (pseudo IPD)	Hybrid decision tree and 3-state PSM; 15 years; 3.0% p.a.	USD258,375 (CHF246,645)	LY: 0.81 (undiscounted) QALY: 0.51	High ICER, unlikely cost-effective. ICER: USD508,530 (CHF485,443)	Study not funded. One author reported potential COI with Novartis
Choe, 2022[170]	United States; healthcare sector and societal	2021 US dollar	Salvage chemotherapy	JULIET SCHOLAR-1	Hybrid decision tree and 3-state PSM; lifetime; 3.0% p.a.	Healthcare sector: USD271,399 (CHF246,712) Societal: USD274,442 (CHF249,479)	QALYs: 2.14	Tisa-cel (≥3 line) cost-effective at WTP of USD150,000 ICER: USD126,593 (healthcare sector; CHF115,078); USD128,012 (societal; CHF116,368)	2 authors reported grants; 1 supported in part by a National Cancer Institute award. One author reported potential COI with Novartis.
Lin, 2019[165]	United States; healthcare payer	2018 US dollar	Salvage chemoimmunotherapy as bridge to SCT (R-DHAP, R-GDP, R-GEMOX, R-ICE)	JULIET trial SCHOLAR-1	Markov cohort; lifetime; 3.0% p.a.	Difference in mean costs: USD352,000–360,000 (CHF336,019–343,656) [A]	Difference in mean LYs: 2.25 to 4.6 Difference in mean QALYs: 1.04 to 2.14 [A]	Possible, but depends on long-term outcomes, which are uncertain. ICER: USD168,000–337,000 (CHF160,373–321,700)	Department of Veterans Affairs

Study ID	Setting; perspective	Costing year; currency	Comparator(s)	Clinical data sources	Methods (model; time horizon; discount rate)	Incremental cost	Incremental effect	Conclusion (Cost effective?)	Potential conflicts/funder
Moradi-Lakeh, 2021[1]	Switzerland; Swiss mandatory health insurance system (societal in sensitivity)	NR; Swiss franc	Salvage chemotherapy (R-GEMOX, R-IVE, R-ESHAP or R-DHAP)	JULIET trial and Schuster 2017 CORAL extension studies	Hybrid decision tree and 3-state PSM; lifetime; 3.5% p.a.	CHF255,835 (2023 CHF254,489)	LYs: 2.63 QALYs: 2.26	Cost-effective at WTP of CHF100,000–150,000. ICER: CHF113,179 (2023 CHF112,584)	Novartis, Switzerland (funder)
Qi, 2021[171]	United States; third-party payer	2020 US dollar	Salvage chemotherapy (R-ICE, R-GDP, R-DHAP, R-GEMOX)	JULIET trial SCHOLAR 1	Hybrid decision tree and 3-state PSM; lifetime; 3.0% p.a.	USD263,761 (CHF245,162)	LYs: 3.71 QALYs: 3.35	Cost-effective at WTP of USD150,000. ICER: USD78,652 (CHF73,106)	Novartis (sponsor)
Wakase, 2021[172]	Japan; healthcare payer (societal in scenario)	2018 Japanese yen	Salvage chemotherapy (R-ICE, R-GDP, R-DHAP, R-ESHAP, R-EPOCH)	JULIET SCHOLAR-1 (pseudo IPD).	Hybrid decision tree and 3-state PSM; lifetime, 2.0% p.a.	JPY15,590,335 (CHF134,777)	LYs: 2.89 QALYs: 2.85	Tisa-cel is clinically important and cost-effective. ICER: JPY5,476,496 (CHF47,344)	Novartis (funder)
Wang, 2021[173]	Singapore, private insurance payer	NR; Singapore dollar and US dollar	Salvage chemotherapy	JULIET and Schuster 2017 (pooled IPD) CORAL extension studies	Hybrid decision tree and 3-state PSM; lifetime; 3.0% p.a.	-SGD8,477 (i.e. cost saving) (-CHF5,736)	LYs: 2.96 QALYs: 2.78	Likely cost-effective. ICER: tisa-cel dominant.	Novartis Singapore (funder)

Abbreviations:

CHF = Swiss franc, **COI** = conflict of interest, **DLBCL** = diffuse large B-cell lymphoma, **ICER** = incremental cost-effectiveness ratio, **IPD** = individual patient data, **LY** = life year, **NR** = not reported, **PSM** = partitioned survival model, **QALY** = quality-adjusted life year, **R-DHAP** = rituximab, dexamethasone, cisplatin, cytarabine, **R-EPOCH** = rituximab, etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide, doxorubicin hydrochloride, **R-ESHAP** = rituximab, etoposide, methylprednisolone, cytarabine and cisplatin, **R-GDP** = rituximab, gemcitabine, dexamethasone, cisplatin, **R-GEMOX** = rituximab, gemcitabine, oxaliplatin, **R-ICE** = rituximab, ifosfamide, carboplatin, etoposide, **R-IVE** = rituximab, ifosfamide, epirubicin and etoposide, **r/r** = relapsed or refractory, **SCT** = stem cell transplantation, **tisa-cel** = tisagenlecleucel, **WTP** = willingness-to-pay.

Notes:

[A] Results reported as difference in mean outcomes (mean outcomes estimated over 100,000 simulations for each scenario). Base case results reported across 3 scenarios, based on varying assumed percentage of patients with PFS at 5 years. Range captures the variation in results across these scenarios.

8.1.2.2 Findings: cost-effectiveness

8.1.2.2.1 Study characteristics

The retrieved studies included economic evaluations from Canada,[166] China,[164] Japan,[161,172] the Netherlands,[160] Singapore,[162,169,173] Spain,[158] Switzerland,[1] and the United States.[157,159,163,165,167,168,170,171] Most studies evaluated the cost-utility of CAR T-cell therapies (tisa-cel and/or axi-cel) over a lifetime horizon, except one study with a long-term time horizon of 15 years.[169]

Overall, 7 studies evaluated tisa-cel for adults with r/r DLBCL,[1,165,169-173] while 8 studies evaluated tisa-cel for children or young adults with r/r B-ALL.[1,157-163] Most studies evaluating axi-cel assessed its cost-effectiveness as a treatment for adults with r/r LBCL, which combines DLBCL, PMBCL and transformed follicular lymphoma. This aligns with the population included in the ZUMA-1 trial.[141] In total, 3 studies evaluated axi-cel for adult patients with r/r LBCL.[166-168] Two studies evaluated axi-cel for DLBCL, although they also used clinical data from the ZUMA-1 trial.[164,165]

Of the 7 studies evaluating tisa-cel in DLBCL, 4 were funded by the company (Novartis) that developed Kymriah® (tisa-cel proprietary drug),[1,171-173] while 5 of the 8 studies evaluating tisa-cel in B-ALL were supported by Novartis.[1,158,160-162] Two of 3 studies evaluating axi-cel in LBCL were funded by the company (Kite, a Gilead company) that developed Yescarta® (axi-cel proprietary drug).[166,167] Modelling techniques employed across each of these groups of company-funded studies appear to be similar. For example, several tisa-cel studies funded by Novartis used a hybrid decision tree and 3-state partitioned survival model (PSM) with a 1-month cycle length and a lifetime horizon.[1,161,162,171-173] Both Gilead-funded studies used 3-state PSM.[166,167]

For studies including a population of adults with DLBCL, the comparator was typically defined as a blend of various salvage chemotherapy/chemoimmunotherapy regimens, followed by SCT in some patients (generally, based on the proportion receiving subsequent SCT in the clinical trials informing the efficacy estimates). For studies including a population of adults with LBCL, the comparator included salvage chemotherapy or best supportive care (BSC) chemotherapy, followed by SCT in some patients. Clinical data were sourced from either the CORAL extension studies or the SCHOLAR-1 trial.[174-176]

For studies including a population of children and young adults with B-ALL, the comparators included salvage chemotherapy (fludarabine, cytarabine and idarubicin), clofarabine monotherapy, clofarabine combination therapy (clofarabine, cyclophosphamide and etoposide) or blinatumomab, followed by SCT in some patients. Clinical data were sourced from a range of studies, depending on the comparator being considered.[177-182]

8.1.2.2.2 Model features

Most studies used a hybrid decision tree and 3-state PSM structure,[1,161,168,169,171,172,183-185] or a 3-state PSM structure without mention of a decision tree.[160,166,167,186] Where employed, the decision tree was used to separate infused versus non-infused patients (CAR T-cell therapy arm only), responders versus non-responders, and/or recipients of subsequent SCT prior to entry into the PSM. This allowed survival analysis to be incorporated separately for the different groups (e.g. infused vs non-infused patients) and/or for costs to be differentially assigned (e.g. by response status). The PSMs included the health states of either PFS, progressed disease and dead (for DLBCL and LBCL populations) or event-free survival (EFS), progressed disease and dead (for B-ALL populations). Where specified, EFS was defined as the time from treatment initiation to the earliest of either treatment failure, relapse or death.[161] For one model, an additional Markov component, which was used beyond year 5 of the PSM simulation, was described.[184] Two studies used a Markov cohort model,[157,165] while another used a microsimulation state transition model.[159] All studies used a 1-month cycle length.

8.1.2.2.3 Previous HTAs

Several HTA bodies have assessed—and, in some cases, re-assessed—the cost-effectiveness of axi-cel and/or tisa-cel in the indications considered for this HTA, including: NICE (UK), the Canadian Agency for Drugs and Technologies in Health (CADTH; Canada), the Institut National d'Excellence en Santé et en Services Sociaux (INESSS; Canada), the Haute Autorité de Santé (HAS; France), and the Zorginstituut Nederland (the Netherlands). Where cost-effectiveness has been assessed, manufacturer-submitted cost-effectiveness analyses have been considered. For the indication of r/r B-ALL, the Zorginstituut Nederland did not consider cost-effectiveness, given the expected budget impact was low.

For the purposes of informing modelling methodologies, the models submitted to NICE, CADTH and INESSS and the accompanying HTA review groups critiques, were reviewed in detail during HTA protocol development. All 3 organisations have published HTAs assessing tisa-cel for adult patients with r/r DLBCL,[187-189] tisa-cel for children and young adults with r/r B-ALL,[190-192] and axi-cel for adult patients with r/r LBCL.[193-196] NICE has assessed axi-cel for adult patients with r/r LBCL twice, once in 2019 and again in 2023.[193,194] For each indication, all 3 organisations considered economic evaluations submitted by the manufacturer of either tisa-cel or axi-cel. The modelling methodologies used in these submissions appear similar to those used in the published company-funded economic evaluations. A summary table for the included HTAs is provided in ***Appendix G***. A more detailed discussion of previous HTAs, including how they compare to this HTA, is provided in ***Section 11.3***.

8.1.2.2.4 The York mock model

As part of a mock technology appraisal commissioned by NICE to review its methods and processes for appraising regenerative medicines and cell therapy products, an exemplar case study on CAR T-cell therapy for treating ALL was developed.[197] This included the development of an exemplar economic model to assess the cost-effectiveness of CAR T-cell therapy relative to SoC (clofarabine in the base case) for children and young adults with 2 or more relapses or refractory ALL.[197]

Two de novo decision models were developed to model the costs and outcomes of CAR T-cell therapy under different target product profiles. One model considered CAR T-cell therapy itself to be a curative-intent treatment, while the other considered CAR T-cell therapy to be a bridge to SCT.[197] The bridge-to-SCT model included a short-term (2-month) decision tree to predict the remission and transplant status of the cohort in the immediate period following CAR T-cell therapy or comparator therapy. This was followed by a series of PSMs to predict the survival of patients, conditional on remission and transplant status. The curative-intent model was a simple 3-state PSM that included the following health states: alive and event free, alive post-event, dead. State occupancy was derived via the direct extrapolation of EFS and OS curves.

Both models used a lifetime horizon and a 1-month cycle length and measured health effects in terms of QALYs.[197] Patients who were alive at 5 years were assumed to be long-term survivors of ALL. The costs and consequences of treatment-related AEs (CRS, B-cell aplasia, encephalopathy, hypotension, febrile neutropenia, neutropenia, anaemia, thrombocytopenia, leukopaenia, hypocalaemia, hypophosphataemia) were all—apart from B-cell aplasia in the curative intent model—captured at the start of the evaluation. For some patients, treatment for B-cell aplasia is expected to persist beyond the first year post-CAR T-cell therapy.[197] In the curative-intent model, the costs and consequences of B-cell aplasia were modelled by estimating the probability of patients having B-cell aplasia over time.

8.1.2.2.5 Study results

Economic evaluation of the cost-effectiveness of tisa-cel in DLBCL was identified in 7 studies.[1,165,169-173] Among them, Lin 2019[165] and Moradi-Lakeh 2021[1] investigated 2 interventions and 2 populations, respectively. In Lin 2019, tisa-cel and axi-cel were assessed separately in adults with r/r DLBCL.[165] This study showed that from the US healthcare payer perspective, the ICERs for both tisa-cel and axi-cel were high but could be cost-effective if the long-term outcomes are optimistic.[165] Moradi-Lakeh 2021 reported base case ICERs of CHF36,419 (2023 CHF36,277) relative to blinatumomab for B-ALL, and CHF113,179 (2023 CHF112,584) relative to salvage chemotherapy for LBCL, in a Swiss setting.[1] This study was funded by Novartis.[1] Among the remaining 5 studies evaluating tisa-cel in DLBCL,[170-173,198] tisa-cel was a cost-effective treatment at the cited WTP threshold in most (k=4) studies.[170-173] Three of

the 4 studies were funded by Novartis.[171,172,183] An extremely high ICER was reported for tisa-cel by Cher 2020.[169] A Singapore healthcare payer perspective and 15-year time horizon were adopted for this evaluation.[169] This study was not company-funded.

Three economic evaluations of the cost-effectiveness of axi-cel versus salvage chemotherapy in adults with r/r LBCL were identified.[166-168] They all found that axi-cel was considered cost-effective over the lifetime horizon of the evaluation. The reported perspectives varied between the studies. Two of the 3 were company-funded.[166,167] Two studies evaluated the cost-effectiveness of axi-cel versus salvage chemotherapy in patients with r/r DLBCL.[164,165] Lin 2019 reported a potentially positive result,[165] while a Chinese study argued that, at a WTP threshold of USD31,120 (CHF28,926), axi-cel was not a cost-effective modality from the perspective of China's healthcare system.[164] Results of one-way sensitivity analysis supported this conclusion, while a probabilistic sensitivity analysis (PSA) showed that the probability of axi-cel being cost-effective exceeds 50% at a WTP threshold of USD80,000 (CHF74,359).[164] This study was not company-funded.

In addition to Moradi-Lakeh 2021,[1] which reported a positive result in both populations, the cost-effectiveness of tisa-cel for children or young adults with r/r B-ALL was evaluated by 7 other economic studies. [157-163] All found tisa-cel to be cost-effective or potentially cost-effective over a lifetime horizon. One of the US studies held a critical view that tisa-cel is cost-effective only if it can keep a significant proportion of patients in remission without transplantation.[157] Most (k=7) of the analyses were from the perspective of the healthcare payer, although a number considered the societal perspective in sensitivity/scenario analysis.[1,157,158,160-163] Among the 8 studies, 5 were funded by Novartis.[1,158,160-162]

A summary of findings of the existing HTAs is provided in ***Section 11.3***.

8.1.2.3 Applicability: cost-effectiveness

8.1.2.3.1 Applicability of the evidence

One directly applicable study was identified. This study assessed, from the perspective of the Swiss mandatory health insurance system (i.e. the Swiss healthcare payer), the cost-effectiveness of tisa-cel compared to salvage chemotherapy in adults with DLBCL, and compared to clofarabine combination therapy, blinatumomab or salvage chemotherapy in children and young adults with B-ALL.[1]

The remaining studies were only partially applicable to this HTA, having been conducted in healthcare contexts outside of Switzerland. None of the studies were judged as inapplicable. Moreover, most studies assessing the cost-effectiveness of axi-cel considered a combined population of adults with LBCL. This does not directly translate to the PICOs of this HTA (***Section 5***), which considers DLBCL and PMBCL populations separately. Nevertheless, it is noted that the pivotal study assessing axi-cel included a combined population of r/r LBCL patients;[144] therefore, a combined r/r LBCL population has

also been considered in this HTA. One study considered CAR T-cell therapy in both second-line (axi-cel and tisa-cel) and third-line (tisa-cel only) settings.[170] Data on the subpopulation of patients receiving third-line or above tisa-cel was applicable to the research question.[170]

8.1.2.3.2 Quality of reporting of the evidence

The one directly applicable study fulfilled 24 of the 28 CHEERS checklist items,[1,156] indicating a high quality of reporting.

8.1.2.4 Findings: additional economic evidence

Fifteen additional economic analyses were identified, including 7 observational studies,[152,199-204] 5 modelling studies,[205-209] 2 budget impact analyses (from the German statutory health insurance perspective; not discussed further here),[210,211] and one efficiency frontier analysis[212].

Comparisons in resource use between BSC or autologous SCT and CAR T-cell therapy were analysed by 2 studies.[201,207] For patients with DLBCL, Foglia 2023 found that compared with BSC, CAR T-cell therapy required more resources, excluding the cost associated with the product itself.[201] However, in an analysis conducted by Ring 2022, treatment with autologous SCT was 29% more expensive than CAR T-cell therapy after excluding the CAR T-cell product cost for BCL patients.[207] One study assessed treatment costs of third-line interventions in DLBCL (BSC, allogenic SCT, tisa-cel, axi-cel) and combined these with estimates of median OS to generate an efficiency frontier.[212] The efficiency frontier showed allogeneic SCT and axi-cel to be the most efficient interventions; however, costs differed substantially—EUR73,829 (CHF79,378) and EUR340,458 (CHF366,046), respectively. In a retrospective cohort claims analysis across 3 US databases,[204] Broder 2020 estimated rates of neurologic AEs and total healthcare costs for patients with and without neurologic AEs within 30 days of treatment with CAR T-cell therapy, high-intensity cytotoxic therapy, low-intensity cytotoxic therapy, or targeted therapy.[204] Patients with neurologic AEs had higher healthcare costs than patients without across all treatment types; however, the difference was most pronounced in patients receiving CAR T-cell therapy.

Nine studies reported on cost specific aspects associated with CAR T-cell therapies.[152,199,200,202,203,205,206,208,209] Three studies considered both axi-cel and tisa-cel individually.[152,200,205] Badaracco 2023 estimated costs associated with the management of CRS and neurologic events in patients with r/r LBCL. The overall weighted average per-patient cost of treating the events was USD47,665 and USD42,538 (CHF44,304 and CHF39,538) for axi-cel and tisa-cel, respectively.[205] Maziarz 2022 assessed costs for both axi-cel and tisa-cel in adult patients with r/r DLBCL,[152] while Huguet 2021 assessed the costs of hospitalisation for 3 subpopulations: tisa-cel for ALL, tisa-cel for DLBCL and axi-cel (patient cohort NR). Mean costs per hospital stay were EUR372,400

(CHF395,360) for tisa-cel in ALL, EUR342,903 (CHF364,045) for tisa-cel in DLBCL, and EUR366,562 (CHF389,162) for axi-cel.[200] CAR T-cell product expenses accounted for more than 80% of these costs.

Two studies analysed the cost of CAR T-cell therapy (axi-cel and tisa-cel in combination) for LBCL and DLBCL patients.[199,202] These studies found that CAR T drug cost accounted for the majority of the overall cost and that AEs can increase the total cost.[199,202] For example, Chacim 2022 reported that CAR T-cell product costs account for 97.0% of overall medical costs. Excluding the product price, inpatient care accounted for 57% of remaining costs.[202] This was supported by 2 studies that considered costs associated with tisa-cel only.[208,209] Both reported that the largest cost component was the list price of CAR T, either for treating young patients with r/r B-ALL or for adult patients with r/r DLBCL. The major driver of additional costs related to AE management.[208,209]

Lyman 2020 and Snyder 2021,[203,206] found that the total cost of care and the cost associated with travelling were both higher for those in the academic hospital setting cohorts. The authors suggested that availability of CAR T therapy will increase if it could be used in non-academic hospitals.

8.2 Methodology for the economic evaluation

8.2.1 Research question

The target population, interventions (axi-cel, tisa-cel) and comparator (SoC) are as previously described (***Section 5***). The remaining aspects of the research question are addressed below: perspective, time horizon, outcome measures and a representative definition of SoC required for the economic analyses.

8.2.2 Perspective

A Swiss healthcare payer perspective was adopted. Direct medical costs for services principally covered by mandatory health insurance were included, irrespective of the actual payer (e.g. health insurer, other social insurer, government [federal, canton, community] or patient). Non-medical and indirect costs (e.g. travel, informal care or productivity losses) were not considered. Costs were reported in Swiss francs for a common costing year of 2023.

8.2.3 Time horizon

The time horizon of an economic evaluation should be sufficient to capture in full the differences in costs and effects of the options being compared.[213] To capture these differences fully, a lifetime horizon was required, as CAR T-cell therapies are intended to improve the prognosis of patients with cancer. This required extrapolation of observed data, increasing uncertainty in the evaluation. Scenario analyses with reduced time horizons were undertaken to explore the impact of this uncertainty on economic outcomes.

8.2.4 Outcomes

Health outcomes were measured in LYs and QALYs lived. Incremental cost, incremental LYs gained and incremental QALYs gained with CAR T-cell therapies relative to SoC were reported. The end result of the economic evaluation is the ICER, reflected as both the incremental cost per LY gained and the incremental cost per QALY gained. Both costs and effects were discounted at 3.0% per annum, with alternative rates of 0.0% and 6.0% per annum used in sensitivity analyses.

8.2.5 Relevant comparators to the Swiss context

Discussions with a clinical expert highlighted that SoC for patients with relapsed or refractory disease is highly variable—some patients may receive salvage therapy, others may receive SCT, palliation (e.g. palliative radiotherapy) or off-label therapies funded under specific agreements between hospitals and health insurers. This level of detail could not be incorporated into the economic analyses. Instead, a representative definition of likely SoC for the target populations in Switzerland was constructed to guide the targeted literature searches for clinical evidence, the assessment of applicability of the available evidence to the Swiss context, and the costing of the comparator arm. Targeted literature searches were performed in addition to the clinical searches described in ***Section 7*** with the aim of retrieving survival outcome data for the economic modelling.

Swiss clinicians (n=3; general fields of expertise: oncology [n=2] and paediatric oncology [n=1]) were provided a list of potential comparators to CAR T-cell therapy (given in the third-line setting) and asked to identify the one or two most relevant or most commonly used (see ***Appendix G*** for full list of comparators). The following comparators were identified in this way:

Paediatric ALL:

- inotuzumab
- blinatumomab
- palliation

One clinical expert noted that the comparator could be individualised bridge-to-transplant, including compassionate use of inotuzumab or blinatumomab. Furthermore, it was suggested that although palliation is an option, patients would often still receive an initial treatment (as mentioned above) without proceeding to transplant.

Adult DLBCL:

- salvage therapy with either rituximab, gemcitabine and oxaliplatin (R-GEMOX); rituximab and bendamustine; POLA-BR; tafasitamab and lenalidomide; or gemcitabine and oxaliplatin (GEMOX)
- palliation

One clinical expert noted that the approved salvage therapy regimens are not intended to cure but are generally given as a bridging therapy.

Adult PMBCL:

Options available for patients with PMBCL are the same as those available for patients with DLBCL. In addition, pembrolizumab (Keytruda®) is approved and reimbursed and will be given to patients who are fit enough (around 50%) for a median duration of 6 months (8 cycles).

8.2.6 Decision regarding the need for de novo modelling

One directly applicable study with a high quality of reporting was identified in the systematic literature searches.[1] This study provides useful information on the cost-effectiveness of tisa-cel in 2 target populations. Nevertheless, it has a conflict of interest, having been funded by the company (Novartis) that developed Kymriah® (tisa-cel proprietary drug). Moreover, since the existing evaluations were run, longer-term follow-up data for 2 cohorts (ELIANA and JULIET) have been published and not all identified comparators were considered.

A data gap remains regarding the cost-effectiveness of axi-cel relative to SoC for adults with DLBCL or PMBCL in Switzerland. De novo economic modelling, guided by the existing evidence base, was required to assess the cost-effectiveness of axi-cel in these populations. To ensure consistency across the HTA, de novo modelling was undertaken for all 3 populations included in this HTA. Existing evidence for these 2 populations is reported narratively alongside the results of the de novo evaluations.

8.2.7 Modelling approach

The modelling approach was a hybrid decision tree and 3-state PSM, built around the health states of alive and progression-free or event-free, alive with progressive or relapsed disease, and dead (***Figure 70***). Models were constructed in TreeAge Pro (Version 2022 R2.0).[214]

In a PSM, the proportion of a cohort in each health state is based upon parametric survival equations.[215] This is a common modelling approach for cancer treatments, with separate survival equations for OS and PFS.[215] It required the digitisation of published KM curves and the generation of pseudo-individual patient data, as described in the York mock technology appraisal and a number of published studies.[1,168,169,172,183-185,197] Further details on the required steps are provided below.

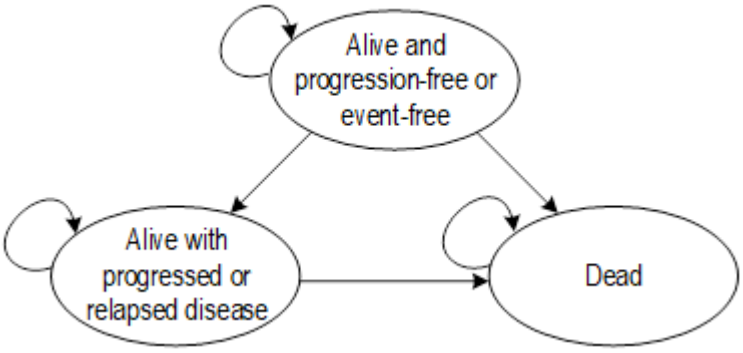
Health state occupancy was determined by the following equations:[197]

Alive and progression-free (t) = *P (PFS, t)*

Alive with progressed disease (t) = *(P (OS, t) – P (PFS, t))*

Dead (t) = *1 – P (OS, t)*

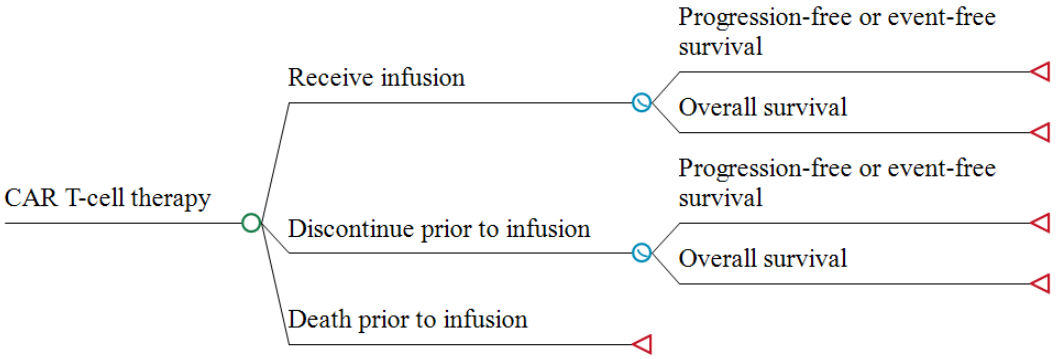
Figure 70 Model structure for a partitioned survival analysis



Source:
Based on the illustration provided for the York mock model.[197]

Treatment discontinuations (i.e. patients in the CAR T-cell therapy arm who discontinue treatment or die prior to infusion) were incorporated as a decision node prior to the 3-state model (see ***Figure 71***). AEs and subsequent SCTs were built into the model as costs and utility reductions.

Figure 71 Combined decision tree and partitioned survival model structure used in TreeAge



Source:
Image exported from TreeAge Pro (Version 2022 R2.0).[214]

Patients who discontinue CAR T-cell therapy prior to infusion (not due to death) were assumed to receive a comparator treatment (blinatumomab for B-ALL population; salvage chemotherapy for LBCL populations). This assumption was applied to only a small percentage of patients. SBST registry data over the period 2019–2021, shows 0% (0/26) of slot requests went without an infusion among B-ALL patients and 12.5% (30/240) of slot requests went without an infusion among DLBCL/PMBCL patients. Of these 30 patients, death occurred prior to CAR T-cell infusion in 26 cases (86.7%). Patients

discontinuing treatment prior to infusion were assigned costs for leukapheresis as well as bridging therapy in a percentage of patients, but no costs for the CAR T-cell therapy product.

The economic evaluation accounted for TRAEs associated with CAR T-cell therapy, including those occurring during the hospitalisation episode for infusion (notably CRS and ICANS), as well as the ongoing costs for IVIG required for prolonged hypogammaglobulinaemia with severe or recurrent infections.

8.2.7.1 Subsequent SCT

Patients may receive subsequent allogenic SCT after CAR T-cell therapy. One clinician suggested subsequent SCT applies for the indication of B-ALL but not for DLBCL or PMBCL. In a review article, Cappell 2023 suggest long-term follow-up data indicate CD19-targeted CAR T-cells are likely to be curative for a subset of patients with B-cell lymphomas, but may need to be combined with consolidative allogenic SCT to enable long-term remissions for patients with B-ALL.[216] However, the review adds that in paediatric B-ALL patients, a substantial proportion of patients have long-term remissions after tisa-cel alone without consolidative allogenic SCT, suggesting that a cure is possible without consolidative allogeneic SCT in some paediatric patients.[216]

Expert advice from a paediatric oncologist suggests it is becoming increasingly clear that many physicians expect CAR T-cell therapy to be more frequently used as a bridge to SCT, depending on the course of aplasia and MRD status. CAR T-cell therapy may be consolidated with SCT if B-cell aplasia is lost early (3 months) and depending on MRD status. The literature notes that the extent to which CAR T-cell therapy is a standalone curative treatment, and whether patients need additional SCT either as consolidation for remission or treatment of relapse post-infusion, remain central and elusive questions.[217]

Subsequent SCTs were not explicitly built into the model structure. Given the reported use of consolidative allogenic SCT in B-ALL patients, costs and disutilities associated with subsequent allogenic SCT were incorporated in the B-ALL model for a proportion of the model cohort in both the CAR T-cell therapy and blinatumomab arms. These proportions were informed by the clinical trials from which survival data were drawn, supplemented with Swiss-specific estimates.

No costs or disutilities for subsequent SCTs were incorporated into the LBCL models, based on feedback that subsequent SCTs do not apply for DLBCL or PMBCL, and that it would be very unlikely to perform a transplant following a comparator therapy in the third-line setting.

8.2.8 Cost inputs

Healthcare resource use relating to CAR T-cell therapies and comparator therapies were identified, measured and valued. Peer-reviewed and grey literature sources were searched for resource utilisation estimates, with preference given to Swiss-specific sources. Furthermore, expert opinion was sought from Swiss clinicians.

Healthcare resources consumed were valued using Swiss diagnosis-related group (DRG) costs for inpatient services, the Spezialitätenliste for medicine costs, the Analysenliste for laboratory costs and TARMED for outpatient medical services.

8.2.9 Clinical inputs

Data sources informing PFS or EFS and OS outcomes for patients receiving CAR T-cell therapies were selected from the studies included in the clinical review (***Section 7***). Data sources were selected for use in the economic evaluation according to their level of evidence. No RCT data and limited NRSI data were identified, therefore data from single-arm studies were considered.

The clinical review was limited to studies including a CAR T-cell therapy arm. As single-arm study data had to be used for the economic evaluation, additional evidence for the comparator arm was needed for the incremental benefit of CAR T-cell therapy to be assessed. A pragmatic approach was taken to identifying potentially relevant data sources for the comparators, including a search of known economic evaluations and HTAs on CAR T-cell therapies as well as clinical practice guidelines for the target populations. Where reasonable, sources used in the existing studies were considered to inform comparative survival outcomes for the modelling. As required, additional literature was sought to inform comparative survival estimates, with either new evidence for newly identified comparators (focusing on key trials) or updated evidence on previously considered comparators (i.e. updated results from previously used trials or from expanded access studies).

As data from single-arm studies were used for the economic evaluation, the incremental benefit of CAR T-cell therapy was based on a naïve treatment comparison between CAR T-cell therapy and the comparator, introducing significant uncertainty into the evaluation.

To estimate QALYs, health state utilities and treatment-related and AE-related disutilities were incorporated into the model. A pragmatic approach was taken to identify potentially relevant sources for utilities and disutilities, including a search of known economic evaluations and HTAs for the populations of interest.

8.2.10 Extrapolation of survival data

Published KM curves for OS and PFS (or EFS in the case of ELIANA) were digitised using WebPlotDigitizer [218] Pseudo-IPD data were then reconstructed using an R Shiny App, as described by Liu 2021.[219,220]

For the extrapolation of published data, a range of survival models were fitted to the extracted data, including exponential, Weibull, log-normal, log-logistic, generalised gamma and Gompertz. More flexible spline-based survival models were also explored. A retrospective comparison of the predictive accuracy of different survival extrapolation methods found mixture cure models (MCMs) and cubic spline models to generate more accurate survival predications for CAR T-cell therapies in r/r LBCL.[221] A retrospective assessment of the accuracy of standard parametric survival models, spline models and MCMs fitted to OS data for immune-checkpoint inhibitors found that spline models and MCMs generally demonstrate the potential to accurately reflect longer-term survival, but there are no definitive features that unquestionably support the use of one specific extrapolation technique.[222] Another retrospective comparison on survival models fitted to the ZUMA-1 trial data reported cure-based models to provide the best fit, relative to standard and spline-based parametric extrapolations.[223] MCMs were not explored in this HTA due to a lack of IPD. Model fitting was performed in R Studio (version 3.4.1), using the flexsurv package.[224,225] For cubic spline models, knot locations were chosen by default from quantiles of the log uncensored death times.[224] Microsoft Excel was used for plotting the extrapolated curves and for constructing piecemeal survival functions (i.e. for the long-term survivorship scenarios). In the analyses, where extrapolated PFS (or EFS) exceeded OS, PFS (or EFS) was set equal to OS. Furthermore, where extrapolated OS exceeded age- and gender-matched general population mortality, OS was set equal to general population mortality.

Goodness-of-fit was assessed using visual inspection, Akaike's information criterion (AIC) and Bayesian information criterion (BIC). Base case survival functions were selected based on an assessment of AIC (curves with the lowest AIC values were selected), combined with visual inspection. A narrative overview of the best fitting models is provided in the results section (***Section 8.4.2***). Figures displaying the fitted standard parametric curves and fitted spline models, and tabulated AIC and BIC statistics for the fitted curves, are provided in the ***Appendices***.

For the B-ALL population, a number of existing studies have assumed that patients remaining alive at 5 years are effectively cured, with ongoing survival modelled according to country-specific life tables adjusted using a standard mortality rate (SMR). In the York mock model, for example, an effective 'cure' point of 5 years was assumed. Across studies, an SMR of 9.05 (95% CI: 7.77 to 10.5), sourced from a Canadian cohort study of 5-year survivors of childhood and adolescent cancer has been used in existing economic evaluation.[226] In the current HTA, the base case assumed survival as modelled by the chosen

distribution (or background mortality, whichever was lower). Scenarios using standard parametric or spline-based distributions followed by assumed long-term survivorship extrapolations beyond year 5 were tested in scenario analysis.

Similarly, some existing studies on LBCL populations also considered an effective 'cure' point in their modelling. In NICE's critique of the manufacturer's submission for DLBCL, assuming long-term survivorship after 5 years (rather than a shorter period) was felt to be appropriate.[187] In the CADTH Optimal Use Report for axi-cel for LBCL, the clinical expert consulted by CADTH considered a 5-year cure point to be appropriate.[195] For LBCL populations, an SMR of 1.09 (95% CI: 0.69 to 1.74) has been used in existing studies. In the current HTA, the base case assumed survival as modelled by the chosen distribution (or background mortality, whichever was lower). Scenario analyses for the LBCL population assumed long-term survivorship beyond year 5.

8.2.11 Accounting for uncertainty

Uncertainties in the base case estimates were explored using one-way deterministic sensitivity analysis (DSA) and scenario analysis.

One-way DSAs allow the key model drivers to be identified. The range over which each parameter is varied reflects 95% CIs (if reported or estimable), highest and lowest values (if a range is available) or is assumed (in the absence of CI or range) by varying the base case estimate by an arbitrary percentage amount (e.g. ±20%).[227,228] Results were presented visually using tornado diagrams.

Scenario analyses varying the time horizon, discount rate, type of survival function and extrapolation assumption, and CAR T-cell product price were undertaken. The impact of the extrapolation assumptions was a key focus. For example, Whittington 2019, who described the use of 5 survival models that account for variation in long-term survival assumptions, found the cost-effectiveness of axi-cel to be uncertain due to variation in results linked to the various survival assumptions.[168] The CAR T-cell product price was also a focus of scenario analysis, given the exact value of this tariff was unknown to the authors of the HTA; however, economic evidence reviewed as part of the literature review demonstrates a high-economic burden of the intervention, driven by product price.

Reporting described how uncertainty in the model inputs affects economic findings. There is no accepted WTP threshold in Switzerland; ICERs are presented without any interpretation of cost-effectiveness. Cost-effectiveness acceptability curves (CEACs) generated through PSAs are also presented.

8.2.12 Summary

Table 33 Overview of the economic analysis

Perspective	Swiss healthcare payer
Patient populations	• children and young adults (up to age 25) with refractory B-ALL or relapsed B-ALL after SCT or at least 2 lines of therapy • adults with refractory or relapsed DLBCL after at least 2 lines of therapy • adults with refractory or relapsed PMBCL after at least 2 lines of therapy
Interventions	• tisa-cel (Kymriah®) • axi-cel (Yescarta®) Note: costs and disutilities associated with subsequent allogenic SCT were included for a proportion of patients in the paediatric and young adult B-ALL model.
Comparator	Standard care, including chemotherapy and immunotherapy Note: costs and disutilities associated with subsequent allogenic SCT were included for a proportion of patients in the paediatric and young adult B-ALL model.
Type of economic evaluation	CUA
Time horizon	Lifetime (10 and 20 years in scenario analysis)
Sources of inputs	Observational studies and/or single-arm studies, Spezialitätenliste, Analysenliste, TARMED, Swiss DRGs, MedStat, expert opinion
Costs	Direct medical costs (2023 CHF) (Pharmaceutical costs, laboratory costs, outpatient and inpatient medical care costs)
Effect measure	LYs and QALYs
Method used to generate results	Hybrid decision tree and 3-state PSM
Discount rate	3.0% per annum for costs and QALYs (0% and 6% in sensitivity analysis)

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **axi-cel** = axicabtagene ciloleucel, **CHF** = Swiss franc, **CUA** = cost utility analysis, **DLBCL** = diffuse large B-cell lymphoma, **DRG** = diagnosis-related group, **LY** = life year, **PMBCL** = primary mediastinal B-cell lymphoma, **PSM** = partitioned survival model, **QALY** = quality-adjusted life year, **SCT** = stem cell transplantation, **tisa-cel** = tisagenlecleucel.

8.3 Methodology for the budget impact analysis

8.3.1 Research question

The intent of this section of the HTA was to explore the potential budget impact of continued funding of CAR T-cell therapies for currently reimbursed populations. This included estimating the size of the eligible population, the number of patients currently utilising CAR T-cell therapies and the potential uptake of CAR T-cell therapies over time.

The potential budget impact of CAR T-cell therapies, from the perspective of the Swiss healthcare payer, was estimated over a 5-year period. CAR T-cell therapies may be a final therapy for some patients, replacing SoC, while others may receive SCT or other follow-up therapies subsequent to cell therapies. Costs for subsequent allogenic SCT in B-ALL patients (following CAR T-cell therapy or comparator treatment) were considered.

To estimate a net cost of treatment, the budget impact model assumed that CAR T-cell therapy may be a substitute for the identified comparator therapies. Nevertheless, CAR T-cell therapy may be an additional therapy for some patients. Additional costs associated with bridging therapies prior to CAR T-cell infusions were accounted for.

8.3.2 Methodology

A budget impact analysis (BIA) compares scenarios defined by sets of interventions, with the starting scenario defined by the current intervention mix for the eligible population.[229] In this case, the intervention—CAR T-cell therapy—is already included in the current intervention mix, having been provisionally listed in Appendix 1 of the Health Insurance Benefits Ordinance.[4] Thus, under the starting scenario, it was assumed that the intervention mix would continue to include CAR T-cell therapy. For the comparator scenario CAR T-cell therapy was not included in the intervention mix.

A number of potential alternatives to CAR T-cell therapies for patients with r/r disease (in the third-line setting) specific to the Swiss context were defined for this HTA (see ***Section 8.2.5***). For the BIA calculations, it was assumed that, in the absence of CAR T-cell therapies, patients would be treated with one of the defined active comparators (i.e. a chemotherapy or immunotherapy regimen, not palliative care). Costs for these comparators were considered a cost offset in the BIA calculations.

8.3.3 Patient numbers

Epidemiological estimates were sourced to provide information on the number of patients within each of the target populations in Switzerland. These estimates were used as a ceiling, since they reflect the maximum number of patients who could receive the therapy, assuming 100% uptake among eligible patients.

The number of Swiss patients currently utilising CAR T-cell therapy was sourced from the SBST registry, which provides information on the annual number of patients in Switzerland treated with CAR T-cell therapy between 2019 and 2022. Differences in utilisation across years provide insight into recent uptake trends of the technology within Switzerland. These trends, or trends in the size of the eligible population (as defined via the epidemiological approach), were used interchangeably to project continued uptake under the scenario in which funding for CAR T-cell therapy by the Swiss mandatory health insurance system is continued.

8.3.4 Cost inputs

Healthcare resource use relating to CAR T-cell therapies and comparator therapies identified, measured and valued for the economic evaluation (as described in ***Section 8.2.8***) were used in the BIA. Specifically, undiscounted treatment and AE management unit costs were used, and assigned to the estimated number of patients within each of the target populations. Costs for patients beginning the

CAR T-cell therapy treatment pathway but discontinuing prior to infusion were considered. In addition, the incidence and associated costs of management of AEs (including costs for extended hospitalisation episodes incurred as part of CAR T-cell infusion as well as long-term monthly IVIG therapy) and subsequent allogenic SCTs for B-ALL patients were captured.

8.3.5 Accounting for uncertainty

Scenario analysis was used to explore the impact of certain assumptions on the results.

8.4 Inputs: costs and cost-effectiveness

8.4.1 Costs

For Swiss DRGs, a base rate of CHF10,500 was assumed (per FOPH advice). An average tax point value (TPV) of 0.89 was assumed for TARMED and Analysenliste costings (per FOPH advice). Outpatient drug costs were calculated by rounding up volume consumed per cycle to the nearest pack size (to account for wastage of single-dose vials) and using the lowest Spezialitätenliste price listing for each pack size if multiple brands were listed (except for IVIG cost calculation, where an average across brands was used).

For all drug cost calculations, body surface areas of 1.79 m^2 (LBCL population) and 1.2 m^2 (B-ALL population), and body weights of 75 kg (LBCL population) and 49.5 kg (B-ALL population) were assumed.[197,230-232]

8.4.1.1 CAR T-cell therapy costs

Costs for CAR T-cell therapy include those for leukapheresis, bridging and lymphodepleting chemotherapies, the CAR T-cell product itself, infusion of the modified CAR T-cells, hospital and ICU stays, TRAEs, subsequent SCT, and a one-off cost upon disease progression.

8.4.1.1.1 Leukapheresis

Leukapheresis can be provided in either the inpatient or outpatient setting. In a process analysis of CAR T-cell therapy and autologous SCT for r/r B-cell lymphoma patients, based on standard operating procedures from the University Hospital Zurich, apheresis was listed under an outpatient phase of the CAR T-cell therapy pathway.[207]

Advice from Swiss clinicians with expertise in oncology states:

- leukapheresis in adults will most often (>95%) be performed in the outpatient setting; outpatient numbers are lower for children (~50%)

- leukapheresis setting depends on the status of the veins; for axi-cel it is often performed in the inpatient setting due to constraints around the collection time of cells
- leukapheresis in paediatric patients is often performed in an inpatient setting for multiple reasons, such as complex management at relapse including bridge to leukapheresis and then to CAR T-cell therapy.

Inpatient care would be covered under the Swiss DRG system, with codes A42A and A42B identified as applicable (and verified via expert consultation). A paediatric oncologist indicates that leukapheresis may need to be performed during admission for leukaemia management. Therefore, in the B-ALL analysis, this cost input was assigned an uncertainty bound, with the lower and upper bounds informed by Swiss DRGs R63E and R63B.

Outpatient care is covered via a lump sum payment, under a special contract between H+ (H+ Die Spitäler der Schweiz; national association of public and private hospitals, clinics and special-care institutions) and SVK (Schweizerischer Verband für Gemeinschaftsaufgaben der Krankenversicherer; Swiss association for joint tasks of health insurers) dated 1 January 2020 and concerning case processing and compensation for cases not regulated by Swiss DRG: services related to haematopoietic stem cell transplantation.[233] Special code SZT30 of this contract ('mobilisation and growth, collection phase') is applicable for the leukapheresis phase.

A summary of the leukapheresis costs used in the model is provided in ***Table 34***.

Table 34 Leukapheresis cost calculations

Resource	Source	Unit cost (CHF) [range]	Proportion of cohort outpatient [range]	Comments
Leukapheresis in adult patients				
Inpatient care	Swiss DRG A42B	18,459.00	0.95 [0.15 to 0.95]	Leukapheresis in adults most often in an outpatient setting (source: expert opinion).
Outpatient care	Contract between H+ and SVK. Special code SZT30	24,600.00		
Leukapheresis in paediatric patients				
Inpatient care	Swiss DRG A42A	28,224.00 [10,290.00 to 38,734.50]	0.00 [0.00 to 0.50]	Leukapheresis in paediatric patients often in an inpatient setting for multiple reasons (source: expert opinion).
Outpatient care	Contract between H+ and SVK. Special code SZT30	24,600.00		

Abbreviations:
CHF = Swiss franc, **DRG** = diagnosis related group, **SVK** = Schweizerischer Verband für Gemeinschaftsaufgaben der Krankenversicherer (Swiss association for joint tasks of health insurers).

8.4.1.1.2 Bridging therapy

Treatment may be given in the period between apheresis and lymphodepleting chemotherapy to slow disease progression. Choices regarding the need for and type(s) of bridging therapy vary between patients. Expert advice states that bridging therapy is used by approximately 66–80% of patients. In a 2-year retrospective experience of a CAR T-cell therapy program at a single Swiss centre, bridging therapy was received by 61% (14 of 23 infused patients).[234] Costs for bridging therapy were assigned to 67% (±20%) of patients in the modelling.

In the Swiss process analysis based on University Hospital Zurich standard operating procedures, one cycle of R-ICE or R-DHAP given in the inpatient setting was included in the CAR T-cell therapy treatment path.[207] Expert advice states that some centres have recently changed to 1–2 cycles of POLA-BR as bridging, usually given on an outpatient schedule. For LBCL populations, costings were undertaken for both inpatient treatment (assuming one cycle of R-ICE or R-DHAP) and outpatient treatment (assuming 1.5 cycles of POLA-BR). An arbitrary split of 2:1 between inpatient rituximab-based regimens and outpatient POLA-BR was assumed to inform a weighted base case input. This was tested in sensitivity analysis.

Expert advice from a paediatric clinician states that bridging chemotherapy is always initiated in the inpatient setting and that—rarely—it is possible to discharge with additional outpatient administration of low-dose chemotherapy. It was emphasised that bridging chemotherapy is often individualised, adding complexity. Inpatient care would be covered under the Swiss DRG system, with codes R63D and R63E identified as applicable (and verified via expert consultation). No surcharge codes were identified for the possible bridging therapies listed in the European Society for Blood and Marrow Transplantation (EBMT)/European Haematology Association (EHA) CAR T-cell handbook, thus none have been included in this cost analysis.[235]

A summary of the bridging therapy costs used in the model is provided in ***Table 35***.

Table 35 Bridging therapy cost calculations

Resource	Source	Unit cost (CHF) [range]	Proportion of total bridging cohort	Comments
Bridging therapy in adult patients				
Inpatient care	Swiss DRG R61D	9,145.00	0.67[A]	Mean LOS 5.6 days; Ring 2022 account for 5 days inpatient time for salvage chemotherapy as bridging.[207]
Inpatient care—drug surcharge	Surcharge code ZE-2023-62-06	887.49	0.67[A]	Rituximab IV, 650–750 mg. Dose of 375 mg/m^2 and BSA 1.79 m^2

Resource	Source	Unit cost (CHF) [range]	Proportion of total bridging cohort	Comments
Outpatient services, 1.5 cycles[B]	TARMED and Analysenliste	1,779.54	0.33[A]	20-min consultation each day for 3 days or 2 days in cycle 1 or 2, respectively; 4.5-, 3.5- and 1.75-hour or 4-5 and 1-hour treatment times in cycle 1 or 2, respectively,[236] and 1 set of laboratory tests in each cycle.
Outpatient care—drug costs, 1.5 cycles[B]	SL	19,086.68	0.33[A]	Polatuzumab IV 1.8 mg/kg day 1, rituximab IV 375 mg/m^2 day 1, bendamustine 90 mg/m^2 day 1 and 2, BSA 1.79 m^2
Bridging therapy in paediatric patients				
Inpatient care	Swiss DRG R63D or R63E	12,495.00 [10,290.00 to 14,700.00]	1.00	Simple average across DRGs. Range reflects R63E and R63D, respectively

Abbreviations:
BSA = body surface area, **CHF** = Swiss franc, **DRG** = diagnosis related group, **IV** = intravenous, **LOS** = length of stay, **SL** = Spezialitätenliste.
Notes:
[A] An arbitrary split of 2:1 between inpatient rituximab-based regimens and outpatient POLA-BR was assumed to inform a weighted base case input. This was tested in sensitivity analysis, varying between all patients receiving inpatient rituximab-based regimens to all patients receiving outpatient POLA-BR.
[B] Cycles 1 and 2 costed for 100% and 50% of patients assumed to receive POLA-BR as bridging, respectively.

8.4.1.1.3 Lymphodepleting chemotherapy

Product information sheets for tisa-cel and axi-cel (Swissmedic)[237] recommend a lymphodepleting regimen of fludarabine and cyclophosphamide at the following doses:

- DLBCL (tisa-cel): fludarabine (25 mg/m^2 IV daily for 3 days) and cyclophosphamide (250 mg/m^2 IV daily for 3 days from first dose of fludarabine)
- LBCL (axi-cel): fludarabine (30 mg/m^2 IV daily for 3 days) and cyclophosphamide (500 mg/m^2 IV daily for 3 days from first dose of fludarabine)
- B-ALL (tisa-cel): fludarabine (30 mg/m^2 IV daily for 4 days) and cyclophosphamide (500 mg/m^2 IV daily for 2 days from first dose of fludarabine).

In the SBST registry, most patients (99.2% LBCL patients; 100% B-ALL patients) received this regimen.

The lymphodepleting regimen may be provided in either the inpatient or outpatient setting. Expert advice varied, with one expert suggesting the majority (>90%) of adults are treated as outpatients and another suggesting they are treated as inpatients. A paediatric clinician suggested lymphodepletion has, to date, always been provided in the inpatient setting for paediatric patients. In the Swiss process analysis, based on University Hospital Zurich standard operating procedures, lymphodepletion was mapped to occur during the hospitalisation for CAR T-cell therapy treatment.[207]

Inpatient lymphodepletion would be covered under the same Swiss DRG as for the infusion of CAR T-cells, without a surcharge code for either drug. Outpatient care would be covered via TARMED, the

Spezialitätenliste and the Analysenliste, as shown in ***Table 36***. Outpatient costs were—conservatively—included in the base case for the LBCL populations. For paediatric and young adult B-ALL patients, lymphodepletion was assumed to occur in the inpatient setting. These assumptions were tested in scenario analysis.

Table 36 Outpatient lymphodepletion cost calculations

Resource	Source	Unit cost (CHF)	Proportion of cohort	Comments
Outpatient lymphodepleting chemotherapy in adult patients				
Outpatient services, 1 cycle	TARMED and Analysenliste	1,014.54	1.00	20-min consultation and 2 hours non-medical care each day for 3 days; one set of laboratory tests
Outpatient care—drug costs, 1 cycle (tisa-cel)	SL	463.29	1.00 in tisa-cel model	3-day course of fludarabine IV 25 mg/m^2 and cyclophosphamide IV 250 mg/ m^2 and BSA of 1.79m^2
Outpatient care—drug costs, 1 cycle (axi-cel)	SL	649.97	1.00 in axi-cel model	3-day course of fludarabine IV 30 mg/m^2 and cyclophosphamide IV 500 mg/m^2 and BSA of 1.79 m^2
Outpatient lymphodepleting chemotherapy in paediatric and young adult patients				
Outpatient services, 1 cycle	TARMED and Analysenliste	1,283.06	0.00	20-min consultation and 2 hours non-medical care each day for 4 days; one set of laboratory tests
Outpatient care—drug costs, 1 cycle	SL	455.14	0.00	4-day course of fludarabine IV 30 mg/m^2 and 2-day course of cyclophosphamide IV 250 mg/ m^2 and BSA of 1.79m^2

Abbreviations:
BSA = body surface area, **CHF** = Swiss franc, **IV** = intravenous, **SL** = Spezialitätenliste.

8.4.1.1.4 CAR T-cell therapy infusion

All CAR T-cell therapy infusions are currently performed in the inpatient setting in Switzerland. Costs are covered under the Swiss DRG system, with an additional surcharge for the CAR T-cell therapy product. Inpatient monitoring is recommended for at least 10 days after the infusion or up to 5 days after resolution of CRS symptoms.[40]

CRS and ICANS are common acute toxicities associated with CAR T-cell infusion. CRS occurs as an acute to subacute event, with a median time to CRS symptom onset of 3 days and a median duration of 8 days.[40] ICANS occurs with a median onset of 5–6 days and a median duration of 6–17 days, depending on the indication and CAR T-cell therapy product used.[40] Management of these acute toxicities would be covered under the Swiss DRG system, within the same episode of care as for the CAR T-cell infusion and an additional surcharge code applicable should tocilizumab be required to treat CRS or ICANS.

8.4.1.1.4.1 Inpatient care

The Swiss DRG applicable to the inpatient care episode for infusion will vary depending on whether complications occur in the period after infusion (e.g. if tocilizumab, ventilation and/or ICU care is needed).

Given that the variability in cost across potentially applicable DRGs is considerable, and the selection of DRG inherently captures the management costs for acute to subacute complications including CRS and ICANS, primary data on Swiss practice was requested from the MedStat database. Swiss DRGs claimed in association with CHOP code 41.0F.13, which covers the transplantation of CAR T-cells, were identified and aggregate data on the relative use of each Swiss DRG was obtained (***Table 37***). Data were obtained for the period 2020–2021 and combined across years. Relative use could be stratified by B-ALL, DLBCL and PMBCL indications; however, data on associated surcharge codes or ATC codes for each hospital separation were unavailable, prohibiting stratification across CAR T-cell products. Given the low number of PMBCL separations, data for DLBCL and PMBCL were combined.

Table 37 Summary of Swiss DRGs codes claimed for CAR T-cell infusion episodes

Swiss DRG	B-ALL (%)	LBCL[A] (%)
A11A	15.4%	6.8%
A15A	38.5%	6.0%
A15C	46.2%	87.2%

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CAR** = chimeric antigen receptor, **DRG** = diagnosis related group, **LBCL** = large B-cell lymphoma.
Note:
[A] DLBCL and PMBCL combined.
Source:
Aggregate data from the MedStat database.

Using the relative utilisation data presented in ***Table 37***, average costs per hospitalisation episode for B-ALL and LBCL populations were obtained (***Table 38***).

Table 38 Inpatient care cost inputs for CAR T-cell infusion, hospital episodes of care

Resource	Source	Unit cost (CHF) [range]	Proportion of cohort	Comments
Inpatient episode of care for CAR T infusion: LBCL populations[A]	Swiss DRG	49,550.58 [37,338.00 to 80,902.50]	1.00	Weighted average cost across Swiss DRGs A15A, A15C and A11A. Range informed by Swiss DRG A15C and A15A.
Inpatient episode of care for CAR T infusion: B-ALL[A]	Swiss DRG	75,707.42 [37,338.00 to 80,902.50]	1.00	Weighted average cost across Swiss DRGs A15A, A15C and A11A. Range informed by Swiss DRG A15C and A15A.

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CAR** = chimeric antigen receptor, **CHF** = Swiss franc, **DRG** = diagnosis related group, **LBCL** = large B-cell lymphoma.
Notes:
[A] excluding cost for CAR T-cell therapy product.

8.4.1.1.4.2 CAR T-cell therapy product

Surcharge codes apply for CAR T-cell therapy products (ZE-2023-192.01, tisa-cel in B-cell lymphoma; ZE-2023-192.02, axi-cel in B-cell lymphoma; ZE-2023-193.01, tisa-cel in ALL); however, the tariffs for these surcharge codes are not published. FOPH advised the following product prices for the base case analysis, with a request for sensitivity analysis on the product price:

- CHF379,500 for axi-cel
- CHF370,755 for tisa-cel.

8.4.1.1.4.3 Tocilizumab

A surcharge code applies should tocilizumab (interleukin-6 receptor inhibitor) be required during the inpatient episode of care to treat CRS or ICANS. In the SBST registry, the following proportions of patients required tocilizumab:

- DLBCL (tisa-cel): 38 of 71 patients (54%)
- LBCL (axi-cel): 25 of 50 patients (50%)
- B-ALL (tisa-cel): 1 of 15 patients (7%).

The recommended dosing for tocilizumab is 8 mg/kg IV over 1 hour for patients ≥30 kg (12 mg/kg for body weight <30kg), repeated every 8 hours if no improvement up to a maximum of 4 doses.[40,237] An average of 3 doses of tocilizumab per treated patient was assumed for the costings.

A summary of tocilizumab surcharge cost calculations is provided in ***Table 39***.

Table 39 Surcharge cost inputs for tocilizumab use following CAR T-cell infusion

Resource	Source	Unit cost (CHF)	Proportion of cohort	Comments
Tocilizumab in adult patients				
Inpatient care—drug surcharge	Surcharge code ZE-2023-47-40	3,403.82	0.50 (axi-cel) 0.54 (tisa-cel)	8 mg/kg dose, assumed body weight 75 kg and average of 3 doses per treated patient
Tocilizumab in paediatric patients				
Inpatient care—drug surcharge	Surcharge code ZE-2023-47-37	2,269.21	0.07	8 mg/kg dose, assumed body weight 49.5 kg and average of 3 doses per treated patient

Abbreviations:
Axi-cel = axicabtagene ciloleucel, **CAR** = chimeric antigen receptor, **CHF** = Swiss franc, **tisa-cel** = tisagenlecleucel.

8.4.1.1.5 Long-term side effects

The most prominent long-term toxicities after CAR T-cell therapy include cytopenias, infection, and long-term B-cell depletion and hypogammaglobulinaemia.[216,238] Clinical evidence on the risk of these events was previously reported in ***Section 7.3***. Costs for long-term IVIG replacement therapy—which is

indicated in the case of low IgG levels (<4g/L) or severe, recurrent or chronic infections (especially pneumonia)[40,239]—were included in the economic evaluation and budget impact analysis.

Cytopenias, including anaemia, thrombocytopenia and neutropenia, are common acute toxicities, but can also persist for ≥3 months after CAR T-cell therapy.[216] Leading clinical complications of long-lasting cytopenias are infectious complications, for which antimicrobial prophylaxis can be considered,[40] although costs for prophylaxis have not been included in the cost analysis. The incidence of severe infections >1 month after CAR T-cell therapy is low relative to their incidence within the first month of infusion.[216] Survivors of lymphoma are known to have increased long-term risks of infection, making interpretation of the effects of CAR T-cell therapy difficult.[216] Costs specifically attributed to managing infections were not included in the cost analysis; however, costs for IVIG replacement therapy—which may be used in the case of severe, recurrent or chronic infections—were captured.

Tisa-cel and axi-cel have a B-cell depleting effect, making hypogammaglobulinaemia an expected, delayed-onset side effect.[40] For patients with low IgG levels (<4 g/L) or severe, recurrent or chronic infections (especially pneumonia), IVIG replacement therapy is performed.[40,239] The clinical evidence review reported B-cell aplasia rates of 64% (95% CI: 0.49 to 0.78) for patients with B-ALL (***Figure 19***), 55% (95% CI: 0.33 to 0.76) for patients with LBCL receiving axi-cel (***Figure 43***) and 1% (95% CI: 0.00 to 0.05) for patients with LBCL receiving tisa-cel (***Figure 64***). The certainty of evidence (GRADE) was assessed as very low for this outcome across all 3 indications. Data from long-term follow-up studies indicate persistent B-cell depletion in 25–38% of patients, even several years after CAR T-cell infusion.[216]

The clinical evidence review reported IVIG utilisation among 77% (95% CI: 48% to 97%) of patients with B-ALL (***Figure 23***), 32% (95% CI: 23% to 42%) of patients with LBCL receiving axi-cel (***Figure 46***), and 17% (95% CI: 11% to 24%) of patients with LBCL receiving tisa-cel (***Figure 67***). GRADE assessments were not made for these outcomes. Expert advice states that 30% of patients will have profound B-cell depletion with recurrent infections and require substitution therapy (IVIG) once every 4 weeks. In the SBST registry, the following proportions of patients require IVIG:

- B-ALL (tisa-cel): 9 of 15 patients (60%)
- LBCL (axi-cel): 24 of 50 patients (48%)
- DLBCL (tisa-cel): 49 of 71 patients (69%).

The cost analysis accounted for the ongoing cost of monthly IVIG replacement therapy where required. Expert advice states that, where possible, IVIG treatment should be given on an outpatient schedule. A monthly cost of treatment (i.e. cost per infusion) was calculated based on TARMED positions, the Spezialitätenliste and the Analysenliste.

The duration of IgG substitution may be lifelong or last until recovery of functional B-cells and plasma cells.[239] In the base case, IVIG has been costed for a duration of 12 months for the percentage of patients requiring IVIG per SBST registry data for each cohort (***Table 40***). Given the uncertainty in this area, the duration of IVIG substitution is tested in a sensitivity analysis.

Table 40 Monthly care costs for IVIG substitution therapy after CAR T-cell infusion

Resource	Source	Unit cost (CHF)	Proportion of cohort	Comments
Outpatient IVIG services	TARMED and Analysenliste	706.76	0.48–0.69 [A]	15-min consultation, 10-min specialist treatment, 4 hrs non-medical care in oncology day clinic, laboratory tests
IVIG drug costs—B-ALL	SL	1,526.71	0.60[A]	Assumed 0.4 g/kg dose.[231,232,239] Assumed body weight 49.5 kg.[197] Average cost for 20g IVIG across available brands.[B]
IVIG drug costs—LBCL	SL	2,274.67	0.48–0.69 [A]	Assumed 0.4 g/kg dose and body weight 75 kg.[231,232,239] Average cost for 30 g IVIG across available brands.[B]
Additional costs	Expert advice	34.21	0.48–0.6[A]	Paracetamol, anti-allergy medication and medical goods.

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CAR** = chimeric antigen receptor, **CHF** = Swiss franc, **IVIG** = intravenous immunoglobulin, **LBCL** = large B-cell lymphoma, **SL** = Spezialitätenliste.
Notes:
[A] 0.48 for LBCL patients who received axi-cel, 0.69 for DLBCL patients who received tisa-cel and 0.60 for B-ALL patients.
[B] Average cost across Ig Vena Kedrion 5%, Intratect 5%, Intratect 10%, Iqymune, Kiovig, Octagam 10% and Privigen.

8.4.1.1.6 Allogenic SCT

In the ELIANA trial, 21.5% (17 of 79) of tisa-cel-infused patients underwent allogenic SCT during follow-up.[2] This includes 11 patients who were in tisa-cel-mediated remission at the time of transplantation. In data from a single Swiss centre, 36.8% of patients with sufficient follow-up were transplanted (expert advice; data not published).

For the paediatric B-ALL population, cost of subsequent allogenic SCTs was considered part of the CAR T treatment pathway (costed using Swiss DRGs A04A and A04B).

Table 41 Allogenic SCT costs following CAR T-cell infusion in B-ALL patients

Resource	Source	Unit cost (CHF) [range]	Proportion of cohort [range]	Comments
Allogenic SCT for B-ALL cohort	Swiss DRGs A04A and A04B	167,879.25 [153,772.50 to 181,986.00]	0.37 [0.22 to 0.50]	Simple average across DRGs. Range costed using Swiss DRG A04B and A04A, respectively.

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CAR** = chimeric antigen receptor, **CHF** = Swiss franc, **DRG** = diagnosis related group, **SCT** = stem cell transplantation.

8.4.1.1.7 Cost of progression

A one-off cost upon disease progression was built into the analysis using Swiss DRG costings for leukaemia admissions (R63B, R63D or R63E) or lymphoma admissions (R61A-D) for B-ALL and LBCL populations, respectively.

Table 42 Model inputs for a one-off cost upon disease progression

Resource	Source	Unit cost (CHF) [range]	Proportion of cohort	Comments
Progression cost for B-ALL patients	Swiss DRGs R63B, R63D and R63E	21,241.50 [10,290.00 to 38,734.50]	Upon progression	Simple average across DRGs. Range costed using Swiss DRGs R63E and R63B, respectively.
Progression cost for LBCL patients	Swiss DRGs R61A-D	19,887.00 [9,145.50 to 39,984]	Upon progression	Simple average across DRGs. Range costed using Swiss DRGs R61D and R61A, respectively.

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CAR** = chimeric antigen receptor, **CHF** = Swiss franc, **DRG** = diagnosis related group, **LBCL** = large B-cell lymphoma.

8.4.1.2 Comparator costs

Costs considered for comparator therapies included those for relevant chemotherapy or immunotherapy regimens, subsequent allogenic SCT (for B-ALL populations) and a one-off cost upon disease progression.

For the B-ALL population, the economic model compared CAR T-cell therapy (± allogenic SCT) to blinatumomab (± allogenic SCT). A pragmatic approach was taken in comparing CAR T-cell therapy to a single comparator in an exemplar-type fashion. Blinatumomab was prioritised for modelling as it has been considered previously in the literature and by other HTA agencies. Both blinatumomab (± allogenic SCT) and inotuzumab (± allogenic SCT) were included when calculating potential cost offsets in the BIA. A 50-50 split between the 2 regimens was, arbitrarily, assumed for the BIA (see ***Section 8.6.2***).

For the LBCL population, historical control was the primary comparator used in the economic modelling. A simplified costing approach applied R-GEMOX treatment costs to the comparator arm in this comparison (an arbitrary selection). POLA-BR was considered in supplementary analyses, with corresponding treatment costs assigned. These additional analyses allowed for an exploration of how choice of comparator impacts the ICER. The choice to explore this comparator in secondary analyses was an arbitrary selection.

R-GEMOX, GEMOX, POLA-BR, rituximab plus bendamustine, tafasitamab plus lenalidomide and pembrolizumab (for a proportion of PMBCL patients only) were all considered when calculating potential cost offsets for LBCL patients in the BIA. Specifically, pembrolizumab costs were considered for 1.2% of the LBCL cohort (r/r PMBCL accounted for approximately 2.5% of all DLBCL/PMBCL patients;

Section 8.6.2). For the remainder of the LBCL cohort, an average cost across potential salvage regimens (i.e. R-GEMOX, bendamustine and rituximab, POLA-BR, tafasitamab and lenalidomide, GEMOX) was derived, with each regimen assumed to account for 20% of use.

A summary of the costing approaches adopted is provided below.

8.4.1.2.1 Treatment: administration costs

Both inpatient and outpatient administration settings were considered when costing the comparator therapies, with an assumed 50-50 split across settings for LBCL populations. For paediatric B-ALL patients, only inpatient admissions were considered for the costings.

Inpatient administrations were costed using Swiss DRGs R61A-D for LBCL populations and Swiss DRGs R63B, R63D and R63E for the B-ALL population (verified via expert consultation). Surcharge codes were added where applicable (***Section 8.4.1.2.2***).

Outpatient administration cost calculations were based on TARMED positions and the Analysenliste. The calculation included costs for a physician consultation and an oncology day clinic stay for each infusion day of the cycle and laboratory tests once per cycle. Drug costs, based on Spezialitätenliste pricing (***Section 8.4.1.2.2***), were then added.

8.4.1.2.2 Treatment: drug costs

The regimens considered as potential comparators are outlined below. Cost calculations for both the economic modelling and the BIA assumed that patients would receive one of the comparator options. For the inpatient setting, surcharge codes (in addition to the assigned Swiss DRG costings) were applied where appropriate, including rituximab (ZE-2023-62), lenalidomide (ZE-2023-89), pembrolizumab (ZE-2023-137), blinatumomab (ZE-2023-138) and inotuzumab (ZE-2023-166). For the outpatient setting, drug costs per Spezialitätenliste pricings applied.

8.4.1.2.2.1 R-GEMOX

Salvage chemotherapy with R-GEMOX was costed according to the following dosing schedule: 2-week cycle repeated up to 8 cycles; rituximab 375 mg/m^2 IV on day 1, gemcitabine 100 mg/m^2 IV on day 1 and oxaliplatin 100 mg/m^2 IV on day 1.[240] Costing calculations assumed a median of 5 cycles (range: 1 to 8 cycles) across treated patients.[241]

In the base case economic model, costs for R-GEMOX were included for the historical control comparator. A summary of R-GEMOX therapy costs is provided in ***Table 43***.

Table 43 Unit cost inputs for salvage chemotherapy with R-GEMOX for r/r LBCL

Resource	Source	Unit cost (CHF) [range]	Proportion of cohort [range]	Comments
Outpatient services, cycle 1	TARMED and Analysenliste	1,000.17	0.5	20-min consultation, 8 hours treatment time, laboratory tests
Outpatient services, subsequent cycles	TARMED and Analysenliste	738.77	0.5	20-min consultation, 5 hours treatment time, laboratory tests
Outpatient drug costs, per cycle	SL	2,449.49	0.5	Rituximab 375 mg/m^2 IV, gemcitabine 100 mg/m^2 IV and oxaliplatin 100 mg/m^2 IV on day 1
Inpatient services, per cycle	Swiss DRGs R61A-D	19,887 [9,145.50 to 39,984]	0.5	Simple average across DRGs
Inpatient surcharges, per cycle	Code ZE-2023-62-06	887.49	0.5	650–750mg of rituximab, IV

Abbreviations:
CHF = Swiss franc, **IV** = intravenous, **DRG** = diagnosis related group, **LBCL** = large B-cell lymphoma, **R-GEMOX** = rituximab, gemcitabine, and oxaliplatin, **r/r** = relapsed or refractory, **SL** = Spezialitätenliste.

For the BIA, costs for GEMOX were also considered. Salvage chemotherapy with GEMOX was costed according to the same dosing schedule (excluding costs for rituximab) and for an assumed median of 2 cycles.[242] Outpatients visits accounted for 3 hours treatment time.[243]

8.4.1.2.2.2 Polatuzumab (POLA-BR)

Polatuzumab was costed in combination with bendamustine and rituximab as per the dosing schedule listed on SwissMedic (Polivy® Specialist Information Sheet): polatuzumab 1.8 mg/kg IV on day 1, rituximab 375 mg/m^2 IV on day 1 and bendamustine 90 mg/m^2 IV daily on days 1 and 2 (or days 2 and 3 in first cycle) administered as a 3-week cycle and repeated up to 6 cycles.[237] Costing calculations assumed a median of 5 cycles (range: 1 to 6 cycles) across treated patients.[244] POLA-BR is temporarily reimbursed on the Spezialitätenliste for the treatment of adult patients with r/r DLBCL who are ineligible for haematopoietic SCT.[245]

A summary of POLA-BR therapy costs is provided in ***Table 44***.

Table 44 Unit cost inputs for salvage therapy with POLA-BR for r/r LBCL

Resource	Source	Unit cost (CHF) [range]	Proportion of cohort [range]	Comments
Outpatient services, cycle 1	TARMED and Analysenliste	1,341.20	0.5	20-min consultation each day, 4.5-, 3.5- and 1.75-hour treatment time on days 1, 2 and 3, respectively,[236] and 1 set of laboratory tests
Outpatient services, subsequent cycles	TARMED and Analysenliste	876.68	0.5	20-min consultation each day, 4.5-hour and 1-hour treatment time on days 1 and 2, respectively, and 1 set of laboratory tests

Resource	Source	Unit cost (CHF) [range]	Proportion of cohort [range]	Comments
Outpatient drug costs, per cycle	SL	12,724.45	0.5	Polatuzumab 1.8 mg/kg IV and rituximab 375 mg/m^2 IV for 1 day; bendamustine 90 mg/m^2 IV daily for 2 days
Inpatient services, per cycle	Swiss DRGs R61A-D	19,887 [9,145.50 to 39,984]	0.5	Simple average across DRGs
Inpatient surcharges, per cycle	Code ZE-2023-62-06	887.49	0.5	650–750mg of rituximab IV

Abbreviations:
CHF = Swiss franc, **IV** = intravenous, **DRG** = diagnosis related group, **LBCL** = large B-cell lymphoma, **POLA-BR** = polatuzumab, bendamustine and rituximab, **r/r** = relapsed or refractory, **SL** = Spezialitätenliste.

For the BIA, costs for rituximab plus bendamustine regimens were also considered. Salvage therapy with rituximab and bendamustine was costed according to the dosing schedule for POLA-BR (see below), excluding costs for polatuzumab, and for an assumed median of 3 cycles.[244] Outpatient visits accounted for 8 hours and 5 hours treatment time on day 1 for the first and subsequent cycles, respectively, and for 1 hour treatment time on day 2 of each cycle.[246]

8.4.1.2.2.3 Tafasitamab (in combination with lenalidomide)

Tafasitamib was costed in combination with lenalidomide as per the dosing schedule listed on SwissMedic (MINJUVI® Specialist Information Sheet): tafasitamab 12 mg/kg IV daily on day 1, 4, 8, 15 and 22 of cycle 1; day 1, 8, 15 and 22 of cycles 2 and 3; and day 1 and 15 of cycles ≥4; plus oral lenalidomide 25 mg daily on day 1–21 of each 28-day cycle, each administered in a 28-day cycle, with treatment continuing until disease progression occurs .[237] Tafasitamab in combination with lenalidomide and subsequent monotherapy is temporarily reimbursed on the Spezialitätenliste for the treatment of adult patients with r/r DLBCL after ≥1 prior line of systemic therapy for patients for whom autologous SCT is not possible.[245] In one study, median duration of exposure to combination treatment was 6.2 months (IQR: 2.1 to 10.9 months) and to tafasitamab monotherapy was 4.1 months (IQR: 0.4 to 12.6 months).[247] In the costing, 6 cycles of combination therapy and 4 cycles of tafasitamab monotherapy were assumed.

Costs for treatment with tafasitamab and lenalidomide were included in the BIA, but not in the economic evaluation. A summary of costs for this therapy is provided in ***Table 45***.

Table 45 Unit cost inputs for salvage therapy with tafasitamab and lenalidomide for r/r LBCL

Resource	Source	Unit cost (CHF) [range]	Proportion of cohort [range]	Comments
Outpatient services and drug costs, cycle 1	TARMED, Analysenliste and SL	26,699	0.5	20-min consultation and 2 hours treatment time each day for 5 days, and 1 set of laboratory tests Tafasitamab 12 mg/kg daily IV for 5 days and lenalidomide 25 mg daily for 21 days.
Outpatient services and drug costs, cycle 2–3	TARMED, Analysenliste and SL	21,602	0.5	20-min consultation and 2 hours treatment time each day for 4 days, and 1 set of laboratory tests. Tafasitamab 12 mg/kg daily IV for 4 days and lenalidomide 25 mg daily for 21 days.
Outpatient services and drug costs, cycle 4+	TARMED, Analysenliste and SL	11,408	0.5	20-min consultation and 2 hours treatment time each day for 2 days, and 1 set of laboratory tests Tafasitamab 12 mg/kg daily IV for 2 days and lenalidomide 25 mg daily for 21 days
Outpatient services and drug costs, monotherapy period	TARMED, Analysenliste and SL	10,403	0.5	20-min consultation and 2 hours treatment time each day for 2 days, and 1 set of laboratory tests Tafasitamab 12 mg/kg daily IV for 2 days
Inpatient services	Swiss DRGs R61A-D	19,887 [9,145.50 to 39,984]	0.5	Simple average across DRGs
Inpatient surcharges	Code ZE-2023-137.02	6,082.40	0.5	150–250mg lenalidomide, oral

Abbreviations:
CHF = Swiss franc, **IV** = intravenous, **DRG** = diagnosis related group, **LBCL** = large B-cell lymphoma, **r/r** = relapsed or refractory, **SL** = Spezialitätenliste.

8.4.1.2.2.4 Pembrolizumab

Pembrolizumab was costed as per the dosing schedule listed on the Keytruda® specialist information sheet on Swiss Medic (200 mg given as a 30-minute IV infusion once every 3 weeks).[237] Pembrolizumab (Keytruda®) is listed on the Spezialitätenliste under a temporary limitation for use as a monotherapy in r/r PMBCL in adults with at least 2 previous treatments (one of which was rituximab) who are ineligible for autologous SCT or had relapse after transplantation.[245] Treatment was costed for an average of 8 cycles, based on expert advice (see ***Section 8.2.5***).

A summary of pembrolizumab therapy costs, included in the BIA only, is provided in ***Table 46***.

Table 46 Unit cost inputs for salvage therapy with pembrolizumab

Resource	Source	Unit cost (CHF) [range]	Proportion of cohort [range]	Comments
Outpatient services	TARMED and Analysenliste	390.38	0.5	20-min consultation, 1 hour treatment time,[248] and 1 set of laboratory tests
Outpatient drug costs	SL	4,763.85	0.5	
Inpatient services	Swiss DRGs R61A-D	19,887 [9,145.50 to 39,984]	0.5	Simple average across DRGs
Inpatient surcharges	Code ZE-2023-137.02	4,254.13	0.5	150–250 mg pembrolizumab IV

Abbreviations:
CHF = Swiss franc, **IV** = intravenous, **DRG** = diagnosis related group, **SL** = Spezialitätenliste.

8.4.1.2.2.5 Blinatumomab

Blinatumomab was costed as per the dosing schedule listed on the BLINCYTO® specialist information sheet on Swiss Medic (6-week cycles with a continuous 4-week IV infusion and 2 weeks off for up to 5 cycles; body weight ≥45 kg (fixed dose) = cycle 1: 9 µg/day on day 1–7, then 28 µg/day on day 8–28, subsequent cycles: 28 µg/day on day 1–28; body weight <45kg (dose based on BSA) = cycle 1: 5 µg/m^2/day on day 1–7, then 15 µg/m^2/day on day 8–28, subsequent cycles: 15 µg/m^2/day on day 1–28).[237] This aligns with the reported recommended dose determined during a phase 1 study among paediatric patients (age <18 years) of stepwise dosing using 5 µg/m^2/day for the first week of the first cycle, followed by 15 µg/m^2/day for the remaining 3 weeks and subsequent cycles.[178]

Blinatumomab is not listed on the Spezialitätenliste for paediatric patients; however, expert advice states that patients may be treated under compassionate use principles. Blinatumomab therapy was costed as an inpatient service, including costs for an inpatient episode of care plus an additional surcharge for use of blinatumomab. A summary of blinatumomab therapy costs used in the modelling is provided in ***Table 47***.

Table 47 Unit cost inputs for salvage therapy with blinatumomab

Resource	Source	Unit cost (CHF) [range]	Proportion of cohort [range]	Comments
Inpatient services	Swiss DRGs R63B, R63D, R63E	21,241.50 [10,290.00to 38,734.50]	1.0 cycle 1; variable cycles 2+[A]	Simple average across DRGs
Inpatient surcharges – cycle 1	Code ZE-2023-138.10	25,720.54	1.0	5 µg/m^2/day IV days 1–7, then 15 µg/m^2/day IV days 8–28
Inpatient surcharges – cycle 2+	Code ZE-2023-138.11	33,202.88	Variable[A]	15 µg/m^2/day on day 1–28

Abbreviations:
CHF = Swiss francs, **DRG** = diagnosis related group.
Notes:
[A] 39.1% in cycle 2, 12.7% in cycle 3, 5.5% in cycle 4, 4.5% in cycle 5, per utilisation in the RIALTO study.[249]

8.4.1.2.2.6 Inotuzumab ozogamicin

Inotuzumab ozogamicin was costed per the dosing schedule listed on the Besponsa® specialist information sheet on Swiss Medic, that is, fractioned dose of 1.8mg/m^2 over 3 divided doses (day 1, 8, 15) or 1.5mg/m^2 over 3 divided doses once response is achieved.[237] This aligns with the recommended dose used in phase II trials within paediatric populations.[250,251] Inotuzumab ozogamicin is not listed on the Spezialitätenliste for paediatric patients; however, expert advice states that patients may be treated under compassionate use principles. Inotuzumab ozogamicin treatment costs were considered in the BIA; however, inotuzumab ozogamicin was not included as a comparator in the economic modelling. A summary of therapy costs is provided in ***Table 48***.

Table 48 Unit cost inputs for salvage therapy with inotuzumab ozogamicin

Resource	Source	Unit cost (CHF) [range]	Proportion of cohort [range]	Comments
Inpatient services	Swiss DRGs R63B, R63D, R63E	21,241.50 [10,290.00to 38,734.50]	1.0 for 2 cycles [A]	Simple average across DRGs
Inpatient surcharges – cycle 1	Code ZE-2023-166.13	26,405.39	1.0 [A]	1.8mg/m^2 over 3 divided doses (day 1, 8, 15)
Inpatient surcharges – cycle 2+	Code ZE-2023-166.12	21,813.15	1.0 [A]	1.5mg/m^2 over 3 divided doses (day 1, 8, 15)

Abbreviations:
CHF = Swiss francs, **DRG** = diagnosis related group.
Notes:
[A] Median number of cycles 2 (range 1–6), per a phase II study in paediatric patients.[251]

8.4.1.2.3 Allogenic SCT

Among 70 patients treated with the recommended dose in a phase I/II study of blinatumomab in paediatric r/r B-ALL, 25 patients (35.7%) received a subsequent allogenic SCT.[178] In an expanded access study (RIALTO study) 58 of 110 patients (52.7%) received allogenic SCT at any time after the first blinatumomab infusion.[249]

Cost of subsequent allogenic SCTs was considered for an average of 44.2% of treated patients, costed using Swiss DRGs A04A and A04B (***Table 49***).

Table 49 Allogenic SCT costs following blinatumomab in B-ALL patients

Resource	Source	Unit cost (CHF) [range]	Proportion of cohort [range]	Comments
Allogenic SCT for B-ALL cohort, comparator	Swiss DRGs A04A and A04B	167,879.25 [153,772.50 to 181,986.00]	0.46 [0.36 to 0.53]	Simple average across DRGs. Range costed using Swiss DRG A04B and A04A, respectively.

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CHF** = Swiss franc, **DRG** = diagnosis related group, **SCT** = stem cell transplantation.

8.4.2 Survival outcomes

A limited selection of NRSIs was identified in the clinical review; however, none provided complete data to inform the economic analysis (i.e. considered a relevant comparator or reported both OS and PFS). Therefore, data from single-arm studies on the CAR T-cell therapies and comparator therapies were utilised in the analyses.

Single-arm studies on the CAR T-cell therapies were identified in the clinical evidence review (***Section 7***). Additional data on comparator therapies were retrieved via pragmatic searches, allowing the incremental benefit of CAR T-cell therapy to be assessed. Nevertheless, there is very high uncertainty in the comparisons made given the absence of reliable comparative evidence. Moreover, separate parametric models were fitted to individual treatment arms.

8.4.2.1 CAR T-cell therapies

Clinical evidence on CAR T-cell therapies was sourced from the pivotal studies for each population (i.e. ELIANA for tisa-cel in B-ALL; ZUMA-1 for axi-cel in LBCL patients; JULIET for tisa-cel in DLBCL).[2,3,144]

8.4.2.1.1 Tisa-cel for B-ALL

The existing Swiss economic evaluation of tisa-cel in r/r B-ALL used pooled data from the ELIANA trial (data cut-off 13 April 2018), the ENSIGN trial (data cut-off 6 October 2017) and the B2101J trial (data cut-off May 2018).[1]

Since publication of the existing Swiss evaluation, updated outcome data for the ELIANA cohort across a median follow-up time of 38.8 months have been published.[2] Overall, 97 patients were enrolled in the trial and received apheresis, and 79 (81.4%) received a tisa-cel infusion.

EFS data were reported in the ELIANA trial. EFS was defined in the study as the time from infusion to the earliest of: death from any cause after remission, relapse or treatment failure (i.e. no response or discontinuation due to death, AEs, lack of efficacy or progressive disease, or new anticancer therapy). KM curves for OS and EFS based on these updated outcome data were digitised, and parametric survival models were fitted to the reconstructed IPD. The reconstructed KM curve for OS for the ELIANA cohort was reported in ***Figure 7***, alongside results from 5 other single-arm studies that showed similar trends (regardless of sample size) with comparable rates of change (***Section 7.3.9.2***). EFS was not reported in ***Section 7.3.9***. Survival outcomes were modelled for the entire cohort of infused patients (i.e. not stratified by response status). Figures displaying the fitted standard parametric curves and fitted spline models and tabulated AIC and BIC statistics for the fitted curves, are provided in ***Appendix G***.

8.4.2.1.1.1 OS: tisa-cel for B-ALL

The lognormal and Gompertz distributions showed the best statistical fit to the OS data, based on an assessment of AIC (i.e. these curves showed the lowest AIC values). However, the Gompertz extrapolation projections appeared overly optimistic. Specifically, projected OS remained relatively consistent at just over 50% from year 10 onwards, which fails to capture general population mortality beyond this timepoint. At 3, 5 and 10 years, the fitted lognormal curve suggested survival probabilities of 61.0%, 51.2% and 37.9% (***Figure 72***). Of the flexible spline models fitted, 1-knot models using an odds or probit model provided the best statistical fit; projections appeared similar to those of the lognormal distribution (5- and 10-year OS estimates of 50.8–51.0% and 37.2–37.6%, respectively). A lognormal distribution was selected for the base case, with alternative extrapolations (Gompertz; log logistic) tested in scenario analysis. Furthermore, a scenario considering a log-normal distribution until year 5, followed by a switch to SMR-adjusted general population mortality beyond year 5 was also considered.

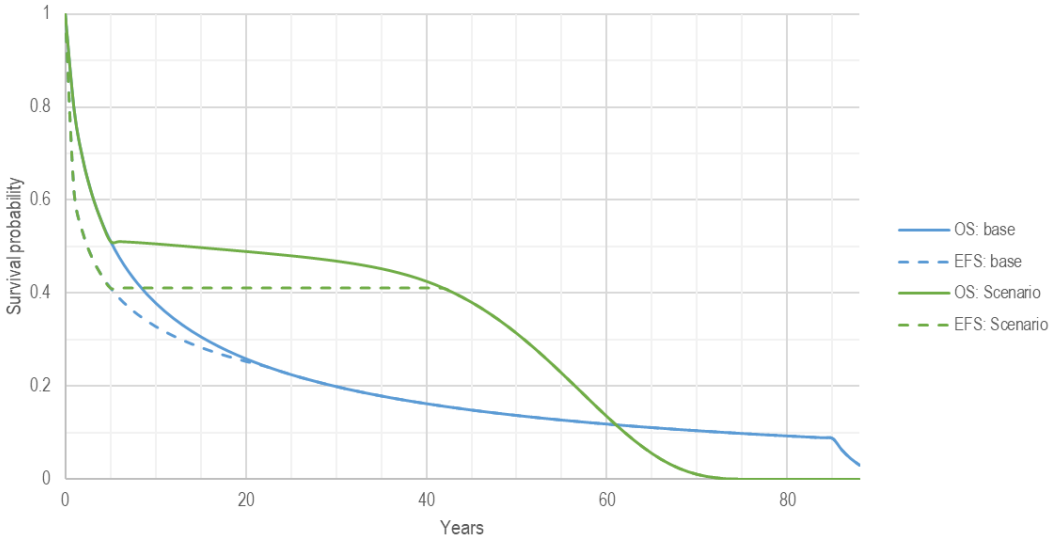
8.4.2.1.1.2 EFS: tisa-cel for B-ALL

The log logistic and lognormal distributions showed the best statistical fit to EFS data, based on an assessment of AIC (i.e. these curves showed the lowest AIC values). Given a lognormal distribution was used to extrapolate OS, a lognormal distribution was also selected to model EFS in the base case. Testing of alternative extrapolations for OS rather than PFS was prioritised for scenario analysis.

As per previous examples, including the York mock model, survival probabilities for EFS were assumed to plateau beyond 5 years until the point at which EFS equalled OS, in scenarios assuming an effective ‘cure’ point at year 5.[197]

Figure 72 shows base case extrapolations for OS and EFS based on a lognormal distribution, along with extrapolations realised in the scenario assuming an effective ‘cure’ point at year 5. The OS curve modelled using the lognormal distribution demonstrates a long tail while the scenario considering a switch to SMR-adjusted general population mortality beyond year 5 demonstrates a more optimistic shape beyond year 5 (***Figure 72***).

Figure 72 Example extrapolated survival outcomes for tisa-cel in r/r B-ALL



Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **EFS** = event-free survival, **OS** = overall survival, **r/r** = relapsed or refractory, **tisa-cel** = tisagenlecleucel
Note:
Start age is assumed to be 11 years of age. Year 0 corresponds to age 11; year 1 to age 12; year 40 to age 51, etc.

8.4.2.1.2 Axi-cel for LBCL

All retrieved studies assessing the cost-effectiveness of axi-cel (r/r DLBCL n=2; r/r LBCL n=3) used data from the ZUMA-1 trial at various cut-off points: 12-month survival data;[167] 11 August 2017 cut-off (median follow-up 15.4 months);[168] 11 August 2018 cut-off (median follow-up 27.1 months, IQR 25.7–28.8 months);[252,253] 3-year ZUMA-1 data (median follow-up 39.1 months; OS only [PFS from 2-year follow-up data])[166].

Long-term follow-up data for r/r LBCL patients treated with axi-cel in the ZUMA-1 study (data cut-off 11 August 2021; median follow-up 63.1 months, range 58.9–68.4 months) are reported by Neelapu 2023.[144] Overall, 111 patients were enrolled in the ZUMA-1 trial and 101 (91.0%) received axi-cel. OS and PFS KM curves published by Neelapu 2023 was digitised and parametric survival models fitted to the pseudo-IPD. The reconstructed KM curve for OS for the ZUMA-1 cohort is shown in ***Figure 28***, along with results from 5 other single-arm studies and the axi-cel arm of 2 NRSIs. The reconstructed KM curve for PFS is shown in ***Figure 30***, along with results from 6 other single-arm studies and the axi-cel arm of 2 NRSIs. Figures displaying the fitted standard parametric curves and fitted spline models, and tabulated AIC and BIC statistics for the fitted curves, are provided in ***Appendix G***.

8.4.2.1.2.1 OS: axi-cel for LBCL

Model diagnostics for the fitted curves indicated the spline models with 2 knots provided the best fit for the data (i.e. showed the lowest AIC values). For the base case, the 2-knot spline model based on a probit model was selected, given it provided the lowest AIC value.

Of the standard parametric distributions, those that provided the best fit (based on AIC) included the Gompertz, generalised gamma and lognormal. Beyond year 5 (60 months), the 2-knot spline model suggested survival probabilities above those suggested by the generalised gamma and lognormal extrapolations but lower than the Gompertz estimates. A parametric distribution (generalised gamma) was tested in scenario analysis. Furthermore, a scenario considering a 2-knot spline model until year 5, followed by a switch to SMR-adjusted general population mortality beyond year 5 was also considered.

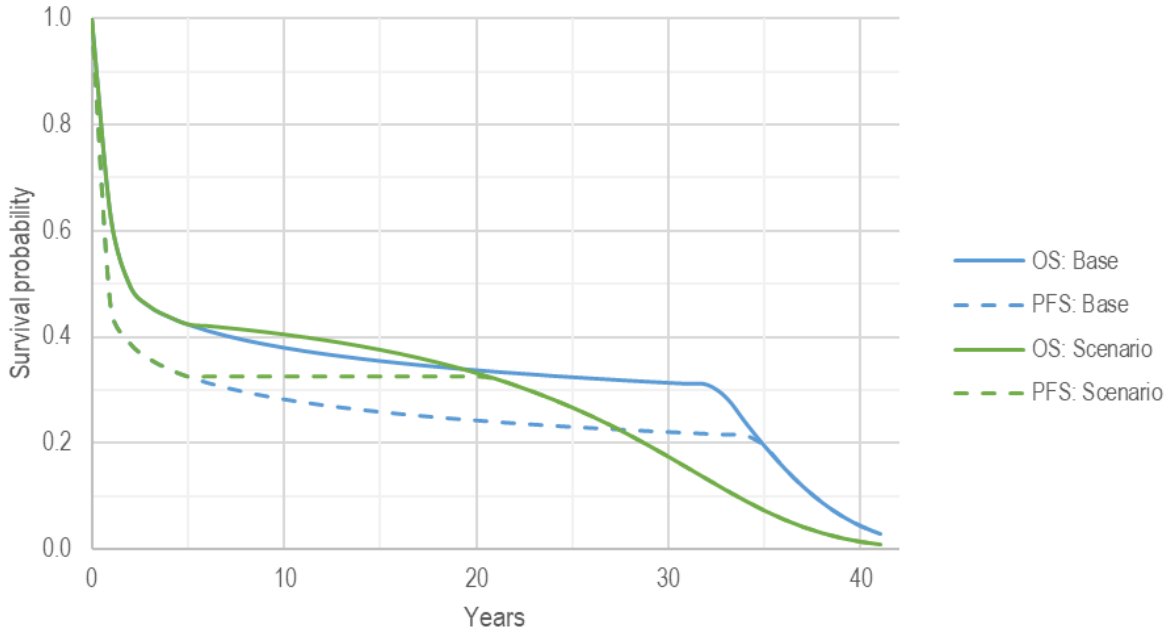
8.4.2.1.2.2 PFS: axi-cel for LBCL

Model diagnostics for the fitted curves indicated 1-knot spline models using odds or hazard models provided the best fit (i.e. showed the lowest AIC values). For the base case, the 1-knot spline model based on an odds model was selected, given it provided the lowest AIC value.

Figure 73 shows base case extrapolations for OS and PFS based on the 2-knot and 1-knot spline models, respectively, along with extrapolations realised in the scenario assuming an effective 'cure' point at year 5. Testing of alternative extrapolations for OS rather than PFS was prioritised for scenario analysis.

Notably, the base case OS curve suggests survival probabilities of 42.4% after 5 years (age of model cohort: 63 years), 38.1% after 10 years (age of model cohort: 68 years), and 31.4% after 30 years (age of model cohort: 88 years) (***Figure 73***). Beyond year 20, OS shown by the base case 2-knot spline model exceeds that shown by the scenario analysis in which background population mortality rates were applied after year 5. This suggests the base case model may be overly optimistic, favouring axi-cel. The impact of this on ICER estimates is explored in the scenario analysis.

Figure 73 Example extrapolated survival outcomes for axi-cel in r/r LBCL



Abbreviations:
axi-cel = axicabtagene ciloleucel, **LBCL** = large B-cell lymphoma, **OS** = overall survival, **PFS** = progression-free survival, **r/r** = relapsed or refractory.
Note:
Start age is assumed to be 58 years of age. Year 0 corresponds to age 58; year 1 to age 59; year 20 to age 78 etc.

8.4.2.1.3 Tisa-cel for LBCL

The existing Swiss economic evaluation of tisa-cel in r/r DLBCL used pooled data from the JULIET trial (data cut-off 11 December 2018) and Schuster 2017.[1]

Long-term follow-up data for r/r DLBCL patients treated with tisa-cel in the JULIET study (data cut-off 20 February 2020; median follow-up 40.3 months, IQR 37.8–43.8 months) are reported by Schuster 2021.[3] Overall, 167 patients were enrolled in the JULIET trial and 115 (68.9%) received tisa-cel. KM curves for OS and PFS published by Schuster 2021 were digitised and parametric survival models were fitted to the reconstructed IPD. The reconstructed KM curve for OS for the JULIET cohort is shown in ***Figure 50***, along with results from 3 other single-arm studies that illustrate similar trends, regardless of sample size, with comparable rates of change (***Section 7.3.13.2***). The reconstructed KM curve for PFS is shown in ***Figure 51***, along with results from 2 other single-arm studies. Figures displaying the fitted standard parametric curves and fitted spline models, and tabulated AIC and BIC statistics for the fitted curves, are provided in the ***Appendices***.

8.4.2.1.3.1 OS: tisa-cel for DLBCL

Model diagnostics for the fitted curves indicated 1-knot spline models using an odds or hazard model provided the best fit (i.e. showed the lowest AIC values). For the base case, the 1-knot spline model based on an odds model was selected, given it provided the lowest AIC value.

Of the standard parametric distributions, those that provided the best fit (based on AIC) included the Gompertz and generalised gamma. Beyond year 4 (48 months), the 1-knot spline model suggested survival probabilities above those suggested by the generalised gamma extrapolation but lower than the Gompertz estimates. A parametric distribution (generalised gamma) was tested in a scenario analysis. A scenario considering a 1-knot spline model until year 5, followed by a switch to SMR-adjusted general population mortality beyond year 5 was also considered.

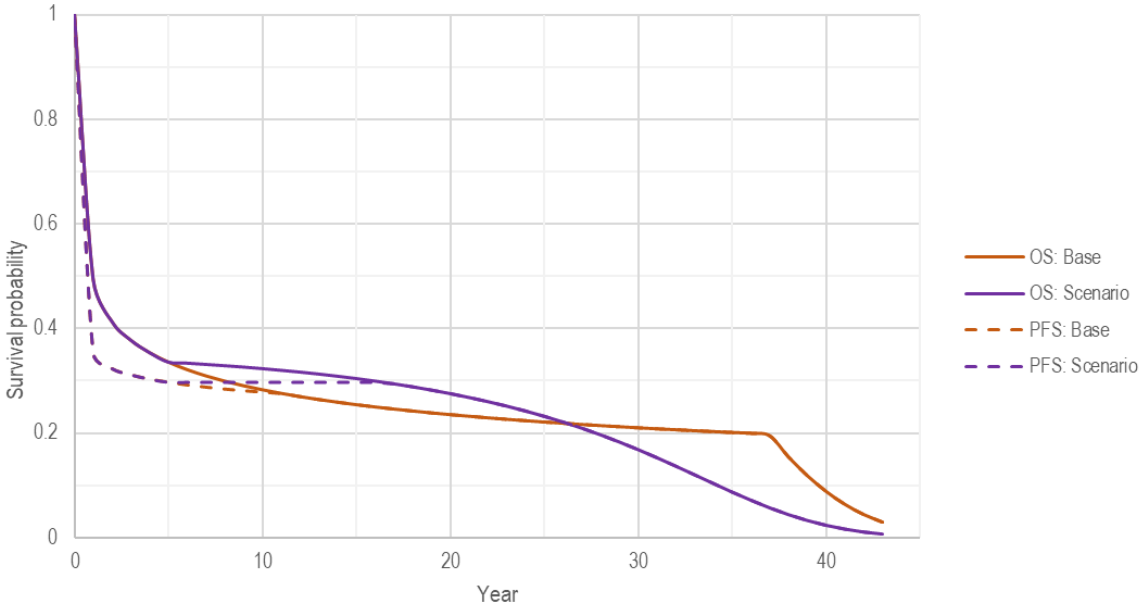
8.4.2.1.3.2 PFS: tisa-cel for DLBCL

Model diagnostics for the fitted curves indicated the spline models with 2 knots provided the best fit for the data (i.e. showed the lowest AIC values). The generalised gamma was the best-fitting parametric distribution, followed by the Gompertz and lognormal. For the base case, the 2-knot spline model based on a probit model was selected, given it provided the lowest AIC value.

Figure 74 shows base case extrapolations for OS and PFS based on the 1-knot and 2-knot spline models, respectively, along with extrapolations realised in the scenario assuming an effective 'cure' point at year 5. Testing of alternative extrapolations for OS rather than PFS was prioritised for scenario analysis.

The base case OS curve suggests survival probabilities of 33.6% after 5 years (age of model cohort: 61 years), 28.3% after 10 years (age of model cohort: 66 years), and 21.0% after 30 years (age of model cohort: 86 years) (***Figure 73***). From year 27 onwards, OS shown by the base case 1-knot spline model exceeds that shown by the scenario analysis in which background population mortality rates were applied after year 5. This suggests the base case model may be overly optimistic beyond this point, in favour of tis-cel. The impact of this on ICER estimates is explored in the scenario analysis.

Figure 74 Example extrapolated survival outcomes for tisa-cel in r/r DLBCL



Abbreviations:
DLBCL = diffuse large B-cell lymphoma, **OS** = overall survival, **PFS** = progression-free survival, **r/r** = relapsed or refractory, **tisa-cel** = tisagenlecleucel.
Note:
Start age is assumed to be 56 years of age. Year 0 corresponds to age 56; year 1 to age 57; year 20 to age 76 etc.

8.4.2.2 Comparator therapies

A pragmatic approach was taken to identify literature on comparators in the third-line setting, beginning with a search of known economic evaluations on CAR T-cell therapies. Where reasonable, sources used in the existing studies were considered to inform comparative survival outcomes for the modelling. Additional literature was sought as required, with either new evidence for newly identified comparators (focusing on key trials) or updated evidence on previously considered comparators (i.e. updated results from previously used trials or from expanded access studies). Applicability of the comparative evidence to the Swiss setting was also explored.

8.4.2.2.1 B-ALL

Alternative therapy options (excluding palliative care) for children and young adults (up to 25 years of age) with refractory B-ALL or relapsed B-ALL after SCT or 2 or more lines of therapy and most relevant in the current Swiss context, include compassionate use of blinatumomab or inotuzumab as a potential bridge to allogenic SCT (see ***Section 8.2.5***).

The existing Swiss economic evaluation considered salvage chemotherapy fludarabine, cytarabine and idarubicin (FLA-IDA), clofarabine combination therapy or blinatumomab as comparators.[1] Clinical evidence was sourced from von Stackelberg 2011 (salvage chemotherapy); Hijiya 2011, Locatelli 2009 and Miano 2012 (clofarabine combination therapy); and von Stackelberg 2016 (blinatumomab, B-ALL).[177-181] Four other retrieved studies also considered blinatumomab as a potential comparator, all

referencing von Stackelberg 2016 as the source of clinical efficacy data.[157,160-162] No existing study considered inotuzumab as a comparator.

Modelling performed for this HTA used blinatumomab as a comparator, to provide a point of comparison with existing literature. While costs for treatment with inotuzumab were considered as part of the cost and budget impact analyses, survival outcomes for inotuzumab are not presented as part of this HTA.

8.4.2.2.1.1 Blinatumomab

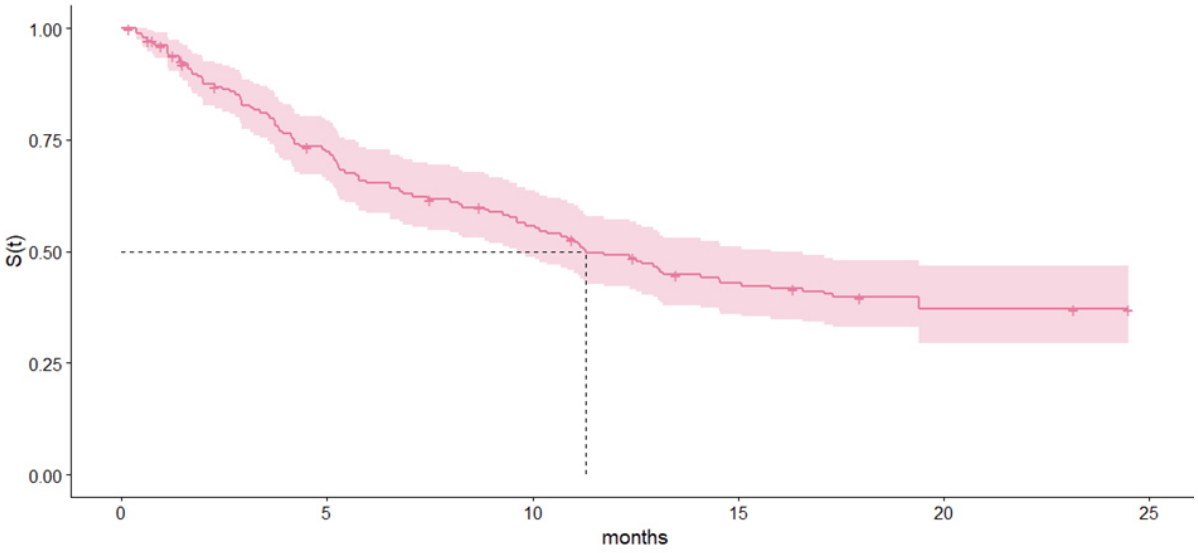
Von Stackelberg 2016 report results of a phase I/II study of blinatumomab in paediatric patients (<18 years of age) with r/r B-ALL and >25% bone marrow blasts, with disease that was either primary refractory, in first relapse after full salvage induction regimen, in second or later relapse, or in any relapse after allogenic SCT.[178] Overall, 70 patients received the recommended dose and were included in the OS analysis. Of these, 27 patients (38.6%) achieved haematologic complete remission within the first 2 cycles.[178] Twenty-five patients received allogenic SCT after blinatumomab, including 13 after blinatumomab-induced complete response (13 of 27; 48.1%).

Locatelli 2020 report results (primary analysis) of an open-label, single-arm, expanded-access study of blinatumomab for paediatric patients (age >28 days to <18 years) with CD19+ r/r B-ALL with second or greater bone marrow relapse (defined as M3 marrow [≥25% morphologic blasts], M2 marrow [≥5% but <25% morphologic blasts] or M1 marrow [<5% morphologic blasts] but with MRD $\geq 10^{-3}$), any bone marrow relapse after allogenic SCT, or refractory to prior treatments (RIALTO study).[254] Locatelli 2022 report final follow-up data for the study, which enrolled 110 patients from January 2015 to July 2018 (data cut-off 10 January 2020).[249] All patients received at least one infusion of blinatumomab; 43 patients (39.1%) completed two cycles, 14 (12.7%) completed three cycles, 6 (5.5%) completed four cycles, and 5 (4.5%) completed five cycles of blinatumomab. Of 110 patients, 69 (63%) achieved complete remission (i.e. morphologic CR; <5% blasts) in the first two cycles and 45 of these patients (65%) proceeded to allogenic SCT.

Survival curves presented in Von Stackelberg 2016 and Locatelli 2022 were digitised and the reconstructed IPD pooled for survival analysis. Survival outcomes were modelled for the entire cohort of treated patients (i.e. not stratified by response status).

Reconstructed KM data from Von Stackelberg 2016 and Locatelli 2022 are plotted in ***Figure 75***. Median OS was reached at 11.3 months (95% CI: 9.6 to 15.8), and overall survival at 12 months was 49.1% (95% CI: 42.1 to 57.2%). Figures displaying the fitted standard parametric curves and fitted spline models, and tabulated AIC and BIC statistics for the fitted curves are provided in ***Appendix G***.

Figure 75 Kaplan Meier curve for blinatumomab OS, generated from reconstructed IPD



Abbreviations:
IPD = individual patient data, **OS** = overall survival.

OS: blinatumomab for B-ALL

The lognormal and generalised gamma distributions showed the best statistical fit to OS data (i.e. showed the lowest AIC values). At 3, 5 and 10 years, the fitted lognormal curve suggested survival probabilities of 23.4%, 14.2% and 6.2%, while the generalised gamma distribution suggested survival probabilities of 26.1%, 17.9% and 10.0%. Of the flexible spline models fitted, 1-knot models using an odds or probit model provided the best statistical fit (i.e. lowest AIC of the flexible spline models). These curves suggested similar extrapolated survival probabilities to the best-fitting parametric models, therefore these have not been considered. A lognormal distribution was selected for the base case as it provided the lowest AIC value and aligns with the modelling used for the intervention in this population. Scenarios using a lognormal distribution followed by assumed long-term survivorship extrapolations beyond year 5 and considering an alternative parametric distribution (generalised gamma) were undertaken.

8.4.2.2.1.1.1 EFS: blinatumomab for B-ALL

An EFS outcome, as defined in the ELIANA trial, was not reported in the blinatumomab studies. Instead, as done in previous evaluations including the York mock model, EFS was derived from the reconstructed OS curve by assuming a constant cumulative HR of 0.83.[1,197,255]

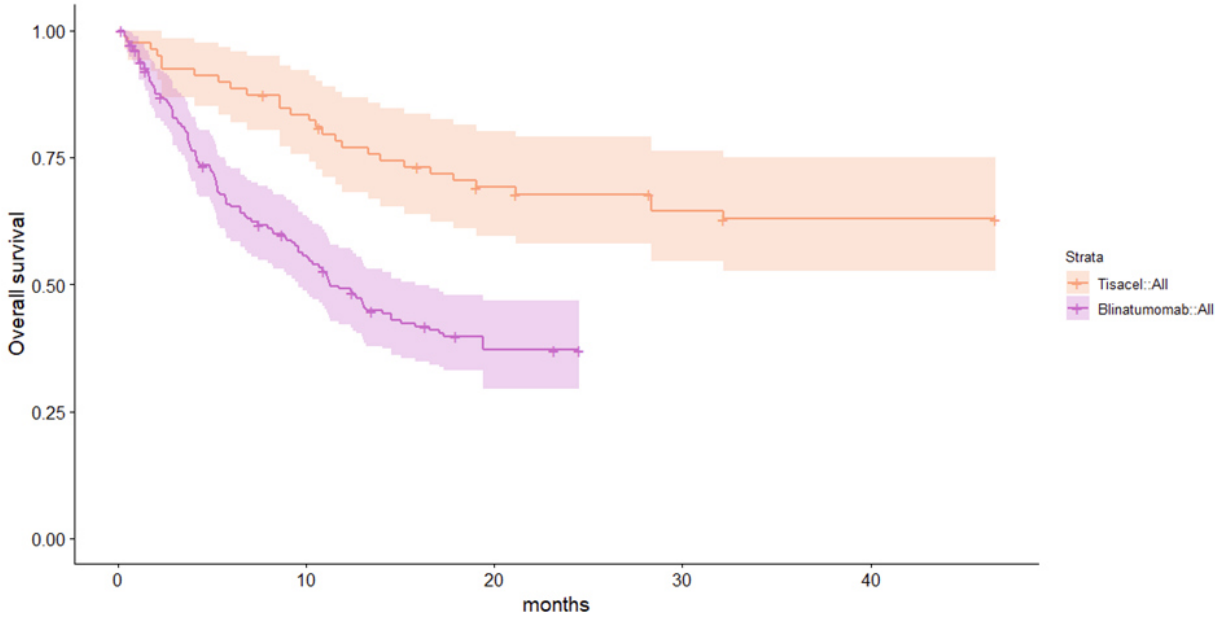
8.4.2.2.1.1.2 Applicability to the Swiss context

Blinatumomab is not listed on the Spezialitätenliste for paediatric patients; however, expert advice states that patients may be treated under compassionate use principles. Further clinical advice states that, in practice, CAR T-cell therapy, blinatumomab and allogenic SCT (as well as inotuzumab) are considered as complementary modalities used in various combinations with one another. The evaluation for this HTA did not capture such complexities, and results should therefore be interpreted in view of this.

8.4.2.2.1.2 Summary of comparative survival

KM plots generated from the reconstructed IPD for OS for tisa-cel and blinatumomab are presented in ***Figure 76***.

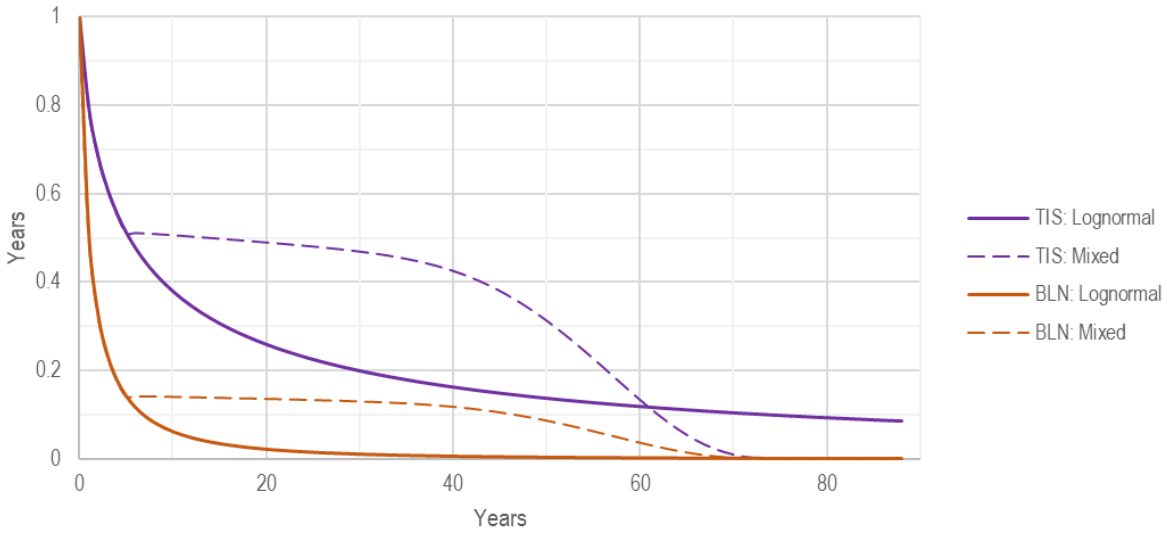
Figure 76 OS Kaplan Meier curves for tisa-cel and blinatumomab, generated from reconstructed IPD



Abbreviations:
IPD = individual patient data, **OS** = overall survival, **tisa-cel** = tisagenlecleucel.

Extrapolations informed by lognormal curves, both with and without a switch to SMR-adjusted background mortality beyond year 5, are shown in ***Figure 77***. After 10 years (age of model cohort: 21 years), survival rates of 37.9% and 6.2% for CAR T-cell therapy and blinatumomab, respectively, were modelled. After 40 years (age of model cohort: 51 years), survival rates of 16.2% and 0.7% were modelled (***Figure 77***).

Figure 77 Extrapolated OS outcomes for tisa-cel and blinatumomab in r/r B-ALL



Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **BLN** = blinatumomab, **OS** = overall survival, **r/r** = relapsed or refractory, **TIS** = tisagenlecleucel.
Notes:
Start age is assumed to be 11 years of age. Year 0 corresponds to age 11; year 1 to age 12; year 40 to age 51 etc.
Mixed survival curves depict survival curves that adopt SMR-adjusted survival beyond year 5.

8.4.2.2.2 LBCL

Alternative active therapy options most relevant to the current Swiss context include salvage chemotherapy with GEMOX, R-GEMOX, rituximab and bendamustine, POLA-BR, or tafasitamab and lenalidomide (***Section 8.2.5***).

Swiss clinical advice states that available options for r/r PMBCL patients are the same as those available to patients with r/r DLBCL, with the added option of pembrolizumab—approved and reimbursed for patients with r/r PMBCL after at least 2 prior lines of therapy.

Of the comparators identified as most relevant to the Swiss context (i.e. GEMOX, R-GEMOX, rituximab and bendamustine, POLA-BR, tafasitamab and lenalidomide; ***Section 8.2.5***), only salvage chemotherapy with R-GEMOX has been previously considered.[1,171,253] The existing Swiss evaluation considered salvage chemotherapy with either R-GEMOX, R-IVE, R-ESHAP or R-DHAP as a comparator, sourcing clinical evidence from the CORAL extension studies.[1]

Briefly, modelling performed for this HTA considered a historic control as a comparator to provide a point of comparison with existing literature. Additional assessments were made relative to POLA BR. These additional assessments are presented as scenario analyses, intended to provide a range of possible ICER values. Regarding other potential comparators identified as relevant in the Swiss context, treatment costs were considered in the BIA; however, comparative cost-effectiveness has not been modelled.

8.4.2.2.2.1 Historical controls

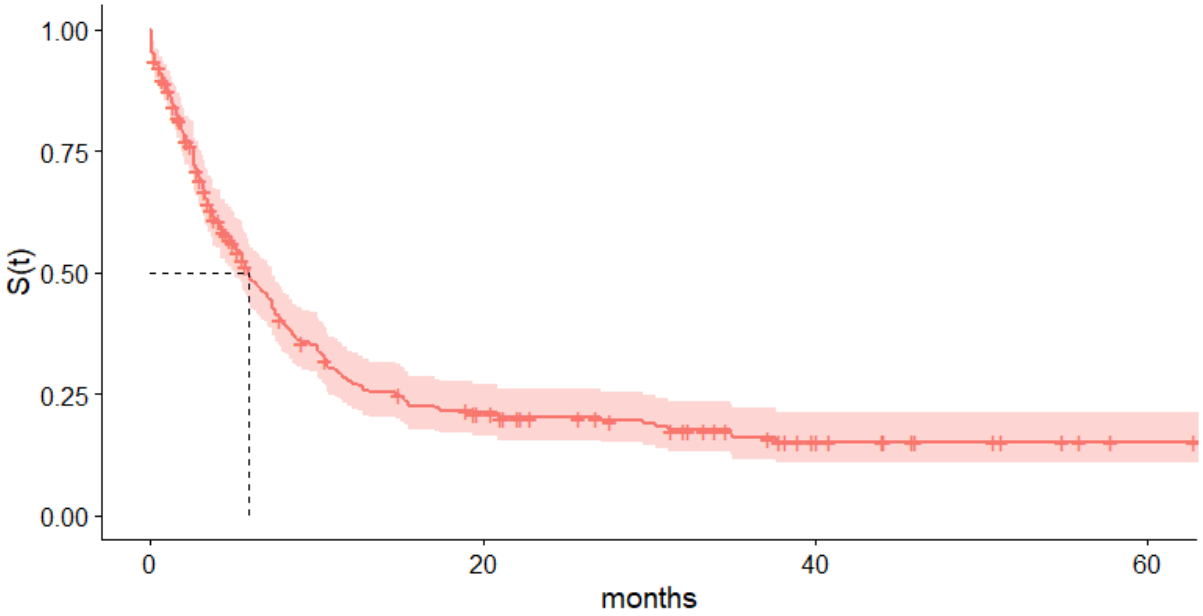
Across existing evaluations, the CORAL study and the SCHOLAR-1 study were the most cited sources of comparative evidence (see ***Table 31*** and ***Table 32***, ***Section 8.1.2***). CORAL was a phase III multicentre RCT that compared R-ICE or R-DHAP prior to high-dose chemotherapy and autologous SCT, with or without rituximab maintenance therapy in adult patients with relapsed DLBCL. Patients who relapsed after autologous SCT or who did not proceed to high-dose chemotherapy plus autologous SCT after salvage chemotherapy were included in 2 extension studies.[174,176] SCHOLAR-1 was a retrospective research study that pooled patient-level data from 4 international cohorts including the CORAL study, the Canadian Cancer Trials Group study (LY-12) and 2 observational cohorts from the United States.[175]

The review group for NICE TA567 considered data from the CORAL extension studies to be relevant to its assessment of tisa-cel for DLBCL.[187] In CADTH's review of axi-cel for LBCL, its clinical expert raised concerns as to whether the salvage chemotherapies used in SCHOLAR-1 adequately reflected contemporary practice.[195] In its review of tisa-cel for DLBCL, CADTH again raised applicability concerns with the SCHOLAR-1 trial (specific chemotherapy regimens not reported), stating that use of the LY-12 and CORAL studies, which include treatments widely available in Canada (R-GDP, R-ICE, R-DHAP), would be more appropriate.[188]

To inform survival outcomes for a historical control for LBCL populations in the evaluation for this HTA, data were selected from the CORAL extension studies. OS curves from these 2 studies were digitised, and the reconstructed IPD were pooled to create a single comparator population reflecting patients who may be eligible for CAR T-cell therapy. The same historical control (CORAL extension) was used in both the axi-cel and tisa-cel comparisons for consistency. It is noted that for axi-cel this deviates from existing literature and HTAs, which have considered SCHOLAR-1 (***Table 31***).

Reconstructed KM data from the CORAL extension cohorts are plotted in ***Figure 78***. Median OS was estimated at 5.9 months (95% CI: 5.1 to 7.3) and OS at 3 years was estimated at 16.1% (95% CI: 11.7 to 22.1%). Figures displaying the fitted standard parametric curves and fitted spline models, and tabulated AIC and BIC statistics for the fitted curves are provided in ***Appendix G***.

Figure 78 Kaplan Meier curve for a DLBCL historical control, generated from reconstructed IPD



Abbreviations:
DLBCL = diffuse large B-cell lymphoma, **IPD** = individual patient data, **OS** = overall survival.

8.4.2.2.2.1.1 OS: historical controls for LBCL

Model diagnostics for the fitted curves indicated the spline models with 2 knots provided the best fit for the data (i.e. showed the lowest AIC values). A 2-knot spline model using a hazard model was selected for the base case, given it provided the lowest AIC value. This model suggested survival probabilities at 3, 5 and 10 years of 16.4%, 13.4% and 10.0%. The generalised gamma was the best-fitting parametric distribution (based on AIC) and it was considered as an alternative selection in the scenario analysis. Beyond year 3, the generalised gamma suggested lower survival probabilities than the base case 2-knot spline model. Specifically, the generalised gamma suggested survival probabilities at 3, 5 and 10 years of 14.6%, 8.4% and 3.3%.

8.4.2.2.2.1.2 PFS: historical controls for LBCL

PFS was not reported for the defined historical control cohort. As in existing evaluations, PFS was derived from OS by assuming a constant cumulative HR of 0.65.[1]

8.4.2.2.2.1.3 Applicability to the Swiss context

A retrospective study describing the outcomes of Swiss patients with DLBCL after high-dose chemotherapy and autologous SCT provides evidence on the management of high-risk or relapsed DLBCL in Switzerland before the availability of CAR T-cell therapies.[256] After autologous SCT, r/r

disease occurred in 42% of patients, and 58% of these patients went on to receive further therapies.[256] Median OS among patients with r/r disease after autologous SCT was 9 months from the time of SCT. A retrospective study using the EBMT database describes the clinical management and outcomes of patients with DLBCL who relapsed after autologous SCT and received active treatment (i.e. not palliative).[257] Median OS from the time of first salvage treatment after autologous SCT was 9.7 months (95% CI: 8.3 to 12.0) and OS at 3 years was 27% (95% CI: 21.9 to 33.3).[257] Notably, these cohorts describe patients relapsing after autologous SCT, while the combined historical control cohort described in ***Figure 78*** includes both patients who relapsed after autologous SCT and patients who did not proceed to high-dose chemotherapy plus autologous SCT after salvage chemotherapy. In the single CORAL extension cohort of patients relapsing after autologous SCT, median OS from the time of relapse was 10.0 months (n=73), with an estimated 1-year OS of 39.1%.[176] For patients who failed to proceed to autologous SCT, median OS from the time of failure of induction therapy, was 4.4 months. (n=193).[174]

In the SBST registry, 26% and 31% of patients receiving axi-cel (for DLBCL or PMBCL) or tisa-cel (for DLBCL), respectively, had prior autologous SCT. Of the pooled CORAL extension cohort, 27.4% (73 of 266) patients had relapsed after autologous SCT.

Chemotherapy regimens used in CORAL extension studies included ICE-type, DHAP-like, gemcitabine-containing and CHOP-like regimens.[174,176] In the retrospective Swiss study described above, regimens administered after SCT failure included chemotherapy (± adjuvant antibodies such as rituximab or radiotherapy), radiotherapy alone, second autologous SCT, allogenic SCT, immunotherapy alone, and the kinase inhibitor ibrutinib.[256] More contemporary comparator regimens often contain rituximab, not reflected in the CORAL extension studies.

A retrospective analysis of a cohort of r/r DLBCL patients not eligible for autologous SCT treated with R-GEMOX in France reported median PFS and OS of 5 months and 10 months, respectively, and 2-year PFS and OS rates of 18% (95% CI:13 to 25) and 32% (95% CI: 26 to 40%).[241] In comparison, PFS and OS predicted by the survival curves used in the base case modelled 2-year PFS and OS rates of 12.9% and 19.8%, respectively. In the retrospective French study, 58% of patients reported 1 line of prior therapy (vs 42% with ≥2 lines); however, further analyses suggested no significant difference in median PFS or OS between patients receiving R-GEMOX in the second- or ≥ third-line (median PFS: 4 vs 5 months, p=0.75; median OS: 10 vs 12 months, p=0.49).[241]

In summary, it is possible that survival outcomes in the comparator arm may be underestimated relative to contemporary practice, biasing the ICER in favour of CAR T-cell therapy.

8.4.2.2.2.2 POLA-BR

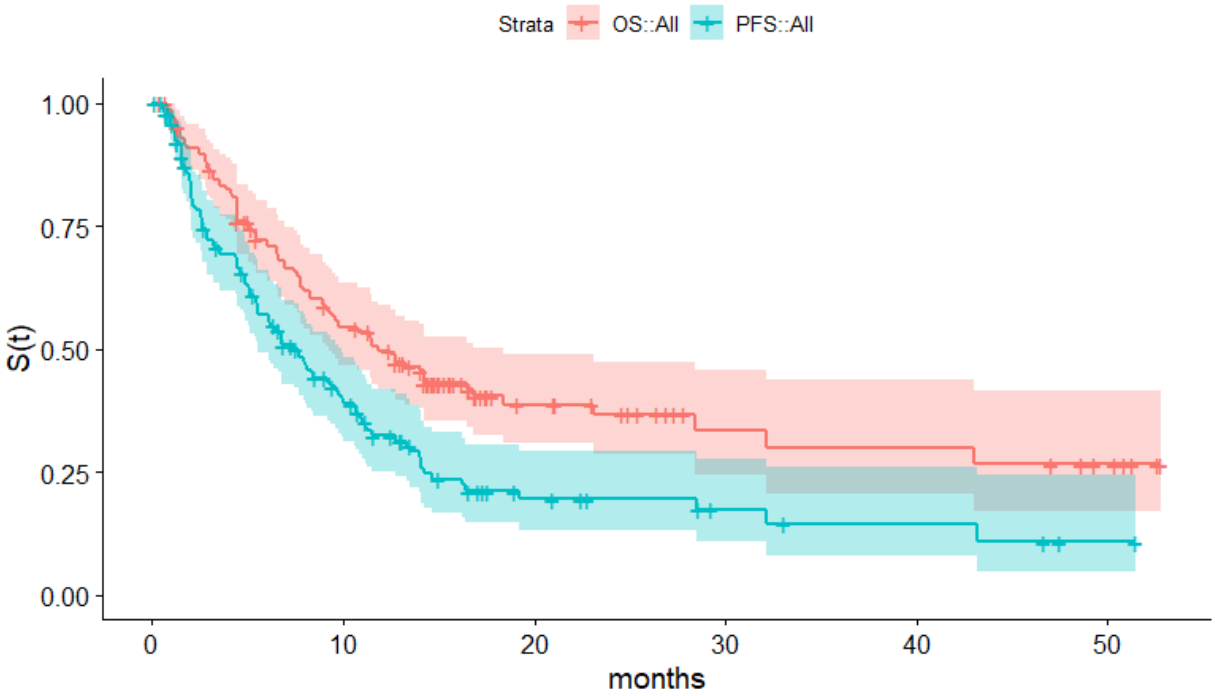
POLA-BR in transplant-ineligible r/r DLBCL patients has been compared to rituximab and bendamustine in a phase II RCT.[244] The median number of prior lines of therapy was 2 (range 1–7) in the POLA-BR arm and 27.5% of patients had only 1 prior line of therapy.

In a subsequent publication, extended follow-up results for the randomised cohort, as well as outcome data for a single-arm extension cohort who received POLA-BR were reported.[258] In the extension cohort, the median number of prior lines of therapy was 2 (range 1–7) and 34.9% had only 1 prior line of therapy.

The EBMT/EHA CAR T-cell handbook suggests patient populations in this pivotal RCT and the expansion cohort are comparable to populations in most CAR T-cell studies.[238] OS and PFS curves for the extended follow-up of the POLA-BR arm from the RCT and for the extension cohort were both digitised and the reconstructed IPD pooled for model fitting. Across both the RCT and extension cohorts (n=146), 9 patients received CAR T-cell therapy after POLA-BR.[258]

Reconstructed KM data from the POLA-BR cohorts are plotted in ***Figure 79***. Median OS and PFS were estimated at 11.8 months (95% CI: 9.3 to 18.4) and 7.6 months (95% CI: 5.5 to 9.9), respectively. Figures displaying the fitted standard parametric curves and fitted spline models and tabulated AIC and BIC statistics for the fitted curves are provided in ***Appendix G***.

Figure 79 OS and PFS Kaplan Meier curves for polatuzumab vedotin, generated from reconstructed IPD



Abbreviations:
IPD = individual patient data, **OS** = overall survival, **PFS** = progression-free survival.

8.4.2.2.2.2.1 OS: Polatuzumab vedotin for LBCL

The best-fitting curve to the OS data was a generalised gamma curve (i.e. it showed the lowest AIC value), followed by 1-knot spline models. Based on the AIC, the generalised gamma distribution was selected for the base case. Scenario analyses focused on the CAR T-cell therapy versus historical control comparisons; testing of alternative extrapolations for POLA-BR was not prioritised.

8.4.2.2.2.2.2 PFS: Polatuzumab vedotin for LBCL

A generalised gamma curve fit the PFS data best, followed by a lognormal model (i.e. they showed the lowest and second lowest AICs, respectively). A generalised gamma distribution was selected for the base case. Compared to the best-fitting flexible spline model (1-knot probit model), the generalised gamma suggested slightly higher survival probabilities beyond year 5 (5- and 10-year probabilities of 20.7% and 12.2% for the 1-knot spline model, and 20.9% and 13.4% for the generalised gamma). Scenario analyses focused on the CAR T-cell therapy vs. historical control comparisons; testing of alternative extrapolations for POLA-BR was not prioritised.

8.4.2.2.2.2.3 Applicability to the Swiss context

Polatuzumab in combination with bendamustine and rituximab (i.e. POLA-BR) is temporarily reimbursed on the Spezialitätenliste for the treatment of adult patients with r/r DLBCL who are ineligible for haematopoietic SCT (temporary limitation until 30 April 2026).[245] POLA-BR may be used as a stand-alone treatment or as a bridging therapy to other treatments, including CAR T-cells. The EBMT/EHA handbook suggests that the potential for polatuzumab to serve as a curative treatment is small if it exists at all, but that it may be a good candidate as a bridging therapy prior to CAR T-cell therapy.[238]

Observational evidence provides some insight to the utilisation patterns of polatuzumab in practice. A retrospective observational study has analysed the outcomes of German patients treated with polatuzumab vedotin under the German compassionate use program.[259] Patients (n=105) were eligible for treatment if they had failed at least 2 lines of therapy and received polatuzumab (± chemotherapy backbone) as a salvage treatment (n=54; 51.4%) or as a bridging treatment (n=51; 48.6%) to CAR T-cell therapy or allogenic SCT. One retrospective observational study analysed the outcomes of Italian patients (n=55) treated with polatuzumab and rituximab (with [n=36] or without [n=19] bendamustine) via an early access program.[260] In this study, polatuzumab was used as a bridge to CAR T-cell therapy in one patient.[260] Another retrospective observational study analysed the outcomes of United Kingdom (UK) patients treated with polatuzumab (n=133) via the Early Access to Medicines Scheme or the Cancer Drugs Fund with the intent to bridge to CAR T-cell therapy (n=40; 31%), as reinduction therapy with planned SCT consolidation (n=13; 9.8%) or as a stand-alone treatment (i.e. no planned CAR T-cell

therapy or SCT; n=78; 58.6%).[261] Expert clinical advice is that some Swiss centres are switching to POLA-BR as a bridging therapy prior to CAR T-cell therapy.

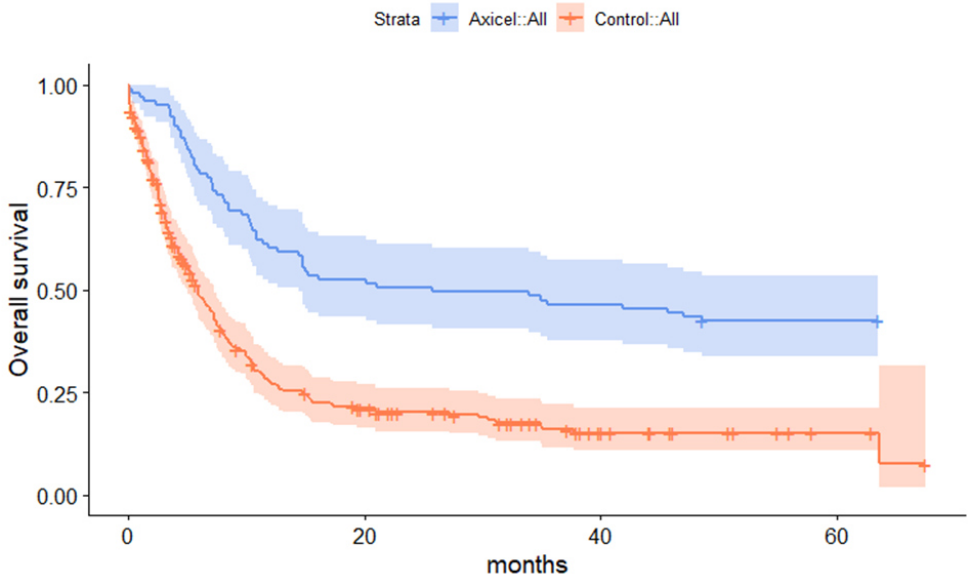
Regarding use of POLA-BR as a stand-alone treatment, POLA-BR may provide an option for patients unable to receive CAR T-cell therapy.[258] In the modelling, it was considered as a comparator to CAR T-cell therapies in scenario analysis.

8.4.2.2.2.3 Summary of comparative survival

8.4.2.2.2.3.1 Axi-cel for LBCL

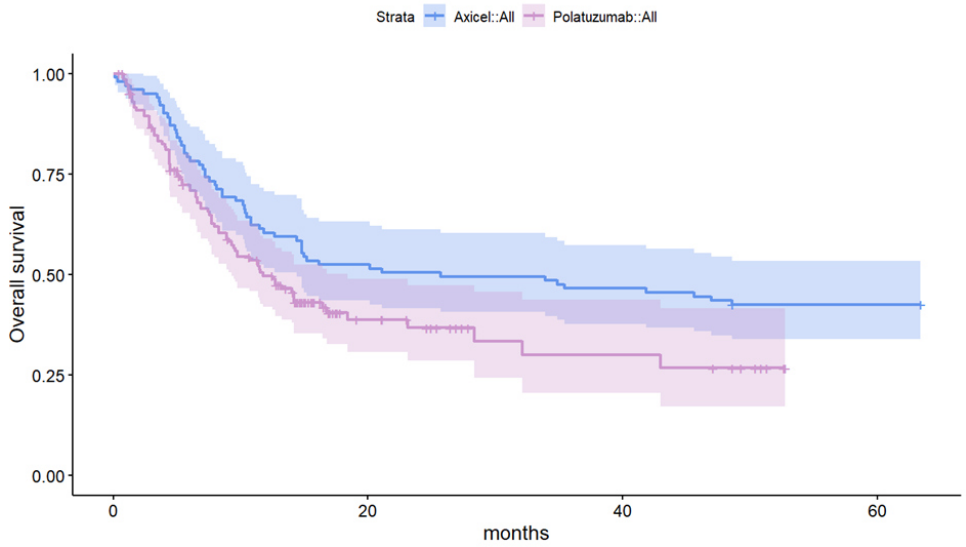
Comparisons made include axi-cel versus a historical control (i.e. the CORAL extension cohorts) and axi-cel versus POLA-BR. KM plots generated from the reconstructed IPD by comparison are provided in ***Figure 80*** and ***Figure 81***.

Figure 80 OS Kaplan Meier curves for axi-cel and a historical control, generated from reconstructed IPD



Abbreviations:
axi-cel = axicabtagene ciloleucel, **IPD** = individual patient data, **OS** = overall survival.

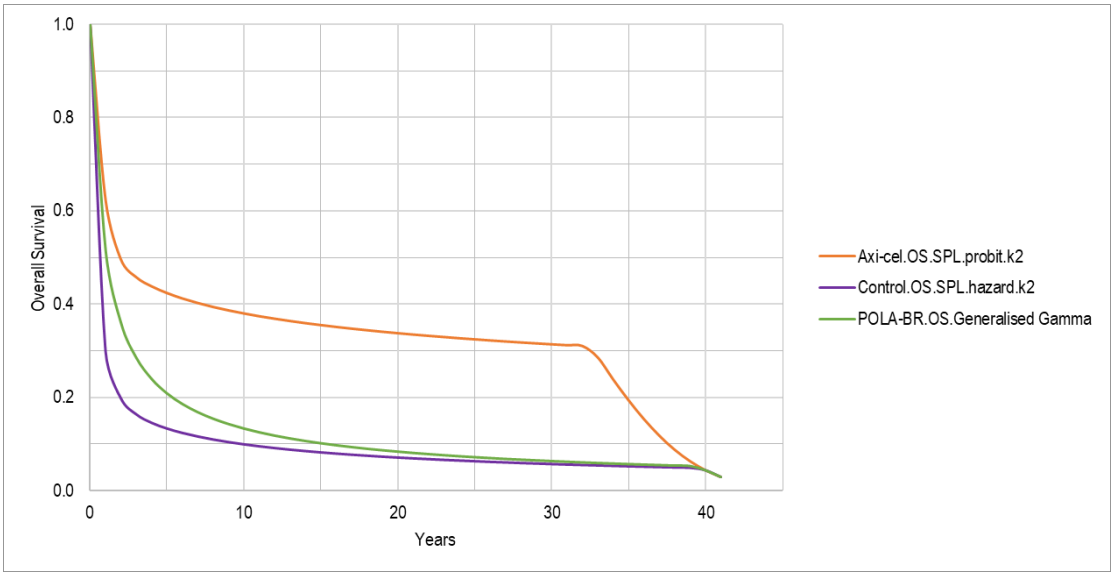
Figure 81 OS Kaplan Meier curves for axi-cel and POLA-BR, generated from reconstructed IPD



Abbreviations:
axi-cel = axicabtagene ciloleucel, **IPD** = individual patient data, **OS** = overall survival, **POLA-BR** = polatuzumab, bendamustine and rituximab.

Extrapolations used in the base case modelling for OS are shown in ***Figure 82***.

Figure 82 Extrapolated OS outcomes for axi-cel and relevant comparators

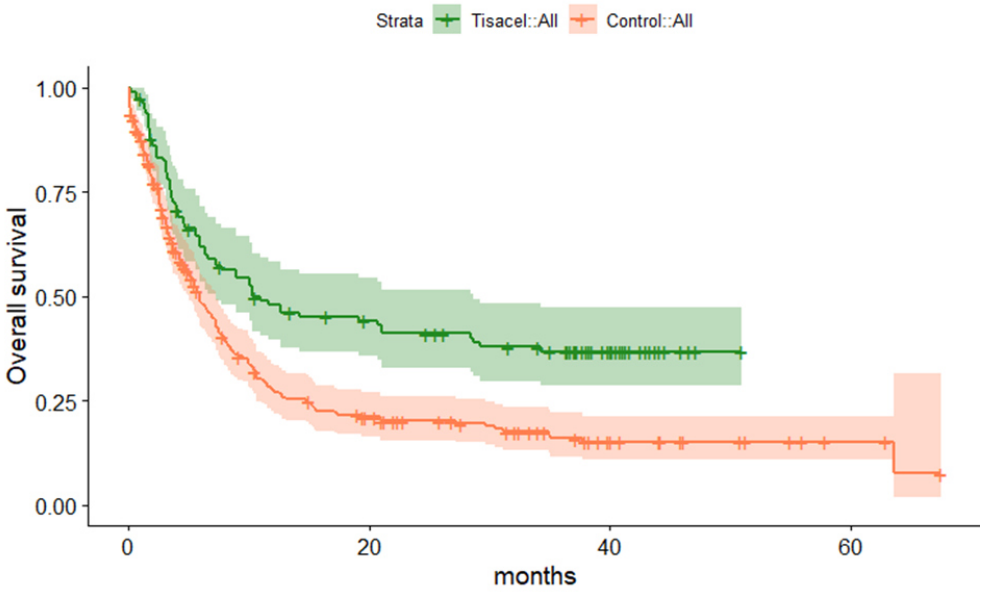


Abbreviations:
axi-cel = axicabtagene ciloleucel, **k1** = 1-knot, **k2** = 2-knots, **OS** = overall survival, **POLA-BR** = polatuzumab, bendamustine and rituximab, **SPL** = spline model.

8.4.2.2.2.3.2 Tisa-cel for DLBCL

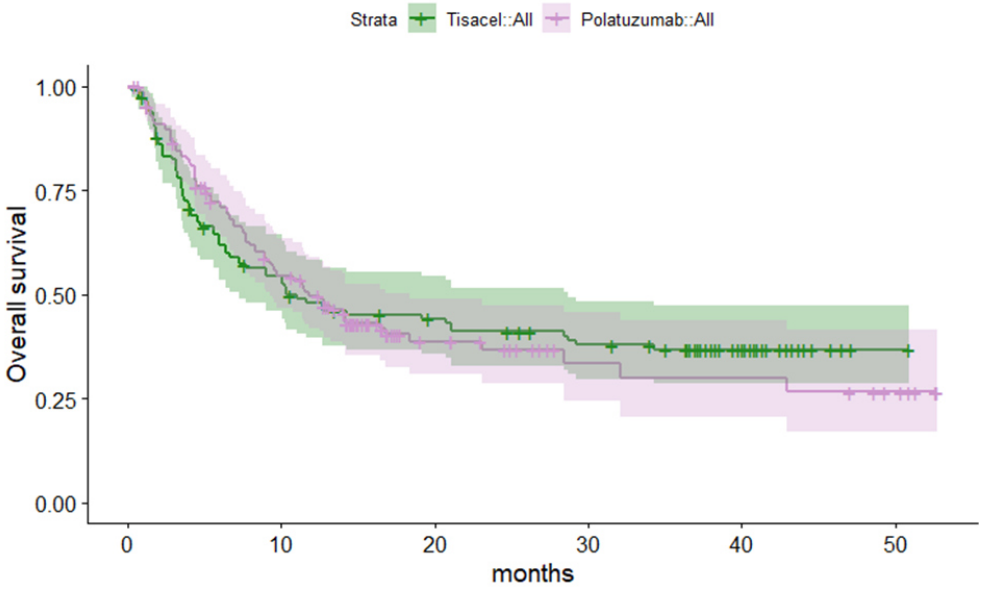
Comparisons made included tisa-cel versus a historical control (i.e. the CORAL extension cohorts) and tisa-cel versus POLA-BR. KM plots generated from the reconstructed IPD by comparison are provided in ***Figure 83*** and ***Figure 84***.

Figure 83 OS Kaplan Meier curves for tisa-cel and a historical control, generated from reconstructed IPD



Abbreviations:
IPD = individual patient data, **OS** = overall survival, **tisa-cel** = tisagenlecleucel.

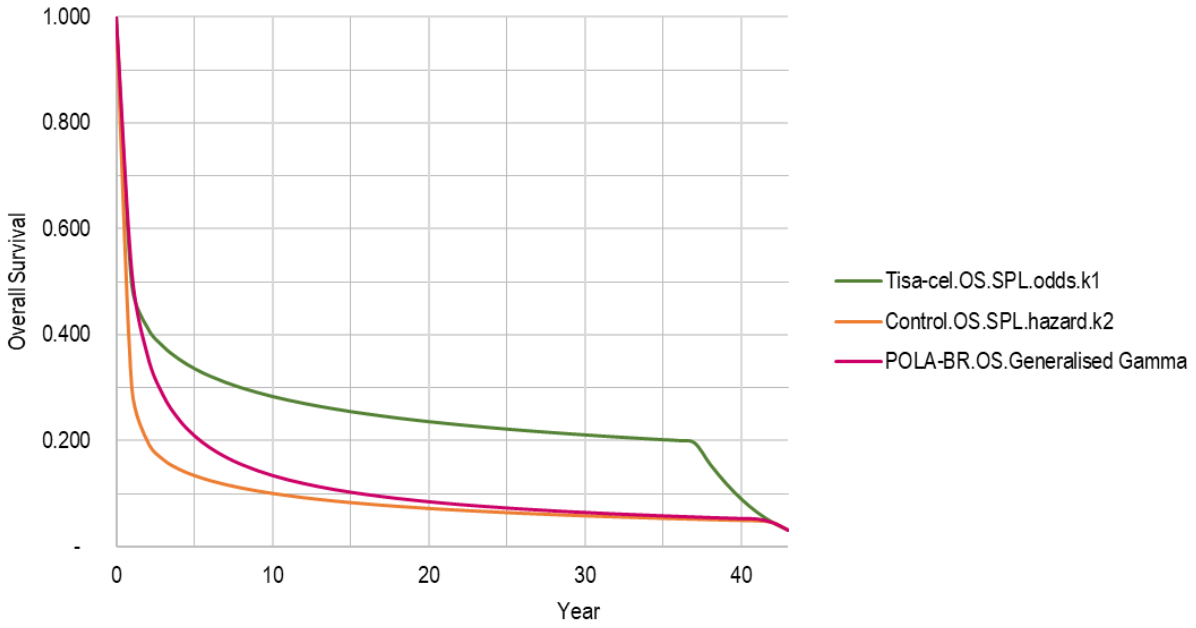
Figure 84 OS Kaplan Meier curves for tisa-cel and polatuzumab, generated from reconstructed IPD



Abbreviations:
IPD = individual patient data, **OS** = overall survival, **tisa-cel** = tisagenlecleucel.

Extrapolations used in the base case modelling for OS are shown in ***Figure 85***.

Figure 85 Extrapolated OS outcomes for tisa-cel and relevant comparators



Abbreviations:
k1 = 1-knot, **k2** = 2-knots, **OS** = overall survival, **POLA-BR** = polatuzumab, bendamustine and rituximab, **SPL** = spline model, **tisa-cel** = tisagenlecleucel.

8.4.3 Health state utilities

Health state utility and disutility values were identified via pragmatic searches, beginning with a search of known economic evaluations on CAR T-cell therapies.

8.4.3.1 B-ALL

8.4.3.1.1 Health state utility values for B-ALL

Across existing B-ALL studies describing health state utility values (HSUVs) for EFS and post-progression health states, the most common source referenced was Kelly 2015.[1,158,161,163,262] The authors present a cost-effectiveness analysis of cranial radiation therapy strategies in patients with T-cell ALL.[262] These utility values were also used in the York mock model.[197]

Two studies included in the literature review—plus the study by Gye 2023 retrieved after the search—used HRQoL data collected in the ELIANA trial to inform HSUVs.[160,162,255] Wang 2022 derived HSUVs from EQ-5D data collected in the ELIANA trial using South Korean preference weights, while Thielen 2020 used a Dutch tariff to derive HSUVs from these EQ-5D data.[160,162] Gye 2023, who presented a cost-effectiveness analysis of tisa-cel from an Australian healthcare system perspective, derived HSUVs from ELIANA EQ-5D data using UK preference weights.[255]

A summary of these HSUVs is provided in ***Table 50***.

Table 50 HSUVs used across existing economic studies for the B-ALL population

Study ID	Event-free HSUV	Post-progression HSUV
Studies referencing Kelly 2015	0.91 (95%: CI 0.87 to 0.95, or 0.87 to 1.00) [A]	0.75 (95% CI: 0.44 to 1.00, or 0.44 to 0.91) [A]
Wang 2022	0.85 (uncertainty NR) [B]	0.76 (uncertainty NR) [B]
Thielen 2020	0.83 (SE: 0.03; beta distribution)	0.68 (SE: 0.05; beta distribution)
Gye 2023	0.80 (uncertainty NR)	0.63 (uncertainty NR)

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **HSUV** = health state utility value, **NR** = not reported, **SE** = standard error.
Notes:
[A] First 95% CI range reflects that provided by Hettle 2017, second reflects that provided by Moradi-Lakeh 2021. Other studies did not report the uncertainty range used.
[B] Publication states that utilities were varied by the 95% CI or range if reported, otherwise they were varied by ±10%.

For this HTA, values reported by Gye 2023 were chosen for the base case for the event-free and post-progression health states across both the tisa-cel and blinatumomab PSMs, given these were based on mapping for the ELIANA EQ-5D data (reported in the clinical evaluation) and used UK preference weights (chosen over the South Korean or Dutch tariffs for applicability to the Swiss context). In a scenario analysis, HSUVs from Kelly 2015 were used.

The existing Swiss study used HSUVs from Kelly 2015 in the base case and EQ-5D utility from the ELIANA trial in a sensitivity analysis. Source of utility was shown to have limited impact on the tisa-cel versus blinatumomab ICER in the DSA conducted in the Swiss evaluation.[1]

An age-associated weighting was also included in this HTA to allow utility to be adjusted as patients aged. Weightings were derived per age category, relative to the 18–24 years category (youngest category reported) for a gender-matched cohort (i.e. 60% male). Data used to derive these weightings comprised gender- and age-specific EQ-5D-3L index population norms for 3 (France, Germany, Italy) of 5 neighbouring countries valued using country-specific time trade-off value sets.[263]

8.4.3.1.2 Disutility values for B-ALL

Across existing B-ALL studies, the most common approach was to apply a treatment disutility for the duration of CAR T-cell therapy or comparator treatment, assuming these disutilities capture utility decrements for all short-term AEs except grade 3–4 CRS and ICU stays. The most referenced source for the disutility value was the study by Sung 2003, which presents a decision analytic model of consolidation treatment options (allogenic bone marrow transplantation or chemotherapy) for young adult patients with acute myeloid leukaemia with a matched sibling donor.[264] Disutility values were quantified via visual analogue scale estimates by 12 physicians.[264] In the York mock model, a treatment disutility was sourced from Sung 2003; however, the duration of disutility for all forms of chemotherapy

was assumed to be the same across treatment arms and treatment disutility, thereby excluding given equivalence across arms.[197]

While Sarkar 2019 report the same up-front treatment disutility as described above, they present additional disutility estimates for CRS, ICU admission, infection, cytopenia, neurotoxicity, anaemia, thrombocytopenia and neutropenia.[159] Thielen 2020 also apply treatment disutilities; however, they source their disutility value from Kwon 2018, who report results of a comprehensive systematic literature review of HSUVs for childhood conditions.[160,265] Lastly, Gye 2023 apply a disutility of 0.1 for all serious AEs (other than grade 3–4 CRS), citing an economic evaluation in chronic lymphocytic leukaemia.[255]

The most common approach to value the disutility associated with grade 3–4 CRS was to assume an HSUV of zero for the duration of the ICU stay (where reported, this varied from 8–11.1 days). This reflects the approach in the York mock model, where an HSUV of zero lasting 1 week was assumed.[197] The only exceptions to this appear to be Sarkar 2019, who reported additional disutility estimates for AEs (as described above), and Thielen 2020, who did not report any additional AE-associated disutilities.[159,160]

Regarding B-cell aplasia, authors of the York mock model highlight that, although there is a large cost burden associated with its ongoing management, there is little evidence of any significant impact on patient utility. Accordingly, no disutility was assumed for cases of B-cell aplasia.[197] Similarly, none of the reviewed evaluations incorporated a disutility for this AE.

Regarding the disutility associated with subsequent allogenic SCTs, the most common approach was to apply a disutility value sourced from Sung 2003 for an assumed duration of 1 year, consistent with the approach described in the York mock model. Alternatively, Thielen 2020 applied a disutility of 0.21 during the SCT treatment period and a disutility of 0.02 for the 6–12 months after SCT.[160] These values were sourced from a systematic review of HSUVs for acute myeloid leukaemia, and reflect utilities mapped from QLQ-C30 data.[266,267]

For this HTA, the example of Thielen 2020 was followed, applying a disutility of 0.20 from the Kwon 2018 systematic review for the duration of therapy. In a meta-regression including the main health utility samples measured using the HUI3, Kwon 2018 report a utility decrement of 0.202 (SE: 0.006; 95% CI: -0.213 to -0.190) relative to baseline for ALL patients on active therapy.[265] In a scenario analysis, the treatment disutility as sourced from Sung 2003 was used. Similarly, the example of Thielen 2020 was followed to model SCT-associated disutilities in the base case for this HTA, and the values of Sung 2003 were used in the scenario analysis.

The approach taken by almost all studies was used, applying an HSUV of zero for grade 3–4 CRS (accounting for the period of ICU admission) and no additional disutility was applied for the ongoing management of B-cell aplasia.

A summary of the approaches chosen for this HTA is provided in ***Table 51***.

Table 51 Summary of HSUVs used in the evaluation for the B-ALL population

	Base case	Scenario analysis
Tisa-cel treatment disutility	0.202 (SE: 0.006) applied for 30 days	0.42 (0.16–0.83) applied for 30 days
Blinatumomab treatment disutility	0.202 (SE: 0.006) applied for 68 days	0.42 (0.16–0.83) applied for 68 days
Disutility for an ICU stay	HSUV of 0 for any ICU stays, applied for 11.1 days	No change
SCT disutility	0.213 (±20%) for 6 months, and 0.016 (±20%) for an additional 6 months	0.57 (0.31–0.87), applied for 12 months

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **HSUV** = health state utility value, **ICU** = intensive care unit, **SCT** = stem cell transplantation, **SE** = standard error, **tisa-cel** = tisagenlecleucel.

8.4.3.2 LBCL

8.4.3.2.1 Health state utility values for LBCL

Base case HSUVs for the progression-free and post-progression health states in the existing Swiss evaluation (Moradi-Lakeh 2021) were derived by mapping SF-36 data from the JULIET trial (data cut-off: 11 December 2018) to utility values.[1] Utility values from Chen 2018 and the NICE technology appraisal guidance for pixantrone monotherapy were considered in the sensitivity analysis. DSA conducted for the tisa-cel versus salvage chemotherapy comparison showed the source of utility to have limited impact on the ICER.[1]

Sources cited by other existing evaluations describing progression-free and post-progression health states include Wang 2018, Chen 2018 and Lin 2018, with Chen 2018 being the most cited. Chen 2018 present modelling analyses exploring the potential cost-effectiveness of precision medicine in DLBCL, using published utility estimates in their modelling from a previous economic evaluation for DLBCL patients receiving R-CHOP.[268] The reports by Lin 2018 and Wang 2018 are both conference abstracts. Lin 2018 present HSUVs for r/r LBCL based on an ad hoc analysis of EQ-5D-5L results from a phase II safety management study of axi-cel for 34 treated patients, valued using US preference weights.[269] Wang 2018 present HSUVs specific to DLBCL for 6 health states, based on EQ-5D-5L responses from 319 DLBCL patients included in the UK's Haematological Malignancy Research Network.[270]

A summary of these HSUVs is provided in ***Table 52***.

Table 52 HSUVs used across existing economic studies for the LBCL population

Study ID	Progression-free HSUV	Post-progression HSUV
Moradi-Lakeh 2021 (base case)	0.83 (95% CI: 0.79 to 0.87)	0.72 (95% CI: 0.66 to 0.78)
Chen 2018	0.83 (range: 0.66 to 1.00), beta distribution with parameters 3.42, 0.7	0.39 (range: 0.31–0.47), beta distribution with parameters 14.86, 23.24
Lin 2018 (conference abstract)	0.80 (SD: 0.14)	0.72 (SD: 0.17)
Wang 2018 (conference abstract)	0.7 (SE: 0.059) [A]	0.59 (SE: 0.093) [B]

Abbreviations:
HSUV = health state utility value, **SD** = standard deviation, **SE** = standard error.
Notes:
[A] For the health state '3rd remission and beyond' (as used in Cher 2020).
[B] For the health state '3rd-line treatment and beyond' (as used in Cher 2020).

The HSUVs used by Moradi-Lakeh 2021 were chosen for the base case analysis for this HTA (for both the tisa-cel and comparator PSMs), given these were based on mapping of the JULIET SF-36 trial data (reported in the clinical evaluation for this HTA). The alternative sources presented above were tested in the scenario analysis.

An age-associated weighting was included to allow utility to be adjusted as patients aged. Weightings were derived per age category relative to the 55–64-year category (assumed start ages of 58 and 56 years for the axi-cel and tisa-cel cohorts, respectively), and for a gender-matched cohort (i.e. 64% and 62% males, respectively). Data used to derive these weightings comprised gender- and age-specific EQ-5D-3L index population norms for 3 (France, Germany and Italy) of 5 neighbouring countries valued using country-specific time trade-off value sets.[263]

8.4.3.2.2 Disutility values for LBCL

Like the B-ALL population, the most common approach was to apply a treatment disutility for the duration of CAR T-cell therapy or comparator treatment, assuming these disutilities capture utility decrements for all short-term AEs except for grade 3–4 CRS and ICU stays. The most referenced source for the disutility value was Guadagnolo 2006, which compared, using a decision analytical model, the cost-effectiveness of alternative follow-up strategies for patients after primary treatment for Hodgkin's disease.[271] In the Guadagnolo 2006 study, utilities were based on prior published studies or clinically plausible values from expert physicians if no prior data were available.

While Cher 2020, describe application of a treatment disutility for the duration of treatment (sourced from Guadagnolo 2006), they additionally describe application of this same disutility value for one episode for the following AEs: diarrhoea, anaemia, febrile neutropenia. Hillis 2022 modelled AE-related utility decrements for AEs associated with CAR T rather than applying an overarching 'treatment-related' disutility.[166] Hillis 2002, conservatively applied no AE-related disutilities to the comparator arm of the

model. Whittington 2019 applied treatment-related disutilities from Sung 2003, consistent with disutilities used in their B-ALL model.

As with the B-ALL models, the most common approach to value the disutility associated with grade 3–4 CRS was to assume an HSUV of zero for the duration of the ICU stay (where reported, this disutility was applied for 8.5 days).

For the analysis for this HTA, the most commonly cited treatment disutility values were chosen. In scenario analysis, the same disutility values were used as by Whittington 2019. The approach taken by almost all studies was used, applying an HSUV of zero for grade 3-4 CRS (accounting for the period of ICU admission) and no additional disutility was applied for the ongoing management of B-cell aplasia.

A summary of chosen approaches is provided in ***Table 53***.

Table 53 Summary of HSUVs used in the evaluation for the LBCL population

	Base case	Scenario analysis
CAR T treatment disutility [A]	0.15 (±20%) applied for 30 days	0.42 (0.16–0.83) applied for 30 days
Comparator treatment disutility	0.15 (±20%) applied for median number of cycles for each regimen	0.42 (0.16–0.83) applied for median number of cycles for each regimen
Disutility for an ICU stay	HSUV of 0 for any ICU stays, applied for 8.5 days	No change

Abbreviations:
HSUV = health state utility value, **ICU** = intensive care unit, **SCT** = stem cell transplantation, **SE** = standard error, **tisa-cel** = tisagenlecleucel.
Notes:
[A] axicabtagene ciloleucel or tisagenlecleucel.

8.5 Results: cost-effectiveness

8.5.1 Tisa-cel for B-ALL

One directly applicable study assessing the cost-effectiveness of tisa-cel in children and young adults with r/r B-ALL was identified (***Section 8.1.2***).[1] Key economic findings are reported narratively, followed by results of the economic modelling performed for the current HTA.

The economic evaluation of tisa-cel relative to blinatumomab for this HTA was informed by indirect treatment comparisons. Results should be interpreted in view of the limitations of such comparisons. The results should also be considered in view of the fact that, in practice, CAR T-cell therapy, blinatumomab and allogenic SCT (as well as inotuzumab) are considered as complementary modalities used in various combinations with one another. The evaluation for this HTA was not constructed to capture such complexities. Instead, the evaluation compared CAR T-cell therapy to blinatumomab, with both therapies followed by allogenic SCT in a proportion of patients. Costs and disutilities were included for patients modelled to receive allogenic SCT.

8.5.1.1 Literature findings

Moradi-Lakeh 2021 presented an economic evaluation of tisa-cel compared to salvage chemotherapy (FLA-IDA), clofarabine combination therapy, and blinatumomab (as 3 separate comparisons) from the perspective of the Swiss mandatory health insurance system (societal perspective in sensitivity analysis).[1] The publication reported an incremental cost for tisa-cel compared to blinatumomab of CHF226,344 (2023 CHF225,154), incremental effects of 6.89 LYs and 6.22 QALYS, and an ICER of CHF36,419 (2023 CHF36,227). Inclusion of productivity gain, the discount rate, HR for the comparator versus tisa-cel, and the time horizon were shown to have the biggest impact on the ICER in a one-way DSA. PSA suggested tisa-cel to have a 100% chance of being cost-effective at a hypothetical WTP of CHF100,000.

8.5.1.2 ICER

Incremental cost-effectiveness of tisa-cel relative to blinatumomab for paediatric and young adult patients (<25 years of age; assumed age of 11 years at treatment initiation) with r/r B-ALL over a lifetime (88-year) time horizon, as estimated in the analyses conducted for this HTA, are presented in ***Table 54***. Findings of the evaluations undertaken for this HTA indicate a higher ICER (CHF70,634) than does the existing economic evidence.

Table 54 Lifetime extrapolated ICER of tisa-cel for patients with r/r B-ALL

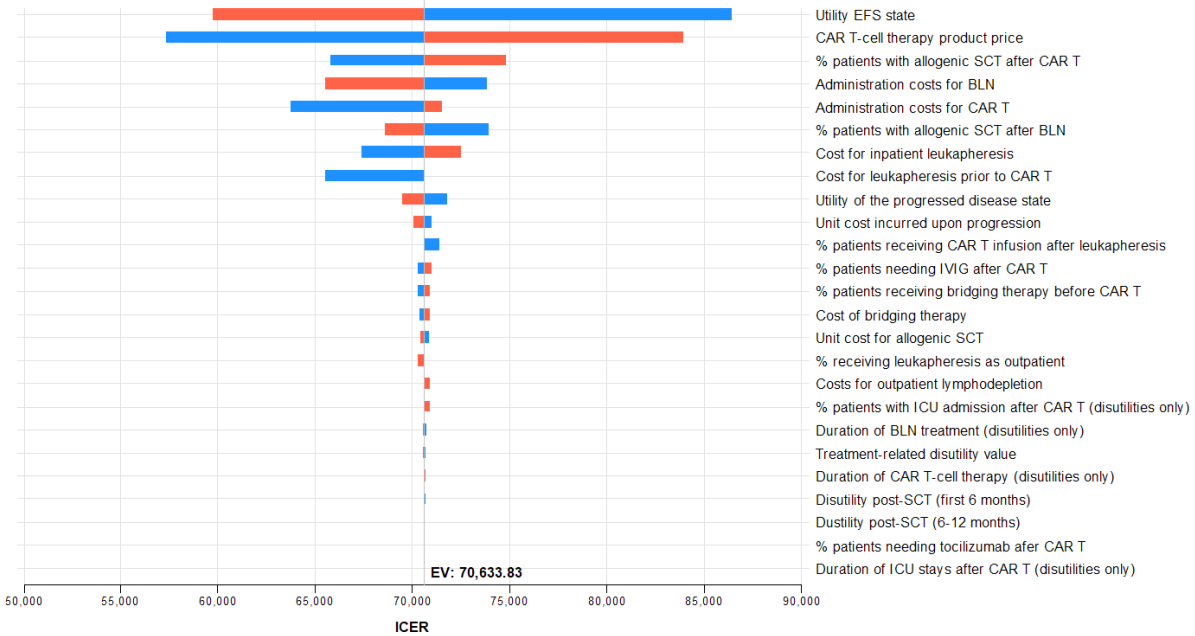
	Tisa-cel	Blinatumomab
Expected cost per patient (CHF)	570,554	177,887
Incremental cost (CHF)	NA	329,668
Expected LYs per patient	9.67	2.50
Incremental LYs	NA	7.17
Expected QALYs per patient	7.41	1.85
Incremental QALYs	NA	5.56
ICER (cost per QALY gained)	NA	**70,634**

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, CHF = Swiss franc, **ICER** = incremental cost-effectiveness ratio, **LY** = life year, **NA** = not available, **QALY** = quality-adjusted life year, **tisa-cel** = tisagenlecleucel.

8.5.1.3 Univariate sensitivity analysis

Figure 86 displays the impact of uncertainty in cost, utility and proportion inputs on the ICER. HSUV for the event-free state (0.8 ±20%) and CAR T-cell therapy product price (CHF370,755 ±20%) demonstrated the greatest impact. ICERs ranged from CHF59,728–86,413 and CHF57,295–83,972 across uncertainty ranges of each variable, respectively. Additional uncertainties introduced by modelling assumptions, including extrapolation assumptions, are discussed in ***Section 8.5.1.5***.

Figure 86 Tornado diagram of uncertainty in parameter input values, B-ALL population



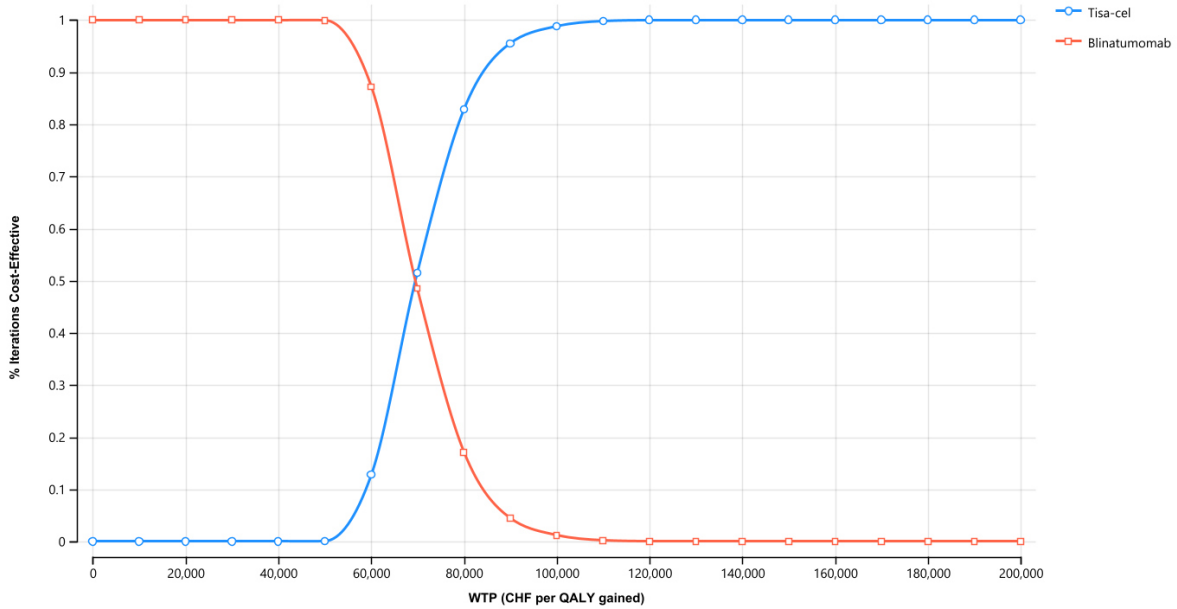
Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **BLN** = blinatumomab, **CAR T** = chimeric antigen receptor T-cell therapy, **EFS** = event-free survival, **EV** = expected value, **ICER** = incremental cost-effectiveness ratio, **ICU** = intensive care unit, **IVIG** = intravenous immunoglobulin, **SCT** = stem cell transplantation.

8.5.1.4 Probabilistic sensitivity analysis

PSA explored the combined uncertainty across cost, utility and patient percentage inputs. Uncertainty introduced through methodological assumptions relating to the time horizon, discount rate, source of HSUV, duration of IVIG for patients requiring replacement therapy after tisa-cel, and extrapolation approach adopted, is not reflected in the PSA results. These were explored through scenario analysis (***Section 8.5.1.5***).

A mean expected ICER of CHF70,879 per QALY gained (95% CI from PSA: CHF55,354 to CHF93,798) was estimated. The CEAC is presented in ***Figure 87***. When considering WTP thresholds of CHF50,000, CHF100,000 and CHF150,000, tisa-cel had probabilities of cost-effectiveness of ≤1.0%, 98.9% and 100%, respectively, compared to blinatumomab.

Figure 87 Cost-effectiveness acceptability curve, B-ALL population



Abbreviations:
CHF = Swiss francs; **QALY** = quality-adjusted life year; **WTP** = willingness-to-pay.

8.5.1.5 Scenario analysis

Scenario analyses tested the impact of time horizon, discount rate, source of HSUV, duration of IVIG for patients requiring replacement therapy after tisa-cel, and extrapolation approach adopted (***Table 55***). The time horizon and discount rate demonstrated the largest impact on the ICER. This impact was larger than the impact of uncertainty in parameter input values shown in ***Figure 86.*** Variations in the ICER across scenarios were largely driven by variations in the incremental QALYs side of the ICER equation. Overall, the benefit of tisa-cel on survival outcomes accumulated over the lifetime horizon is a key driver of the ICER estimate.

Table 55 Scenario analysis impacts on the ICER, B-ALL population

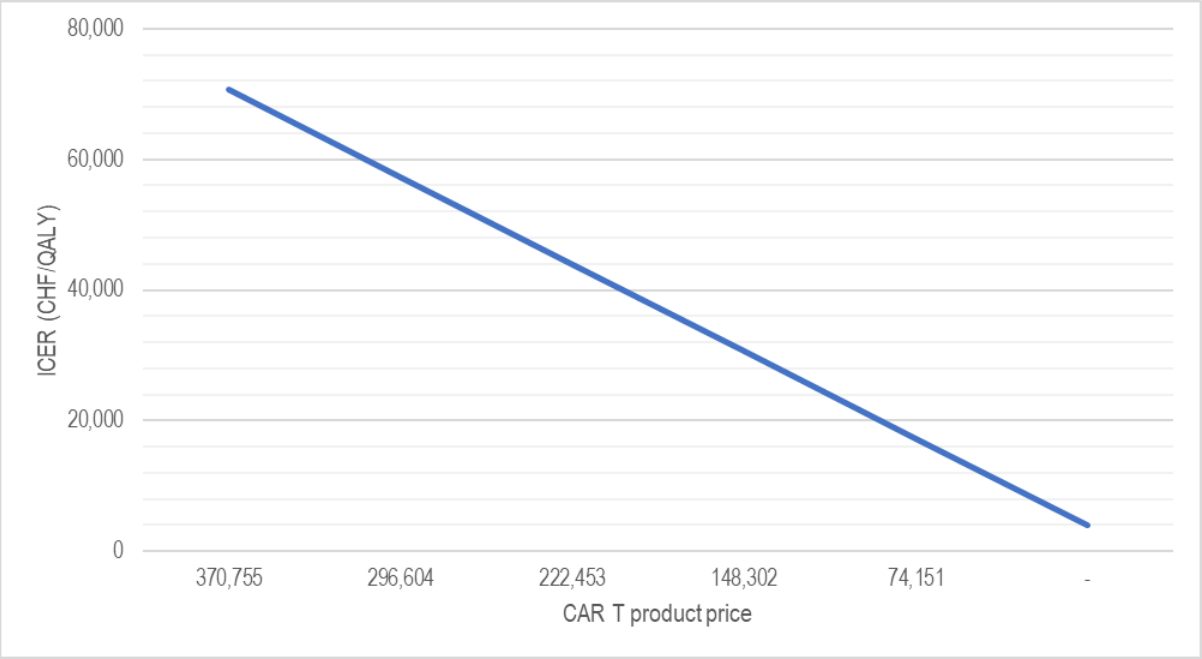
Scenario	Incremental cost (CHF)	Incremental QALYs	ICER (CHF per QALY)	Difference from base
Base case	392,668	5.56	70,634	NA
Time horizon: 10 years	390,999	2.20	178,100	+152%
Time horizon: 20 years	391,582	3.59	109,129	+54%
Discount rate: 0%	396,303	11.52	34,412	-51%
Discount rate: 6%	391,749	3.55	110,237	+56%
Source of HSUV (Kelly 2015)	392,668	6.34	61,904	-12%
Duration of IVIG: 3 years	407,357	5.56	73,276	+4%
Duration of IVIG: 80 years	490,796	5.56	88,285	+25%
Switch to SMR-adjusted mortality beyond year 5 – tisa-cel only	390,660	8.75	44,628	-37%
Switch to SMR-adjusted mortality beyond year 5	391,951	7.04	55,676	-21%
Gompertz – tisa-cel OS	392,417	9.95	39,451	-44%
Gompertz – tisa-cel & BLN OS	392,417	6.91	56,804	-20%
Loglogistic – tisa-cel OS	393,127	4.84	81,147	+15%
Generalised gamma – BLN OS	392,668	5.08	77,297	+9%

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **BLN** = blinatumomab, **CHF** = Swiss franc, **HSUV** = health state utility value, **ICER** = incremental cost-effectiveness ratio, **IVIG** = intravenous immunoglobulin, **OS** = overall survival, **QALY** = quality-adjusted life year, **SMR** = standard mortality rate.

8.5.1.6 Sensitivity analysis on CAR T-cell therapy product price

Surcharge codes apply for CAR T-cell therapy products; however, the tariffs for these surcharge codes are unpublished, so scenario analysis focused on the product price. A base case cost of CHF370,755 was assumed for tisa-cel. A reduction of 0–100% from the assumed base price was considered. ICER outcomes as a function of CAR T-cell product price are shown in ***Figure 88***.

Figure 88 ICER as a function of CAR T-cell therapy product price, B-ALL population



Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CAR** = chimeric antigen receptor, **CHF** = Swiss franc, **ICER** = incremental cost effectiveness ratio, **QALY** = quality-adjusted life year.

8.5.2 Axi-cel for LBCL

No existing economic evidence on axi-cel for the treatment of r/r LBCL in the Swiss healthcare context was identified in the literature (***Section 8.1.2***). Results generated for this HTA are presented.

Base case results are presented for axi-cel relative to a historical control and POLA-BR. Subsequent SCT use was not explicitly modelled (no cost or disutilities for SCT were included in the LBCL model). Modelling was informed by naïve treatment comparisons and results should be interpreted in view of this limitation. Sensitivity analyses were conducted on the model, which compared axi-cel to a historical control. Comparisons against POLA-BR are presented as scenario analyses, providing a range of potential ICER values.

ICER

Incremental cost-effectiveness of axi-cel relative to each comparator for the management of patients with r/r LBCL in the third-line setting over a lifetime horizon (42 years; assumed age of 58 years at treatment initiation) are presented in ***Table 56***.

Axi-cel was associated with higher expected per patient costs, LYs and QALYs relative to all comparators. Axi-cel demonstrated the most favourable cost-effectiveness relative to a historical control, followed by POLA-BR.

Table 56 Lifetime extrapolated ICERs of axi-cel for patients with r/r LBCL

	Axi-cel	Historical control	POLA-BR
Expected cost per patient (CHF)	460,856	79,582	102,831
Incremental cost (CHF)	NA	381,274	358,025
Expected LYs per patient	8.22	2.83	3.82
Incremental LYs	NA	5.39	4.40
Expected QALYs per patient	6.33	2.02	2.83
Incremental QALYs	NA	4.32	3.50
ICER (cost per QALY gained)	NA	**88,346**	**102,220**

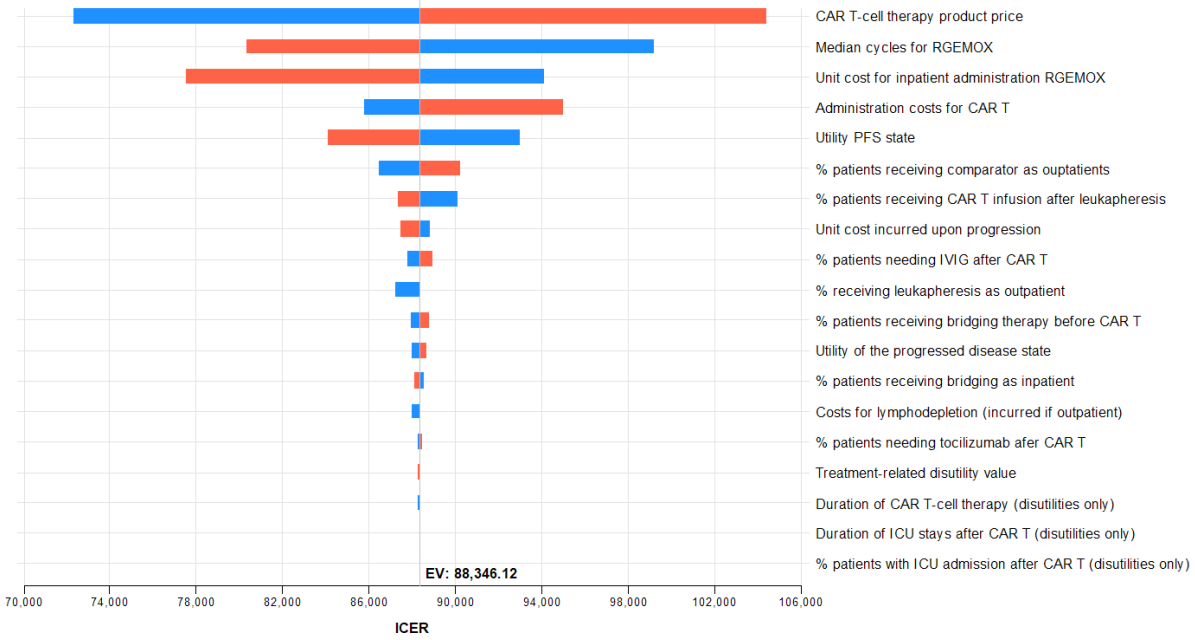
Abbreviations:
axi-cel = axicabtagene ciloleucel, **CHF** = Swiss franc, **ICER** = incremental cost-effectiveness ratio, **LY** = life year, **NA** = not available, **POLA-BR** = polatuzumab, bendamustine and rituximab, **QALY** = quality-adjusted life year.

8.5.2.1 Univariate sensitivity analysis

Figure 89 shows the impact of uncertainty in cost, utility and proportion inputs on the ICER for axi-cel in comparison to a historical control. Major drivers of the ICER included the CAR T-cell therapy product price, and administration costs associated with the hospital episode for treatment with either the comparator or CAR T-cell therapy.

Additional uncertainties introduced by modelling assumptions, including extrapolation assumptions, are discussed in ***Section 8.5.2.3***.

Figure 89 Tornado diagram of uncertainty in parameter values, axi-cel compared to historical control



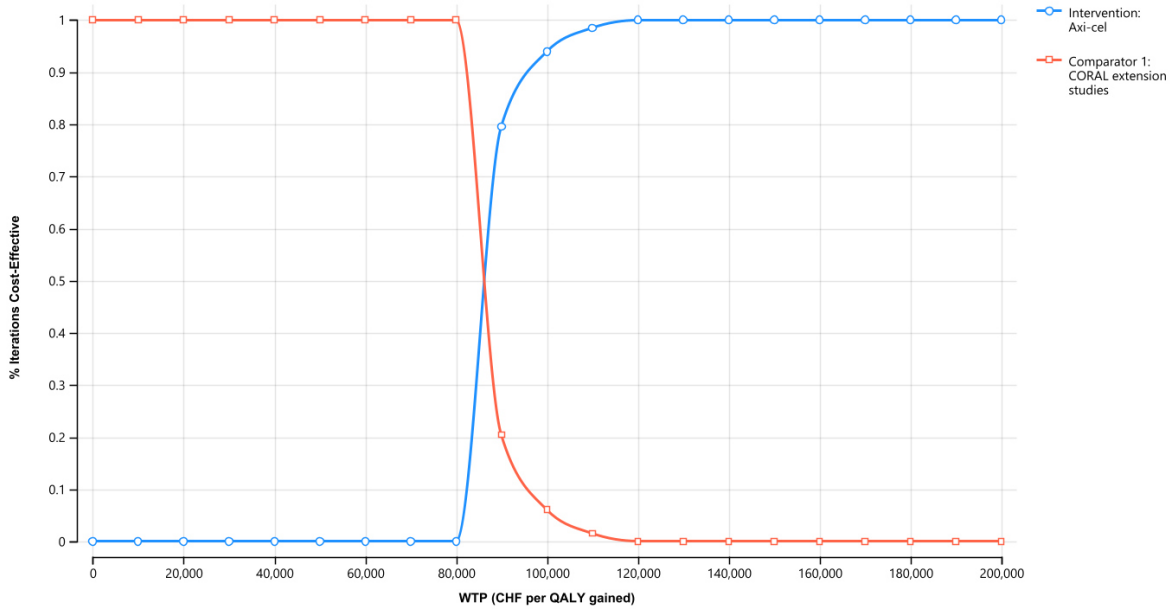
Abbreviations:
axi-cel = axicabtagene ciloleucel, **CART** = chimeric antigen receptor T-cell therapy, **EV** = expected value, **ICER** = incremental cost-effectiveness ratio, **ICU** = intensive care unit, **IVIG** = intravenous immunoglobulin, **PFS** = progression free survival, **RGEMOX** = rituximab, gemcitabine, oxaliplatin.

8.5.2.2 Probabilistic sensitivity analysis

PSA explored the combined uncertainty across cost, utility and patient percentage inputs. Note that uncertainty introduced through methodological assumptions relating to the time horizon, discount rate, source of HSUV, duration of IVIG for patients requiring replacement therapy after tisa-cel, and extrapolation approach adopted, is not reflected in the PSA results. These were explored through scenario analysis (***Section 8.5.2.3***).

A mean expected ICER of CHF88,560 per QALY gained (95% C: from PSA: CHF85,770 to CHF107,259) was estimated. The CEAC is presented in ***Figure 90***. When considering WTP thresholds of CHF50,000, CHF100,000 and CHF150,000, axi-cel had probabilities of cost-effectiveness of 0.0%, 93.9% and 100%, respectively, compared to historical control.

Figure 90 Cost-effectiveness acceptability curve, axi-cel compared to historical control



Abbreviations:
CHF = Swiss francs; **QALY** = quality-adjusted life year; **WTP** = willingness-to-pay.

8.5.2.3 Scenario analysis

Scenario analyses tested the impact of time horizon, discount rate, source of HSUV, duration of IVIG for patients requiring replacement therapy after tisa-cel, included cost components, and extrapolation approach adopted. Results for the comparison with a historical control are shown in ***Table 57***.

Table 57 Scenario analysis impacts on the ICER, axi-cel compared to historical control

Scenario	Incremental cost (CHF)	Incremental QALYs	ICER (CHF per QALY)	Difference from base
Base case	381,274	4.32	88,346	NA
Time horizon: 10 years	379,541	1.82	208,682	+136%
Time horizon: 20 years	379,859	3.09	123,071	+39%
Discount rate: 0%	384,390	6.85	56,120	-36%
Discount rate: 6%	380,008	2.99	127,136	+44%
Source of HSUV (Chen 2018)	381,274	4.40	86,581	-2%
Source of HSUV (Lin 2018)	381,274	4.15	91,801	+4%
Source of HSUV (Wang 2018)	381,274	3.65	104,555	+18%
Switch to PF HSUV beyond year 5 for all patients	381,274	4.31	88,430	+0.1%
Duration of IVIG: 3 years	396,811	4.32	91,946	+4%
Duration of IVIG: 40 years	507,593	4.32	117,616	+33%
Include monthly healthcare expenditure costs for patients post CAR T-cell therapy (lower) [A]	417,812	4.32	96,812	+10%
Include monthly healthcare expenditure costs for patients post CAR T-cell therapy (upper) [A]	500,546	4.32	115,983	+31%
Include terminal care costs [B]	376,629	4.32	87,270	-1%
SMR-adjusted mortality beyond year 5: axi-cel only	381,315	4.01	95,134	+8%
SMR-adjusted mortality beyond year 5: both arms	381,342	3.88	98,345	+11%
SMR-adjusted mortality beyond year 5: both arms *and* switch to PF HSUV beyond year 5 for all patients	381,342	3.80	100,440	+14%
Generalised gamma – axi-cel OS	381,872	3.53	108,096	+22%
Generalised gamma – historical control OS	381,255	5.04	75,632	-14%
Generalised gamma – both arms	381,853	4.26	89,680	+1.5%

Abbreviations:
axi-cel = axicabtagene ciloleucel, **CHF** = Swiss franc, **HSUV** = health state utility value, **ICER** = incremental cost-effectiveness ratio, **IVIG** = intravenous immunoglobulin, **OS** = overall survival, **QALY** = quality-adjusted life year, **SMR** = standard mortality rate.
Notes:
[A] In these scenarios, monthly costs of care were included for the first 2 years after CAR T-cell therapy, based on the mean monthly post-infusion costs reported in a real-world expenditures study from Switzerland.[272] Across the scenarios, 90% of the reported post-infusion mean monthly costs (CHF5,068 and CHF11,342) were included, considering that 10% of real-world health care expenditure is caused by non-disease-specific services. Modelled costs for IVIG and the monthly cost of progression in the first 2 years were excluded.
[B] In this scenario, mean healthcare expenditure in the last 30 days of life reported in a real-world expenditures study from Switzerland (CHF29,193)[272] were applied as a one-off cost upon death in the model, across both treatment arms.

Again, the time horizon and discount rate demonstrated large impacts on the ICER, indicating that the benefit of axi-cel on survival outcomes accumulated through extrapolation over a lifetime horizon is a key driver of the ICER estimate.

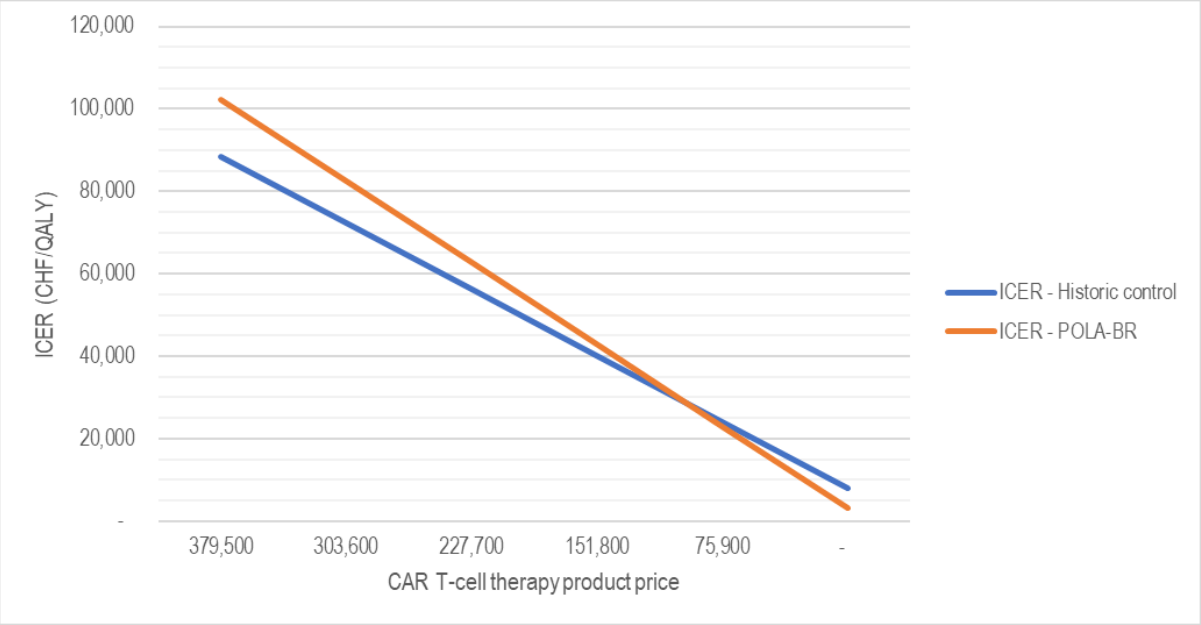
Scenarios including IVIG management costs over a patient's lifetime (40 years) or including mean monthly post-infusion costs for the first 2 years post-infusion had a moderate impact on the ICER estimate. Scenario analyses suggest the impact of CAR T-cell therapy treatment on the need for subsequent therapies and/or ongoing AE management strategies, have a moderate impact on treatment cost-effectiveness. A retrospective insurance claims data analysis of Swiss patients treated with CAR T-cell therapy reported high mean post-infusion health expenditure over 2 years post-infusion (noting—

as discussed by study authors—these findings [which include total healthcare expenditure] are not directly comparable to calculations made in cost-effectiveness studies, which focus on treatment-related costs for a specific disease).[272]

8.5.2.4 Sensitivity analysis of CAR T-cell therapy product price

Results of the scenario analysis of CAR T-cell therapy product price are displayed in ***Figure 91***.

Figure 91 ICER as a function of CAR T-cell therapy product price, axi-cel for patients with r/r LBCL



Abbreviations:
CAR = chimeric antigen receptor, **CHF** = Swiss franc, **ICER** = incremental cost effectiveness ratio, **QALY** = quality-adjusted life year

8.5.3 Tisa-cel for LBCL

One directly applicable study assessing the cost-effectiveness of tisa-cel in adults with r/r DLBCL was identified (see ***Section 8.1.2***).[1] Key economic findings are reported narratively followed by results of economic modelling conducted for the current HTA.

Base case results for the modelling performed for this HTA are presented for tisa-cel relative to historical control and POLA-BR. Subsequent SCT use was not explicitly modelled (no cost or disutilities for SCT were included in the LBCL model). Results are based on naïve treatment comparisons and should be interpreted in view of this limitation. Sensitivity analyses were conducted on the comparison of tisa-cel to a historical control.

8.5.3.1 Literature findings

Moradi-Lakeh 2021 presented an economic evaluation of tisa-cel compared to salvage chemotherapy from the perspective of the Swiss mandatory health insurance system (societal perspective in sensitivity analysis).[1] The publication reported an incremental cost for tisa-cel compared to salvage chemotherapy of CHF255,835 (2023 CHF254,489), incremental effects of 2.63 LYs and 2.26 QALYS, and an ICER of CHF113,179 (2023 CHF112,584). Start age, discount rate, treatment costs for tisa-cel, and the inclusion of productivity gain were shown to have the biggest impact on the ICER in one-way DSA. PSA suggested tisa-cel to have 35% (approximate) and 86.6% probabilities of being cost-effective at WTP thresholds of CHF100,000 and CHF150,000 per QALY, respectively.

8.5.3.2 ICER

Incremental cost-effectiveness of tisa-cel relative to each comparator for the management of patients with r/r DLBCL in the third-line setting over a lifetime horizon (44-year time horizon) is presented in ***Table 58***. Findings of the present evaluation indicate a slightly higher ICER (CHF157,437) than does the existing economic evidence for tisa-cel relative to a historical salvage chemotherapy control (CHF129,840 per QALY). Economic outcomes appear less favourable for tisa-cel relative to the alternative comparator considered in the current analysis (CHF157,437 per QALY compared with POLA-BR).

Table 58 Lifetime extrapolated ICER of tisa-cel for the treatment of r/r DLBCL

	Tisa-cel	Historical control	POLA-BR
Expected cost per patient (CHF)	455,611	78,566	102,800
Incremental cost (CHF)	NA	377,045	352,811
Expected LYs per patient	6.44	2.86	3.85
Incremental LYs	NA	3.58	2.59
Expected QALYs per patient	5.10	2.20	2.86
Incremental QALYs	NA	2.90	2.24
ICER (cost per QALY gained)	NA	**129,840**	**157,437**

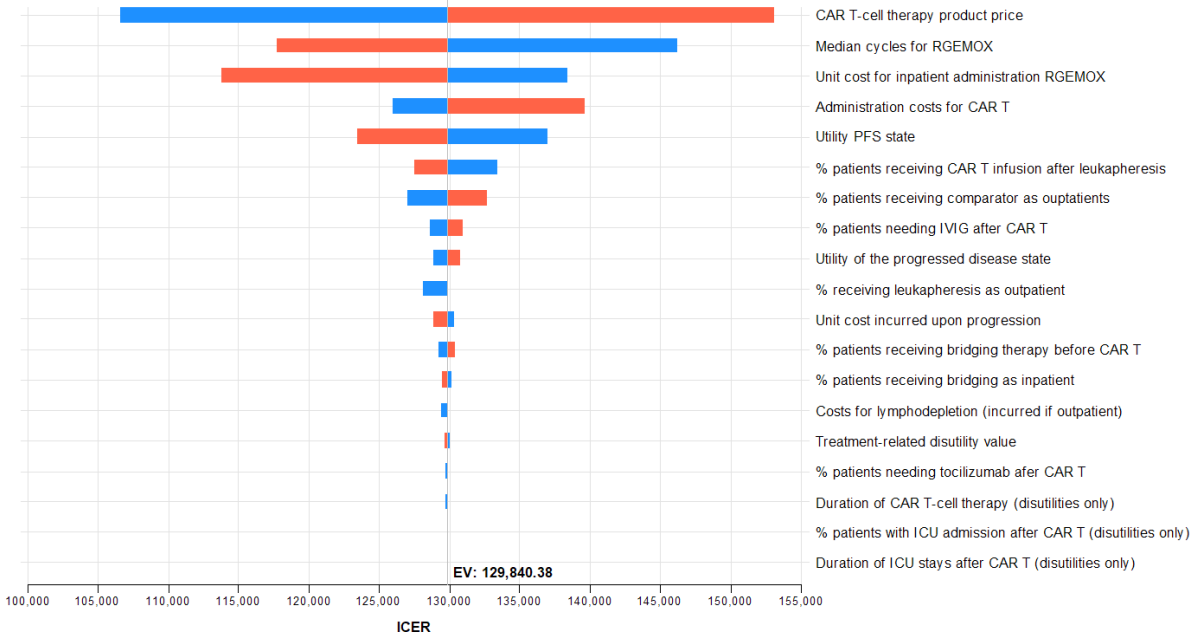
Abbreviations:
CHF = Swiss franc, **DLBCL** = diffuse large B-cell lymphoma, **ICER** = incremental cost-effectiveness ratio, **LY** = life year, **POLA-BR** = polatuzumab, bendamustine and rituximab**, QALY** = quality-adjusted life year, **tisa-cel** = tisagenlecleucel.

8.5.3.3 Univariate sensitivity analysis

Figure 92 displays the impact of uncertainty in cost, utility and proportion inputs on the ICERs of tisa-cel relative to a historical control. CAR T product price (CHF370,755 ±20%), assumed duration of comparator treatment, and hospitalisation costs for the administration of CAR T-cell therapy or the comparator, demonstrated the greatest impact. Across uncertainty ranges for the biggest driver (CAR T-cell therapy product price), the ICER ranged from CHF106,604 to CHF153,077.

Additional uncertainties introduced by modelling assumptions, including extrapolation assumptions, are discussed in ***Section 8.5.3.5***.

Figure 92 Tornado diagram of uncertainty in parameter values, tisa-cel compared to historical control for DLBCL



Abbreviations:
CAR T = chimeric antigen receptor T-cell therapy, **DLBCL** = diffuse large B-cell lymphoma, **EV** = expected value, **ICER** = incremental cost-effectiveness ratio, **ICU** = intensive care unit, **IVIG** = intravenous immunoglobulin, **PFS** = progression free survival, **RGEMOX** = rituximab, gemcitabine, oxaliplatin.

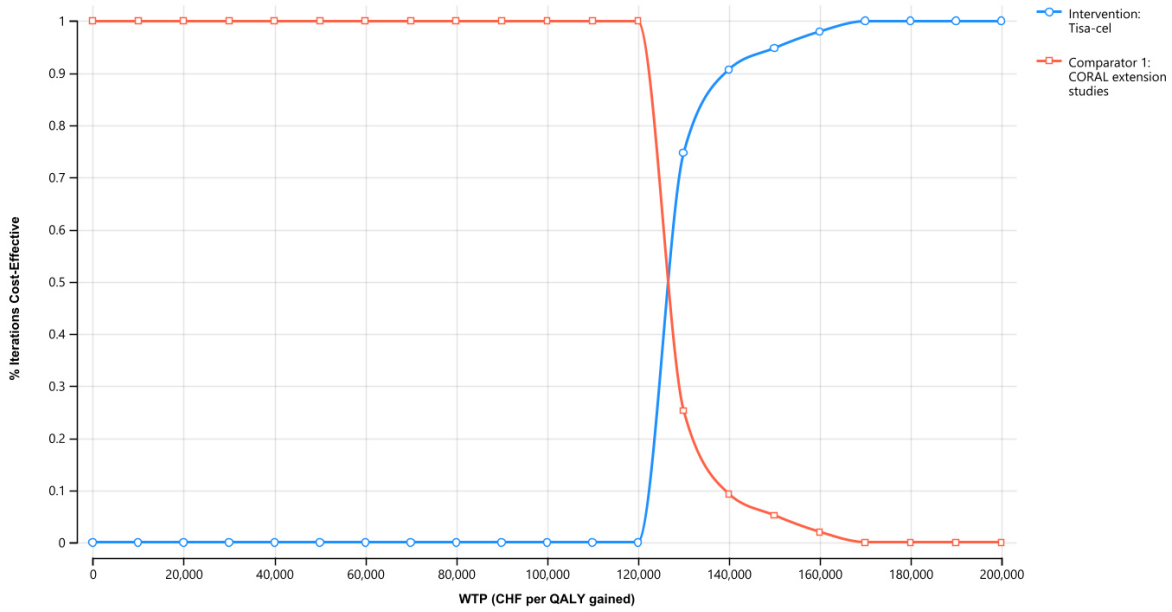
8.5.3.4 Probabilistic sensitivity analysis

PSA explored the combined uncertainty across cost, utility and patient percentage inputs. Note that uncertainty introduced through methodological assumptions relating to the time horizon, discount rate, source of HSUV, duration of IVIG for patients requiring replacement therapy after tisa-cel, and extrapolation approach adopted is not reflected in the PSA results. These were explored through scenario analysis (***Section 8.5.3.5***).

A mean expected ICER of CHF130,157 per QALY gained (95% CI from PSA: CHF126,028 to CHF157,836) was estimated. The CEAC is presented in ***Figure 93***. When considering WTP thresholds

of CHF50,000, CHF100,000 and CHF150,000, tisa-cel had probabilities of cost-effectiveness of 0.0%, 0.0% and 94.8%, respectively, compared to the historical control.

Figure 93 Cost-effectiveness acceptability curve, tisa-cel compared to historical control for DLBCL



Abbreviations:
CHF = Swiss francs; **QALY** = quality-adjusted life year; **WTP** = willingness-to-pay.

8.5.3.5 Scenario analysis

Scenario analyses tested the impact of time horizon, discount rate, source of HSUV, duration of IVIG for patients requiring replacement therapy after tisa-cel, included cost components, and extrapolation approach adopted. Results for the comparison with a historical control are shown in ***Table 59***. Again, time horizon and discount rate demonstrated the largest impact on the ICER. Inclusion of additional longer-term costs post infusion (i.e. monthly IVIG for 40 years or additional mean monthly healthcare costs for 2 years post-infusion), and one-way changes in the selection of extrapolation approach for OS demonstrated moderate impacts.

Table 59 Scenario analysis impacts on the ICER, tisa-cel compared to historical control for the treatment of r/r DLBCL

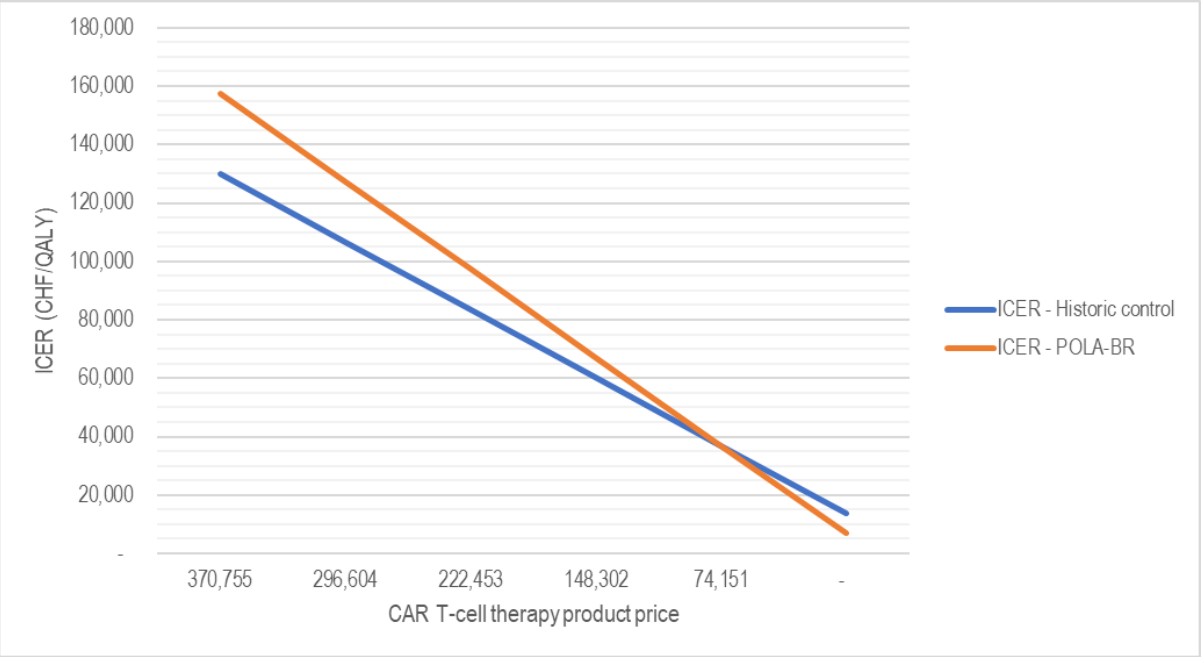
Scenario	Incremental cost (CHF)	Incremental QALYs	ICER (CHF per QALY)	Difference from base
Base case	377,045	2.90	129,840	NA
Time horizon: 10 years	375,641	1.22	309,125	+138%
Time horizon: 20 years	375,919	2.04	184,211	+42%
Discount rate: 0%	379,597	4.72	80,451	-38%
Discount rate: 6%	376,107	1.99	189,244	+46%
Source of HSUVs (Chen 2018)	377,045	3.02	124,819	-4%
Source of HSUVs (Wang 2018)	377,045	2.79	135,129	+4%
Source of HSUVs (Lin 2018)	377,045	2.46	153,428	+18%
Switch to PF HSUV beyond year 5 for all patients	377,045	2.86	131,847	+2%
Duration of IVIG: 3 years	395,250	2.90	136,110	+5%
Duration of IVIG: 40 years	514,599	2.90	177,209	+36%
Include monthly healthcare expenditure costs for patients post CAR T (lower) [A]	401,042	2.90	138,104	+6%
Include monthly healthcare expenditure costs for patients post CAR T (upper) [A]	473,222	2.90	162,960	+26%
Include terminal care costs [B]	373,959	2.90	128,778	-1%
SMR-adjusted mortality beyond year 5: tisa-cel only	377,185	2.96	127,562	-2%
SMR-adjusted mortality beyond year 5: both arms	377,287	2.70	139,945	+8%
SMR-adjusted mortality beyond year 5: both arms *and* switch to PF HSUV beyond year 5 for all patients	377,287	2.67	141,207	+9%
Generalised gamma – tisa-cel OS	377,921	2.24	168,904	+30%
Generalised gamma – historical control OS	376,564	3.70	101,664	-22%
Generalised gamma – both arms	377,440	3.04	124,256	-4.3%

Abbreviations:
CAR T = chimeric antigen receptor T-cell therapy, **CHF** = Swiss franc, **HSUV** = health state utility value, **ICER** = incremental cost-effectiveness ratio, **IVIG** = intravenous immunoglobulin, **OS** = overall survival, **QALY** = quality-adjusted life year, **SMR** = standard mortality rate.
Notes:
[A] In these scenarios, monthly costs of care were included for the first 2 years after CAR T-cell therapy, based on the mean monthly post-infusion costs reported in a real-world expenditures study from Switzerland.[272] Across the scenarios, 90% of the reported post-infusion mean monthly costs (CHF5,068 and CHF11,342) were included, considering that 10% of real-world health care expenditure is caused by non-disease-specific services. Modelled costs for IVIG and the monthly cost of progression in the first 2 years were excluded.
[B] In this scenario, mean healthcare expenditure in the last 30-days of life reported in a real-world expenditures study from Switzerland (CHF29,193)[272] were applied as a one-off cost upon death in the model, across both treatment arms.

8.5.3.6 Sensitivity analysis on CAR T product price

Additional sensitivity analyses of the tisa-cel product price were undertaken across comparisons with a historical control. Tariffs for the CAR T-cell therapy product inpatient surcharge codes are not published. A base case cost of CHF370,755 was assumed for tisa-cel. Reductions of 10–50% from the assumed base price were considered in 10% increments. ICER outcomes as a function of CAR T product price are shown in ***Figure 94***.

Figure 94 ICER as a function of CAR T product price, tisa-cel for DLBCL analysis



Abbreviations:
CAR T = chimeric antigen receptor T-cell, **CHF** = Swiss franc, **ICER** = incremental cost effectiveness ratio, **QALY** = quality-adjusted life year.

8.6 Results: budget impact

Annual numbers of axi-cel or tisa-cel infusions in Switzerland in the target populations were estimated using data from the SBST registry. Predicted utilisation was extrapolated to 2027 based on these data combined with epidemiological estimates. The potential budget impact of axi-cel and tisa-cel in the target populations over the period 2023–2027 was estimated—assuming continued listing in the Health Insurance Benefits Ordinance.

8.6.1 Number of CAR T-cell therapy procedures for target population

8.6.1.1 Current Swiss registry data for CAR T-cell therapy

Annually collected data for axi-cel and tisa-cel were extracted from the SBST registry. This dataset contains pre-, intra- and post-infusion information. The number of requests for CAR T-cell therapy, infusions and patients under evaluation according to the SBST registry over the period 2019–2021 are shown in ***Table 60***.

Table 60 CAR T-cell therapy in Swiss registry, 2019–2021

	Patients in SBST registry (2019-2021)[1]	Total slot requests (2019-2021)[2]	Infusion after slot request (%)
Patients with r/r DLBCL/PMBCL who received axi-cel	59	163	89.6%
Patients with r/r DLBCL who received tisa-cel	87		
Patients with r/r B-ALL who received tisa-cel	20	20	100%

Abbreviations:
B-ALL = B-cell acute lymphoblastic lymphoma, **CAR** = chimeric antigen receptor, **DLBCL** = diffuse large B-cell lymphoma, KLV = Krankenpflege-Leistungsverordnung (Health Insurance Benefits Ordinance), **PMBCL** = primary mediastinal B-cell lymphoma, **r/r** = relapsed or refractory; SBST = Swiss Blood Stem Cell Transplant.
Source:
SBST Registry data provided by the FOPH.

Overall infusion numbers for CAR T-cell therapy (i.e. axi-cel or tisa-cel) have been increasing since 2019 (***Table 61***).

Table 61 CAR T cell therapy recipient numbers by year, 2019-2021

	2019	2020	2021
Patients with r/r DLBCL/PMBCL who received axi-cel [a]	1	23	26
Patients with r/r DLBCL who received tisa-cel [a]	23	25	23
Patients with r/r B-ALL who received tisa-cel [a]	3	4	8

Abbreviations:
B-ALL = B-cell acute lymphoblastic lymphoma, **DLBCL** = diffuse large B-cell lymphoma, **PMBCL** = primary mediastinal B-cell lymphoma, **r/r** = relapsed or refractory; SBST = Swiss Blood Stem Cell Transplant.
Notes:
These data are limited to patients for whom ≥2 prior lines of therapy are recorded in the registry. However, according to SBST registry advice, all patients (i.e. 59, 87 and 20) as reported in ***Table 60*** can be regarded as having had ≥2 prior lines of therapy (meeting the KLV indication for therapy). The above figures (***Table 60***) are used in population projections. Numbers presented in this table are included only for the purposes of exploring trends in use over time.
[a] Patients included in the SBST registry with at least 2 prior lines of therapy recorded (refer to note above).

For patients with LBCL, there has been a significant annual escalation in the utilisation of axi-cel, while treatment with tisa-cel demonstrates relative stability over time without a specific trend. For patients with B-ALL, the yearly increasing trend between 2019 and 2021 was moderate (***Table 61***).

Total slot request data for 2019, 2020 and 2021 were not disclosed. Therefore, percentages of infusions from slot requests were unavailable for these years individually. Moreover, slot request numbers were presented for a combined DLBCL/PMBCL cohort, without stratification by type of CAR T product (***Table 60***).

[1] For 2019-2022, these figures were 100 (axi-cel in DLBCL/PMBCL), 110 (tisa-cel in DLBCL) and 26 (tisa-cel in B-ALL). It was hence estimated that 41, 23 and 6 patients, respectively, were treated in 2022 (difference between 2019-2021 and 2019-2022 figures).
[2] For 2019-2022, these figures were 240 (DLBCL/PMBCL) and 26 (B-ALL). It was hence estimated that there were 77 and 6 slot requests, respectively, in 2022 (difference between 2019-2021 and 2019-2022 figures).

8.6.1.2 Epidemiological estimation for CAR T use in Switzerland

To estimate the number of patients potentially eligible for axi-cel or tisa-cel within the target populations in Switzerland, an epidemiological approach was used, requiring the following estimates:

- population size of Switzerland
- incidence of DLBCL, PMBCL and B-ALL in the Swiss population
- proportion of patients with r/r disease
- step-by-step proportions of r/r patients eligible for CAR T-cell therapies (based on clinical management pathways of different indications).

In the context of this PICO, all indications have varying treatment pathways and response rates. Prevalent cases have a relatively more complex treatment history and less comparable treatment sequence. It is difficult to make appropriate assumptions about the proportion of CAR T-cell therapy candidates or the prior treatments and responses of these patients. Thus, this analysis exclusively considered annual incident case numbers (i.e. patients with newly diagnosed DLBCL, B-ALL or PMBCL). Prevalent cases (patients with established disease) were excluded from the calculation.

Epidemiological estimates were made for the period 2018–2022, and these historical estimates used to inform the number of potentially eligible patients over the assessment period (i.e. 2023–2027). Given similarities in treatment pathways between DLBCL and PMBCL, combined estimates across DLBCL and PMBCL were made.

Data sources for each of the parameters listed above and the estimated number of CAR T-cell therapy-eligible (i.e. axi-cel- or tisa-cel-eligible) patients in Switzerland within the target populations over the period 2018–2022 derived using the epidemiological approach, are provided in ***Table 62.*** Based on the calculations, it was estimated that approximately 209 patients with DLBCL/PMBCL in Switzerland were eligible for CAR T-cell therapy (i.e. axi-cel- or tisa-cel) in 2022, for example. This estimated number of patients indicated an upper limit. In practice, the actual number of patients receiving CAR T-cell therapy was typically equal to or lower than this estimate, especially considering the policy changes and regulatory updates for the relevant conditions since 2022 (details presented in ***Section 8.6.1.3***).

It was estimated that approximately 4 incident patients with B-ALL may be eligible for CAR T-cell therapy, annually (***Table 62***). In practice, the number of patients receiving CAR T-cell therapy annually was observed to be higher than this, highlighting uncertainty in the calculations. Data from the SBST registry were used as a starting point for the budget estimates.

Table 62 Epidemiologically estimated number of CAR T-eligible patients, 2018–2022

Parameter	2018	2019	2020	2021	2022	Data sources
Population of Switzerland at year end	8,544,527	8,606,033	8,670,300	8,738,791	8,815,400	Swiss population was 8,815,400 people on 31 December 2022, annual growth rate 0.9% Federal Statistical Office
DLBCL/PMBCL						
Number of Swiss patients newly diagnosed with DLBCL/PMBCL annually	675	680	685	690	696	Rate of DLBCL+PMBCL: 0.079 per 1,000. Informed by age-specific incidence rates from UK source (HMRN)[273]
Proportion of patients who will develop r/r disease after 1st-line treatment	33.3%	33.3%	33.3%	33.3%	33.3%	Friedberg 2011[274]
Proportion of patients with r/r disease eligible for SCT	50%	50%	50%	50%	50%	Gisselbrecht 2018[275]
Proportion of patients who respond to 2nd-line treatment and continue treatment with SCT	40%	40%	40%	40%	40%	Crump 2017[175]
Proportion of patients with disease relapse after SCT	50%	50%	50%	50%	50%	Crump 2017[175]
Proportion of patients who do not respond to 2nd-line treatment and move to 3rd-line	60%	60%	60%	60%	60%	Schuster 2019[147]
Number of DLBCL/PMBCL patients eligible for CAR T-cell therapy	202[A]	204	205	207	209	Includes patients eligible for CAR T-cell therapy following relapse after SCT and eligible for CAR T-cell therapy after 2nd-line therapy.
B-ALL						
Number of paediatric/young adult Swiss patients newly diagnosed with B-ALL annually	43	43	44	44	44	Rate of 0.02 per 1,000. Informed by age-specific incidence rates from UK source (HMRN)[273]
Proportion of patients who will develop r/r disease after first-line treatment	15%	15%	15%	15%	15%	Schrappe 2012[276], Bhojwani 2013[277], Hunger 2015[278], Stolpa 2022[279]
Proportion of patients with r/r disease eligible for SCT	50%	50%	50%	50%	50%	Nietfeld 2008[280]
Proportion of patients with disease relapse after 1st SCT	30%	30%	30%	30%	30%	Poon 2013[281], Crotta 2018[282]
Proportion of patients who respond to 2nd-line treatment and move on to 2nd SCT	17.3%	17.3%	17.3%	17.3%	17.3%	Crotta 2018[282]
Proportion of patients whose disease ultimately relapses after 2nd SCT	55%	55%	55%	55%	55%	Tallen 2010[283], Freyer 2011[283], Sellar 2018[284]

Parameter	2018	2019	2020	2021	2022	Data sources
Number of paediatric/young adult B-ALL patients eligible for CAR T-cell therapy	4[B]	4	4	4	4	Included number of patients needed to treat following relapse after 1st SCT and 2nd SCT, and number of SCT ineligible patients needed to treat following relapse after 1st SCT.

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CAR T**= chimeric antigen receptor T-cell, **DLBCL** = diffuse large B-cell lymphoma, **HMRN** = Haematological Malignancy Research Network, **PMBCL** = primary mediastinal B-cell lymphoma, **r/r** = relapsed or refractory, **SCT** = stem cell transplantation.
Notes:
A: Calculation: 202 = 675*33.3%*50%*40%*50% + 675*33.3%*50% + 675*33.3%*50%*60%
B: Calculation: 4 = 43*15%*50%*30% + 43*15%*50%*30%*17.3%*55% + 43*15%*50%

8.6.1.3 Projected number of CAR T-cell therapy procedures for target population

Extrapolated numbers of CAR T procedures for patients within target populations (DLBCL/PMBCL and B-ALL separately) over the period 2023–2027 are presented in ***Table 63***. Both were extrapolated using patient number estimates for 2022, derived from SBST registry data as a starting point.[3] For DLBCL/PMBCL, combined estimates of CAR T-cell therapy procedure numbers were made. Costing calculations were made based upon the relative use of axi-cel and tisa-cel as observed in the SBST registry for 2022.

DLBCL/PMBCL populations were extrapolated based on historical data of CAR T infusions in the SBST registry. Compared to epidemiological estimates, this approach captured a potential continued increasing trend of CAR T uptake among potentially eligible patients over future years. The chosen extrapolation approach was varied in scenario analysis. In Swiss practice, eligible patients and overall infusion numbers for CAR T-cell therapy (i.e. axi-cel- or tisa-cel) may be less than extrapolated. Uncertainties associated with this extrapolation have to be considered, including increasing the number of patients receiving CAR T-cell therapy in the second line and the introduction of a third CAR T-cell therapy product (Breyanzi®; i.e. lisocabtagene maraleucel) onto the market for lymphoma patients. B-ALL populations were extrapolated based on trends in growth in the eligible population (i.e. in the epidemiological estimates) (***Table 62***). In this population, extrapolation based on historical SBST registry data were not used, mainly due to varying and non-linear characteristics from 2019–2022. This meant it was hard to determine any trend in uptake among eligible patients. It was thus assumed that uptake among eligible patients would be relatively stable over future years. Extrapolated CAR T numbers do

[3] CAR T-cell therapy recipient numbers were available for the periods 2019-2021 (***Table 60***) and 2019-2022 (see footnotes to ***Table 60***). These estimates included patients who, according to the SBST registry, meet KLV criteria irrespective of the number of prior lines of therapy recorded in the registry. Difference between these 2 figures, for each treatment/indication, were estimated to determine the number of CAR T-cell therapy recipients in 2022.

not vary much across years (n=6, 2023; n=7, 2027) perhaps due to the relatively low incidence of the disease (***Table 63***). Moreover, only a proportion of patients with r/r disease may be eligible for CAR T-cell therapy.

Extrapolations were based on successfully treated patients (i.e. patients receiving CAR T-cell infusion) because annual data across the period 2019–2022 were available to inform future trends for CAR T-cell infusion numbers. Total slot request numbers were then back-calculated from extrapolated infusion numbers. Linear trend extrapolations of patients eligible for infusion were performed. It is acknowledged that this is a simplifying approach.

Table 63 Extrapolated CAR T-cell therapy numbers for patients within target population, 2023–2027

Parameter	2022	2023	2024	2025	2026	2027	Extrapolation
DLBCL/PMBCL							
Total number of patients eligible for infusion	64	77	89	101	113	125	Extrapolated based on trends in historical use of CAR T-cell infusions in SBST registry, 2019–2022
Total slot requests	77	92	107	121	136	150	Using the percentage of 83.1% in 2022 (i.e. assuming projected infusion numbers reflect 83.1% of all slot requests for the year)
B-ALL							
Total number of patients eligible for infusion	6	6	6	6	6	6	Extrapolated based on observed growth in epidemiological estimates, 2018–2022 (i.e. accounting for population growth only) (***Table 62***)
Total slot requests	6	6	6	6	6	6	Using the percentage of 100% in 2019–2022

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CAR** = chimeric antigen receptor, **DLBCL** = diffuse large B-cell lymphoma, **PMBCL** = primary mediastinal B-cell lymphoma.

8.6.2 Projected costs of CAR T procedures and comparators for target population

Projected CAR T-cell therapy costs and comparator costs were derived using the cost estimates described in ***Section 8.4.1***.

In both target populations, it was assumed that all patients submitting slot requests either underwent leukapheresis and bridging immunochemotherapy in the CAR T scenario, or received comparator management in the comparator scenario. However, costs associated with the remaining aspects of the CAR T treatment pathway (i.e. lymphodepleting chemotherapy, CAR T product price, hospital stay for CAR T infusion [including management of acute AEs], subsequent allogenic SCTs [B-ALL population only], and the management of longer-term AEs [i.e. ongoing IVIG]), were only calculated for patients who received an infusion. According to the SBST registry, the majority (n=26/30, 86.7%) of patients

submitting slot requests without infusion progressed quickly and died before planned infusion, so no additional treatment costs were considered.

Regarding the comparator therapies, an average cost across potential comparator regimens was derived. For r/r PMBCL only, pembrolizumab is reimbursed and will be given to patients who are fit enough (around 50%). SBST registry data for the period 2019-2021 indicates r/r PMBCL accounts for approximately 2.5% of the total DLBCL/PMBCL cohort.[4] Costs for pembrolizumab in 50% of PMBCL patients (approximately 1.2% of the total cohort) were included. For the remaining patients, an average cost across potential salvage chemotherapy regimens (i.e. R-GEMOX, bendamustine and rituximab, POLA-BR, tafasitamab and lenalidomide, GEMOX) was derived, with each regimen assumed to account for 20% of use. These comparators are applicable for patients with r/r DLBCL or r/r PMBCL. For the B-ALL population, blinatumomab and inotuzumab were each assumed to account for 50% of use.

In the target population of DLBCL/PMBCL, expected proportions of patients receiving axi-cel and tisa-cel were determined based on SBST registry data in 2022. Among 64 patients with DLBCL/PMBCL,[5] 41 (64%) received axi-cel, while 23 (36%) were treated with tisa-cel. The relative use of axi-cel and tisa-cel was assumed to remain consistent over the extrapolation period; however, there has been growth in the relative use of axi-cel over time in Switzerland (***Table 62***). The majority of inputs were estimated for the DLBCL/PMBCL population overall therefore this assumption is expected to have a minimal impact on budget impact projections (i.e. the assumption only affected the CAR T cell-therapy product cost assigned).

Project costs for CAR T-cell therapy over the period 2023–2027 are shown in ***Table 64***.

Table 64 Projected cost of CAR T-cell therapy in patients with r/r DLBCL/PMBCL, 2023–2027

Resource	Unit cost (CHF)	Proportion	2023	2024	2025	2026	2027
CAR T-cell therapy costs (CHF)							
No. of patients			77	89	101	113	125
Total slot requests (shown in integers)			92	107	121	136	150
Leukapheresis	24,293	100% of total slot requests	2,236,355	2,590,079	2,943,803	3,297,527	3,651,251
Bridging therapy	11,179	67% of total slot requests	686,064	794,579	903,094	1,011,609	1,120,123
Lymphodepleting chemotherapy	1,597 [A]	100% of infusions	122,194	141,521	160,849	180,176	199,503

[4] 3 of 121 patients with DLBCL/PMBCL included in the KLV analysis population
[5] Calculated as difference between 2019-2021 and 2019-2022 figures

Resource	Unit cost (CHF)	Proportion	2023	2024	2025	2026	2027
CAR T infusion, hospital episode	51,324 [B]	100% of infusions	3,926,283	4,547,303	5,168,323	5,789,343	6,410,363
CAR T product, tisa-cel	370,755	36% of infusions	10,192,866	11,805,071	13,417,276	15,029,481	16,641,686
CAR T product, axi-cel	379,500	64% of infusions	18,598,465	21,540,183	24,481,901	27,423,619	30,365,337
Longer-term IVIG	33,172 [C]	60% of infusions	1,530,986	1,773,141	2,015,297	2,257,453	2,499,609
Total cost of CAR T			37,293,213	43,191,878	49,090,543	54,989,208	60,887,873
Comparator therapy costs (CHF)							
R-GEMOX	60,038	19.8%	1,091,682	1,264,353	1,437,024	1,609,696	1,782,367
BR	36,037	19.8%	655,267	758,911	862,554	966,198	1,069,842
GEMOX	20,988	19.8%	381,622	441,984	502,345	562,706	623,067
POLA-BR	83,953	19.8%	1,526,536	1,767,988	2,009,440	2,250,892	2,492,344
Tafasitamab & lenalidomide	190,552	19.8%	3,464,863	4,012,900	4,560,937	5,108,974	5,657,011
Pembrolizumab	117,181	1.2%	133,728	154,880	176,032	197,184	218,336
Total average cost of comparators			7,253,699	8,401,016	9,548,333	10,695,650	11,842,967
Net cost of CAR T (CHF)			30,039,514	34,790,862	39,542,210	44,293,558	49,044,906

Abbreviations:
axi-cel = axicabtagene ciloleucel, **BR** = bendamustine and rituximab, **CAR T** = chimeric antigen receptor T-cell, **CHF** = Swiss franc, **DLBCL** = diffuse large B-cell lymphoma, **GEMOX** = gemcitabine and oxaliplatin, **IVIG** = intravenous immunoglobulin, **PMBCL** = primary mediastinal B-cell lymphoma, **POLA-BR** = polatuzumab, bendamustine and rituximab, **R-GEMOX** = rituximab, gemcitabine, and oxaliplatin, **r/r** = relapsed or refractory, **tisa-cel** = tisagenlecleucel.
Notes:
[A] Accounts for varying regimens across axi-cel and tisa-cel, weighted based on utilisation of axi-cel and tisa-cel per 2022 SBST registry estimates.
[B] Unit cost includes weighted average DRG cost for hospital episode (CHF49,551) and surcharge codes for tocilizumab use in 52.1% of patients (CHF1,773). According to SBST registry data (2019–2021), 63/121 treated DLBCL or PMBCL patients required tocilizumab.
[C] Accounts for monthly IVIG (CHF3,016 per month) for an assumed average duration of 11 months. The assumed average duration was based upon NICE TA567.[187] According to SBST registry data (2019–2021), 73/121 treated DLBCL or PMBCL patients required at least one course of IVIG substitution.

The annual cost of CAR T-cell therapy reflects the combined costs of both axi-cel and tisa-cel therapies. Annual costs were projected to range from CHF37.29 million in 2023 to CHF60.89 million in 2027 (***Table 65***). The annual cost of comparators is anticipated to range from CHF7.25 million in 2023 to CHF11.84 million in 2027 (***Table 65***).

Over the period 2023–2027, net costs for CAR T-cell therapy in patients with DLBCL or PMBCL were estimated to range from CHF30.04 million in 2023 to CHF49.04 million in 2027 (***Table 65***).

Table 65 Projected cost of CAR T-cell therapy in patients with r/r B-ALL, 2023–2027

Resource	Unit cost (CHF)	Proportion	2023	2024	2025	2026	2027
CAR T-cell therapy costs							
No. of patients			6	6	6	6	6
Total slot requests (shown in integers)			6	6	6	6	6
Leukapheresis	28,224	100% of total slot requests	170,301	171,258	172,214	173,171	174,128
Bridging therapy	12,495	86.7% of total slot requests [A]	65,366	65,733	66,101	66,468	66,835
Lymphodepleting chemotherapy	1,738	0% of infusions [B]	0	0	0	0	0
CAR T infusion, hospital episode	75,866 [C]	100% of infusions	457,769	460,341	462,913	465,485	468,057
CAR T product, tisa-cel	370,755	100% of infusions	2,237,099	2,249,667	2,262,236	2,274,804	2,287,373
Longer-term IVIG	15,118 [D]	91% of infusions	83,010	83,476	83,943	84,409	84,875
Subsequent allogenic SCT	167,879	36.8% of infusions	372,772	374,866	376,960	379,055	381,149
Total cost of CAR T			3,386,317	3,405,342	3,424,367	3,443,392	3,462,418
Comparator therapy costs							
Blinatumomab	80,609	50%	243,192	244,559	245,925	247,291	248,658
Inotuzumab	90,702	50%	273,642	275,179	276,717	278,254	279,792
Subsequent allogenic SCT	167,879	44.2% [E]	447,731	450,247	452,762	455,278	457,793
Total average cost of comparators			964,566	969,985	975,404	980,823	986,242
Net cost for CAR T			2,421,751	2,435,357	2,448,963	2,462,569	2,476,175

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CAR** = chimeric antigen receptor, **CHF** = Swiss franc, **IVIG** = intravenous immunoglobulin, **r/r** = relapsed or refractory, **SCT** = stem cell transplantation, **tisa-cel** = tisagenlecleucel.
Notes:
[A] SBST registry data for the period 2019–2021 indicates that 13 of 15 (86.7%) treated r/r B-ALL patients received bridging therapy.
[B] Assumed to occur in the inpatient setting for paediatric patients in the base case.
[C] Unit cost includes weighted average DRG cost for hospital episode (CHF75,705) and surcharge codes for tocilizumab use in 7% of patients (CHF159). According to SBST registry data (2019–2021), 1/15 (7%) of treated r/r B-ALL patients required tocilizumab.
[D] Accounts for monthly IVIG (CHF2,268 per month) for an assumed average duration of 200 days across 91% of infused patients, per ELIANA trial results.[2]
[E] Average subsequent SCT rates across 2 blinatumomab studies (range 35.7–52.7%; ***Section 8.4.1.2***).[178,249] A retrospective study of inotuzumab by compassionate use (n=51) and 2 phase II trials indicate subsequent SCT rates of 41.2%, 43.8% and 51.8%, falling within range of the blinatumomab input.[250,251,285]

For the B-ALL target population, annual cost of CAR T-cell therapy is expected to range from CHF3.39 million in 2023 to CHF3.46 million in 2027, while the cost of comparators ranges from CHF0.96 million in 2023 to CHF0.99 million in 2027 (***Table 65***). Over the 5-year period, net healthcare costs are predicted to range from CHF2.42 million in 2023 to CHF2.48 million in 2027 (***Table 65***).

8.6.3 Uncertainty analyses

Thirteen scenarios for the DLBCL/PMBCL population and 5 scenarios for the B-ALL population that considered uncertainties among the key assumptions or data inputs were considered, including estimated annual numbers of eligible patients, assumed growth rates in patient numbers, different combinations of comparator regimens, and CAR T-cell therapy procedure costs. Uncertainty values and corresponding results are provided in ***Table 66***, ***Table 67*** and ***Table 68***. The number of CAR T infusions and slot requests is reported where applicable.

Overall, anticipated net costs for DLBCL/PMBCL were estimated to range between CHF28.27 million (n=72 and n=87) and CHF85.12 million (n=217 and n=261) in 2027; anticipated net costs for B-ALL were estimated to range between CHF1.84 million (n=5 and n=5) and CHF2.52 million (n= 6 and n=6) in 2027. The estimated cost of CAR T ranged between CHF34.96 million (n=72 and n=82) and CHF105.67 million (n=217 and n=261) for DLBCL/PMBCL, and between CHF2.58 million (n=5 and n=5) and CHF3.51 million (n=6 and n=6) for B-ALL.

8.6.3.1 Uncertainty analyses in DLBCL/PMBCL population

Scenario 1: Assumed percentage of infusions from slot requests (87.5%)

In the base case analysis, the annual number of slot requests was calculated based on the rate of 83.1% in 2022 (used as the basis for future extrapolations). This ensures that the estimate is grounded in the most recent data available, since both starting numbers (i.e. total number of patients eligible for infusion and total slot requests) align with data from the SBST registry. However, in this scenario, the rate of 87.5% from 2019–2022—representing an average rate over a broader time span—was used instead. When the assumed percentage of infusions from slot requests increased to 87.5%, the estimated cost of CAR T and the net cost was CHF60.65 million and CHF49.40 million, respectively, in 2027 (n=125 and n=143).

Scenario 2: Assumed growth rate from epidemiological approach

The growth rate in CAR T infusion numbers was assumed based on recent utilisation trends; however, it is uncertain how closely future trends will align with historical trends. In this scenario, the possibility was considered that future growth in the uptake of CAR T utilisation could be slower than recent trends suggest. In this scenario, the assumed growth rate in infusion numbers was based on growth in the epidemiological estimates (i.e. population growth only). Under this scenario, the number of CAR T infusions and slot requests were 72 and 87, respectively, in 2027. The estimated cost of CAR T and net costs were CHF35.10 million and CHF28.27 million, respectively.

Scenario 3: Assumed percentage of infusions from slot requests (87.5%) and growth rate from epidemiological approach

In this scenario, 2 assumptions used in estimating the annual number of CAR T infusions and slot requests were altered: (1) growth rate based on epidemiological approach (i.e. Scenario 2), and (2) percentage of infusions from slot requests of 87.5% (Scenario 1). When both assumptions are altered simultaneously, the numbers of CAR T infusions and slot requests were 72 and 82, respectively, in 2027. The estimated cost of CAR T and net costs were CHF34.96 million and CHF28.47 million, respectively.

Scenario 4: All lymphodepleting chemotherapy provided as inpatient

In the base case analysis, the unit cost of lymphodepleting chemotherapy was estimated based on the assumption that all lymphodepleting chemotherapies are administered as outpatient services. However, this assumption is subject to uncertainty (i.e. lymphodepletion may be given in the inpatient setting prior to infusion). As previously mentioned, when lymphodepleting chemotherapy is provided in an inpatient setting, relevant cost is covered under the same Swiss DRG as for the CAR T infusion without a surcharge. The estimated cost of CAR T and net cost is CHF60.69 million and CHF48.85 million, respectively, in 2027 (n=125 and n=150).

Scenario 5 and 6: All bridging chemotherapy provided as inpatient or outpatient

In the base case, bridging chemotherapy was assumed to occur across both the inpatient and outpatient settings. Experts suggest that most bridging chemotherapy is administered as inpatient treatment, but some Swiss centres are switching to polatuzumab as a bridging therapy provided in an outpatient setting. Under scenarios assuming all bridging chemotherapy varies from 100% inpatient to 100% outpatient, the estimated cost of CAR T varied from CHF60.77 million to CHF61.12 million in 2027. The corresponding net costs varied between CHF48.93 million and CHF49.27 million (for both scenarios, n=125 and n=150).

Scenario 7: All Infusions of CAR T-cells have no/little ICU stay and no tocilizumab

DRG codes for CAR T infusion are classified based on different levels of care and treatment required, ranging from those with no or minimal need for ICU stay (Scenario 7) to the most challenging and severe cases of complications (Scenario 8). When all patients were assigned to the DRG code involving no or little ICU stay and no tocilizumab, the estimated cost of CAR T was CHF59.14 million and the estimated net cost was CHF47.30 million in 2027 (n=125 and n=150).

Scenario 8: All infusion of CAR T requires ICU stay and ~3 doses tocilizumab, and occasional ventilation

In this scenario, it was assumed that 100% of CAR T leads to SAEs or complications that demand extensive intervention and ICU monitoring. Considering that the cost of this DRG is the highest, this scenario can be considered as representing the upper bound of the analysis, given the uncertainty regarding the cost of CAR T administration. When all patients were assigned to the DRG code involving the most complexity and the most resources usage, estimated cost of CAR T and net cost was CHF65.01 million and CHF53.16 million, respectively, in 2027 (n=125 and n=150).

Scenario 9: Full uptake – assumed number of patients receiving CAR T using epidemiological estimates

Not all patients eligible for CAR T-cell therapy will receive infusions. This extreme scenario provided an estimation of the maximum number of patients receiving CAR T-cell therapy (n= 217 and n=261), by using the estimated number of patients from the epidemiological approach. The estimated cost of CAR T-cell therapy and net costs were CHF105.67 million and CHF85.12 million, respectively, in 2027.

Scenario 10: IVIG administration for patients who receive comparator therapy

IVIG is needed for some patients receiving comparator therapy, but information on the proportion of such patients is currently unavailable. The proportion of patients who received IVIG in the CAR T arm (60%) was directly utilised for the calculation. The estimated cost of CAR T and the net cost is CHF60.89 million and CHF46.05 million, respectively, in 2027 (n=125 and n=150).

Scenario 11, 12 and 13: Different combinations of comparator regimens

The comparator regimen cost per patient is highest for tafasitamab + lenalidomide (CHF190,552), and lowest for GEMOX (CHF20,988). It was assumed that no patient received tafasitamab + lenalidomide in scenario 11, and all patients received GEMOX in scenario 12. In scenario 13, both tafasitamab + lenalidomide and POLA-BR were assumed to be excluded because they can be provided in second-line treatment. For the 3 scenarios, the estimated cost of CAR T is CHF60.89 million in 2027. The net cost ranged from CHF53.21 million to CHF57.55 million (n=125 and n=150).

Table 66 Uncertainty analyses on projected net cost of CAR T-cell therapy vs comparators in DLBCL/PMBCL population

Scenario	2023	2024	2025	2026	2027
Scenario 1: Assumed percentage of infusions from slot requests (87.5%)					
CAR T infusions	77	89	101	113	125
Slot requests	87	101	115	129	143
CAR T costs (CHF)	37,146,257	43,021,678	48,897,099	54,772,520	60,647,941

Scenario	2023	2024	2025	2026	2027
Comparator costs (CHF)	6,888,941	7,978,565	9,068,188	10,157,811	11,247,435
Net cost (CHF)	30,257,316	35,043,113	39,828,911	44,614,709	49,400,506
Scenario 2: Assumed growth rate from epidemiological approach					
CAR T infusions	66	67	69	70	72
Slot requests	79	81	83	85	87
CAR T costs (CHF)	31,978,759	32,757,968	33,537,177	34,316,386	35,095,594
Comparator costs (CHF)	6,220,013	6,371,573	6,523,133	6,674,692	6,826,252
Net cost (CHF)	25,758,746	26,386,395	27,014,044	27,641,693	28,269,343
Scenario 3: Assumed percentage of infusions from slot requests (87.5%) and growth rate from epidemiological approach					
CAR T infusions	66	67	69	70	72
Slot requests	75	77	79	80	82
CAR T costs (CHF)	31,852,745	32,628,884	33,405,022	34,181,160	34,957,298
Comparator costs (CHF)	5,907,236	6,051,174	6,195,112	6,339,051	6,482,989
Net cost (CHF)	25,945,510	26,577,710	27,209,910	27,842,109	28,474,309
Scenario 4: All lymphodepleting chemotherapy provided as inpatient					
CAR T infusions	77	89	101	113	125
Slot requests	92	107	121	136	150
CAR T costs (CHF)	37,171,019	43,050,356	48,929,694	54,809,032	60,688,369
Comparator costs (CHF)	7,253,699	8,401,016	9,548,333	10,695,650	11,842,967
Net cost (CHF)	29,917,320	34,649,341	39,381,361	44,113,382	48,845,403
Scenario 5: All bridging chemotherapy provided as inpatient					
CAR T infusions	77	89	101	113	125
Slot requests	92	107	121	136	150
CAR T costs (CHF)	37,222,891	43,110,434	48,997,976	54,885,518	60,773,061
Comparator costs (CHF)	7,253,699	8,401,016	9,548,333	10,695,650	11,842,967
Net cost (CHF)	29,969,193	34,709,418	39,449,643	44,189,869	48,930,094
Scenario 6: All bridging chemotherapy provided as outpatient					
CAR T infusions	77	89	101	113	125
Slot requests	92	107	121	136	150
CAR T costs (CHF)	37,433,855	43,354,766	49,275,676	55,196,587	61,117,497
Comparator costs (CHF)	7,253,699	8,401,016	9,548,333	10,695,650	11,842,967
Net cost (CHF)	30,180,157	34,953,750	39,727,344	44,500,937	49,274,530
Scenario 7: All infusion of CAR T has no/little ICU stay and no tocilizumab					
CAR T infusions	77	89	101	113	125
Slot requests	92	107	121	136	150
CAR T costs (CHF)	36,223,286	41,952,721	47,682,156	53,411,591	59,141,025
Comparator costs (CHF)	7,253,699	8,401,016	9,548,333	10,695,650	11,842,967
Net cost (CHF)	28,969,588	33,551,705	38,133,823	42,715,941	47,298,059
Scenario 8: All infusion of CAR T requires ICU stay and ~3 doses tocilizumab, and occasional ventilation					
CAR T infusions	77	89	101	113	125
Slot requests	92	107	121	136	150
CAR T costs (CHF)	39,816,363	46,114,114	52,411,866	58,709,617	65,007,369

Scenario	2023	2024	2025	2026	2027
Comparator costs (CHF)	7,253,699	8,401,016	9,548,333	10,695,650	11,842,967
Net cost (CHF)	32,562,664	37,713,099	42,863,533	48,013,968	53,164,402
Scenario 9: Full uptake – assumed number of patients receiving CAR T using epidemiological estimates					
CAR T infusions	210	212	214	215	217
Slot requests	253	255	257	259	261
CAR T costs (CHF)	102,555,080	103,334,296	104,113,512	104,892,728	105,671,944
Comparator costs (CHF)	19,947,427	20,098,988	20,250,549	20,402,110	20,553,671
Net cost (CHF)	82,607,653	83,235,308	83,862,963	84,490,618	85,118,273
Scenario 10: IVIG administration for patients who receive comparator therapy (60% of total slot requests)					
CAR T infusions	77	89	101	113	125
Slot requests	92	107	121	136	150
CAR T costs (CHF)	37,293,213	43,191,878	49,090,543	54,989,208	60,887,873
Comparator costs (CHF)	9,085,945	10,523,068	11,960,191	13,397,315	14,834,438
Net cost (CHF)	28,207,268	32,668,810	37,130,351	41,591,893	46,053,435
Scenario 11: Different combinations of comparator regimens, omitting tafasitamaib & lenalidomide for patients with DLBCL (24.7% each for other 4 regimens)					
CAR T infusions	77	89	101	113	125
Slot requests	92	107	121	136	150
CAR T costs (CHF)	37,293,213	43,191,878	49,090,543	54,989,208	60,887,873
Comparator costs (CHF)	4,702,613	5,446,425	6,190,236	6,934,048	7,677,860
Net cost (CHF)	32,590,600	37,745,453	42,900,306	48,055,159	53,210,012
Scenario 12: Different combinations of comparator regimens, all patients with DLBCL (98.8%) receive GEMOX comparator therapy					
CAR T infusions	77	89	101	113	125
Slot requests	92	107	121	136	150
CAR T costs (CHF)	37,293,213	43,191,878	49,090,543	54,989,208	60,887,873
Comparator costs (CHF)	2,041,840	2,364,798	2,687,756	3,010,714	3,333,671
Net cost (CHF)	35,251,372	40,827,080	46,402,787	51,978,494	57,554,201
Scenario 13: Different combinations of comparator regimens, taken out tafasitamaib & lenalidomide and POLA-BR for patients with DLBCL (32.9% each for other 3 regimens)					
CAR T infusions	77	89	101	113	125
Slot requests	92	107	121	136	150
CAR T costs (CHF)	37,293,213	43,191,878	49,090,543	54,989,208	60,887,873
Comparator costs (CHF)	3,681,348	4,263,626	4,845,905	5,428,183	6,010,462
Net cost (CHF)	33,611,865	38,928,252	44,244,638	49,561,025	54,877,411

Abbreviations:
CAR = chimeric antigen receptor, **CHF** = Swiss franc, **DLBCL** = diffuse large B-cell lymphoma, **GEMOX** = gemcitabine and oxaliplatin, **ICU** = intensive care unit, **IVIG** = intravenous immunoglobulin, **PMBCL** = primary mediastinal B-cell lymphoma, **POLA-BR** = polatuzumab, bendamustine and rituximab.

8.6.3.2 Uncertainty analyses in B-ALL population

Scenario 1: Assumed number of patients potentially eligible for CAR T using epidemiological estimates

In the BIA base case estimates, the utilisation data for 2022 in the SBST registry were used as the basis for extrapolations, while the assumed growth in utilisation was based on trends observed in the epidemiological estimates (i.e. population growth only). By using the estimated number of patients from the epidemiological approach in this scenario an alternate estimate was provided. The estimated costs of CAR T-cell therapy and net costs were CHF2.58 million and CHF1.84 million, respectively, in 2027 (n= 5).

Scenario 2: All lymphodepleting chemotherapy provided as outpatient

As previously discussed in the sensitivity analysis for scenario 4 within the DLBCL/PMBCL population, when lymphodepleting chemotherapy is provided as inpatient treatment, relevant cost is covered under the same Swiss DRG as for the CAR T-cell infusion without a surcharge. In this scenario, when lymphodepleting chemotherapy is provided as an outpatient treatment, an outpatient surcharge has to be considered. The estimated cost of CAR T and net cost is CHF3.47 million and CHF2.49 million, respectively, in 2027 (n= 6).

Scenario 3: All Infusion of CAR T has no/little ICU stay and no tocilizumab

As for the sensitivity analysis for scenario 7 in the DLBCL/PMBCL population, uncertainties arise when allocating patients to specific DRG codes, given that these codes take into account the complexity and resource needs of individual patients. When 100% of the population required no or little ICU stay and no tocilizumab, the estimated cost of CAR T and net cost is CHF3.22 million and CHF2.24 million, respectively, in 2027 (n= 6).

Scenario 4: All infusion of CAR T requires ICU stay and ~3 doses tocilizumab, and occasional ventilation

Similar to the sensitivity analysis for scenario 8 in the LBCL population, when assuming all patients developed SAEs that require extensive intervention and ICU monitoring, estimated cost of CAR T and net cost is CHF3.51 million and CHF2.52 million, respectively, in 2027 (n= 6).

Scenario 5: Assumed number of patients receiving CAR T-cell therapy annually, upper bound

In the BIA base case estimates, the utilisation data for 2022 in the SBST registry were used as the basis for extrapolations. However, utilisation data for 2022 were below 2021 figures (n=6 vs n=8). An upper bound analysis was undertaken, setting the number of CAR T-cell infusions for 2023 to 10 (20% increase

on the observed 2021 figure of 8). Estimated cost of CAR T and net cost is CHF5.67 million and CHF4.07 million, respectively, in 2027 (n= 10).

Table 67 Uncertainty analyses on projected net cost of CAR T vs comparators in B-ALL population

	Scenario	2023	2024	2025	2026	2027
	Scenario 1: Assumed number of patients potentially eligible for CAR T using epidemiological estimates					
A	CAR T infusions	4	4	5	5	5
B	Slot requests	4	4	5	5	5
C	CAR T costs (CHF)	2,501,966	2,520,976	2,539,986	2,558,996	2,578,006
D	Comparator costs (CHF)	712,665	718,080	723,495	728,910	734,325
E	Net cost (CHF)	1,789,301	1,802,896	1,816,491	1,830,086	1,843,681
	Scenario 2: All lymphodepleting chemotherapy provided as outpatient					
F	CAR T infusions	6	6	6	6	6
G	Slot requests	6	6	6	6	6
H	CAR T costs (CHF)	3,396,805	3,415,889	3,434,973	3,454,057	3,473,141
I	Comparator costs (CHF)	964,566	969,985	975,404	980,823	986,242
J	Net cost (CHF)	2,432,239	2,445,904	2,459,569	2,473,234	2,486,899
	Scenario 3: All infusion of CAR T has no/little ICU stay and no tocilizumab					
K	CAR T infusions	6	6	6	6	6
L	Slot requests	6	6	6	6	6
M	CAR T costs (CHF)	3,153,841	3,171,560	3,189,279	3,206,998	3,224,717
N	Comparator costs (CHF)	964,566	969,985	975,404	980,823	986,242
O	Net cost (CHF)	2,189,275	2,201,575	2,213,875	2,226,175	2,238,475
	Scenario 4: All infusion of CAR T requires ICU stay and ~3 doses tocilizumab, and occasional ventilation					
P	CAR T infusions	6	6	6	6	6
Q	Slot requests	6	6	6	6	6
R	CAR T costs (CHF)	3,430,397	3,449,670	3,468,943	3,488,216	3,507,488
S	Comparator costs (CHF)	964,566	969,985	975,404	980,823	986,242
T	Net cost (CHF)	2,465,831	2,479,685	2,493,539	2,507,392	2,521,246
	Scenario 5: Number of patients receiving CAR T annually, upper bound					
U	CAR T infusions	10	10	10	10	10
V	Slot requests	10	10	10	10	10
W	CAR T costs (CHF)	5,612,153	5,631,178	5,650,203	5,669,228	5,688,253
X	Comparator costs (CHF)	1,598,577	1,603,996	1,609,416	1,614,835	1,620,254
Y	Net cost (CHF)	4,013,575	4,027,181	4,040,787	4,054,393	4,067,999

Abbreviations:
B-ALL = B-cell acute lymphoblastic lymphoma, **CAR** = chimeric antigen receptor, **CHF** = Swiss franc, **ICU** = intensive care unit.

8.6.3.3 Scenario analysis: CAR T product price

Uncertainty surrounds the current and future pricing of CAR T products. Surcharge codes apply but the tariffs for these codes are unpublished, so scenarios focusing on the product price were conducted. Base case costs of CHF379,500 and CHF370,755 were assumed for axi-cel and tisa-cel, respectively. A sensitivity analysis where the assumed product price for CAR T-cell therapies was reduced between

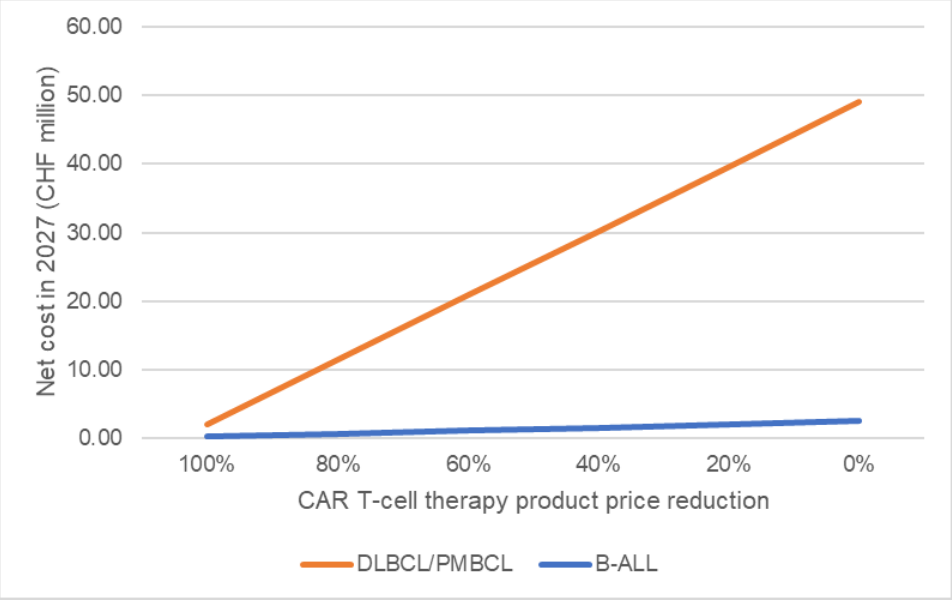
0–100% (in 20% increments) from the assumed base case price is outlined in ***Table 68*** and ***Figure 95***. When the assumed cost of the CAR T product was reduced by 20% to 100% from the assumed base case price, estimated net costs varied from CHF39.64 million to CHF2.04 million for DLBCL/PMBCL, and from CHF2.02 million to CHF0.19 million for B-ALL in 2027.

Table 68 Scenario analysis on 20–100% price reduction of CAR T product cost (net cost)

	2023 (CHF)	2024 (CHF)	2025 (CHF)	2026 (CHF)	2027 (CHF)
DLBCL/PMBCL					
Current price	30,039,514	34,790,862	39,542,210	44,293,558	49,044,906
20% price reduction	24,281,248	28,121,811	31,962,375	35,802,938	39,643,502
40% price reduction	18,522,982	21,452,761	24,382,539	27,312,318	30,242,097
60% price reduction	12,764,716	14,783,710	16,802,704	18,821,698	20,840,693
80% price reduction	7,006,449	8,114,659	9,222,869	10,331,078	11,439,288
100% price reduction	1,248,183	1,445,608	1,643,033	1,840,459	2,037,884
B-ALL					
Current price	2,421,751	2,435,357	2,448,963	2,462,569	2,476,175
20% price reduction	1,974,331	1,985,424	1,996,516	2,007,608	2,018,701
40% price reduction	1,526,912	1,535,490	1,544,069	1,552,647	1,561,226
60% price reduction	1,079,492	1,085,557	1,091,622	1,097,687	1,103,751
80% price reduction	632,072	635,623	639,175	642,726	646,277
100% price reduction	184,653	185,690	186,727	187,765	188,802

Abbreviations:
B-ALL = B-cell acute lymphoblastic lymphoma, **CAR** = chimeric antigen receptor, **CHF** = Swiss franc, **DLBCL** = diffuse large B-cell lymphoma, **PMBCL** = primary mediastinal B-cell lymphoma.

Figure 95 Budget impact for CAR T-cell therapy product price reduction scenarios



Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia; **CAR T** = chimeric antigen receptor T-cell; **CHF** = Swiss francs; **DLBCL** = diffuse large B-cell lymphoma; **PMBCL** = primary mediastinal B-cell lymphoma

9 Ethical, legal, social and organisational issues

Summary statement ethical, legal, social and organisational issues

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Of the 7 publications included, 5 addressed organisational issues associated with CAR T-cell therapies and 2 assessed ethical issues. No publications met the inclusion criteria for legal or social issues.

A core ethical issue relates to equity of access within a European healthcare context. Patient access to CAR T is often delayed due to long wait times, issues with patient referrals (i.e. doctors' limited knowledge about referral pathways and/or the treatment), and acquiring confirmation of cost coverage prior to treatment.

Four organisational issues were highlighted in the published literature (European and US healthcare contexts). The first issue was the management of patient deterioration between leukapheresis and infusion. The second issue was the identification, management and treatment of toxicities (i.e. CRS, ICANS and/or TLS) associated with CAR T-cell therapy. The third issue was ensuring comprehensive education of medical practitioners (i.e. nurses, physicians) around CAR T-cell therapy product and process. This included the ability of medical practitioners to clearly communicate the CAR T-cell therapy process to patients and their caregivers. The final organisational issue was the use of fewer hospital resources for CAR T-cell therapies (when manufacturing was excluded) than for autologous SCT.

9.1 Methodology: ethical, legal, social and organisational issues

The social, legal, ethical and organisational analyses were informed primarily by the EUnetHTA Core Model Version 3.0.[286] The systematic literature searches detailed in ***Section 7.1.1*** were used to identify literature relevant to the legal, social, ethical and organisational issues related to CAR T-cell therapies. Additional targeted non-systematic keyword searches for literature addressing these domains were conducted. Systematic reviews, literature reviews, RCTs, non-randomised studies, single-arm studies, ethnographic studies, phenomenological studies, narrative research and case studies were considered for inclusion. The included literature was ordered in tables describing the study characteristics and key findings. The results were synthesised narratively.

9.2 Results: ethical, legal, social and organisational issues

A total of 7 publications were relevant to the ethical and organisational domains. No publications were identified addressing the legal and social issues. The study designs, aims and main outcomes grouped by themes are summarised in ***Table 69***.

9.2.1 Study characteristics

The included publications consisted of one qualitative study,[287] one process analysis,[207] one expert opinion review,[288] 3 reviews,[289-291] and one HTA report including an ethical analysis.[292] From these publications, only those by Jommi 2022 and Ring 2022 were based within a European healthcare context.[207,290] The remaining publications were based within a US or Canadian healthcare context. To maintain generalisability to a Swiss healthcare context, information regarding the ethical issues of access and equity reported in publications based within the US or Canadian healthcare contexts were not included in this HTA.

9.2.2 Evidence table

The ethical, legal, social and organisational evidence is summarised in ***Table 69***.

Table 69 Characteristics of included studies for ethical, legal, social, and organisational issues

Study; country	Indication; sample size (n)	Design; duration; setting	Outcomes
Ethical issues			
Jommi 2022[290] Italy	DLBCL NA CAR T-cell: • Tisa-cel • Axi-cel	Review NA Italian health system	Barriers to access: • long wait times • patient referral system • pre-treatment funding approvals
CADTH 2019[292] Canada	DLBCL NA CAR T-cell: • Tisa-cel	HTA report including ethical analysis NA Canadian health system	• Balancing safety and effectiveness • Cost • Informed choice about treatment options
Legal issues			
NR	NR	NR	NR
Social issues			
NR	NR	NR	NR
Organisational issues			
Cunningham 2021[289] USA	B-ALL & DLBCL NA CAR T-cell: • Tisa-cel	Review NA Outpatient care	• Nurses' role in CAR T-cell therapy care

Study; country	Indication; sample size (n)	Design; duration; setting	Outcomes
Gajra 2022[288] USA	B-ALL & DLBCL NA CAR T-cell: • Tisa-cel • Axi-cel	Opinion NA USA health system	• Management of toxicities • Importance of practitioner-patient communication
Gajra 2020[287] USA	CAR T-cell: • Tisa-cel • Axi-cel Medical oncologists, medical haematologists n=114	Qualitative study 10 mo USA health system: • community-based • hospital-based	• Patient decline between leukapheresis and CAR T-cell therapy infusion • Lack of in-depth knowledge of which CAR T-cell therapy to select • Importance of practitioner-patient communication
Kansagra 2020[291] USA	B-ALL & LBCL NA CAR T-cell: • Tisa-cel • Axi-cel	Review NA Outpatient care	• Management of toxicities • Patient decline between leukapheresis and CAR T-cell therapy infusion
Ring 2022[207] Europe	LBCL NA CAR T-cell: • Tisa-cel • Axi-cel	Process analysis 10 mo Inpatient hospital	• Hospital resource use

Abbreviations:
Axi-cel: axicabtagene ciloleucel; **B-ALL:** B cell lymphoblastic leukaemia, **DLBCL:** diffuse large B cell lymphoma; **LBCL:** lymphoblastic B cell leukaemia**; mo:** month**; n:** number; **NA:** not applicable; **NR:** not reported; **Tisa-cel:** tisagenlecleucel; **USA:** United States of America.

9.2.3 Findings: ethical issues

Two studies detailed ethical issues related to CAR T-cell therapies for the treatment of B-ALL and DLBCL within the Italian and Canadian healthcare contexts.[290,292]

The Italian publication highlighted that the main ethical issues relate to equity of access to CAR T-cell therapies.[290] The first issue related to patients being unable to receive CAR T-cell treatment immediately, due to long wait times.[290] The second issue related to how patients were referred for treatment. Patient referrals to CAR T centres are often late in disease progression due to doctors having limited knowledge of the novel therapy and/or of how to refer patients to the respective centres.[290] This issue can be further compounded by distance, if the only available CAR T-cell centres are outside of the immediate area.[290] Patients may have to travel greater distances to access treatment, likely accompanied by caregivers for support and transport due to their weakened health state.[290] The final impediment to accessing CAR T-cell therapy relates to the financial cost, which was highlighted in both publications.[290,292] In Italy, CAR

T-cell centres require confirmation of complete cost coverage for both the treatment product and process prior to commencement of therapy.[290] The confirmation process causes delays to the ability of critically ill patients to access treatment. Further inequity in the process can occur if a patient is referred to a CAR T centre outside of their local area. This means that inter-regional confirmation of cost and eligibility needs to occur.[290] Each of the aforementioned issues can delay a patient with progressive disease from receiving treatment.

In addition to issues of access, CADTH's ethical analysis highlighted issues relating to balancing ***benefits and harms, costs,*** and ***informed consent***:[292]

Regarding ***balancing benefits and harms***, several key points were raised: first, tisa-cel was found to be associated with SAEs; second, there is uncertainty surrounding long-term safety and efficacy; and finally, patients who do not receive treatment face deterioration or death.[292] It was noted that there is no expert consensus around ethically justifiable frameworks for effectively balancing these issues, and that decisions will thus be made subjectively.[292] Further, it should be noted that substantial evidentiary uncertainty exists in relation to the relative effectiveness of CAR T-cell therapies in the third line, due to the absence of direct comparative evidence identified in the current HTA. As such, treatment decisions made with substantial uncertainty should be supported through post-market surveillance in order to ensure that benefits and harms are balanced accordingly.[292]

Regarding ***costs***, 2 key points were raised. First, it was noted that the total cost associated with treatment is often not covered under reimbursement arrangements, and additional extra-therapeutic costs to patients and caregivers can include travel and lodging, among other things.[292] Second, a high-level discussion of opportunity costs was presented, in which the high cost associated with CAR T-cell therapies may present an ethical dilemma related to the opportunity costs and the fair distribution of burdens and benefits within the health system.[292] These issues should be considered when deciding on the reimbursement of high-cost medical therapies.

Regarding ***informed consent***, it was argued that uncertainty around the relative safety and effectiveness of CAR T-cell therapies creates ethical challenges to providing informed consent to patients.[292] These issues are particularly highlighted due to the vulnerable nature of the eligible populations that have limited treatment options available. Ultimately, issues of informed consent are best overcome through education of patients, caregivers and medical staff involved in providing CAR T-cell therapies,[292] and responsibility for providing education within the health system should be clearly assigned.

9.2.4 Findings: organisational issues

The 5 included publications highlighted 4 potential organisational issues related to the treatment of B-ALL and LBCL with CAR T-cell therapies.[207,287-289,291]

The first organisational issue is the progression of disease that may occur during the manufacturing of CAR T-cells.[288,291] Given that B-ALL and LBCL are aggressive conditions, it is not uncommon for patients to deteriorate between leukapheresis and the CAR T-cell infusion. The disease progression that may occur during the manufacturing process can result in patients being deemed ineligible for the infusion once the CAR T cells are received by the treatment centre, or can result in death for some patients.[287,291] Provision of bridging chemotherapy may be a way to address the disease progression that may occur during the CAR T-cell therapy manufacturing process.[287,288]

The second organisational issue is the management of toxicities (i.e. CRS, ICANS, TLS) associated with CAR T-cell therapy.[288,291] These toxicities can be life-threatening and need to be treated immediately.[288,291] The general treatment for both CRS and ICANS is tocilizumab and corticosteroids.[288,291] TLS is generally treated using SoC.[288] Due to the severity of these toxicities, medical staff involved in patient care must be able to identify the conditions and provide early intervention.[288,289]

The third organisational issue is resource utilisation.[207] Ring 2022 states that within the European healthcare context, when the resource utilisation related to the manufacturing of the CAR T product is excluded, the therapy utilises less resources than autologous SCT.[207]

The final organisational issue is that of ensuring the ongoing education of treating medical practitioners (e.g. nurses, physicians) in CAR T-cell therapy and the corresponding treatment processes.[287,289] A barrier to the integration of CAR T-cell therapy into the health system is the lack of knowledge surrounding patient eligibility, treatment processes and the product itself.[287,289] In the US, 59% of referring physicians let the treatment centres determine which of the 2 CAR T-cell therapies (i.e. axi-cel or tisa-cel) the patient should receive, because they feel they possess insufficient information about the products or process.[287] In addition, treating physicians in the US were unaware that bridging chemotherapy can be used to slow disease progression during the CAR T-cell therapy manufacturing process.[287] Nurses have been highlighted as being vital to ensuring successful patient management throughout the CAR T-cell therapy process,[289] because they guide the patient through the multistep process of CAR T-cell therapy and help to identify and manage AEs (e.g. toxicities).[289] To ensure that CAR T-cell therapy reaches its full potential in benefiting patients it is paramount that medical practitioners are familiar with the treatment process and are able to clearly communicate the process to patients and their caregivers.[287-289,291]

10 Additional issues

10.1 Clinical practice recommendations and guidelines

In total, 15 clinical practice guidelines, consensus-based recommendations and technology appraisal guidance documents were identified through the systematic search and targeted searches (***Appendix H***).[55,194,293-305] Four were technology appraisal documents[194,293-295] and 11 were clinical practice guidelines or consensus-based recommendation publications.[55,296-305] The issuing organisations were from Europe, UK, Germany, Spain, Canada and USA (multiple publications were identified for some countries).

The guidelines and recommendations were generally in agreement for the use of tisa-cel in children and young adults with refractory B-ALL or relapsed B-ALL after SCT or ≥2 lines of prior therapy. The guidelines and recommendations were generally in agreement for the use of tisa-cel or axi-cel for the treatment of adults with r/r DLBCL after ≥2 lines of prior therapy, but consensus was not reached as to whether tisa-cel or axi-cel is preferred in this patient population. Finally, although PMBCL is a much rarer diagnosis, clinical guidelines recommend that adults with r/r PMBCL be managed in the same way as those with r/r DLBCL. It is important to note that only the use of axi-cel is approved for use in adults with r/r PMBCL after ≥2 lines of prior therapy.

Several guidelines and recommendations have also been developed to address CAR T-cell therapy-specific considerations, rather than the overall management of individual cancer populations (e.g. B-ALL, DLBCL, PMBCL).[296,304,305] In these publications, recommendations are made for how to manage patients who will undergo CAR T-cell therapy, including assessment of eligibility, screening, therapies prior to CAR T-cell therapy (e.g. leukapheresis, bridging), processes and procedures of manufacturing/administering CAR T-cells, management of AEs and short, medium and long-term follow-up timepoints, and post-administration tests.

During targeted searches, it was also discovered that the American Society of Haematology is currently developing new clinical practice guidelines for the treatment of adolescents and young adults with ALL. These guidelines will be published in 2024.

Further details on each clinical practice guideline, consensus-based recommendation and technology appraisal guidance document are provided in ***Appendix H***.

10.2 Ongoing clinical trials

Ten ongoing clinical trial records were identified in the clinical trial databases (summarised in ***Appendix I***), of which 3 will be conducted in a mixed population of B-ALL and LBCL patients, 6 will be conducted in LBCL or B-cell NHL patients, and 1 will be conducted in children and young adults with B-ALL. No studies will solely investigate PMBCL; however, these patients will be included in trials investigating LBCL patients. Of the ongoing clinical trials, 4 will evaluate axi-cel, 3 will evaluate tisa-cel and 3 will evaluate multiple CAR T-cell therapies (including axi-cel, tisa-cel and/or others). All ongoing trials are single-arm cohort studies or case-control studies with unclear comparator arms, thus will not contribute new information to warrant reconsideration of the evidence for axi-cel or tisa-cel in the proposed populations in the near future.

10.3 Risk of insertional mutagenesis

On 28 November 2023, the FDA issued a statement outlining reports of T-cell malignancies occurring in patients that had received CD-19-directed CAR T-cell therapies.[306] These reports had been received by the FDA from clinical trials and/or postmarking adverse event data sources. The specific CAR T-cell therapies that were implicated were not named, rather, the entire class of CD-19-directed therapies was implicated, including tisa-cel and axi-cel.[306] At the time of writing this HTA, the FDA are currently investigating the risk of T cell malignancy with serious outcomes, including hospitalisation and death, and recommend all patients treated with a CD-19-direct CAR T-cell therapy be monitored for secondary malignancy for the remainder of their lives.[306] The statement also noted that, despite these reports, the overall benefits of these products continue to outweigh the potential risks for their approved uses.[306]

11 Discussion

The objective of this HTA is to evaluate the clinical effectiveness/efficacy, safety, costs, cost-effectiveness and budget impact of the CAR T-cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) compared to current SoC for the treatment of B-ALL, DLBCL and PMBCL.

11.1 Evidence gaps

The most significant gap in the evidence relates to the lack of high-quality comparative evidence comparing CAR T-cell therapies to SoC treatments in B-ALL, DLBCL and PMBCL patients. The conduct of well-designed RCTs and NRSIs will be of great value to address the research question of interest.

Limited evidence was available to directly compare CAR T-cell therapies to SoC treatments. The majority of the clinical evidence was single-arm. Due to the scarce and low-quality evidence available, this HTA was unable to draw evidence-based conclusions for head-to-head effectiveness/efficacy and safety of CAR T-cell therapies compared to SoC.

Regarding the outcomes of interest, comparative evidence was unavailable for TFI, HRQoL, SAEs, AEs, TRAEs/TEAEs, B-cell aplasia, B-cell aplasia duration, cytopenia, hypogammaglobulinemia, IVIG usage, infections, TLS and secondary malignancies.

All ongoing clinical trials are single-arm cohort studies or case-control studies, thus unlikely to alter the findings of this HTA.

11.2 Strengths and limitations of the HTA

11.2.1 Limitations of the included trials

A limitation of the included studies was the grouping of DLBCL, PMBCL and tFL (transformed follicular lymphoma) patients within a broader ‘LBCL’ population. These data could not be stratified, therefore separate comparisons for DLBCL and PMBCL populations, as defined in the PICO, could not be made.

The criteria used to define eligible children and young adults with refractory B-ALL or relapsed B-ALL after SCT or ≥2 lines of prior therapy were often unclear. It was often unclear whether patients met the eligibility requirements to receive tisa-cel based on whether patients were refractory or relapsed after SCT, or had failed ≥2 lines of therapy. Future studies should endeavour to describe the included population in a clear manner.

The majority of studies reported outcome data over a short period of time, with only the larger, industry-funded studies reporting long-term follow-up. Patient-relevant outcomes such as HRQoL were rarely

reported in the included studies. As CAR T-cell therapies are relatively new, ongoing clinical trials may address these limitations. Future trials will benefit from a greater focus on patient-relevant outcomes and longer follow-up of patients treated with CAR T-cell therapies.

The majority of included studies measured survival outcomes (i.e. OS, PFS) from the time of CAR T-cell therapy infusion, which may introduce bias into the results. Patients that have a slot request or undergo leukapheresis but do not undergo the infusion (e.g. due to death, disease progression, CAR T manufacturing problems) will not be represented in the analyses, biasing in favour of CAR T-cell therapies. This issue can be overcome by using an ITT population from the time of slot request; however, only one included study did this.[127]

Finally, the included studies were largely unable to directly answer the research questions regarding relative safety, effectiveness and cost-effectiveness due to their study design. No RCTs on the eligible population were identified. The identified NRSIs were methodologically limited—the majority of studies were single-arm. Future studies with comparative study designs (i.e. RCTs or NRSIs with appropriate methods to control for confounding domains) are needed to inform these research questions with a higher degree of certainty.

11.2.2 Limitations of the review methodology

The methodology of this review has numerous notable advantages, primarily stemming from its systematic approach and thorough search strategies. Utilising a protocol established *a priori* enhances a review's quality and reduces bias, so a protocol was established before commencing this review. In addition, the comprehensive search strategy and the independent review of studies by 2 reviewers provides confidence that the included studies accurately reflect the available evidence base.

It is essential to acknowledge that systematic reviews have shortcomings. Studies with fewer than 10 participants were excluded from this HTA, which could have resulted in the omission of relevant data; however, given the limited sample sizes and single-arm study design of these excluded studies, their inclusion would not have changed the interpretation of the findings of the HTA. Publications that reported the use of CAR T-cell therapy as a bridge to another therapy (e.g. systematic planned use of SCT following CAR T infusion) were also excluded during study selection. This criterion was established to reduce confounding by co-medication, as exposure to such therapies will influence the true effect of CAR T-cell therapies on outcomes of interest. It is noted that although these studies may be relevant, only the sole effectiveness and safety of CAR T-cell therapies was the focus of this HTA report. It is currently unclear what proportion of patients in Swiss practice receive CAR T-cell therapies as a bridge to additional therapies.

11.2.3 Limitations in the economic evaluation

The methodology for the assessment of costs, cost-effectiveness and budget impact included a systematic review of full economic evaluations and additional economic literature (e.g. costing studies) to provide an overview of the economic aspects of CAR T-cell therapies. Costs across the entire CAR T-cell therapy process, from leukapheresis to discharge after infusion and ongoing IVIG use, were estimated within the Swiss context using Swiss tariffs. Notably, costs for inpatient care—which can pose a significant cost burden due to the management of acute AEs—were informed by primary data on DRG use.

A major limitation of the economic evaluation is the reliance on naïve treatment comparisons to estimate the incremental benefit of CAR T-cell therapy. It is recognised that this introduces significant uncertainty into the estimates of incremental cost-effectiveness. Additionally, the comparisons made relied on the digitisation of published KM curves rather than the use of primary IPD, and separate parametric models were fitted to individual treatment arms. Moreover, best fitting curves were selected based on AIC criteria as opposed to clinical face validity checks. The extrapolations of OS and PFS are at high risk of bias.

While comparisons made against historical controls align with comparisons considered in previous economic evaluations (including previous HTAs), current practice appears to be deviating from the historical landscape, with new therapies becoming available to patients (e.g. POLA-BR or tafasitamab-lenalidomide in LBCL and pembrolizumab in PMBCL). Furthermore, there is complexity in the relationship between CAR T-cell therapy and the nominated comparators, which may be used to complement CAR T-cell therapy (e.g. as a bridging therapy) rather than as alternative treatment options. For example, feedback noted that in B-ALL, blinatumomab is often used to bridge to CAR T-cell therapy. Feedback also raised concerns with the POLA-BR comparison given the expense of this treatment.

Additional costs for subsequent SCTs were not included in the LBCL models, based on feedback that these are applicable to the indication of B-ALL but not DLBCL or PMBCL; that it would be unlikely to perform transplants in the third-line setting; and that, after CAR-T cell therapy or a comparator, autologous SCTs would not be given and allogenic SCTs would be rare. Nevertheless, only a fraction of the SBST registry cohort (26% and 31% of LBCL patients receiving axi-cel or tisa-cel, respectively) and the CORAL extension cohort (27%) had failed a prior autologous SCT. Assuming no subsequent SCTs in the modelling is a simplification of actual treatment pathways and a potential limitation of the modelling.

An additional limitation in the methodology was the pragmatic approaches taken to identify sources of survival data for the comparator treatments and utility and disutility values. This meant that modelling undertaken in the current HTA largely drew from the data sources and input values used in the existing

evidence base (albeit different extrapolation approaches were adopted). While this is not a limitation in itself, it is noted that a considerable percentage of the included studies were industry-funded. Moreover, it is possible that more contemporary evidence in relation to these aspects could have been overlooked.

Finally, average costs for the inpatient episodes of care for CAR T-cell infusion were derived from aggregate data on relative use across Swiss DRGs. While this allowed for real-world analysis of inpatient care costs associated with CAR T-cell infusion and the management of acute AEs (notably, CRS and ICANS), costs could not be stratified across CAR T-cell products because data on associated surcharge codes or ATC codes for each hospital separation were unavailable. The model input for this cost component across the axi-cel and tisa-cel comparisons thus reflects an overall average cost for LBCL patients rather than product-specific average costs.

11.3 Comparison to existing HTA reports

Several HTA bodies have evaluated—and, in many cases, re-evaluated—tisa-cel in r/r B-ALL, axi-cel in r/r DLBCL/PMBCL, and/or tisa-cel in r/r DLBCL. Relevant documentation was identified on the websites of HAS, the Zorginstituut Nederland, NICE, the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG; Germany), Gemeinsamer Bundesausschuss (G-BA; Germany), CADTH, INESSS, and the Medical Services Advisory Committee (MSAC, Australia). The nature of the documentation varied, including company-submission documents, review group critiques, budget impact analyses, re-evaluation reports and public summary documents. For the purposes of providing context and points of comparison for this HTA, existing HTA reports from CADTH, INESSS, NICE and the Zorginstituut Nederland were prioritised.

11.3.1 Tisa-cel in B-ALL

11.3.1.1 Clinical evaluation

The CADTH 2019 HTA focused on tisa-cel in both B-ALL and DLBCL patients, separately.[307] For B-ALL, 3 studies were included to inform the HTA—ELIANA, ENSIGN and B2101J.[120,122,308] The B2101J study was excluded from the current HTA because child and adult B-ALL patients were combined and could not be stratified, thus this study did not fit the inclusion criteria of this HTA (only including children and young adults up to age 25).[308] The CADTH HTA concluded that tisa-cel has the potential to cause severe AEs and demands significant resources, necessitating a well-established infrastructure to guarantee the safe administration of this treatment in accordance with protocol standards.

The INESSS 2019 HTA focused on tisa-cel in B-ALL patients and also included the same core studies (ELIANA, ENSIGN, B2101J) as the CADTH 2019 HTA;[120,122,192,307,308] however, a naïve indirect comparison was conducted using study MT-103-205 on blinatumomab and an additional study on

clofarabine in combination with etoposide and cyclophosphamide.[178,179] Therefore the results are not comparable to this HTA. The INESSS 2019 HTA noted that tisa-cel will need to be reassessed in view of new, more robust data.

The NICE 2018 HTA focused on tisa-cel in B-ALL patients, and likewise included the same core studies (ELIANA, ENSIGN, B2101J) as both the CADTH 2019 HTA and the INESSS 2019 HTA.[120,122,190,192,307,308] The NICE 2018 HTA concluded that tisa-cel is clinically effective. (It is unclear how this conclusion was reached). The comparative effectiveness could not be assessed due to the studies being single-arm. Furthermore, there was no robust evidence that tisa-cel has a curative effect, and a lack of data beyond 30 months was noted. The HTA assessed outcomes at longer follow-up timepoints; however, the scarcity of comparative data is an issue, with the curative effect of tisa-cel also in question.

The Zorginstituut Nederland 2018 HTA also focused on tisa-cel in B-ALL patients.[309] However, the HTA conducted indirect treatment comparisons against blinatumomab (studies not provided but assumed to be similar to the above HTAs), so the results are not comparable to this HTA. The HTA concludes that the effect of tisa-cel on survival is clinically relevant, but it is also associated with a high risk of SAEs. This risk-benefit profile of tisa-cel must be considered.

11.3.1.2 Economic evaluation

The cost-effectiveness of tisa-cel in paediatric and young adult B-ALL patients has been considered by CADTH, INESSS and NICE.[190-192] All 3 organisations considered economic evaluations submitted by the manufacturer. Cost-effectiveness for this indication was not considered by the Zorginstituut Nederland 2018 HTA because of a low expected budget impact.[309] Tisa-cel was compared to salvage chemotherapy in the submission to CADTH; to salvage chemotherapy, clofarabine monotherapy and blinatumomab in the submission to INESSS; and to blinatumomab and salvage chemotherapy in the submission to NICE. INESSS had concerns regarding the comparison with salvage chemotherapy and retained comparisons with the clofarabine-based regimen and blinatumomab only. The literature review performed for the current HTA identified one published, company-sponsored cost-effectiveness evaluation of tisa-cel relative to salvage chemotherapy (FLA-IDA), clofarabine combination therapy and blinatumomab within the Swiss context. Additional modelling was undertaken to compare tisa-cel to blinatumomab using updated outcomes data from the ELIANA trial. Only a comparison with blinatumomab was considered in the current HTA (based on clinical feedback regarding the most relevant comparators).

In the NICE submission, tisa-cel was found to have an ICER of GBP18,392 (CHF23,424) compared to blinatumomab in the company base case and GBP27,732 (CHF35,319) in the expert review group's

base case. Further exploratory analyses by the expert review group, focused on uncertainty in SCT uptake and IVIG duration, reported ICERs of between GBP23,900 and GBP46,133 (CHF30,439–CHF58,755). It was noted that the majority of QALYs gained were accrued over the period of extrapolation as a result of additional LYs gained. Significant uncertainty was noted due to the use of historical control data to establish the effectiveness of the comparator therapies, an issue that also features in results of the current HTA.

Both CADTH and INESSS also highlight high uncertainty due to the lack of comparative efficacy and safety data. In INESSS's updated scenario 1 (scenario based on the parametric distributions that best approximate EFS and OS curves), tisa-cel was shown to have an ICER of CAD62,074 (CHF45,643) relative to blinatumomab, or CAD92,606 (CHF68,093) if IVIG users required replacement therapy until death or recurrence. Nevertheless, INESSS notes that these results are dependent on the persistence of clinical benefit over the longer-term. Scenario analyses conducted as part of the current HTA similarly found the benefit of tisa-cel on survival outcomes accumulated over a lifetime time horizon to be a key driver of the ICER estimate.

11.3.2 Tisa-cel in LBCL

11.3.2.1 Clinical evaluation

The CADTH 2019 HTA focused on tisa-cel in both B-ALL and DLBCL patients, separately.[307] For DLBCL, 2 studies were included to inform the HTA—JULIET and A2101J.[147,310] The A2101J study was not included in the current HTA as it included patients with follicular lymphoma and those treated with CAR T as a second-line therapy.[310] As previously mentioned, the CADTH HTA concluded that tisa-cel has the potential to cause SAEs and demands significant resources, necessitating a well-established infrastructure to guarantee the safe administration of this treatment in accordance with protocol standards.

The INESSS 2019 HTA focused on tisa-cel in DLBCL and included the same core studies (JULIET and A2101J) as the CADTH 2019 HTA;[147,189,307,310] however, a naïve indirect comparison was conducted using the CORAL and SCHOLAR-1 studies.[174,175] Therefore, the results are not comparable to this HTA as naïve indirect comparisons were not conducted. The INESSS 2019 HTA concluded that the evidence base was too immature for the authors to confidently recognise the therapeutic value of tisa-cel. Due to the lack of a standard, effective third-line therapy in this population, additional data should be generated to inform the clinical effectiveness and safety of tisa-cel in LBCL patients.

The NICE 2019 HTA focused on tisa-cel in DLBCL and included the same core studies (JULIET and A2101J) as the CADTH 2019 HTA and INESSS 2019 HTA.[147,187,189,307,310] The NICE 2019 HTA concluded that tisa-cel is clinically effective. (It is unclear how this conclusion was reached.)

Comparative effectiveness could not be assessed due the studies being single-arm. Furthermore, the evidence base was assessed to be immature—leading to uncertainty in the survival data—and tisa-cel was found to be associated with a high degree of SAEs.

The Zorginstituut Nederland 2019 HTA also focused on tisa-cel in LBCL patients;[311] however, this HTA conducted indirect treatment comparisons between the JULIET and the SCHOLAR-1 studies (utilising salvage chemotherapy), therefore the results are not comparable.[147,175] The authors conclude that a clinically relevant difference was not observed between tisa-cel and salvage chemotherapy. The quality of the evidence was considered to be very low. Based on these findings, advice was given by Zorginstituut Nederland to not include tisa-cel for this indication in the insurance package.

11.3.2.2 Economic evaluation

The cost-effectiveness of tisa-cel for patients with r/r DLBCL has been considered by CADTH, INESSS and NICE.[187-189] All 3 organisations considered economic evaluations submitted by the manufacturer comparing tisa-cel to salvage chemotherapy. In submissions to CADTH and INESSS, data from SCHOLAR-1 were used to inform efficacy estimates for the comparator; however, CADTH noted that the LY-12 or CORAL studies may have been more appropriate, and INESSS felt that the use of SCHOLAR-1 may over-estimate long-term OS. In the submission to NICE, the manufacturer sourced data from a UK-based observational study of pixantrone monotherapy; however, the expert review group preferred data from the CORAL extension studies or PIX301 for those ineligible for SCT. Cost-effectiveness was not mentioned in the Zorginstituut Nederland 2019 HTA.

The literature review performed for the current HTA identified one published, company-sponsored cost-effectiveness evaluation of tisa-cel relative to salvage chemotherapy for patients with r/r DLBCL within the Swiss context. The evaluation considered data from the CORAL extension studies to inform efficacy estimates for the comparator. De novo modelling was undertaken during the current HTA to compare tisa-cel to salvage chemotherapy using updated outcomes data from the JULIET trial, and to consider POLA-BR as an alternative comparator.

In the NICE submission, the company base case found tisa-cel to have an ICER of GBP47,684 (CHF60,730) compared to R-GEMOX. In alternative base cases presented by the expert review group, ICERs of GBP49,964 (CHF63,634) and GBP67,568 (CHF86,054) were reported, compared to PIX301 or CORAL extension study cohorts, respectively, when using MCM for tisa-cel survival. When using a one-knot spline model until year 5 followed by general population mortality, ICERs of GBP62,345 (CHF79,402) and GBP93,862 (CHF119,542), respectively, were reported. Key uncertainties identified by the expert review group relate to the extrapolation of OS for tisa-cel, structural assumptions associated with cure, and the uncontrolled nature of the comparisons.

In the submission to CADTH, the manufacturer reported an ICER of CAD143,018 (CHF105,188) for tisa-cel relative to salvage chemotherapy, while CADTH reanalysis suggested an ICER of CAD211,870 (CHF155,828). Base case results calculated for this HTA suggest an ICER between these 2 estimates (CHF129,840). A lack of head-to-head comparative data was raised as a key limitation. In INESSS's updated scenario 1 (i.e. scenario based on best-fitting parametric distributions), an ICER of CAD174,814 (CHF128,574) was reported. INESSS considered the available evidence to be too immature to confidently recognise the therapeutic value of tisa-cel; however, it did recognise the severity of the disease and the significance of the unmet need.

11.3.3 Axi-cel in LBCL

11.3.3.1 Clinical evaluation

The CADTH 2019 HTA report investigated the use of axi-cel in patients with r/r LBCL.[312] The CADTH 2019 HTA utilised data from only one pivotal study—ZUMA-1—to answer the research question; this study was identified and included in the current HTA.[143] As such, the results of the CADTH 2019 HTA are generally in-line with the current HTA. However, the current HTA included a larger subset of studies to investigate the effectiveness and safety of axi-cel in LBCL patients. Both HTAs identified the need for longer follow-up durations and direct comparative evidence to fully understand the risk-benefit profile of axi-cel in the treatment pathway of LBCL.

The INESSS 2019 HTA focused on axi-cel in patients with r/r LBCL.[196] The INESSS 2019 HTA also primarily utilised the ZUMA-1 study data; however, in the absence of comparative studies, indirect unanchored comparisons were made between axi-cel and salvage chemotherapies based on data from the ZUMA-1 and SCHOLAR-1 studies.[143,175] The INESSS 2019 HTA concluded that the available evidence was too immature to confidently discern the incremental therapeutic benefits of axi-cel. However, INESSS recognised the presence of a significant unmet need for the treatment of LBCL in those who had previously failed 2 lines of therapy.

The NICE 2019 HTA focused on axi-cel in patients with r/r DLBCL and PMBCL, in combination.[193] Similar to the CADTH 2019 HTA and the INESSS 2019 HTA, the NICE 2019 HTA also utilised data from the ZUMA-1 study.[143,193,196,312] The HTA concluded that axi-cel is clinically effective (unclear how this conclusion was reached); however, comparative effectiveness could not be assessed due the ZUMA-1 study being single-arm. Axi-cel was also found to be associated with a high degree of SAEs.

The Zorginstituut Nederland 2019 HTA focused on axi-cel in patients with r/r DLBCL or PMBCL, with a comparison drawn against chemotherapy (± SCT) based on data from the ZUMA-1 and SCHOLAR-1 studies.[141,175] Despite noting that the quality of the evidence was very low, the authors considered that the beneficial effects of axi-cel were clinically relevant compared to those of chemotherapy (±SCT). The

authors acknowledged the high incidence of AEs (including CRS) associated with axi-cel; however, they concluded that the AEs were acceptable given their treatability, the introduction of risk-reducing measures, and the severity of the disease.

11.3.3.2 Economic evaluation

The cost-effectiveness of axi-cel for patients with r/r LBCL was considered by CADTH and INESSS, and twice by NICE and the Zorginstituut Nederland.[193-196] All 4 organisations considered economic evaluations submitted by the manufacturer comparing axi-cel to BSC/salvage chemotherapy based on clinical data from SCHOLAR-1. CADTH expressed concerns as to whether salvage chemotherapies used in SCHOLAR-1 adequately reflect current contemporary practice. Comparisons with salvage chemotherapy based on clinical data from the CORAL extension studies were considered in the current HTA. In addition, a scenario including a more contemporary comparator (POLA-BR) was considered.

In the original submission to NICE, the company base case found axi-cel to have an ICER of GBP67,323 (CHF85,742) compared to BSC.[193] In an alternative base case presented by the expert review group, the ICER exceeded GBP100,000 (exact value not recorded). In the more recent submission—which used the same modelling approach as the original submission but with 60-month OS data for axi-cel—the committee concluded that the most plausible probabilistic ICER was below GBP50,000 (CHF63,680).[194] Similarly, findings from the Zorginstituut Nederland were more favourable in their 2021 re-evaluation relative to the original 2019 review. In 2019, the Zorginstituut Nederland concluded that the ICER was very uncertain, presenting a large potential range of values; however, in 2021 the Zorginstituut Nederland reported the manufacturer's ICER of EUR83,184 (CHF89,436), noting there was now less uncertainty about the effects of axi-cel on OS.

In the submission to CADTH, the manufacturer reported an ICER of CAD84,030 (CHF61,787) for axi-cel relative to salvage chemotherapy. In a reanalysis performed by CADTH, the start age was increased to 67 years, changes to the extrapolation of OS across both arms were made, the full ITT population from ZUMA-1 was considered, and costs of bridging therapy were included for 56% of patients. CADTH's reanalysis suggested an ICER of CAD226,131 (CHF166,275). Key uncertainties identified by both NICE and CADTH relate to the lack of head-to-head comparative efficacy and safety data, the modelling around assumptions of cure, and—for the submission to NICE—use of the modified ITT population, which implied model entry for patients receiving axi-cel occurred from the point of infusion (not leukapheresis).

In INESSS's updated analysis, ICERs of CAD156,000 (CHF114,707) to CAD350,000 (CHF257,356), depending on whether the therapy is considered curative, were reported. INESSS restricted the time horizon to 20 years in its updated analysis. INESSS felt it was too early to definitively attribute an

incremental therapeutic value to axi-cel and stated that there is considerable uncertainty regarding the long-term safety associated with the treatment.

The economic analysis presented in the current HTA utilised long-term follow-up data from the ZUMA-1 trial, (data cut-off 11 August 2021; median follow-up 63.1 months; range 58.9–68.4 months). Economic outcomes were found to be more favourable than those reported in previous HTAs (excluding the most recent assessments by NICE and the Zorginstituut Nederland, which also showed more favourable outcomes in comparison to the earlier assessment).

12 Conclusions

Limited, very low certainty comparative evidence was available to evaluate the relative effectiveness and safety of tisa-cel compared to standard care for the treatment of B-ALL and LBCL. Limited, moderate to very low certainty evidence reported favourable outcomes for axi-cel compared to salvage chemotherapy or no axi-cel, respectively, for effectiveness outcomes, and did not report safety data. Overall, the majority of evidence was single-arm in nature, which is unable to inform research questions regarding relative safety and effectiveness. Given the lack of ongoing comparative studies, the prospect of better evidence in the future is unlikely.

Due to a lack of comparative evidence comparing CAR T-cell therapies to alternative therapy options, naïve comparisons were relied upon to estimate the incremental benefit of axi-cel and tisa-cel in the economic evaluation. This introduces high levels of uncertainty into the results. Comparisons drawn against historical controls align with comparisons made in existing publications and HTAs. These comparisons suggest ICERs of approximately CHF70,000 for tisa-cel for r/r B-ALL relative to blinatumomab, and of CHF88,000 for axi-cel in r/r LBCL and CHF130,000 for tisa-cel in r/r DLBCL relative to historical salvage chemotherapy controls. Nevertheless, the use of historical controls to establish the incremental benefit of CAR T-cell therapy raises applicability concerns to contemporary Swiss clinical practice. It is possible that base case ICERs (LBCL populations) are biased in favour of CAR T-cell therapy due to the reliance on historical control. Scenario analyses suggested higher ICERs for axi-cel for r/r LBCL and tisa-cel for r/r DLBCL relative to more contemporary alternatives such as POLA-BR (approximately CHF102,000 and CHF157,000, respectively). However, there are also concerns in these comparisons due to cross-trial differences between study populations. In summary, there are important limitations underpinning the ICERs, including a lack of comparative safety and efficacy evidence, applicability of the comparator evidence to contemporary practice, and uncertainty in the extrapolation of survival outcomes.

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