Health Technology Assessment (HTA)

HTA Protocol

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
Technology	tisagenlecleucel (Kymriah®), axicabtagene ciloleucel (Yescarta®)
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Executive Summary

The CAR T cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) are provisionally listed in Appendix 1 of the Health Insurance Benefits Ordinance, and are reimbursed by Swiss mandatory health insurance for the treatment of diffuse large B cell lymphoma (DLBCL; Kymriah® and Yescarta®), B cell acute lymphocytic leukaemia (ALL; Kymriah®) and primary mediastinal B cell lymphoma (PMBCL; Yescarta®) until 31 December 2024. This proposed health technology assessment will evaluate the safety, efficacy/effectiveness, costs, cost-effectiveness and budget impact of tisagenlecleucel and axicabtagene ciloleucel separately in these indications. In addition, ethical, legal, social and organisational issues associated with these therapies will be investigated.

A systematic review of 4 databases (MEDLINE [Ovid], Embase [Ovid], Cochrane Library, INAHTA database) will be conducted to capture contemporary literature. CAR T cell therapies are novel technologies, therefore only studies from 1 January 2010 onwards will be considered. Recent systematic reviews and meta-analyses that answer the research questions will be considered. Primary studies will be included in the absence of, or to update, existing health technology assessment (HTA) reports, systematic reviews and meta-analyses. Included studies will be evaluated for risk of bias using study design-specific tools. Where more than 2 comparative studies report on outcomes of interest, a pairwise random-effects meta-analysis will be performed using an inverse-variance model. Single-arm studies will be summarised narratively.

A systematic literature search of Medline, Embase and Econlit for existing economic studies was conducted up to 25 October 2022 to inform the economic modelling approach for the HTA. Based on the search results, it is likely that a *de novo* economic evaluation will be performed. The planned modelling approach will be a hybrid decision tree and 3-state model built around the health states of alive and progression free, alive with progressive or relapsed disease, and dead. Treatment discontinuations, adverse events and subsequent therapies (notably, subsequent stem cell transplantation) will also be incorporated. Current cost data from Switzerland as well as utility, clinical effectiveness and safety data—likely from international sources—will serve as inputs for the model. Confidentiality of the CAR T cell therapy product prices will be maintained throughout the HTA process, where necessary. A budget impact analysis will be performed.

Social, legal, ethical and organisational issues will be addressed through systematic and targeted searches. Issues highlighted in studies within the clinical section will also be included. The findings will be summarised narratively.

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Abbreviations and acronyms

axi-cel	Axicabtagene ciloleucel
B cell ALL	B cell acute lymphoblastic leukaemia
BIA	budget impact analysis
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
CRS	cytokine release syndrome
CT	computed tomography
DLBCL	diffuse large B cell lymphoma
DNA	deoxyribonucleic acid
DRG	diagnosis-related group
DSA	deterministic sensitivity analysis
EFS	event-free survival
EQ-5D	EuroQol 5 Dimensions
FOPH	Federal Office of Public Health
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
INESSS	Institut National d'Excellence en Santé et en Services Sociaux
IPD	individual patient data
ITT	intention-to-treat
kg	kilogram
LY	Life years
NHL	non-Hodgkin lymphoma
NICE	National Institute for Health and Care Excellence
NRSI	non-randomised studies of interventions
PET	positron emission tomography
PFS	progression-free survival
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
RCT	randomised controlled trial
RNA	ribonucleic acid
SCT	stem cell transplantation
SD	standard deviation
SF-36	Short Form 36
tisa-cel	Tisagenlecleucel
WHO	World Health Organization

Objective of the HTA Protocol

Based on a preliminary screening of the literature, the objective of the health technology assessment (HTA) protocol is to formulate the research question; to define the population, intervention, comparator, outcomes (PICO); and to describe the methodology to conduct a systematic literature search and extract, analyse and synthesise the data for an HTA report on the topic. Key questions are defined to address the main HTA domains of efficacy/effectiveness/safety, cost/budget impact/cost-effectiveness and ethical/legal/social and organisational issues.

1 Policy question

Each HTA topic entails a policy and a research question. In healthcare, a ***policy question*** is a request to regulate a reimbursement policy; it is aimed at securing financing of health technologies. This HTA report addresses the following policy issue brought forward by the applicant:

The CAR (chimeric antigen receptor) 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.[1] The therapies are reimbursed as third-line therapies for patients with refractory or relapsed B cell acute lymphoblastic leukaemia (B cell ALL; Kymriah®), patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL; Kymriah® and Yescarta®), and for patients with primary mediastinal B cell lymphoma (PMBCL; Yescarta®). In order to inform future reimbursement decision for these CAR T cell therapies, the contemporary available evidence is to be re-evaluated.

An HTA will be conducted to evaluate the available evidence regarding efficacy, effectiveness and safety of tisa-cel and axi-cel compared to standard care. The proposed HTA will also evaluate the costs, cost-effectiveness and budget impact of these CAR T cell therapies and explore the ethical, legal, social and organisational issues.

2 Medical background

2.1 Medical context, disease description and main symptoms

Leukaemia and lymphoma are blood cancers characterised by the abnormal proliferation of cells derived from multipotential 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;[2] those originating in blood-forming tissue such as bone marrow are referred to as leukaemias,[3] while those originating in the lymphatic system are referred to as lymphomas.[2,4] Subtypes of leukaemia and lymphoma can be further differentiated based on morphology, immunophenotype, and cytogenic or molecular analysis.[5,6] As noted in ***Section 1***, there are 3 indications of interest to this project: B cell ALL, DLBCL, and PMBCL.

2.1.1 B cell ALL

B cell 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 generation of immature cells, rather than mature cells.[5] Despite its acute characteristics, B cell ALL in children and young adults under

the age of 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.[7]

The symptoms associated with B cell ALL arise due to the increasing insufficiency of normal blood cell production, as well as 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).[8]

Predisposing factors in children include inherited genetic susceptibility and environmental exposure to pesticides, ionising radiation, and childhood infections;[9] predisposing factors in adults are not well understood.[5]

B cell ALL is primarily diagnosed in children, with three-quarters of cases diagnosed in those <6 years of age, and occurs more frequently in male patients than female patients.[10] Annually, the overall incidence rate of ALL and lymphoblastic lymphoma in Europe is 1.28 per 100,000 individuals.[11] 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 ages 45–54 years (0.53 per 100,000) and then increases with age thereafter (1.45 per 100,000 at 75-99 years).[11] The incidence of ALL is significantly higher in southern Europe in comparison to other European regions.[11]

2.1.2 DLBCL

DLBCL is a malignancy of mature B cells originating in the lymphatic system.[6] It is the most common subtype of non-Hodgkin lymphoma (NHL) in adults, accounting for approximately 25% of NHL cases worldwide.[12] DLBCL is an aggressive disease; however, up to 50% of patients can achieve complete remission after first line therapies.[13] The majority of DLBCL cases−approximately 80%−are defined as “not otherwise specified” according to the current WHO classification of lymphomas, and as such typically lack defining characteristics and symptoms.[2]

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 in the neck, groin or abdomen; however, extra nodal involvement in other organs is common.[14] In addition to a solid mass, systemic “B” symptoms (e.g. fever, weight loss, night sweats) are experienced by approximately up to 30% of patients.[13]

Predisposing risk factors for DLBCL include a 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.[15,16]

DLBCL is more commonly diagnosed in male patients (55%) than female, with median age of diagnosis 64 years and incidence steadily increasing with age.[17,18] In Europe, the crude incidence of DLBCL is 3.8

per 100,000 per year.[11] The incidence of DLBCL is significantly lower in eastern (1.79 per 100,000) and northern (0.79 per 100,000) Europe in comparison to other European regions.[11] Per the EUROCARE-5[19] population-based study conducted across Europe, the age-standardised 5-year relative survival of DLBCL increased from 42.0% (1997–1999) to 55.4% (2006–2008).

2.1.3 PMBCL

PMBCL is an aggressive, rare subtype of NHL, representing approximately 2–3% of NHL diagnoses.[20] 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.[21] It is a rapidly growing cancer, which can spread to parenchymal organs after recurrence.

The prognosis of PMBCL after first line therapies is favourable, with a 5-year estimated survival rate of approximately 70-85%;[20] however, the prognosis of patients with refractory disease that do not respond to salvage chemotherapy is poor.[22]

PMBCL is most commonly diagnosed in white female patients between the age of 30–39.[20] To date, only a single population-based study conducted in the USA has been able to estimate the incidence of PMBCL.[23] This study reported the annual incidence of PMBCL to be 0.4 per million in a US population.[23]

3 Technology description

3.1 CAR T cell therapy overview

CAR T cell therapies use genetically modified, autologous T cells to target and destroy cancer cells.[24] The therapy involves expressing engineered receptors (known as CARs) in a patient's immune cells (i.e. a T cell), to direct their action to specific cancer cells.[25] As noted, 2 CAR T cell therapies that are provisionally reimbursed in Switzerland are the focus of this evaluation: tisa-cel (Kymriah®) and axi-cel (Yescarta®).

3.2 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.[26] In the 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).[24] This is accomplished using either viral or non-viral methods.[25] 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; additional methods to insert RNA/DNA include chemical transfection, electroporation and the use of nanoparticles.[25,27] After selection of modified cells, the cells are cultured (i.e. grown in expanded numbers) until there are enough of them for clinical use.[25] The CAR T cells are generally returned to the hospital for infusion into the patient 3-4 weeks after leukapheresis.[28] In the meantime, patients may receive bridging chemotherapy to control their disease while the CAR T cells are being manufactured.[28] 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.[29-32] To decrease potential reactions to the CAR T infusion, it is recommended that prior to the infusion (30 to 60 minutes), patients are pre-medicated with, e.g. paracetamol and antihistamines.[33,34] Finally, patients receive the CAR T cells as a one-off intravenous infusion, and are then monitored for adverse events in the in-patient setting. The dose of CAR T cells administered to patients is dependent on the patients' diagnosis (i.e. ALL, DLBCL, PMBCL), body weight, and type of therapy (i.e. axi-cel, tisa-cel).[33,34]

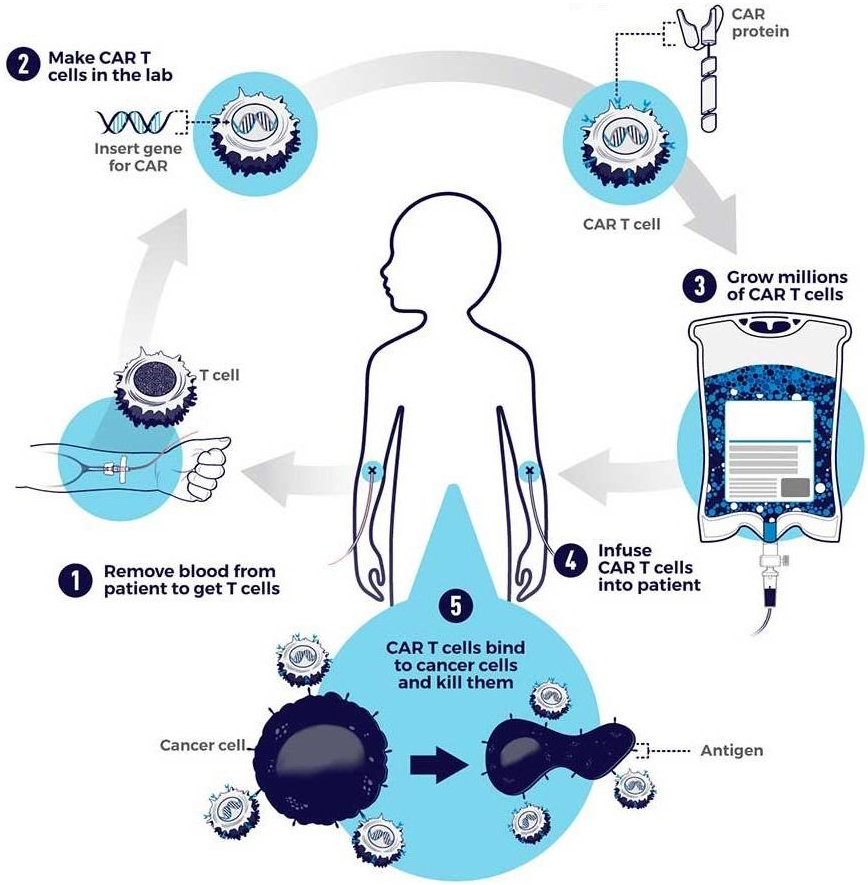


Figure 1 CAR T cell therapy process

Source: National Cancer Institute[35]

3.3 Adverse events

CAR T cell therapies are associated with a range of potential adverse events, which 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, and require urgent medical attention.[29-31,36] Another potentially severe side effect is immune effector cell-associated neurotoxicity syndrome, 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).[37] Longer-term side effects of CAR T cell therapies can include cytopaenia (i.e. reduced blood cell count) and hypogammaglobulinaemia (i.e. reduced serum immunoglobulin).[37] Other common adverse events include, but are not limited to, infections and B cell aplasia (i.e. reduced B cell count).[36] Owing to the adverse events associated with CAR T cell therapies, Onkopedia guidelines (non-binding) recommend the treatment be reserved for highly specialised centres with extensive experience in managing cellular immunotherapies, including direct access to an intensive care unit.[36]

3.4 Contraindications

Contraindications to tisa-cel include known hypersensitivity to tisa-cel or any of the excipients (e.g. dimethyl sulfoxide, dextran 40, sodium gluconate, sodium acetate, potassium chloride, magnesium chloride, sodium-N-acetyltryptophanate, sodium caprylate, aluminium).[30,32] In addition, contraindications to lymphodepleting chemotherapy should be considered.[32] Similarly, contraindications to axi-cel are limited to hypersensitivity to axi-cel or any of the excipients (i.e. cryostor CS10, sodium chloride, human albumin), or to any substances listed as contraindications for fludarabine or cyclophosphamide.[29,31]

4 PICO criteria

The PICO and study selection criteria for the planned HTA are outlined in ***Table 1***, ***Table 2*** and ***Table 3***, and described in the subsequent ***Sections 4.1*** to ***4.4***.

Table 1 PICO and study selection criteria, population 1

Population	Children and young adults (up to age 25) with refractory B cell ALL or relapsed B cell ALL after stem cell transplantation or 2 or more lines of therapy *Excluded: patients 26 years of age or above*
Intervention(s)	Tisagenlecleucel (Kymriah®) therapy (i.e. the entire treatment complex of CAR-T cell therapy)
Comparator	Standard care
Outcome(s)	Overall survival (OS) Progression-free survival (PFS) Complete response rate (CRR) Overall response rate (ORR) Treatment-free interval (TFI) Quality of life (QoL) [a] Treatment discontinuation [b] Adverse events [c]
Economic outcome(s)	Costs, utilities, LYs, QALYs, cost-effectiveness/cost-utility, ICER, budget impact
Publication type	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 effectiveness trials relating to the intervention will be included. Single-arm trials that report safety outcomes will be included *Excluded: narrative reviews, letters to the editor, conference abstracts, opinion articles.* For the economic literature review, only full economic evaluations will be included.
Limits	Publication date from 1 January 2010 No language limitations applied

Abbreviations

ALL = acute lymphocytic leukaemia, **CAR T cell** = chimeric antigen receptor T cell, **CRR** = complete response rate, **HTA** = health technology assessment, **ICER** = incremental cost-effectiveness ratio, **LY** = life year, **ORR** = overall response rate, **OS** = overall survival, **PFS** = progression-free survival, **QALY** = quality-adjusted life year, **QoL** = quality of life, **TFI** = treatment-free interval.

Note(s)

[a] Including any verified scale.

[b] Defined: production failure, patient died waiting for infusion, patient decided against infusion during pre-infusion therapies.

[c] Including, cytokine release syndrome, B cell aplasia, cytopaenia, hypogammaglobulinaemia, infection, etc.

Table 2 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)
Comparator	Standard care
Outcome(s)	Overall survival (OS) Progression-free survival (PFS) Complete response rate (CRR) Overall response rate (ORR) Treatment-free interval (TFI) Quality of life (QoL)[a] Treatment discontinuation [b] Adverse events [c]
Economic outcome(s)	Costs, utilities, LYs, QALYs, cost-effectiveness/cost-utility, ICER, budget impact
Publication type	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 effectiveness trials relating to the intervention(s) will be included. Single-arm trials that report safety outcomes will be included *Excluded: narrative reviews, letters to the editor, conference abstracts, opinion articles.* For the economic literature review, only full economic evaluations will be included.
Limits	Publication date from 1 January 2010 No language limitations applied

Abbreviations

DLBCL = diffuse large B cell lymphoma, **CAR T cell** = chimeric antigen receptor T cell, **CRR** = complete response rate, **HTA** = health technology assessment, **ICER** = incremental cost-effectiveness ratio, **LY** = life year, **ORR** = overall response rate, **OS** = overall survival, **PFS** = progression-free survival, **QALY** = quality-adjusted life year, **QoL** = quality of life, **TFI** = treatment-free interval. **WHO** = World Health Organization.

Note(s)

* The analysis will evaluate tias-cel and axi-cel compared to placebo separately; tisa-cel and axi-cel will not be compared directly or indirectly.

[a] Including any verified scale.

[b] Defined: production failure, patient died waiting for infusion, patient decided against infusion during pre-infusion therapies.

[c] Including, cytokine release syndrome, B cell aplasia, cytopaenia, hypogammaglobulinaemia, infection, etc.

Table 3 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)
Comparator	Standard care
Outcome(s)	Overall survival (OS) Progression-free survival (PFS) Complete response rate (CRR) Overall response rate (ORR) Treatment-free interval (TFI) Quality of life (QoL) [a] Treatment discontinuation [b] Adverse events [c]
Economic outcome(s)	Costs, utilities, LYs, QALYs, cost-effectiveness/cost-utility, ICER, budget impact
Publication type	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 effectiveness trials relating to the intervention will be included. Single-arm trials that report safety outcomes will be included *Excluded: narrative reviews, letters to the editor, conference abstracts, opinion articles.* For the economic literature review, only full economic evaluations will be included.
Limits	Publication date from 1 January 2010 No language limitations applied

Abbreviations
CAR T cell = chimeric antigen receptor T cell, **CRR** = complete response rate, **HTA** = health technology assessment, **ICER** = incremental cost-effectiveness ratio, **LY** = life year, **ORR** = overall response rate, **OS** = overall survival, **PFS** = progression-free survival, **PMBCL** = primary mediastinal B cell, **QALY** = quality-adjusted life year, **QoL** = quality of life, **TFI** = treatment-free interval.
Note(s)
[a] Including any verified scale.
[b] Defined: production failure, patient died waiting for infusion, patient decided against infusion during pre-infusion therapies.
[c] Including, cytokine release syndrome, B cell aplasia, cytopaenia, hypogammaglobulinaemia, infection, etc.

4.1 Population(s)

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

- children and young adults (up to age 25) with refractory B cell ALL or relapsed B cell ALL after stem cell transplantation or 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).

4.2 Intervention(s)

The proposed HTA will be limited to 2 of the CAR T cell therapies provisionally reimbursed in Switzerland: tisa-cel (Kymriah®) and axi-cel (Yescarta®).[1] The evaluation of these therapies will consider the entire treatment complex as a whole, i.e. inclusive of leukapheresis up to infusion, and post-infusion follow-up (see ***Section 6.5.1*** for follow-up timepoints). However, follow-up SCT will be excluded as it is patient specific and is not part of a routine of CAR T treatment cycle.[38,39]

4.3 Comparator(s)

The population of interest for this HTA specifically requires patients to have refractory or relapsed 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 cell ALL, the main goal in the management of relapsed patients is to achieve complete remission, and to enable subsequent stem cell transplantation (SCT).[8] The choice of comparator depends on the nature of the relapse (e.g. 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), prior therapies, comorbidities, and the suitability for allogenic SCT.[5,8] Depending on the clinical characteristics of the patients, standard care may include immunotherapy with blinatumomab or inotuzumab, 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).[5,8]

For patients with relapsed or refractory DLBCL, standard care includes salvage chemotherapy (R-DHAP [rituximab, dexamethasone, cytarabine and cisplatin], R-ICE [rituximab, ifosfamide, carboplatin and etoposide], R-GEMOX (rituximab, gemcitabine, oxaliplation) or R-GDP [rituximab, gemcitabine, dexamethasone and cisplatin]) and / or by high-dose therapy (BEAM [carmustine, etoposide, cytarabine, melphalan]) and autologous SCT.[40,41] Alternatively, patients may receive palliation (i.e. care aimed at improving quality of life/relieving suffering of patients and their families) or allogenic SCT.[40-42]

For relapsed or refractory PMBCL, salvage treatments are similar to those for DLBCL, and include immunotherapy (e.g. pembrolizumab, nivolumab, etc.), attempting reinduction with non-cross-resistant agents followed by consolidation with high-dose chemotherapy and autologous SCT in patients with chemosensitive disease.[43-45]

4.4 Outcome(s)

The primary purpose of CAR T cell therapies is to cure (e.g. remove and prevent reoccurrence of malignant tumours), improve the prognosis and quality of life of patients with cancer. The outcomes under investigation in the planned HTA have been chosen to address the intent of the treatment. All outcomes are planned to be measured at longest follow-up. As such, the following outcomes will be investigated:

- Overall survival (OS)
- Progression-free survival (PFS), defined as the time from randomisation, or study enrolment in the case of NRSI and single-arm studies, to disease progression or death from any cause, or to last follow-up.[36,46]
- Complete response rate (CRR), also known as complete remission, is defined as the disappearance of all of signs of cancer. This does not indicate that the cancer has been 'cured'.[47,48]
- Overall response rate (ORR), is defined as the proportion of patients that have a complete or partial response to cancer therapy.[48]
- Treatment-free interval (TFI), defined as the time of the discontinuation of cancer treatment to the start of cancer progression. To be considered TFI, the cancer progression has to occur after treatment discontinuation.[49] TFI is used as a surrogate for a state of good health, as it assumed that the patients are clinically stable and that they are not subject to treatment tolerability and toxicity issues.[49]
- Quality of life, measured with a reliable and valid instrument (e.g. Short Form 36 [SF-36],[50] EuroQol-5 Dimension [EQ-5D],[51] Functional Assessment of Cancer Therapy-Lymphoma [FACT-Lym],[52] FACT-General [FACT-G],[53] European Organization for Research and Treatment of Cancer quality of life [EORTC QLQ-C30], etc.).[54]
- Treatment discontinuation (i.e. production failure, patient died waiting for infusion, patient decided against infusion during pre-infusion therapies)
- Adverse events (e.g. cytokine release syndrome, B cell aplasia, cytopaenia, hypogammaglobulinaemia, infection, immune effector cell-associated neurotoxicity syndrome, etc.)

5 HTA key questions

To evaluate the technology, the following key questions covering the central HTA domains will be addressed:

1. In children and young adults (up to age 25) with refractory B cell ALL or relapsed B cell ALL after stem cell transplantation or 2 or more lines of therapy, is tisa-cel safe and efficacious/effective compared to standard care?
2. In adults with refractory or relapsed 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 refractory or relapsed PMBCL after at least 2 lines of therapy, is axi-cel safe and efficacious/effective compared to standard care?
4. Compared to standard care, is tisa-cel cost-effective for the treatment of children and young adults (up to age 25) with relapsed or refractory B cell ALL after SCT or 2 or more lines of therapy?
5. Compared to standard care, are axi-cel and tisa-cel cost-effective for treatment of adult patients with relapsed or refractory DLBCL after at least 2 lines of therapy?
6. Compared to standard care, is axi-cel cost-effective for the treatment of adult patients with relapsed or refractory PMBCL after at least 2 lines of therapy?
7. What is the potential budget impact of continued funding of CAR-T 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?

6 Methodology: Clinical evaluation

The proposed methods have been developed with reference to the Cochrane Handbook for Systematic Reviews of Interventions.[55] They are described in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[56]

6.1 Databases and search strategy

A systematic literature search will be conducted in 4 databases (Medline, Embase, Cochrane Library, INAHTA HTA database). CAR T cell therapies are novel technologies, therefore only studies from 1 January 2010 onwards will be considered.[36] The search strategy includes filters to exclude non-human studies. No other filters will be used during the searches. Searches will also be 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 planned search strategy for each database. The results of the draft search strategy have been cross-checked against the included studies from existing published reviews on the topic.[36,57,58]

6.2 Study selection

Results from the literature searches will be imported into Rayyan (Rayyan Systems Inc, United States).[59] Rayyan functions similarly to EndNote but allows for easy blinding of reviewers and management of study inclusion conflicts. The search results will be screened against the predetermined eligibility criteria (***Section 4***) by 2 reviewers. To ensure that the inclusion criteria are interpreted consistently between reviewers, 2 separate training samples (k = 250 and k = 250 citations) will be used to establish inter-rater reliability. Both reviewers will select studies independently in both training samples, with selections compared between reviewers. The first sample will be a training sample only, whereas the second sample will be used to calculate inter-rater reliability; a minimum kappa score of 0.7, representing substantial agreement between reviewers,[60] will be required. Further training samples of 250 citations will be used until the minimum kappa score is achieved, after which point, screening of the remainder of the articles by title and abstract will be split between the reviewers. In cases where a reviewer is unsure about whether to include an article, the article will be included for further review by full text. Following the title and abstract screen, all articles deemed potentially relevant will be reviewed in full text by each reviewer independently. Conflicts between reviewers on study inclusion will be settled via consensus. If consensus cannot be reached, a third reviewer will decide whether to include or exclude the citation. The reasons for excluding articles at full-text review will be documented, and the results of the study selection will be reported in a PRISMA flow diagram.

6.3 Data extraction

One reviewer will independently extract data (on a study-arm level, where applicable) into a standardised template, which will be checked against the original study record by a second reviewer. Disagreements will be settled by discussion or utilisation of a third independent reviewer. Data of interest include:[61,62]

- study information: study identifier, study 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, gender, ethnicity, comorbidities, diagnosis, pervious SCT (i.e. autologous, allogeneic), pervious lines of therapy (e.g. 2, 3, 4, etc.).
- intervention and comparator: type of CAR T cell therapy, type of lymphodepleting chemotherapy, pre-medication regimen, pre-medication administration route (i.e. oral, intravenous), 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 4.4***).
- any noteworthy features (e.g. effect modifiers), limitations or differences in the study.

For studies that report outcomes graphically instead of numerically, *WebPlotDigitizer* will be used to estimate numerical values.[63]

6.4 Quality appraisal

Assessment of the quality of evidence will be performed by one reviewer and checked by a second reviewer. Any differences will be settled via consensus. If consensus cannot be reached, a third reviewer will be consulted. The quality and risk of bias of included evidence will be assessed using different tools depending on the research design. Systematic reviews will be evaluated using the ROBIS risk of bias tool;[64] Randomised controlled trials (RCTs) will be evaluated using Cochrane Risk of Bias 2.0 (RoB 2.0);[65] Non-randomised studies of interventions (NRSIs) will be evaluated using the Cochrane Risk of Bias in Non-randomised Studies – of Interventions (ROBINS–I) tool.[66] The quality of reporting in single arm studies will be evaluated using the IHE quality appraisal checklist.[67] Quality assessments of primary studies conducted by included systematic reviews will not be repeated unless they were conducted with a tool not listed above.

The overall certainty of the reported outcomes will be appraised using the GRADE approach.[68] Results of the assessments for each domain (i.e. risk of bias, inconsistency, indirectness, imprecision, other considerations) will be 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' tables will be produced for each intervention and population group (i.e. tisa-cel + B cell ALL, tisa-cel + DLBCL, axi-cel + DLBCL, axi-cel + PMBCL). Separate summary of findings tables will be produced for each level of evidence (i.e. RCTs, NRSIs, single-arm studies).

6.5 Data analyses of efficacy, effectiveness and safety outcomes

6.5.1 Data synthesis

The method of data synthesis will depend on whether relevant systematic reviews or meta-analyses are available. *De novo* analysis will not be performed if existing systematic reviews meet the inclusion criteria. In such cases, the results from included systematic reviews will be reported for the relevant outcomes and synthesised into a GRADE summary of findings table.

A *de novo* meta-analysis will be performed for specific outcomes of interest from primary research reports of RCTs and NRSIs where there are no existing systematic reviews with meta-analyses available. Meta-analysis will be performed using R software. Random-effects models using the generic inverse variance method will be used as the basis for the primary analysis. Fixed-effects models using the generic inverse variance method will only be used in cases where it is reasonable to assume that the studies are measuring the same treatment effect (i.e. due to low clinical and statistical heterogeneity between included studies), in all other cases random-effects models will be used. Meta-analysis will be performed for outcomes reported by at least 2 studies.

Except for health-related quality of life (HRQoL), all outcomes included in the review will be dichotomous. Each dichotomous outcome will be reported as a risk ratio or odds ratio with 95% confidence intervals, and the unit of measurement will be the number of patients experiencing an event. HRQoL will be reported as mean difference between treatment arms with 95% confidence intervals. Where included studies report different HRQoL scales, standardised mean differences with 95% confidence intervals will be used. Standardised mean differences will be interpreted using generic standard deviation units and also re-expressed as the most commonly reported scale of HRQoL included in the analysis.

All outcomes will be reported at longest follow-up. Depending on data availability, data will be stratified at 30 days, 3 months, 6 months, 9 months, 1 year, 2 years, and over 2 years. The 30 days timepoint will be limited to reporting the point estimates for HRQoL and safety outcomes. The timepoints are based on published literature.[36,69,70]

Given the limited treatment options for patients with refractory or relapsed ALL, DLBCL or PMBCL after at least 2 lines of therapy, and because it is not possible to account of the personalised nature of last-line therapies into planned meta-analysis techniques, it will be assumed that all 'standard care' is equivalent across trials.

6.5.2 Assessment of heterogeneity

Heterogeneity will be assessed graphically through the presentation of forest plots. Heterogeneity will be 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 will be as proposed in the Cochrane handbook (I^2 = 0–40% might not be important; 30–60% moderate heterogeneity; 50–90% substantial; 75–100% considerable heterogeneity). Where substantial heterogeneity is evident, the causes of this will be explored through subgroup analysis as described in ***Section 6.5.4***.

6.5.3 Publication bias

Publication bias will be assessed using tests for funnel plot asymmetry for outcomes with a minimum of 10 studies.

6.5.4 Subgroup and sensitivity analysis

Subgroup and sensitivity analysis will be used to investigate possible causes of heterogeneity in meta-analyses due to effect modifiers (e.g. dose, risk of bias, etc.). Subgrouping will be used to explore a subset of effect modifiers from comparative studies.[55] The subgroup analyses will use random effects models with an assumption of a normal distribution. A two-tailed Z-test will be used to determine if the difference between the two groups is statistically significant. The difference between subgroups will be considered statistically significant if there is less than 5% of difference occurring by chance alone (i.e. $p < 0.05$). Given that none of the subgroup analyses include two or more groups, a Q-test will not be performed. If there are only 10 trials in the subgroup analyses Tau^2 will be calculated using trials in both subgroups. However, if the subgroup analyses included more than 10 trials, a separate Tau^2 will be calculated for each individual subgroup. These will include:[33,34]

- <u>All populations</u>
    - Previous SCT (i.e. autologous, allogeneic).
    - Previous lines of therapy (e.g. 2, 3, 4, etc.).
- <u>Tisa-cel in B cell ALL or relapsed B cell ALL</u>
    - Dosage concentration (i.e. patients weight $\leq$ 50 kg, patients weight $>$ 50 kg).
    - Type of lymphodepleting chemotherapy (e.g. fludarabine and cyclophosphamide, cytarabine and etoposide).

    - Pre-medication regimen (e.g. H1 antihistamine, etc.) administered as part of the CAR T cell therapy.
- Tisa-cel in relapsed or refractory DLBCL
    - Type of lymphodepleting chemotherapy (e.g. fludarabine and cyclophosphamide or bendamustine).
    - Pre-medication regimen (e.g. H1 antihistamine, etc.) administered as part of the CAR T cell therapy.
- Axi-cel in relapsed or refractory DLBCL
    - Dosage concentration (i.e. patient weight $<$ 100 kg, patient weight $\geq$ 100 kg).
    - Pre-medication diphenhydramine administration route (i.e. oral or intravenous).
- Axi-cel in refractory or relapsed PMBCL
    - Dosage concentration (i.e. patient weight $<$ 100 kg, patient weight $\geq$ 100 kg).
    - Pre-medication diphenhydramine administration route (i.e. oral or intravenous).

Sensitivity analyses will be conducted to investigate the impact of methodological factors on the reported results of the clinical evaluation of RCTs and NRSIs.[61] The sensitivity analyses will be conducted using the methods described in ***Section 6.5.1*** and ***6.5.2***. These will include:

- Risk of bias due to confounding
- Risk of bias due to selection bias
- Risk of bias due to information bias

6.5.5 Imputation methods for dealing with missing values

Missing SDs will be 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 are unavailable to calculate SD, it will be imputed using the 'impute_SD' function in the *R* (version 1.4) package 'metagear', following the imputation methods described by Braken et al., 1992.[71-74] Where continuous values need to be combined, formulae detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.1)* will be used. For studies that report outcomes graphically, *WebPlotDigitizer* will be used to convert graph points into numerical values.[63]

6.5.6 Narrative synthesis

If fewer than 2 comparative studies report an outcome, meta-analysis will not be possible. In such cases, the results will be tabulated and described narratively in the text. For continuous outcomes, the mean change from baseline or final follow-up score and standard deviation will be reported for each study arm, as well as the mean difference and 95% confidence interval comparing the mean effects between groups. For dichotomous outcomes, event rates for each trial arm will be reported along with a risk ratio or odds ratio and 95% confidence interval comparing the event rates between groups.

If only single-arm studies are available for the intervention, meta-analysis will not be conducted. In this situation, the results for each study will be tabulated and reported narratively. Indirect, naïve comparisons to single-arm studies of comparator interventions will not be conducted, owing to the methodological concerns associated with this approach.[55]

7 Methodology: Health economic evaluation

Here, the systematic literature review informing the proposed methodology (***Section 7.1***) and the planned approaches for the economic and budget impact analyses (***Section 7.3*** and ***Section 7.4***) are discussed.

7.1 Review of existing cost-effectiveness studies

7.1.1 Methods

7.1.1.1 Study selection

The target populations, interventions (axi-cel and tisa-cel) and comparator (standard care) components of the PICO guiding the review of economic studies were previously described (***Section 4***). Regarding the outcomes, only full economic evaluations (studies that value both costs and benefits of different treatments) were included.

The search strategy outlined in ***Table 12***, ***Table 13*** and ***Table 14***, ***Appendix B*** was used to identify full economic evaluations assessing the cost-effectiveness of axi-cel or tisa-cel compared to standard of care in either population (adults with relapsed or refractory DLBCL or PMBCL, or children or young adults with relapsed or refractory B cell ALL). Searches were conducted in Ovid (Medline and Embase), and Econlit. Previous HTAs that have considered the intervention(s) of interest within the target population were identified via searches of the International HTA Database.

For axi-cel, studies considering relapsed or refractory large B cell lymphoma (LBCL)—a broader population than those defined in the population components of the PICOs—were also included.

7.1.1.2 Data extraction, analysis and synthesis

Data pertaining to the following domains were extracted from the identified cost-effectiveness analyses and are presented in the ***HTA Protocol***: first author, publication year, country, perspective, target population, intervention(s), comparators(s), analysis methods (model type and structure, time horizon and discount rate), sources of clinical evidence, quality of life inputs, adverse events, conflicts of interest. At this stage of the HTA process, the purpose of the systematic review of cost-effectiveness studies was to inform the economic evaluation methodology. Results data have therefore not been included in the ***HTA Protocol***, but will be extracted and presented in the ***HTA Report.***

The extraction template is available in ***Table 15***, ***Appendix C***. Findings are described narratively (***Section 7.1.2.2***).

In addition, data relating to several of these domains were extracted from the identified HTAs, along with associated concerns raised in critiques of manufacturers' submissions. This was a high-level extraction to guide the economic evaluation methodology; thus, not all information available in the HTA reports and accompanying critiques are included. Nevertheless, the extraction template is provided in ***Table 19*** (***Appendix D***). Results of both the original submission and any reanalyses will be extracted and presented in the ***HTA Report***.

7.1.1.3 Assessment of applicability

Each cost-effectiveness analysis was assessed against the applicability checklist items outlined by the National Institute for Health and Care Excellence (NICE).[75] The applicability appraisal template is available in ***Table 16***, ***Appendix C***. This checklist asks one 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 depending on whether all applicability criteria were met and if these were unmet, whether this misalignment could change or was likely to change the conclusions about cost effectiveness. Judgements were largely based on the alignment of each study with the PICO criteria and on the setting in which the evaluation was conducted. Only Swiss-specific evaluations were judged as directly applicable.

The purpose of this assessment was to guide our decision regarding the necessity of *de novo* modelling. The applicability of the existing evidence to the evaluation context is described narratively (***Section 7.1.2.3***).

7.1.1.4 Assessment of study reporting quality

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 (see ***Table 18***, ***Appendix C***).[76] Results of the assessment(s) are described narratively (***Section 7.1.2.4***).

7.1.2 Results of the literature review

7.1.2.1 Search results

A PRISMA flowchart summarising the overall systematic literature search will be included in the ***HTA Report***. Lists of the included economic evaluations and HTAs are available in ***Appendix C***. In brief, 16 cost-effectiveness studies (***Section 7.1.2.2.1*** and ***Section 7.1.2.2.2***) and 9 HTAs with an economic evaluation component (***Section 7.1.2.2.3***) were identified.

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 (***Section 7.1.2.2.4***).

7.1.2.2 Summary of findings

7.1.2.2.1 Study characteristics

The retrieved studies included economic evaluations from Canada,[77] Japan,[78,79] the Netherlands,[80] Singapore,[81-83] Spain,[84] Switzerland[85] and the United States.[86-92] All studies evaluated the cost-utility of CAR T cell therapies (tisa-cel and/or axi-cel) over a lifetime horizon.

Overall, 6 studies evaluated tisa-cel for adults with relapsed or refractory DLBCL,[78,81,82,85-87] while 8 studies evaluated tisa-cel for children or young adults with relapsed or refractory B cell ALL.[79,80,83-85,89,91,92] Most studies evaluating axi-cel assessed its cost-effectiveness as a treatment for adults with relapsed or refractory large B cell lymphoma (LBCL), which combines DLBCL, PMBCL and transformed follicular lymphoma. This aligns with the population included in the ZUMA-1 trial.[93] In total, 3 studies evaluated axi-cel for adult patients with LBCL.[77,88,90] One study evaluated axi-cel for DLBCL, although it also used clinical data from the ZUMA-1 trial.[86]

Of the 6 studies evaluating tisa-cel in DLBCL, 4 were funded by the company (Novartis) who developed Kymriah® (tisa-cel proprietary drug),[78,82,85,87] while 5 of the 8 studies evaluating tisa-cel in B cell ALL were supported by Novartis.[79,80,83-85] Two of 3 studies evaluating axi-cel in LBCL were funded by the

company (Kite, a Gilead company) who developed Yescarta® (axi-cel proprietary drug).[77,88] Modelling techniques employed across each of these groups of company funded studies appear similar.

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 stem cell transplantation (SCT) in some patients. For studies including a population of adults with LBCL, the comparator included salvage chemotherapy or BSC chemotherapy, followed by SCT in some patients. Clinical data were sourced from either the CORAL extension studies or the SCHOLAR-1 trial.[94-96]

For studies including a population of children and young adults with B cell 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.[97-102]

7.1.2.2.2 Model features

Most studies used a hybrid decision tree and 3-state partitioned survival model (PSM) structure,[78,79,81-83,85,87,90,91] or a 3-state PSM structure without mention of a decision tree.[77,80,84,88] Where employed, the decision tree was used to separate infused versus non-infused patients (CAR T 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, progressed disease and dead (for B cell ALL populations). Where specified, event-free survival was defined as the time from treatment initiation to the earliest of either treatment failure, relapse or death.[79] For one model, an additional Markov component, which was used beyond year 5 of the PSM simulation, was described.[91] Two studies used a Markov cohort model,[86,92] while another used a microsimulation state transition model.[89] All studies used a 1-month cycle length.

7.1.2.2.3 Previous HTAs

Published HTAs including economic evaluation sections were identified from 3 organisations: NICE (the United Kingdom), the Canadian Agency for Drugs and Technologies in Health (CADTH) (Canada) and the Institut National d'Excellence en Santé et en Services Sociaux (INESSS) (Canada) (see ***Appendix D***).

All 3 organisations have published HTAs assessing tisa-cel for adult patients with relapsed or refractory DLBCL,[103-105] tisa-cel for children and young adults with relapsed or refractory B cell ALL,[106-108] and axi-cel for adult patients with relapsed or refractory LBCL.[109-111] 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.

7.1.2.2.4 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.[112] This included the development of an exemplar economic model to assess the cost-effectiveness of CAR T cell therapy relative to standard care (clofarabine in the base case) for children and young adults with 2 or more relapses or refractory ALL.[112]

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.[112] 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, and dead. State occupancy was derived via the direct extrapolation of event-free survival and OS curves.

Both models used a lifetime horizon and 1-month cycle length, and measured health effects in terms of QALYs.[112] Patients who were alive at 5 years were assumed to be long-term survivors of ALL. The costs and consequences of treatment-related adverse events (cytokine release syndrome, B cell aplasia, encephalopathy, hypotension, febrile neutropaenia, neutropaenia, anaemia, thrombocytopaenia, 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.[112] 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.

7.1.2.3 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 cell ALL.[85]

The remaining studies were only partially applicable to this HTA, having been conducted in healthcare contexts outside of Switzerland. 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 4***), which consider DLBCL and PMBCL populations separately.

The results of all identified studies will be compared with the Swiss-specific estimates derived for this HTA.

7.1.2.4 Quality of reporting of the evidence

The one directly applicable study fulfilled 24 of the 28 CHEERS checklist items (see ***Table 18***, ***Appendix C***),[76,85] indicating a high quality of reporting.

7.2 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.[85] This study may provide useful information for this HTA about the cost-effectiveness of tisa-cel in the 2 target populations. Nevertheless, this study has a conflict of interest, having been funded by the company (Novartis) who developed Kymriah® (tisa-cel proprietary drug). Until the clinical review is underway, it cannot be judged whether the estimates of baseline outcomes and relative treatment effects are from the best available sources, or if the assumptions made are reasonable. A full assessment of the study limitations (e.g. using NICE's study limitations checklist items)[75] will be undertaken as part of the HTA. If no major limitations are identified, the existing evidence for these 2 populations could be reported narratively.

Nevertheless, a data gap remains regarding the cost-effectiveness of axi-cel relative to standard care for adults with DLBCL or PMBCL in Switzerland. *De novo* economic modelling, guided by the existing evidence base, will therefore be required to assess the cost-effectiveness of axi-cel in these populations. To ensure consistency across the HTA, it is likely that *de novo* modelling will be undertaken for all 3 populations included in this HTA, and a comparison made with existing evidence, including any re-analyses performed from previous HTAs.

Given the need for *de novo* analysis, the planned modelling approach is outlined below. Reporting of the *de novo* economic evaluation(s) would follow the CHEERS statement.[76]

7.3 Economic evaluation methodology

7.3.1 Research question

The target population, interventions (axi-cel and tisa-cel) and comparator (standard care) were previously described (***Section 4***). Remaining aspects of the decision problem are addressed below. These include the perspective, time horizon, outcome measures and a representative definition of standard care required for the economic analyses.

7.3.1.1 Perspective

A Swiss healthcare payer perspective will be adopted. Direct medical costs for services covered by mandatory health insurance will be included, irrespective of the actual payer (e.g. health insurers, other social insurers, the government (federal government, cantons, communities) or patients). Non-medical and indirect costs (e.g. travel costs, informal care or productivity losses) will not be considered. Costs will be reported in Swiss Francs (CHF) for a common costing year of 2023.

7.3.1.2 Time horizon

The time horizon of an economic evaluation should be long enough to capture in full the differences in costs and effects of the options being compared.[113] To capture these differences fully, a lifetime horizon will likely be required as CAR T cell therapies are intended to improve the prognosis of patients with cancer. Nevertheless, this would require extrapolation of observed data, increasing uncertainty in the evaluation.

7.3.1.3 Outcomes

Health outcomes will be measured in terms of life years (LYs) and quality-adjusted life years (QALYs) lived.

Incremental cost, incremental LYs gained and incremental QALYs gained with CAR T cell therapies relative to standard care will be reported. The end result of the economic evaluation will be the incremental cost-effectiveness ratio (ICER), reflected as both the incremental cost per LY gained and the incremental cost per QALY gained. Both costs and effects will be discounted at 3.0% per annum, with alternate rates of 0% and 6% per annum used in sensitivity analysis.

7.3.1.4 Relevant comparators to the Swiss context

Discussions with a clinical expert highlighted that standard care for patients with relapsed or refractory disease is highly variable—some patients may receive salvage chemotherapy, 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 cannot be incorporated into the cost analysis. Instead,

a representative definition of what standard care is likely to look like for the target populations in Switzerland has been constructed to guide the targeted literature searches for clinical evidence (if required), the assessment of applicability of the available evidence to the Swiss context and the costing of the comparator arm.

To identify the most representative examples of standard care for the economic model, 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 2 most relevant or most commonly used (the list of comparators given to the experts is provided in ***Section 11.4.6***, ***Appendix D***). 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 whilst palliation is also an option, patients One clinical expert noted that the comparator could be individualised bridge to transplant, including would often still receive an initial treatment (as mentioned above) without going on to transplant.

Adult DLBCL:

- Salvage chemotherapy, with any of the following regimens: rituximab, gemcitabine, and oxaliplatin; rituximab and bendamustine; rituximab, polatuzumab and bendamustine; tafasitamab and lenalidomide; gemcitabine and oxaliplatin
- Palliation

One clinical expert noted that the approved salvage chemotherapy regimens are not intended to cure but are generally given as a bridge [to allogenic SCT].

Adult PMBCL:

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

7.3.2 Planned modelling approach

The planned modelling approach is a hybrid decision tree and 3-state model, built around the health states of alive and progression free, alive with progressive or relapsed disease, and dead. Treatment

discontinuations (i.e. patients in the CAR T arm who discontinue treatment or die prior to infusion), subsequent therapies (notably, subsequent SCT) and, potentially, response to treatment may be incorporated as decision nodes prior to the 3-state model. Adverse events will likely be built into the model as costs and utility reductions.

In our model, patients who discontinue CAR T cell therapy prior to infusion will either be assumed to receive an active comparator or palliative care (yet to be decided). In NICE's critique of the manufacturer's submission for B cell ALL, it was felt that assuming CAR T cell therapy patients not receiving the infusion receive comparator therapies instead is problematic, as these patients have faced a significant delay in treatment and/or have experienced adverse events and are therefore likely to be in poorer health and proceed to palliative care.[106]

Most published studies have used PSMs. In a PSM, the proportion of a cohort in each health state is based upon parametric survival equations.[114] This is a common modelling approach for cancer treatments, with separate survival equations for OS and PFS.[114] Were this approach to be adopted in this HTA, it would likely require the digitisation of published Kaplan Meier curves and the generation of pseudo-individual patient data using a published algorithm,[115] as described in the York mock technology appraisal and a number of published studies.[78,81-83,85,90,91,112]

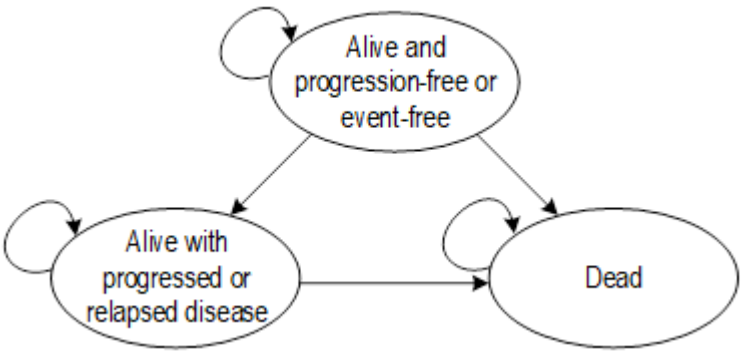
If a 3-state PSM approach was adopted (example provided in ***Figure 2***), health state occupancy would be determined by the following equations:[112]

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 2 Planned structure for a partitioned survival analysis



Source:
Based on the illustration provided for the York mock model.[112]

Alternatively, a 3-state Markov cohort model, considering similar states as described for the PSM (***Figure 2***), could be utilised, with monthly probabilities of progression/relapse and death derived from available data.

It is likely that an assumed timepoint beyond which patients would be considered long-term survivors will be built into the analysis. Based on existing models, this could be between 2 and 5 years, depending on the population,[77-80,82,85,88,91] although the most appropriate timepoint will be further explored in the HTA. 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.[103]

The economic evaluation will also account for treatment-related adverse events associated with CAR T cell therapy and comparator therapies. For CAR T cell therapy, these include cytokine release syndrome, neurological toxicity, infection, B cell aplasia and viral re-activation. Additional adverse events relating to CAR T cell therapy, as well as those associated with the comparator therapies will be informed by the clinical review. Some adverse events are likely to occur during the hospitalisation episode for infusion. Costs and consequences relating to such adverse events could be accounted for at the beginning of the simulation. Other adverse events, such as B cell aplasia, may require ongoing treatment and would be incorporated accordingly into the model.

7.3.2.1 The role of SCT

Patients may receive subsequent SCT after CAR T cell therapy. Clinical advice is that, when CAR T is given in the third-line setting, all subsequent SCTs would be allogenic, not autologous. Further clinical advice suggests that, for paediatric patients, it is becoming increasingly clear that many physicians expect CAR T to be more frequently (in up to 50% of patients) used as a bridge to SCT. It is likely that receipt of SCT will be incorporated into the decision tree component of the model. Adverse events associated with SCT will be considered when determining costs and utility decrements associated with SCT. The proportion of patients receiving SCT could be based directly on Swiss registry data. Nevertheless, this dataset is yet to mature, with longer-term (e.g. 12-month) follow-up available for a limited number of patients only. Care will be taken in interpreting the available data.

Regarding the comparator arm, it seems SCT plays a smaller role, with clinical advice suggesting SCTs are unlikely in the third-line setting. Nevertheless, individualised bridges to transplant may be considered for paediatric patients.

7.3.3 Clinical inputs

Data sources informing PFS, OS, treatment discontinuation and adverse event rates for patients receiving CAR T cell therapies will be selected from the studies included in the clinical review (***Section 6***).

Data sources will be selected for use in the economic evaluation according to their level of evidence. Data obtained from RCTs will be prioritised, as they provide estimates for both CAR T cell therapies and comparator therapies in comparable patient groups. In the absence of RCT evidence, NRSIs will be considered. In the absence of any comparative evidence, data from single-arm studies will be utilised.

The clinical review will be limited to studies including a CAR T cell therapy arm. If single-arm study data are required for the economic evaluation, additional evidence for the comparator arm will be needed so that the incremental benefit of CAR T cell therapy can be assessed. A pragmatic approach would be taken to identify 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. This would be supplemented with targeted literature searches for the specific treatment regimens outlined previously (***Section 7.3.1.4***).

If data from single-arm studies are used for the economic evaluation, the incremental benefit of CAR T cell therapy will be based upon a naïve treatment comparison between CAR T cell therapy and the comparator. A critical review of the patient populations included in the single-arm studies would be undertaken to critically analyse the comparability of the populations. Nevertheless, such comparisons would introduce significant uncertainty into the evaluation.

To estimate QALYs, health state utilities and treatment-related and adverse event-related disutilities will be incorporated into the model. Health state utilities may already account for the impact of treatment-related adverse-events on patient quality of life—care will be taken to ensure that there is no double-counting. A pragmatic approach will be taken to identify potentially relevant sources for utilities and disutilities, including a search of known economic evaluations and HTAs for the populations of interest, as well as targeted literature searches as required.

7.3.4 Cost inputs

Cost components relating to CAR T cell therapies and comparator therapies, including those around patient follow-up and subsequent therapies (e.g. SCT) are summarised below (***Section 7.3.4.1*** and ***Section 7.3.4.2***).

Healthcare resource use for each of the components listed, will be identified, measured and valued as part of the HTA. Resource utilisation will be informed by peer-reviewed or grey literature sources, with preference given to Swiss-specific sources. If only international sources are identified, consideration will be given to the applicability of the data to the Swiss context. Where data gaps remain, expert opinion will be sought.

Swiss-specific cost data will be sourced using resources such as 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.

7.3.4.1 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 intensive care unit stays, treatment-related adverse events, subsequent SCT, other subsequent therapies (as relevant), patient follow-up and terminal care.

Discussions with clinical experts have indicated that, in Switzerland:

- leukapheresis may be provided in either the inpatient or outpatient setting with a lump sum payment (more often inpatient for paediatric patients)
- bridging chemotherapy (used by two thirds to 80% of patients) is generally provided in an inpatient setting (for approximately 60% of adults and the majority of children), while bridging radiotherapy is general provided in the outpatient setting (predominantly in adults)
- lymphodepleting chemotherapy may be provided in either an inpatient or outpatient setting (typically inpatient for paediatric patients)
- infusion of CAR T cells would occur in an inpatient setting
- follow up after CAR T cell therapy varies between patients. It may—for patients achieving a long-term response—include weekly blood tests (30-minute clinical visit) for the first month, which will be extended to every 2–3 weeks, then every 3 months
- PET/CT scans will be done at month 3 and 6 to ensure remission, and as clinically indicated thereafter
- some patients will require monthly intravenous immunoglobulin after CAR T cell therapy for an unknown duration to treat B cell aplasia (cost coverage from health insurance)
- in paediatrics, CAR T is sometimes used as a bridge to allogenic SCT.

Swiss Registry data will be used as a source of information on the number of patients experiencing certain adverse events, requiring IVIG to treat B cell aplasia, or receiving post-CAR T anti-tumour therapies (including SCT) or other treatments within the Swiss context. However, this dataset is yet to mature; therefore, care will be taken in interpreting the available data.

Confidentiality of the CAR T cell therapy product prices will be maintained throughout the HTA process, where necessary. An external price will be used and sensitivity analysis in relation to the CAR T product price undertaken. This will include one-way DSA as well as an exploration of the required product price for the ICER to meet various threshold values.

7.3.4.2 Comparator costs

Costs for comparator therapies may include those for chemotherapy, immunotherapy or palliative care (e.g. palliative radiotherapy) as well as subsequent SCT, treatment-related adverse events, patient follow-up and terminal care. The comparator arm will be costed according to the representative examples outlined in ***Section 7.3.1.4***.

7.3.5 Accounting for uncertainty

Uncertainties in the base case estimates will be explored using one-way deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA).

One-way DSAs will allow the key model drivers to be identified. The range over which each parameter is varied will reflect 95% confidence intervals if reported or estimable, highest and lowest values if a range is available or, in the absence of a confidence interval or range, be assumed by varying the base case estimate by an arbitrary percentage amount (e.g. ±20%).[116,117] Results will be presented both visually using tornado diagrams and in table format.

PSAs capture the joint uncertainty across model parameters, giving decision-makers information on the overall certainty of the economic outcomes. Distributions representing uncertainty around the mean estimate will be imposed on model inputs. The choice of distribution will depend on the information available and the nature of the input parameter. For example, a gamma distribution may be used for cost data, a beta distribution for utility data, or a lognormal distribution for relative risks or hazard ratios.[116,117] Consistency will be sought between the ranges used in DSA and the distribution parameters used in the PSA. Results will be presented as scatter plots with 95% confidence ellipses on the cost-effectiveness plane. Cost-effectiveness acceptability curves (CEACs) will also be produced.

Should a PSM approach be adopted, further sensitivity analyses would be undertaken to vary the type of survival function.[114] Whittington et al. describe the use of 5 survival models that account for variation in long-term survival assumptions.[90]

Reporting will describe how uncertainty in the model inputs effect economic findings. There is no accepted willingness to pay (WTP) threshold in Switzerland. Using CEAC curves produced via PSAs, the probability of cost-effectiveness will be expressed as a function of WTP.

7.3.6 Summary

Table 4 Overview of the planned economic analysis

Perspective	Swiss healthcare payer
Patient populations	• children and young adults (up to age 25) with refractory B cell ALL or relapsed B cell 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**: used either as a bridge to SCT or with curative intent
Comparator	Standard care, including chemotherapy, immunotherapy and/or palliative care **Note**: in some instances, standard care may be used as a bridge to SCT
Type of economic evaluation	CUA
Time horizon	Lifetime
Sources of inputs	Published meta-analyses, RCTs, observational studies and/or single-arm studies, Spezialitätenliste, Analysenliste, TARMED, Swiss DRGs, 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	Planned approach is hybrid decision tree and 3-state model (PSM or Markov cohort)
Discount rate	3.0% per annum for costs and QALYs (0% and 6% in sensitivity analysis)

Abbreviations

ALL = acute lymphoblastic leukemia, **axi-cel** = axicabtagene ciloleucel, **BSC** = best supportive care, **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, **RCT** = randomised controlled trial, **SCT** = stem cell transplantation, **tisa-cel** = tisagenlecleucel.

7.4 Budget impact analysis

7.4.1 Research question

The intention of this section of the HTA will be to explore the potential budget impact of continued funding of CAR T cell therapies for currently reimbursed populations. This will include 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, will be estimated over a 5-year period. CAR T cell therapies may be a final therapy for some patients, replacing standard care, while others may receive SCT or other follow-up therapies subsequent to cell therapies. The budget impact model will consider that CAR T cell therapy may be either a substitute for or an addition to the comparator, standard care.

7.4.2 Planned 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.[118] 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.[1]

Under one scenario, the intervention mix will continue to include CAR T cell therapy, while in the comparator scenario, CAR T cell therapy would not be included in the intervention mix (i.e. all patients receive comparator standard care). The BIA will consider the differences in healthcare costs between these 2 scenarios.

7.4.2.1 Patient numbers

Epidemiological estimates will be sourced to provide information on the number of patients within each of the target populations in Switzerland. Such estimates would be 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 will be sourced from the Swiss CAR T cell therapy registry, which provides information on the annual number of patients in Switzerland treated with CAR T cell therapy between 2019 and 2021. This information is available separately for each population defined in the PICO (***Section 4***). Differences in utilisation across years may provide insight into recent uptake trends of the technology within Switzerland. This could be used to project continued uptake under the scenario in which funding for CAR T cell therapy by the Swiss mandatory health insurance system is continued. Nevertheless, additional factors, such as the number of centres using CAR T cell therapies or the recent COVID-19 pandemic, may also need to be factored into the projected uptake estimates.

7.4.2.2 Cost inputs

Undiscounted yearly costs from the first 5 years of the economic model will likely be extracted to inform the annual per patient costs for each strategy. In year 1 of the BIA, fist year costs for incident patients would be valued as the year 1 costs from the economic model. In year 2 of the BIA, incident patients from year 1 would incur the year 2 costs extracted from the model while new incident patients would incur the extracted first year costs. If this approach were adopted, the mortality of earlier-year incident patients as well as the incidence and associated costs of adverse events (including B cell aplasia) and subsequent therapies (including SCT) would be quasi-automatically captured.

7.4.2.3 Accounting for uncertainty

All major assumptions will be tabulated, as will all input parameters and their data sources. Scenario analyses will be used to explore the impact of certain assumptions on the results, while one-way sensitivity analysis will be undertaken to identify key drivers of the BIA.

8 Methodology: legal, social, ethical and organisational issues

The social, legal, ethical and organisational analyses will be informed primarily by the EUnetHTA Core Model Version 3.0.[119] In addition, the evaluation of legal issues associated with CAR T cell therapies will be structured using a perspectival framework, considering outside and inside perspectives, as described by Widrig and Tag.[120]

The systematic literature searches detailed in ***Section 6.1*** will be 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 will be conducted. Systematic reviews, literature reviews, RCTs, non-randomised studies, single-arm studies, ethnographic studies, phenomenological studies, narrative research and case studies will be considered for inclusion. The included literature will be ordered in tables describing the study characteristics and key findings. The results will be synthesised narratively.

9 Summary and outlook

The proposed HTA will evaluate the safety, efficacy/effectiveness, costs, cost-effectiveness and budget impact of tisa-cel and axi-cel, separately, in patients with B cell ALL, DLBCL and PMBCL.

For the clinical evaluation, meta-analysis will be conducted if at least two comparative studies evaluating tisa-cel or axi-cel to a relevant comparator exist; in the absence of comparative evidence, the clinical evaluation will synthesise published single-arm evidence on tisa-cel and axi-cel, separately; indirect comparisons between each CAR T therapy and a comparator will not be conducted.

For the economic evaluation, it seems likely that a naïve treatment comparison between CAR T-cell therapy and comparator therapies will be required, introducing uncertainty into the analysis. This will require targeted literature searches for clinical data on comparator regimens. In Switzerland, confidential net price agreements between health insurance and licence holder companies enable the reimbursement of the CAR T cell therapy products. The economic evaluation and budget impact analysis is therefore likely to be based upon uncertain, external product prices.

The HTA protocol is followed by production of the HTA report. The external review group that was consulted during the protocol phase is consulted again during the HTA phase. Subsequently the HTA draft report is presented to the stakeholders for consultation. Communication with the reviewers and the stakeholders is coordinated by the FOPH.

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11 Appendices

11.1 Appendix A: Literature sources and search strings

Table 5 Search strategy – Ovid (Medline and Embase)

PICO domain	#	Search term
Intervention terms	1	Tisagenlecleucel*.tw.
	2	Kymriah*.tw.
	3	Axicabtagen*
	4	Yescarta*
	5	axi-cel*
	6	CART-19.tw.
	7	CAR19.tw.
	8	CART 19.tw.
	9	"ctl 019".tw.
	10	ctl019.tw.
	11	Receptors, Antigen, T cell.sh.
	12	Receptors, Chimeric Antigen.sh.
	13	Immunotherapy, Adoptive.sh.
Intervention 1	**14**	**1 OR 2 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13**
Intervention 2	**15**	**3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13**
Population 1	16	B cell acute lymphoblastic leukaemia.tw.
	17	B cell acute lymphoblastic leukemia.tw.
	18	acute lymphocytic leukaemia.tw.
	19	acute lymphocytic leukemia.tw.
	20	B cell ALL.tw.
	21	Precursor B cell lymphoblastic leukemia-lymphoma.sh.
	22	**16 OR 17 OR 18 OR 19 OR 20 OR 21**
Population 2	23	Diffuse large B cell lymphoma.tw.
	24	DLBCL.tw.
	25	lymphoma, large B cell, diffuse.sh.
	26	Lymphoma, Non-Hodgkin.sh.
	27	Lymphoma, B cell.sh.
	28	**23 OR 24 OR 25 OR 26 OR 27**
Population 3	29	Primary mediastinal large B cell lymphoma.tw.
	30	MPMBCL.tw.
	31	PBCL.tw.
	32	PMBCL.tw.
	33	mediastinal neoplasms.tw.

	34	**29 OR 30 OR 31 OR 32 OR 33**
	35	14 AND 22
	36	(14 OR 15) AND 28
	37	15 AND 34
Combined search	**38**	**35 OR 36 OR 37**
Limits	39	Limit 38 to human, publication from 1/1/2010

Table 6 Search strategy – The Cochrane Library

PICO domain	#	Query
Intervention terms	1	(Tisagenlecleucel*):ti,ab,kw
	2	(Kymriah*):ti,ab,kw
	3	(Axicabtagen*):ti,ab,kw
	4	(Yescarta*):ti,ab,kw
	5	(Axi-cel*):ti,ab,kw
	6	(CART-19):ti,ab,kw
	7	(CAR19):ti,ab,kw
	8	(CART 19):ti,ab,kw
	9	(ctl 019):ti,ab,kw
	10	(ctl019):ti,ab,kw
Combined search	**11**	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13**

Table 7 Search strategy – Econlit

PICO domain	#	Query
Intervention terms	1	TX Tisagenlecleucel*
	2	TX Kymriah*
	3	TX Axicabtagen*
	4	TX Yescarta*
	5	TX Axi-cel*
	6	TX CART-19
	7	TX CAR19
	8	TX CART 19
	9	TX ctl 019
	10	TX ctl019
	11	TX car t-cell therapy
Combined search	**11**	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13**

Table 8 Search strategy – International HTA Database

PICO Domain	#	Query
Intervention terms	1	Tisagenlecleucel
	2	Kymriah
	3	Axicabtagen*
	4	Yescarta
	5	CAR T*
	6	CAR-T*
Combined search	**7**	**1 OR 2 OR 3 OR 4 OR 5 OR 6**

Table 9 Search strategy – Clinicaltrials.gov

PICO Domain	#	Query
Intervention terms	1	Tisagenlecleucel
	2	Axicabtagene*
	3	Yescarta
	4	Kymriah
Combined search	**5**	**1 OR 2 OR 3 OR 4**

Table 10 Search strategy – EU Clinical trials registry

PICO Domain	#	Query
Intervention terms	1	Tisagenlecleucel
	2	Axicabtagene*
	3	Yescarta
	4	Kymriah
Combined search	**5**	**1 OR 2 OR 3 OR 4**

Table 11 HTA agency websites

HTA Websites	
Global	
INAHTA HTA Database	
Australia	
Adelaide Health Technology Assessment (AHTA)	https://www.adelaide.edu.au/ahta/pubs/
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S)	https://www.surgeons.org/research-audit/research-evaluation-inc-asernips
Austria	
Austrian Institute for Health Technology Assessment (AIHTA)	https://aihta.at/page/homepage/en

Gesundheit Österreich GmbH (GOG)	http://www.goeg.at
Argentina	
Institute for Clinical Effectiveness and Health Policy (IECS)	http://www.iecs.org.ar
Belgium	
Belgian Health Care Knowledge Centre (KCE)	http://kce.fgov.be
Brazil	
National Committee for Technology Incorporation (CONITEC)	http://conitec.gov.br/en/
Agência Nacional de Saúde Suplementar/ National Regulatory Agency for Private Health Insurance and Plans (ANS)	https://www.gov.br/ans/pt-br
Canada	
Institute of Health Economics (IHE)	http://www.ihe.ca
Institut National d'Excellence en Santé et en Services (INESSS)	https://www.inesss.qc.ca/en/home.html
The Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/
Ontario Health (OH)	https://www.ontariohealth.ca/
Colombia	
Instituto de Evaluación Tecnológica en Salud (IETS)	http://www.iets.org.co
Denmark	
Social & Health Services and Labour Market (DEFACTUM)	http://www.defactum.net
Finland	
Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	https://www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/HTA-julkaisuja.aspx
France	
French National Authority for Health (Haute Autorité de Santé; HAS)	http://www.has-sante.fr/
Assistance Publique – Hôpitaux de Paris	http://cedit.aphp.fr
Germany	
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA)	https://www.g-ba.de/english/
Ireland	
Health Information and Quality Authority (HIQA)	http://www.hiqa.ie
Italy	
Agenzia Sanitaria e Sociale Regionale (ASSR)	http://www.inahta.org/members/assr/
HTA Unit in A. Gemelli Teaching Hospital (UVT)	https://www.policlinicogemelli.it/
National Agency for Regional Health services (Agenas)	http://www.agenas.it
Kazakhstan	
Ministry of Public Health of the Republic of Kazakhstan, Republican Centre for Health Development (RCHD)	http://www.rcrz.kz
Korea	
National Evidence-based healthcare Collaborating Agency (NECA)	www.neca.re.kr/eng
Malaysia	
Health Technology Assessment Section, Ministry of Health Malaysia (MaHTAS)	http://www.moh.gov.my
The Netherlands	
The Netherlands Organisation for Health Research and Development (ZonMw)	http://www.zonmw.nl
Zorginstituut Nederland (ZIN)	https://www.zorginstituutnederland.nl/

Norway	
The Norwegian Institute of Public Health (NIPHNO)	http://www.fhi.no/
Peru	
Institute of Health Technology Assessment and Research (IETSI)	http://www.essalud.gob.pe/ietsi/
Poland	
Agency for Health Technology Assessment and Tariff System (AOTMiT)	http://www.aotm.gov.pl
Republic of China, Taiwan	
Center for Drug Evaluation (CDE)	http://www.cde.org.tw
Singapore	
Agency for Care Effectiveness (ACE)	Agency for Care Effectiveness (ACE) (ace-hta.gov.sg)
Spain	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I / Health Technology Assessment Agency (AETS)	http://publicaciones.isciii.es/
Agency for Health Quality and Assessment of Catalonia (AQuAS)	http://aquas.gencat.cat
Andalusian HTA Agency	http://www.aetsa.org/
Basque Office for Health Technology Assessment (OSTEBA)	http://www.euskadi.eus/web01-a2ikeost/en/
Galician Agency for Health Technology Assessment (AVALIA-T)	http://acis.sergas.es
Health Sciences Institute in Aragon (IACS)	http://www.iacs.es/
Sweden	
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
Switzerland	
Swiss Federal Office of Public Health (SFOPH)	http://www.bag.admin.ch/hta
Tunisia	
INEAS – National Authority for Assessment and Accreditation in Healthcare, TUNISIA	http://www.ineas.tn/fr
United Kingdom	
Healthcare Improvement Scotland (HIS)	http://www.healthcareimprovementscotland.org
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
Health Technology Wales (HTW)	http://www.healthtechnology.wales
National Institute for Health Research (NIHR), including HTA programme	http://www.nets.nihr.ac.uk/programmes/hta
United States	
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/research/findings/index.html

Source:
Based on the INAHTA members list[121]

11.2 Appendix B: Economic search results

Table 12 Economic search results: Ovid (Medline and Embase)

#	Query	Results from 7 Nov 2022
1	(Tisangenlecleucel* or Kymriah* or CART-19 or CAR19 or CART 19 or "ctl 019" or ctl019).tw. or Receptors, Antigen, T cell.sh. or Receptors, Chimeric Antigen.sh. or Immunotherapy, Adoptive.sh.	39,454
2	(B cell acute lymphoblastic leukaemia or B cell acute lymphoblastic leukemia or acute lymphocytic leukaemia or acute lymphocytic leukemia or B cell ALL).tw. or precursor B cell lymphoblastic leukemia-lymphoma.sh.	18,914
3	1 and 2	852
4	(Axicabtagen* or Yescarta* or axi-cel* or KTE-C19 or CART 19 or "ctl 019" or ctl019).tw. or Immunotherapy, Adoptive.sh. or Receptors, Antigen, T cell.sh. or Receptors, Chimeric Antigen.sh.	39,309
5	1 or 4	40,129
6	(Diffuse large B cell lymphoma or DLBCL).tw. or lymphoma, large B cell, diffuse.sh. or Lymphoma, Non-Hodgkin.sh. or Lymphoma, B cell.sh.	105,893
7	5 and 6	1,936
8	(Primary mediastinal large B cell lymphoma or MPMBCL or mediastinal neoplasms).tw. or lymphoma, large B cell, diffuse.sh. or Lymphoma, Non-Hodgkin.sh. or Lymphoma, B cell.sh.	68,661
9	4 and 8	1,103
10	3 or 7 or 9	2,648
11	limit 10 to human	2,500
12	Economics/	271,380
13	Cost/	112,410
14	exp Health Economics/	2,632,178
15	budget*.ti,ab,kf.	80,064
16	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	598,852
17	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	858,896
18	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	473,547
19	(value adj2 (money or monetary)).ti,ab,kf.	6,782
20	Statistical Model/	270,506
21	economic model*.ab,kf.	9,905
22	Probability/	194,464
23	markov.ti,ab,kf.	63,559
24	monte carlo method/	79,505
25	monte carlo.ti,ab,kf.	117,580
26	Decision Theory/	2,773
27	Decision Tree/	30,893
28	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	80,715

29	or/12-28	4,143,286
30	11 and 29	266
31	Remove duplicates from 30	230

Table 13 Economic search results: Econlit

#	Query	Results from 7 Nov 2022
1	TX Tisagenlecleucel*	0
2	TX Kymriah*	1
3	TX Axicabtagen*	0
4	TX Yescarta*	1
5	TX Axi-cel*	0
6	TX CART-19	0
7	TX CAR19	0
8	TX CART 19	13
9	TX ctl 019	0
10	TX ctl019	0
11	TX car t-cell therapy	1
12	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13**	**15**

Table 14 Economic search results: International HTA Database

#	Query	Results from 7 Nov 2022
1	Tisagenlecleucel	9
2	Kymriah	4
3	Axicabtagen*	8
4	Yescarta	3
5	CAR T*	20
6	CAR-T*	11
7	**1 OR 2 OR 3 OR 4 OR 5 OR 6**	**32**

11.3 Appendix C: List of included economic studies

11.3.1 Published studies

1. Hillis C, Vicente C, Ball G. The Cost Effectiveness of Axicabtagene Ciloleucel Versus Best Supportive Care in the Treatment of Adult Patients with Relapsed or Refractory Large B-Cell Lymphoma (LBCL) After Two or More Lines of Systemic Therapy in Canada. *Pharmacoeconomics* 2022;40(9):917-28.

2. Wakase S, Teshima T, Zhang J, et al. Cost Effectiveness Analysis of Tisagenlecleucel for the Treatment of Adult Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma in Japan. *Transplant Cell Ther* 2021;27(6):506.e1-06.e10.

3. Wakase S, Teshima T, Zhang J, et al. Cost-Effectiveness Analysis of Tisagenlecleucel for the Treatment of Pediatric and Young Adult Patients with Relapsed or Refractory B Cell Acute Lymphoblastic Leukemia in Japan. *Transplant Cell Ther* 2021;27(3):241.e1-41.e11.

4. Thielen FW, van Dongen-Leunis A, Arons AMM, et al. Cost-effectiveness of Anti-CD19 chimeric antigen receptor T-Cell therapy in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia. A societal view. *Eur J Haematol* 2020;105(2):203-15.

5. Cher BP, Gan KY, Aziz MIA, et al. Cost utility analysis of tisagenlecleucel vs salvage chemotherapy in the treatment of relapsed/refractory diffuse large B-cell lymphoma from Singapore's healthcare system perspective. *J Med Econ* 2020;23(11):1321-29.

6. Wang XJ, Wang YH, Li SCT, et al. Cost-effectiveness and budget impact analyses of tisagenlecleucel in adult patients with relapsed or refractory diffuse large B-cell lymphoma from Singapore's private insurance payer's perspective. *J Med Econ* 2021;24(1):637-53.

7. Wang XJ, Wang YH, Ong MJC, et al. Cost-Effectiveness and Budget Impact Analyses of Tisagenlecleucel in Pediatric and Young Adult Patients with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia from the Singapore Healthcare System Perspective. *ClinicoEcon* 2022;14:333-55.

8. Maria J, Santasusana R, De Andres Saldana A, et al. Cost-effectiveness analysis of tisagenlecleucel in the treatment of relapsed or refractory B-cell acute lymphoblastic Leukaemia in children and young adults in Spain. *ClinicoEconomics and Outcomes Research* 2020;12(pp 253-264)

9. Moradi-Lakeh M, Yaghoubi M, Seitz P, et al. Cost-Effectiveness of Tisagenlecleucel in Paediatric Acute Lymphoblastic Leukaemia (pALL) and Adult Diffuse Large B-Cell Lymphoma (DLBCL) in Switzerland. *Adv Ther* 2021;38(6):3427-43.

10. Lin JK, Muffly LS, Spinner MA, et al. Cost Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Multiply Relapsed or Refractory Adult Large B-Cell Lymphoma. *J Clin Oncol* 2019;37(24):2105-19.

11. Qi CZ, Bollu V, Yang H, et al. Cost-Effectiveness Analysis of Tisagenlecleucel for the Treatment of Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma in the United States. *Clin Ther* 2021;43(8):1300-19.e8.

12. Roth JA, Sullivan SD, Lin VW, et al. Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States. *J Med Econ* 2018;21(12):1238-45.

13. Sarkar RR, Gloude NJ, Schiff D, et al. Cost-Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Pediatric Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia. *J Natl Cancer Inst* 2019;111(7):719-26.

14. Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term Survival and Cost-effectiveness Associated With Axicabtagene Ciloleucel vs Chemotherapy for Treatment of B-Cell Lymphoma. *JAMA netw* 2019;2(2):e190035.

15. Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term Survival and Value of Chimeric Antigen Receptor T-Cell Therapy for Pediatric Patients With Relapsed or Refractory Leukemia. *JAMA Pediatr* 2018;172(12):1161-68.

16. Lin JK, Lerman BJ, Barnes JI, et al. Cost Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Relapsed or Refractory Pediatric B-Cell Acute Lymphoblastic Leukemia. *J Clin Oncol* 2018;36(32):3192-202.

11.3.2 HTAs with an economic evaluation component

National Institute of Health and Care Excellence (NICE):

1. National Institute for Health and Care Excellence. Single Technology Appraisal. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167]. Committee Papers.. 2018. https://www.nice.org.uk/guidance/ta554.

2. National Institute for Health and Care Excellence. Single Technology Appraisal. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]. Committee Papers.. 2019. https://www.nice.org.uk/guidance/TA559.

3. National Institute for Health and Care Excellence. Single Technology Appraisal. Tisagenlecleucel-T for treating relapsed or refractory diffuse large B-cell lymphoma [ID1166]. Committee Papers.. 2019. https://www.nice.org.uk/guidance/ta567.

Canadian Agency for Drugs and Technologies in Health (CADTH):

1. CADTH. Axicabtagene Ciloleucel for Diffuse Large B-Cell Lymphoma: Economic Review Report. *CADTH Optimal Use Report* 2019; vol. 9(no. 1d). https://www.cadth.ca/axicabtagene-ciloleucel-adults-relapsed-or-refractory-large-b-cell-lymphoma.

2. CADTH. Tisagenlecleucel for Diffuse Large B-Cell Lymphoma: Economic Review Report. *CADTH Optimal Use Report* 2019; vol. 8(no. 3e). https://www.cadth.ca/tisagenlecleucel-kymriah-pediatric-acute-lymphoblastic-leukemia-and-diffuse-large-b-cell-lymphoma.

3. CADTH. Tisagenlecleucel for Acute Lymphoblastic Leukemia: Economic Review Report. *CADTH Optimal Use Report* 2019; vol. 8(no. 3f). https://www.cadth.ca/tisagenlecleucel-kymriah-pediatric-acute-lymphoblastic-leukemia-and-diffuse-large-b-cell-lymphoma.

Institut National d'Excellence en Santé et en Services Sociaux (INESSS) (Canada):

1. Institut National d'Excellence en Santé et en Services Sociaux (INESSS). Tisagenlecleucel pour le traitement du lymphome diffus à grandes cellules B récidivant ou réfractaire. 2019. https://www.inesss.qc.ca/publications/repertoire-des-publications/publication/avis-sur-le-tisagenlecleucel-pour-le-traitement-du-lymphome-diffus-a-grandes-cellules-b-recidivant-ou-refractaire.html.

2. Institut National d'Excellence en Santé et en Services Sociaux (INESSS). Tisagenlecleucel pour le traitement de la leucémie lymphoblastique aiguë à cellules B récidivante ou réfractaire. 2019. https://www.inesss.qc.ca/publications/repertoire-des-publications/publication/avis-sur-le-tisagenlecleucel-pour-le-traitement-de-la-leucemie-lymphoblastique-aigue-recidivante-ou-refractaire.html.

3. Institut National d'Excellence en Santé et en Services Sociaux (INESSS). Axicabtagene ciloleucel pour le traitement des lymphomes à grandes cellules B récidivants ou réfractaires. 2019. https://www.inesss.qc.ca/publications/repertoire-des-publications/publication/avis-sur-laxicabtagene-ciloleucel-pour-le-traitement-des-lymphomes-a-grandes-cellules-b-recidivants-ou-refractaires.html.

11.4 Appendix D: Economic evidence tables

11.4.1 Study characteristics

Table 15 Economic evidence table 1: characteristics of the included

Author, year	Country, perspective	Population	Intervention	Comparator(s)	Potential conflicts
Cher 2020	Singapore Healthcare payer	r/r DLBCL after 2 or more lines of systemic therapy. Hypothetical cohort of adults with a median start age of 56 years.	Tisa-cel with or without subsequent SCT, with salvage chemotherapy for patients who do not receive tisa-cel infusion.	Salvage chemotherapy with or without subsequent SCT. Note: For salvage chemotherapy, patients were assumed to receive either R-ICE or R-DHAP in the third-line, or R-GDP following response failure to either therapy.	Study was not funded. One author reports a potential COI with Novartis.
Hillis 2022	Canada Healthcare payer and societal	r/r LBCL (including DLBCL, PMBCL and transformed follicular lymphoma) after 2 or more lines of systemic therapy. Hypothetical cohort of adults with start age of 56 years.	Axi-cel, with subsequent SCT for patient who relapsed or were refractory to CAR T.	BSC, defined as a blended comparator of several chemotherapy options including gemcitabine, etoposide, and cyclophosphamide, with or without subsequent SCT.	Gilead Sciences Canada (funder)
Lin 2019	United States Healthcare payer	r/r DLBCL after 2 or more lines of systemic therapy or relapsed 12 or fewer months after SCT. Hypothetical cohort of adults with a mean age of 58 years.	Axi-cel or tisa-cel, with salvage chemoimmunotherapy for those who do not receive CAR T infusion due to manufacturing failure, and no additional therapy for those who do not receive infusion due to adverse events.	Salvage chemoimmunotherapy, modelled as a bridge to SCT. A mix of the following 4 regimens were considered: R-DHAP, R-GDP, R-GEMOX, and R-ICE, with or without SCT.	Department of Veterans Affairs

Author, year	Country, perspective	Population	Intervention	Comparator(s)	Potential conflicts
Lin 2018	United States Healthcare payer	Paediatric patients with r/r B cell ALL.	Tisa-cel, followed by SCT or alternate therapy in a minority of patients. Blinatumomab for those who do not receive CAR T infusion due to manufacturing failure, and no additional therapy for those who do not receive infusion due to adverse events.	Blinatumomab, clofarabine combination therapy (clofarabine, cyclophosphamide and etoposide), and clofarabine monotherapy; modelled as bridges to SCT (in the month after initial remission, a proportion of patients proceed directly to SCT). If SCT unavailable, a 2-year course of chemotherapy.	Supported in part by a Veterans Affairs Office of Academic Affiliations advanced fellowship. One author reports potential COI with Novartis.
Maria 2020	Spain Spanish National Health System	Paediatric and young adult patients up to 25 years of age with B cell ALL that is refractory, in relapse post-transplant or in second or later relapse.	Tisa-cel, with or without subsequent SCT. Patients not receiving the infusion receive salvage chemotherapy (FLA-IDA).	Salvage chemotherapy (FLA-IDA), with or without SCT.	Novartis
Moradi-Lakeh 2021	Switzerland Swiss mandatory health insurance system, and societal (sensitivity analysis)	1. r/r B cell ALL in paediatric and young adult patients up to 25 years of age that is refractory or in second line or later relapse. 2. r/r DLBCL in adult patients who have received 2 or more lines of chemotherapy and have either failed autologous SCT or were ineligible for or did not consent to autologous SCT.	Tisa-cel with or without SCT. Patients who did not have CAR T infusion were assumed to receive a comparator treatment.	1. For B cell ALL: salvage chemotherapy (fludarabine, cytarabine and idarubicin), clofarabine combination therapy (clofarabine, cyclophosphamide and etoposide) or blinatumomab, with or without SCT. 2. For DLBCL: salvage chemotherapy (R-GEMOX, R-IVE, R-ESHAP or R-DHAP), with or without SCT.	Novartis, Switzerland (funder)
Qi 2021	United States Third-party payer	Adult patients with r/r DLBCL after 2 or more lines of systemic therapy. The hypothetical model cohort had a start age of 56 years.	Tisa-cel, with or without subsequent SCT.	Salvage chemotherapy, including 4 regimens: R-ICE, R-GDP, R-DHAP and R-GEMOX, with or without subsequent SCT.	Novartis (sponsor)

Author, year	Country, perspective	Population	Intervention	Comparator(s)	Potential conflicts
Roth 2018	United States Healthcare payer	Adult patients with r/r LBCL after 2 or more lines of systemic therapy.	Axi-cel, with or without subsequent SCT.	Salvage chemotherapy (R-DHAP), with or without subsequent SCT. Note: as the effects of SCT were already represented in survival outcomes of each study, no additional effects were modelled.	Kite, a Gilead Company (funder)
Sarkar 2019	United States Third party payer (primary base-case analysis) and societal	Paediatric patients with r/r B cell ALL. The standard base patient was defined as a 12-year-old boy with a weight of 40kg and a body surface area of 1.4m^2.	Tisa-cel. Patients who failed to respond to CAR T received SOC as salvage. In the base case, responders did not have SCT. Note: patients who responded to CAR T were given IVIG monthly for 18 months to treat B cell aplasia.	SOC, which was defined as clofarabine, etoposide and cyclophosphamide; followed by SCT in responders.	National Institutes of Health (funder)
Thielen 2020	The Netherlands Healthcare payer and societal, reported separately (base case defined from a societal perspective)	Paediatric patients with r/r B cell ALL. The hypothetical cohort had a start age of 12 years.	Tisa-cel, with or without subsequent SCT.	One of either: (1) clofarabine, (2) clofarabine, etoposide and cyclophosphamide, or (3) blinatumomab; with or without subsequent SCT.	Novartis (funding)
Wakase 2021	Japan Healthcare payer and societal (in scenario analysis)	Adults with r/r DLBCL who are ineligible for, or relapsed after, auto-SCT.	Tisa-cel, with or without subsequent SCT. Patients not receiving the infusion assumed to receive comparator salvage chemotherapy.	Salvage chemotherapy, including the following regimens: R-ICE, R-GDP, R-DHAP, R-ESHAP and R-EPOCH; with or without subsequent SCT.	Novartis (funder)
Wakase 2021	Japan Healthcare payer and societal (in sensitivity analysis)	Paediatric and young adult patients up to 25 years of age with r/r B cell ALL.	Tisa-cel, with or without subsequent SCT. Patients who discontinued prior to infusion were assumed to receive the comparator therapy.	Blinatumomab (base case), or clofarabine combination therapy (sensitivity analysis); with or without SCT.	Novartis (funder)

Author, year	Country, perspective	Population	Intervention	Comparator(s)	Potential conflicts
Wang 2022	Singapore Healthcare payer	Paediatric and young adult patients with r/r B cell ALL.	Tisa-cel, with or without subsequent SCT. Patients not receiving infusion assumed to receive salvage chemotherapy.	Blinatumomab or salvage chemotherapy, with or without subsequent SCT.	Novartis Singapore (funder)
Wang 2021	Singapore Private insurance payers	Adults with r/r DLBCL with 2 or more prior lines of systemic therapy. The hypothetical cohort had a start age of 56 years.	Tisa-cel, with or without subsequent SCT. Patients who did not receive the infusion after leukapheresis were assumed to receive salvage chemotherapy.	Salvage chemotherapy with or without subsequent SCT.	Novartis Singapore (funder)
Whittington 2019	United States Public payer perspective and commercial payer perspective	Adult patients with r/r LBCL. The hypothetical cohort had a start age of 58 years.	Axi-cel, with or without subsequent SCT. Patients who discontinue prior to infusion due to a manufacturing failure receive the active comparator, while patients who discontinue due to an adverse event receive palliative care.	Chemotherapy (R-DHAP), with or without SCT.	Institute for Clinical and Economic Review providing funding for a prior CAR T review. No additional funding for this article.
Whittington 2018	United States Healthcare payer	Patients less than 25 years of age with B cell ALL that is refractory or in second or later relapse.	Tisa-cel, with or without subsequent SCT. Patients who discontinue prior to infusion due to a manufacturing failure receive the active comparator, while patients who discontinue due to an adverse event receive palliative care.	Clofarabine monotherapy, with or without subsequent SCT. Note: clofarabine monotherapy was selected because the trial population most closely matched the populations from the tisa-cel trial in regard to demographics and disease severity.	Institute for Clinical and Economic Review (funder)

Abbreviations:
AE = adverse event, **ALL** = acute lymphoblastic leukaemia, **axi-cel** = axicabtagene ciloleucel, **BSC** = best supportive care, **CAR T** = chimeric antigen receptor T cell, **COI** = conflict of interest, **CRS** = cytokine release syndrome, **DLBCL** = diffuse large B cell lymphoma, **FLA-IDA** = fludarabine, cytarabine and idarubicin, **ICU =** intensive care unit, **IVIG** = intravenous immunoglobulin, **LBCL** = large B cell lymphoma, **PMBCL** = primary mediastinal B cell lymphoma, **r/r** = relapsed or refractory, **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, **SCT** = stem cell transplantation, **SOC** = standard care, **tisa-cel** = tisagenlecleucel.

11.4.2 Modelling methodology considerations

Table 16 Economic evidence table 2: modelling methods used in the included studies

Author, year	Analysis methods	Source(s) of efficacy inputs	Utilitites	Adverse events
Cher 2020	**Analysis**: Incremental cost per LY and per QALY. **Model**: Hybrid decision tree and 3-state PSM. The decision tree determines if tisa-cel infusion is successful (tisa-cel arm only) and if SCT is received (both arms). PSM includes PFS, progressive disease and death. Cycle length was 1 month. **Time horizon**: 15 years. **Discount**: 3.0% p.a. for costs and effects.	**For tisa-cel**, pseudo-IPD data from the JULIET trial for OS and PFS.[122] **For salvage chemotherapy**, pseudo-IPD data from the CORAL-1 extension study for OS;[94] PFS estimated by applying a HR to OS. Modelled separately for patients with vs without subsequent SCT. Note: standard parametric models were fitted to the IPD. To account for a potential curative effect, MCMs and spline models were also fitted to the tisa-cel and chemotherapy with SCT data.	**Health state utilities:** 0.7 (0.58-0.82) for progression-free (including long term survivors); 0.59 (0.47-0.71) for progressed disease. **Treatment-related disutility:** –0.15 applied for 26 days for tisa-cel and 21 days for salvage chemotherapy. **AE-related disutility:** –0.7 for CRS applied for duration of ICU stay (5.5 days); –0.15 for other AEs (diarrhea [1 day], anaemia [3.3 days], febrile neutropenia [12 days]). **SCT-related disutility:** –0.15 applied for 42 days.	Diarrhea, anaemia, and febrile neutropenia were considered in both the tisa-cel and standard care arms. CRS resulting in ICU, CRS requiring1 dose tocilizumab, CRS requiring2 doses tocilizumab, and hypogammaglobulinemia requiring IVIG were included for the tisa-cel arm only.
Hillis 2022	**Analysis**: Incremental cost per QALY. **Model**: 3-state PSM, which includes the following states: pre-progression, post-progression, and death. Cycle length was 1 month. **Time horizon**: Lifetime. **Discount**: 1.5% p.a. for costs and effects.	**For axi-cel**, IPD from ZUMA-1 for OS and PFS.[93] **For BSC**, IPD from SCHOLAR-1 for OS using propensity score methods.[95] PFS derived from OS by assuming the ratio between PFS and OS was the same for BSC as for axi-cel. Note: MCMs were fitted to the axi-cel trial data. Standard parametric models were used for BSC. Patients who did not experience progression after 2 years were assumed to have achieved long-term remission, with mortality equal to that of the general Canadian population, with a SMR.	**Health state utilities:** 0.72 for progression-free state, 0.65 for progressed disease, population norm values for patients who remained in the PFS state for >2 years. **AE-related disutility:** –0.15 (SE: 0.01) for encephalopathy, febrile neutropenia, hypophosphatasemia, hypotension, leukopenia, lymphocyte count decreased; neutrophil count decreased, white blood cell count decreased; –0.12 (SE: 0.01) for anaemia; –0.11 (SE: 0.01) for platelet count decreased, pyrexia, thrombocytopenia; –0.09 (SE: 0.01) for neutropenia. Note: AE-related disutility applied for the first model cycle.	Grade 3 to 4 AEs associated with axi-cel were included. Costs associated with all AEs, with the exception of B cell aplasia, were assumed to occur during the hospital stay for initial treatment. It was assumed that the BSC arm would not incur AE-related costs.

Author, year	Analysis methods	Source(s) of efficacy inputs	Utilitites	Adverse events
Lin 2019	**Analysis**: Incremental cost per QALY. **Model**: Markov cohort model. Main health states included: remission (stratified by response: complete, partial or none), progression, remission after SCT (stratified by response), progression after SCT, long-term remission, and death. Cycle length was 1 month. **Time horizon**: Lifetime. **Discount**: Costs and effects discounted at 3% p.a.	**For axi-cel**, rates of remission, survival, and relapse were informed by the ZUMA-1 trial.[93] **For tisa-cel**, they were informed by the JULIET trial.[122] **For comparator**, they were informed by the SCHOLAR-1 trial.[95] Note: after 5 years of continuous remission, patients were considered to have achieved long-term remission.	**Health state utilities:** ***CAR T:*** 0.50 (0.40-0.60) for month 1-2 of axi-cel and 0.58 (0.55-0.61) for month 1-2 of tisa-cel—utilities for individual side effects were used to model QoL during CAR T, 0.7 (0.47-0.89) for remission after CAR T treatment state. ***Chemoimmunotherapy:*** 0.63 (0.58-0.68) during treatment; 0.71 (0.65-0.76) for remission after treatment. ***Autologous SCT:*** 0.43 (0.23-0.64) for month 1-2; 0.70 (0.47-0.89) for month 3 (if in remission); 0.70 (0.47-0.89) for remission after treatment. ***Allogenic SCT:*** 0.35 (0.16-0.57) for month 1-2; 0.45 (0.25-0.65) for month 3 (if in remission); 0.68 (0.46-0.86) for remission after treatment state. ***Progression:*** 0.45 (0.40-0.50).	Short-term grade 3 or 4 AEs, including anaemia, neutropenic fever, thrombocytopenia, thrombosis, CRS (grade 2, 3 or 4), neurotoxicity. Long-term costs of IVIG for B cell aplasia were also included, assuming IVIG is given for 12 months. Note: to estimate QoL during CAR T treatment, the following AEs were considered: CRS, neurologic manifestations and febrile neutropenia.
Lin 2018	**Analysis**: Incremental cost per QALY. **Model**: Markov cohort model. Main health states included: remission, relapse or refractory, remission after transplantation, relapse after transplantation, cure, and death. Cycle length was 1 month. **Time horizon**: Lifetime. **Discount**: Costs and effects discounted at 3% p.a. Note: Upon relapse, patients receive palliative chemotherapy until death.	**For tisa-cel,** rates of remission, survival, and relapse from aggregated data from 3 single arm trials (one pivotal and 2 supportive).[123,124] **For the comparator,** rates of remission, survival, and relapse from aggregated data from 5 single arm studies.[98-102] Data from the transplantation literature informed long-term overall and relapse-free survival after SCT. Note: patients who achieve 5 years of continuous remission were considered effectively cured.	**Health state utilities:** ***Treatment*:** 0.78 (0.71-0.85) for tisa-cel, 0.78 (0.74-0.82) for blinatumomab, 0.71 (0.67-0.75) for clofarabine therapies. ***Post induction chemotherapy:*** 0.75 (0.72-0.78), 0.77 (0.74-0.80); 0.79 (0.75-0.83); and 0.83 (0.79-0.87) for consolidation, intensification, continuation, and maintenance. ***Remission:*** 0.88 (0.82-0.93) if <5 years since initial therapy and 0.92 (0.82-0.98) if >5 years. ***Relapse:*** 0.76 (0.70-0.82). ***Post-SCT:*** 0.64 (0.56-0.71) for month 1; 0.62 (0.54-0.70), 0.63 (0.55-0.71), 0.80 (0.74-0.86), and 0.86 (0.80-0.91) for months 2, 3, 4-60 and ≥60 if in remission; 0.56 (0.48-0.64), 0.57 (0.49-0.65), and 0.73 (0.67-0.79) for months 2, 3, and >3 if with relapsed disease.	Short-term grade 3 or 4 AEs that were reported to occur in at least 5% of patients in either treatment group (complete list is available in the study's appendices). Note: To estimate QoL during CAR T treatment, the following AEs were considered: CRS (modelled as severe sepsis and shock), infection, febrile neutropenia and anaemia.

Author, year	Analysis methods	Source(s) of efficacy inputs	Utilitites	Adverse events
Maria 2020	**Analysis:** Incremental cost per LY and per QALY. **Model:** A 3-state PSM, with the following states: EFS, progressive/relapsed disease, death. Cycle length of 1 month. **Time horizon:** Lifetime. **Discount:** Costs and effects discounted at 3% p.a.	**For tisa-cel,** OS and EFS obtained by fitting parametric curves to pooled data from the ITT populations of the ELIANA, ENSIGN and B2101J trials.[123,125-128] **For the comparator,** OS obtained by fitting parametric survival curves to data from Von Stackelberg et al. (2011).[97] EFS derived from the OS curve. Note: from year 5 onwards, those who remained alive were assumed long-term survivors. EFS curves were assumed to flatten until they reached OS, which was modelled according to Spanish life tables with a SMR.	**Health state utilities:** 0.91 for the EFS state and 0.75 for the progressive/relapsed disease state. **Treatment-related disutility:** –0.42 for tisa-cel and salvage chemotherapy (FLA-IDA), applied during the hospital stay. **ICU-related disutility:** –0.91 for duration of an ICU stay (assumption of zero utility during ICU stay). **SCT-related disutility:** –0.57, assumed to last for 1 year. Note: age-related disutilities were also applied.	Short-term grade 3 or 4 AEs that were reported to occur in at least 5% of patients in either treatment group (complete list is available in the study's appendices).
Moradi-Lakeh 2021	**Analysis**: Incremental cost per LY and per QALY. **Model**: Hybrid decision tree and 3-state PSM. Decision tree determined infused vs non-infused patients (tisa-cel arm only). For B cell ALL, the PSM included EFS, progressive disease and death. For DLBCL, it included PFS, progressive disease, and death. Cycle length was 1 month. **Time horizon**: Lifetime. **Discount**: 3.5% p.a. for costs and effects.	**For tisa-cel**, for B cell ALL, OS and EFS derived from pooled IPD from ELIANA, ENSIGN, and B2101J;[125-127] for DLBCL, OS and PFS derived from pooled IPD from JULIET and pseudo-IPD from Schuster et al. (2017).[129,130] **For comparators**, for B cell ALL, pseudo-IPD from several published studies,[97-101] most with limited follow-up so HRs from MAIC were used to extrapolate up to year 5; for DLBCL, pseudo-IPD from the 2 CORAL extension studies.[94,96] Note: beyond year 5 for B cell ALL and year 3 for DLBCL, patients were considered long-term survivors; the same mortality risk being used for all arms, based on SMR-adjusted survival.	**Health state utilities:** for B cell ALL, 0.91 (0.87-1.00) for EFS and 0.75 (0.44-0.91) for progressive disease; for DLBCL, 0.83 (0.79-0.87) for PFS and 0.72 (0.66-0.78) for progressive disease. **Treatment-related disutility:** for B cell ALL, –0.03 for tisa-cel (infused patients) and clofarabine combination therapy; –0.02 for blinatumomab and –0.04 for salvage chemotherapy, applied for duration of treatment (or hospitalisation for tisa-cel); for DLBCL, –0.02 for tisa-cel and salvage chemotherapy, applied for duration of induction chemotherapy (or of hospitalisation for tisa-cel.) **AE-related disutility:** a utility of zero was assumed for grade 3-4 CRS with ICU stay or ICU stay not due to CRS (for duration of ICU stay). **Subsequent SCT disutility:** –0.30, assumed to last for 1 year. Note: the model considered additional age-related decrements.	Grade 3-4 AEs with greater than 5% rates in any arms (in the trials specified in the supplementary document). For tisa-cel and blinatumomab, CRS was considered. For tisa-cel only, low immunoglobulin levels requiring IVIG was also considered.

Author, year	Analysis methods	Source(s) of efficacy inputs	Utilitites	Adverse events
Qi 2021	**Analysis**: Incremental cost per LY and per QALY. **Model**: Hybrid decision tree and 3-state PSM. Decision tree stratified patients according to their response status (responders vs non-responders; tisa-cel arm only). Health states in the PSM include: PFS, progressive disease, and death. Cycle length of 1 month. **Time horizon**: Lifetime. **Discount**: 3.0% p.a. for costs and effects.	**For tisa-cel**, OS and PFS derived by fitting survival models to IPD from the JULIET trial, separately for patients with vs without a response,[122] up to 5 years. MCMs used to account for the potentially curative effect for patients with a response. Standard and spline-based parametric models for non-responders. **For salvage chemotherapy**, OS derived by fitting survival models to data from SCHOLAR-1.[95] PFS derived from OS by applying a HR, informed by the JULIET trial.	**Health state utilities:** 0.83 for PFS and 0.39 for progressive disease. **Treatment-related disutility:** –0.15, for a duration of 72.2 days for salvage chemotherapy, and for 27.9 days for tisa-cel. **ICU stay disutility:** –0.83 (i.e. assumed zero utility during ICU stay), applied for 8.5 days for ICU stay due to CRS, and for 0.9 days for ICU stay not due to CRS. **Subsequent SCT disutility:** –0.30 applied for a duration of 1 year (assumption).	Grade 3-4 AEs affecting at least 5% of patients receiving either treatment (complete list not provided). This included the following tisa-cel specific AEs: grade 3-4 CRS, grade 3-4 neurotoxicity events, and B cell aplasia.
Roth 2018	**Analysis**: Incremental cost per LY and per QALY. **Model**: 3-state PSM, including the following states: pre-progression, post-progression, and death. A 1-month cycle length was used. **Time horizon**: Lifetime. **Discount**: Costs and effects discounted at 3% p.a.	**For axi-cel**, OS and PFS derived by fitting survival models to IPD from ZUMA-1, extrapolated to 5 years.[93] **For salvage chemotherapy**, OS derived by fitting survival models to data from SCHOLAR-1 (up to 10 years).[95] PFS imputed using a time-dependent ratio of PFS to OS, per the ratio observed in ZUMA-1. Note: for axi-cel, beyond-study survival was extrapolated up to 5 years. It was assumed patients who had not progressed by 5 years had no subsequent progressions. In the salvage chemotherapy arm, patients alive at 10 years were assigned mortality rates based on US life tables.	**Health state utilities:** ***Treatment:*** 0.74 (0.68-0.80) for axi-cel on treatment, 0.672 (0.623-0.773) for salvage chemotherapy on treatment. ***Remission:*** 0.782 (0.736-0.828) for the in remission for <6 months follow-up health state (for both strategies), 0.823 (0.741 to 0.905) for the in remission for ≥6 months follow-up health state (for both strategies). ***Progressive disease:*** 0.39 (0.31-0.47) for the progressive disease state.	For axi-cel, grade 3 to 4 CRS, and hypogammaglobulinemia and treated with IVIG were considered. For salvage chemotherapy, grade 3 to 4 AEs for the following were included: febrile neutropenia, infection, fatigue, nausea and thrombosis/embolism.

Author, year	Analysis methods	Source(s) of efficacy inputs	Utilitites	Adverse events
Sarkar 2019	**Analysis**: Incremental cost per QALY. **Model**: microsimulation state-transition model. Health states included: treatment, remission, recurrence/progression, and death. Patients may experience acute or long-term toxicity but remain in the same health state. A 1-month cycle length was used. **Time horizon**: Lifetime. **Discount**: Costs and effects discounted at 3% p.a.	**For tisa-cel**, outcomes were derived from Maude et al. (2018).[123] **For SOC**, for the base case, outcomes were derived from Hijiya et al. (2011).[99] Note: it was assumed that, after a SCT, if patient survived for 2 years, they had experienced a successful transplant.	**Health state utilities:** 0.94 (SD: 0.188) for the baseline ALL utility. **Treatment-related disutility:** –0.42 (SD: 0.084) **AE-related disutility:** –0.47 (SD: 0.09) for CRS, –0.16 (0.03) for ICU admission, –0.23 (SD: 0.04) for infection, –0.19 (SD: 0.04) for cytopenia, neurotoxicity and anaemia, –0.11 (SD: 0.02) for thrombocytopenia, –0.25 (SD:0.05) for febrile neutropenia. **SCT-related disutility:** –0.57 (SD: 0.114). **Disease progression-related disutility:** –0.64 (SD: 0.13).	**CAR-T:** CRS, ICU admission, tocilizumab (for CRS), infection, cytopenia, neurotoxicity, febrile neutropenia. **Standard of care:** anaemia, thrombocytopenia, febrile neutropenia, infection.
Thielen 2020	**Analysis**: Incremental cost per LY and per QALY. **Model**: 3-state PSM, with the following health states: EFS, progressive disease, death. A 1-month cycle length was used. **Time horizon**: Lifetime. **Discount**: Costs were discounted at 4% p.a. and effects at 1.5% p.a.	**For tisa-cel**, EFS and OS were derived by fitting survival models to pooled data from the ELIANA, ENSIGN and B2101J trials.[125-127] **For the comparator**, OS derived by fitting survival models to literature-based values,[98,99] while EFS was considered proportional to OS, using a validated ratio. Note: patients who remained in the EFS state after 5 years were assumed to be long-term survivors; OS for these patients was modelled using SMR-adjusted survival. Beyond year 5, the EFS curve was assumed to flatten until it reached the OS curve.	**Health state utilities:** 0.83 (SE: 0.03) for EFS and 0.68 (SE:0.05) for progressed disease **Treatment-related disutility:** –0.20 (SE: 25% of mean), applied for 26 days for tisa-cel, 66 days for clofarabine monotherapy, 47 days for clofarabine combination therapy, and 61 days for blinatumomab, with disutility value of –0.20. Note: age-related utility decrements were also incorporated.	Costs for grade 3 or 4 AEs reported in more than 5% of patients in any of the treatment arms were included. For long-term costs to treat B cell aplasia, that model assumed 73% of tisa-cel patients would be treated with IVIG for an average duration of 11.4 months.

Author, year	Analysis methods	Source(s) of efficacy inputs	Utilitites	Adverse events
Wakase 2021	**Analysis**: Incremental cost per LY and per QALY. **Model**: hybrid decision tree and 3-state PSM. The decision tree (tisa-cel arm only) determined patients who did vs didn't receive tisa-cel infusion. The PSM included PFS, progressive or relapsed disease, and death. Cycle length was 1 month. **Time horizon**: Lifetime. **Discount**: Costs and effects were discounted at 2% p.a.	**For tisa-cel**, OS and PFS derived from the JULIET trial data, until year 3.[122] **For salvage chemotherapy**, OS obtained from the SCHOLAR-1 study (pseudo IPD data from KM curves), until year 3.[95] PFS was derived by applying a HR to OS. Note: at the end of year 3, patients who remained alive were assumed to be long-term survivors, with mortality based on Japanese life tables, adjusted using a SMR.	**Health state utilities:** 0.83 for PFS and 0.39 for progressive/relapsed disease. **Treatment-related disutility:** –0.15, applied for 28 days for tisa-cel and 62 days for salvage chemotherapy. Note: treatment disutility assumed to capture utility decrements for all short-term AEs, with the exception of CRS (requiring ICU stay). **Disutility due to ICU stay:** –0.83 (i.e. patients assumed to have zero utility during ICU stay), applied for 8.5 days if ICU stay due to CRS and 0.9 days if ICU stay not due to CRS. **SCT-related disutility:** –0.30, applied for 1 year.	Authors noted that the duration of hospital stay for treatment already included inpatient stays due to AEs, therefore additional costs were not modelled separately, with the exception of CRS requiring ICU stay and B cell aplasia requiring IVIG. I.e. costs for grade 3 or 4 CRS requiring ICU stay, and B cell aplasia were included.
Wakase 2021	**Analysis**: Incremental cost per LY and per QALY. **Model**: hybrid decision tree and 3-state PSM. The decision tree determined patients who did vs. didn't receive tisa-cel infusion. Health states in the PSM included: EFS, progressive disease, and death. A 1-month cycle length was used. Note: EFS was defined as the time from treatment initiation to the earliest among death, relapse, or treatment failure. **Time horizon**: Lifetime. **Discount**: 2.0% p.a. for costs and effects.	**For tisa-cel**, OS and EFS (without censoring subsequent SCT) estimated based on pooled data from ELIANA, ENSIGN, and B2101J.[125-127] Trial data were used to model OS until year 5. **For comparators**, for blinatumomab, informed by von Stackelberg et al. (2016);[98] for clofarabine combination therapy, pooled data from 3 studies was used.[99-101] Note: comparator studies had <5 years follow-up; HRs derived from MAIC analyses were used to extrapolate survival up to year 5. Note: patients alive at the end of year 5 were assumed to be long-term ALL survivors, with survival based on Japanese life tables, adjusted using a SMR.	**Health state utilities:** 0.91 for EFS and 0.75 for progressive disease. **Treatment-related disutility:** –0.42, applied for 32 days for tisa-cel, 61 days for blinatumomab, and 47 days for clofarabine combination therapy. Note: treatment disutility assumed to capture utility decrements for all short-term AEs, with the exception of CRS. **CRS-related disutility:** –0.91 (i.e. patients assumed to have zero utility during ICU stay), applied for 11 days. **SCT-related disutility:** –0.57, applied for 1 year.	Grade 3-4 CRS for patients receiving either tisa-cel or blinatumomab, as well as B cell aplasia for tisa-cel patients.

Author, year	Analysis methods	Source(s) of efficacy inputs	Utilitites	Adverse events
Wang 2022	**Analysis:** Incremental cost per LY and per QALY. **Model:** Hybrid decision-tree and 3-state PSM. Decision tree determines patients who receive vs. don't receive infusion (tisa-cel arm only). PSM has the following state: EFS, progressive disease, and death. Cycle length of 1 month. **Time horizon:** Lifetime (88 years). **Discount:** 3% p.a. for costs.	**For tisa-cel**, pooled data from the ELIANA, ENSIGN and B2101J trials.[123,125,131] Observed OS and EFS trial data, based on ITT, were used until year 3. **For the comparators**, OS derived from pseudo IPD derived from published KM curves from von Stackelberg et al. (2011) and von Stackelberg et al. (2016).[97,98] OS was extrapolated until year 3 via parametric extrapolation. EFS derived from the OS curve. Note: patients alive at the end of year 3 were assumed long-term ALL survivors, with mortality based on SMR-adjusted Singapore life tables.	**Health state utilities:** 0.85 for EFS and 0.76 for progressive disease. **Treatment-related disutility:** –0.42, applied for 10 days for tisa-cel, 30 days for salvage chemotherapy, and 211 days for blinatumomab. **Disutility due to ICU stay:** –0.85 (i.e. patients assumed to have zero utility during ICU stay), applied for 11.1 days if ICU stay due to CRS, and for 1.73 days if ICU stay not due to CRS. **Disutility due to SCT:** –0.57, applied for 1 year. Note: age-related utility decrements were also incorporated.	ICU not due to CRS, CRS with ICU stay, B cell aplasia (requiring IVIG), and other serious AEs. Note: the specifics of 'other AEs' not provided. They are defined/modelled separately for tisa-cel (infused), tisa-cel (non-infused), Blinatumomab and salvage chemotherapy.
Wang 2021	**Analysis**: Incremental cost per LY and per QALY. **Model**: hybrid decision tree and 3-state PSM. The decision tree determined patients who received vs didn't receive CAR T infusion (tisa-cel arm only). The PSM included PFS, progressive/relapsed disease, and death. 1-month cycle length. **Time horizon**: Lifetime (44 years). **Discount**: 3.0% p.a. for costs and effects.	**For tisa-cel**, OS and PFS based on pooled IPD from the JULIET and Schuster et al. (2017) trials, up to 3 years.[122,129] **For salvage chemotherapy**, OS used pseudo-IPD from the 2 CORAL extension studies.[94,95] PFS derived by applying a HR to the available OS curves. Note: patients who remained alive at 3 years assumed to be long-term survivors of DLBCL, with mortality based on SMR-adjusted Singapore life tables.	**Health state utilities:** 0.90 (SE: 0.01) for PFS and 0.82 (SE: 0.02) for progressive disease. **Treatment-related disutility:** –0.15, applied for 16 days for tisa-cel, and for 84 days for salvage chemotherapy. **Disutility due to ICU stay:** –0.90 (i.e. patients assumed to have zero utility during ICU stay), applied for 8.5 days if ICU stay due to CRS, and for 0.9 days if ICU stay not due to CRS. **Disutility due to SCT:** –0.30, applied for 1 year.	CRS, B cell aplasia (tisa-cel), and other serious AEs. Note: the specifics of 'other AEs' not provided. They are defined/modelled separately for tisa-cel (infused), tisa-cel (non-infused), and salvage chemotherapy.

Author, year	Analysis methods	Source(s) of efficacy inputs	Utilitites	Adverse events
Whittington 2019	**Analysis**: Incremental cost per LY and per QALY. **Model**: hybrid decision tree and 3-state semi-Markov PSM. Decision tree decides who receives CAR T infusion (Axi-cel arm), who responds to treatment (both arms), and who receive SCT (both arms). Health states in the PSM are: alive and responding to treatment (complete or partial response), alive and not responding (these patients assumed to have palliative chemotherapy), and death. Cycle length of 1 month. **Time horizon**: Trial-based (24 months) and lifetime. **Discount**: 3% p.a. for costs and effects.	**For axi-cel**, PFS and OS were derived by fitting survival models to pseudo-IPD from ZUMA-1.[93] **For chemotherapy**, OS derived by fitting survival models to pseudo-IPD from SCHOLAR-1.[95] PFS derived from OS by assuming a proportional relationship between PFS and OS. Note: 5 different survival models were used to extrapolate survival, including standard parametric, flexible parametric, MCM (assuming those alive and responding to treatment at the end of the trial were cured), MCM (assuming all patients alive at the end of the trial were cured, regardless of response status), and flexible parametric mixture.	**Health state utilities:** 0.39 for the alive and not responding to treatment state, 0.83 for the alive and responding to treatment and the long-term survivor states. **Treatment-related disutility:** –0.42 for chemotherapy, applied for the duration of treatment, including for pre-CAR-T chemotherapies. **SCT-related disutility:** –0.57, applied for duration of decision tree (and includes all decrements due to AEs).	Unit costs for all grade 3-4 AEs reported for either treatment arm were included.

Author, year	Analysis methods	Source(s) of efficacy inputs	Utilitites	Adverse events
Whittington 2018	**Analysis**: Incremental cost per LY and per QALY. **Model:** hybrid decision tree and 3-state semi-Markov PSM. Decision tree decides who receives CAR-T infusion (tisa-cel arm), responds to treatment (both arms), and receives SCT (both arms). Health states in the PSM are: alive and responding to treatment (complete or partial response), alive and not responding to treatment (these patients assumed to receive palliative chemotherapy), and death. The PSM runs until year 5. Beyond year 5, a Markov model models the outcomes of long-term survivors. Cycle length of 1 month. **Time horizon:** Lifetime. **Discount:** 3% p.a. for costs and effects.	**For tisa-cel,** EFS and OS were derived from parametric fits to pooled pseudo-IPD from 3 trials (B2202, B2205J and B2101J), extrapolated until year 5. **For clofarabine monotherapy,** OS was derived from parametric fits to pseudo-IPD from Jeha et al. (2006)[102], extrapolated until year 5. The EFS curve was derived from OS, by assuming the same proportional relationship as for tisa-cel. Note: patients alive and responding to treatment after 5 years were assumed to be long-term survivors.	**Health state utilities:** 0.75 for the alive and not responding to treatment state, 0.91 for the alive and responding to treatment and long-term survivor states. **Treatment-related disutility:** –0.42 for chemotherapy, applied for the duration of treatment, including for pre-CAR-T chemotherapies. **SCT-related disutility:** –0.57, applied for duration of stage 1 (and includes all decrements due to AEs).	Unit costs for all grade 3-4 AEs reported for either treatment arm were included.

Abbreviations:

AE = adverse event, **ALL** = acute lymphoblastic leukaemia, **axi-cel** = axicabtagene ciloleucel, **BSC** = best supportive care, **CAR T** = chimeric antigen receptor T cell, **CRS** = cytokine release syndrome, **DLBCL** = diffuse large B cell lymphoma, **EFS** = event free survival, **EQ-5D** = EuroQoL 5 dimensions, **FLA-IDA** = fludarabine, cytarabine and idarubicin, **HR** = hazard ratio, **ICU** = intensive care unit, **IPD** = individual patient data, **ITT** = intention to treat, **IVIG** = intravenous immunoglobulin, **KM** = Kaplan-Meier, **LBCL** = large B cell lymphoma, **LY** = life year, **MAIC** = match-adjusted indirect comparison, **MCM** = mixture cure model, **OS** = overall survival, **PFS** = progression-free survival, **PSM** = partitioned survival model, **QALY** = quality-adjusted life year, **QoL** = quality of life, **SCT** = stem cell transplantation, **SD** = standard deviation, **SE** = standard error, **SMR** = standard mortality ratio, **SOC** = standard care, **tisa-cel** = tisagenlecleucel, **US** = United States.

11.4.3 Applicability assessment

Table 17 Applicability assessment of the existing economic evidence using NICE's appraisal checklist items

	1.1 Is the study population appropriate for the review question?	*1.2 Are the interventions appropriate for the review question?*	*1.3 Is the system in which the study was conducted sufficiently similar to the current Swiss context?*	*1.4 Is the perspective for costs appropriate for the review question?*	*1.5 Is the perspective for outcomes appropriate for the review question?*	*1.6 Are all future costs and outcomes discounted appropriately?*	*1.7 Are QALYs or an appropriate social care-related equivalent used as an outcome?*	***Overall Judgement***
tisa-cel in adults with r/r DLBCL								
Cher 2020	Yes	Yes	Partly. Singaporean healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Lin 2019	Yes	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Moradi-Lakeh 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	***Directly applicable***
Qi 2021	Yes	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Wakase 2021a	Yes	Yes	Partly. Japanese healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Wang 2021	Yes	Yes	Partly. Singaporean healthcare setting	Yes	Yes	Yes	Yes	*Partly applicable*
tisa-cel in children or young adults with r/r B cell ALL								
Lin, 2018	Yes	Yes	Partly, United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Maria, 2020	Yes	Yes	Partly. Spanish healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Moradi-Lakeh 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	***Directly applicable***
Sarkar 2019	Yes	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Thielen 2020	Yes	Yes	Partly. Dutch healthcare setting	Yes	Yes	Yes	Yes	*Partly applicable*

	1.1 Is the study population appropriate for the review question?	*1.2 Are the interventions appropriate for the review question?*	*1.3 Is the system in which the study was conducted sufficiently similar to the current Swiss context?*	*1.4 Is the perspective for costs appropriate for the review question?*	*1.5 Is the perspective for outcomes appropriate for the review question?*	*1.6 Are all future costs and outcomes discounted appropriately?*	*1.7 Are QALYs or an appropriate social care-related equivalent used as an outcome?*	***Overall Judgement***
Wang, 2022	Yes	Yes	Partly. Singaporean healthcare setting.	Yes	Yes	Unclear if outcomes are discounted.	Yes	*Partly applicable*
Wakase 2021b	Yes	Yes	Partly. Japanese healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Whittington 2018	Yes	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Axi-cel in adults with DLBCL								
Hillis 2022	Partly. DLBCL combined with other LBCLs.	Yes	Partly. Canadian healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Lin 2019	Yes	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Roth 2018	Partly. DLBCL combined with other LBCLs.	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Whittington 2019	Partly. DLBCL combined with other LBCLs.	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Axi-cel in adults with PMBCL								
Hillis 2022	Partly. PMBCL combined with other LBCLs.	Yes	Partly. Canadian healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Roth 2018	Partly. PMBCL combined with other LBCLs.	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Whittington 2019	Partly. PMBCL combined with other LBCLs.	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*

Abbreviations:
ALL = acute lymphoblastic leukemia, **DLBCL** = diffuse large B cell lymphoma, **LBCL** = large B cell lymphoma, **PMBCL** = primary mediastinal B cell lymphoma, **QALY** = quality-adjusted life year.

11.4.4 Assessment against the CHEERS reporting checklist

Table 18 CHEERS checklist items for the existing Swiss study

Item	Section	Topic	Y/N	Comments
1	Title	Title	Y	Title specifies intervention (tisa-cel), target populations (B cell ALL, DLBCL), and setting.
2	Abstract	Abstract	Y	
3	Introduction	Background and objectives	Y	
4	Methods	Health economic analysis plan	N	
5		Study population	Y	
6		Setting and location	Y	
7		Comparators	Y	
8		Perspective	Y	
9		Time horizon	Y	
10		Discount rate	Y	
11		Selection of outcomes	Y	
12		Measurement of outcomes	Y	
13		Valuation of outcomes	Y	
14		Measurement and valuation of resources and costs	Y	
15		Currency, price, data, and conversion	Y	
16		Rationale and description of model	Y	PSM, a typical approach in oncology and has been used in prior submissions to NICE and CADTH.
17		Analytics and assumptions	Y	During B cell ALL model development, clinical experts were consulted to evaluate efficacy inputs and long-term extrapolation from a clinical perspective. The assumption that DLBCL patients are cured after year 3 was, according to the authors, validated by NICE submission of tisa-cel, with this approach being preferred by the NICE committee.
18		Characterizing heterogeneity	N	
19		Characterizing distributional effects	N	
20		Characterising uncertainty	Y	
21		Approach to engagement with patients and others affected by the study	Partial	Authors note the Swiss clinical experts were consulted on various issues. Engagements with patients or payers were not described.
22	Results	Study parameters	Y	
23		Summary of main results	Y	
24		Effect of uncertainty	Y	
25		Effect of engagement with patients and others affected by the study	Y	Swiss clinical experts provided input regarding comparators, diagnostic and therapeutic procedures, clinical evidence, and costs, which were used to inform the models.

Item	Section	Topic	Y/N	Comments
26	Discussion	Study findings, limitations, generalizability and current knowledge	Y	
27	Other relevant information	Source of funding	Y	
28		Conflicts of interest	Y	

Abbreviations:

ALL = acute lymphoblastic leukaemia; **CADTH** = Canadian Agency for Drugs and Technologies in Health, **DLBCL** = diffuse large B cell lymphoma, **NICE** = National Institute of Health and Care Excellence, **PSM** = partitioned survival model, **tisa-cel**: tisagenlecleucel.

11.4.5 Overview of the existing HTAs with an economic evaluation component

Table 19 Summary of existing HTAs with an economic evaluation component

HTA identifier	Population	Intervention and comparator(s)	Summary of the economic evidence considered
NICE, UK			
NICE TA554	B cell ALL that is refractory, in relapse post-transplant, or in second or later relapse, in people aged up to 25 years. Mean age of the cohort at model entry of 12 years.	**Intervention**: tisa-cel. Those discontinuing prior to infusion were assumed to receive either blinatumomab or salvage chemotherapy. *Note: the review group considered the assumption that tisa-cel patient not receiving the infusion receive comparator therapies is problematic, as these patients have faced a significant delay in treatment and include a proportion of patients who do not receive infusion due to AEs.* **Comparator**: Blinatumomab or salvage chemotherapy (FLA-IDA). **Subsequent therapies**: subsequent allogenic SCT after intervention or comparator therapies.	**About**: company submission from Novartis **Analysis**: incremental cost per QALY gained **Model**: hybrid decision tree and 3-state PSM was used. The decision tree accounted for patients who are assigned for tisa-cel treatment but who did not receive the infusion. The PSM included the following states: EFS, relapsed/progressed disease, and death. 1-month cycle length. **Data sources (efficacy)**: OS and EFS for tisa-cel arm derived from pooled analysis of IPD from 3 trials (ELIANA, ENSIGN and B2101J).[125-127] IPD data were not available for the comparators; the model therefore had to rely on published summary data. OS and EFS for tisa-cel were extrapolated using a MCM approach. This approach was also used for blinatumomab. For salvage chemotherapy, a standard parametric survival approach was used. *Note: the review group notes that a central feature of the company's model is the concept of cure.* **Time horizon**: lifetime horizon (88 years). **Discount**: costs and effects were both discounted at 3.5% p.a.
NICE TA559	Adult patients with r/r DLBCL, PMBCL and transformed follicular lymphoma who are ineligible for autologous SCT.	**Intervention:** axi-cel. **Comparator:** BSC, defined as a blended comparator of the following options: GEM, GEM-P, RGCVP and RVP. All were assumed to share the same safety and efficacy profile with each other and with the regimens used in SCHOLAR-1. **Subsequent therapies:** subsequent SCT (all allogenic in base case) after intervention or comparator. *Note: review group highlights the potential impact of SCT on HRQoL was not formally captured.*	**About:** Company submission from Kite, a Gilead Company **Analysis:** Incremental cost per QALY gained **Model**: 3-state PSM (pre-progression, post-progression, and death). 1-month cycle length. *Note: the review group noted that use of data for the modified ITT population (for axi-cel) implies model entry for patients receiving axi-cel occurs from the time point of infusion (not leukapheresis).* **Data source (efficacy):** IPD from modified ITT population from ZUMA-1 trial for OS and PFS of axi-cel.[93,95] MCM used for OS; standard parametric curve used for PFS (for axi-cel). IPD from SCHOLAR-1 study for OS of comparator (extrapolated using standard parametric curve). PFS derived from OS, assuming the same ratio between OS and PFS as observed in ZUMA-1. **Time horizon:** Lifetime horizon (44 years). **Discount:** 3.5% p.a. for costs and effects.

HTA identifier	Population	Intervention and comparator(s)	Summary of the economic evidence considered
NICE TA567	Adult patients with r/r DLBCL who have failed 2 or more lines of systemic therapy. Mean age of the cohort at model entry is 54 years.	**Intervention**: tisa-cel. **Comparator:** salvage chemotherapy, including R-GEMOX,R-GDP, or pixantrone monotherapy (generally considered to be palliative). **Subsequent therapies:** SCT after tisa-cel; model assumes no patients treated with a comparator therapy would receive SCT. *Note: review group's clinical advisor noted patients could be given a non-cross resistant salvage therapy with a view to possible autologous SCT.*	**About**: Company submission from Novartis **Analysis**: Incremental cost per QALY gained **Model**: A hybrid decision tree and 3-state PSM was used. The decision tree accounted for patients assigned to tisa-cel who did not receive the infusion (tisa-cel arm only). The PSM included the following states: PFS, progressed disease, and death. A 1-month cycle length was considered. **Data sources (efficacy)**: OS and PFS for tisa-cel arm derived from pooled analysis of IPD from JULIET and Schuster et al. (2017), extrapolated using MCMs.[122,129] Pseudo-IPD from the Eyre et al. (2016) UK observational study was used for the comparator, extrapolated using a standard parametric approach.[132] Patients were considered to be long-term survivors after 2 years. *Note: the review group considered data from the CORAL extension studies to be relevant. The review group considered the assumption of long-term survivorship reasonable, but that a 5-year time point may be more appropriate.* **Time horizon**: Lifetime horizon (46 years). **Discount**: Costs and effects were both discounted at 3.5% p.a.
CADTH, Canada			
Optimal Use Report, Vol.9 Issue 1D	Adult patients with LBCL (median age 58 years) that is refractory or has relapsed after 2 or more lines of systemic therapy and who are ineligible for autologous SCT or relapsed after autologous SCT.	**Intervention:** axi-cel. **Comparator:** BSC, defined as a combination of salvage mono-chemotherapies; specifically, gemcitabine, etoposide and cyclophosphamide. *Note: The clinical expert consulted by CADTH raised concerns as to whether the salvage chemotherapies regimens used in SCHOLAR-1 adequately reflect current contemporary practice.*	**About**: Manufacturer's submission **Analysis**: Incremental cost per QALY gained **Model**: 3-state PSM which included the following health states: progression free, progressed disease, and death. *Note: Methodological concerns remain with the use of a PSM. The use of mixture cure rates in the PSM limits transparency given that there is no explicitly defined state of cure in PSM. CADTH noted the estimated cure fraction used is highly uncertain.* **Data sources (efficacy)**: OS and PFS for axi-cel arm derived from IPD from ZUMA-1 using an MCM.[93] OS for the comparator was derived by fitting a parametric survival model on selected IPD from SCHOLAR-1.[95] PFS for the comparator was derived from OS, by applying time-dependent HR. *Note: The clinical expert consulted by CADTH considered a 5-year cure point to be appropriate.* **Time horizon**: Lifetime horizon (44 years). **Discount**: 1.5% p.a. for costs and effects.

HTA identifier	Population	Intervention and comparator(s)	Summary of the economic evidence considered
Optimal Use Reort, Vol. 8. No. 3e	Adult patients with r/r DLBCL who are ineligible for or relapse after autologous SCT. (Average age of 54 years at model entry)	**Intervention:** tisa-cel. **Comparator:** salvage chemotherapy (assumed to consist of rituximab, gemcitabine, cisplatin, and dexamethasone). *Note: CADTH noted that it is unclear whether the salvage chemotherapy regimens used in the SCHOLAR-1 trial represent standard practices in Canada (specific salvage chemotherapies used in the included evidence is NR). They felt it would have been more appropriate to derive PFS and OS from the LY-12 and CORAL studies, which included treatments widely available in Canada (R-GDP, R-ICE and R-DHAP).*	**About**: Manufacturer's submission **Analysis**: Incremental cost per QALY gained **Model:** 3-state PSM which included the following health states: progression free, progressed disease, and death. Cycle length of 1 month. **Data sources (efficacy)**: OS and PFS for tisa-cel derived by fitting parametric curves to pooled IPD from JULIET and Schuster et al. (2017).[122,129] For salvage chemotherapy, the OS data were based on parametric survival model fitted using SCHOLAR-1, while PFS was derived from OS based on the assumptions of a constant cumulative HR between OS and PFS. *Note: CADTH noted the impact of subsequent SCT was only partially accounted for.* **Time horizon:** 20 years. **Discount**: 1.5% p.a. for costs and effects.
Optimal Use Report, Vol. 8 No. 3f	Paediatric and young adult patients (aged 3 to 25 years of age) with r/r B cell ALL. The modelled patients were assumed to be, on average, 12 years of age (SD: 5.2 years) at model entry.	**Intervention**: tisa-cel. **Comparator**: salvage chemotherapy. *Note: CADTH had concerns around the generalisability of OS data from the von Stackelberg et al. (2011) study to Canadian patients. Moreover, CADTH noted that the impact of subsequent SCT was only partially captured. Only costs and disutility were accounted for; potential impacts of SCT in delaying progression and improving patient survival were not considered.*	**About**: Manufacturer's submission **Analysis**: Incremental cost per QALY gained **Model:** 3-state PSM which included the following health states: event free, progressive disease, and death. Cycle length of 1 month. EFS was defined as the earliest among death, relapse and treatment failure. **Data sources (efficacy)**: OS and EFS for tisa-cel derived by fitting parametric curves to pooled IPD from ELIANA, ENSIGN, and B2101J.[125-127] For salvage chemotherapy, the OS data were based on parametric survival model fitted to data from the curative arm of the von Stackelberg et al. (2011) study.[97] EFS for the comparator was estimated from OS by assuming a constant HR between OS and EFS over time. From year 5 onwards, the predicted OS based on the literature of ALL long-term survivors was applied to both arms. *Note: CADTH suggested it was inappropriate to pool data from ELIANA, ENSIGN, and B2101J trials due to differences in cell doses and study designs.* **Time horizon:** 70 years. **Discount**: 1.5% p.a. for costs and effects.

HTA identifier	Population	Intervention and comparator(s)	Summary of the economic evidence considered
INESSS, Canada			
Non provided	Adults with r/r DLBCL.	**Intervention:** tisa-cel. **Comparator:** salvage chemotherapy.	**About**: manufacturer's submission **Analysis**: Incremental cost per QALY gained **Model:** 3-state PSM which included the following health states: PFS, progressive disease, and death. *Note: INESSS felt it would have been relevant to model a decision tree for tisa-cel arm to consider the fact that certain patients selected will not receive the therapy.* **Data sources (efficacy)**: JULIET and Schuster et al. (2017) for tisa-cel,[122,129] SCHOLAR-1 for comparator,[95] with safety data for salvage chemotherapies from the literature. After 39 months it was assumed the probability of death in the tisa-cel arm was equal to OS data from SCHOLAR-1. *Note: INESSS did not retain the study by Schuster et al. (2017); only the JULIET study was considered. Probabilities of death between the 2 arms set equal after 24 months. They took safety data for the comparator from LY-12 study. INESSS felt use of SCHOLAR-1 to estimate deaths may overestimate long-term OS of patients receiving salvage chemotherapy.* **Time horizon:** 20 years. **Discount:** 1.5% p.a. for costs and effects.
Non provided	Children and young adults with r/r B cell ALL.	**Intervention:** tisa-cel. **Comparator**: salvage chemotherapy; and in sensitivity analyses: clofarabine monotherapy, clofarabine based regimens and blinatumomab. *Note: INESS felt, regarding the comparison with salvage chemotherapy—von Stackelberg et al. (2011)—comparisons with tisa-cel data are difficult as recruitment took place more than 20 years ago, since which time clinical practice—e.g. with regard to SCT—has evolved. Only the clofarabine-based regimen and blinatumomab were retained.*	**About**: manufacturer's submission **Analysis**: Incremental cost per QALY gained **Model:** 3-state PSM which included the following health states: event free, progressive disease, and death. *Note: INESSS felt that it would have been relevant for a decision tree to be modelled for tisa-cel arm to take into account the patients who do not receive an infusion.* **Data sources (efficacy)**: for tisa-cel, OS and PFS from B2202, B2205J and B2101J; for the comparator, OS from Hijiya et al. (2011) for clofarabine-based regimen and von Stackelberg et al. (2016) for blinatumomab.[98,99] PFS for comparators derived from OS curves. After 5 years, patients still alive were assumed to be cured. *Note: INESSS felt it was not appropriate to combine data from studies B2202, B2205J and B2101J, and retained data from B2202 only.* **Time horizon:** 70 years. **Discount:** 1.5% p.a. for costs and effects.

HTA identifier	Population	Intervention and comparator(s)	Summary of the economic evidence considered
Non provided	Adults with r/r LBCL.	**Intervention**: axi-cel. **Comparator:** salvage chemotherapies.	**About**: manufacturer's submission **Analysis**: Incremental cost per QALY gained **Model:** 3-state PSM. **Data sources (efficacy):** Survival data for axi-cel and salvage chemotherapy derived from an unanchored adjusted indirect comparison of data from ZUMA-1 and SCHOLAR-1.[93,95] This data were extrapolated using, for axi-cel, both parametric models and MCMs (given the potentially curative nature of axi-cel), and for the comparator, only parametric models (*according to experts consulted, salvage chemotherapy cannot be considered curative).* **Time horizon**: lifetime (44 years) used by manufacturer; *INESSS used a 20-year horizon in their update.* **Discount**: 1.5% p.a.for costs and effects.

Abbreviations:

AE = adverse event, **ALL** = acute lymphoblastic leukaemia, **axi-cel** = axicabtagene ciloleucel, **BSC** = best supportive care, **CADTH** = Canadian Agency for Drugs and Technologies in Heath, **CAR T** = chimeric antigen receptor T cell, **DMBCL** = diffuse large B cell lymphoma, **EFS** = event free survival, **GEM** = gemcitabine and methylprednisolone, **GEM-P** = gemcitabine, methylprednisolone, and cisplatin, **HR** = hazard ratio, **HRQoL**: health-related quality of life; **INESSS** = Institut National d'Excellence en Santé Sociaux, **IPD** = individual patient data, **ITT** = intention to treat, **LBCL** = large B cell lymphoma, **MCM** = mixture cure model, **NICE** = National Institute for Health and Care Excellence, **NR** = not reported, **OS** = overall survival, **PFS** = progression free survival, **PMBCL** = primary mediastinal B cell lymphoma, **PSM** = partitioned survival model, **QALY** = quality-adjusted life year, **RGCVP** = rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisolone, **r/r** = relapse or refractory, **R-GDP** = rituximab, gemcitabine, dexamethasone, cisplatin, **R-GEMOX** = rituximab, gemcitabine, oxaliplatin, **RVP** = rituximab, vinblastine, and prednisolone, **SCT** = stem cell transplantation, **SD** = standard deviation, **tisa-cel** = tisagenlecleucel.

11.4.6 Questions for clinical experts regarding the comparator therapies

Question
The draft HTA protocol on CAR T cell therapies identifies a range of 'standard care' alternatives to CAR T. It will not be possible to model the clinical or cost-effectiveness for all possible treatment options in each patient group; for the purposes of conducting the evaluation, we need to narrow down this list to the most important or commonly used comparators. The following is a list of potential comparators to CAR-T therapy, when given in the **third-line** setting. We ask that you identify the one or two **most relevant** or **most commonly used** comparators, based on your experience: ***Paediatric ALL:*** • Blinatumomab • Inotuzumab • Chemotherapy (if selected, please specify which regimen/(s) would be most commonly prescribed) • Tyrosine kinase inhibitor • Palliation • Other (please specify) ***Adult DLBCL:*** • Salvage chemotherapy (if selected, please specify which regimen/(s) would be most commonly prescribed) • Salvage chemotherapy followed by high-dose therapy and autologous SCT (if selected, please specify which chemotherapy regimen/(s) would be most commonly prescribed) • Palliation • Other (please specify) ***Adult PMBCL:*** • Salvage chemotherapy (if selected, please specify which regimen/(s) would be most commonly prescribed) • Salvage chemotherapy followed by high-dose therapy and autologous SCT (if selected, please specify which chemotherapy regimen/(s) would be most commonly prescribed) • Palliation • Other (please specify)