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CADTH Reimbursement Recommendation

Tisagenlecleucel (Kymriah)

Indication: For the treatment of adult patients with relapsed or refractory grade 1, 2, or 3a follicular lymphoma after 2 or more lines of systemic therapy

Sponsor: Novartis Pharmaceuticals Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Kymriah?

CADTH recommends that Kymriah be reimbursed by public drug plans for the treatment of adults with relapsed or refractory follicular lymphoma (FL) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Kymriah should only be covered to treat adults who have grade 1, 2, or 3a FL whose disease did not respond to a second or later line of treatment, returned within 6 months after 2 or more treatments, or returned after an autologous stem cell transplant (SCT).

What Are the Conditions for Reimbursement?

Kymriah should only be reimbursed for patients who have not already received a chimeric antigen receptor (CAR) T-cell therapy, are in relatively good health, and the cost of Kymriah is reduced. Kymriah should be prescribed and administered by clinicians with expertise in blood cancers in a hospital setting with adequate resources to treat patients and manage side effects.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial suggested that treatment with Kymriah resulted in durable responses and that it may improve overall survival time and the time until disease progression or death.
- Kymriah may be an effective treatment option for patients who are seeking new treatments that have durable responses and may prolong survival.
- Based on CADTH's assessment of the health economic evidence, Kymriah does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Kymriah is estimated to cost the public drug plans approximately $192,483,483 over the next 3 years.

Additional Information

What Is FL?

FL is a common type of lymphoma that develops when the body makes abnormal blood cells that cluster together to form lumps in lymph nodes or other tissues. Even though, in general, FL progresses slowly over many years, patients have shortened life expectancy if they do not respond to

Summary

the treatment or if FL returns after a response to previous treatments. It is estimated that 1 in 3,000 people have FL.

Unmet Needs in FL

Patients with FL that does not respond to, or returns after, treatment have a poor prognosis and limited treatment options. Furthermore, not all patients benefit from the available treatments. Additional treatments that can prolong survival, cure the disease, and improve quality of life are needed.

How Much Does Kymriah Cost?

Treatment with Kymriah is expected to cost approximately $450,000 per infusion.

Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that tisagenlecleucel be reimbursed for the treatment of adults with relapsed or refractory grade 1, 2, or 3a FL after 2 or more lines of systemic therapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One ongoing phase II, multicentre, single-arm, open-label trial (ELARA; N = 98) demonstrated that tisagenlecleucel resulted in benefits in response rates for adults with relapsed or refractory FL after 2 or more lines of systemic therapy. The complete response rate (CRR) in the efficacy analysis set was 68.1% (95% confidence interval [CI], 57.7 to 77.3) and met the prespecified primary end point (i.e., the lower bound of the 95% CI for CRR exceeded 15%). The overall response rate (ORR) was 86.2% (95% CI, 77.5 to 92.4). The observed responses in the ELARA trial were deemed clinically meaningful by clinical experts compared with expected outcomes in adults with relapsed or refractory grade 1, 2, or 3a FL. Tisagenlecleucel was associated with potential benefits in survival outcomes; after a median follow-up time of 28.9 months, median overall survival (OS) and progression-free survival (PFS) were not reached. Among all treated patients, the 30-month OS rate was 82.6% (95% CI, 70.2 to 90.2) and the 24-month PFS rate was 57.4% (95% CI, 46.2 to 67.0). pERC considered that the ELARA trial suggested that treatment with tisagenlecleucel may not have a detrimental impact on health-related quality of life (HRQoL), but all HRQoL measures were at risk of bias due to lack of comparative evidence, open-label design, and missing data.

Patients identified a need for more effective treatments that extend survival and disease remission and improve quality of life. Furthermore, patients indicated that there is a need for easier access to new therapies such as CAR T-cell therapy. pERC considered that tisagenlecleucel offers a subsequent therapy for a heavily pretreated population in the form of a single treatment. Given the totality of the evidence, pERC concluded that tisagenlecleucel may meet some of the needs identified by patients, in that it has durable responses and may prolong survival. While recognizing the uncertainty in the evidence, pERC agreed that tisagenlecleucel was associated with manageable toxicity and acknowledged that HRQoL may be maintained with tisagenlecleucel treatment.

The committee considered analyses conducted by CADTH that evaluated the cost-effectiveness of tisagenlecleucel relative to the current standards of care used to treat adults with relapsed or refractory grade 1, 2, or 3a FL after 2 or more lines of systemic therapy. Given the uncertainty associated with the magnitude of benefit of PFS and OS, relative to current standards of care, and the durability of such a benefit, CADTH could not estimate a robust single base-case estimate of cost-effectiveness for tisagenlecleucel. Using the sponsor's submitted price for tisagenlecleucel and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio ranged from $193,516 to $434,036 per quality-adjusted life-year gained based on CADTH reanalyses that explored possible ranges of the extrapolated OS benefits for tisagenlecleucel. In all reanalyses, a price reduction would be required for tisagenlecleucel to achieve an incremental cost-effectiveness ratio of $50,000 per quality-adjusted life-year gained.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Tisagenlecleucel should be reimbursed in adults with relapsed or refractory grade 1, 2, or 3a FL defined as one of the following: 1.1. refractory to a second or later line of systemic therapy (including anti-CD20 antibodies and alkylating agents) or relapsed within 6 months after completion of a second or later line of systemic therapy 1.2. relapsed during anti-CD20 antibody maintenance (following at least 2 lines of therapies, including anti-CD20 antibodies and alkylating agents) or within 6 months after maintenance completion. 1.3. relapsed after autologous HSCT.	In the ELARA trial, treatment with tisagenlecleucel demonstrated a clinical benefit in adults with relapsed or refractory grade 1, 2, or 3a FL with the characteristics listed in this condition.	–
2. Patients must: 2.1. have good performance status 2.2. be 18 years of age or older.	The ELARA trial enrolled patients who had an ECOG PS of 0 or 1 and who were 18 years of age or older.	–
3. Patient must not have had any of the following: 3.1. grade 3b FL 3.2. prior anti-CD19 therapy 3.3. prior adoptive T-cell therapy 3.4. active CNS involvement.	No evidence was identified to support a beneficial effect of tisagenlecleucel when used in patients with grade 3b FL, prior anti-CD19 therapy, prior adoptive T-cell therapy, or active CNS involvement as these patients were excluded from the ELARA trial.	pERC agreed with the clinical experts consulted by CADTH that as long as the CNS disease is being treated and the patient is neurologically stable, a patient should not be excluded from consideration for tisagenlecleucel.
Prescribing		
4. Treatment with tisagenlecleucel is a 1-time therapy.	At this time, CAR T-cell therapy re-treatment has not been established as an efficacious strategy and is not considered standard of care. In the ELARA trial, re-treatment was not allowed; therefore, there is insufficient evidence to support re-treatment.	Patients should receive a 1-time infusion with appropriate lymphodepleting chemotherapy before tisagenlecleucel infusion. In the ELARA trial, all patients were required to receive lymphodepleting chemotherapy before tisagenlecleucel infusion.
5. Tisagenlecleucel should only be prescribed by clinicians with expertise in the treatment of hematological malignancies. Tisagenlecleucel should be administered in specialized centres	To ensure that tisagenlecleucel is prescribed only for appropriate patients and adverse events are managed in an optimized and timely manner.	pERC acknowledges that the availability of specialized centres with adequate infrastructure and resources to administer CAR T-cell

Reimbursement condition	Reason	Implementation guidance
with adequate infrastructure, resources, and expertise to facilitate treatment with CAR T-cell therapy.		therapy in Canada is a barrier that needs to be addressed.
Pricing		
6. A reduction in price	Based on CADTH reanalyses, a price reduction of 71% to 82% would be required for tisagenlecleucel to be cost-effective at a WTP threshold of $50,000 per QALY gained relative to current standards of care. This range reflects uncertainty around the extrapolation of survival in the absence of long-term data. The magnitude of the survival benefit is uncertain given the limitations with comparative evidence for tisagenlecleucel and current standards of care. As outstanding uncertainty remains, it was noted that greater price reductions may be required.	—
Feasibility of adoption		
7. The feasibility of adoption of tisagenlecleucel must be addressed.	At the submitted price, the incremental budget impact of tisagenlecleucel is expected to be more than $40 million in years 1 and 3.	—

CAR = chimeric antigen receptor; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FL = follicular lymphoma; HSCT = hematopoietic stem cell transplant; pERC = CADTH Pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year; WTP = willingness to pay.

Discussion Points

- As there was uncertainty associated with the single-arm study design of the ELARA trial, pERC deliberated on tisagenlecleucel considering the criteria for significant unmet need described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews. Considering the severity of relapsed or refractory grade 1, 2, or 3a FL in adults and the unmet need for effective treatments in third-line and later lines of therapy, the committee concluded that the available evidence reasonably suggests that tisagenlecleucel could substantially reduce morbidity and mortality associated with the disease.
- Due to the noncomparative study design of the ELARA trial, pERC considered a submitted retrospective matched cohort study, comparing tisagenlecleucel versus standard therapies including chemotherapy, anti-CD20 antibody monotherapy, a PI3K inhibitor, high-dose chemotherapy, autologous or allogeneic SCT, and radio-immunotherapy. The results favoured tisagenlecleucel in comparison to standard therapies for the OS and PFS outcomes. However, pERC agreed that no definitive conclusions could be drawn on the relative efficacy of tisagenlecleucel versus comparators due to several limitations in the analyses, including small sample sizes, heterogeneity across the

study designs and populations, and the inability to adjust for all potential effect modifiers and prognostic variables.

- pERC acknowledged that 1 of the requirements of the conditional market authorization for tisagenlecleucel is to conduct a confirmatory phase III randomized controlled trial (RCT) comparing tisagenlecleucel with investigator's choice of treatment in patients with relapsed or refractory FL. The primary end point will be PFS, and the secondary end points will include OS and ORR. This confirmatory RCT is planned to start in August 2023 and estimated to be completed at the end of 2028.
- pERC agreed with the clinical experts that the response rates observed in the trial appeared compelling and clinically relevant in this heavily pretreated patient population in a setting that does not currently have standard of care treatment options. pERC noted the durability of response, as the median duration of response (DoR) had not been reached in the ELARA trial.
- pERC agreed with the clinical experts that the safety profile of tisagenlecleucel appeared consistent with other CAR T-cell therapies, and no unexpected safety signals were observed in the ELARA trial. Although tisagenlecleucel was associated with short-term toxicity, it is a 1-time therapy. However, ongoing monitoring and support for the prevention of infection are needed after receiving tisagenlecleucel. pERC could not draw definitive conclusions about the safety of tisagenlecleucel relative to other currently available treatments as all patients in the ELARA trial received the same treatment.
- pERC noted that uncertainties remain regarding the implementation of CAR T-cell therapy and the systems needed to optimize timely access and deliverability of tisagenlecleucel in the real-world setting. Furthermore, patients identified the need for improved access to CAR T-cell therapies. Tisagenlecleucel must be administered at specialized treatment centres with the infrastructure and resources required to administer the treatment and manage adverse events (AEs). However, a limited number of centres in Canada have the expertise and resources to deliver CAR T-cell therapy and it is unlikely that qualified centres will be available in all jurisdictions. pERC considered that some patients may be unable to travel outside their province or country to receive therapy. The need for adequate financial supports to facilitate equitable access and mitigate cost-related barriers to access that are exacerbated by geography was also discussed.
- Regarding ethical considerations in the treatment of FL with tisagenlecleucel, pERC discussed whether there are any subpopulations of patients with FL who should be prioritized for treatment, and that consideration should be given to addressing socioeconomic and structural barriers to equitable access. pERC also discussed how uncertainties in the evidence for tisagenlecleucel in the treatment of FL have implications for considering the stewardship of limited health budgets, as well as how the ongoing collection of RCT and real-world evidence could contribute to a more robust understanding of safety and efficacy. Finally, regarding health system considerations, pERC discussed the need for fair and equitable priority setting criteria if the demand for therapy exceeds manufacturing or delivery capacity, and the overall need for considering the sustainability of the health care system,

fair resource allocation, and the potential opportunity costs within and beyond the hematological-oncological space.

Background

FL is the second most common subtype of non-Hodgkin lymphoma (NHL) in western countries. FL is a relapsing and remitting disease, characterized by recurrent disease progressions, shorter remission periods, and decreased survival (i.e., OS or PFS) with each treatment course. Even though FL manifests as an indolent clinical course over many years in general, most patients eventually develop increasingly resistant disease, which results in patients with relapsed or refractory FL having reduced treatment options and poor prognosis. The overall prevalence of FL was estimated to be 1 per 3,000 people. The overall incidence of FL is also low, with rates ranging from 2.2 to 3.5 per 100,000 new cases per year in Asia, Australia, Europe, and the US. Although Canadian-specific mortality data for FL could not be identified, in 2022, it was projected that there will be 3,000 deaths due to NHL in Canada.

Patients with relapsed or refractory FL in the third-line setting and beyond represent a heavily pretreated patient population with few treatment options. A heterogenous mix of immunochemotherapy regimens (for most patients) and SCT (for a minority of patients) are the current treatment options in this population.

Tisagenlecleucel is a second-generation autologous CAR T-cell therapy directed at the cell-surface protein CD19, which is only expressed on B cells or their precursors. Tisagenlecleucel has received a Health Canada Notice of Compliance with Conditions for adults with relapsed or refractory grade 1, 2, or 3a FL after 2 or more lines of systemic therapy. The sponsor's reimbursement request is the same as the Health Canada indication. It is available as an IV infusion, and the dosage recommended in the product monograph is 0.6 to 6.0×10^6 CAR-positive viable T cells.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of a phase II, open-label single-arm study in patients with relapsed or refractory grade 1, 2, or 3a FL
- patients' perspectives gathered by 1 patient group, Lymphoma Canada (LC)
- input from the public drug plans and cancer agencies that participate in the CADTH review process
- a panel of 4 clinical specialists with expertise diagnosing and treating patients with FL
- input from 2 clinician groups, the Cell Therapy Transplant Canada and the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to tisagenlecleucel from published literature.

Stakeholder Perspectives

Patient Input

One patient group, LC, provided input to the Kymriah submission. LC is a national Canadian registered charity that collected inputs from patients with relapsed or refractory FL through an online anonymous survey from November 2022 to January 2023. Out of the 44 respondents, only 1 had experience with tisagenlecleucel. In addition, LC obtained patient feedback from a French patient organization called Ensemble Leucemie Lymphomes Espoir, which collected feedback on CAR T-cell therapy from 162 patients, including 19 responses from those with experience with tisagenlecleucel from January 2019 to September 2020 in France.

Based on the patient input, FL has significant negative impact on patients' physical and psychosocial well-being, affecting their everyday life, work, and family.

Patients indicated that there is a need for more therapeutic options that provide longer disease remission, longer life span, and improve quality of life. Patients indicated that all people living in Canada should have easy access to new therapies.

Patients who had experience with tisagenlecleucel indicated that the drug is effective; AEs were reported but manageable.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical panel indicated that for patients with FL, the most important goals for an ideal treatment are to prolong survival (i.e., OS and PFS) and improve the patient's quality of life. However, patients with relapsed or refractory FL relapse after the frontline therapies or are refractory to the available treatments, which subsequently impacts their long-term PFS and quality of life. In addition, some patients may not tolerate current treatments well due to the related AEs or complications associated with SCT.

The clinical panel noted that many factors (e.g., patient characteristics, previous treatments, treatment effects and toxicity, whether a treatment is reimbursed by drug plans, disease progression and transformation, and patient preference) need to be considered before deciding which treatment to provide. "Watch and wait" is a common approach for many patients with FL, even after disease relapse. Patients who need active treatments typically receive bendamustine, or rituximab-based therapies such as bendamustine plus rituximab, R-CVP (rituximab plus cyclophosphamide plus vincristine plus prednisone), R-CHOP (rituximab plus cyclophosphamide plus doxorubicin plus vincristine plus prednisone), or rituximab plus lenalidomide. Patients with relapsed disease after the treatment with chemoimmunotherapy, particularly those who progress within 2 years, may receive autologous SCT if they are suitable candidates. After all these treatments, some patients maintain the indolent status and some transform to large cell lymphoma. The clinical panel suggested that tisagenlecleucel be used as a third or later line of treatments for patients with relapsed or refractory FL. There are not many options available for the patients at this stage.

The clinical panel indicated that, while a more selective population would be suitable for treatment with CAR T-cell therapy in clinical trials of relapsed or refractory FL, in practice, CAR T-cell therapy can be used in a broader patient population (e.g., patients with certain comorbidities or disease status). In clinical practice, suitable patients can be identified based on clinical judgment, which combines medical history, laboratory and imaging findings, and often a lymph node biopsy. The panel noted that patients who are likely to benefit from other available treatments or with Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 3 or higher are least suitable for tisagenlecleucel. The panel also noted that there is not a specific patient characteristic that can be used to predict which patient would respond better to tisagenlecleucel compared to the others.

The panel indicated that in clinical practice, patients are evaluated and followed in a similar manner as described in the clinical trials of FL. Remission and survival are measured, and physical exams and imaging exams are routinely conducted to assess the patient's response to CAR T-cell therapy.

The panel suggested that meaningful responses to treatment with tisagenlecleucel would be a high complete remission rate as well as durability of treatment response and long-term PFS and OS. The panel noted that after CAR T-cell therapy, the clinicians will assess the treatment response (e.g., using CT scan) at 3 months, or sooner if needed.

The panel emphasized that a multidisciplinary team involving hematologists, infectious disease specialists, neurologists, intensive care units, and all other specialists is required to diagnose, treat, and monitor the patients who would receive tisagenlecleucel, to ensure the safe and effective delivery of this treatment.

Clinician Group Input

Two clinician groups provided input for the review of tisagenlecleucel: Cell Therapy Transplant Canada and the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee.

In general, the clinician group input was consistent with the input provided by the experts consulted by CADTH for the tisagenlecleucel review. They also suggested tisagenlecleucel be used in patients with relapsed or refractory FL who are not eligible to receive an allogeneic or autologous SCT as third-line therapy or beyond. In addition, in their opinion, CD19 CAR T-cell therapy, including tisagenlecleucel, will only be considered in patients without significant organ dysfunction.

The clinician groups noted that assessing response to treatment should be based on the standard lymphoma response criteria using clinical exams and imaging scans such as CT and PET. Outcomes such as remission rates, PFS, patient safety, and HRQoL should be measured.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
There was no direct comparator in the phase II information submitted by the sponsor. PAG notes that current treatments for relapsed or refractory FL after 2 lines of systemic therapy vary and can include a CD20-targeted medication (e.g., rituximab, obinutuzumab) plus various chemotherapy backbones if they were not used previously (e.g., GDP, ICE), lenalidomide plus rituximab, and SCT.	Comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
The Health Canada indication for tisagenlecleucel is specific to relapsed or refractory grade 1, 2, 3a FL after 2 or more prior lines of systemic therapy. The ELARA trial excluded those with grade 3b FL. Are patients with relapsed or refractory grade 3b FL eligible for treatment with tisagenlecleucel?	The clinical experts noted that grade 3b FL accounts for a small proportion of all FL and behaves more like DLBCL. Patients with grade 3b FL have an unmet need and a poor prognosis. These patients are usually excluded from the clinical trials. Although there is insufficient evidence to inform this decision, the clinical experts agreed that it might be reasonable to generalize the ELARA trial's results to patients with grade 3b FL. The clinical experts noted that another CAR T-cell therapy has been approved for use in patients with grade 3b FL and DLBCL. pERC noted that the approved Health Canada indication does not include grade 3b FL; therefore, pERC cannot provide guidance on this population.
PAG noted that patients with the following characteristics were excluded from the ELARA trial. If recommended for reimbursement, will these patients be excluded from treatment with tisagenlecleucel? Those with: • an ECOG PS > 1 • prior CD19-targeted therapy (e.g., tafasitamab) • prior allogeneic SCT • prior CAR T-cell therapy • active CNS involvement • other types of low-grade lymphomas (e.g., marginal zone, Waldenström macroglobulinemia, MALT lymphoma).	pERC agreed with the clinical experts that it would be reasonable to generalize the ELARA trial's results to patients with good performance status. The clinical experts noted that patients with an ECOG PS of 0, 1, or 2 are eligible for treatment with tisagenlecleucel in many centres, while those with an ECOG PS of 3 or 4 are not. The clinical experts noted that it may be reasonable to generalize the ELARA trial's results to patients who had received prior CD19-targeted therapy and in whom CD19 positivity was confirmed. pERC noted that there is no evidence to support using tisagenlecleucel in patients who received prior CD19-targeted therapy. pERC agreed with the clinical experts that it may be reasonable to generalize the ELARA trial's results to patients who had prior allogeneic SCT. These patients represent a small proportion of the population in practice and are generally excluded from clinical trials. pERC agreed with the clinical experts that the ELARA trial's results should not be generalized to patients with prior CAR T-cell therapy, patients with active CNS disease, and patients with other types of low-grade lymphomas. pERC agreed with the clinical experts consulted by CADTH that as long as the CNS disease is being treated and the patient is neurologically stable, they should not be excluded from consideration for tisagenlecleucel.

Implementation issues	Response
What bridging therapies can be considered for tisagenlecleucel in patients with relapsed or refractory FL?	The clinical experts noted that in practice, radiation would be used as bridging therapy for localized FL. Steroids, rituximab, R2, and chemotherapies are also used in clinical practice. pERC agreed with the clinical experts that selection of bridging therapies should be at the discretion of the treating physicians.
Is there sufficient evidence to support re-treatment with tisagenlecleucel in cases of disease relapse in the future?	Re-treatment was not permitted in the ELARA trial. The clinical experts and pERC agreed that there is currently a lack of data to support re-treatment with tisagenlecleucel in patients with disease relapse.
Considerations for prescribing of therapy	
The manufacturer indicates that tisagenlecleucel can be given in either the inpatient or outpatient setting, provided that it is a CAR T-cell therapy certified centre.	Comment from the drug programs to inform pERC deliberations.
Delivery of tisagenlecleucel must take place at specialized treatment centres that are accredited and certified by the manufacturer. There continues to be limited access to CAR T-cell services in Canada. While access is expanding, interprovincial travel or out-of-country funding remains necessary in many parts of Canada. Due to geographical site limitations, patients may need to travel for treatment, which requires interprovincial agreements to ensure equitable access.	Comment from the drug programs to inform pERC deliberations.
Generalizability	
Should patients who recently started their third-line systemic therapy be allowed to switch to CAR T-cell therapy provided all other criteria are met?	pERC agreed with the clinical experts that if patients respond to their current third-line systemic therapy and do not have progressive disease, there is no need to switch them to CAR T-cell therapy. However, if progressive disease is a concern, the patients would be allowed to switch to CAR T-cell therapy, provided all other criteria are met.
Funding algorithm	
This is a complex therapeutic space with multiple lines of therapy, subpopulations, or competing products.	Comment from the drug programs to inform pERC deliberations.
Care provision issues	
CRS is sometimes managed with tocilizumab. The product monograph of tisagenlecleucel indicates that 2 doses of tocilizumab should be onsite before the tisagenlecleucel infusion is started and that additional doses can be obtained within 8 hours, if needed. In the event of a tocilizumab shortage, is there another treatment that can be used to manage CRS?	The clinical experts noted that when tocilizumab is not available, other treatments used to manage CRS can include steroids, siltuximab, or anakinra (an interleukin-1 receptor inhibitor). pERC agreed with the clinical experts.
Acetaminophen and diphenhydramine, as premedication, within 30 to 60 minutes before tisagenlecleucel infusion are recommended. Systemic corticosteroids should be avoided.	Comment from the drug programs to inform pERC deliberations.

Implementation issues	Response
Other care provision issues include that patients need to stay within 2 hours of travel of a qualified clinical facility for at least 4 weeks following infusion.	Comment from the drug programs to inform pERC deliberations.
System and economic issues	
The feasibility of adoption (including budget impact) must be addressed. Given the anticipated patient volumes, PAG is concerned that existing capacity may not be able to meet demand.	Comment from the drug programs to inform pERC deliberations.
There have been significant manufacturing delays for tisagenlecleucel. How does the delayed turnaround time impact the clinical effectiveness of tisagenlecleucel?	The clinical experts indicated that manufacturing delays are a significant clinical problem, especially for the patients who progress quickly and have more disease burden. In these cases, tisagenlecleucel may not be as effective as for other patients who do not have disease progression. In addition, some patients may not be able to receive tisagenlecleucel after leukapheresis and bridging therapies. pERC acknowledged the response by the clinical experts.

CAR = chimeric antigen receptor; CNS = central nervous system; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FL = follicular lymphoma; GDP = gemcitabine, dexamethasone, and cisplatin; ICE = ifosfamide, carboplatin, and etoposide; MALT = mucosa-assisted lymphoid tissue; PAG = Provincial Advisory Group; pERC = CADTH Pan-Canadian Oncology Drug Review Expert Review Committee; R2 = lenalidomide + rituximab; SCT = stem cell transplant.

Clinical Evidence

Pivotal Studies and RCT Evidence

Description of Studies

One clinical study, ELARA, was included in the systematic review. The ELARA trial (N = 98) is an ongoing phase II, open-label, single-arm study that evaluated the efficacy and safety of tisagenlecleucel in patients with relapsed or refractory grade 1, 2, or 3a FL after 2 or more lines of systemic therapy. The primary end point was CRR by independent review committee (IRC) through 24 months. Secondary end points included ORR, OS, PFS, DoR, and HRQoL (assessed by Functional Assessment of Cancer Therapy – Lymphoma [FACT-Lym], 36-Item Short Form Survey [SF-36], and 3-Level EQ-5D [EQ-5D-3L]). Data up to 30 months of follow-up were available at the time of this review (data cut-off date of March 29, 2022). The median age observed in the overall relapsed or refractory FL population was 57 years (range, 29 to 73), more males (68.1%) were enrolled than females (31.9%), and most patients (84.0%) were white. Almost all patients (97%) had a baseline ECOG PS between 0 to 1. Most patients also had grade 1 to 2 (90.4%) and stage III to IV (80%) disease. Enrolled patients had received a median of 4 (range, 2 to 13) prior lines of treatments. Of the 98 patients included, 77.6% were refractory to their last line of antineoplastic therapy. The proportion of patients who progressed within 24 months from first-line anti-CD20 monoclonal antibody–containing therapy was 64.9%.

Efficacy Results

At the data cut-off of March 29, 2022, among the 97 patients who were treated with tisagenlecleucel, the CRR was 68.1% (95% CI, 57.5 to 77.3), ORR was 86.2% (95% CI, 77.5 to 92.4) and partial response rate was 18.1% (95% CI, not reported) at the 24 month follow-up, per IRC assessment. The results from the local assessment were consistent with the IRC assessment. Median DoR was not reached with tisagenlecleucel at the respective median follow-up times in the ELARA trial.

In the ELARA trial, median OS was not reached at the 24 month follow-up (cut-off date of March 29, 2022). Thirteen deaths had occurred in the study and the OS rate was 87.7% (95% CI, 78.3 to 93.2) and 82.6% (95% CI, 70.2 to 90.2) at the 24 month and 30 month follow-up, respectively.

The median PFS per IRC was not reached at the time of the data cut-off (March 29, 2022) and there were 38 PFS events in total (disease progression or death). The PFS rate was 77.8% (95% CI, 67.7 to 85.1), 67.2% (95% CI, 56.3 to 75.9), and 57.4% (95% CI, 46.2 to 67.0) at 6 month, 12 month, and 24 month follow-up, respectively.

Over time, there were no notable changes in the proportion of patients who reported improved, stable, or deteriorated FACT-Lym and SF-36 scores post-tisagenlecleucel infusion for most patients. Overall, 70% to 88% of patients reported no deterioration in HRQoL based on the FACT-Lym and SF-36 at 12 months, with similar trends observed at 18 months and 24 months. Results of the EQ-5D-3L Visual Analogue Scale (VAS) score showed that HRQoL was maintained from baseline following the tisagenlecleucel infusion. The mean VAS score was 69.4 at baseline, and increased to 72.5 at 6 months, 75.9 at 12 months, and 71.9 at 24 months. However, these results should be interpreted with caution because the 24-month results were based on approximately half of the patients enrolled in the study.

Harms Results

At the data cut-off date of March 29, 2022, 99% of the 97 patients evaluable for safety experienced at least 1 AE. The most commonly reported AEs of patients at any time post infusion were cytokine release syndrome (CRS) (49.5%), neutropenia (43.3%), anemia (25.8%), diarrhea (25.8%), headache (23.7%), decreased white blood cell count (22.7%), pyrexia (18.6%), thrombocytopenia (18.6%), fatigue (17.5%), nausea (17.5%), decreased neutrophil count (17.5%), constipation (16.5%), and hypogammaglobulinemia (15.5%). Serious adverse events (SAEs) were reported in 46.4% patients at any time post infusion. The most commonly reported SAEs included CRS (19.6%), pneumonia (10.3%), and febrile neutropenia (8.2%). There were 13 deaths (13.3% of patients) reported post-tisagenlecleucel infusion in the ELARA study: 7 patients died due to the study indication (occurred due to progression of the underlying disease) and 6 died because of other reasons (AEs for 5 patients and euthanasia for 1 patient).

In terms of AEs of special interest, more than 40% of patients experienced any grade CRS (49.5%), hematological disorders that included cytopenias (78.4%), and infections (55.7%). Across hematological disorders that included cytopenias, at least 25% of the patients reported neutropenia (43.3%) and anemia (25.8%). Overall, the majority of patients (74.2%) experienced hematological events of grade 3 or higher severity. Infections occurring at any time post infusion were reported in 54 patients (55.7%), 16 of whom

(16.5%) had infections suspected to be related to tisagenlecleucel. Most of the patients had either grade 1 or 2 infections, while grade 3 or higher infections were reported in 21.6% of patients (9% of whom had AEs suspected to be related to tisagenlecleucel). Death due to infection (pneumonia) was reported in 1 patient. Any grade serious neurologic adverse reactions were reported in 12 patients (12.4%), of which, 10 patients experienced these events within 8 weeks of their tisagenlecleucel infusion. Grade 3 or 4 AEs (i.e., SAEs), were reported in 3 patients (3.1%), of which, 1 patient recovered.

According to the clinical experts consulted by CADTH, the safety profile of tisagenlecleucel is consistent with other CAR T-cell therapies, and no unexpected safety signals were observed in the ELARA trial.

Critical Appraisal

The single-arm, noncomparative study design for the ELARA trial is 1 of the key limitations for this study. Interpreting the results of studies with this design is difficult because it may not be apparent whether the results are from the effect of the intervention, a placebo effect, or the effect of natural history. Although it is acknowledged that this study design has so far predominated in the evaluation of CAR T-cell therapies for advanced cancers across a variety of tumour types, and there may be practical limitations to conducting an RCT in patients with relapsed or refractory FL, there is no clear rationale that makes an RCT infeasible. Subsequently, the lack of a comparator still makes it difficult to determine whether the magnitude of the treatment effect would be replicated in a larger comparative trial or in the real world. Another limitation of the ELARA trial is its relatively small sample size and selective study population.

The study's follow-up time was likely sufficient for assessing tumour response and safety outcomes associated with tisagenlecleucel in general. However, the follow-up duration was not long enough to fully capture the effects on OS and PFS; thus, these results are considered immature. In addition to the duration of the study and the noncomparative design, subsequent treatments make it difficult to interpret the OS and PFS results. The survival results (i.e., OS and PFS) should be considered in the context of subsequent treatments, as it may be difficult to tell which treatment has more impact on patients' survival, especially when there is a lack of comparative data in the ELARA study.

The ELARA trial was open label, which can result in a bias in the measurement of subjectively assessed outcomes such as response, PFS, HRQoL, and AEs. In addition, the study presented patient-reported outcomes and HRQoL data up to 24 months; however, there is a risk of attrition bias and drawing conclusions on a select population because the analyses at 24 months were based on half of the study population from baseline and the results could be biased in favour of tisagenlecleucel.

According to the clinical experts consulted by CADTH, the study population of the ELARA trial generally represents the patients in the population with relapsed or refractory FL in Canada who would be receiving tisagenlecleucel. However, the clinical experts noted that patients seen in clinical practice would include those with poorer performance status (the ELARA trial only included patients with an ECOG PS of 0 or 1), those who received prior CD19-targeted therapy, and those who have more comorbidities.

Indirect Comparisons

Description of Studies

One indirect treatment comparison was submitted by the sponsor and included in CADTH's clinical review. Due to the lack of a common comparator, the sponsor conducted an unanchored matched-adjusted indirect comparison (MAIC) to estimate ORR, CRR, OS, and PFS comparisons between tisagenlecleucel and axicabtagene ciloleucel (2×10^6 CAR T cells per kg) in patients with relapsed or refractory FL after 2 or more lines of therapy. While the comparator treatment used in the MAIC has not yet been reviewed by pERC for this patient population, the indirect treatment comparison was used to inform the sponsor's pharmacoeconomic model and therefore reviewed by the clinical team. The MAIC was based on individual data of patients who received tisagenlecleucel during the ELARA trial and aggregate-level data of patients who received axicabtagene ciloleucel during the ZUMA-5 trial.

Efficacy Results

The MAIC analysis included 52 patients from the ELARA trial efficacy-evaluable set who were receiving nonbridging chemotherapy compared to 86 patients in the ZUMA-5 trial efficacy-evaluable set who had at least 24 months of follow-up. Compared to axicabtagene ciloleucel, the MAIC estimated a response difference for tisagenlecleucel in ORR and CRR of −3.03% (95% CI, −13.67 to 7.61) and −5.03% (95% CI, −23.85 to 13.80), respectively. Compared to axicabtagene ciloleucel, the MAIC analysis estimated the hazard of death and disease progression for tisagenlecleucel to be 0.49 (95% CI, 0.16 to 1.49) and 0.84 (95% CI, 0.37 to 1.90), respectively.

Harms Results

Fifty-three patients from the ELARA trial infused set who received nonbridging chemotherapy and 124 patients in the ZUMA-5 infused set were included in the MAIC of safety outcomes. At least 1 AE of any grade was reported in 44.6% of patients in the ELARA trial and 78.2% of patients in the ZUMA-5 trial. No grade 3 or higher AEs were reported among patients in the ELARA trial, and 6.5% of patients in the ZUMA-5 trial experiences grade 3 or higher AEs. Management of CRS with corticosteroids was documented in 3.0% and 15.3% of patients in the ELARA and ZUMA-5 trials, respectively. CRS management with tocilizumab was documented in 9.9% and 45.2% of patients in the ELARA and ZUMA-5 trials, respectively. Neurologic events of any grade were documented in 9.5% of patients in the ELARA trial and in 56.5% of patients in the ZUMA-5 trial. Grade 3 and higher neurologic events were reported among 0.2% and 15.3% of patients in the ELARA and ZUMA-5 trials, respectively.

Critical Appraisal

For an unanchored MAIC to produce unbiased treatment effect estimates, all effect modifiers and prognostic variables need to be adjusted for in the analysis. However, MAICs are rarely able to overcome the strict assumption and the bias resulting from missing covariates is very difficult to quantify. Key methodological differences between the ELARA and ZUMA-5 trials that could not be adjusted for and failure to match on key covariates may have confounded the study results. Furthermore, MAICs cannot account for unknown cross-trial differences; thus, MAIC estimates are susceptible to bias from unknown confounding. An evaluation of potential bias from residual confounding was not reported; therefore, the magnitude of this bias in the

relative treatment effect estimates is unclear. There is also concern with the loss of precision in the results given the reduction in the effective sample size. Overall, the direction of bias could not be determined due to the previously mentioned limitations and the CADTH team could not draw any strong conclusions from the MAIC. Outcomes other than treatment response and survival that are important to patients, clinicians, and drug plans (e.g., HRQoL and symptoms) were not analyzed in the MAIC.

Studies Addressing Gaps in the Pivotal Trial and RCT Evidence

Two studies provided additional context to the effectiveness and safety of tisagenlecleucel for the treatment of relapsed or refractory FL. One study compared tisagenlecleucel to standard chemotherapy (ELARA versus ReCORD-FL), and the other study was a single-arm, noncomparative trial.

ELARA Versus ReCORD-FL

Description of Study

In the absence of a direct head-to-head comparison of tisagenlecleucel to standard of care, the sponsor compared the treatment effect of tisagenlecleucel as observed in ELARA to standard of care (defined as standard chemotherapy) as documented in the ReCORD-FL study. ReCORD-FL is a noninterventional, multicentre, retrospective chart review conducted by the sponsor with the purpose of providing patient-level data to form a historical control group for comparison of standard chemotherapy to the ELARA trial. Patient-level data were collected from patients treated for relapsed or refractory FL between 1998 and 2020 from 10 sites across Europe and North America, including 1 Canadian site (n = 12). Where feasible, the ReCORD-FL study adopted the same inclusion and exclusion criteria as the ELARA trial. Propensity score matching was used to achieve an approximate balance on the number of prior lines of therapy while also balancing other key baseline prognostic variables between the ELARA and ReCORD-FL studies. The distribution of the weighted time-to-event end points of OS and PFS were estimated using Kaplan-Meier (KM) analysis, while hazard ratio (HR) was estimated using Cox proportional-hazard regression. At the time for data cut-off, 97 and 143 patients with relapsed or refractory FL from the ELARA trial (March 29, 2022) and the ReCORD-FL trials (December 31, 2021), respectively, were included. After weighting, patients included in the ELARA (n = 97) and ReCORD-FL (effective sample size = 47.5) trials had a mean age of 55.4 and 56.5 years old, respectively, were mostly males (67% to 72%), and just over a third had prior documented autologous SCT therapy. Approximately 68% and 70.2% of patients in the ELARA and ReCORD-FL trials, respectively, were documented as double refractory; and 77.3% and 63.9% were refractory to their last prior therapy.

Efficacy Results

At the time of data cut-off, death events were observed in 13.4% of patients in the ELARA trial and 45.2% of patients in the ReCORD-FL trial. Median OS was not estimable (NE) for the ELARA trial. Among patients in the ReCORD-FL study, the median OS was 36.6 months (95% CI, 25.8 to NE). The KM estimate for OS at 24 months was 90.8% (95% CI, 84.7 to 96.9) and 64.8% (95% CI, 49.5 to 80.0) for the ELARA and ReCORD-FL studies, respectively. Compared to standard chemotherapy, tisagenlecleucel was associated with an estimated risk reduction in death of 72% (HR = 0.28; 95% CI, 0.07 to 0.49).

At the time of data cut-off, disease progression was observed in 42.3% of patients in the ELARA trial and 63.7% of patients in the ReCORD-FL trial. Median PFS was NE for the ELARA trial. Among patients in the ReCORD-FL trial, the median PFS was 11.5 months (95% CI, 5.9 to 35.6). The KM estimate for PFS at 24 months was 58.6% (95% CI, 48.6 to 68.6) and 38.3% (95% CI, 22.7 to 53.8) for the ELARA and ReCORD-FL trials, respectively. Compared to standard chemotherapy, tisagenlecleucel was associated with an estimated risk reduction in death or starting a new anticancer therapy of 47% (HR = 0.53; 95% CI, 0.25 to 0.81).

Harms Results

Harms outcomes were not compared between the ELARA and ReCORD-FL trials.

Critical Appraisal

The nonrandomized comparison of the ELARA trial and the ReCORD-FL trial makes interpretation of the efficacy of tisagenlecleucel relative to standard chemotherapy challenging. To mitigate potential differences in baseline prognostic factors related to OS and PFS: the ELARA trial's inclusion and exclusion criteria were applied to the ReCORD-FL trial, and eligible patients from the ReCORD-FL study were systematically selected based on highest propensity scores. Moreover, comparison by weighting by odds was conducted to assess the causal effects of prescribing tisagenlecleucel versus chemotherapy. However, several of the ELARA study's inclusion and exclusion criteria could not be applied to the ReCORD-FL study. Moreover, prognostic factors considered important by the clinical experts consulted by CADTH for the purpose of this review, such as baseline ECOG PS and Follicular Lymphoma International Prognostic Index (FLIPI) scores, were not included in the propensity model. Consequently, there is uncertainty around the comparative treatment effects of tisagenlecleucel relative to standard chemotherapy due to selection bias and unmeasured and residual confounding that cannot be entirely ruled out. Baseline characteristics post weighting were well balanced as evident with absolute mean differences of less than 25%. However, the complete baseline demographic and disease characteristics for patients in both studies were not reported after matching. Therefore, it is unclear what effect the weighting had on the balance of other relevant patient characteristics. The applications of weights resulted in a reduced effective sample size of 45.7, in which 52% of enrolled patients in the ReCORD-FL study were lost. The reduction in sample size may contribute to imprecision, leading to uncertainty of the results. Regarding the PFS efficacy outcome, date of disease progression was not available for most patients in the ReCORD-FL trial. Moreover, radiographic assessment of disease progression tends to be less frequent in the real-world setting than in clinical trial protocols. Accordingly, date of disease progression was considered at the time of starting a new anticancer therapy in both the ReCORD and ELARA trials for comparison analysis of PFS and censoring was redefined to occur at the last contact date versus the last assessment date of the ELARA trial to avoid bias due to timing of assessment. Uncertainty of outcome assessment is further compounded due to inconsistencies in the assessments of the patients included in the ReCORD study. As assessments across patients included in the ReCORD-FL trial were not planned according to a uniform protocol, physicians may have used subjective criteria to assess clinical response. Based on input from the clinical experts, the patients included in the comparison of the ELARA and ReCORD-FL trials appeared to be younger than what is typically seen in the clinical setting. The clinical experts noted that the selected anticancer treatments were appropriate standard of care regimens;

however, whether the change in PFS definition for the purpose of efficacy comparison between the studies is an appropriate surrogate for the standard definition of PFS is uncertain.

Schuster et al.

Description of Study

The study by Schuster et al. was a single-centre, single-arm, phase IIa clinical trial conducted in the US. Its objective was to estimate the efficacy of a single infusion of tisagenlecleucel in patients with NHL and chemotherapy-relapsed or -refractory CD19+ lymphomas. Patients were eligible if they had CD19+ diffuse large B-cell lymphoma or FL with no curative treatment options, a limited prognosis (less than 2 years of anticipated survival), and a partial response or stable disease after the most recent therapy. Patients with FL were eligible if they had measurable disease less than 2 years after the second line of immunochemotherapy (excluding single-drug monoclonal antibody therapy). A total of 15 patients with relapsed or refractory FL were enrolled in this study, of whom 14 patients received the tisagenlecleucel treatment. The median age of the 14 patients was 59 years (range, 43 to 72). There was an equal distribution of male and female patients (50%). All patients (100%) had a baseline ECOG PS of 0 to 1. Overall, 64% of the patients had grade 1 to 2 FL and 86% had stage IV FL. Patients had received a median of 5.0 (range, 2 to 10) prior lines of treatment. The intervention of interest in this study was tisagenlecleucel, which was administered as a 1-time, single infusion of CAR-positive viable T cells by IV injection (total dose of 1 to 5 x10^8 CAR-positive viable T cells). The median total dose of tisagenlecleucel was 5.00 × 10^8 (range, 1.79 × 10^8 to 5.00 × 10^8), and the median dose of tisagenlecleucel per kg of body weight was 5.79 × 10^6 (range, 3.08 × 10^6 to 8.87 × 10^6). The median number of days from apheresis to infusion was 39 (range, 27 to 145). All 14 patients with FL received lymphodepleting chemotherapy before the tisagenlecleucel infusion. The primary outcome in the Schuster et al. study was ORR at 3 months in patients with NHL. The secondary outcomes were CRR, partial response, DoR, OS, PFS, and time to next treatment. Patient-reported outcomes were not included in the Schuster et al. study.

Efficacy Results

In Schuster et al., the median OS was not reached at either 28.6 or 49 months of median follow-up, and the OS rate was 93% at 28.6 months of median follow-up. The median PFS was also not reached at 28.6 months; however, a decline was observed at longer follow-up intervals (median PFS of 32.4 months and 26.2 months at a median follow-up of 49 months and 60 months, respectively). The estimated PFS probabilities were 77%, 70%, and 43% at a median follow-up of 11.4 months, 28.6 months, and 60 months, respectively. The Schuster et al. study assessed the response rate at shorter follow-up intervals (3 months and 6 months). This study reported ORR of 79% at both assessment points. CRR was 50% at 3 months and 71% at both 6 months and 49 months. The median DoR was not reached with tisagenlecleucel at the respective median follow-up times.

Harms Results

The main AEs were CRS of any grade and grade 3 or 4 experienced by 42.9% and 14.3% of patients with FL, respectively. Tisagenlecleucel was administered as a single-time infusion; therefore, no patients discontinued treatment in the Schuster et al. study. One patient with FL who had encephalopathy had progressive neurologic deterioration that resulted in death. Data for other AEs of special interest were only

reported for the overall NHL population in the Schuster et al. study. Eleven patients (39%) reported neurologic toxicities, including encephalopathy in 3 patients (27%), delirium in 2 patients (18%), and tremor in 2 patients (18%). In addition, cognitive disturbance, confusion, involuntary movements, and memory impairment were reported in 1 patient (5%) each.

Critical Appraisal

The main limitations of the Schuster et al. study are the single-arm design, lack of comparator, and open-label nature of the study, which limits interpretation of effect. Moreover, the sample size calculation for this study was based on the overall NHL population and was not specific to the FL subgroup, which could limit the detection of magnitude of effect among the FL subgroup.

In terms of generalizability, this study was conducted in the US, which may have different health systems and treatment conditions compared to Canada. The patient population of this study had a baseline ECOG PS of 0 to 1. It is not clear if the results are generalizable to the patients with poorer performance status.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Adults with relapsed or refractory grade 1, 2, or 3a FL after 2 or more lines of systemic therapy
Treatment	Tisagenlecleucel
Dose regimen	One-time infusion of tisagenlecleucel, cell suspension of 0.6 to 6.0 × 10^8 cells (non–weight-based dose)
Submitted price	Tisagenlecleucel: $450,000 per 1-time infusion
Treatment cost	One-time cost of $450,000
Comparators	SoC, axicabtagene ciloleucel SoC is composed of chemotherapy (89%) and ASCT (11%) Chemotherapy includes 6 different regimens: • R-CVP (rituximab + cyclophosphamide + vincristine + prednisone) • R-CHOP (rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone) • O-CHOP (obinutuzumab + cyclophosphamide + doxorubicin + vincristine + prednisone) • R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin) • BR (rituximab + bendamustine) • R-ICE (rituximab + ifosfamide + carboplatin + etoposide).
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs

Component	Description
Time horizon	Lifetime (30 years)
Key data sources	• Tisagenlecleucel: single-arm, phase II ELARA trial (data cut-off date: March 29, 2022) • SoC: The ReCORD-FL study chemotherapy subgroup (data cut-off date: December 31, 2020) • Axicabtagene ciloleucel: The ZUMA-5 study efficacy-evaluable subgroup (data cut-off date: March 31, 2021) • Tisagenlecleucel was compared to SoC through propensity score matching to the ReCORD-FL trial and to axicabtagene ciloleucel through a MAIC to the ZUMA-5 trial
Key limitations	• The sponsor's choice of a dependent parametric model for OS and PFS was not appropriate given that the assumption that patients receiving tisagenlecleucel would have a similar disease course as those receiving SoC was invalid. • Beyond month 38 of the model (i.e., longest follow-up time in the ELARA trial at the March 2022 data cut-off), the sponsor assumed the same OS and PFS rate of decline between tisagenlecleucel and SoC and that the incremental benefit favouring tisagenlecleucel would be sustained for the remainder of the model lifetime horizon. • The magnitude and durability of the survival benefit with tisagenlecleucel is highly uncertain in the absence of more robust evidence. Clinical experts indicated that it is plausible for the OS of tisagenlecleucel to converge with that of SoC within the model's lifetime horizon; that is, for tisagenlecleucel's treatment effect to wane within the patients' lifetime. • The sponsor assumed that 45% of patients who receive SoC incur the costs associated with receiving CAR T-cell therapy as subsequent therapy in the fourth line without experiencing the full extent of the survival benefit associated with it. This assumption reduced the incremental cost of tisagenlecleucel relative to SoC, thereby introducing a cost-effectiveness bias in favour of tisagenlecleucel. • The sponsor failed to consider the upfront costs associated with the assessment of CAR T-cell therapy eligibility. Moreover, the pretreatment cost of leukapheresis considered by the sponsor for patients receiving CAR T-cell therapy was underestimated. • While the sponsor included axicabtagene ciloleucel as a comparator, it is not specifically indicated for FL, not currently reimbursed by participating cancer organizations, and not currently used off-label. In contrast, the sponsor omitted rituximab and lenalidomide (Revlimid) from the analysis despite evidence that the therapy is used off-label in current Canadian clinical practice.
CADTH reanalysis results	• CADTH reanalyses were derived by making changes to the following model parameters: applying independent models to estimate the OS and PFS of tisagenlecleucel and SoC; using parametric distributions based on the ELARA and ZUMA-5 trial data to extrapolate the OS and PFS of tisagenlecleucel and axicabtagene ciloleucel for the entire time horizon of the model; including a CAR T-cell eligibility assessment cost and updating the pretreatment cost associated with apheresis; aligning subsequent therapies among patients receiving SoC in the third line with the observed proportion of patients in the ReCORD-FL trial's chemotherapy subgroup; and excluding axicabtagene ciloleucel as a comparator. Given the magnitude of uncertainty surrounding OS for tisagenlecleucel, its comparative efficacy against SoC, and the durability of such a benefit, CADTH conducted separate analyses involving different parametric assumptions for OS. • In CADTH reanalysis A, the OS for tisagenlecleucel was modelled using the exponential distribution (assuming a treatment effect for 17.5 years post infusion before any waning of effect). Tisagenlecleucel was associated with an ICER of $193,516 per QALY gained compared to SoC (incremental costs = $420,926; incremental QALYs = 2.18). A price reduction of 71% would be required for tisagenlecleucel to be cost-effective at a WTP threshold of $50,000 per QALY gained. • In CADTH reanalysis B, tisagenlecleucel's OS was modelled using the log-normal distribution (assuming a treatment effect for 7.9 years post infusion before any treatment waning). Tisagenlecleucel was associated with an ICER of $434,036 per QALY gained compared to SoC (incremental costs = $420,063;

Component	Description
	incremental QALYs = 0.97). Under this reanalysis, a price reduction of 82% would be required for tisagenlecleucel to be cost-effective at a WTP threshold of $50,000 per QALY gained.

ASCT = autologous stem cell transplant; CAR = chimeric antigen receptor; FL = follicular lymphoma; ICER = incremental cost-effectiveness ratio; LY = life-year; MAIC = matching-adjusted indirect comparison; OS = overall survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; SoC = standard of care; WTP = willingness to pay.

Budget Impact

CADTH identified the following limitations in the sponsor's base case: the projected market size is underestimated, the projected market share of tisagenlecleucel is underestimated, both the inclusion of axicabtagene ciloleucel and the exclusion of the rituximab and lenalidomide (Revlimid) regimen as relevant comparators is not supported by current Canadian clinical practice, and CAR T-cell therapy pretreatment costs are underestimated. CADTH reanalysis included changes to address these limitations. Based on the CADTH base case, the estimated budget impact associated with the reimbursement of tisagenlecleucel for the treatment of relapsed or refractory grade 1, 2, or 3a FL after 2 or more lines of systemic therapy is expected to be $109,216,203 in year 1, $37,814,864 in year 2, and $45,452,416 in year 3, with a three-year total of $192,483,483. A scenario analysis based on the assumption that axicabtagene ciloleucel would be a relevant comparator in the third- and fourth-line new drug scenarios resulted in a decrease of tisagenlecleucel's estimated 3-year budget impact to $147,117,573, indicating that the budget impact is highly sensitive to the inclusion of other CAR T-cell therapies in the comparator space.

Ethical Considerations

Normative and empirical literature on CAR T-cell therapies, as well as past CADTH ethics reports, were reviewed to summarize the ethical considerations associated with the use of CAR T-cell therapies for the treatment of hematological cancers. Ethical considerations specific to the use of tisagenlecleucel for the treatment of FL were identified from a review of patient and clinician group and drug program input as well as consultation with the clinical experts engaged by CADTH for this review.

- Ethical considerations arising in the context of hematological cancers include the unmet need for durable, life-prolonging treatment for patients with relapsed or refractory disease, as well as disparities in incidence, diagnosis, treatment, and outcomes in hematological cancers, especially how these affect patients from racialized, structurally marginalized, and lower income groups, as well as those residing in rural areas. Patients with relapsed or refractory FL have limited third-line therapeutic options, especially if they are ineligible for SCT, and have a need for therapies with fewer toxicities that offer more durable response. Patients who become chemotherapy refractory have no remaining therapeutic options available and thus have an unmet need for treatment that can delay disease progression.
- Ethical considerations arising in the evidence used to evaluate CAR T-cell therapies indicate limitations in the representativeness of the clinical trial populations, the absence of long-term safety and efficacy data, and the absence of comparative effectiveness data. Uncertainty about the

magnitude of clinical benefit can present challenges for the pharmacoeconomic assessment of CAR T-cell therapies and the assessment of opportunity costs, and may expose payers to greater financial risks. Budget forecasting may underestimate the overall budget impact of reimbursing CAR T-cell therapies if they are implemented fairly and as needed. Clinical experts noted that given the availability of other therapeutic options for the treatment of FL past second-line therapies, they would prefer to have a higher level of evidence—including long-term efficacy outcomes and comparative effectiveness data collected from a phase III trial—to inform clinical decision-making with respect to tisagenlecleucel.

- Several access considerations arise in the context of CAR T-cell therapies in Canada, including those related to geographical access, especially as they may disproportionately impact racialized, structurally marginalized, and lower income groups and those lacking caregiver support, as well as inequities that may arise during referral or treatment. Considerations related to privacy and culturally sensitive practices also arise in the context of cell and tissue ownership, as well as informed consent, shared decision-making, and balanced communication related to CAR T-cell therapies. While tisagenlecleucel is proposed for use beyond second-line therapy in FL, the clinical experts noted that there are other third-line therapies available to treat FL. Owing to the heterogeneity of FL and availability of other third-line therapies, the clinical experts discussed how the decision to recommend tisagenlecleucel for the treatment of FL would include a consideration of all available therapeutic options, as well as a patient's individual presentation of the disease and circumstances. Shared decision-making may be part of this process given the range of therapies available and individualized risk-benefit calculations.
- Ethical considerations for health systems include challenges associated with the capacity to manufacture and deliver CAR T-cell therapy and scale CAR T-cell centres across Canada due to complex infrastructure and personnel requirements. Fair priority setting criteria are required if demand for the therapy exceeds manufacturing or delivery capacity. Reimbursing high-cost, resource-intensive therapies such as CAR T-cell treatment presents opportunity costs for health systems within and beyond the hematological-oncological cancer space. Resources for health information infrastructure may be required to support postmarket surveillance, collection of real-world evidence, or the implementation of alternative pricing or financing models. Variability in funding for FL treatment, and oncological drugs more broadly, across Canadian jurisdictions could result in inequities for accessing tisagenlecleucel if it were reimbursed in a piecemeal manner for patients in Canada.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Catherine Moltzan,

Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik

Meeting date: July 12, 2023

Regrets: One expert committee member did not attend.

Conflicts of interest: None

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