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Abbreviations

CAR	chimeric antigen receptor
CD19	cluster of differentiation 19
CIBMTR	Center for International Blood and Marrow Transplant Research
CRS	cytokine release syndrome
DLBCL	diffuse large B-cell lymphoma
EBMT	European Society for Blood and Marrow Transplantation
EMA	European Medicines Agency
FACT	Foundation for the Accreditation of Cellular Therapy
HSCT	hematopoietic stem cell transplant
IEC	immune effector cells
JACIE	Joint Accreditation Committee International Society for Cell and Gene Therapy-Europe and European Society for Blood and Marrow Transplantation
LLSC	Leukemia & Lymphoma Society of Canada
NCA	national coverage analysis
NHL	non-Hodgkin lymphoma
NHS	National Health Service
pCODR	CADTH pan-Canadian Oncology Drug Review
r/r	relapsed or refractory
SOP	standard operating procedures

Protocol Amendments

Amendment	Page
Following Health Canada's issuance of a Notice of Compliance for axicabtagene ciloleucel and publication of the final product monograph, the confirmed indication was used to inform a revision of the indication in the population eligibility criterion for the review (i.e., instances of "non-Hodgkin lymphoma" were changed to "large B-cell lymphoma" throughout except for the Patients' and Caregivers' Perspectives and Experiences review, where the larger disease category of non-Hodgkin lymphoma was retained).	All (including title page and all footers)
Changed label for the study design used for the analysis of implementation issues in the published literature from a "rapid qualitative evidence synthesis" to a "narrative summary."	6

Executive Summary

Background

Axicabtagene ciloleucel (marketed as Yescarta by Gilead Sciences) is the second chimeric antigen receptor (CAR) T-cell therapy to be approved in Canada. Following a priority review, Health Canada approved axicabtagene ciloleucel on February 13, 2019, for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.[1]

As part of CADTH's health technology assessment of axicabtagene ciloleucel,[2] an implementation analysis and ethics review was conducted to help Canadian jurisdictions structure the provision of axicabtagene ciloleucel to adults with large B-cell lymphoma.

Ethics Review

Methods

A review of the empirical and normative ethics literature was conducted to identify literature relevant to the identification and analysis of the potential ethical, legal, and social issues related to the use of axicabtagene ciloleucel for adults with r/r large B-cell lymphoma.

Summary of Findings

Axicabtagene ciloleucel is a CAR T-cell therapy for the treatment of r/r large B-cell lymphoma and the second CAR T-cell therapy to be approved for use in Canada. Given continuing evidentiary uncertainty concerning the long-term clinical benefits and harms, and similar uncertainty around substantial economic impact,[3,4] from an ethics perspective, it is best understood as an experimental therapy. This means striking a balance between the protection of vulnerable persons and the promotion of therapeutic benefit. Key ethical considerations include balancing safety and effectiveness, both short and long term; addressing barriers to or limitations on equitable access, including geographic constraints, supply constraints, and patient selection; and considering the total cost of axicabtagene ciloleucel, including its affordability at the health system, institutional, and patient levels.

These considerations underline the importance of informed choice and consent in treatment decision-making as well as recognition of psychological and emotional benefits and burdens. There may also be legal questions associated with the ownership of the genetically modified T cells. Clinical and policy implications shed light on how some of these concerns may be addressed in practice and illuminate considerations for the implementation of axicabtagene ciloleucel.

Implementation Analysis

Methods

The implementation analysis synthesized information from several sources, including patient and stakeholder input; relevant information from the clinical, economic, and ethics reviews conducted as part of the broader CADTH health technology assessment; industry documents; a rapid qualitative evidence synthesis of patients' and caregivers' perspectives

and experiences of advanced or terminal hematologic cancer; and a narrative summary of implementation issues relating to axicabtagene ciloleucel.

Summary of Findings

Structuring the provision of axicabtagene ciloleucel raises a number of challenges. The management of toxicities and potential for severe adverse events, coupled with the need for ongoing data collection, point to the need to manage potential risks of the therapy and its implementation and help to shape potential models of delivery. The process for onboarding of sites suggests that widespread diffusion of the therapy may take time, and that care may remain situated with specialized hematopoietic stem cell transplant centres. Supporting care across and within jurisdictions through reimbursement mechanisms and resources for patient travel (financial and logistical) may mitigate risks of potential geographic inequalities. Deciding on which organizations are most suited to provide oversight of treatment sites — namely, the role of the Foundation for the Accreditation of Cellular Therapies (FACT) and the manufacturer — involves complex considerations. The presence of multiple CAR T-cell products makes this a more pressing issue as treatment sites grapple with multiple levels of oversight and accreditation for multiple products. Patient selection will likely involve the selection of patients who are less stable than those in the pivotal trial supporting regulatory approval of axicabtagene ciloleucel, and bridging therapy will also likely be used in practice. Patient selection may occur across the process of receiving the therapy and processes for allocating manufacturing slots as they become available will be needed. Uncertainty around long-term clinical effectiveness and safety raises challenges for regulatory agencies and payers when making decisions, highlighting the need for long-term data collection.

Background and Purpose

Axicabtagene ciloleucel (marketed as Yescarta by Gilead Sciences) is the second chimeric antigen receptor (CAR) T-cell therapy to be approved in Canada. Following a priority review, Health Canada approved axicabtagene ciloleucel on February 13, 2019, for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.[1]

CAR T-cell therapy involves collecting a patient's own immune cells (T cells) and genetically altering the collected cells to express a CAR, which in the case of axicabtagene ciloleucel is cluster of differentiation 19 (CD19). Once reinfused back into the patient, the CAR T cells attach to the cancer cells because of the modified receptor and attack the cancer cells.

Manufacturing and infusion of axicabtagene ciloleucel involves multiple steps. Once a manufacturing slot is secured for a patient, the patient must be stable enough to undergo leukapheresis — a process by which a patient's white blood cells are collected to make the product. The patient's blood is then handled through rigorous procedures for packaging, labelling, and shipping through specialized courier to the manufacturer's centralized facility in the US. At the centralized manufacturing facility, the T cells are processed, genetically modified using retroviruses, expanded, washed, then frozen, packed, and shipped back to the treating facility. In ZUMA-1, the clinical trial supporting the regulatory approval of axicabtagene ciloleucel, the time between leukapheresis and infusion was on average 24 days (range of 16 days to 73 days).[2] Patients must undergo lymphodepleting chemotherapy to prepare them for subsequent reinfusion, and are monitored post-infusion for potentially serious adverse events, including cytokine release syndrome (CRS) and neurologic symptoms associated with T-cell expansion and activity.

This therapy is currently indicated for patients whose cancer is r/r. These patients are young adults and adults who have relapsed, perhaps more than once, or patients whose cancer never went into remission. With salvage chemotherapy, patients are typically given a prognosis of months, with a median overall survival of six months.[5] In a medically fragile state, they face ongoing deterioration in their health due to an aggressive disease.

As part of a health technology assessment of axicabtagene ciloleucel, CADTH conducted an implementation analysis and an ethics review to help Canadian jurisdictions structure the provision of axicabtagene ciloleucel for adults with large B-cell lymphoma. The purpose of the implementation analysis was to provide evidence-based information and an analysis of implementation considerations, including travel, hospital stays, and health care resource use and costs that bear on the implementation of axicabtagene ciloleucel. A rapid qualitative evidence synthesis was conducted as part of the implementation analysis to describe patients,' caregivers,' and providers' experiences and perspectives with advanced hematologic cancers. The purpose of the ethics review was to identify, describe, and provide guidance on how to address the major ethical issues raised by the implementation of axicabtagene ciloleucel for adults with large B-cell lymphoma. Clinician input and patient input submissions were also collected to inform this assessment to ensure opportunities for considering stakeholders' and patients' experiences.

Policy Question

The analyses reported here inform the following policy question:

How should the provision of axicabtagene ciloleucel be structured for treating adults with eligible types of relapsed or refractory large B-cell lymphoma?

Ethics Review

Objectives and Approach

Ethical principles can serve as a guide to assessing and implementing new therapies such as axicabtagene ciloleucel. Common ethical principles include:

- promoting overall net benefit to individual patients through access to safe and effective therapies (beneficence) and minimizing risk of harm (nonmaleficence)
- respecting the importance of informed and voluntary patient choice (autonomy)
- ensuring a fair distribution of benefits and burdens across affected patients (equity)
- protecting the public from harm (nonmaleficence) and fostering public confidence in the health system (accountability)
- promoting the responsible use of health resources based on best available evidence (stewardship).

It is common in ethical analyses to consider ethical issues as well as broader legal and social issues (referred to as ELSI). While the primary emphasis of this ethics review is on ethical issues arising in the implementation of axicabtagene ciloleucel, legal and social issues were also considered in the analysis.

Principles of procedural justice are also important in health policy, particularly where there may be competing ethical principles, reasonable disagreement about how different principles ought to be balanced or prioritized, or uncertainty in the policy context. The "accountability for reasonableness" framework outlines five conditions of a legitimate and fair decision-making process toward publicly defensible decisions and decision-maker accountability.[6,7]

Table 1: Accountability for Reasonableness Framework[6,7]

Relevance	Decisions should be based on reasons (i.e., evidence, principles, values, and arguments) that fair-minded people can agree are relevant under the circumstances.
Publicity	Decision processes should be transparent and decision rationales should be publicly accessible.
Revision	There should be opportunities to revisit and revise decisions in light of further evidence or arguments, and there should be a mechanism for resolving disputes.
Empowerment[7]	There should be efforts to optimize effective opportunities for participation in priority setting and to minimize power differences in the decision-making context.
Enforcement	There should be a leadership commitment to ensure that the first four conditions are met.

The findings of this ethics review illustrate the relevance of these principles to the proposed implementation of axicabtagene ciloleucel, including where more than one principle may be in conflict or need to be balanced and where consideration of procedural justice may be relevant.

Two research questions guided the ethics review.

- What are the major ethical issues raised by the implementation of axicabtagene ciloleucel for adults with relapsed or refractory non-Hodgkin lymphoma?
- How might these issues be addressed?

The ethics review used a two-step approach to identify, describe, and analyze potential ethical issues. Further details about the methods used can be found in an a priori published protocol.[8] The first step was a literature review of explicit ethical issues described in the literature on axicabtagene ciloleucel. A search was performed by an information specialist using a peer-reviewed search strategy to retrieve citations from the ethics, clinical, and health policy and health services literature on axicabtagene ciloleucel. Retrieved citations were screened for inclusion. To be eligible, studies had to include explicit descriptions of ethical issues or provide existing analyses of ethical considerations in the use of axicabtagene ciloleucel. Appendix 5 presents a flowchart of the article selection process based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) process.[9] Details about the included articles can be found in Appendix 6.

The second step was a *de novo* ethical analysis of the potential ethical, legal, and social issues related to the use of axicabtagene ciloleucel. Using the included studies and gaps identified in the literature review, the analysis drew on ethical concepts to identify potential ethical issues with the implementation of axicabtagene ciloleucel for adults with r/r large B-cell lymphoma. The ethics review approach was inductive and iterative, and was responsive to results emerging from the clinical, economic, and implementation reviews, including patients' and stakeholders' perspectives, conducted as part of the full health technology assessment.

Ethics Review Findings

Axicabtagene Ciloleucel as "Experimental Therapy"

Axicabtagene ciloleucel may offer a therapy of last resort for some adults with r/r large B-cell lymphoma. While axicabtagene ciloleucel has demonstrated some potential for clinical benefit in patients with r/r disease who have exhausted all other curative options, it is also associated with high risks due to short-term toxicity and a high degree of uncertainty about long-term effectiveness and harms.[2] Several authors have drawn attention to the "hype" surrounding CAR T-cell therapy,[10-15] which has been described by one author as a form of "experimental therapy" that blurs the line between research and clinical care.[16] Given this, the ethical status of axicabtagene ciloleucel may be examined from both a research ethics and a clinical ethics paradigm, the former focusing on protection of vulnerable persons and the latter focusing on promotion of therapeutic benefit.[17]

Implementing the provision of axicabtagene ciloleucel involves balancing distinct ethical imperatives of protecting vulnerable persons from harm (nonmaleficence) while also guarding against paternalism and respecting patients as autonomous decision-makers capable of deciding to pursue a therapy that comes with risk (respect for persons, autonomy), and enabling patients to access potentially beneficial therapies (beneficence). Jecker et al. describe therapeutic benefit as existing along a continuum "from the complete uncertainty associated with standard research, to an intermediate stage where evidence of benefit mounts and reaches a peak, to a final stage of clearly demonstrated benefit that is sufficient to gain approval for clinical applications." (p. 393).[17] Furthermore, they argue that patients may have greater ethical claims to accessing therapies if evidence of therapeutic

benefit mounts. As is discussed subsequently, the evidentiary uncertainty surrounding axicabtagene ciloleucel's long-term safety, effectiveness and cost-effectiveness has ethical implications for its implementation in practice.[3,4]

Key Ethical Considerations

Balancing Safety and Effectiveness

A primary ethical consideration for implementing axicabtagene ciloleucel, as with any therapy, is determining how to weigh therapeutic risks and benefits.[17] Although available evidence indicates that axicabtagene ciloleucel has demonstrated clinical benefit to some patients,[3] its risk profile is ethically relevant in three key respects. First, axicabtagene ciloleucel has known severe adverse events that can occur within several weeks of administration; these can be life threatening but are treatable.[3] Second, there is uncertainty surrounding axicabtagene ciloleucel's intermediate and long-term safety and effectiveness.[3] Third, patients eligible for axicabtagene ciloleucel are r/r and are at high risk of death, so the risks associated with treatment remain relative to the known risks of the patient's untreated condition.[11,18] Among the articles included in this review, there is no expert consensus concerning what constitutes an ethically justifiable or appropriate balance of risks and benefits when using axicabtagene ciloleucel for the treatment of r/r large B-cell lymphoma. Some authors have underlined the net benefit to patients of a therapy that is both life- and quality-of-life-preserving, even in the face of serious adverse events such as severe CRS.[14,19] This is echoed by some patients,[18] including those who contributed to the patient input submissions for CADTH's review in Appendix 3. However, some patients contributing to the patient input submission also expressed uncertainty in whether they would decide to undergo treatment with potentially serious side effects even if recommended by their physician (see Appendix 3). Patients reported assessing the risks and benefits of axicabtagene ciloleucel in comparison with the risks and benefits of previous or alternative treatments, such as chemotherapy or stem cell transplants, which also bear serious risks (see Appendix 3).[11,18]

Considering whether a therapy offers net benefit over harm in the long term also has implications for both patients and members of the public. Evidentiary uncertainty about the therapy's long-term safety and effectiveness and the lack of data concerning axicabtagene ciloleucel's effectiveness compared with other CAR T-cell therapy,[3] such as tisagenlecleucel, poses a challenge for clinical and policy decision-making. Evidentiary uncertainty also limits the accuracy of cost-effectiveness assessments,[4,15,20] which are used to support stewardship and public accountability in resource allocation. Evidence-generating measures, such as active post-market surveillance, are required by regulators to inform clinical and policy decision-making that serve the interests of patients and the public.[12,21-23]

Access

There are several ethical considerations associated with accessing axicabtagene ciloleucel. Three commonly cited access concerns include geographic constraints on access, supply constraints, and patient selection. These concerns underline ethical tensions between safety and equity (geographic constraints), timely access and quality control (constraints on supply), and patient need and procedural fairness (patient selection).

Geographic Constraints

Given the need to onboard treatment sites, it is likely that axicabtagene ciloleucel will be initially administered at a limited number of hematopoietic stem cell transplant (HSCT) treatment centres with the resources and highly trained clinical staff required to properly administer the therapy, manage potential adverse events, and ensure safe treatment (see the Implementation Analysis section). While this may foster safety in the provision of axicabtagene ciloleucel, patients and caregivers who live remotely from these treatment centres will bear a disproportionate burden in accessing care compared with those patients and caregivers located in closer proximity to treatment centres.[12,21,24-26] As noted in the published literature,[18,24,25,27] Appendix 1, and Appendix 3, some patients and caregivers face additional costs associated with travel, lodging, and absence from work, as well as psychological burdens associated with spending time away from family and communities, especially during a time of need. Moreover, patients are required to remain close to the treatment facility during the period in which the risk of severe adverse events is highest (the first four weeks after treatment), and then require follow-up care at multiple points over the subsequent year (see the Implementation Analysis section). As patients relocate, patient–provider relationships may be disrupted and care continuity may be impacted (see Appendix 1). Coordination between referring and providing institutions is essential to facilitate successful and continuous care and support for patients and caregivers prior to and following treatment.[28] These geographic constraints and the duration of treatment together place additional burdens on patients and caregivers who live far away from treatment facilities and may exacerbate existing inequities in access to care (see the Implementation Analysis section).[21,27,29] Hence, the geographic location of treatment centres illuminates not only an ethical tension between minimizing harm (nonmaleficence) and ensuring equitable access; it may also act as a barrier to access for some patients who are unable to shoulder the out-of-pocket costs associated with travel and short-term relocation, and further impact the balance of benefits and burdens associated with the therapy.

Owing to the novel nature of the therapy and limited existing infrastructure, the manufacturer is expected to have a high degree of involvement in the implementation of axicabtagene ciloleucel, including in patient and clinician education, site selection, and site accreditation and auditing (see the Implementation Analysis section). A consideration of what the appropriate role of the manufacturer ought to be going forward is warranted. For example, site selection criteria may need to consider population-level needs and the promotion of equitable access across Canada.

Constraints on Supply

T-cell collection, access to manufacturing slots, and delivery and monitoring processes may present additional barriers to access. As axicabtagene ciloleucel is manufactured individually for each patient, supply is limited by access to highly trained personnel and facilities capable of collecting cells, shipping and handling the cells, administering the therapy, managing potential adverse events, and collecting follow-up safety and effectiveness data (see the Implementation Analysis section).[11,27,30] This could have significant implications for patient outcomes given a limited treatment window — namely, patients must be sick enough to be eligible for treatment but well enough to wait between two and three weeks on average while their T cells are processed for infusion.[3,11,30] Some authors flagged additional concerns about possible off-label use for CAR T-cell therapy, which could introduce production delays for currently approved products and indications.[31] Although not borne out through international experiences to date, with potentially limited

resources for collecting, processing, and reinfusing patients' modified T cells, the demand for axicabtagene ciloleucel may exceed supply. Additionally, the potential for long-term B-cell aplasia in a portion of patients who receive CAR T-cell therapy may require follow-up and long-term intravenous immunoglobulin treatment.[3,32,33] As the number of patients who receive CAR T-cell therapy grows, it may be important to consider existing issues with the supply of intravenous immunoglobulin in Canada.[34] On one hand, this underlines the need for efficient and high-quality production processes. On the other hand, supply constraints may entail setting priorities among patients for access to axicabtagene ciloleucel.

Patient Selection

Considerations of distributive and procedural justice may arise if the demand for axicabtagene ciloleucel exceeds manufacturing and administration capacities. Jecker et al. have proposed a set of selection criteria for prioritizing patient participation in CAR T-cell clinical trials.[17] First, they recommend setting a minimum threshold of expected benefit sufficient to justify the potential risk of harm (beneficence). Next, among eligible participants, they recommend giving priority to the sickest patients in order to save the most lives and improve the well-being of the worst-off (equity). Finally, in the absence of ethically salient criteria to prioritize remaining participants, they recommend using a fair procedure (e.g., random lottery) to give each patient a fair opportunity to be selected (procedural fairness).

While the appropriateness of these criteria within a therapeutic context requires further consideration, Jecker et al.'s assertion that patients are entitled to a fair selection process is translatable to clinical contexts where there is an analogous need for just criteria for prioritizing access to limited therapies. For example, in a clinical setting, a fair selection process for a therapy for patients with little or no therapeutic alternatives may prioritize beneficence, such as by taking into account need and potential for benefit as assessed by standardized clinical criteria rather than a random lottery. Indeed, it may be the case that if evidence of axicabtagene ciloleucel's benefit increases, there might be a shift in criteria from prioritizing the sickest patients (saving lives) to prioritizing patients who are most likely to benefit from therapy (promoting better outcomes and maximizing overall therapeutic impact).[17] Moreover, as patients with greater disease burden are more likely to experience severe CRS,[35] earlier placement in the treatment pathway may be preferable to help mitigate toxicity.[11,36] Whatever criteria may be chosen, fairness suggests the importance of a common set of selection criteria to ensure consistency across similar patients and to alleviate decision-making burden from clinicians.[37] Procedural fairness, including transparency about the patient selection process, consistency in the application of selection criteria, and potentially having an appeals mechanism, can help foster patient and public trust.

Priority-setting criteria may be needed to determine which CAR T-cell product should be made available to a patient, given that some patients with r/r large B-cell lymphoma who are eligible for axicabtagene ciloleucel may also qualify for tisagenlecleucel. Stakeholders consulted raised the suggestion that a centralized, pan-Canadian mechanism for referral and prioritization could be adopted for CAR T-cell therapy, such as is used in organ transplant triage (see the Implementation Analysis section). A pan-Canadian approach may promote more equitable inter-regional access to axicabtagene ciloleucel and contribute to fair selection processes by promoting the consistent use and application of patient selection criteria. However, triage models from HSCT may be more appropriate than those for organ transplants. With organ transplants, the limited resource is the organ, so the triage model centres on ensuring the organ's survival. By contrast, CAR T-cell therapy involves engineering the patient's own cells, hence the limited resource is manufacturing and

processing capacity rather than the cells. A pan-Canadian approach that focuses on achieving the best outcomes for the patient may be more appropriate in the context of CAR T-cell therapy.

Cost

The high cost of axicabtagene ciloleucel is commonly identified as an ethical challenge for individual patients, clinicians, treatment sites, and health system funders.[10-13,19,24,26,29,30,38] In jurisdictions where access to CAR T-cell therapy is not publicly funded, high costs can contribute to significant financial burdens and inequities in access for patients who are uninsured or under-insured.[29,30] Although it is possible that price negotiations may reduce the cost of axicabtagene ciloleucel, the total cost is likely to remain high because the price of the product is only one component of the total cost of the therapy. The total cost of axicabtagene ciloleucel includes pre- and post-infusion treatment costs and extra-therapeutic costs, such as travel and lodging.[4] As noted in the Economic Review section, the total costs of axicabtagene ciloleucel exceed the costs that were factored into the manufacturer's cost-effectiveness assessments.[4] Treatment costs tend to be borne by health systems, but some costs such as travel and lodging are borne in part by patients and their caregivers (see the Implementation Analysis section).[24,39] Treatment centres may also face cost pressures related to data collection and monitoring for long-term safety and effectiveness, and increased capacity demands in those institutions where multiple CAR T-cell and related cancer therapies may be offered (see the Implementation Analysis section).[4]

Funding highly expensive and last-resort therapies is sometimes defended with reference to a "rule of rescue," by which society might have an obligation to provide available, beneficial treatment to patients who face severe or terminal illness and have run out of therapeutic options.[40] For example, some agencies in other jurisdictions, such as the National Institute for Health and Care Excellence in the UK, give extra weight to quality-adjusted life-years gained at the end of life.[20] However, at the policy level, axicabtagene ciloleucel's likely high cost and budget impact presents an ethical challenge related to the opportunity cost of funding some benefits but not others and the fair distribution of burdens and benefits.[12,13,29,38] With increasing availability of CAR T-cell products, policy-makers will be faced with the opportunity costs associated with funding these therapies over other potentially valuable therapies (for other conditions) within constrained budgets. Limit-setting is necessary within budgetary constraints and raises questions about ethically appropriate criteria for constraining and prioritizing access to axicabtagene ciloleucel based on resource availability (e.g., monetary, human resources, institutional capacity) and other health resource demands, including forgone benefits elsewhere in the health care system as well as considerations of long-term sustainability.[13] Concerns about long-term system sustainability in various jurisdictions is prompting innovation in alternative pricing and reimbursement models (e.g., outcome-based pricing), technology assessment methods, and regulatory mechanisms for personalized medicines, such as CAR T-cell therapy, with uncertain safety and effectiveness profiles and high cost.[15,20,41,42] Public trust of Canada's regulatory system may turn on how the first CAR T-cell products, including axicabtagene ciloleucel, are implemented.[13] Procedural justice, enacted in part through clear public communication about decisions involving new therapies (e.g., whether to publicly fund axicabtagene ciloleucel, eligibility criteria), can contribute to sustaining patient and public trust (see the Implementation Analysis section).[13,26,30,41]

Informed Choice About Treatment Options

Evidence gaps about safety and effectiveness underline the importance of informed consent processes,[3] on one hand, and the need for clinical aids to assess patient-level risk and suitability for axicabtagene ciloleucel, on the other. Patients describe axicabtagene ciloleucel as offering "hope for the hopeless," conferring greater benefits or lower risks than treatment alternatives, such as bone marrow transplant (see Appendix 3), "hope for a cure" where no alternatives previously existed (p. 3),[18] and hope for a treatment with fewer side effects compared with chemo-radiation and stem cell transplant therapies. Patients also describe a "fear of the unknown" (p. 3)[18] about long-term effectiveness and safety — in particular, possible neurotoxicity and its long-term impact on quality of life.[16] However, several authors noted concerns about the unique vulnerability of patients with few therapeutic options who may pursue high-risk treatment in a context of "false promises" if benefits are overstated or harms are understated.[12,13,24,38,43,44] Nevertheless, it is important to be wary of paternalism and recognize that patients are capable of making autonomous, rational decisions to pursue high-risk therapies.[13,43] Some have argued that the term "cure" ought to be eschewed or used with caution to prevent misleading hope or promoting false hope for patients, given that the long-term clinical effectiveness of CAR T-cell therapy is unknown.[10,18] This underscores the importance of patient and caregiver education as integral to informed consent and effective treatment.[45,46]

Considerations about patient vulnerability and autonomy draw attention to the importance of establishing robust informed consent and education strategies for patients and caregivers.[13,24,38,43,44,47] As one patient advocate argued, patient education and anticipatory guidance is essential in setting expectations related to potential benefits and risks, especially when hype exceeds available evidence.[45] Similarly, patient and caregiver education is important for enabling patients to identify and report side effects.[28,46] The need for a balanced presentation of potential benefits and risks was emphasized by several authors.[12,24,38,48] For example, paying attention to how side effects are characterized in trial results by avoiding subjective language (e.g., manageable, tolerable), especially when not validated by patients, can help guard against giving an erroneous impression of more favourable risk–benefit profiles.[49] Consenting to treatment is best understood as an ongoing and iterative process. Given that axicabtagene ciloleucel involves a lengthy pre- and post-infusion process with many individual procedures, it has been recommended that consent processes be accompanied by continuous education and discussion with patients and caregivers to allow them to express concerns and make informed choices.[45]

Existing clinical guidelines also recommend that patients should be informed that, even if CAR T cells are manufactured successfully, infusion remains contingent on the patient's continued clinical eligibility.[21] In developing consent processes, it will be necessary to consider the extent to which patients ought to be informed and provide consent related to the use of their health information or the use of their cells in the event of non-reinfusion (e.g., due to death or product failure).[10,18,48] A further consideration will be to determine who should be responsible for patient and caregiver education within the health care system (e.g., clinicians, health administrators), including at transitions of care. In other jurisdictions (European Union, US) where axicabtagene ciloleucel is licensed, the manufacturer provides clinician and staff training and patient education as well as on-site accreditation. While the manufacturer is well placed to provide product-specific educational materials that have been vetted by regulators, independent clinicians may be better placed to educate patients specific to their unique clinical needs as well as conduct and obtain informed consent from

patients, as clinicians are bound by a fiduciary duty to always act in the patient's best interest (beneficence).

Beyond Clinical Harms and Benefits

In addition to the clinical harms and benefits associated with axicabtagene ciloleucel and associated medical procedures, patients who undergo intensive and lengthy treatment, and their caregivers and family members, are likely to face emotional and psychological burdens. Treatments that have serious side effects or require long-term hospitalization may contribute to emotional and psychological harms, including post-traumatic stress, for patients undergoing the treatment as well as caregivers and family members who witness severe side effects and are involved in caring for ill patients, often over long periods of time.[18,45] Patients may also experience anxiety associated with the fear of recurrence or additional anxiety and stress associated with the financial burdens of treatment.[22] Moreover, appropriate education and open communication with patients and caregivers throughout treatment can contribute to the safety and psychological well-being of patients.[22,45] Age-appropriate education for children of adults undergoing treatment can also support their coping needs and aid patients.[22] Furthermore, some clinicians cited that administering CAR T-cell therapy can be a stressful process when patients become extremely ill due to CRS (see the Implementation Analysis section). They suggested that adequate training and support are required to assist clinicians in caring for their patients. Some authors also identified societal benefits and harms emphasizing, for example, the importance of fostering and maintaining public trust and pursuing overall benefits through mechanisms such as post-market surveillance of long-term safety and effectiveness, fair decision-making processes, and public reporting.[13,21]

Legal Considerations

There is a paucity of litigation and legal scholarship relevant to the ethical considerations of axicabtagene ciloleucel or CAR T-cell therapy, likely because they remain nascent technologies. Litigation related to CAR T-cell therapy is thus far confined to intellectual property disputes between manufacturers in the US.[50,51] Similarly, legal scholarship on CAR T-cell therapy is primarily confined to intellectual property issues,[51] including defining CAR T-cell therapy as a genetic therapy,[52,53] or ownership and commodification of cells in pre-market research.[54] Other jurisdictions, such as in Europe, are also grappling with how to regulate CAR T-cell therapy (e.g., as a genetic therapy, immunotherapy, medications, biological samples) and balance considerations of risk assessment with promoting innovation and access to potentially life-saving treatment.[55,56] As axicabtagene ciloleucel involves the creation of genetically modified T cells using a proprietary method, questions remain about who owns the modified cells — the patient whose T cells have been modified, the health system, or the manufacturer — and at what point ownership is transferred; what happens to the modified T cells if a patient is no longer eligible for or dies prior to reinfusion; and for what purposes and under what conditions any remaining modified T cells may be used.

In the absence of legal scholarship, it is possible to look to the ethics literature on biobanking to identify legal and ethical concerns that may arise with respect to axicabtagene ciloleucel. In biobanking, the primary ethical concerns about ownership of tissues or genetic material emphasize human dignity (related to identity and consent), benefit sharing (related to potential consequences of ownership, including financial and intellectual), and trust (related to the perceived intentions and trustworthiness of the owner).[57,58] For axicabtagene ciloleucel, considerations of human dignity may raise questions about the ownership of

specimens (e.g., do genetically modified T cells belong to patients?) and its implications for consent (e.g., the extent to which patients can dictate the use of modified cells, obligations to keep patients apprised of research conducted using their cells). The ownership of cells can also constrain the extent and nature of the benefits (therapeutic, financial, or intellectual) that patients, members of the public, and manufacturers accrue from the cells. Finally, ownership of biospecimens also relates to patient and public trust, which relates to legitimacy. Empirical research about biobanking with Canadian cancer patients suggests that patients place greater trust in public institutions, such as hospitals or research institutes, than for-profit companies,[57] signalling that private manufacturers may need to take additional measures to secure patient trust, particularly if the manufacturer is determined to have ownership of the biospecimens.

Clinical and Policy Implications

Clinical Implications

A number of clinical implications emerged through the ethics review. This included key strategies to address or mitigate the risks associated with using axicabtagene ciloleucel in a clinical context. These focused on the need for:

- patient and caregiver education, including what to expect before, during, and after the treatment and how to identify and manage potential adverse events
- health care provider education to support the role of health care providers in caring for patients and responding to caregiver needs
- effective communication with patients to support informed choice (e.g., use of translators)
- informed consent based on a balanced presentation of benefits and risks and an iterative process of shared decision-making
- consideration of the impact of CAR T-cell therapy on caregivers as well as patients (e.g., financial costs, psychological and emotional support, time commitment).

Policy Implications

The ethics review also identified policy implications relevant to the institutional- and system-level implementation of axicabtagene ciloleucel and the broader public. These focused on the need for legitimate and fair priority-setting and allocation processes, including the selection of treatment sites and the requirement of expert trained staff in these sites. Capacity building and dedicated resources are necessary to support facilities and institutions involved in the resource-intensive process of administering CAR T-cell therapy. As more CAR T-cell therapies are introduced, further considerations about investments in capacity building and infrastructure to support the adoption of additional CAR T-cell therapies may be required. Such investments include monitoring and oversight of the overall implementation process. Owing to high evidentiary uncertainty about the safety and effectiveness of axicabtagene ciloleucel,[3] post-market surveillance measures are ethically necessary and required by regulators to gather long-term effectiveness and safety data.[12,20,59,60] Evidence-generating measures are in the public interest but are also resource-intensive both for individual sites and for health systems, which will be an important factor in implementation design. Finally, clear and transparent communication with the public about the benefits and risks associated with CAR T-cell therapy will be important to mitigate “hype” that may unduly affect clinical and policy decisions.[10,47,48] Differences in eligibility criteria internationally,

which arise in part from the limited clinical evidence, may also present policy challenges as patients in certain jurisdictions may feel "as if they are missing out."[15] Similarly, clear justification and transparent communication with patients and members of the public about policy decisions that balance expanding access to innovative therapies with long-term sustainability will be important as more CAR T-cell products are licensed and the therapeutic and regulatory landscape continues to change.

Limitations

The ethics literature concerning axicabtagene ciloleucel in particular and CAR T-cell therapy in general is limited. Similarly, there is little legal scholarship describing axicabtagene ciloleucel and the use of CAR T-cell therapy. As a result, the ethics review drew both on a systematic review of existing literature and on an original ethical analysis, which included references to related bodies of ethics literature to identify additional ethical issues that may arise in the implementation of axicabtagene ciloleucel.

Implementation Analysis

Objectives and Approach

The implementation analysis was guided by two research objectives:

- to provide a detailed description of potential pathways of care for patients to receive axicabtagene ciloleucel, and the resources needed to do so (e.g., health and human resources, training, organizational)
- to provide an overview of feasibility and capacity considerations relating to the provision of axicabtagene ciloleucel at the level of the individual patient and provider (i.e., micro level), hospital or health care organization such as health authority or region (i.e., meso level), and the provincial, territorial, and federal levels (i.e., macro level).

The analysis synthesized information and results from several sources, including patient and stakeholder input; relevant information from the clinical, economic, and ethics reviews conducted as part of CADTH's broader assessment; industry documents; a rapid qualitative evidence synthesis of patients', families', and providers' perspectives and experiences; a narrative summary of implementation issues relating to axicabtagene ciloleucel.

The information and results from these sources were synthesized using a framework approach.[61] Further details about the a priori methods are detailed in a published protocol.[8] The analysis takes a pan-Canadian perspective on issues about structuring the provision of axicabtagene ciloleucel.

Implementation Findings

The findings are presented by three interconnected themes — access, patient selection, and uncertainty. Access refers to the models through which health care systems and clinicians might provide access to patients. Patient selection refers to both the development criteria for patient selection by health care systems and the process of selecting individual patients. Uncertainty describes challenges faced when structuring access to axicabtagene ciloleucel that result from limited evidence and experience with its use.

Access

Proposed Models of Access

Two key features of axicabtagene ciloleucel bear on how access to the therapy may be structured: its safety profile and limited long-term data on clinical effectiveness and harms. Concerns relating to the safety profile of axicabtagene ciloleucel refer to the risk of severe adverse events, including CRS and neurologic events and the need for coordinated and specialized clinical skills and heath care resources to treat them.[3] These concerns have led regulatory agencies in other jurisdictions (i.e., FDA, European Medicines Agency [EMA]) to approve the therapy with risk management plans that include limiting access to axicabtagene ciloleucel to manufacturer-approved or -certified sites.[62,63]

The US FDA approved axicabtagene ciloleucel for adults with r/r large B-cell lymphoma with a Risk Evaluation and Mitigation Strategy requirement.[62] As part of this requirement, hospitals delivering axicabtagene ciloleucel must be certified by the manufacturer by undergoing training activities, and the manufacturer must audit sites on an annual basis to ensure their continued compliance with training and certification requirements. Among additional requirements, treatment sites must have two doses of tocilizumab per patient receiving axicabtagene ciloleucel available on-site for the management of CRS.[62] Further pharmacovigilance requirements specified by the FDA are discussed in subsection Long-Term Uncertainties.

The EMA recommended axicabtagene ciloleucel for market authorization in the European Union with a risk management plan that includes a controlled distribution program.63 The controlled distribution program requires that only qualified sites that have completed manufacturer training be allowed to deliver axicabtagene ciloleucel, and that sites have four doses of tocilizumab per patient receiving axicabtagene ciloleucel available on-site.63 Additional pharmacovigilance requirements specified by the EMA are discussed in subsection Long-Term Uncertainties.

The National Health Service (NHS) in England is rolling out the delivery of axicabtagene ciloleucel at sites that are accredited by the international association for the accreditation of cellular therapies for the delivery of immune effector cells (IEC) (i.e., the Foundation for Accreditation for Cellular Therapy [FACT]-Joint Accreditation Committee International Society for Cell and Gene Therapy-Europe and European Society for Blood and Marrow Transplantation [JACIE] [together known as FACT-JACIE]).[64] The NHS England has itself selected the sites that are able to deliver the therapy through a process that called for expressions of interest.[65] The NHS then reviewed interested sites' applications. These were scored, considering a number of factors that included access to an intensive care unit, apheresis, a pharmacy, and immune effector cell storage. Experience with CAR T-cell products, including in trials or studies, was also part of the scoring and was weighted the highest.[65] Based on highest scores and geographic distribution, the NHS selected nine sites to undergo on-site, independent inspections conducted by JACIE.[65] In Canada, the model of access proposed by the manufacturer is that axicabtagene ciloleucel only be delivered at HSCT sites that have undergone manufacturer training and qualification. The product monograph advises that delivery sites should have four doses of tocilizumab on-site prior to infusion.[64]

Manufacturer certification of treatment sites involves on-site inspections and ongoing auditing. These cover technical training for clinical, pharmacy, and lab staff; confirm standard operating procedures (SOPs); assure there are processes for cell collection, storage, and shipping and maintaining chain of identify of the product — including labelling; and the management of adverse events. In the US and the European Union, regulatory

agencies have assigned this role of certification of treatment sites to the manufacturer as part of risk mitigation strategies.[62,63]

Stakeholder Views on Manufacturer Oversight of Treatment Sites

Based on stakeholder consultations, there is wide variation in views on the appropriate role of manufacturers in supporting the delivery of CAR T-cell therapy. Some stakeholders saw the manufacturer as needing to have had experience with the therapy and managing severe adverse events, which when coupled with their experience with clinician education and training, meant their role in certifying and training sites was appropriate and welcomed. Others consulted described their views that manufacturers of CAR T-cell products should not have a role in the certifying sites. Rather, FACT accreditation and/or oversight by Health Canada through the Safety of Human Cells, Tissues and Organs for Transplantation Regulations (CTO Regulations)[66] was viewed as rigorous and sufficient. The addition of manufacturer certification was described by consulted stakeholders as adding an unnecessary level of oversight over and above that provided by FACT and Health Canada, which was described as resource-intensive in terms of the number and hours of staff required to attend training and accompany manufacturers while on-site for auditing This was all the more so when treatment sites were aiming to use multiple CAR T-cell products. In the US, where there are currently two CAR T-cell products on the market for DLBCL (tisagenlecleucel and axicabtagene ciloleucel), approximately half of those sites delivering CAR T-cell therapy are delivering both products.[67] These sites have reported capacity and feasibility issues with being certified or qualified by more than one manufacturer, both in terms of start-up training requirements and ongoing auditing, due to similar but slightly different protocols.[67] Once certified or qualified, these different protocols are described as burdensome,[67] and were viewed by stakeholders as introducing unnecessary potential for human error. Some professional societies have noted the importance of standardized SOPs across CAR T-cell products in terms of safety and operations.[68]

Manufacturer oversight may also lead to differences in toxicity management between products (see, for example, Neelapu, 2018, versus Teachey, 2018).[69,70] While these differences may be accounted for by differences between products and their indications, some stakeholders consulted felt that it should be the clinicians' role to develop evidence and SOPs for the management of toxicities, not manufacturers. A further and related issue is the need for standardization of toxicity grading and management algorithms across products to enable the study of toxicity management.[71,72] The need for these standardized, non-product–specific SOPs point to the role of a third party in providing oversight for treatment sites delivering CAR T-cell therapy. This may become more important as more CAR T-cell products are approved for the market.

Stakeholder Views on the Accreditation of Treatment Sites by the Foundation for the Accreditation of Cellular Therapies

FACT HSCT or IEC accreditation was seen by many hematologists (including many of those consulted for this review) as an indicator that an HSCT centre has the resources necessary to manage the risks associated with the delivery of CAR T-cell therapy.[73-76] Situating axicabtagene ciloleucel within FACT-JACIE accredited sites is seen as mitigating risks by facilitating the appropriate management of toxicities and severe adverse events that can occur post-infusion. Additionally, such oversight facilitates the collection of data for assessing long-term clinical effectiveness and safety, as FACT requires sites to collect data using standardized forms for ongoing evaluation and accreditation.[62,63,75,77]

Within Canada, all jurisdictions have at least one HSCT centre with the exception of Prince Edward Island and the territories.[78] Five provinces currently have FACT-accredited adult HSCT centres: British Columbia (n = 1), Alberta (n = 1), Manitoba (n = 1), Ontario (n = 3), and Quebec (n = 3).[79] The remaining five provinces (Saskatchewan, New Brunswick, Prince Edward Island, Nova Scotia, Newfoundland and Labrador) and the three territories (Yukon, Nunavut, Northwest Territories) do not currently have FACT-accredited adult HSCT centres.

Based on consultations with hematologists it is likely that many of the FACT HSCT accredited centres in Canada will be applying for FACT IEC accreditation, which is specific to immune cell and CAR T-cell therapies.[75,80] Among the hematologists consulted, FACT accreditation was seen an important marker of quality assurance and improvement as it meant the accredited site had SOPs, reviewed them regularly to improve care, and was undertaking data collection to track outcomes. FACT accreditation was additionally seen as encouraging harmonization of both the delivery of the therapy and collection of data necessary for the evaluation of long-term clinical effectiveness and safety.[81] Many of the stakeholders consulted saw FACT accreditation as becoming the norm in Canada — in order to be able to deliver CAR T-cell therapy — and desirable, both for its ability to improve care and as a source of pride for offering high-quality care. For those centres with FACT HSCT accreditation, seeking additional accreditation for FACT IEC standards was described by clinician experts as not requiring a great deal of additional work, particularly as centres in Canada are sharing knowledge and SOPs to support each other.

However, some stakeholders described FACT accreditation as a burden. Seeking FACT HSCT accreditation was described as a costly and resource-intensive, multi-year process, after which ongoing activities must be undertaken to maintain accreditation. Some sites described how, to become FACT accredited, a site needs full-time dedicated staff (approximately two full-time equivalent positions), organizational and institutional support, and a champion to lead the initiative. Ongoing data collection is an important component of FACT accreditation, and stakeholders in Canada described how sites use a variety of dedicated and non-dedicated staff positions to collect and enter data.

Some stakeholders reported that HSCT centres already have rigorous oversight by Health Canada under CTO Regulations.[66] Compliance with the CTO Regulations was often described by Canadian transplant specialists as equivalent to or exceeding the standards assured through FACT HSCT accreditation. However, the CTO Regulations were developed as a specific response to the concerns of working with allogeneic products, not autologous products such as axicabtagene ciloleucel. While the CTO Regulations may provide a framework for the oversight of HSCT sites in Canada, they were not designed to address the specific risks associated with CAR T-cell therapy.

Facilitating Access Across and Within Canadian Jurisdictions

Given the certification process and the need to ensure sites are prepared to deliver axicabtagene ciloleucel, it is likely that the therapy will be phased in over a period of time.[64] As a result, there may be limited initial access across Canadian jurisdictions. Even as the therapy is rolled out to all potential HSCT centres, there will likely be times where travel within a jurisdiction, or to other jurisdictions, will be required to access the therapy.

Opportunities exist to maximize access to axicabtagene ciloleucel by ensuring an appropriate number of sites that can receive out-of-jurisdiction (either out-of-province or -territory or -catchment) patients, and by ensuring the resources and arrangements for cross-jurisdiction treatment of patients. Selecting treatment sites that have capacity to

accept patients outside their catchment may help minimize geographic inequalities. According to some clinicians, in some jurisdictions, out-of-country treatment may remain a feasible option to provide ready access to the therapy and, depending on the home location and given the geographic breadth of Canada, may in some cases minimize the need for travel. With the need to travel for treatment comes the need for financial and logistical support for patients and their caregivers to travel for assessment, apheresis, and infusion and monitoring, as well as post-treatment follow-up.

With the phasing in of axicabtagene ciloleucel, and the likely need for ongoing transfer of patients across jurisdictions, interprovincial/interterritorial billing that accounts for the process of delivering axicabtagene ciloleucel (i.e., assessment, apheresis, lymphodepletion, infusion, and monitoring and management of adverse events) may be required. As these tend to be funded by different sources (e.g., provincial health plans, cancer agencies, global hospital budgets) across jurisdictions, reciprocal billing arrangements may become complex. Some of the clinicians consulted for this review described inconsistent reimbursement criteria as a current challenge in caring for out-of-province HSCT patients. As such, there may be an opportunity to consider reimbursement criteria and opportunities to maximize consistency across jurisdictions for the purposes of fairness and equity in access.

The addition of a resource-intensive treatment such as axicabtagene ciloleucel may pose challenges to the existing capacity of HSCT centres. In recent years, capacity issues have been raised in the Canadian media, specifically in Ontario for adults requiring HSCT,[82] leading to additional resources being made available. Consultations with stakeholders identified the need for highly trained nursing staff for apheresis and the monitoring and management of adverse events, and technicians for the processes of packaging, shipping, and handling of cellular products. These needs would compound any existing capacity issues at HSCT centres and may influence the pace at which axicabtagene ciloleucel is phased in across Canadian jurisdictions.

Patient-Specific Considerations for Access

Given the aggressiveness of their disease and the wait time between T-cell collection and infusion, patients will benefit from timely access to treatment throughout the pathway of receiving axicabtagene ciloleucel.[83] Based on conversations with patient groups, patients who are indicated to receive axicabtagene ciloleucel likely anticipate being able to access the therapy as it is approved for use in Canada. Communicating the rollout of axicabtagene ciloleucel and CAR T-cell therapy to patients and the public can help inform accurate expectations of when and how access will be provided.

The model of delivery and Canada's geography mean that travel and short-term relocation will likely be necessary for many patients to access axicabtagene ciloleucel. Travel will include travel for assessment, travel for apheresis, and short-term relocation (likely a minimum of four weeks) for reinfusion and monitoring of adverse events. Travel will also be required for follow-up at regular intervals during the first year post-treatment.

Travel and short-term stays for cancer care impact patients and their families in a multitude of ways. The act of travel is itself physically exhausting for some, particularly given that eligible patients are medically fragile (see Appendix 1). Travel and short-term stays also come with direct and indirect patient and family-borne costs, including transportation, lodging, and food (see Appendix 3). Many patients report having to leave their job or reduce their hours due to the cancer and its treatment, and that travel additionally required their caregiver (often a partner) to take a leave from work. Depending on their household

structure, many patients have to keep two households at the same time (see Appendix 1). These additional economic burdens added stress and tension to families already experiencing a health crisis (see Appendix 1).

Travel and short-term stays also disrupt patients' and caregivers' social networks. Being away from their social supports and homes, patients and their caregivers often must cope with being in an unfamiliar environment (see Appendix 1). Transferred to a new health care facility, patients and caregivers must forge new relationships with health care providers at the delivery site and work to build trusting and communicative relationships in the short term with a new health care team (see Appendix 1).[84]

Given its geography and demography, travelling for care is routine or expected in many parts of Canada. For some patients, urban centres are seen as being able to provide better care due to the availability of greater resources. As such, travel is viewed positively in this sense, as it was perceived as affording access to high-quality health care (see Appendix 1). Transitioning back to local treatment centres after being cared for at a highly specialized centre, however, leads some patients to feel that were losing access to the highest-quality health care (see Appendix 1).

Given the burden patients and their caregivers experienced when travelling to access cancer care, there is a need to coordinate and enhance existing resources to support travel and short-term relocation for accessing axicabtagene ciloleucel. Support could include financial resources as well as support in coordinating logistics, such as securing appropriate lodging for short-term stays.

With the potential for life-threatening adverse events, the psychosocial needs of patients and caregivers will also need to be supported throughout care and follow-up (see the Ethics Review section and Appendix 1). These include providing access to psychological and social supports (e.g., social workers, peer support networks) and building clear and trusting relationships with clinical staff.

Patient Selection

Stakeholder Views on Patient Selection

Health Canada approval for axicabtagene ciloleucel includes the conditions for which the therapy is indicated and counter indications. However, clinicians expressed that they did not expect that all patients who meet the clinical indication are appropriate to undergo treatment, in large part due to the potential for severe adverse events. Those patients with aggressive disease and who were likely unable to wait two to three weeks for manufacturing may not be appropriate candidates for the therapy. Real-world evidence suggests that manufacturing times in clinical practice in the US are similar to those seen in the clinical trial, with a median of 26 days compared with a median of 24 days in ZUMA-1.[85]

In general, clinicians described that patient selection for axicabtagene ciloleucel for the indicated population ought to be consistent with the trial population in which effectiveness and safety has been assessed. The patients of ZUMA-1 may have reflected a group of patients with more clinically stable disease, based in part on the inclusion of patients with an Eastern Cooperative Oncology Group performance status of zero or one, the exclusion of patients based on the need for urgent therapy due to tumour mass effects, and the fact that bridging therapy was not permitted.[3]

Consultations with stakeholders indicated that clinicians were likely to see and treat patients who had a poorer performance status than those included in the trial population. Emerging real-world evidence from the US suggests that clinicians have been selecting patients with poorer performance status than patients enrolled in ZUMA-1 and have been using bridging chemotherapy when treating patients with axicabtagene ciloleucel.[85-87] Thus, it is likely that clinicians, in clinical practice, will deviate from the patient selection criteria used in the trial.

Patients have expressed a concern that not all clinicians of potentially eligible patients will know about the therapy and how to access it, particularly those not affiliated with a treatment site. Informing clinicians across Canada about the therapy and how to access it should alleviate some concerns about patient selection due to proximity to treatment site. No matter what criteria are developed for patient selection, they will benefit from being transparent, evidence-based, and consistently applied. Early communication with patient groups, professional associations, referring sites, and physicians may aid in improving uptake and acceptance of criteria for patient selection.

Potential Challenges in Selecting Patients

Stakeholders expressed a range of views on whether there is a role for a centralized referral or selection process. Some hematologists pointed to the system used in organ donations in Canada, where a centralized mechanism of allocation is used. Additionally, many clinicians reported their HSCT sites already use case reviews as part of deciding on patient treatment and felt that this model could be extended to CAR T-cell therapy. In the US, many institutions reported using a clinical review committee as part of patient selection for CAR T-cell therapy.[68] Typically, this was reported as an HSCT committee but other types included immunotherapy or cell therapy committees, high-cost drug committees, and pharmacy and therapeutics committees.[68] In England, the NHS has established a centralized mechanism for selecting patients for CAR T-cell therapy through a multidisciplinary panel, the National CAR T Multi-Disciplinary Teams, which considers equity, capacity, and clinical considerations.[64]

Timing may play an important role in selecting patients for axicabtagene ciloleucel as the patient population for whom this is indicated typically has an aggressive disease that rapidly worsens. As axicabtagene ciloleucel is shipped to the manufacturer as a fresh product, the timing of apheresis is coordinated with the availability of a manufacturing slot. This may mean that, of patients selected for axicabtagene ciloleucel, the allocation of the manufacturing slot may depend on real-time clinical assessment of candidates to ensure they are able to undergo apheresis. Additionally, during the time between apheresis and when the treatment centre receives the product, patients' conditions may deteriorate such that they are no longer able to handle the toxicities associated with treatment.

Patient-Specific Considerations for Patient Selection

Given the potential for patients to be selected to undergo treatment with axicabtagene ciloleucel but be unable to use a manufacturing slot because of deterioration in their condition since time of selection, it may be important to clearly communicate with patients the steps involved in receiving the treatment and the possibility of challenges that might occur at each step. In the event of changes in clinical status that affect patients' ability to undergo a procedure in the treatment pathway (e.g., apheresis, lymphodepletion, and reinfusion), communication with patients and their caregivers about options and timing may support patient decision-making. This may also flag the need for clinicians to provide opportunities not just to carry forward with treatment but also to opt out, particularly in light of

concerns of hype and hope of CAR T-cell therapy (see the Ethics Review section) and potential pressures to pursue aggressive therapies.[15] Patients will additionally benefit from information on what long-term follow-up is required so that they understand the travel required and data collection activities when consenting to undergo treatment with axicabtagene ciloleucel.

Uncertainty

Decision-Making With Uncertainty

The uncertainty surrounding the long-term clinical effectiveness and safety of axicabtagene ciloleucel poses challenges for decision-makers. Adding to these challenges is the expected increase in both the number of eligible patients due to anticipated expansion of the indications for which axicabtagene ciloleucel may seek approval (see Appendix 4) and the number of CAR T-cell products approved for use in Canada for hematologic cancers. With multiple CAR T-cell products, including allogeneic or "off-the-shelf" products, in various stages of development,[88] this is a therapeutic area that continues to shift and evolve. Moreover, the models of access and reimbursement that are used for the first commercial CAR T-cell products are likely to set in place infrastructure and policies that will influence how subsequent products are delivered and reimbursed. For example, in England, it is anticipated that future CAR T-cell products for solid tumours will also be delivered within FACT IEC-accreditedsites.[64] The high cost of CAR T-cell products have led to consideration being given to value-based pricing and reimbursement models such as pay-for-performance models of payment.[18]

Reimbursement decisions for axicabtagene ciloleucel are still underway across international jurisdictions where it has received regulatory approval. In the UK, the National Institute for Health and Care Excellence recommended reimbursement of axicabtagene ciloleucel for adults diagnosed with large B-cell lymphoma in January 2019.[89] This reversed draft guidance issued in August 2018, which did not recommend axicabtagene for reimbursement for this indication.[90] The current recommendation for reimbursement is conditional upon a managed access agreement that includes an agreement with the manufacturer to make axicabtagene ciloleucel available to the NHS at a confidential discount.[89]

In the US, reimbursement of axicabtagene ciloleucel is currently inconsistent across private plans, with clinicians citing the absence of reimbursement policies and codes for CAR T-cell therapy as a significant barrier to implementation.[91] In the public insurance system, UnitedHealthcare, a provider of Medicare Advantage insurance, requested that the Centers for Medicare & Medicaid Services perform a National Coverage Analysis (NCA) of CAR T-cell therapy for cancer, which would include the use of axicabtagene ciloleucel for adults with r/r large B-cell lymphoma.[88] The Centers for Medicare & Medicaid Services has since issued a draft NCA proposal that includes a Coverage with Evidence Development designation.[76] The draft NCA proposal describes the conditions for which sites can be reimbursed for CAR T-cell therapy and details requirements to collect real-world evidence on FDA-approved CAR T-cell products.[76] The final NCA is forthcoming.

Treatment Uncertainties

Patients who submitted input described CAR T-cell therapy as providing "hope for the hopeless" and as expecting the therapy to offer the possibility of remission, longer survival, and improved quality of life (see Appendix 3). The absence of long-term data on the durability of remission has raised concerns about the potential for CAR T-cell therapy to provide false hope (see the Ethics Review section).[15] Building on this concern is research

that highlights the ways that clinicians working in HSCT centres face challenges when discussing end of life and palliation (see Appendix 1). The reticence of some clinicians to discuss end of life may contribute to patients' decision-making to pursue aggressive treatment, creating the space for false hope and potentially unrealistic expectations of treatment (see Appendix 1).

Situating the discussion about possible benefits of treatment within the context of known limitations of available data will support patients in making informed decisions about consenting to treatment, or not. Providing informational resources for patients and providers may also support shared decision-making around undergoing CAR T-cell therapy.

As part of the treatment uncertainty, there are questions around the ideal placement of axicabtagene ciloleucel in the pathway of care for patients with large B-cell lymphoma. The limited available evidence on the durability of remissions leaves uncertainty around whether axicabtagene ciloleucel is a definitive therapy or whether it is a bridge to other therapy (i.e., stem cell therapy). Understanding the mechanisms of resistance — including antigen loss, absence of T-cell persistence, and T-cell exhaustion — has been described as a high-priority research area.[92] Clinical trials are underway exploring the combined use of CAR T-cell therapy and other agents, including immune checkpoint inhibitors, immunomodulators, and tyrosine kinase inhibitors.[92]

In addition, patient groups and clinicians report waiting for evidence that supports the use of axicabtagene ciloleucel earlier in the clinical pathway; for instance, positioning it as a second-line therapy for r/r large B-cell lymphoma (see Appendix 3 and Appendix 4). While some clinician experts felt any clinical response in this patient population offered an opportunity for remission, patients may benefit from understanding what can be expected after treatment, including potential next steps. This becomes important in the context of patients' expectations of treatment which includes not only increased overall survival but also improved quality of life (see Appendix 2), which may be affected by the subsequent need for treatment.

It remains to be seen how products that do not meet the specified release criteria in terms of cell number for clinical efficacy will be handled in Canada (i.e., out-of-specification products). The product has a low rate of manufacturing failure, with only one manufacturing failure observed in ZUMA-1's cohort I (n = 81).[3] In the European Union, it has been reported that 97% of the manufactured product has met the specifications for commercial release.[93] Consulted clinicians described that, given the opportunity, they would likely still infuse an out-of-specification product with a lower cell count for several interrelated reasons: the poor prognosis of their patient without the therapy, the challenge in collecting more cells and waiting for another infusion, and the chance that the product might still work to reduce or eliminate the patient's disease burden. At the bedside, patients and providers may have to decide on what to do in the event of the manufacture of an out-of-specification product, highlighting once more the continuous nature of decision-making and consent involved in CAR T-cell therapy.

Long-Term Uncertainties

Given the lack of evidence around long-term clinical effectiveness and safety of axicabtagene ciloleucel, the FDA and EMA — as part of their market authorizations — have required the manufacturer to conduct studies with a long-term follow-up of 15 years.[62,63] These studies are intended to collect and analyze data to assess effectiveness, serious

adverse events, and other safety concerns related to immunogenicity and mutagenicity over the long term.[62,63]

To collect and house these data on long-term outcomes, the manufacturer is collaborating with the Center for International Blood and Marrow Transplant Research (CIBMTR) in the US, and its European counterpart (EBMT Registry).[94] These registries house data from HSCT sites and provide FACT-JACIE data for site audit. Data from HSCT sites in Canada are sent to the CIBMTR, which then shares Canadian data with the Canadian Blood and Marrow Transplant Group Registry. The CIBMTR-EBMT Registry has developed standardized and validated forms for the collection of clinical data for advanced cellular therapies, including CAR T-cell therapy.[94] Within Canada, clinicians described that FACT-accredited sites already capture data as required by FACT and are thus experienced and have processes for collecting patient-level data. However, clinicians at several sites described that data collection requires resources (i.e., staff to collect data); in the context of existing resource constraints, the addition of further site-level resources would facilitate data collection.

Limitations

The purpose of the implementation analysis is to provide information about options and issues surrounding the provision of axicabtagene ciloleucel for adults diagnosed with r/r large B-cell lymphoma in Canadian jurisdictions. The analysis describes the policy landscape in which axicabtagene ciloleucel may be situated, and the resources needed and capacity issues that may arise with the provision of axicabtagene ciloleucel. While the review team engaged with physician stakeholders, the perspectives of non-physician health professionals and staff involved in the provision of axicabtagene ciloleucel were not directly included. As a result, there may be additional areas of resource constraint or implementation considerations beyond those identified by this analysis. Although effort was made to ensure the information in this review was current up to the date of publication, regulatory approvals for and the implementation of axicabtagene ciloleucel and other CAR T-cell products is active and ongoing in Canada and in other parts of the world. The consequence is that the reported analyses may not reflect current practice.

Appendix 1: Patients' and Caregivers' Perspectives and Experiences Review

Research Approach and Question

As part of CADTH's larger health technology assessment of axicabtagene ciloleucel,[2] a rapid qualitative evidence synthesis of the literature exploring the perspectives and experiences of patients, their family members, and their health care providers relative to advanced hematologic malignancies was conducted.[8] Specifically, this rapid qualitative evidence synthesis was used to identify and describe key issues pertaining to the implementation of axicabtagene ciloleucel. Direct patient input was also collected through CADTH's CAR T-cell therapy patient submission process (see Appendix 2 and Appendix 3).[8] Together, patient input submissions and the findings of this qualitative evidence synthesis brought the concerns, experiences, and perspectives of patients and their caregivers into the analysis of considerations when implementing axicabtagene ciloleucel.

Due to the novel nature of axicabtagene ciloleucel and experience gained through a recently completed rapid qualitative evidence synthesis for the similarly indicated CAR T-cell therapy tisagenlecleucel,[95] it was assumed that little to no qualitative literature focused specifically on either the product or broader intervention (CAR T-cell therapy) would be found. As such, the research question directing the synthesis remained broad and explored experiences with the pathway of care in which patients eligible for axicabtagene ciloleucel find themselves and with the treatment of advanced or end-of-life hematologic cancers.

The research question guiding this rapid review was:

What are the experiences and perspectives of patients, their family members, and their health care providers regarding advanced or terminal hematologic cancer in relation to treatment and health care?

Further details about the methods can be found in an a priori published protocol.[8] In brief, the literature search was performed by an information specialist using a peer-reviewed search strategy. Articles published in English or French that used qualitative data collection and analysis methods to investigate the experiences of patients with advanced or end-of-life hematologic cancers, their family members, and their health care providers were eligible for this review. A "best fit framework" approach to data analysis was planned.[96] Eligible articles were to be imported into NVivo 11[97] for data analysis, with the goal of creating categories that comprehensively describe the perspectives and experiences of patients, family members, and providers across the pathway of care (i.e., diagnosis, decision-making, treatment, and outcome) in which axicabtagene ciloleucel will be offered and delivered.

Following both title and abstract, and full-text screening of articles retrieved through the literature search and subsequent updates, the research team identified four studies that were not included in the previously published rapid qualitative evidence synthesis of patients' and caregivers' perspectives and experiences relating to the pathway of care for tisagenlecleucel.[95] The remaining 17 eligible studies were all included studies in the tisagenlecleucel review. Upon reviewing the full text of these four additional studies, the review team concluded that their content corroborated, rather than enhanced or modified, the analysis of patients' and caregivers' perspectives and experiences within that report.[95] Based on this — and the fact that both reviews were guided by the same research question, and used the same search concepts and the same methods of literature selection and

analysis — conducting an update in lieu of a *de novo* review was appropriate. While tisagenlecleucel is indicated for both adult and pediatric populations and axicabtagene ciloleucel for adults, the tisagenlecleucel report only included studies situated with the adult population and so no studies needed to be removed due to eligibility criteria.

The key findings from the tisagenlecleucel rapid qualitative evidence syntheses are summarized for the purposes of this review. The following lists the studies included in the rapid qualitative evidence synthesis of patients' and caregivers' perspectives and experiences for tisagenlecleucel, as well as additional studies identified.

Summary of Results

Table 2 reports on details on the included studies and Table 3 outlines the characteristics of patients and caregivers included in those studies.

Patients' and caregivers' experiences of living with and undergoing treatment for advanced or terminal hematologic cancers often move through and around the interrelated concepts of travel, finances, and temporal uncertainty.

Travel poses a problem for those individuals who may live outside the reach of a specialist hospital or treatment centre. Whether requiring temporary relocation over the course of months, shorter spurts of overnight travel, or even quicker day trips, this need to often be on the move could exacerbate already tenuous living situations. For those with families, the extra expenses associated with travel (e.g., time off work) complicated the desire to be around one's family. As such, patients and their families (or other caregivers) were, at times, confronted with difficult decisions around access to treatment and time with family or financial survival. If the family decides to relocate as a whole, there is a risk of further economic hardship due to loss of both incomes. If the patient travels alone, the separation from their support unit could make it difficult to cope during an already difficult time. Even when separated, the cost of keeping up two households (e.g., groceries and phone bills) could be burdensome.

With the difficulties of travel in mind, the opportunity to be treated locally was expressed as preferred across several publications. Local care allows patients to remain immersed in their support groups and mitigates the financial pressures associated with travel. As such, local care was noted as allowing patients to remain focused on their health and provide a morale boost. However, there are situations in which travel to specialized centres was accepted by patients, as it was a means of accessing specialists and technologies that could only be found in larger centres. Sometimes, the transition back to local care was disruptive for patients as it meant ending their relationship with their care providers and having to establish (or re-establish) relationships in their local community.

Due to the advanced stages of participants' hematologic malignancy, decision-making and conversations with care providers at the end of life were explored across a number of studies. While patients and caregivers generally had faith that their provider would help them make the appropriate decision, studies examining hematologic specialists' negative perspectives on end-of-life conversations or palliative care complicate this picture. Whether due to sentiments that referral to palliative care is akin to admitting professional failure, or the desire to push younger patients toward further treatment as they could potentially have more of a life ahead of them, professionals at times distanced themselves from end-of-life conversations. This distance could have a detrimental effect on the patient's ability to make

an informed decision, as such decisions may be made by the physician without the patient understanding the severity of their situation.

Limitations

The primary limitations of this review relate to the use of rapid review methods. Rapid reviews necessitate high-level engagement with a circumscribed set of literature and result in an analysis that is largely descriptive rather than conceptually driven. While this in no way lessens the importance of the findings from this review, it does create a situation where findings become subsumed within the realm of “apparent,” “obvious,” or “common sense.” As an example, in the case of this rapid review, an area rich for exploration is the ripple effect on decision-making that results from the expressed tendency of hematologic specialists to pursue treatment over creating space for end-of-life conversations. The use of rapid review methods did not enable further engagement with the concept and instead resulted in a simple recognition and declaration that this can indeed happen. The use of rapid review methods also entailed the decision to not conduct formal quality appraisal due to time constraints. As such, the credibility, dependability, confirmability, and transferability of the included studies were not explicitly accounted for when synthesizing the findings.

Studies Included in the Rapid Qualitative Evidence Synthesis of Patients’ and Caregivers’ Perspectives and Experiences for Tisagenlecleucel[95]

1. Dunn E, Arber A, Gallagher A. The Immediacy of illness and existential crisis: Patients' lived experience of under-going allogeneic stem cell transplantation for haematological malignancy. A phenomenological study. *Eur J Oncol Nurs*. 2016 Apr;21:90-96.
2. Grech A, Depares J, Scerri J. Nurses' experiences providing end-of-life care to adults with hematologic malignancies. *J Hosp Palliat Nurs*. 2018;20(3):237-244.
3. Hoff L, Hermeren G. Identifying challenges to communicating with patients about their imminent death. *J Clin Ethics.* 2014;25(4):296-306.
4. Horinuki F, Noguchi-Watanabe M, Takai Y, et al. The experience of persons with hematological malignancy when communicating with health care professionals. *Qual Health Res*. 2018;28(3):479-490.
5. LeBlanc TW, O'Donnell JD, Crowley-Matoka M, et al. Perceptions of palliative care among hematologic malignancy specialists: a mixed-methods study. *J Oncol Pract*. 2015 Mar;11(2):e230-238.
6. Loggers ET, Lee S, Chilson K, Back AL, Block S, Loberiza FR. Advance care planning among hematopoietic cell transplant patients and bereaved caregivers. *Bone Marrow Transplant*. 2014 Oct;49(10):1317-1322.
7. McGrath P. End-of-life care in hematology: update from Australia. *J Soc Work End Life Palliat Care*. 2013;9(1):96-110.
8. McGrath P. Findings on family issues during relocation for hematology care. *Oncol Nurs Forum*. 2015 May;42(3):E250-256.
9. McGrath P. ‘You never leave work when you live on a cattle property’: special problems for rural property owners who have to relocate for specialist treatment. *Aust J Rural Health.* 2015 23:286-290.
10. McGrath P. Overcoming the distance barrier in relation to treatment for haematology patients: Queensland findings. *Aust Health Rev.* 2015 39:344-350.
11. McGrath P. 'The bills that were coming in...': out of pocket costs during relocation for specialist treatment for haematological malignancies. *Support Care Cancer*. 2016 07;24(7):2893-2903.

12. McGrath P. Financial distress during relocation for treatment of a hematological malignancy: Findings for social work. *Soc Work Health Care*. 2016 04;55(4):265-279.
13. McGrath P. Haematology patients' desire to access metropolitan hospital expertise. *Aust Health Rev*. 2016;40(3):251-256.
14. McGrath P. Financial assistance for patients who relocate for specialist care in hematology: practical findings to inform nursing supportive care. *Nurs Forum*. 2017;52(1):55-61.
15. Odejide OO, Salas Coronado DY, Watts CD, Wright AA, Abel GA. End-of-life care for blood cancers: a series of focus groups with hematologic oncologists. *J Oncol Pract*. 2014 Nov;10(6):e396-403.
16. Orlowska D, Selman LE, Beynon T, et al. 'It's a traumatic illness, traumatic to witness': a qualitative study of the experiences of bereaved family caregivers of patients with cutaneous T-cell lymphoma. *Br J Dermatol*. 2018 Oct;179(4):882-888.
17. Prod'homme C, Jacquemin D, Touzet L, Aubry R, Daneault S, Knoops L. Barriers to end-of-life discussions among hematologists: A qualitative study. *Palliat Med*. 2018;32(5):1021-1029.

Additional Identified Studies

1. Alnasser Q, Abu Kharmah SD, Attia M, Aljafari A, Agyekum F, Ahmed FA. The lived experience of autologous stem cell-transplanted patients: Post-transplantation and before discharge. *J Clin Nurs*. 2018 Apr;27(7-8):e1508-e1518.
2. McCaughan D, Roman E, Smith A, Garry A, Johnson M, Patmore R, Howard M, Howell D. Perspectives of bereaved relatives of patients with haematological malignancies concerning preferred place of care and death: A qualitative study. *Palliat Med* 2019; 00(0):1-13.
3. Sabo B, McLeod D, Couban S. The experience of caring for a spouse undergoing hematopoietic stem cell transplantation: opening Pandora's box. *Cancer Nurs*. 2013 Jan-Feb;36(1):29-40.
4. Selman LE, Beynon T, Radcliffe E, et al. 'We're all carrying a burden that we're not sharing': a qualitative study of the impact of cutaneous T-cell lymphoma on the family. *Br J Dermatol*. 2015 Jun;172(6):1581-1592.

Table 2: Characteristics of Included Publications

First Author (Publication Year), Country, Funding	Study Design	Study Objectives	Sample Size	Inclusion Criteria	Data Collection Type; Sampling Method
Alnasser (2018),[98] Saudi Arabia, NR	Descriptive phenomenological analysis	To explore the lived experience of the patients' post-HSCT and specifically after engraftment and before discharge	15 post-HSCT recipients	Physically and mentally stable post-HSCT	Multiple interviews; purposive sampling
Dunn (2016),[99] UK, Guys and St Thomas' Foundation Trust	Phenomenology	To explore lived experiences of patients undergoing allogeneic stem cell transplant for hematologic cancer	15 patients	Patients > 18 who could communicate in English and had undergone allogeneic stem cell transplant between 3 months and 1 year prior	Semi-structured interviews; purposive sampling
Grech (2018),[100] Malta, NR	Phenomenology	To explore experiences of nurses providing end-of-life care for patients with hematologic malignancies	5 nurses from 1 hematologic oncology unit	Nurses presently working at the hematologic oncology unit and having more than 1 year of experience working in that unit	In-depth semi-structured interviews; purposive sampling
Hoff (2014),[101] Sweden, Lund University, Sodalitium Majus Lundense, Foundation of Birgit and Sven Hakan Ohlsson	NR	To identify challenges in communicating with patients about imminent death	7 patients 10 hematologists	NR	Repeated interviews with patients, interviews with clinicians; NR
Horinuki (2018),[102] Japan, Policy-Based Medical Service Foundation	Constructivist grounded theory	To explore experiences of persons with hematological malignancies in communicating with health care professionals	14 family members	Bereaved family members aged 20 years or older who were the primary caregiver of a patient who died in acute care ward within 2 months to 2 years prior	Interviews; primary physician referrals
LeBlanc (2015),[103] US, National Palliative Care Research Center, National Center for Advancing	NR	To explore differences in referral practices and perspectives of palliative care among hematologic oncologists and solid tumour oncologists	23 hematologic oncologists 43 solid tumour oncologists	NR	In-depth semi-structured interviews; purposive sampling

First Author (Publication Year), Country, Funding	Study Design	Study Objectives	Sample Size	Inclusion Criteria	Data Collection Type; Sampling Method
Translational Sciences, University of Pittsburgh Department of Medicine					
Loggers (2014),[104] US, National Cancer Institute	NR	To explore the effect of pre-transplant discussions on mortality risk and advance care planning on survivors' or caregivers' confidence of the medical team, the commitment of the medical team to help patient through transplant, and personal hope that patient would survive	18 patient "survivors" 11 bereaved caregivers	English-speaking adults ≥ 21 years of age, free of major, uncontrolled psychiatric illness Stem cell transplant survivors had to have received their transplants 6 months to12 months prior Caregivers' of patients who had a transplant 6 months to 12 months prior and died within 6 months of the transplant	Interviews; "identified via clinical databases"
McCaughan (2019),[105] UK, Bloodwise and Marie Curie Grants Scheme	Qualitative design, not otherwise specified, using "the Framework" method	To explore bereaved family carers of patients with hematological malignancies perspectives of (1) preferred place of care and death, (2) reflections on experiences following the patient's death, including perceptions of factors influencing the attainment of preferences, and (3) changes that could promote achievement of preferences	10 bereaved caregivers	Primary bereaved family care provider(s) of patients with leukemia, lymphoma, or myeloma, who had died within the previous 2 years (maximum)	Interviews; purposive sampling done "ethically and pragmatically"
McGrath (2016),[106] Australia, Leukaemia	Descriptive qualitative	To provide evidence on the financial impact of relocating for	45 patients	Patients with hematologic malignancies that needed to	In-depth interviews; purposive sampling

First Author (Publication Year), Country, Funding	Study Design	Study Objectives	Sample Size	Inclusion Criteria	Data Collection Type; Sampling Method
Foundation of Queensland		hematological treatment and its contribution to poverty		travel or relocate for specialist care	
McGrath (2016),[107] Australia, Leukaemia Foundation of Queensland	Descriptive qualitative	To understand out-of-pocket costs for patients with hematologic cancers in relocating for specialist treatment	45 patients	NR	In-depth interviews; purposive sampling
McGrath (2015),[108] Australia, Leukaemia Foundation of Queensland	Descriptive qualitative	To provide findings on issues impacting rural property owners who need to travel to metropolitan areas for specialist care for hematologic cancer	45 patients	NR	In-depth interviews; purposive sampling
McGrath (2015),[109] Australia, Leukaemia Foundation of Queensland	Descriptive qualitative	To explore experiences of relocating for specialist care for patients with hematologic malignancies	45 patients	NR	In-depth interviews; purposive sampling
McGrath (2016),[106] Australia, Leukaemia Foundation of Queensland, Senior Research Fellowship	Descriptive qualitative	To explore the economic and psychosocial aspects of relocating for specialized hematologic cancer treatment in patients	45 patients	Patients with hematologic malignancies who needed to travel or relocate for specialist care	In-depth interviews; purposive sampling
McGrath (2013),[110] Australia, Leukemia Foundation of Queensland	Qualitative design, not otherwise specified	To provide findings on perceptions and experiences about end-of-life care for patients with hematologic cancer	50 patients	Adults with a hematologic malignancy who were at least 1 year post-diagnosis	Open-ended interviews, focus groups; purposive sampling
Odejide (2014),[111] US, NR	NR	To determine how hematologic oncologists identify the end-of-life phase of a disease, to identify factors that characterize factors initiating end-of-life care,	20 hematologic oncologists	Hematologic oncologists eligible if they spent at least 25% of their time attending to patients and provided longitudinal care for adult patients with blood cancers	Focus groups; purposive sampling

First Author (Publication Year), Country, Funding	Study Design	Study Objectives	Sample Size	Inclusion Criteria	Data Collection Type; Sampling Method
		and to examine perspectives on current end-of-life care			
Orlowska (2018),[112] UK, Dimbleby Cancer Care	NR	To explore experiences of bereaved caregivers of patients' cutaneous T-cell lymphoma up to and beyond the death	15 family members	Bereaved relatives of patients that had CTCL as the primary or secondary cause of death	Semi-structured interviews; identified from patient database at supra-region CTCL clinic
Prod'homme (2018),[113] France, NR	Grounded theory	To explore hematologists' perspectives of end-of-life discussions with patients with recurring hematologic cancer	10 hematologists	Hematologic specialist members of the European Cooperator Oncology Group located in 1 of the 4 study sites	In-depth semi-structured interviews; NR
Sabo (2013),[114] Canada, International Society of Nurses in Cancer Care	Mixed-methods exploratory	To explore caregiver experiences with caring for a spouse undergoing HSCT	11 spouses or partners	Spouses or partners of HSCT recipients who were the primary caregiver, 18 or older, and fluent in English	Interviews and questionnaires; NR
Selman (2015),[115] UK, Dimbleby Cancer Care	Qualitative design, not otherwise specified	To describe the impact of CTCL on family members and how they cope and adjust, to inform support services	14 caregivers	Informal (unpaid) caregivers of patients with CTCL, 18 or older	Semi-structured interviews; NR

CTCL = cutaneous T-cell lymphoma; HSCT = hematopoietic stem cell transplant; NR = not reported.

Table 3: Characteristics of Study Participants

First Author (Publication Year), Country	Sample Size	Sex (% Male)	Age (Range in Years)	Conditions	Severity of Conditions; Special Population
Alnasser (2018),[98] Saudi Arabia	15 post-HSCT recipients	47%	21 to 59	"(L)ymphoma relapsed patients"	Advanced; none
Dunn (2016),[99] UK	15 patients	60%	22 to 68	Hodgkin lymphoma, acute myeloid leukemia acute lymphoblastomic lymphoma, aplastic anemia, myelofibrosis, myelodysplastic syndrome, lymphoma, peripheral T-cell lymphoma	Patients undergoing stem cell transplant; NR
Grech (2018),[100] Malta	5 nurses	0%	25 to 55	NA	NA; health care providers to patients at the end of life
Hoff (2014),[101] Sweden	7 patients 10 hematologists	Patients: 43% Hematologists: 70%	Patients: 37 to 80 Hematologists: NR	Malignant hematologic disease	Patients at the end of life; health care providers whose patients are at the end of life
Horinuki (2018),[102] Japan	14 family members	NR	Above 20	Hematological malignancies	NA; family members of patients who died
LeBlanc (2015),[103] US	23 hematologist-oncologists 43 solid tumour oncologists	Hematologist-oncologists: 70% Solid tumour oncologists: 65%	NR	NA	NA; health care providers working in palliative care
Loggers (2014), US[104]	18 patient "survivors" 11 caregivers	Patients: 44% Caregivers: 18%	Patients: 33 to 67 Caregivers: 37 to 65	Acute myeloid leukemia, acute lymphoblastic leukemia, lymphoma, multiple myeloma, chronic myelogenous leukemia, other	NR; stem cell transplant survivors and bereaved caregivers
McCaughan (2019),[105] UK	10 bereaved caregivers	Bereaved caregivers: 20% Deceased (not involved in study, but reported): 70%	Bereaved caregivers: NR Deceased (not involved in study, but reported): 66 to 81	Patients had leukemia, lymphoma, or myeloma	End of life or deceased; bereaved caregivers

First Author (Publication Year), Country	Sample Size	Sex (% Male)	Age (Range in Years)	Conditions	Severity of Conditions; Special Population
McGrath (2016),[106-109,116,117] Australia	45 patients	44%	18 to 70	Hodgkin disease, NHL, acute myeloid leukemia, acute lymphoblastic leukemia, acute promyelocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, myeloma, myelodysplastic syndrome, myeloproliferative neoplasm-essential thrombocythemia, hemolytic anemia	NR; patients from rural and remote areas
Odejide (2014),[111] US	20 hematologic oncologists	75%	NR	Leukemia, lymphoma, myeloma, hematologic malignancies	NA; health care providers working with patients at the end of life
Orlowska (2018),[112] UK	15 family members	33%	Under 42 to over 66	CTCL	NA; family members of patients who died
Prod'homme (2018),[113] France	10 hematologists	40%	33 to 56	Myeloma, lymphoma; myeloproliferative disease; acute myeloid leukemia, allograft	NA; health care providers working with patients at the end of life
Sabo (2013),[114] Canada	11 spouses or partners of HSCT recipients	36%	30 to 70	HSCT recipients: NHL, multiple myeloma, myelodysplastic disease, acute myelogenous leukemia, and aplastic anemia	Advanced; NA
Selman (2015),[115] UK	14 caregivers	29%	39 to 85	CTCL	NA; NA
Hoff (2014)[101]	7 patients 10 hematologists	Patients: 43% Hematologists: 70%	Patients: 37 to 80 Hematologists: NR	Malignant hematological disease	Patients at the end of life; health care providers whose patients are at the end of life
Loggers (2014)[104]	18 patient “survivors” 11 caregivers	Patients: 44% Caregivers: 18%	Patients: 33 to 67 Caregivers: 37 to 65	Acute myeloid leukemia, acute lymphoblastic leukemia, lymphoma, multiple myeloma, chronic myelogenous leukemia, other	NR; stem cell transplant survivors and bereaved caregivers

First Author (Publication Year), Country	Sample Size	Sex (% Male)	Age (Range in Years)	Conditions	Severity of Conditions; Special Population
McGrath (2013)[110]	50 patients	52%	22 to 77	Multiple myeloma, lymphoma, leukemia, and other	End of life
Grech (2018)[100]	5 nurses	0%	25 to 55	NA	NA; health care providers to patients at the end of life

CTCL = cutaneous T-cell lymphoma; HSCT = hematopoietic stem cell transplant; NA = not applicable; NHL = non-Hodgkin lymphoma; NR = not reported.

Appendix 2: Summaries of Patient and Clinician Input Submissions

Summary of Patient Group Input Submissions

Description of Patient Groups That Submitted Input

Two patient input submissions were received through the CAR T-cell patient submission input process and summarized by CADTH staff. One was received from Lymphoma Canada and one from the Leukemia & Lymphoma Society of Canada.

Lymphoma Canada is Canada's only national organization focused entirely on lymphoma. Lymphoma Canada provides education materials, peer and caregiver support groups, and advocacy on behalf of patients. Lymphoma Canada also funds Canadian research (https://www.lymphoma.ca/about-us).

The mission of the Leukemia & Lymphoma Society of Canada is to cure leukemia, lymphoma, Hodgkin disease and myeloma, and improve the quality of life of patients and their families (http://www.llscanada.org).

The full patient input submissions can be found in Appendix 3. They were used to inform the clinical, economics, and ethics reviews and the implementation analysis.

Patients' Experiences of Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Patients' experiences of relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) centred on their diagnosis and prior treatments. Treatment for aggressive B-cell non-Hodgkin lymphoma subtypes were described as starting at the time of diagnosis, where patients were often given multi-agent chemotherapy regimens. At this point, patients with r/r DLBCL had undergone one or more first-line therapies (i.e., chemotherapy, radiation, and stem cell transplant) and possibly many years of cancer treatment. Their prior diagnoses and treatments affected their physical, emotional, and mental health in a multiplicity of ways.

Physically, patients undergoing treatment for DLBCL treatment were described as experiencing a host of side effects. Fatigue and changes in their ability to be physically active, hair loss, pain, constipation, and nausea and vomiting were reported as treatment-related side effects that greatly affected patients' lives.

Treatment also affected patients' mental health. Patients described the stress of living with DLBCL — living with fear, anxiety, depression, brain fog, fatigue, and having difficulties sleeping. The financial well-being of patients and their families was also strained by patient-borne costs of treatment and the reduced ability to work. In addition to being unable to work and sometimes having to give up their career, a partner or other family member often also had to leave work or reduce their hours in order to act as a caregiver. Those patients who had caregiving responsibilities (e.g., children who still lived at home or elders for whom they cared) struggled to fulfill their family responsibilities.

Patients' Experiences with Current Treatments for Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Treatments for r/r DLBCL had a substantial and negative impact on many respondents' ability to work, travel, and participate in daily activities because of fatigue, side effects, number of clinic visits, infusion time, number and frequency of infections, and infusion reactions. The absence from work or school for treatment also added a serious financial burden to some patients and their families.

Patients' Expectations for Chimeric Antigen Receptor T-Cell Therapy

In terms of expectations of treatment for r/r DLBCL, patients expressed that they desired remission, longer survival, and improved quality of life. Chimeric antigen receptor (CAR) T-cell therapy and axicabtagene ciloleucel were described as a last resort for many patients with r/r DLBCL. Patients described that they hoped the therapy would enable them to go into remission and live longer with fewer side effects. Patients felt that CAR T-cell therapy should be the standard of care for patients with r/r DLBCL who have failed two lines of treatment.

Patients responding to the patient group input submissions expressed a range of views of the tolerability of side effects associated with CAR T-cell therapy. Some described it as easier than autologous stem cell transplant while others described it as a very difficult treatment.

Costs associated with travel were noted as being a substantial concern as they included having to travel for initial assessment, for T-cell collection, and for infusion and monitoring for adverse events. Patient-borne costs were a negative dimension of the treatment burden associated with patients' access to CAR T-cell therapy.

The perspectives of patients with r/r DLBCL who died after receiving treatment or who were otherwise unable to participate are not represented in the patient input submissions received by CADTH. The experiences of these patients may not be reflected in the input received.

Summary of Clinician Input Submission

One clinician input submission was received through the CAR T-cell therapy stakeholder submission input process in November 2018 and summarized by CADTH staff. The full clinician input submission can be found in Appendix 4. It was used to inform the ethics review and the implementation analysis.

Description of Clinicians Who Submitted Input

Nine clinicians from across Canada completed the CAR T-cell therapy review's clinician input submission for axicabtagene ciloleucel.

Overview of Need and Place in Therapy

In terms of the current treatment for adult patients with r/r DLBCL, the submitting clinicians described that there are few options available and that this is a population with a high unmet treatment need. As of the time of submission, the standard treatment for patients was non-curative care (radiation therapy, oral chemotherapy, intravenous chemotherapy). Clinical trials, when available, were described as being prioritized as a treatment option. Clinicians described the treatment population as a group of patients that has exhausted all of their therapeutic options, including autologous stem cell transplant, allogeneic stem cell transplant, and standard therapies.

The submitting clinicians considered cluster of differentiation 19 (CD19) CAR T-cell therapy to be "essential treatment" for patients with r/r DLBCL. They expressed a great deal of expectation for CD19 CAR T-cell therapy to be the standard of care for r/r DLBCL patients in the future and for it to provide long-term disease control. Submitting clinicians also felt clinical trials would be needed to determine the superiority of CD19 CAR T-cell therapy as compared with other second-line therapies (i.e., chemotherapy and autologous stem cell transplant), and that if these trials were favourable, CD19 CAR T-cell therapy could replace other second-line therapies.

At the time of submission, CAR T-cell therapy was available in Canada only through clinical trials. The submitting clinicians reported that the limited number of Canadian patients who have been treated with axicabtagene ciloleucel were located at the Vancouver General Hospital and Princess Margaret Cancer Centre in Toronto. They expected that once CAR T-cell therapy is being offered, patients will be sent to expert centres (not further specified) to determine their eligibility for treatment due to their prolonged disease state and toxicity (related to treatment).

Regarding eligibility, from the perspective of submitting clinicians, patient characteristics needed to determine eligibility are routinely collected in clinical practice. Clinicians felt that some patients may not be eligible for treatment with axicabtagene ciloleucel because of their condition or disease progression, but the submitting clinicians did not know this proportion due to a lack of data at the time of the submission. Immunohistochemistry testing to determine whether CD19 is expressed on a patient's tumour can be offered prior to CD19 CAR T-cell therapy. It was noted that while this testing has not been routine, it could be performed on archival tissue, meaning a new biopsy prior to CD19 CAR T-cell therapy would not be required.

CADTH

Appendix 3: Patient Input Submissions for Axicabtagene Ciloleucel for Large B-Cell Lymphoma

CADTH OPTIMAL USE REPORT

Axicabtagene Ciloleucel for Large B-Cell Lymphoma — Patient Input Submissions

Patient Group Input Submissions Were Received From the Following Patient Groups:
Leukemia & Lymphoma Society of Canada
Lymphoma Canada

CADTH received patient group input for this review on or before November 2018.

The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations.

While CADTH formats the patient input submissions for posting, it does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no personal information is included in the submission. The name of the submitting patient group and all conflict of interest information are included in the posted patient group submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

CADTH

Patient Input Template for CADTH Chimeric Antigen Receptor T-Cell Therapy Reviews

Name of the Drug and Indication	Yescarta (Axicabtagene ciloleucel) for relapsed or refractory large B-cell lymphoma, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
Name of the Patient Group	The Leukemia & Lymphoma Society of Canada (LLSC)

1. About Your Patient Group

If you have not yet registered with CADTH, describe the purpose of your organization. Include a link to your website.

Leukemia and Lymphoma Society of Canada

The mission of the Leukemia & Lymphoma Society of Canada (LLSC) is: Cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families.
http://www.llscanada.org/

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

An online survey was posted on Survey Monkey and distributed by LLSC staff asking for input from patients who were currently in treatment or in remission from relapsed or refractory large B-cell lymphoma, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. The link to the survey was distributed through social media and email. We received 15 responses (10 Canadians, 5 from United States of America). Of these 15 respondents, 9 are patients and 6 are immediate family and caregivers.

The survey addressed questions regarding Yescarta including whether or not patients are being treated with the drug, costs associated with the treatment and side effects experienced with this drug treatment.

The Leukemia & Lymphoma Society of Canada (LLSC) realizes this is a small sample, but since there was a great degree of similarity in people's responses, we think this information still has value to the pCODR process.

Who are the respondents?	Number of respondents
Patient over 18 years of age	9
Spouse of a patient	2
Immediate family member of a patient	2
Caregiver	2
Other	0

Age of Diagnosis	Number of respondents
19 and younger	0
20-29	1
30-39	1
40-49	2
50-59	6
60-69	4
70 -79	1
80 and older	0

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

Non-Hodgkin lymphoma (NHL) is the term that encompasses a diverse group of blood cancers that share a single characteristic—they all arise from lymphocytes. Lymphocytes are white blood cells that are part of our immune system. They can be either B cells, T cells or natural killer cells. Lymphomas begin when a cell undergoes a change (mutation) in a lymph node or in some other lymphatic structure, eventually crowding out healthy cells and creating tumors. Lymphomas are found in the skin, the gastrointestinal tract, or other sites in the body. One way that NHL subtypes are designated is by cell type. Some NHL subtypes involve lymphocytes called "B cells" (e.g., diffuse large B-cell lymphoma (DLCBL) and follicular lymphoma [FL]). Aggressive lymphoma subtypes (also called "high-grade NHL") account for about 60 percent of all NHL cases. Diffuse large B-cell lymphoma is the most common aggressive NHL subtype. Slow-growing (indolent) subtypes represent about 40 percent of all NHL cases. Follicular lymphoma is the most common subtype of indolent NHL.

Approximately 43,335 Canadians are living with, or are in remission from a lymphoma: 36,175 with non-Hodgkin lymphoma. The median age at diagnosis of non-Hodgkin lymphoma is 66 years of age. It is the sixth most commonly diagnosed cancer in Canada.

All respondents were diagnosed as adults. Most patients who are diagnosed with NHL show symptoms that are also associated with a number of other less serious diseases such as: fever, fatigue, frequent minor infections, discomfort in bones or joints, enlarged spleen, liver or lymph nodes and shortness of breath. It is therefore crucial that patients displaying these symptoms do a "complete blood count" (CBC) test at their local clinic or doctor's office.

All respondents indicated that, as a result of the diagnosis, they experienced some disruptions to their daily lives. They are listed in the chart below, ranked on a scale of 1 (no impact) to 5 (extremely large impact):

Symptom	Respondents who rated a four or more	Total number of respondents	Rating average
Fatigue/lack of energy	4	13	4.25
Loss of appetite	1	14	4.0
Unexplained weight loss	2	14	4.0
Rash	0	13	0
Fever	2	13	4.0
Night sweats	4	13	4.25
Bone pain	1	13	5.0
Chest pain	0	13	0
Abdominal pain	2	13	4.0
Lumps	4	14	4.25
Cough	3	13	4.67

Common symptoms of such as fatigue, fever/night sweats and lumps under the skin, were experienced by 4 respondents. However, it can be noted that most respondents reported that their initial symptoms had minimal disruptions to their daily lives. In fact most diagnoses occurred either during routine check-ups or during doctor visits for some other issues. One patient stated that she "went for a routine mammogram and enlarged ganglions were seen in my underarms". Biopsy later confirmed diagnosis. 7 of the 15 respondents visited their physicians due to visible lumps under their skin. Biopsies of these led to their diagnoses. 6 of the 15 respondents received diagnoses while testing for other issues, such as persistent cough, bronchitis, infections, and progressively worsening fatigue.

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers. Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

Patients' Experience with Current Therapy

The main types of treatment used for HNL subtypes are chemotherapy, radiation therapy, drug therapy and autologous or allogeneic stem cell transplants. For patients without symptoms and with indolent subtypes of NHL, the treatment may be the watch-and-wait approach, meaning treatment is deferred or delayed until signs of disease progression occur. Treatment for aggressive B-cell NHL subtypes starts at the time of diagnosis. Patients with fast-growing NHL are frequently treated with chemotherapy that consists of four or more drugs. Chemotherapy can be supplemented by radiation therapy in select cases, for instance, when large NHL masses are found during the diagnostic and staging process.

Of all the respondents, 11 reported having received treatment; 4 respondents did not specify treatments being received or symptoms associated with treatment. Of the 11 respondents, 10 have received chemotherapy and in addition, 3 have received radiation.

All of the respondents surveyed were asked if they had difficulty accessing their treatments and 8 reported little to no difficulties in accessing treatment or health services during first-line treatment. 2 respondents indicated that in their opinion, the current treatment did not do a sufficient job in managing their cancer.

All respondents reported having some variation of side effects associated with their treatments and therapies. When asked about the impact of each of the side effects of lymphoma treatment on their quality of life, on a scale of 1 (no impact) to 5 (extremely important):

Symptom	Percentage of respondents who rated a four or more	Total number of respondents	Rating average
Neutropenia (low white blood cell count)	45	11	4.0
Fever	37	11	4.0
Nausea	36	11	4.25
Vomiting	0	11	0
Pain	27	11	4.3
Neuropathic pain	30	10	4.0
Constipation	30	10	4.3
Hair loss	36	11	4.5
Organ damage	0	10	0
Vision	0	10	0
Movement or ability to take part in physical activities	20	10	5.0
Mental health and general happiness	40	10	4.25
Difficulty eating	10	10	4.0

Symptom	Percentage of respondents who rated a four or more	Total number of respondents	Rating average
Changes to physical activity	45	11	4.6
Anxiety	18	11	4.5
Social development	11	9	4.0
Educational development	0	10	4.0

In terms of impact that these side effects had on their life, 9 of the 11 respondents stated that there was some effect on their mental health and general happiness as well as anxiety levels. 10 out of 11 respondents stated that their treatment's side effects impacted their physical ability as a whole. They experienced sore back and joint, susceptibility to UTIs, fatigue and stomach issues. 2 respondents also mentioned the negative effect it had on their families and close relationships.

Patient Experiences with Second-Line Therapy

Most patients achieve an initial remission. However, in some patients, NHL does not respond to initial treatment. This is called "refractory" disease. In other patients, the lymphoma returns, even though these patients had achieved a remission. This is called "relapsed" disease. Most patients with refractory or relapsed disease receive second-line therapy, in some cases followed by allogeneic (from a donor) or autologous (from the patient) stem cell transplantation.

Of the 15 respondents, 4 received additional chemotherapy as a second-line treatment, 3 of which also received additional radiation therapy followed by a stem-cell transplant. 1 person was receiving immunotherapy drugs. Side effects for all of the respondents of the second-line treatments predominantly revolve around fatigue, nausea, low white blood cell count, low platelet count, hair loss and diarrhea. One respondent reported an infection after transplant, requiring hospitalization, antibiotics and blood/platelet transfusions. One caregiver mentioned that the second-line chemotherapy only served to "just slowed it down a bit and gave him more time." One patient reported that "The treatments haven't work, each failed treatment causes fear and anxiety and depression. It is a tough row to hoe"

5. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

Please see under Section 6.

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families. How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared with any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways?

The patient who has had experience with Yescarta responded to follow up questions regarding his/her experiences with the drug. The patient reported serious side effects such as: Cytokine release syndrome (CRS), fever and pain. And some more controllable side effects such as: dizziness, headaches, vomiting and nausea and low white blood cell count (neutropenia). Although reporting that Yescarta compared to other treatment was "more difficult" this patient agreed that Yescarta has improved his/her quality of life compared to other treatments received. "It has given us hope."

The respondents who have never taken Yescarta responded to a series of follow-up questions regarding their expectations for the new drug. When we asked “If you have not had Yescarta treatment, but would be ready to consider it, why would you be willing to tolerate the side effects?” They responded:

- “CAR T represents the best hope for cure were I to relapse.”
- “It becomes a life or death decision. He’s not done living.”
- “Because after 2 separate failed chemo therapies, I am out of options in our standard of care.”

Respondents were also asked “When making a decision about a new treatment for cancer, what are the most important factors you consider?” The possible impact on the disease, doctor’s recommendations and quality of life were the top three deciding factors. 4 of the respondents gave their final comments on lymphoma treatments: all revolve around having access to CAR T-cell therapy here in Canada and the hope that it provides to patients. “I can stress enough how important CAR T-cell therapy is to patients that it can help. In the US it is standard protocol after two failed lines of treatment. That needs to be the case here in Canada as well”

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

Not Applicable.

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

Yescarta is a treatment for large B-cell lymphoma that has failed conventional treatment. T cells are removed from a person with lymphoma and genetically engineered to produce a specific T-cell receptor. The resulting chimeric antigen receptor T-cells or "CAR T-cells" that react to the cancer are then given back to the person to populate the bone marrow. The FDA granted approval for the second-line treatment of diffuse large B-cell lymphomas.

Our survey asked respondents about their knowledge and experience with Yescarta. All 15 patient respondents were asked if “they were currently on or have ever used Yescarta.” 1 respondent is currently receiving Yescarta. 1 respondent is awaiting approval of a grant to receive the treatment and one other is actively perusing the treatment. Since Yescarta is not offered in Canada, they requiring funding to travel to the USA for treatment. The remaining respondents have either not received this treatment or did not respond to the question.

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Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.
2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.
3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of 50,000
Nadine Prevost (LLSC), Novartis CAR T-Cell Consultation Meeting, Info gathering for patient materials, February 2018. Partnerships for patients programs			x	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

CADTH

Patient Input Template for CADTH Chimeric Antigen Receptor T-Cell Therapy Reviews

Name of the Drug and Indication	Axicabtagene ciloleucel for diffuse large B-cell lymphoma
Name of the Patient Group	Lymphoma Canada

1. About Your Patient Group

www.lymphoma.ca

2. Information Gathering

Lymphoma Canada (LC) conducted 2 anonymous online surveys of diffuse large B cell lymphoma (DLBCL) patients from April 18th – June 15th, 2018. Links to the surveys were sent via e-mail to patients registered on the LC database. The links were also made available via LC Twitter and Facebook accounts, Canadian and American Cancer Society message boards, Facebook groups organized for lymphoma patients and survivors, and international lymphoma organizations' own contacts. The surveys had a combination of multiple choice, rating and open - ended questions. Skipping logic was built into surveys so respondents were asked questions only relevant to them. Open-ended responses to surveys that reflected the sentiment of a majority are included verbatim to provide a deeper understanding of patient perspectives.

Overall, 107 patients provided input. Of patients who provided their demographic information (see Tables 1 and 2), 90% live in Canada, 62% are female, 53% are ≥ 60 years-old, 33% are 40-59 years-old and 14% are < 40 years-old

Table 1: Country of survey respondents (107 respondents)

Respondents	CANADA	US	Other	Skipped	Total
Patients with CAR T therapy experience	2	3	0	4	9
Patients without CAR T therapy experience	85	5	2	6	98

Table 2: Gender and Age of Survey Respondents

Respondents	Age Range					Gender		
	< 20	20-39	40-59	≥ 60	skipped	Female	Male	Skipped
Patients with CAR T therapy experience	0	1	1	3	4	3	2	4
Patients without CAR T therapy experience	2	11	31	48	6	57	35	6

3. Disease Experience

Symptoms of DLBCL that most commonly affected respondents' quality of life at diagnosis (98 respondents) were fatigue or lack of energy (72%), enlarged lymph nodes (49%), drenching night sweats (37%), unexplained weight loss (28%), loss of appetite (25%), flu-like symptoms (18%), and persistent cough (18%). Other symptoms affecting quality of life for ≥ 10% of respondents included itching, chest pain and trouble breathing.

Respondents were asked which aspects of their life have been NEGATIVELY impacted by DLBCL. Notably, 56% and 42% indicated that DLBCL had a negative impact on their ability to work or attend to family obligations, respectively. Additional responses are summarized in Table 3.

Table 3: Effect of DLBCL on day-to-day life of patients (95 respondents)

Aspect of life NEGATIVELY impacted by DLBCL	# of respondents	% of respondents
Ability to work	53	56%
Family obligations	40	42%
Personal image	36	39%
Intimate relations	27	28%
None of these	23	24%
Friendships	21	22%
Ability to attend school	2	2%

The majority of respondents (85%) also reported that their quality of life has been negatively affected by mental and emotional problems associated with their disease or treatments (Table 4).

Table 4: Impact of DLBCL on patients' mental and emotional well-being (98 respondents

Symptom	# of respondents	% of respondents
Fear of disease recurrence	66	67%
Memory loss	41	41%
Anxiety/worry	38	38%
Problems concentrating	37	38%
Difficulty sleeping	28	29%
Loss of sexual desire	25	26%
Stress of diagnosis	18	18%
Depression	17	20%
None of these	15	15%

As described by four patients:

" [Fear of disease recurrence] is very high and consumes a lot of my thought process almost every day. Even after two years since my chemo treatments finished and I had a complete response."

"I retired early due to memory loss, lack of concentration, and ongoing depression."

"It affected our personal lives my husband had to stay home from work to help me. We had no income. Very stressful. Our community did a couple benefits which helped us pay our bills. Big life changer for sure."

"I was an avid exerciser and have difficulty walking right now. The cancer is in my pelvis; it's a sizable tumour and limits my movements. In the last year I have sold my businesses and am now retired. I could not manage business, family, daily activities. There were times I had brain fog or chemo brain, not good for decision-making. I try to do daily activities, laundry, cooking etc. The trial I am on right now has given me more fatigue, so I rest more than ever."

4. Experiences With Currently Available Treatments

Ninety-six (96) respondents provided information about their experience with DLBCL treatments. All respondents had received at least one line of treatment or were undergoing first-line treatment for DLBCL, 46% had received more than one line of treatment, and 5% had received three or more lines of treatment. The most commonly reported first-line treatment (84% of respondents) was the chemoimmunotherapy regimen R-CHOP. Of those who received more than one line of treatment (44 respondents), 25% had undergone an autologous stem cell transplant and 5% had undergone an allogeneic stem cell transplant.

Side effects of current treatments: The most common side effects respondents experienced during their DLBCL treatments are listed in Table 5.

Table 5: Side effects from treatment (96 respondents)

Side effect	% of resp.	Side effect	% of resp.	Side effect	% of resp.
Hair loss	92%	Mouth sores	47%	Trouble breathing	23%
Fatigue	86%	Thrombocytopenia	35%	Cough	22%
Memory problems or confusion	73%	Infections	35%	Other	22%
Neutropenia	67%	Anemia	32%	Loss of menstruation	19%
Nausea	61%	Diarrhea	27%	Irregular heartbeat	16%
Constipation	50%	Pain	27%	Viral reactivation	7%
Peripheral neuropathy	50%	Skin rashes (severe) itching	23%	Bowel obstruction	7%

When asked which side effects they found most difficult to tolerate, respondents most often reported fatigue (32/80; 40%), nausea/vomiting (15/80; 19%), chemo brain (13/80; 16%), and hair loss (8/80; 10%). Eighty (80) respondents provided responses to this question.

Impact of treatments on quality of life: When asked about the impact of various aspects of treatment on daily living (on a scale of 1 – 5, where 1 = No impact and 5 = significant negative impact), respondents noted that treatment-related fatigue and other side effects had the most significant impact on their quality of life (Table 6).

Table 6: Impact of treatment on quality of life (96 respondents)

Treatment aspect	Weighted average	Significant negative impact (rating = 4-5)	Number of responses
Fatigue	3.8	63%	95
Side effects	3.6	57%	93
# of clinic visits	2.4	22%	93
Infusion time	2.4	21%	92
# of infections	2.4	24%	91
Infusion reaction	2.4	21%	92
Frequency of infections	2.2	21%	92

Treatment also had a very significant impact on many respondents' ability to work, travel, and participate in daily activities (Table 7).

Table 7: Impact of treatment on daily living (95 respondents)

Activity	Weighted average	Significant negative impact (rating = 4-5)	Number of responses
Work	4.0	61%	94
Travel	3.9	64%	94
Activities	3.9	69%	94
Intimate relations	3.3	45%	92
Family	2.9	36%	91
Friendships	2.5	23%	93
School	2.1	6%	85

As reported by three respondents:

"I needed to make extra visits to emergency or to the clinic between treatments as a result of fever. Eventually I was given Neupogen injections after treatments to keep my white blood cells at a better level (these were daily in my home for several days - impact, had to be home)."

"Learning to not to push myself with physical activity, i.e., yard work, house renos etc.
Not taking on extra duties at work, and possibly retiring early in age"

"There is always some stress getting time off work to attend check-ups with oncologist. I am tired after work so I do very little during the work week to make sure I will have enough energy for my job."

When asked about the financial implications of treatment, almost half of respondents from Canada (40/85; 47%) reported that their absence from work or school impacted them financially.

As reported by two respondents:

"Had to give up a new career and job to have treatment"

"I was unable to continue working so I had to retire early, and therefore I lost my salary and health benefits"

Additional financial costs for respondents living in Canada are reported in Table 8.

Table 8: Financial implications of treatment for DLBCL patients in Canada (85 Canadian resp.)

Financial impact	% of respondents	Number of respondents
Absence from work or school	47%	40
Cost of medications	33%	28
None	24%	20
Travel	13%	11
Other	13%	11
Accommodation	8%	7
Drug administration supplies	4%	3
Clinical trial charges	0%	0

5. Improved Outcomes

Patient preferences: Respondents were asked to rate, on a scale of 1 -5 (1 = not important; 5 = extremely important), the importance of various factors regarding a new drug or therapy for DLBCL. “Longer survival” and “longer remission” than current therapies were rated as the most important outcomes for a new therapy (Table 9). “Fewer side effects” was rated as the least important outcome, overall.

Table 9: Treatment preferences (94 respondents)

Treatment outcome or factor	Rating = 5 (Extremely important)	Weighted average	Number of responses
Longer survival	90%	4.9	94
Longer remission	87%	4.8	94
Better quality of life	77%	4.6	94
Fewer side effects	55%	4.1	94

Respondents were also asked if they would choose a treatment with known side effects, potentially serious, if their doctor recommended it was the best option for them. Of the 94 respondents who answered this question, 49% selected “Yes,” while only 3% selected “No.” The remaining 49% of respondents selected “I’m not sure.” Furthermore, 42% or respondents would be willing to tolerate potential side effects if the benefits were short term, while only 7% were not.

6. Experience With Drug Under Review

Nine respondents from Canada and the US reported that they had been treated with CAR T therapy for diffuse large B-cell lymphoma. Most patients received CHOP +/- R as their first-line of treatment. All but one of the respondents were diagnosed from 2014 to 2016 and treated with CAR T therapy between 2015 and 2018 (the lone exception was diagnosed in 2011 and treated in 2012). Two patients received tisagenlecleucel (Kymriah), one received KTE-C19 (Yescarta), two received JCAR017, and four did not specify what type of CAR T therapy they had received. All of the respondents received CAR T therapy through a clinical trial. Four patients are currently in remission, one remains in treatment with CAR T therapy and four patients did not indicate their current status. Patients who provided demographic information are profiled below:

- A male patient from Ontario (50 to 59 years old) was interviewed. He was diagnosed in 2014 and treated with CHOP +/- R, followed by CHEOP +/- R, GCVP +/- R, DHAP +/- R and radiation therapy. The patient indicated that he had exhausted the available lines of treatment prior to his enrolment in the clinical trial. He began CAR T therapy (CTL019) in July 2016 and has been in remission for one to two years. He commented that: “*I did not experience any significant adverse effects from the treatment.*”
- A female patient from the US (70 to 79 years old) was diagnosed in 2016. She was treated with CHOP +/- R, followed by GemOx +/- R, cisplatin, ibrutinib + buparlisib and high-dose methotrexate. She was treated with CAR T therapy (JCAR017) beginning in March 2018 and is newly in remission. She was admitted to hospital four days prior to the infusion and remained for five weeks, due in part to a C. difficile infection.
- A male patient from the US (60 to 69 years old) was diagnosed in 2015. He was treated with CHOP +/- R, followed by lenalidomide +/- rituximab and HDT + auto-SCT. He was treated with CAR T therapy (JCAR017) beginning in May 2017 and has been in remission for six months to one year. He suffered from skin issues related to his therapy that lasted for more than two months. He remarked that “*I was supposed to be dead last April. I couldn’t walk 5 feet. After CAR T therapy, I am now in remission and I just golfed 18 holes. Life is good.*”
- A female patient from Canada (20 to 29 years old) was diagnosed in 2015. She was previously treated with CHOP +/- R and began CAR T therapy (CTL019) in June 2017. She is currently in remission.
- A female patient from the US (60 to 69 years old) was diagnosed in 2011. She began CAR T therapy (KTE-C19) in 2018 and remains in treatment.

Side Effects: Neutropenia was the most commonly reported side effect of CAR T therapy followed by decreased appetite, cytokine release syndrome, and febrile neutropenia. Only one patient required hospitalization to manage side effects due in part to a *C. difficile* infection and one patient reported side effects that lasted longer than two months (skin issues).

Quality of Life: Five respondents answered a question asking them to rate the impact of different aspects of their CAR T therapy on a scale of 1 (no negative impact on my life) to 5 (significant negative impact on my life). None of the weighted averages for these responses was higher than 3 and only 1 of 5 respondents gave a rating > 3 for any aspect of CAR T therapy, suggesting that CAR T therapy had a reasonably benign effect of their quality of life.

Table 10: Impact of CAR T therapy on Patients' Lives (5 respondents)

Aspect of CAR T therapy	Weighted Average
Number of clinic visits	2.8
Travel to treatment centre	2.8
CAR T-cells infusion	2.6
Short-term side effects of treatment	2.5
Activity level	2.5
Treatment-related fatigue	2.5
Lasting side effects of treatment	2.0
Leukapheresis	1.8

As reported by one patient:
"For all intents and purposes, despite having reviewed and discussed all of the potential side effects with respect to the CAR T therapy program, the experience was fairly uneventful. I did not experience any significant adverse effects from the treatment." (Male, 50-59, Ontario)

Recommend CAR T therapy: When asked to describe the positive and negative effects of CAR T therapy, patients provided these two responses:

"Nothing negative, but the cost for travel. It was so much easier than the auto stem cell transplant." (Male, 60 to 69, US).

"Positive, in that it removed the cancer. But it was a very difficult treatment." (Female, 70 to 79, US).

When asked if they would recommend CAR T therapy to other DLBCL patients based on their own experience, patients answered:

"After 25 days I am cancer free, so that was worth it, since nothing else worked." (Female, 70 to 79, US).

"I would recommend it to any patient with relapsed DLBCL." (Male, 60 to 69, US).

Companion Diagnostic Test

CD19 CAR T therapy requires expression of CD19 on the tumour cells. Hematologists and oncologists with knowledge of CAR T therapy and experience treating DLBCL indicated that this is a routine test that can be performed on archival biopsy tissue using readily available laboratory testing and would not need to be performed on new tissue prior to the initiation of CAR T therapy.

7. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

Adam Waiser, an independent consultant, helped promote the patient surveys, analyzed the survey data for patients with CAR T-cell therapy experience, and wrote the “Experience With Drug Under Review” section of the submission.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

Adam Waiser, an independent consultant, helped promote the patient surveys, analyzed the survey data for patients with CAR T-cell therapy experience, and wrote the “Experience With Drug Under Review” section of the submission.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of 50,000
Novartis			X	
Gilead			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Elizabeth Lye

Position: Scientific Advisor

Patient Group: Lymphoma Canada

Date: June 20, 2018

CADTH

Appendix 4: Clinician Input Submission — Original Submission

Clinician Input Template for CADTH CAR T-Cell Therapy Reviews

Before completing this template, be sure to register with CADTH Collaborative Workspaces. Please visit https://cadth.ca/cadth-collaborative-workspaces-registration for information about the registration process.

1. About the Registered Clinician

Name of Registered Clinician	**John Kuruvilla**
Title	**Chair, Scientific Advisory Board, Lymphoma Canada**
Disease Specialty (if applicable)	**Hematology**
Province	**Ontario**
Organization Membership (if applicable, national or provincial)	
Email	**John.kuruvilla@uhn.ca**
Telephone Number	**416 946 2821**

If this is a joint clinician input submission, please list the names of the other clinicians and disease site specialty (if applicable). Please note that all clinicians listed must also register with CADTH and complete conflict of interest declaration forms.

Dr. Mohamed Elemary, Dr. Kevin Song,
Dr. Pamela Skrabek, Dr. Kerry Savage,
Dr. Graeme Fraser, Dr. Carolyn Owen,
Dr. Mona Shafey, Dr. Nizar Samad

2. About the Therapy and Indication Under Review

CADTH Project Number	CT0002
Generic Drug Name	Axicabtagene ciloleucel
Indication	Relapsed or refractory large B-cell lymphoma
Review Request	Seeking approval for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
Health Canada Status	Under review
FDA	October 17, 2018 For the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
European Medicines Agency Status	August 23, 2018 For the treatment of adult patients with relapsed or refractory DLBCL and PMBCL after two or more lines of systemic therapy

3. Key Questions for Clinician Input

3.1 Current Treatment(s) for the Indication Under Review:

- Please list the current standard treatment(s) you use for the defined patient population in the funding request.
- If more than one treatment is funded in your province, identify the treatment(s) that would be the most appropriate comparator for the therapy under review.

Patients in this setting are typically managed palliatively. Most of these patients have not responded to aggressive chemotherapy and are no longer candidates for curative approaches, such as autologous stem cell transplantation (ASCT). The other group in this patient population consists of patients who have developed disease progression post-ASCT. Current treatment strategies include radiation therapy, palliative chemotherapy (either oral strategies such as prednisone, etoposide, cyclophosphamide or IV treatments such as gemcitabine, vinblastine etc.). Clinical trials are also prioritized when available. A selected group of patients would potentially be considered for allogeneic stem cell transplantation (Allo-SCT). These patients typically require chemosensitive disease and need to be younger age (up to 70 years) which no significant medical comorbidities and an available donor. Please note that allo-SCT is associated with significant toxicities including non-relapse mortality (NRM) of approximately 10% by day 100 post-cell infusion and up to 20-35% with mature follow-up. ASCT is associated with NRM in the range of 1-3% typically although patients above age 60 may have rates of NRM between 5-10%.

3.2 Eligible Patient Population

Describe the patients for whom you would use the new treatment. Examples can include, but are not limited to, the following questions:

- Does the patient population in the reimbursement request align with the need identified in your clinical practice? Is there an unmet need?
- Can the inclusion and exclusion criteria of the clinical trial be applied in clinical practice?
- Is there a subgroup of patients beyond the study population for which you would like to use the new treatment? Is there a subgroup of patients within the study population that the new treatment should be limited to?

The funding request represents a population with an extremely high unmet need; one for which we currently have no effective therapies. The inclusion/exclusion criteria are typical characteristics routinely evaluated in clinical practice. An historical population with similar criteria were identified in an international collaboration with Canadian participation as having consistently poor OS (median 6.4 months) with currently available salvage therapies (Crump SCHOLAR-1, Blood 2017). It is important to note that this population would have utilized all potential available therapies including both ASCT and allo-SCT, along with conventional palliative and experimental therapies. The largest patient group in the review was from Canada.

If CD19 CAR-T cell therapies are available in this indication, it is very likely that ALL potential patients included in the funding request will be considered for this treatment. CD19 CAR-T cell therapy appears to offer an unprecedented benefit over other standard and experimental treatments currently available in this indication. Given the potential for prolonged disease control and significant toxicity, the majority of these patients will be sent to expert centres for evaluation regarding potential candidacy for this treatment. It is expected that a proportion of patients (unknown at this time due to lack of data) would not ultimately receive the therapy (or have the CAR-T cell product manufactured) if they were deemed ineligible for medical issues or if their disease

tempo precluded this type of treatment.

3.3 Relevance to Clinical Practice

Do you have experience with using the treatment (through clinical trials, manufacturer's access program, private insurance) under review?

☒Yes ☐No

- How or when would you use the new treatment? Is there any population or subpopulation where you particularly want to use this therapy?
- How is the new treatment different than currently available treatments with respect to efficacy, safety, and tolerability?
- Are there contraindications to using the new treatment? Are there contraindications to current treatments that would make the new treatment favourable?

Please note: Scientific published references are not required, as CADTH has access to current scientific literature through the manufacturer's submission and a rigorous, independent literature search.

CD19 CAR-T therapy is now an essential treatment for patients with DLBCL who have exhausted all curative treatment options. There is an extremely high unmet need in DLBCL (the most common lymphoma – the 6th most common cancer in Canada) for potentially curative treatment in this setting. With a typical median survival of approximately 6 months with available therapies, the potential to transform care in this setting is unprecedented.

Unfortunately, CAR-T cell trials have been largely limited to the US for initial clinical trial populations. There are a limited number of patients that have had therapy in Canada – centres involved in these clinical trials (multiple companies with patient accrued) have included the Vancouver General Hospital (VGH), Juravinski Cancer Centre and Hopital Maisonneuve Rosemont. Axicabtagene Ciloleucel has been used at Princess Margaret and VGH on the Zuma-1 clinical trial and there multiple sites in Canada accruing patients using this product on the Zuma-7 randomized trial (earlier in the disease course).

3.4 Sequencing and Priority of Treatments

- Please describe how the new treatment could be sequenced with current treatment(s), if appropriate.
- In your opinion, in the event that the therapy under review becomes available for funding in your jurisdiction, would the new treatment be a replacement of current treatment(s) or another option?

Currently, CD19+ CAR-T would be considered standard of care in patients who are no longer eligible for curative treatment (ie beyond second-line therapy). In patients eligible for additional aggressive treatment strategies, this would clearly become a new standard in the palliative setting, given the potential for long-term disease control. It is very likely that this would displace potential allo-SCT in this setting given the favourable results in terms of disease control and lack of meaningful late effects given current follow-up.

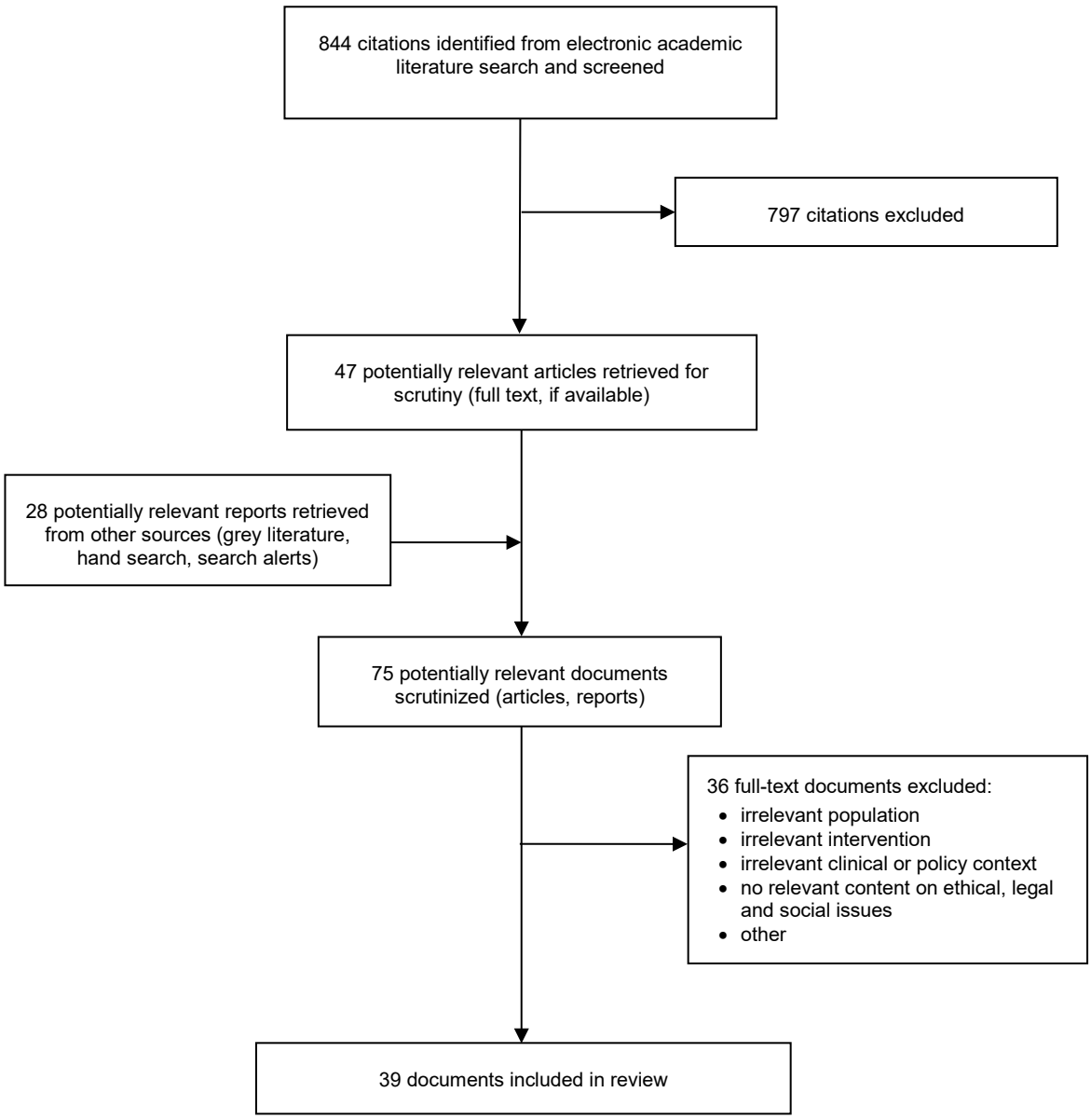
Randomized controlled trials will determine the potential superiority of CAR-T in the second-line curative setting. CD19+ CAR-T cells could replace salvage chemotherapy and ASCT if this generation of clinical trials is positive.

3.5 Companion Diagnostic Testing

- If companion diagnostic testing is required for the new therapy, is the test available in your jurisdiction? Is it funded by your jurisdiction? What concerns, if any, do you have on the test and turnaround time for test results? Are there specific considerations to a testing algorithm that you think would be important to share with CADTH's Health Technology Expert Review Panel?

In theory, CD19 CAR-T cell therapy requires expression of CD19 on tumour – this is a routine study that can be performed on tissue using immunohistochemistry. However, this has not been a routine inclusion/exclusion criterion for the trials given the lack of sensitivity for CD19 expression using immunohistochemistry. Thus, while it would be very reasonable to require demonstration of the target on archival tissue this is not routinely practice. As other anti-CD19-based therapy is not routine, it is highly unlikely that CD19 negative disease would arise through standard therapy.

Appendix 5: Study Selection Flow Diagram — Ethics Review



Appendix 6: Table of Included Publications — Ethics Review

First Author (Publication Year), Country	Publication Type	Topic(s)	Key Claims and Findings
Atilla (2018), Turkey[12]	Review	CAR T-cell therapy as experimental therapy — hype Balancing safety and effectiveness Access: Location of treatment sites Cost: Affordability Informed choice	Discusses general ethical issues related to safety and unknown risks, access to therapy limited by available treatment sites, affordability to health systems and patients, and post-market surveillance of cellular therapies, including CAR T-cell therapy. Notes specific ethical issues related to clinical trials, including patient and data confidentiality, consent, decisional vulnerability of patients with severe illness and few options, and importance of honest communication about the benefits and risk of treatment to mitigate hype.
Beaupierre (2019), US[28]	Review	Access: Location of treatment sites Informed choice	Describes practices for managing and coordinating care for patients who are receiving CAR T-cell therapy across multiple care settings. Discusses strategies across six stages of therapy, from consultation and workup to long-term follow-up, with an emphasis on nursing. Owing to the centralized and specialized nature of delivery sites, notes the importance of continued and concerted coordination between care providers and settings, as well as patient education, to ensure safe and effective care.
Brigand (2018), Belguim[41]	Report	Cost: System-level affordability	Asks at what price CAR T-cell therapies, which are effective and available for patients without additional options, warrant public coverage in Europe. Takes issue with the “value-based pricing” model, which determines price based on the treatment’s value to patient outcomes and society, noting that the value provided by a treatment depends on inputs and that the data used by manufacturers is not publicly available. Discusses the impact of public funding for research that has led to the development of CAR T-cell technologies and that the decision to patent CAR T cells is neglecting “public involvement and the need for affordable medicines.” Notes the debate over CAR T cells will be highly politicized given their therapeutic potential, the lack of alternatives for patients, public pressure for timely access, and budgetary constraints and considerations of sustainability.

First Author (Publication Year), Country	Publication Type	Topic(s)	Key Claims and Findings
			Recommends making CAR T-cell therapy prices "more understandable" and ensuring "more transparency in pricing," including through intergovernmental collaboration by payers on increasing transparency, HTA efforts, and price negotiations.
Buitrago (2019), US[22]	Review	Balancing safety and effectiveness Beyond clinical harms and benefits	Notes that there is limited survivorship data for adults receiving CAR T-cell therapy, but as the survivor population grows, information about the physiologic and psychosocial needs of adult survivors should be gathered to inform interventions. In addition to incurring physical side effects, survivors may face anxiety associated with recurrence. Moreover, caregivers, family members, and children may require support and education, and can help psychosocial aspects of recovery. Survivors and caregivers may also face financial burdens associated with the costs of treatment, travel, lodging, and time off work, which can contribute to further anxiety or stress.
Carvalho (2017), Portugal[19]	Review	Cost: Barrier to patient access, affordability	Identifies inequities in patient access related to patient-level affordability. Suggests current high costs may be offset by potential long-term benefits, resulting in reduced health system utilization.
Cossu (2018), UK[13]	Primary research and review; normative analysis	Balancing safety and effectiveness Informed choice about treatment options Beyond clinical harms and benefits Policy implications	Raises concern about how hope of cure and false promises may exacerbate patient vulnerability. Underlines the importance of informed consent and efforts to support patient autonomy to make life choices and, at the same time, avoiding unjustified paternalism. Argues that consideration of benefits and risk are not limited to direct benefits/risks at the patient level, but also apply to broader population-level considerations, including distributive justice, opportunity costs associated with providing these benefits, and trust in health care systems. Emphasizes principles of procedural justice (e.g., transparency) to protect patients, maintain public trust, and enable social licence for emerging technologies.
Couzin-Frankel (2017), US[31]	Editorial	Access: Constraints on supply, patient selection	Addresses ethical issues associated with supply of CAR T-cell therapy, including how to fairly allocate supply and what factors should be considered in allocating resources. Notes potential impact on supply of "off-label" use. Identifies difficulty of balancing efforts to meet the sickest patients' needs and keep other patients stable enough to be eligible for treatment. Raises question about age-

First Author (Publication Year), Country	Publication Type	Topic(s)	Key Claims and Findings
			based selection criteria ("If Novartis's product is approved for leukemia patients up to 28 years old, say, and you have a 28.1-year-old, does that mean you can't treat them?").
Darrow (2015), US[43]	Primary research; normative analysis	Informed choice about treatment options	Addresses difficulty of respecting patient autonomy and supporting informed consent in the context of evidentiary uncertainty and information asymmetries associated with investigational drugs. Cautions against paternalism because patients are rational actors capable of making decisions based on their own risk–benefit thresholds. Argues for greater deference to patient autonomy when the stakes are highest (i.e., imminent or likely death).
de Lima Lopes (2018), US[30]	Opinion	Access: Barriers based on cost to patients and time delays Cost: Affordability, transparency, clinician role	Discusses cost of CAR T-cell therapy as an ethical issue with a number of dimensions: the high cost of CAR T-cell therapy potentially justified if it offers a cure; affordability (including for total costs, i.e., hospital, supportive, and outpatient treatment) as a potential barrier to access for patients; duration of reimbursement approval processes as a potential barrier to access for patients whose health status declines to point of clinical ineligibility while waiting for approval; and the need for greater transparency about pricing given public investment in research and development. Asserts that physicians should be aware of costs in clinical decision-making to help mitigate inefficient or wasteful health care spending.
Ertl (2011), US[44]	Commentary	CAR T-cell therapy as experimental therapy	Describes ethical dilemma in balancing societal benefit in knowledge creation and the potential for therapeutic benefit in design of early phase research involving CAR T cells. Addresses challenges associated with the accurate disclosure of risks and benefits and appropriate informed consent involving seriously ill patient–subjects with few therapeutic options.
Fernandez (2017), Canada[38]	Blog — ethical analysis	CAR T-cell therapy as experimental therapy — hype Informed choice Cost: Patient- and system-level affordability	Identifies two key ethical challenges related to CAR T-cell therapy: over-promising the benefits of a new therapy, and justice. Argues for caution in discussing benefits and risks, including lack of evidence on long-term effects, with patients and caregivers faced with limited treatment options. Raises concerns about the financial implications of CAR T-cell therapy for patients and caregivers, opportunity costs of expanded use beyond current indications, and competing health priorities over the short and long term.

First Author (Publication Year), Country	Publication Type	Topic(s)	Key Claims and Findings
Gyawali (2018), Japan[49]	Primary research; normative analysis	Informed choice about treatment options	Asserts the importance of transparent reporting of harms in cancer trials and cautions against using subjective language such as "acceptable," "manageable," "favourable," or "tolerable" to describe risk–benefit profiles from trials as the experience of therapy and side effects is individual to the patient. Additionally, general concepts, especially when used in place of transparently reported risk profiles, may give the impression of a better risk–benefit profile than supported by evidence. Recommends asking patients about acceptability and quality of life while noting the limitations of these approaches as well.
Gumer (2018), US[29]	News	Cost: Patient-level affordability	Identifies that financial burdens on patients may exacerbate existing inequities in ability to pay for health care.
Hammer (2016), US[118]	Case analysis	CAR T-cell as experimental therapy — research ethics paradigm	Identifies the Belmont principles (respect for persons, beneficence, and justice) as relevant ethical tenets for participation in gene therapy clinical trials and studies. Raises concern about whether marginalized people with poor access to health care will have a chance to benefit and whether some patients will be better informed than others based on education level.
Hayden (2018), US[54]	Primary research — legal analysis	Legal considerations	Describes trend of individuals refusing to contribute biological materials for research purposes without monetary compensation.
Hernandez (2018), US[39]	Primary research — economic analysis	Cost	Estimates total costs of CAR T-cell therapies, including axicabtagene ciloleucel. Notes that ancillary costs associated with treatment compare with or exceed costs of many expensive medications, and that an outcomes-based pricing model does not reimburse ancillary costs should treatment fail. Recommends more accurate assessments of total drug costs to understand the treatment's true costs and value.
Holmes (2018), US[25]	Interview	Access: Location of treatment centres	Describes constraints on access due to limited number of treatment centres, which may be justified on grounds of ensuring appropriate management of toxicity but has implications for patient access.
Imbach (2018), US[21]	Primary research — normative analysis	Balancing safety and effectiveness Access: Geographic constraints Cost	Identifies ethical issues associated with CAR T-cell therapy across the various stages of development and implementation — from pre-clinical to post-market. Claims that minimizing harm to research participants and patients is a challenge that cuts across various stages of the therapeutic life cycle. Identifies challenge of managing

First Author (Publication Year), Country	Publication Type	Topic(s)	Key Claims and Findings
		Policy implications	patient and public expectations and minimizing hype, which involves balancing the benefits of excitement (e.g., increased awareness and funding) with the actual uncertainty around the long-term effectiveness. Raises concern about potential exacerbation of health inequities based on the cost of treatment and location of treatment centres. Underlines importance of studying safety and effectiveness in order to preserve public trust.
Institute for Clinical and Economic Review (2018), US[18]	Technology Assessment Report – patient perspectives	Balancing safety and effectiveness Cost Informed choice about treatment options Beyond clinical harms and benefits	Reports findings of consultation with patients and caregivers about tisagenlecleucel and axicabtagene ciloleucel. Describes how patients with no other options hoped therapy would offer a cure and perceived it to be less toxic than alternative treatments; how patients also expressed fear of the unknown related to limited evidence, not knowing if they would experience a serious side effect; and uncertainty associated with long-term side effects (especially neurological). Stresses the importance of detailed patient education regarding what to expect. Patients incurred various non-medical costs associated with treatment (accommodation, taking time off work, etc.) "but they felt that they had no choice; parents, in particular, spoke of doing anything for their child with leukemia." Notes that both patients and caregivers experience distress associated with experiencing or witnessing severe side effects and that emotional and psychological support are required to mitigate the post-traumatic stress following treatment and the emotional toll of cancer.
Jecker (2017), US[17]	Primary research — normative analysis	CAR T-cell as experimental therapy — clinical and research ethics paradigms Access: Patient selection, age	Characterizes breakthrough therapies such as CAR T-cell therapy as existing between therapy and research. Argues that while individuals may not be entitled to receive an experimental therapy, they are entitled to a fair selection process and protection from risks. Proposes selection criteria for prioritizing clinical trial participants for CAR T-cell. Discusses additional selection criteria such as age, based on a fair innings argument. Argues that as evidence of therapeutic benefit increases, obligations of justice shift from protection from harm to ensuring fair access to benefits, which may mean modification of selection criteria.
Jecker (2017), US[119]	Blog — ethical analysis	CAR T-cell as experimental therapy — clinical and research ethics paradigms	Proposes that, with respect to breakthrough therapies, benefit should be understood as a continuum from complete uncertainty

First Author (Publication Year), Country	Publication Type	Topic(s)	Key Claims and Findings
			about benefit to clearly demonstrated benefit. Argues that as evidence of benefit increases, the ethical claim for access increases. Outlines a framework for prioritizing access along the continuum — earlier in the continuum, priority should be given to those with the greatest medical need to justify risk of participation; later in the continuum, priority should be given to those most likely to benefit on the basis of available evidence.
Jönsson (2019), Sweden, UK, Germany, France[20]	Primary research — economic and legal analysis	Balancing safety and effectiveness Cost: System-level affordability	Discusses challenges facing HTA of ATMPs, including CAR T-cell therapy in Europe. Presents recommendations to promote values-based and sustainable health care. Identifies three key challenges: uncertainty, discounting, and health outcomes and value. Evidentiary uncertainty complicates HTA and can be mitigated through evidence-generating efforts, but these are also resource-intensive and should be evaluated in terms of their incremental costs and benefits. Suggests that outcomes-based pricing contracts or performance-based risk-sharing agreements may be appropriate in such contexts and "coverage with evidence" approaches can promote post-marketing surveillance. Recommends establishing an international multidisciplinary forum to study the economic, social, and ethical implications of selecting a specific discounting rate for ATMPs, given that the choice of rate impacts the favourability of an assessment. Lower discount rates support therapies whose upfront costs are high and outcomes are in the future, as are benefits to future generations. Similarly, recommends a reconsideration of how value, especially social value beyond health gains, is assessed for ATMPs. Notes that how value is determined varies across jurisdictions, especially around the valuation of "cure" vs. wider incremental value. Some, such as the UK's National Institute for Health and Care Excellence, value quality-adjusted life-years gained at the end of life more than those at other time points on the assumption that society prioritizes treating patients at the end of life. Notes that patients may be willing to undergo high-risk treatment that offers the potential for long-term survival (referred to as the "value of hope").
Krackhardt (2018), Germany[55]	Review	Legal considerations	Describes the legal and regulatory landscape for CAR T-cell therapy in Germany and the European Union. Notes that challenges arise in

First Author (Publication Year), Country	Publication Type	Topic(s)	Key Claims and Findings
			translating innovative CAR T-cell therapy in the clinical setting as therapy is understood both as gene therapy medicinal products and cancer immunotherapies, which have different regulatory motivations associated with risks and innovation. Notes that discussions of ethical issues associated with risk–benefit assessments and costs of safety measures for innovation should include not only researchers, clinicians, and regulators but also patients, health care providers, and politicians.
Kim (2018), US[51]	Primary research — legal analysis	Legal considerations	Analyzes whether the current understandings of medical procedure exemptions and experimental use exemptions to patent infringement leave clinicians, researchers, and academic institutions who use patented therapies — such as CAR T-cell therapy — to treat patients liable for patent infringement under US law.
Kimmelman (2015), Canada[47]	Primary research — normative analysis	CAR T-cell therapy as experimental therapy Informed choice	Discusses cancer gene therapies, primarily in the context of early-stage clinical trials. Discusses ethical importance of managing public expectations about breakthrough therapies as well as participant expectations for the purpose of informed consent.
Kodish (2017), US[16]	Opinion	CAR T-cell therapy as experimental therapy	Describes CAR T-cell therapy as an example of “experimental therapy” (or alternatively, “therapeutic research”) characterized by “high risk, high reward” and “high cost” at the intersection of research and therapy.
Kuehn (2017), US[11]	News article	CAR T-cell therapy as experimental therapy Balancing safety and effectiveness Access: Constraints on supply, patient selection Cost: System-level and long-term impacts	Discusses the hope and hype surrounding CAR T-cell therapy and patient willingness to accept severe side effects (toxicities) for potential benefit. Raises a concern about the impact of production timelines on patient outcomes. Cites a physician claiming that treating patients earlier in the course of cancer may help minimize CRS. Describes systems-level impacts (e.g., insufficient intensive care unit beds if such therapies became widely available). Suggests that CAR T-cell therapy may be cost-effective and reduce future costs if it proves to be curative.
The Lancet (2018), UK[15]	Editorial	CAR T-cell as experimental therapy	Considers whether the benefits of CAR T-cell therapy, including axicabtagene ciloleucel, justify the high costs or are “a case of hype

First Author (Publication Year), Country	Publication Type	Topic(s)	Key Claims and Findings
		Balancing safety and effectiveness Cost: System-level and long-term impact	and overpromise." Identifies the lack of comparative effectiveness studies between CAR T-cell therapy and the standard of care as posing a challenge to determining the value of CAR T-cell therapy. Cites the high incidence of serious adverse events associated with axicabtagene ciloleucel as requiring long-term follow-up and cautious communication. Notes that the excitement surrounding CAR T-cell therapy may cause patients to feel "that they are missing out on a new wonder drug" and that this phenomenon may be exacerbated by international differences in eligibility criteria, despite the subjective nature of these decisions made on the basis of limited clinical evidence.
Locke (2017), US[23]	Editorial	Balancing safety and effectiveness	Discusses regulatory challenges associated with CAR T-cell therapy in the US context, including related to post-market surveillance, reimbursement, and maintenance of biological samples and data. Notes that while CAR T-cell therapy are approved on the basis of surrogate end points, confirmatory trials, clinical trials and post-marketing surveillance are required to establish morbidity, mortality, and efficacy. Asserts that the long-term viability of CAR T-cell therapies hinges on the early regulatory environment that will shape their use and implementation.
Levine (2017), US[120]	Opinion	Balancing safety and effectiveness	Argues for restraint in expanding CAR T-cell therapy "too far and too fast" given evidentiary uncertainty and risk. Recommends giving priority to meeting the needs of worst-off patients (i.e., those for whom there are no other options, not those with earlier-stage cancers who have a wider array of options), ensuring there are processes in place to address risks, developing educational materials for patients, and coordinating with patient advocacy groups on communications.
Madden (2018), US[48]	Review	CAR T-cell as experimental therapy Informed choice — patient education Beyond clinical harms and benefits	Cautions against hype and discusses the need for transparent and realistic reporting of research findings and clear, accurate, and balanced education and discussion with patients about both benefits and risks.
Maschke (2017), US[24]	Commentary	Balancing safety and effectiveness	Notes that many patients without alternative therapeutic options are willing to undergo investigational treatments that bear serious risk of

First Author (Publication Year), Country	Publication Type	Topic(s)	Key Claims and Findings
		Access: Geographic constraints Cost Informed choice about treatment options	harm. Underlines the importance of informed consent and open communication about the risk–benefit profile. Argues that post-licensing monitoring of side effects is required, especially for drugs approved through priority-review mechanisms. Also argues that access to therapy needs to be balanced with safety in determining treatment locations (i.e., those equipped to manage toxicities); however, raises concern about treatment costs (including informal costs to patients and families who must travel to receive treatment) and impact on sustainability of health care systems.
McConville (2017), US[45]	Primary research and review — empirical analysis	Informed choice Beyond clinical harms and benefits	Describes consent as ongoing process and the importance of iterative education of patients and caregivers to informed decision-making and consent. Identifies the need for appropriate education processes and materials for pediatric patients. Links education to safety and the psychological well-being of patients and caregivers. Identifies role of anticipatory guidance in reducing stress and anxiety for patients and caregivers. Underlines impact of treatment on caregivers and the requirement to address caregiver needs and concerns.
Mullin (2018), US[27]	Editorial	Access: Geographic constraints	Addresses implications of risk mitigation in limiting the number of treatment centres with expertise in managing side effects. Includes the burden on sick patients to travel long distances to receive care and the exacerbation of existing health inequities (e.g., cancer patients in rural US states have poorer health outcomes). Also notes limited supply of clinicians with relevant expertise and argues that, in the immediate term, priority should be given to safety considerations over access considerations.
Prasad (2018), US[26]	Opinion	Access: Geographic constraints, patient selection Cost	Identifies four policy considerations for tisagenlecleucel, which also apply generally to CAR T-cell therapy, including axicabtagene ciloleucel: cost and the lack of transparency around pricing; cost to payers, including total costs beyond just the therapy itself; access, including whether all eligible patients will have access given that the limited number of treatment facilities may introduce geographic constraints (including cases where patients are not stable enough to travel to treatment facilities); implications for adult patient populations for whom CAR T-associated toxicities, especially CRS, may be more difficult to manage at an advanced age.

First Author (Publication Year), Country	Publication Type	Topic(s)	Key Claims and Findings
Rial-Sebbag (2018), France[56]	Primary research — normative and legal analysis	Legal considerations	Discusses the regulatory and legal challenges in France and the European Union associated with CAR T cells as products that follow the logic of pharmaceuticals, with an emphasis on post-market surveillance for safety, and on biobanking in the context of transplants.
Seigel (2018), US[46]	Opinion	Informed choice	Discusses the role of patient advocates in promoting patient safety by informing patients and caregivers about the importance of recognizing and reporting even minor symptoms following immunotherapy. Highlights the importance of patient and caregiver education and clear communication by physicians.
Shah (2018), US[42]	Primary research — economic and regulatory analysis	Cost: System-level affordability and long-term impact	Describes challenges and opportunities for realizing values-based care models for therapies such as CAR T-cell therapy across various domains, including system capacity, standardization across institutions, diversity, and disparities in access, patient quality of life, and costs.
Sherkow (2018), US[53]	Primary research — legal analysis	Legal considerations	Analyzes challenges associated with intellectual property and surrogate licensing in particular, in the context of research and development of precision medicines.

ATMP = advanced therapy medicinal products; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; HTA = health technology assessment; vs. = versus.

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