Cost-effectiveness of Chimeric Antigen Receptor T-cell Therapy for Treating Large B-cell Lymphoma Patients in Canada

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Background/Aim: Chimeric antigen receptor (CAR) T-cell therapy is a novel cell therapy for treating hematological cancers including multiply relapsed large B-cell lymphoma in adults. Although for some patients it can produce long-term remission who would have otherwise run out of treatment options, it is very expensive, costing $373,000 U.S. dollars per patient. There are other additional hospital costs related to management of severe adverse events. The first two Health Canada approved CAR T-cell therapy products were reviewed by the Canadian Agency for Drugs and Technologies in Health (CADTH) and recommended for funding. Because CAR T-cell therapies have not been administered before in Canadian hospitals, there are certain logistical concerns with implementation that are unique.

The first aim of this thesis is to describe processes of developing CAR T-cell therapy and administering it to patients, as well as describe the challenges to implementation and considerations for long-term sustainability of cell and gene therapy in Canada. The second aim is to evaluate the cost-effectiveness of axicabtagene ciloleucel, a CAR T-cell therapy for treating adult lymphoma patients, compared to salvage chemotherapy.

Methods: A qualitative interview study was conducted with 13 CAR T-cell therapy stakeholders including scientists, clinicians, and policy-makers in Canada. Questions were asked related to CAR T-cell therapy development, treating patients, challenges to implementation, and suggestions for logistical planning at the healthcare system level.

A partitioned survival model was developed in TreeAge Pro Software from a Canadian public payer perspective. Patients with large B-cell lymphomas were modeled and their health outcomes from being treated with axicabtagene ciloleucel or salvage chemotherapy were extrapolated over a lifetime time horizon. The cost-effectiveness was evaluated by the incremental cost-effectiveness ratio.

Results: The results from the qualitative interviews were summarized into 4 main themes: novel, patient characteristics and experiences, processes from "bench to bedside", and future state of CAR T-cell therapy in Canada, including both challenges and recommendations to ensure sustainability.

The ICER generated for the cost-effectiveness analysis was $170,380 per QALY. At a willingness-to-pay threshold of $150,000 per QALY, CAR T-cell therapy is not cost-effective. There is some uncertainty in the long-term efficacy of CAR T-cell therapy and in the cost of CAR T-cell therapy.

Conclusions: Valuable perspectives from CAR T-cell therapy stakeholders on the current and future state of CAR T-cell therapy were highlighted from a Canadian perspective. In addition, a reduction in price of CAR T-cell therapy and reduced uncertainty through collection of long-term health outcomes can improve the cost-effectiveness to ensure value-for-money.

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Table of Contents

List of Figures

List of Tables

List of Abbreviations

ALL	Acute Lymphoblastic Leukemia
CADTH	Canadian Agency for Drugs and Technologies in Health
CAR	Chimeric Antigen Receptor
CEA	Cost-effectiveness analysis
COREQ	Consolidated Criteria for Conducting Qualitative Research
CRS	Cytokine Release Syndrome
DLBCL	Diffuse Large B-cell Lymphoma
FACT	Foundation of the Accreditation of Cellular Therapy
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
NICE	National Institute for Health and Care Excellence
NHL	Non-Hodgkin lymphoma
pCODR	pan Canadian Oncology Drug Review
pCPA	pan Canadian Pharmaceutical Alliance
pERC	pCODR Expert Review Committee
PMBCL	Primary mediastinal B-cell lymphoma
PSM	Partitioned Survival Model
QALY	Quality-adjusted life year
SCT	Stem cell transplant
U.S.	United States

CHAPTER 1

Introduction and Background

1.1 Large B-cell Lymphomas

Large B-cell lymphomas are a type of non-Hodgkin lymphoma in which tumours develop from the rapid production of abnormal B-lymphocytes, a type of white blood cell, in the lymph nodes.[1,2] Worldwide, Diffuse Large B-cell Lymphoma (DLBCL) is the most common type of NHL, accounting for 30 to 40 percent of cases.[1,2] DLBCL is characterized by lymphocytes that are larger in size than normal lymphocytes, and arranged in a diffuse pattern. Other subtypes of DLBCL include primary mediastinal B-cell lymphoma (PMBCL) and DLBCL transformed follicular lymphoma (TFL). These types of lymphomas often present quite aggressively as advanced stage disease.[1,2]

In 2017, it was estimated that there were 8,300 new cases and 2,700 deaths from NHL in Canada.[20] In 2019, it is estimated that there will be 10,000 new cases and 2,700 deaths from NHL. Although DLBCL can occur at any age, most people are diagnosed in their mid sixties.[3] In Canada, the five-year net survival rate for non-Hodgkin lymphoma is 68%, indicating that about 68% of people diagnosed with NHL will survive for at least 5 years, although this varies by prognostic factors such as age and stage of disease.[3]

1.2 Treatment Guidelines and Typical Patient Prognosis

Most patients with DLBCL (approximately 60%) are successfully treated with chemo-immunotherapy as a first line therapy, and the remaining (30 to 40%) will likely experience a relapse and require second-line therapy.[2,4-5] Upon failure of first line treatment, patients will often receive a second chemo-immunotherapy.[5] If patients respond effectively to chemotherapy but their cancer recurs, they may go on to receive high dose chemotherapy followed by a stem cell transplant.[6-8]

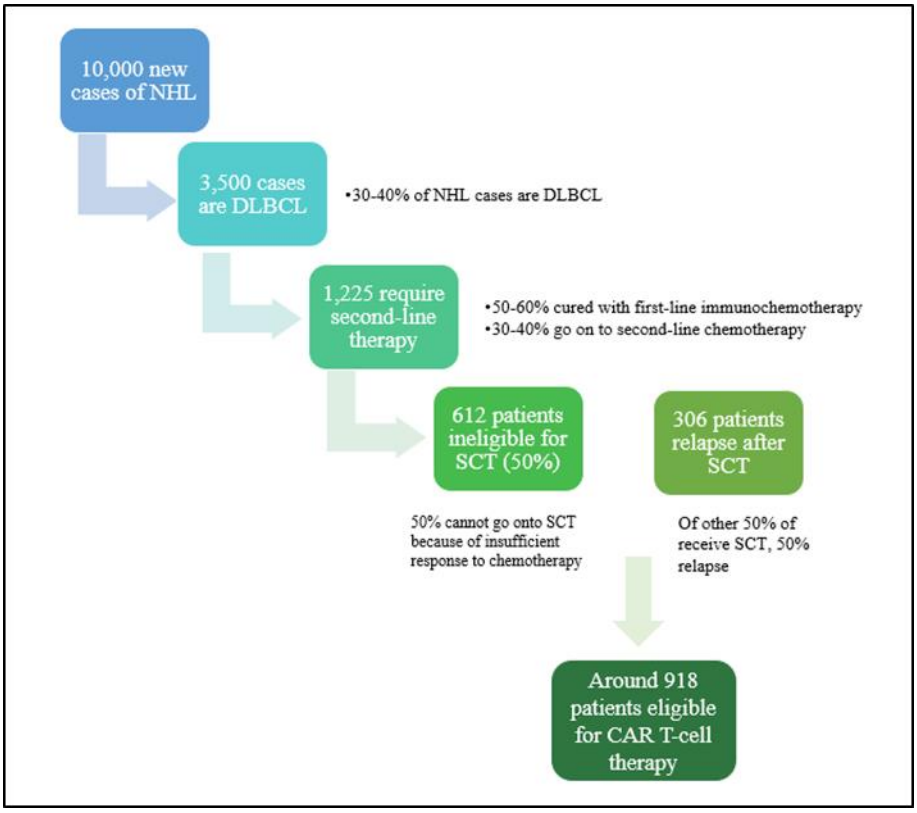
Approximately half of patients who receive subsequent chemotherapy will fail to achieve a response sufficient to proceed to autologous hematopoietic cell transplantation, therefore the other 50% of patients

treated with second-line chemotherapy will proceed to a stem-cell transplant.[8] About half of patients who undergo a stem-cell transplant will relapse.[9] Patients who do not respond effectively to these treatments, experience resistance to chemotherapy, or relapse again following a stem-cell transplant have very few options and a poor prognosis.[7]

The median overall survival reported in a retrospective study of 636 patients receiving salvage chemotherapy with aggressive B-cell lymphoma that was primary refractory or relapsed less than 12 months after autologous transplant was about 6.3 months.[10] However, with the development of a novel gene therapy called chimeric antigen receptor (CAR) T-cell therapy, relapsed and refractory patients may be able to receive a potentially life-saving treatment and go into long-term remission.[11-12] CAR T-cell therapy is indicated for patients who have relapsed after two or more lines of therapy which include a stem-cell transplant, or patients who have refractory disease. If patients do not receive CAR T-cell therapy, they would likely only receive supportive care and stop active treatment.[6,11-12]

Based on the number of new NHL cases in 2019 and estimated proportion of those patients with DLBCL, as well as the estimated percentage of relapsed/refractory patients who were 1) refractory to chemotherapy 2) ineligible for SCT or 3) relapsed following SCT, it is estimated there could be at least 918 cases in Canada. This is based on the number on the incidence of NHL in 2019 in Canada and not the overall prevalence.

Figure 1.1 Estimated number of patients in Year 1 of CAR T-cell therapy available in Canada for adult large B-cell lymphoma patients



1.3 CAR T-cell Therapy

CAR T-cell therapy utilizes a patient's own T-cells to develop a therapy that targets a specific tumour antigen. T-cells are classified as lymphocytes (white blood cells) which have several roles in the body. These include recognizing foreign antigens and infections, activating the immune system to attack them, and producing cytokines that direct response in other immune cells.[13,14] These processes occur through the T-cell receptor, which recognizes antigens only when presented on the surface of cells bound to a major histocompatibility complex (MHC) molecule.[14] In a CAR T-cell, the T-cell receptor is replaced by a synthetic engineered receptor, which enhances the T-cell response and recognizes antigens independent of the MHC .[13] This tumour-targeted recombinant antigen receptor includes an intracellular domain involved in T-cell activation and signalling, and an extracellular domain that is specific to a target antigen.[15-16] . In large B-cell lymphomas, the target antigen is CD19. CD19 is a protein expressed in over 95% of B-cell

malignancies, referred to as CD19-postive malignancies.[15] The mechanism by which the CAR T-cell attacks cancerous cells is through elimination of CD19 expressing tumour through effector and cytolytic processes. When a CAR T-cell recognizes the target antigen, it is activated through its effector function and able to kill tumour cells through its cytolytic function.[17-18] There are several different generations of CAR T-cells, which refer to variations in the intracellular signalling domain, and they grow more complex with later generations.[14] Second or later generation CARs contain co-stimulatory domains, which improve T-cell activation and anti-tumour efficacy.[15] The two Health Canada approved products, axicabtagene ciloleucel, and tisagenlecleucel, are both second generation anti-CD19 CARs.[21]

1.4 Manufacturing CAR T and Administering it to Patients

CAR T is unique because it is highly personalized, can lead to long-term remission, and comes at a very high cost. To develop CAR T-cell therapy, a T-cell sample is required from a patient and is produced through a process called leukapheresis. Leukapheresis involves the separation of the components of white blood cells and the isolation of T-cells.[20] The T-cell sample is then sent to the drug manufacturer where it is genetically engineered to express the CD19 antigen. The CAR gene is transfected into T-cells using retroviral or lentiviral vectors. The genetically engineered cells are then grown in large numbers in a lab and the final product in frozen and sent back to treating centre.[20] Patients typically undergo lymphodepleting chemotherapy prior to the infusion of the engineered immune cells to improve the success of the therapy by reducing the number of competing lymphocytes.[15-17,20] Once the patient has received the therapy through infusion in a hospital, they must be monitored for severe side effects such as cytokine release syndrome (CRS) and neurotoxicity over the next few days to a few weeks.[11-12]

1.5 CAR T-cell Therapy Commercialized Products for Large B-cell Lymphomas

To date, two different CAR T-cell therapy products for refractory large B-cell lymphomas in adults have been approved by Health Canada. Axicabtagene ciloleucel is a therapy developed by Kite Pharma (a Gilead Sciences company) that targets the CD19 antigen. It was approved by the FDA in 2017 and by Health

Canada in early 2019.[21] The cost of axicabtagene ciloleucel is $373,000 U.S. dollars.[22] The indication for this particular CAR T-cell product is 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 (transformed follicular lymphoma, or TFL).[21] Tisagenlecleucel is another CAR T-cell therapy developed by Novartis which also targets the CD19 antigen, and is indicated for the similar adult patient population who have relapsed or refractory DLBCL after receiving at least two lines of therapy, as well as for pediatric acute lymphoblastic leukemia.[12,21] It was approved by the FDA and Health Canada and costs $475,000 U.S. dollars.[22]

For use in Canada, both therapies require the T- cell sample to be shipped to the site of the manufacturer to be genetically engineered and shipped back to the hospital site delivering the therapy.[20] The typical turnaround time from manufacturing to infusion is between two to three weeks.[11,20] For patients with relapsed/refractory disease who have not responded effectively to prior treatments, it is critical to receive this therapy in a timely manner, while maintaining stable physical health.

1.6 CAR T-cell Therapy Efficacy and Safety

Axicabtagene Ciloleucel

Axicabtagene ciloleucel, or Yescarta, is a second-generation CD19 CAR T-cell.[11] The pivotal clinical trial, ZUMA-1, enrolled 7 patients in the Phase 1 trial and 111 patients in Phase 2 with refractory DLBCL, PML, or follicular lymphoma, which was defined as progressive or stable disease as the best response to the most recent chemotherapy regimen or disease progression or relapse within 12 months after autologous stem-cell transplantation. In the Phase 2 trial, axicabtagene ciloleucel was successfully manufactured in 110 patients (99%) and 101 patients received axicabtagene ciloleucel (91%) with median time from leukapheresis to delivery of axicabtagene ciloleucel to the treating facility of 17 days.[11] Response was evaluated one month after infusion, with objective response (complete and partial response) as the primary

outcome. At the primary analysis at an median of 8.7 months of follow-up, the objective response rate was 82% and complete response rate was 54%. At the updated data cut-off at a median follow-up of 15.4 months, 42% of still patients had a response, including 40% with a complete response. At 8 months, the overall rate of survival was 52%. Common adverse events included cytokine release syndrome of 93% of patients with most cases being Grade 1 or 2 severity (81%), and neurologic events in 64% of patients, with 28% being Grade 3 or higher.[11]

Tisagenlecleucel

The Phase II JULIET trial enrolled patients with relapsed or refractory DLBCL who were ineligible for or had disease progression after autologous stem-cell transplantation. There were 111 patients were treated with tisagenlecleucel aged 18 years or older with DLBCL, and 93 patients included in the efficacy analysis of patients who had 3 months or more of follow-up or had discontinued participation in the study before 3 months. Prior to receiving the infusion, 92% of patients underwent bridging chemotherapy and 93% received lymphodepleting chemotherapy.[12]

The best overall response rate was 52%, with 40% of patients having a complete response and 12% having a partial response. The most common adverse events of any grade were cytokine release syndrome (58%), anemia (48%), pyrexia (35%), decreased neutrophil count (34%), decreased platelet count (33%), decreased white-cell count (33%), and diarrhea (32%).[12]

The most common grade 3 or 4 adverse events of special interest included cytokine release syndrome (22%), neurologic events (12%), cytopenias lasting more than 28 days (32%), infections (20%), and febrile neutropenia (14%).[12]

CAR T-cell Therapy Adverse Events

For both CAR T-cell therapy products, the most common Grade 3 or 4 adverse events included cytokine release syndrome and neurologic events. Cytokine released syndrome results from a systemic inflammatory

response characterized by fever and an elevated level of cytokines. Symptoms of cytokine release syndrome include pyrexia, hypotension, hypoxia, tachycardia.[11]

In the JULIET trial, median time from infusion to onset of symptoms of CRS of any grade was 3 days and the median duration was 7 days. Patients with CRS in the JULIET trial were treated with one or two doses of tocilizumab, as well as other treatments including supportive care, oxygen supplementation, endotracheal intubation, high-dose vasopressors and dialysis in a proportion of patients.[12]

Neurologic event symptoms can include delirium and confusion, speech disturbances, seizures and focal neurological deficits.[15] These symptoms can be treated with supportive care including glucocorticoids. In the JULIET trial, the median time to onset of neurologic events of any grade was 6 days and the median duration was 14 days.[12]

CRS and neurotoxicity are common side effects from immunotherapies that most often occur with days to two weeks of infusion. However, symptoms can range from mild to life threatening. The majority of cases are treated within a few weeks, but there is a risk that symptoms can be severe and life threatening.[11] Grade 3 or 4 CRS or neurotoxicity often requires the patient to be in the intensive care unit (ICU) for up to weeks depending on the severity. Of the patients who had CRS, 24% were admitted to the intensive care unit. During the first week post-infusion, patients are monitored closely in the hospital and while side effects are treated.[23]

Monitoring Post Infusion

After side effects have resolved, patients will likely have office visits twice a week with a clinician for 1 month followed by weekly visits for the second month, then ongoing monthly visits.[24] After treatment, many patients require monthly intravenous immunoglobulin infusions to prevent infections in patients with B-cell aplasia, which results from normal B-cell lineage cells being significantly reduced or eliminated from treatment.[14-16] The persistence of CAR T-cell therapy in the body is not well understood, however

some patients have experienced a sustained complete response to the therapy at or past 39 months following treatment even after CAR cells are no longer detectable.[25]

1.7 CAR T-cell Therapy in Drug Regulatory Landscape in Canada

In Canada, new cancer therapies must undergo several steps in the regulatory and approval process to be funded in the provinces. First, a drug must be approved by Health Canada which is based on the available safety and efficacy data in the pivotal clinical trial. After a drug or therapy receives a Notice of Compliance (NOC) from Health Canada, it will be reviewed by the Canadian Agency for Drugs and Technologies in Health (CADTH). Typically, the pan Canadian Oncology Drug Review (pCODR) branch of CADTH reviews the clinical evidence, cost-effectiveness, patient perspectives and feasibility of new cancer drugs to inform a recommendation made by the pCODR Expert Review Committee (pERC) about whether the provinces should fund the therapy for patients. After a recommendation is issued, the pan Canadian Pharmaceutical Alliance (pCPA) works to negotiate the price with the drug manufacturer, and each province ultimately decides if they will fund the therapy for patients.[26] The two CAR T-cell therapies were approved by Health Canada based on efficacy and safety data from single-arm trials showing a high percentage of complete responses, and then reviewed by CADTH. Because of the unique features of CAR T-cell therapy, it was reviewed through the health technology assessment process for medical devices and clinical interventions rather than through pCODR.[27] CADTH's approach was to evaluate the clinical evidence, and cost-effectiveness in addition to ethical and legal considerations with adoption in Canada and summarize the findings in an "Optimal Use Report". Currently, the Health Canada approved CAR T-cell therapy products are not yet widely funded for Canadians and administered in Canadian hospitals except for in special circumstances. The reports confirmed that there is a clinical benefit from the therapies and some of the unique regulatory, reimbursement and implementation issues were highlighted. [28,29] CADTH recommended that the therapies be funded with certain conditions to be met.

1.8 Growth of cell and gene therapies

There has been tremendous growth of the number of clinical trials in the CAR T-cell therapy space. At the end of 2016 there were 220 documented CAR T-cell clinical trials, and this number continues to grow.[30] Based on search of ClinicalTrials.gov, there were over 500 ongoing, completed or unknown status clinical trials (Phase I to Phase IV) related to CAR T-cell therapy.[31] With the first two CAR T-cell therapies undergoing the regulatory process in the past two years, government and regulatory agencies have adapted their processes to fit the unique and novel features of this therapy.[28,29] The majority of clinical trials with CAR T-cell therapy are for treating hematological cancers, followed by solid tumours and rare diseases.[30] It is expected that there will be more personalized and high cost treatments will be in the regulatory and market access phase as medicine advances and CAR T-cell therapy will pave the way for others in the future.

1.9 Knowledge Gap and Thesis Objectives:

There are two important knowledge gaps in the drug current reimbursement context in Canada that will be addressed in this thesis. The first is that the capacity of the health care system to support the implementation of CAR T-cell therapy Canada is currently unknown. In addition, challenges and barriers associated with implementation of regenerative medicines and feasibility of implementation are poorly understood despite the momentum that CAR T-cell therapy has gained in the last few years in terms of clinical research. The research conducted will provide a better understanding of the current landscape of CAR T-cell therapy specific to Canada and the unique challenges the country faces with adoption and implementation.

The second knowledge gap is that a cost-effectiveness analysis of CAR T-cell therapy for treating adult patients with large B-cell lymphomas in a Canadian context has not been published in a journal for research intent. There is however a Canadian economic evaluation of tisagenlecleucel in pediatric patients with acute lymphoblastic leukemia.[32] In 2019, CADTH published the findings from their reviews of axicabtagene ciloleucel and tisagenlecleucel for treating adult patients with large b-cell lymphomas, with the caveat that

certain parts of the data supporting the economic analyses are redacted due to confidentiality with the drug manufacturers. The conducted economic evaluation will contribute to a health technology assessment (HTA) of CAR T-cell therapy in a Canadian context and can be used by decision-makers in the drug reimbursement space.

1.10 Objectives

There are 2 main objectives of this thesis.

1. Conduct qualitative interviews to understand processes of developing CAR T-cell therapy and administering it to patients and identify challenges to developing and delivering CAR T-cell therapy in Canada.
2. Develop an economic model for CAR T-cell therapy for treatment of adult patients with large B-cell lymphoma to support decision-making regarding the adoption of this therapy in Canada.
    a. Integrate all relevant evidence including effectiveness, safety, and costs
    b. Project the health and economic burden.
    c. Perform uncertainty analyses and assess the impact on the results.

There is limited literature available about the current and future state of regenerative medicine, specifically CAR T-cell therapy in Canada. Determining barriers to implementation and system capacity are important to the understanding of the context of where CAR T-cell therapy fits in the bigger picture. A Canadian qualitative interview study on this topic is novel and has not been completed to date.
To determine whether this therapy is a feasible option for certain Canadian patients, it is critical to evaluate the cost-effectiveness and the overall impact on the healthcare system. To date, a cost-effectiveness analysis for axicabtagene ciloleucel in the adult aggressive lymphoma population has not been conducted in a Canadian context. The results will provide an evidence-based assessment of the projected health and economic burden that CAR T-cell therapy will have in Canada. The proposed economic model will integrate evidence of effectiveness, safety, cost, and patient and public preferences

to support decision-making regarding CAR T-cell therapy treatment in the future. Results of this research will provide an overview of the CAR T-cell therapy in a Canadian healthcare system context, and a cost-effectiveness analysis of CAR T-cell therapy in patients with large B-cell lymphomas from a Canadian perspective.

Chapter 1 will address the first objective and describe the qualitative interview study that was conducted. Chapter 1 will give an overview of why understanding the processes of developing CAR T-cell therapy and administering it to patients from the perspectives of scientists and clinicians in Canada is important. The methods for recruiting participants for the study, interviewing them, and analyzing the qualitative data will be described. Lastly, the results of the qualitative study will be described through the main themes that arose related to the study objectives.

Chapter 2 will give an overview of economic evaluations as part of health technology assessments to inform decision-making around funding new drugs. The methods for conducting a cost-effectiveness analysis (CEA) of axicabtagene ciloleucel compared to salvage chemotherapy in adult patients with large b-cell lymphomas will described in detail, and the results of the base-case analysis will follow. The results from a probabilistic sensitivity analysis as well as one-way sensitivity analyses will be shared.

CHAPTER 2

Qualitative Study

2.1 Introduction

Certain cell and gene therapies are considered disruptive to the healthcare system because they are highly personalized, resource intensive, and very costly per patient. With a number of these therapies recently evaluated by policy-makers in Canada and recommended for funding, the anticipated impact on current healthcare system capacity is great, requiring hospitals and healthcare professionals with specialized skills to develop and deliver them effectively. In Canada, CADTH conducts reviews of new drugs, clinical interventions, or health technologies, and makes funding recommendations based on four domains: clinical evidence, cost-effectiveness, patient perspectives, and feasibility of implementation.[33] Chimeric antigen receptor (CAR) T-cell therapy is one of the first disruptive interventions to undergo the regulatory approval process in Canada and therefore is not well understood in this context. As discussed in Chapter 1, there are currently two CAR T-cell therapy products that have been recommended for funding in the provinces by CADTH, tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta). The processes of manufacturing CAR T-cell therapy and administering it to patients are unique and have not been described qualitatively through views of key stakeholders in a Canadian setting. Although CADTH has published some ethical and implementation challenges of CAR T-cell therapies identified by stakeholders in reports[34-35], barriers to the adoption of CAR T-cell therapy in the healthcare system have not been well documented or described in a Canadian context.[38,39] With more therapies of this nature being developed and undergoing clinical trials, it is important to understand current barriers to the adoption and implementation of these therapies in the Canadian healthcare system. Qualitative analyses help inform healthcare policy by "clarifying the interplay between stakeholders, health systems and context." In addition, they help us to understand values and preferences of individuals and assess the acceptability and feasibility of health interventions.[36]

The collective perspectives of CAR T stakeholders including scientists and researchers, clinicians, policy-makers and regulatory agencies have yet to be described in this context. The purpose of this study was to gather qualitative data through interviews with important stakeholders to understand the processes of developing CAR T-cell therapy and delivering it to patients, and understand the challenges to the widespread adoption of CAR T-cell therapy in the healthcare system.

2.2 Methods

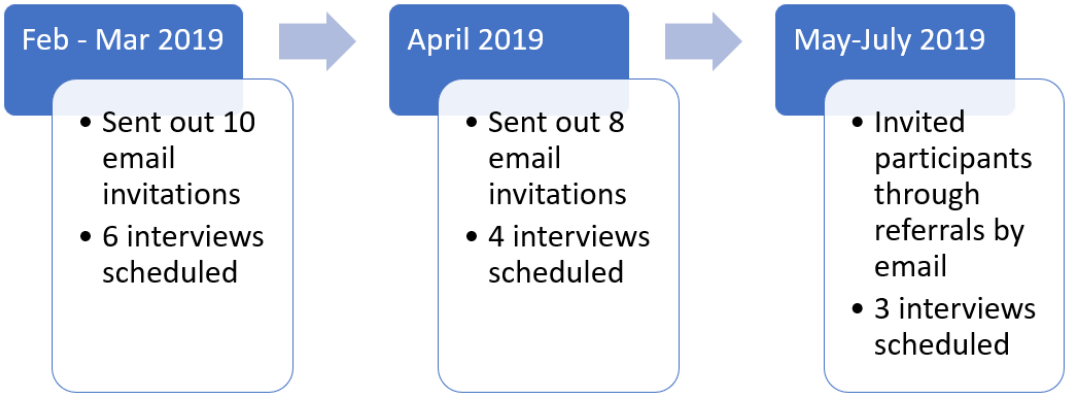
This study was approved by the University of Waterloo Research Ethics Board prior to conducting research. The consolidated criteria for conducting qualitative research (COREQ) checklist was used for reporting results.[39] Interview questions were designed to address the purpose of the study and were approved in January 2019. The initial interview questions were revised to add additional questions at two different points. Questions were designed for the three different target participant groups. These included: scientists involved in CAR T manufacturing, clinicians who treat pediatric or adult hematological cancers, and policy makers who work in regulation of pharmaceuticals in Canada. Semi-structured interview questions were developed to learn about the specific processes of developing CAR T-cell therapy and administering it to patients, the patient experience, and the processes of drug regulatory approval. Open ended questions were also developed to understand the views of participants on challenges to implementation. Depending on the participant's role they were asked semi-structured questions most relevant to them as well as all open-ended opinion questions. Questions were adjusted for policy-makers because of their unique expertise in the drug regulatory space. Appendix B1 for the full set of interview questions.

2.3 Recruitment

Participants were recruited using a combination of purposive sampling and snowball sampling and were initially recruited because of their known role in CAR T-cell related projects. During interviews, the participants were asked if they could refer suitable interview candidates and in some cases these individuals were contacted by the researcher. An initial invitation email was sent out in February 2019 to 10 individuals

with four interview confirmations. A reminder email was sent in March to the other 6 people and two more interviews were confirmed. A second round of invitation emails were sent in April to 8 more individuals resulting in four confirmed participants. Emails were sent out three more times in May, June, and July, based on referrals and other known CAR T stakeholders who were not initially contacted. 3 more interviews were conducted in this time. After participants confirmed interest in participating, an interview consent form was sent out to be signed and returned prior to the set interview date. The consent form can be found in Appendix B2. The interview questions were sent out ahead of time so that participants given time to prepare answers as some questions required technical responses. Thirteen interviews in total were conducted between March and July 2019.

Figure 2.1. Interview participant recruitment



2.4 Interviews

One-on-one semi-structured interviews were conducted by video call using Zoom or by phone with audio only. Interviews were scheduled for 1 hour and were between 30 minutes and 1 hour in length. Participants were notified that they would not be personally identified and only their perspectives would be shared. Interviews were recorded using Zoom when this platform was used or with a recording device if by phone. Participants were asked a set of questions most relevant to their field: scientist, clinician, or policy-maker. Probing and follow-up questions were asked by the interviewer to encourage more detailed responses. After

role-specific questions were asked, participants were asked open-ended questions about perceived challenges to the adoption of CAR T-cell therapy, potential changes in the healthcare system, and broadly why CAR T-cell therapy is unique. Interviews were coded throughout the interview process to determine when the saturation of ideas and themes was reached. Interviews were stopped after saturation was reached. This occurred after 13 interviews.

2.5 Analysis

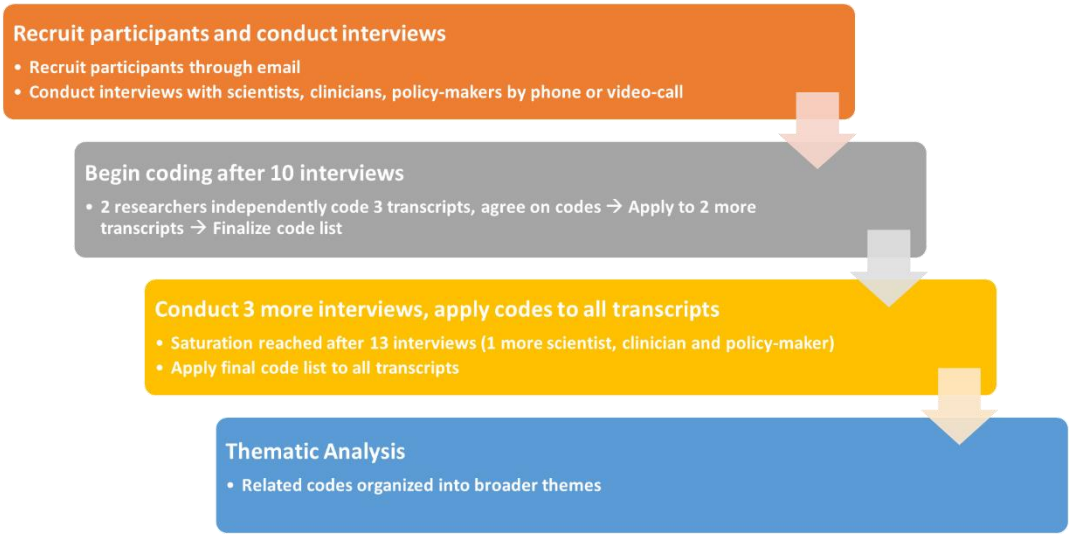
Each interview was transcribed using a transcription service and each participant was given a unique identifier using a number and their role in the study as a scientist, clinician or policy-maker. Data analysis was completed in four stages: **1) Independent coding by 2 researchers to reduce bias.** The interviewer and another researcher independently coded 3 transcripts of three different types of participants and met to refine codes. Another researcher was consulted to resolve differences in coding schemes. **2) Agreement on codes and applying to new transcripts.** The 2 researchers agreed on a set of common codes and then applied these codes to two more transcripts of the three different participant groups. **3) Finalize codes and apply to all transcripts.** The two researchers then defined additional codes and finalized the list of codes. This set of codes was then applied to all the transcripts using Nvivo qualitative data analysis software. 4) **Thematic analysis.** Related codes were organized into broader themes.

Deductive coding was used when participants were directly asked questions about certain processes and therefore organized in this manner (Eg. Manufacturing process). Inductive coding was used to understand responses to open-ended questions and to allow unanticipated themes emerge. After codes were applied to all transcripts, the codes were organized into a matrix and a set of themes was generated. Themes were created with sub categories aligning with the codes that were applied.

After ten interviews were conducted, the researchers began qualitative analysis and found that saturation was reached through the reiteration of ideas in interviews. Saturation was determined through the repetition of ideas and themes in the developed code categories.[40-41] When no new codes or themes were developed

after conducting 10 interviews, it was determined that saturation was reached. At this point, the research questions were able to be answered.[40-41] 3 more interviews were conducted after this to fill in any gaps identified by the primary researcher and to confirm saturation had been reached. Adding additional participants did not result in new themes but did help to clarify processes and timelines described for developing CAR T-cell therapy and administering it to patients and showed that there was consistency in answers about challenges to implementation and suggestions for ensuring long-term sustainability of CAR T-cell therapy across the three different participant groups.

Figure 2.2. Interview and analysis process



2.6 Participants

The sample of participants included 3 Scientists/Researchers, 5 Clinicians in hematology, and 5 policy makers in the drug regulatory space. All participants were Canadian-based, and their locations were recorded. Participants identified as either male or female. Participants were given a unique identifier based on their role with the prefix C for clinician, P for policy-maker, and S for Scientist followed by a number assigned by the researcher.

2.7 Results

Four key themes were identified through qualitative analysis:

- **Novel:** CAR T-cell therapy is novel in many ways; its unique mechanism of action as a gene therapy, it is highly personalized, it has a high per patient upfront cost, it can lead to long-term survival and remission in patients, and requires significant hospital resources. These characteristics make CAR T-cell therapy difficult to classify as a typical drug, but rather a complex clinical intervention.
- **Patient characteristics and experiences:** This theme includes: characteristics of patients who are eligible to receive CAR T-cell therapy based on the Health Canada approved indications, the impact of CAR T on patients, the current unmet need for patients who have not been successfully treated with previous lines of therapy, and why equitable access to CAR T-cell therapy for patients across Canada needs to be considered.
- **Processes from "bench-to-bedside"**: There are specific processes and requirements to: effectively manufacture a CAR T product for each individual patient, prepare the patient to receive treatment, transport the product to the treating facility, and administer the therapy to the patient in a hospital.
- **Future state of CAR T in Canada**: This theme is defined as: current barriers and challenges to the implementation of CAR T-cell therapy in the healthcare system, suggestions and predictions for long-term sustainability of CAR T, ways to enhance and improve existing healthcare programs and address current barriers, and planning logistics of implementation of CAR T across Canada.

Novel:

When asked to describe CAR T-cell therapy in their own words or about why it is unique, participants often described CAR T-cell therapy as difficult to classify because it is more than just a drug. One participant said, "*CAR T-cell therapy, at least the first two that have come through for review, have been disruptive*

innovators. In so far as they provide options, fundamentally new ways of treating particular indications. They're introduced and delivered in a way that is different from the kind of treatments(…) in terms of the complexity. So it's not a drug." Another participant stated *"Well it's unique because it's really a game changer, that's one thing. Second of all it's completely different in terms of it's not a drug, at least not as we see it presently. It's a cellular therapy, it's got its whole set of complications and its got a significant cost. It needs special expertise in terms of manufacturing."*

CAR T-cell therapy was also described by participants as extremely expensive and highly personalized. In addition, participants stated that CAR T-cell therapy offers patients a potentially curative and life-saving treatment option where otherwise patients would receive salvage chemotherapy or palliative care, as the current Health Canada approved indications are for patients who are relapsed or refractory to two or more lines of therapy. When asked about the most important benefits of CAR T-cell therapy, one clinician stated *"It's the only chance at cure, or at complete responses. So I think it has the ability to prolong life which is what the current regimens for relapsed or refractory disease don't have,"* and another clinician stated, *"I think it's definitely a high priority, based on the emerging evidence thus far and that these patients really had the ... the only treatments for these patients before was really palliative care. This is certainly providing ... the evidence that has come out of the typical trials certainly shows that this therapy is very effective for certain patients"*

CAR T-cell therapy was also described by participants as novel in terms of the infrastructure and resources required to effectively deliver CAR T, and that it poses a unique challenge with ensuring equitable access across Canada with CAR T requiring such a specialized expertise to develop and deliver. Policy makers emphasized that it will be a challenge to ensure patients across the country can get access to this therapy due to the specialized resources and personnel required. They felt that not every province would be able to deliver the therapy, therefore it was important to consider how patients across Canada could access CAR T-cell therapy equitably. On equity, a participant stated, *"there have been a lot of discussions around equity, the fact that there really isn't. Even if the drug was available and cheap, the access is a different*

issue because of the fact that... because of how it's supposed to be delivered, because of expertise required, because of the infrastructure that's required."

Although many participants commented on CAR T-cell therapy being novel in some way, participants also recognized that the complexity of delivering CAR T-cell therapy equitably is similar to a bone marrow transplant, which has set a precedent for CAR T-cell therapy. Participants felt that CAR T-cell therapy is similar in terms of the resources required in comparison to some existing interventions, with one participant stating, *"It's more similar to administering stem cell therapy where it's kind of a stem cell transfer versus administering chemo."*

Patient characteristics and experiences

Clinicians were asked to describe patients who would be eligible to receive CAR T-cell therapy based on the current Health Canada approved indications and their general characteristics in their own words. The current approved indications are for pediatric and young adults with acute lymphoblastic leukemia (ALL) who are refractory, have relapsed after allogenic stem cell transplant (SCT) or are otherwise ineligible for SCT, or have experienced second or later relapse; and for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. Participants indicated that these patients do not have other treatment options and a poor prognosis. One clinician stated, "*For refractory ALL, it actually is causes disease remission and for refractory lymphoma, likewise. That's kind of a big important thing. It meets an unmet need*." Clinicians described patients as very sick but must be physically well enough to survive until the CAR T-cell manufacturing process of a few weeks is completed to receive the therapy. One participant said, *"You have to make sure that the patient can ... these very sick patients can withstand that timeline, in order to create therapy for them, in order to be able to be well enough to receive that therapy."*

Patients must also be able to provide a sufficient cell sample for the CAR T-cell product to be developed from. During the time while the therapy is being manufactured and the patient is waiting, clinicians

explained that patients would be treated with chemotherapy in the weeks leading up to the infusion. One clinician's response summarized this, stating, *"The challenge is to just give them just enough chemotherapy to keep them well, but not enough that you make them sick and land them in the hospital or get them and result in an infection, because that all delays getting to the CAR T-cells."*

After being infused with CAR T-cell therapy, which was described as a straightforward inpatient procedure, patients are monitored for side effects. Clinicians discussed two common side effects that can be life threatening and require immediate treatment: CRS and neurotoxicity, which occurred in most of the patients in the pivotal clinical trials for the two Health Canada approved CAR T-cell products. When summarizing these adverse events, one clinician said, *"…It all depends on what it is. If we're talking about, let's say, cytokine release syndrome. I said 80% develop it. Then it depends what kind of degree you have. If you have a grade 1, if you just have a fever, this is something that, yes, you would admit the patient but just to a regular ward. If that's all they have then that's it. If they have higher degrees of CRS then they may need ICU care, they may need (vaso)pressors, they may need to be on the ventilator, they may need dialysis…Neurotoxicity, same thing. Sometimes they just get hallucinations... but that is something you just watch and you don't do much. Again, that would be a regular ward kind of scenario. We have seen patients who become completely encephalopathic and need ICU care. That's the other extreme of that. Again, it depends on the severity of the symptoms."*

These side effects can occur within days of the infusion and last from days to almost two weeks, with one participant reporting, *"systematic reviews say it's about five or seven days with CRS and seven to twelve days for neurotoxicity"*. Clinicians noted that depending on the severity of the symptoms, some patients will need to be in the intensive care unit (ICU) short-term, around "30 to 40%" of patients.

Clinicians indicated that patients would be heavily monitored during the first week after the infusion as an inpatient and treated for side effects if they occur. After the first week of heavy monitoring, clinicians would likely see the patient every week for a few weeks after the patient returns home, and monthly for a few months. One clinician stated *"Well if the risk-period for CRS and neurotoxicity is over, so if they haven't*

developed that, then I'd say 10 days they'd probably go home. Their ongoing follow-up, remember these are our patients with active malignant would be once or twice a week in clinic, blood count checks, like that, for the rest of the month, and then less frequently if they're doing well."

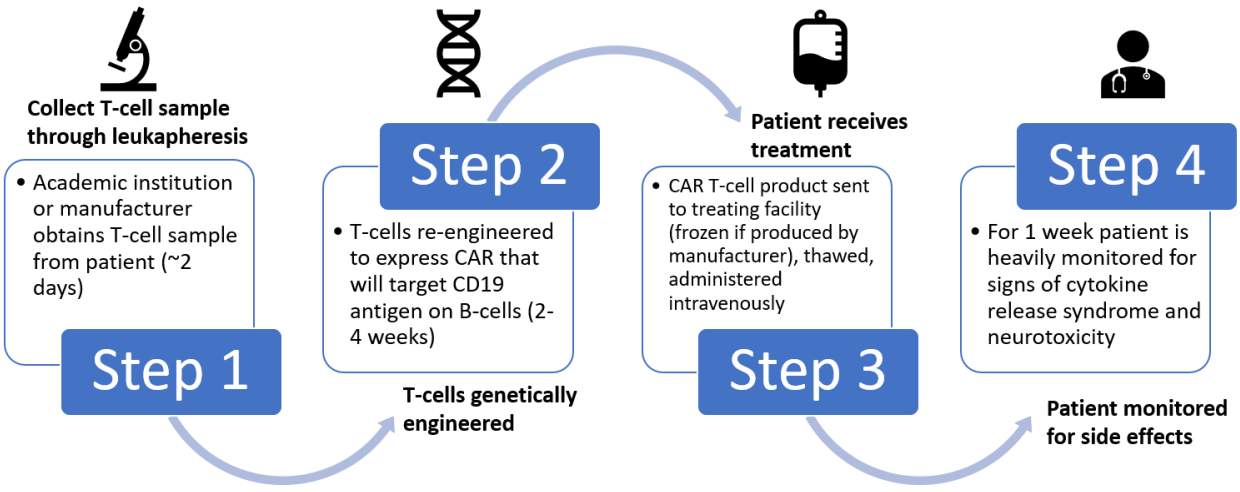
However, as the Health Canada approved CAR T-cell products have not yet been funded for use in Canada in certain hospitals, some clinicians only had knowledge and experience with the patient receiving the treatment in the United States and returning to Canada following the resolution of side effects. Once the therapies are funded, they will be administered to patients in Canadian hospitals.

Processes from "bench to bedside"

One of the primary outputs from the interviews were detailed descriptions of processes including manufacturing CAR T-cells and administering the therapy to patients in the hospital. These descriptions included things such as steps to complete processes, length of time, personnel and resources required, and errors that can occur. These processes were organized into a flowchart showing how CAR T-cell therapy is developed and how it is administered to the patients. Participants described manufacturing CAR T-cells in two contexts: academia and industry. In academia, CAR T-cell products are developed at academic centres for research and product development and for clinical trials. In industry, there are two commercial products that have been approved by Health Canada that are developed at the manufacturing sites of the drug companies Novartis and Kite Pharma (a Gilead Sciences company) in the United States.[21] Participants described the process of leukapheresis, the collection and isolation of white blood cells from a blood sample to be used to create the CAR T product. A patient will give a blood sample and machine will isolate the white blood cells. This can be done at a hospital facility in Canada with the proper resources to generate the cell sample and deliver the therapy and was described as a "routine process". The cell sample is then transported to the manufacturing facility, where the processes of reengineering the cells by combining the cell sample and the lentivirus and growing them in large numbers occur to produce the final product. With commercial products, the final CAR T-cell product is frozen and sent back to the treating hospital in some cases, or, prior to the regulatory approval of the commercial products in Canada, some patients received

the therapy in the United States. The average time for manufacturing the individualized product reported by participants ranged from three to four weeks, with an average of 17 days reported by Kite Pharma in the clinical trial for axicabtagene ciloleucel for patients with DLBCL. Researchers developing products in Canada noted that the manufacturing turnaround time is around two weeks. In addition, participants discussed that to develop a functional CAR T-cell therapy product, a Good Manufacturing Practice (GMP) facility is required, which includes a rigorous process to ensure employees are trained properly and that quality standards are met for products. Participants with experience in manufacturing were also asked to discuss errors that could occur in manufacturing that would lead to a failure, which occurred in a small percentage of patients in the clinical trials for tisagenlecleucel in pediatric ALL and axicabtagene ciloleucel in DLBCL. A participant stated "*So you know, the 7% manufacturing failure that we saw with Novartis when the studies were published, that was because (they) couldn't expand enough cells to make it a viable CAR T product. Nowadays the manufacturing failures are often related to the functionality of the product*," indicating that although errors can still occur, the cause of them has changed over time.

Figure 2.3. Processes from bench to bedside



Future State of CAR T in Canada - Challenges

Participants were asked about current challenges to effective implementation of CAR T-cell therapy in Canada and asked about for their recommendations ensure long-term sustainability of CAR T-cell therapy. Some key challenges identified were:

- the high cost of CAR T to the healthcare system and maintaining funding
- limited capacity of manufacturers and hospitals to develop and deliver CAR T
- government and regulatory agencies working with short-term efficacy data and having to make decisions for the future with limited evidence

Challenge 1 - High Cost to Healthcare System

Participants noted that not only is the cost of CAR T-cell therapy products very expensive, there are many additional hospital costs associated with CAR T-cell therapy. The cost for the approved CAR T-cell products ranges from $373,000 USD to $475,000 USD.[22] Because administering CAR T products to patients is new to Canadian hospitals, clinicians noted that patients would likely be admitted as an inpatient in the days leading up to the therapy and may stay in the hospital for 1 to 2 weeks. Some patients who experience serious adverse events may need to be transferred to the intensive care unit (ICU) which also increases costs. Summarizing this theme, one participant stated *"Well, the biggest challenge is clearly the costs associated with it, right? The commercial products that are coming out of the US companies have costs of hundreds of thousand dollars per product on top of the actual clinical treatment costs are associated with that."*

Challenge 2 – Limited Capacity

Across all areas of expertise, participants felt that one of the largest barriers to implementation is capacity. Participants spoke about capacity in the context of the current healthcare system not currently being able to meet the demand for CAR T-cell therapy. Participants agreed that even if CAR T-cell therapy were affordable, hospitals are currently at capacity with other procedures such as bone marrow transplants, which

clinicians noted is similar to CAR T-cell therapy in terms of the hospital resources required. Hospitals with expertise in bone marrow transplants were discussed by participants as being the best equipped to effectively deliver CAR T. Participants were concerned about the number of patients that would eligible for CAR T and the limited hospital resources, specifically regular ward beds and ICU beds. One participant stated *"Everything you need to treat these complicated patients as we're short of. And we've been working to improve that, so we're just sort of catching up on the transplant side and then these guys came along", and another saying "at this point, we don't have enough bed space in the province to meet the need for the number of patients who would be eligible for CAR-T in the province"* referring to Ontario.

Challenge 3 – Limited Evidence

Based on interview responses, "limited evidence" is defined as short-term efficacy data for the approved CAR T-cell therapy products. Participants discussed that decisions are being made at the government level about funding and implementation of CAR T-cell therapy based on data from single-arm clinical trials that ranged from 14 to 27 months of follow-up.[11,12] It was noted that cost-effectiveness and value for money is important when using healthcare budget dollars for innovative cancer therapies. Working with limited data, participants shared that there is some uncertainty in the long-term benefit and cost-effectiveness of CAR T, although early data is very promising and suggests many patients can go into long-term remission. A quote illustrating this theme is *"…we also don't have long term data on the products that are currently marketed. And so when you try to do planning at a system level it becomes very difficult because you're not planning for today or even the year after, you're trying to plan five to 10 years down the road. So trying to estimate the numbers of patients that would require this therapy and then the proper resources as far as health human resources, capital infrastructure… to care for these patients and what their long term needs might be is quite difficult. So, the costs of not just purchase of the CAR T-cell but the cost of the actual care and management of these patients, there is limited information to go on. Even the clinical trials that have occurred have fairly small numbers when you compare them to clinical trials in other therapeutic areas of*

breast cancer, or so forth. That's a big challenge for us in the planning phase." This quote shows the challenge of working short-term data to make long-term decisions about healthcare.

Future State of CAR T-cell Therapy – Planning at the System Level

Responses to many questions focused on recommendations for sustainability of CAR T-cell therapy and other cell and gene therapies. These fell under three main categories:

- Coordination among stakeholders
- Implement infrastructure, training and education
- Consider reimbursement strategies and cost-effectiveness
- Adapt to emerging evidence

Recommendation 1 – Coordination Among Stakeholders

Participants discussed the need for CAR T-cell therapy stakeholders to be aligned to ensure patients can get timely and maintained access to CAR T-cell therapy. Key stakeholders include government and regulatory agencies, industry, clinicians, hospitals, and patients.

A quote illustrating this is *"I think the manufacturer working with the provinces to achieve a price that's equitable, sustainable for the success of CAR T. The first step. I think that's one. In terms of other steps to maintain or improve the success, or sustainability of the treatments, I think we need to continue with research, which we're doing. It can't stop with these three indications, or two indications that exist in the market. If the technology is going to be sustainable, you need the evidence to support funding it."* Another participant stated, *"I have to say that my perception is that there's a lot of people on the various levels that are involved being in politics, being in health administration, being at the hospitals, that there's a lot of good will, enthusiasm to make this happen."* Participants felt that there is a will by CAR T-cell therapy stakeholders to achieve effective and efficient implementation.

Recommendation 2 – Implement Infrastructure, Training and Education

Participants recognized that infrastructure is an important consideration regarding which hospitals would be best suited to deliver CAR T-cell therapy and what resources are required. Most participants agreed that there is already some infrastructure in place that can be built upon. For example, participants reported that establishing centres of excellence that are accredited through the Foundation of Accreditation for Cellular Therapy (FACT) will be required to effectively deliver CAR T-cell therapy. FACT is a globally recognized standard for hospitals that do stem cell transplants and treat patients with other cellular therapies.[42] To summarize these points, a participant stated, *"In terms of treating patients, a lot of the infrastructure already exists, so if sites administer, for example, allogeneic stem cell transplant, a lot of these procedures already exist to accommodate CAR T therapies. It's one of the main reasons why some of the first centers that we approach are the FACT certified center. They have the infrastructure, for the most part, to accommodate these therapies."* Along with infrastructure comes training and education within manufacturing facilities and hospitals. Participants agreed that safely and effectively delivering CAR T-cell therapy in the hospital requires specific training as illustrated by one participant stating, *"I think in Canada what we need to do is get the infrastructure in place, which we're beginning to do now, get the training ... It'd take a lot of training to get people up to speed so the technicians who run the machines, the people who ... the docs who give the treatment. They have to become familiar with what to expect and how to treat it and so on, and all that has to be built"*.

Recommendation 3 – Consider Reimbursement Strategies and Cost-Effectiveness

Another key area for system-level planning was reimbursement. While funding was mentioned as one of the most prominent challenges, it was noted that provinces will have to make decisions about which budget the funding for these therapies will come from for reimbursement. When describing the regulatory processes for evaluating a new cancer drugs and pricing negotiations, a participant stated, *"So, in essence, all of that is the same for CAR T except who is actually funding it. It's a bit different depending on the jurisdiction. So it may come out of the hospital or whether it may come out of the cancer agency or it*

whether it may come out of something else. That's a bit of a challenge, and a bit of a uniqueness to this particular product. And I'm not really sure entirely whether every single province and territory have sorted out exactly where the money or the funding is going to come from". Some participants also discussed the importance of establishing value-for-money for CAR T-cell therapy before making a large investment and novel solutions to implementation issues may be required. Summarizing this, one participant said *"In terms of sustainability, I think again, we have to do everything we can to negotiate the prices down as far as we can to make sure that, because we do have limited healthcare dollars, and we're in a socialized medicine environment, we do need to make sure that we're using our money wisely. And so, if we can negotiate the prices down, and maybe even come up with novel ways of administering the therapy. So, like, maybe moving it to the out-patient setting in the hospitals, could result in less cost to the tax payer."*

Recommendation 4 - Adapt to Emerging Evidence

Participants discussed that while there are two Health Canada approved indications for CAR T-cell therapies at present, there are many more being developed and tested which should be accounted for in long-term planning. Participants discussed new indications for CAR T-cell therapies and gene therapies, as well as clinical trials for CAR T-cell therapy used in earlier lines of therapy. Participants also discussed that as the eligible patient population grows, the healthcare system needs to be able to manage the increased capacity and adapt to emerging evidence. A quote illustrating this is *"I think we have to change our mindset and say we have to deliver these drugs, or these therapies, in a different way. We have to approach it differently because they're gonna continue to evolve. This is not the end. This is the very ... I'm gonna sound very Churchill-like. This is the end of the beginning. We really are beginning to see these expand and if you keep going at it in a one-at-a-time in the sort of side-level approach of pharma, it'll take 50 years"*. Thinking ahead, participants recognized that in its current state, the healthcare system is not fully prepared to implement CAR T-cell therapy for the approved products for the anticipated number of patients. A participant shared, *"But, having said that, if in fact the indications stand and grow and CAR T becomes more commonplace, then we do have to look at how would it be more broadly available? We can't rely on*

just a handful of sites in the province, or in the country to do this. So, where should we be planning and how should we be training these individuals for this therapy?".

Many participants discussed the need for the healthcare system to consider more than just what is happening today in the CAR T-cell world, but what is to come, if Canada is going to adopt other innovative therapies in the future. Participants were hopeful that eventually CAR T-cell therapy could be an outpatient procedure which would reduce costs. In addition, a few participants discussed the idea of CAR T-cell therapy being manufactured within Canada at academic or research hospital centres rather than solely by manufacturers because of the evolving nature of CAR T-cells. On the topic of an outpatient model, a participant stated *"U.S. institutions who have done this a bit longer than we have actually are working with an outpatient model. That's where we are going as well. Then once the patients develop signs of side effects, then that's the time when you would admit them, but not routinely admit them just because they got CAR T cells."* On the topic of developing CAR T-cell products in Canada and the evolution of CAR T cells, one scientist stated *"There is a push to,…to allow centers that have bone marrow expertise but are not necessarily set up for GMP labs, to have a manufacturing facility to actually make these CAR T-cells on machines that you can just put in your lab as we normally do, for cell sorting during the transplant process and in a way like that, produce CAR T-cells that meet all the criteria to be given to a patient."* Another participant stated *"The other thing that we need to mention is not just that the CAR T-cells are being investigated for other diseases, but also the particular CAR T product itself is undergoing a revolution. First generation, second generation, et cetera, et cetera, and that impacts what the future might look like. Whether the costs will change, whether the risk benefit will change, and so forth."*

2.8 Discussion

The results of this study highlight the challenges that policy-makers face with the implementation of CAR T-cell therapy in the Canadian healthcare system. The qualitative interviews led to the development of four key themes: novel, patient experiences with CAR T-cell therapy, processes from "bench to bedside" and the future of CAR T-cell therapy in Canada including challenges to implementation and considerations for

long-term sustainability. Participants consistently described CAR T-cell therapy as novel in terms its therapeutic benefit and the way it is developed and administered to patients. In addition, participants focused on the patient experience living with acute lymphoblastic leukemia or large B-cell lymphoma and their experiences with CAR T, focusing on two common but serious adverse events: cytokine release syndrome and neurotoxicity. With both scientist and clinician perspectives, processes ranging from collecting cells and manufacturing CAR T-cell therapy in a lab to administering the therapy in the hospital and monitoring patients were described in detail. Lastly, participants in all fields outlined key barriers to implementation including high drug cost and hospital costs, and that many hospitals currently lack the capacity to effectively deliver an additional resource intensive therapy. Participants commented on the future of CAR T-cell therapy in Canada, giving recommendations for planning at the system level, and looking ahead to what is next in the cell therapy space. To facilitate implementation of CAR T-cell therapy, participants noted that alignment and coordination with stakeholders, tailored training and education at hospitals, and establishing cost-effectiveness and negotiating a fair price are all important.

Currently, there is an unmet need for relapsed or refractory pediatric ALL patients and adult LBCL patients and CAR T-cell therapy is a potentially life-saving treatment for eligible patients. There are challenges to delivering this high-cost and novel therapy across Canada, however, the interviews illustrated that from the perspective of participants, stakeholders are working together to ensure the long-term sustainability of CAR T-cell therapy and other novel therapies.

The results presented in this study align with other reports on challenges with implementing CAR T-cell therapy in the healthcare system, although they have not been described qualitatively through interviews in a Canadian context. In the Optimal Use reports published by CADTH for the approved CAR T-cell therapy products, ethical, legal, and implementation issues were highlighted as part of a comprehensive review. CADTH highlighted views from stakeholders about how to roll out the delivery of CAR T-cell therapy. This included stakeholder views on manufacturer oversight of treatment sites, accreditation of treatment sites by FACT, selecting eligible patients, and handling uncertainty with clinical trial data. The report also

highlighted key ethical consideration which included: balancing safety and effectiveness of the therapies, ensuring equitable access across the country and equitable patient selection, high cost of CAR T-cell therapy, patients having an informed choice of treatment options, and the burden of going through treatment on the patient and their caregivers and families.[34-35]

2.9 Limitations

This study had several limitations to be noted. Although saturation was reached, there was a small sample size of 13 participants (3 scientists/researchers, 5 clinicians, 5 policy-makers). In addition, this study did not include patients, who are at the centre of discussions about CAR T-cell therapy. Future research would benefit from the patient perspective on their own experiences with CAR T-cell therapy and their views on challenges to implementation. Another limitation is that the majority of participants (12) were from Ontario with only 1 participant from British Columbia. The perspectives are limited to the experiences of participants in these areas and may not be generalizable to the perspectives across all of Canada. This was the case due to certain national drug regulatory agencies located in Ontario, the leadership demonstrated by Ontario and British Columbia with developing CAR T-cell therapy products, and the location of currently specialized hospital centres in delivering cell and gene therapies.

2.10 Conclusions

The goal of this study was to understand challenges to the implementation of CAR T-cell therapy in Canada and the various processes involved in developing CAR T-cell therapy and administering it to patients from the perspectives of key CAR T-cell therapy stakeholders. Participants included scientists, clinicians and policy-makers. Their views highlighted unique challenges to Canada to the successful implementation and adoption of CAR T-cell therapy in the healthcare system, and some challenges that have been reported previously. Canada-specific views on barriers to implementation and recommendations for planning at the system-level had not been well documented prior to this study. Future research would benefit from the

perspectives of Canadian patients and their experiences with accessing CAR T-cell therapy before and following funding approval.

CHAPTER 3

Cost-effectiveness of CAR T-cell Therapy in Adults with Relapsed or refractory Large B-cell Lymphoma from a Canadian Perspective

3.1 Background

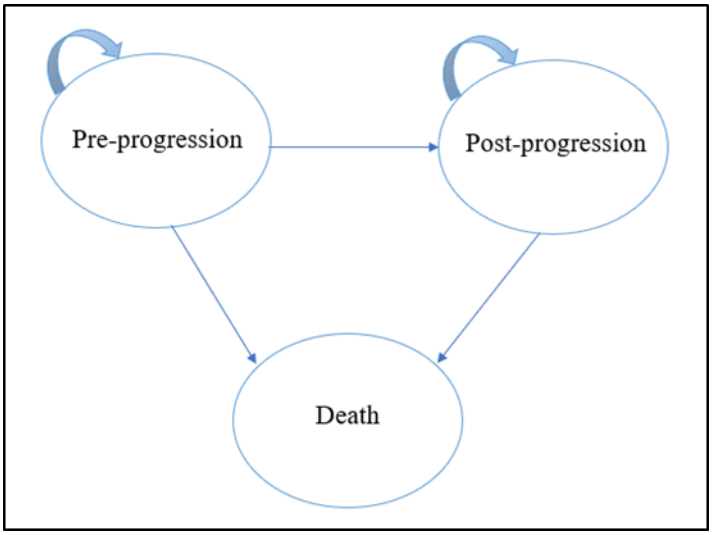
With the two FDA and Health Canada approved CAR T-cell therapy products having such a high cost per patient, it is important to establish cost-effectiveness of CAR T-cell therapy when compared to standard treatment. As discussed in Chapter 1, patients would likely receive salvage chemotherapy after experiencing multiple relapses or being refractory to treatment. Establishing cost-effectiveness of new cancer therapies ensures that limited healthcare dollars are providing value-for-money.[43] Cost-effectiveness is determined using the incremental cost-effectiveness ratio (ICER), which is the cost per additional quality-adjusted life year (QALY) gained.[42] QALYs are a measure of both the quantity and quality of health and allow for health interventions to be compared using a "common currency".[44] If a treatment is at or below a certain willingness-to-pay threshold, it is commonly considered to be cost-effective. A WTP threshold of $50,000 is not explicitly by CADTH but is often used as a benchmark in economic evaluations and is cited in many of their economic reports.[45] Specific to the pan Canadian Oncology Drug Review process, there are cases of therapies being approved with an ICER of up to $140,000 per QALY based on an evaluation of pCODR recommendations between 2011 and 2017.[46]

As many cancer therapies are covered through public provincial drug plans for Canadians, it is appropriate to conduct a CEA from the perspective of the Ministries of Health in the provinces. To conduct a CEA in patients with large B-cell lymphomas, the eligible patient population can be simulated moving through the health states of progression-free, progressed and death. The probability of being in these health states can be informed by the progression-free survival (PFS) and overall survival (OS) curves of patients treated with CAR T-cell therapy and with standard treatment from published clinical trial data. This structure is called a partitioned-survival model (PSM) and is commonly used in cost-effectiveness analyses of cancer therapies

in part because PFS and OS are commonly measured and reported outcomes of clinical trials for cancer therapies to determine efficacy.[47]

Utility values between 0 and 1 are assigned to the progression-free, progressed, and death health states, where 0 is death and 1 is perfect health.[44] These utility values allow the incremental QALYs gained or lost to be calculated. As patients move through these health states, costs occur at the time of treatment and throughout follow-up care and monitoring. Costs are not limited to the costs of the therapies, but can also include hospital costs, adverse event management, office visits and consultations for follow-up care, and subsequent treatments.[43]

Figure 3.1. Partitioned survival model structure



3.2 Previous Published Cost-Effectiveness Analyses of CAR T-cell Therapy for Adults with Large B-cell Lymphomas

In the "Optimal Use" report published by CADTH in which a health technology assessment of CAR T-cell therapies was conducted, one component was an economic evaluation. The economic evaluation compared axicabtagene ciloleucel to best supportive care. This model was developed by the manufacturers and submitted to CADTH for review. CADTH reviewed and critiqued the economic models and provided reanalyses incorporating information that they felt addressed the limitations in the analyses. The submitted

model was a partitioned survival model (PSM) with three health states, and the baseline patient characteristics were based on the ZUMA-1 trial.[28]

In the CADTH reanalysis of the economic evaluation of axicatagene ciloleucel, CADTH reported that the total costs of axicabtagene ciloleucel were $626,104 and $106,415 for BSC leading to an incremental cost of $519,689. The total quality-adjusted life years gained for axicabtagene ciloleucel was 4.47 and 2.17 for BSC leading to incremental QALYs of 2.30. The incremental cost-effectiveness ratio was $226,131 per QALY gained.[28,29] Limitations of the manufacturer's model noted by CADTH were: the lack of head-to-head trials between comparators, lack of generalizability of the ZUMA-1 patient population median age in the real-world clinical setting, the time at which patients were considered cured and were considered to have a similar risk of death than a general Canadian population, not censoring patients treated with subsequent therapies, uncertainty in PFS data for BSC due to a lack of available data, and uncertainty in some cost values. Key assumptions made in CADTH's reanalysis were the adjustment of the average age to be 67 rather than 58 in the manufacturer's original submission, using an assumption that patient who remain progression-free for five years instead of two years are considered cured, and that the cured population has a higher risk of death of than the general Canadian population.

Other CEAs have also been published from a U.S. third party payer perspective comparing axicabtagene ciloleucel to salvage chemotherapy between 2018 and 2019.[48-50] In a CEA published by Lin et al in 2019, a state-transition model was developed to assess the cost-effectiveness. At 40% 5-year PFS, axicabtagene ciloleucel resulted in an additional 3.72 QALYs at a cost of $129,000 per QALY ($89,000 to $219,000 per QALY) gained compared with salvage chemoimmunotherapy, however, at 30% 5-year PFS, axicabtagene ciloleucel resulted in an additional 2.96 QALYs at a cost of $159,000 per QALY ($105,000 to $284,000 per QALY) gained, with fewer QALYs and greater ICERs at lower percentage of patients cured.[48] In another U.S. CEA published by Roth et al in 2018 that utilized a PSM, the reported incremental cost was $380,184, incremental effectiveness was 6.54 QALYs leading to an ICER of $58,146.[49] Besides the structural differences in these models, there are differences in assumptions such as salvage chemotherapy

regimen selected for comparator, data used to inform efficacy, efficacy extrapolation methods, utilities used for health states, and adjustments made to account for patient differences in the clinical trials.

3.3 Economic Evaluation Model of CAR T-cell Therapy Compared to Salvage Chemotherapy in Adult Patients with Large B-cell Lymphomas

Comparators

This study compared treatment strategies for adult large B-cell lymphoma patients. In the primary analysis, axicabtagene ciloleucel was compared to salvage chemotherapy in patients with multiply relapsed or refractory lymphoma. Axicabtagene ciloleucel was chosen as the drug of interest because of its demonstrated efficacy in the clinical trials and the lack of published CEAs from a Canadian perspective. There is currently no standard treatment for multiply relapsed LBCL, however patients would likely receive salvage or palliative chemotherapy. There are several chemotherapy combinations that may be used for salvage chemotherapy including: rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP), as well as rituximab, dexamethasone, cytarabine and cisplatin (R-DHAP), and less commonly rituximab, isofamide, carboplatin, etopisode (R-ICE).[5] A Canadian clinical pharmacist in hematology and bone marrow transplantation was consulted to understand estimations of the proportion of patients who would receive each of these combinations and it was determined that R-GDP is the most common in the Canadian setting for adult patients with LBCL.

3.4 Methods – Model Structure and Key Model Inputs

Type of Economic Analysis

This analysis conducted was a cost-utility analysis with cost-effectiveness assessed by the incremental cost in Canadian dollars per quality-adjusted life year gained and is from a publicly funded healthcare payer perspective (the Ministries of Health in the provinces in Canada). One-way sensitivity analyses were also conducted. The model was discounted at a rate of 1.5% annually as per the CADTH Guidelines for

Economic Evaluation of Health Technologies, and the model used a lifetime (30 year) time horizon to capture all meaningful costs and effects.[43] A lifetime time horizon is appropriate as the goal of therapy is long-term remission and therefore capture costs over a long period of time.[43]

The analysis assessed the cost-effectiveness at willingness-to-pay thresholds of $50,000 per QALY, $100,000 per QALY, $150,000 per QALY, and $200,000 per QALY. Most costs used in the model were taken from Canadian sources apart from the price of the CAR T-cell therapy, axicabtagene ciloleucel, which were converted from U.S. to Canadian dollars. The U.S. prices of axicabtagene ciloleucel was sourced from the Micromedex Redbook using the wholesale acquisition price and converted to Canadian dollars using the Purchasing Power Parity (PPP) using the ratio of the prices of a good or service paid in the U.S. compared to Canada in 2018.[51] All other costs were adjusted to 2019 Canadian dollars using the Consumer Price Index (CPI) from Statistics Canada for health and personal care when required. Specifically, the annual national average CPI for all of Canada was used to calculate the costs used in the model.[52]

A partitioned-survival model (PSM) was developed using the TreeAge Pro 2019 software package. Baseline parameters for the assumptions, costs, and utilities are provided in Table 1.

Target Population

The population in this analysis included patients with large B-cell lymphoma who are refractory to or have experienced relapse after at least two lines of prior therapy. The mean age of the modeled population is 58 years based on the median age in the pivotal trial for axicabtagene ciloleucel (ZUMA-1).[11]

Model

A PSM was used to represent three health states a patient with LBCL can be in, which includes progression-free, progressed, and death. Patients could experience adverse events in the first cycle of the model and costs of adverse events were applied in this cycle. At 5 years, patients who remained in the progression-free or progressed health states state were considered to be in long-term remission. It was assumed that past 5 years patients were in remission based on the CEA by Roth et al, in which patients who remained

progression-free at 5 years did not experience subsequent progression. This was based on 2 studies that assessed long-term outcomes in patients with DLBCL and the low probability of progression past this point.[53-54] The probability of death of the general population was sourced from the 2015-2017 Statistics Canada Life Table for males.[55]

In the model, each cycle is 1 month in length. In addition, a patient could only be in one health state at a time and they could not move back to a previous health state. Patients in any of the health states could progress more quickly than the standard model and move into the death state.

3.5 Assumptions

Costs

Total costs included for the axicabtagene ciloleucel arm of the comparison included wholesale acquisition cost of the drug, cost of pre-treatment, cost of leukapheresis, cost of hospitalization for 16 days, cost of drug administration by a physician, costs of adverse events, and cost of monitoring including office visits. Primary data sources for costs included the Ontario Case Costing Initiative, Canadian Institute for Health Information hospital data, Schedule of Benefits and Fees for Physician Services, and the Ontario Drug Benefit. Sources for costs can be found in Table 1. Costs of drugs where the dose is weight-based were calculated using an average body surface index (BSA) of $1.7m^2$.[56]

Utilities

Utility values for the progression-free and progressed health states came from quality-of-life data collected from a safety management cohort from the ZUMA-1 trial using the EQ-5D-5L instrument.[57] The EQ-5D-5L instrument allows patients to self report their through answering questions in five domains. Patients can select one of five options for each question ranging from no problems to extreme problems related to five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[58]

In the quality-of-life study, a total of 34 patients with relapsed/refractory LBCL treated with axicabtagene ciloleucel were initially part of the study, with a median follow-up of 5.1 months. The mean EQ-5D-5L index was 0.80 (SD = 0.14) for progression-free health state and 0.72 (SD = 0.17) for progressed disease.[57]

Adverse Events

Adverse events experienced by patients in the ZUMA-1 and JULIET trial that were Grade 3 or higher in greater than 10% of patients were included in the model.[11,12] A cost was applied for the proportion of patients that experienced. Adverse event costs were obtained from the Ontario Case Costing Initiative.[58] A utility decrement was not applied for these adverse events. Key adverse events associated with axicatagene ciloleucel included pyrexia (14%), neutropenia (78%), anemia (43%), thrombocytopenia (38%), febrile neutropenia (31%), hypotension (14%) encephalopathy (21%), and white-blood cell count decreased (29%).

Cytokine release syndrome (CRS) was included for 13% of patients treated with axicabtagene ciloleucel.[11] For the duration of the first 2 cycles the utility for patients with CRS was 0.[56] Patients with Grade 3 or 4 CRS were estimated to be in the intensive care unit (ICU) for an average of 6 days for axicabtagene ciloleucel.[28] The average cost of a day in the ICU was obtained from the Canadian Institute for Health Information and was based on the average per diem ICU cost in Ontario.[60] The cost of 2 doses of tocilizumab was also included in the CRS cost.

For salvage chemotherapy, adverse events were not reported in the trial used for efficacy data, so it was assumed that the adverse events that occurred and the proportion of patients matched the adverse events of a clinical trial in which transplant-ineligible patients with refractory/relapsing B-cell lymphoma received "Gem-Ox"[61]. Gem-Ox is a salvage chemotherapy combination of gemcitabine and oxaliplatin.[61] This was used as an assumption in the CADTH Economic Review Report of tisagenlecleucel in adult LBCL patients compared to salvage chemotherapy.[29]

3.6 Methods – Efficacy

To estimate efficacy of each treatment option over a lifetime time horizon, a method reported by Guyot et al[62] was used to generate patient-level data from published Kaplan-Meier survival curves from clinical trials. In this report, an algorithm was used to reconstruct survival curves using digital software, which allowed the use of various survival distributions to be tested to extrapolate survival over a lifetime time horizon.[62] PFS and OS curves from the long-term follow-up of the ZUMA-1 trial[63] (median of 27.1 months) for axicabtagene ciloleucel and OS curve from the SCHOLAR-1 trial for salvage chemotherapy[10] were first reconstructed using the Plot Digitizer computer application. The SCHOLAR-1 trial only reported the OS and not the PFS. To generate an estimated PFS curve for salvage chemotherapy, it was assumed that the ratio of the PFS curve to the OS curve was proportionate to the ratio PFS and OS curves in the ZUMA-1 trial at each time point.[49]

The PFS and OS curves were uploaded to Plot Digitizer and manually replicated by using the mouse to click along the curve to produce a table of the data points for probability of remaining progression-free and probability of death for the follow-up period. The PFS curve shows the probability of progressing over time in months and the OS curve shows the probability of death over time in months.[47] To address human error during the clicking process, an Excel function was used to look for data points that did not follow the correct ascending or descending order and were removed. The data points of the PFS and OS curves were then processed in R software to generate the best fitting parametric survival distributions to predict longer term outcomes. Parametric survival analysis techniques are "designed to allow the characterization and summary of the observed time-to-event distributions in the form of mathematical models (or equations) that reflect the patterns of change in the risk of the events of interest". These distributions can be used to predict longer term outcomes beyond the length of follow-up from a clinical trial.[64-66]

A range of parametric survival models were fitted to the reconstructed survival curves, and the selection of the most appropriate parametric function for each one was based on visual inspection and plausibility, goodness-of-fit statistics including Akaike Information Criterion (AIC) and Bayesian Information Criterion

(BIC), and clinical rationale.[66] The tested parametric survival models for data extrapolation included Loglogistic, Weibull, Lognormal, Gamma, and Exponential.

The best fitting distribution for each PFS and OS curve for axicabtagene ciloleucel, the OS curve for salvage chemotherapy, and the estimated PFS curve data for salvage chemotherapy were used in the analysis. The SCHOLAR trial collected data up to 15 years. To allow for the parametric distribution to more closely match the first 3 years of data for the OS curve for patients treated with salvage chemotherapy, only data up to 3 years was used to generate the extrapolated curve. The parametric distributions were extrapolated for 5 years, based on the assumption that the cancer is cured and at this point the probability of progression or death stops decreasing and remains constant. The data points for the extrapolated were exported to tables and used in TreeAge to estimate patients moving from progression-free to progressed and from progressed to death. The fitted parametric distributions for each survival curve are shown in Appendix 3A,3B and 3C. The selected parametric distributions are shown in the table below for OS and PFS for axicabtagene ciloleucel and for OS for salvage chemotherapy.

To calculate the patients in the progressed health state, the function is OS-PFS and to calculate those in the death state, the function is 1-OS. These functions were applied in the model.[47]

Sensitivity Analyses

One-way

One-way sensitivity analyses were conducted on all variables by varying the point estimate of each parameter by +/- 25%Typically, one-way sensitivity analyses should be conducted using the 95% Confidence Interval, but when these values are not known, lower and upper values for all parameters should still be assessed[67]. The cure point was also included in the sensitivity analysis and was varied from 2 to 5 years before a patient experiences the same probability of death as the general population. In addition, the second-best fitting parametric distributions for the extrapolation of PFS and OS for CAR T-cell therapy and

for OS for salvage chemotherapy were tested in one-way sensitivity analyses. The top 15 values influencing the ICER were reported in a tornado diagram. Because the cost of CAR T-cell therapy in Canadian dollars is a highly uncertain value, it was tested at different values in one-way sensitivity analyses. These included price increases and decreases based on the base-case price used.

Based on the economic report by CADTH evaluating axicabtagene ciloleucel in adult patients with LBCL, several limitations were noted in the manufacturer's model and addressed by CADTH in sensitivity analyses or in their reanalyses. One parameter that CADTH tested in a sensitivity analysis was the starting age in the model. The manufacturer's model used 58 years based on the ZUMA-trial, but CADTH noted that the mean age of Canadian patients with this disease may be higher and used in a sensitivity analysis.

Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was conducted using a Monte Carlo simulation with 10,000 iterations. A PSA utilizes statistical distributions for each parameter rather than point estimates to account for uncertainty in values.[42] Costs used a Gamma distribution, probabilities (including PFS and OS patient-level data as well as proportions of patients experiencing adverse events and receiving SCT) used a beta distribution, utilities used a beta distribution, and other time related variables such as the average age and average number of days in hospital used a normal distribution

Table 3.1 Assumptions, Costs, Probabilities, Utilities

Parameter	**Value**	**Source**	**Year**	**Distribution**
Total regular ward hospital days during treatment	16	Qualitative interview study (assume in hospital for 2 weeks plus 2 days before for pretreatment)	2019	Normal
Total ICU days	6	CADTH Report - axicabtagene ciloleucel in adult DLBCL	2018	Normal
Monitoring	Office visit every day for 2 weeks and then once a week up to 1 month followed by once a month visit up to 3 months, and PET scan at 3 months, 6 months, 1 year and yearly up to 5 years	Interviews	2019	
		Costs		
Parameter	**Value**	**Source**	**Year**	**Distribution**
Leukapheresis	$2,508.00	Ontario Case Costing Initiative	2017/2018	Gamma
Administration of CAR T	$105.15	Ontario Physician Schedule of Benefits and Fees, Code G359 for special single agent or multi agent therapy with major toxicity-require frequent monitoring	2016	Gamma
Administration of chemo	$75.00	Ontario Physician Schedule of Benefits and Fees, Code G345 for a complex single agent or multi agent therapy with potential for some toxicities needing intervention by physician	2016	Gamma
Pre-treatment - Axicel	$212.67	Product monograph (fludarabine and cyclophosphamide) and hospital pharmacist	2019	Gamma

		Costs continued		
Parameter	**Value**	**Source**	**Year**	**Distribution**
Axicabtagene ciloleucel	373,000 USD→ $464,385 CAN	U.S. List Price converted to CAN using PPP	2017	Gamma
Salvage chemotherapy (R-GDP for 6 cycles of 21 days)	21470.14	Dose from BC Cancer Protocol for R-GDP for Lymphoma and Myeloma and costs from ODB 2019 (hospital pharmacist)	2019	Gamma
Hospital day (regular ward)	$1851.40	CIHI Patient cost estimator (Intervention with Lymphoma)-Ontario - All Lymphoma -adults age 18-59	2017/2018	Gamma
Hospital day (intensive care unit)	$3,710.00	CIHI - Ontario Provincial Average of ICU cost per diem	2017	Gamma
Office consultation, hematology	$157.00	Ontario Physician Schedule of Benefits and Fees, Code A615	2016	Gamma
PET Scan	$1,506.20	TRIUMF, The Use of Positron Emission Tomography (PET) for Cancer Care Across Canada Time for a National Strategy	2011	Gamma
Stem cell transplant	$155,611.00	CADTH Economic Report of axicabtagene ciloleucel: Ministry of Health and Long-Term Care Interprovincial Billing Rates for Designated High Cost Transplants	2019	Gamma
Complete blood count	$3.98	OHIP Schedule of Laboratory Services	2019	Gamma
Terminal care for lymphoma- 12 months	$59,202.00	de Oliveria et al. Phase specific and lifetime costs of cancer care in Ontario	2009	Gamma
Bridging chemo	$19,816.24	CADTH Report	2019	Gamma
Tocilizumab	2452.80	Dose from axi-cel product monograph (2 doses, costs from Ontario Drug Benefit)	2019	Gamma
		Costs continued		

Parameter	Value		Source	Year	Distribution
Febrile Neutropenia	$6,776.00		OCCI	2017/2018	Gamma
Infections	$350.00		OCCI	2017/2018	Gamma
Pyrexia	$424.00		OCCI	2017/2018	Gamma
Neutropenia	$507.00		OCCI	2017/2018	Gamma
Anemia	$8,150.00		OCCI	2017/2018	Gamma
Thrombocytopenia	$436.00		OCCI	2017/2018	Gamma
Hypotension	$560.00		OCCI	2017/2018	Gamma
White-blood cell count decreased	$433.00		OCCI	2017/2018	Gamma
Encephalopathy	$4,055.00		OCCI	2017/2018	Gamma
Probabilities					
Proportion of patients receiving bridging chemo	Tisagenlecleucel	92%	JULIET trial	2019	Gamma
	Axicabtagene ciloleucel	0%	ZUMA-1 trial	2017	Gamma
Proportion of patients getting SCT after therapy	Axicel	10%	CADTH Economic Report of axicabtagene ciloleucel	2019	Beta
	Tisagen	5%			Beta
	Salvage chemotherapy	29.9%			Beta
Axicabtagene ciloleucel proportion with Grade 3-4 adverse events					
Anemia	43%		ZUMA-1 trial	2017	Beta
Febrile neutropenia	31%		ZUMA-1 trial	2017	Beta
Encephalopathy	21%		ZUMA-1 trial	2017	Beta
Hypotension	14%		ZUMA-1 trial	2017	Beta
Neutropenia	78%		ZUMA-1 trial	2017	Beta
Pyrexia	14%		ZUMA-1 trial	2017	Beta
Thrombocytopenia	38%		ZUMA-1 trial	2017	Beta
White blood cell count decreased	29%		ZUMA-1 trial	2017	Beta
Utilities					
Parameter	**Value**		**Source**	**Year**	**Distribution**

Progression-free health state	0.75	Health Utilities for Patients with Relapsed or Refractory Large B-Cell Lymphoma (R/R-LBCL): Ad Hoc Analysis From an Axicabtagene Ciloleucel (Axi-cel) Safety Management Study	2018	Beta
Progressed health state	0.72	Health Utilities for Patients with Relapsed or Refractory Large B-Cell Lymphoma (R/R-LBCL): Ad Hoc Analysis From an Axicabtagene Ciloleucel (Axi-cel) Safety Management Study	2018	Beta
CRS Disutility	-0.13 over 2 cycles (utility of 0 for the first 2 months after CAR T treatment is assumed)	CADTH Economic Report, Lin et al Cost-effectiveness of		Beta
Salvage chemotherapy disutility	-0.15 (for duration of treatment)	CADTH Economic Report		Beta

3.7 Results

Validation

The projected PFS and OS curves were validated by comparing the original patient-level data obtained from the published survival curves to the R projection using parametric survival distributions and to the TreeAge projection. The model generated survival curves that closely match the patient-level data from the clinical trials. These analyses are shown in appendix C4, C5 and C6.

Base-case Analysis

In the base-case analysis, axicabtagene ciloleucel led to an additional cost of $165,266 and additional effectiveness of 3.10 QALYs. This led to an ICER of $170,380. At willingness-to-pay thresholds of $50,000 per QALY and $100,000 per QALY, and $150,000 per QALY, CAR T-cell therapy is not cost-effective based on the base-case analysis.

Table 3.2 Base-case analysis

Treatment	**Total Costs**	**Incremental Cost of axicabtagene ciloleucel**	**Total QALYs**	**Incremental QALYs of axicabtagene ciloleucel**	**ICER**
Standard therapy (Salvage chemotherapy)	$165,266		1.76		
CAR T (Axicabtagene ciloleucel)	$693,173	$527,907	4.86	3.10	$170,380

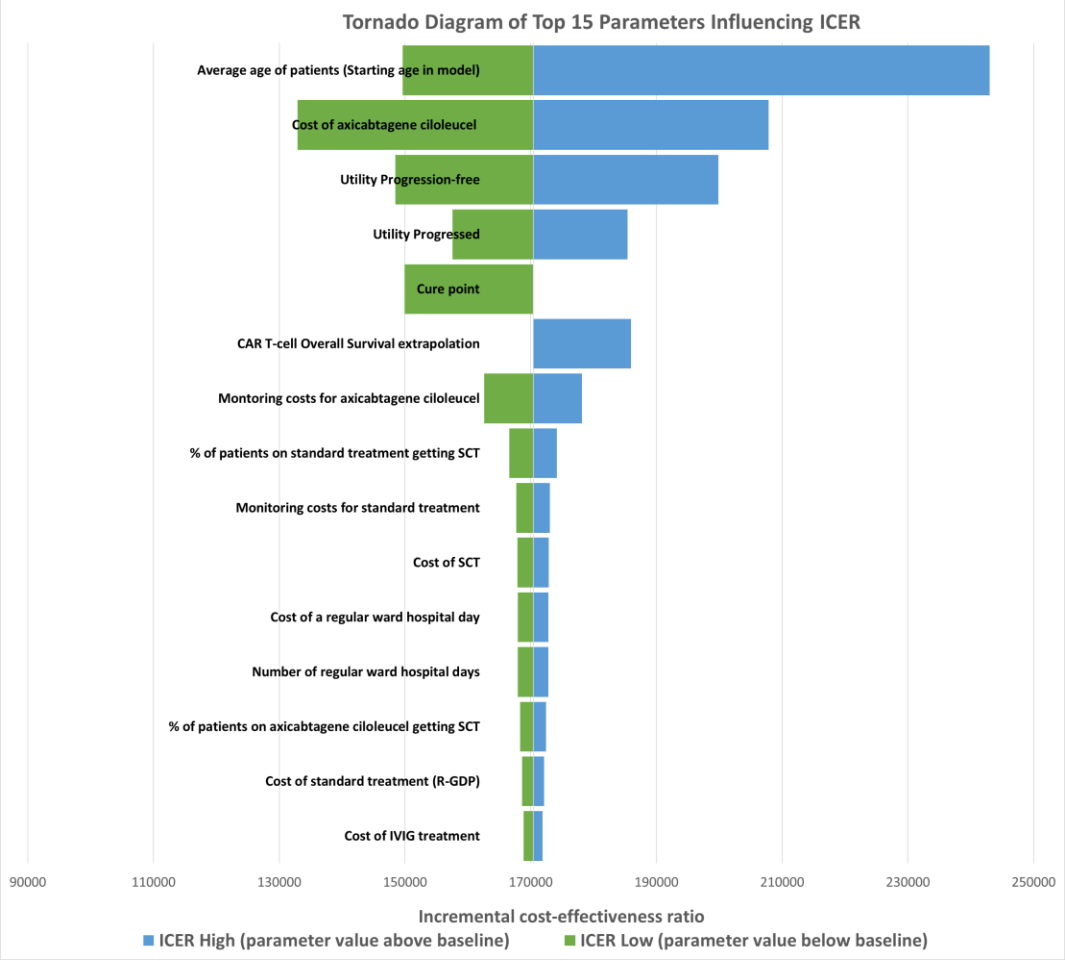
In the base case analysis, at 5 years, 17% of patients treated with axicabtagene ciloleucel remain in the progression-free health state.

One-way sensitivity analyses

A tornado diagram representing the top variables that impact the ICER in either direction from the base case ICER is displayed in Figure 3.3 The top 5 variables were the average age of patients in the model (the starting age in the model), the cost of axicabtagene ciloleucel, the utility for progression-free, the utility for progressed, and the cure point.

As the price of CAR T-cell therapy was determined be one of the top variables impacting the ICER, a threshold analysis was conducted to determine at what price axicabtagene ciloleucel would have to be to achieve an ICER of $100,000 per QALY. At a cost of $246,320, which is a 52% reduction in price, the ICER would be $100,000 per QALY.

Figure 3.2 Tornado diagram



Assuming that patients are cured prior to 5 years in remission, effectiveness of CAR T-cell therapy is improved in the model which is reflected in the ICER. The results are shown in Table 3.3. The average age was increased to 67 and tested in a one-way sensitivity analysis in Table 3.4, and higher led to a higher ICER due to a decreased health from CAR T-cell therapy. Lastly, the second-best fitting parametric distributions to extrapolate long-term PFS and OS for CAR T-cell therapy and OS for salvage chemotherapy were tested. The Log-logistic distribution was the second-best fitting distribution based on the curve with the second lowest AIC and BIC statistics. The impact of the using the Log-logistic curve rather than Log-normal was the greatest for CAR T-cell therapy OS and led to an increased ICER. The impact of using the Log-logistic curve rather than Log-normal for CAR T-cell therapy PFS and salvage chemotherapy OS was minimal. The results of this are shown in Table 3.5.

Table 3.3 Cure Assumption

Assumption	**Incremental Cost**	**Incremental QALYs**	**ICER (Cost per QALY)**	**% remaining progression-free/progressed at cure point**	**% remaining progression-free/progressed at 5 years**
Cure at 2 years in remission	$539,118	3.59	$149,967	48.9%	46.7%
Cure at 3 years in remission	$536,873	3.49	$154,039	38.5%	37.2%
Cure at 4 years in remission	$532,325	3.28	$162,143	31.6%	30.8%

Table 3.4 Increased Average Age to 67

Treatment	**Total Cost**	**Incremental Cost of axicabtagene ciloleucel**	**Total QALYs**	**Incremental QALYs of axicabtagene ciloleucel**	**ICER**	**Change from base case**
Standard therapy (Salvage chemotherapy)	$157,636		1.42			
CAR T (Axicabtagene ciloleucel)	$676,157	$518,521	3.92	2.49	$208,083	$37,703

Table 3.5 Second-best fitting parametric distributions to extrapolate PFS and OS

PFS/OS	Incremental Cost	Incremental QALYs	ICER (Cost per QALY)	Change from Base Case
CAR T – OS (Log-logistic)	$521,333	2.80	$185,986	$15,606
CAR T – PFS (Log logistic)	$527,571	3.09	$170,755	$375
Salvage chemotherapy – OS (Log-logistic)	$527,907	3.10	$170,380	-

Probabilistic Sensitivity Analysis

To account for uncertainty and ensure robustness in the results, a PSA was run with 10,000 iterations and the results are shown in Table 3.6. The results showed that in 90% of iterations, the ICER was above a $50,000 per QALY. In 89% of iterations, the ICER was above $100,000 per QALY and 0.43% below $150,000 per QALY. In 77% of iterations the ICER was above $150,000 and 13% less than $150,000 per QALY and in 56% of iterations were above $200,000 per QALY and 34% of iterations were below $200,000. At all willingness-to-pay thresholds, 10% of iterations resulted in CAR T-cell therapy being inferior in terms of effectiveness.

In the PSA, uncertainty in the efficacy data was accounted for by sampling values from a lower and upper bound of the mean values over time based on the extrapolated PFS and OS curves. The results of the PSA showed that the incremental cost was $497,105 and the incremental QALYs were 1.88 leading to an ICER of $264,418. In the PSA, the incremental cost ranged from $331,766 to $607,409, the incremental QALYs ranged from 0.74 to -0.9, and the ICER ranged from $448,331 to -674,899 per QALY.

A PSA was also run with uncertainty in efficacy excluded and the results are shown in Table 3.7. The results showed incremental costs of $523,436, incremental QALYs of 3.03 leading to an ICER of $172,751 per QALY, which is greater than the base case ICER by only $2,371.

Table 3.6 Probabilistic sensitivity analysis

Treatment	**Total Costs**	**Incremental Cost of axicabtagene ciloleucel**	**Total QALYs**	**Incremental QALYs of axicabtagene ciloleucel**	**ICER**
Standard therapy (Salvage chemotherapy)	$178,428		2.38		
CAR T (Axicabtagene ciloleucel)	$675,533	$497,105	4.26	1.88	$264,418

*Incorporates uncertainty in the extrapolated PFS and OS curves for CAR T-cell therapy and salvage chemotherapy

Table 3.7 PSA excluding uncertainty in PFS and OS

Treatment	**Total Costs**	**Incremental Cost of axicabtagene ciloleucel**	**Total QALYs**	**Incremental QALYs of axicabtagene ciloleucel**	**ICER**
Standard therapy (Salvage chemotherapy)	$164,348		1.73		
CAR T (Axicabtagene ciloleucel)	$687,784	$523,436	4.76	3.03	$172,751

*Uses base case extrapolation of PFS and OS for CAR T-cell therapy and salvage chemotherapy

3.8 Discussion

CAR T-cell therapy has the potential to improve many patients lives by inducing long-term durable remission in patients who have run out of treatment options, despite the high cost for the therapy and hospital costs.

The results of the CEA show that CAR T-cell therapy is not cost-effective in adult patients with large B-cell lymphomas based on the current estimated price and the current published efficacy data at a willingness-to-pay threshold of $150,000 per QALY. If the cost of CAR T-cell therapy is reduced and

health outcomes are improved for patients including more complete responses and fewer adverse events, the ICER will improve and CAR T-cell therapy may become cost-effective. This result is consistent with the findings of the economic evaluation by CADTH, and with results reported by Lin et al the United States.[48] Based on the deterministic base case analysis, the cost of CAR T-cell therapy would have to be reduced by 52% to meet a willingness-to-pay threshold of $100,000 per QALY. As more data is published on efficacy of axicabtabgene ciloleucel including real world outcomes, it should be incorporated in further economic evaluations to ensure value for money is achieved based on longer-term data.

With an assumption of cure only at or past 5 years in progression-free or progressed health states as in the base-case, CAR T-cell therapy is not cost-effective. However, if it is assumed that patients are cured at 2 years and it is highly unlikely that they will relapse beyond this point, then the ICER decreases to $149,967 per QALY, which would be cost-effective at a WTP threshold of $150,000 per QALY.

When uncertainty was incorporated through a probabilistic sensitivity analysis, the mean ICER was higher than the deterministic ICER by $94,038, indicating that there is some variability in the parameter values and that the ICER may in fact be even higher.

In this patient population, CAR T-cell therapy was initially rejected by the United Kingdom's National Institute of Health and Care Excellence because it was too expensive, but after negotiating the price with Gilead Sciences, LBCL patients are now able to receive CAR T-cell therapy through the National Health Service in England. In Canada, axicabtagene ciloleucel and tisagenlecleucel were recommended by CADTH provided that there are clear eligibility criteria, interprovincial agreements to ensure equitable access, and the collection of real-world evidence data about patients' outcomes for future reassessment of safety, efficacy and cost-effectiveness.[68]

With more cell and gene therapies expected to be undergoing the approval process in Canada in the near future, regulatory agencies will be faced with prioritization of them based on value for money.

3.9 Limitations

A limitation of the model is that the efficacy data from two single-arm trials for CAR T-cell therapy and salvage chemotherapy were compared directly as though the comparators were a in head-to-head clinical trial. This resulted in differences between the two patient populations that were not accounted for in the model. Because of the lack of comparative trials of CAR T-cell therapy, this was considered appropriate to use in the model. Another limitation is that the SCHOLAR-1 trial used for OS data for salvage chemotherapy did not report PFS and a method proposed by Roth et al to generate an artificial PFS curve. The PFS data used was generated by assuming a proportional ratio of OS to PFS as in the ZUMA-trial and actual reported PFS data from the SCHOLAR trial is not available.

Uncertainty in certain parameters is another limitation of this analysis. Highly uncertain values include the actual Canadian cost of axicabtagene ciloleucel, the number of years at which a patient can be considered cured or in long-term remission, and the long-term efficacy of CAR T-cell therapy. To account for this uncertainty, sensitivity analyses were conducted on these parameters. Uncertainty in long-term efficacy was tested in one-way sensitivity analyses by using the second-best fitting distributions for the extrapolation of survival curves, and was incorporated into the PSA.

Additional limitations of include that neurotoxicity was not explicitly included in the model. However, a one-time cost for cancer-related death was included which incorporates some palliative costs. It was assumed that patients who experience Grade 3-4 CRS and receive ICU care account for the costs from neurotoxicity as well. The cost of palliative care was also not included in the model, but it was assumed that because both the CAR T-cell therapy and standard treatment arm would have palliative care costs that it does not impact the model. There was also a one-time cost of death from cancer which is expected to include some palliative care costs.

In addition, the included adverse events for salvage chemotherapy were based on another trial in which another salvage chemotherapy, Gem-Ox was used in relapsed and refractory patients with DLBCL. This

was based on the published economic report of tisagenlecleucel comparted to salvage chemotherapy in adult LBCL patients by CADTH. The manufacturer's model used the trial to estimate proportions of patients with adverse events treated with salvage chemotherapy although CADTH noted that this is not an appropriate assumption because it does not match the salvage chemotherapy in the model. However, the SCHOLAR-1 trial did not report adverse events so an exception was made to include this data to account for some patient adverse events that could occur from salvage chemotherapy.

3.9 Conclusion

The results of this cost-effectiveness analysis compared axicabtagene ciloleucel to salvage chemotherapy and produced an ICER beyond a WTP threshold of $150,000 per QALY. With efficacy data on CAR T-cell therapy limited to around 2 years, there is uncertainty with predicting long-term health outcomes of patients. The cost-effectiveness of CAR T-cell therapy depends heavily on the price of the drug itself and the expected long-term health benefit. At a lower price and with a higher cure rate, the ICER is improved. Overall, CAR T-cell therapy does offer a health benefit over salvage chemotherapy. As with other cancer therapies, federal and provincial agencies in Canada will work to negotiate fair pricing with manufacturers to ensure patients can access therapies. Although the base-case analysis showed that CAR T-cell therapy is not cost-effective, it has the potential to become cost-effective with collection of data on long-term patient outcomes and with a reduction in price. For multiple relapsed or refractory lymphoma patients, CAR T-cell therapy may be their only treatment option and has been very successful in some patients. Canada may consider novel pricing and reimbursement strategies to ensure patients can get access to CAR T-cell therapy and that the cost-effectiveness is re-evaluated when more data is available to confirm value-for-money.

CHAPTER 4

Conclusions

4.1 Summary of Results

The results of Chapter 2 show the views of key CAR T-cell therapy stakeholders in Canada on the processes of developing a CAR T-cell product, how to administer CAR T-cells to a patient, and the patient experience with B-cell lymphoma after relapsing or being refractory to treatment. The results of the qualitative study also highlight some of the unique challenges to Canada with the implementation of a highly personalized and expensive-to-deliver therapy, and considerations for the future of novel cell and gene therapies entering the Canadian healthcare system. There were 4 key themes that arose from the analysis of qualitative data: novel, patient experiences with CAR T-cell therapy, processes from "bench to bedside" and the future of CAR T-cell therapy in Canada including challenges to implementation and considerations for long-term sustainability. Describing the landscape of CAR T-cell therapy for treating cancer in a Canadian context qualitatively allowed for rich description of processes and situations and avoided oversimplification of them. The findings from this study can be used to inform policy-makers in Canada and other countries and the public about logistical and feasibility concerns with implementing CAR T-cell therapy and other cell and gene therapies. As the first two CAR T-cell therapy products have been undergoing the approval process throughout 2019, this is a new area to be studied and was previously not well described in the literature.

The results of Chapter 3 show that CAR T-cell therapy is not cost-effective even at a willingness-to-pay threshold of $150,000 per QALY. The ICER in the deterministic base-case analysis was $170,380 per QALY. Therefore, the price of CAR T-cell therapy would have to reduced by over 50% using the base case analysis assumptions for CAR T-cell therapy to be cost-effective at a WTP threshold of $100,000 per QALY. While the best available data was used in the analysis to compare CAR T-cell therapy to salvage chemotherapy, there is a great deal of uncertainty in the long-term efficacy of CAR T-cell therapy because

only 27 months of follow-up data on patients treated with axicabtagene ciloleucel was available. The probabilistic analysis was able to incorporate uncertainty into the analysis and showed that the mean ICER was higher than the deterministic value by $94,038 When making decisions based upon short-term clinical trial data and uncertain model parameters, it is important to incorporate uncertainty in models to ensure the results are consistent and robust. These results indicate that more data is needed on the long-term health outcomes from CAR T-cell therapy to reduce uncertainty in the results.

4.2 Thesis Contributions

Currently, there are no qualitative interview studies using interviews that have investigated the opinions of Canadian CAR T-cell therapy stakeholders on the logistical concerns of the implementation of CAR T-cell therapy or other novel cell and gene therapies in Canada. With the excitement surrounding novel cancer gene therapies and the potential for curative treatments, it is also important to understand the reality of Canadian approval and regulatory landscape. As the Canadian government must work within a constrained budget to deliver healthcare, there are many considerations when approving high cost personalized therapies, and value-for-money is important. This study highlights many of these important considerations and provided insight into the high-level planning that is required before allowing novel therapies to be used across Canada. Although there are some similarities to the U.S. in terms of some of the challenges to effective implementation of CAR T-cell therapy, Canada's single-payer system, and the ongoing CAR T-cell therapy product development within Canada outside of the drug manufacturer's lead to a unique situation that has not been well described in the literature.

The CEA comparing axicabtagene ciloleucel to salvage chemotherapy in adult patients with LBCL demonstrated that even at willingness-to-pay threshold of $200,000 per QALY, when accounting for uncertainty in efficacy data, CAR T-cell therapy is not cost-effective at the present wholesale acquisition price. This study confirms what CADTH reported in their published economic evaluation report of the same comparison. Depending on the average age of the eligible population and the negotiated price of the therapy,

the ICER can change greatly. In addition, it was determined that there is a great deal of uncertainty in the efficacy data supporting the approval of axicabtagene ciloleucel.

4.4 Future Work

Future work related to understanding processes of developing CAR T and delivering it to patients as well as well understanding challenges to implementation would benefit from the patient perspective. Due to time constraints, patients were not interviewed as part of the qualitative study. However, it is important to engage with patients throughout the different stages of healthcare research to ensure they are heard, and their needs are being met. In addition, this study was conducted prior to the widespread use of CAR T-cell therapy in Canada. A qualitative study to understand processes of obtaining CAR T-cell therapy products and administering them to patients post implementation will provide insight into the real challenges in Canadian hospitals and whether anticipated challenges are in fact the actual challenges seen.

The accuracy of the cost-effectiveness analysis would be improved with reduced uncertainty in specific parameters. For example, longer follow-up for efficacy data for CAR T-cell therapy will reduce uncertainty in the long-term health outcomes as a result of CAR T-cell therapy. In addition, a head-to-head trial between CAR T-cell therapy and the most appropriate comparator would reduce uncertainty in the efficacy data from the comparison between two single-arm trials. If collection of this data is not feasible, uncertainty in efficacy data could also be improved by using administrative databases once CAR T-cell therapy has been utilized in Canadian hospitals to assess the efficacy in the real-world clinical setting.

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Appendix

Figure A1. Treatment Pathway

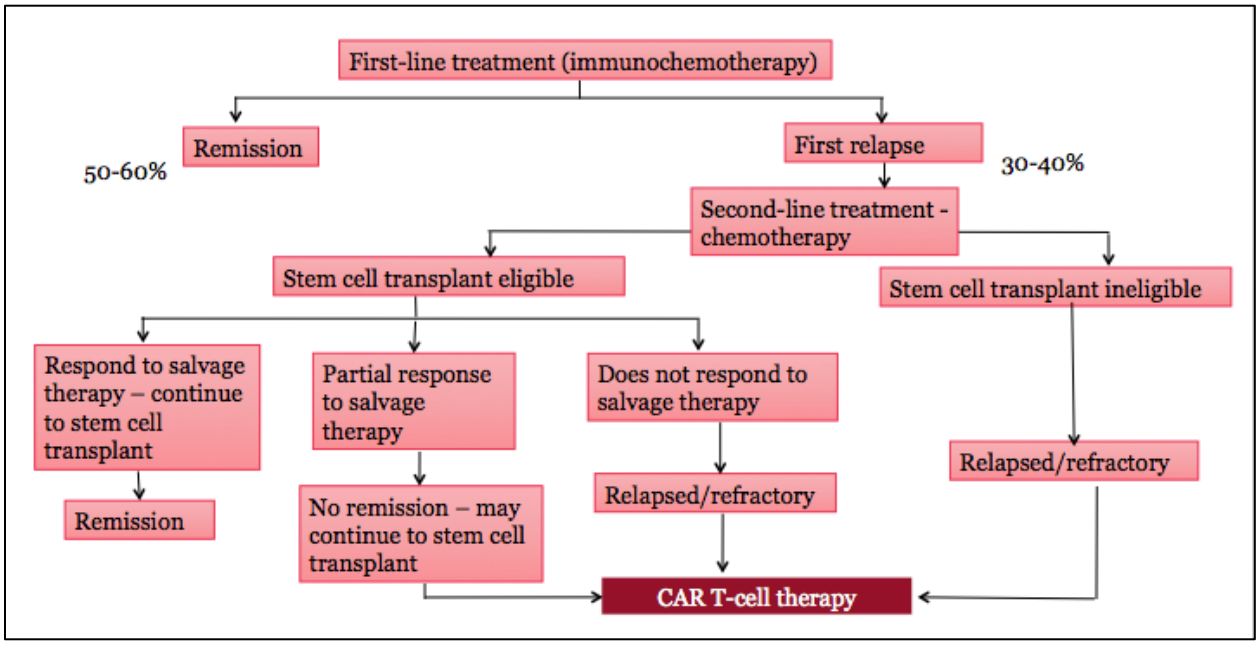

Table A1. Qualitative interview questions

Interviewee	Questions
Scientist	1. Describe the process of obtaining a T-cell sample from a patient who will undergo therapy. Follow up questions: o Describe the resources and health professionals that are required for this process. o How long does it take to obtain a sample? 2. Is your lab/facility able to manufacture CAR T-cell therapy? 3. Based on your knowledge, how many facilities/labs in Canada can produce CAR T-cell therapy (other than the manufacturer)? o What is the capacity of these centres? (Number of patients?) o How many hospitals in Canada /Ontario can administer the therapy? 4. Based on my understanding, CAR T-cells are generated from a patient's blood sample, which is then genetically engineered to express a certain antigen. Describe the process of generating CAR T-cells at your facility/centre. Probe, if needed: (If/when sent to the manufacturer, what steps must be completed first, and which steps does the manufacturer complete? Follow-up questions: o What resources and health professionals are required for this process? o Where is the therapy manufactured? o What is the typical turnaround time from leukapheresis to infusion? 5. Can errors occur during the manufacturing process? o Could you estimate the percentage or number of patients who undergo leukapheresis but do not receive a CAR T infusion? o What are the reasons why a patient may not receive an infusion after initiating the process to receive treatment? o Could you estimate the manufacturing failure rate? 6. What do you estimate the average time (or wait time) is for: o Leukapheresis? o Manufacturing of cells (time from cells sent to centre for manufacturing and sent back to treatment facility) o Transport from facility with cell sample to manufacturing facility, then from manufacturing facility to treatment centre o Infusion once the therapy is transported to the treatment centre 7. What are the challenges with developing the therapy for use?
Clinician	1. Describe the standard (s) of care of treatment that would be used if a patient was not able to receive CAR T-cell therapy. (Probe: What combination of chemotherapy drugs?) Follow-up questions: o What are the most important benefits of CAR T-cell therapy compared to standard therapy? (How many rounds of treatment is required for CAR T?) o What are the differences? Or disadvantages? (Probe: cost?) 2. Where does CAR T-cell therapy fit in to the current clinical treatment pathway? (When would it be used?)

	3. What are the most common and serious side effects and how are they managed? 4. Describe the types of patients who are eligible to receive CAR T-cell therapy? (Probe: Patient and disease characteristics, age, sex, stage, type of cancer, previous treatments) Follow-up questions: o Is there a specific subgroup? What percentage of patients do you estimate are eligible of the patients with (aggressive DLBCL or ALL)? (Or do you know where I could find this information?) o Which patient group should be prioritized to receive this therapy? o How many patients are there with DLBCL/ALL in Canada? (Or do you know where I could find this information?) o What is the typical prognosis for a patient with aggressive DLBCL/ALL (at initial diagnosis, and following the trajectory to be eligible for CAR T ?) 5. My understanding is that a patient may receive chemotherapy while waiting to get CAR T, and they may need to remain close to the treatment centre. Can you describe what happens during the period of time while a patient is waiting to receive CAR T? (Treatment, travel, how long will they have to wait) 6. Describe the process of administering the treatment to the patient Follow-up questions: o Where is it done? (E.g. Hospital) o Who administers the therapy? o How long does the treatment take? o How long is patient monitored during administration? o Which health care providers are involved? o What resources are required? o What errors have you seen occur with administering CAR T-cell therapy? 7. What does follow-up look like during treatment (after infusion) and in the following weeks? (Inpatient versus outpatient care, when they leave the hospital)? Follow-up questions: o How many days are required in the hospital? How many days in the ICU? o Are there any adverse events that significantly impact length of stay in the hospital? o After the patient leaves the hospital how are they monitored? How many office visits are required? o Are patients required to be close to a treatment centre after they leave the hospital? And for how long? o Could you compare monitoring and follow-up of patients who have received CAR T-cell therapy to those that would receive the standard of care? o If a patient progresses after treatment, how is this handled? 8. Which processes (developing therapy, delivering it, monitoring/side effects, administration) use the most resources? How does this differ from the standard of care?

	9. Could you estimate the number of hospitals/centres in Canada or Ontario that can administer CAR T-cell therapy? (Number of patients/beds?) If clinician is familiar with all processes: 10. Can you describe the process of 1) obtaining T-cells from the patients, 2) genetically engineering the cells, and 3) administering the therapy to the patient?
Policy makers	1. Describe your understanding of CAR T-cell therapy from a system-level perspective. (Economic, reimbursement, policy, healthcare) 2. Describe the role that you have for CAR T-cell therapy in the Canadian healthcare system. 3. What are the challenges to providing CAR T-cell therapy in Canada? (Probe: Policy angle, clinical angle) 4. Based on your knowledge of cancer drug reimbursement, how would CAR T-cell therapy fit within the current budget for cancer therapies in Canada? (Probe: Is it much different than other cancer drugs? Do you anticipate it to be a high priority? Will it displace other drugs?) 5. Compare CAR T-cell therapy to other novel treatments such as other cancer drugs. What is unique about CAR T in the context of drug reimbursement, the approval process, and pricing? How will this be assessed and managed for CAR T? What path is CAR T likely to follow for coverage? o Are there any treatments that have been approved that are similar to CAR T-cell therapy in terms of its novelty, cost, and potential for long-term survival? 6. Could you estimate the average time for reimbursement approval by CCO following a patient/clinician's request for a patient to receive CAR T?
General questions	Thinking about CAR T from a system level… 1. What do you expect the biggest challenges to be with adopting this new therapy? (Or with each area of the process) 2. What do you think may need to be changed for this therapy to be adopted in Canada? (Or do you think there is anything?) 3. How does therapy differ than what is currently done? (How is it unique) 4. From your perspective, to implement CAR T in Canada effectively, what do you think Canada needs to prioritize to facilitate access? 5. What do you think needs to be implemented for the sustainability of patient access to high-cost cancer therapies?

Figure A2. Interview Consent Form

INFORMED CONSENT FORM FOR INTERVIEW PARTICIPATION

Study Title: Developing a system-level policy model for regenerative medicine and cell therapy in oncology

Principal Investigator: William Wong, PhD
Assistant Professor, School of Pharmacy,
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Telephone: 519-888-4567 ext. 21323

Sponsor: BioCanRx Networks of Centres of Excellence

INVITATION TO TAKE PART

You are being asked to take part in this research study because you have experience with CAR T-cell therapy (eg. as a researcher, clinician, pharmacist, lab personnel, policy maker, etc) and have a unique perspective. Before you decide if you would like to take part in this research, please read this information about the study and its risks and benefits. You should take as much time as you need to make your decision and ask the Research Coordinator to explain anything that you do not understand. Make sure that all your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish. Taking part in this study is voluntary.

BACKGROUND AND PURPOSE

CAR T-cell therapy is a novel treatment in the cancer world. This cutting-edge therapy combines gene therapy and immunotherapy, and has demonstrated high efficacy in some relapsed or refractory hematological cancers. In 2017 there were two CAR T-cell therapies approved by the Food and Drug Administration (FDA) in the United States. In 2018, one of these, tisagenlecleucel (Kymriah) was approved by Health Canada for two indications. At this stage, regenerative medicines such as CAR T-cell therapy are costly and resource intensive, but offer the potential to cure some cancers. In the near future it is expected that Canada will have to make decisions regarding the adoption of CAR T-cell therapy, so it is important to conduct a health technology assessment by incorporating clinical evidence, cost-effectiveness analyses, and consider potential feasibility issues with this treatment.

The objectives of the study are to:

1) Understand the capacity of the healthcare system to support the implementation of CAR T-cell therapy in Canada by learning about the processes of developing and delivering the treatment, and understand the current challenges associated with the implementation of this therapy.
2) Develop a policy model and conduct an economic evaluation to estimate the health and economic burden of this therapy in the context of the Canadian healthcare system, and estimate the cost-effectiveness of the treatment compared to the current standard of care.

The interviews will contribute valuable information to this project. Interviews with individuals who have various perspectives will be conducted to ensure that the qualitative evidence generated is representative of the current state of CAR T-cell therapy in Canada. Interviews will be conducted by Kristina Ellis, research assistant or by Stephen Tully, study coordinator.

PROCEDURE

Participation in this study means taking part in one interview where we will ask you questions related to the following themes:

1. To understand the processes of developing the CAR T-cell therapy, administering it to patients and monitoring them
2. To understand the challenges or facilitators of the adoption of CAR T-cell therapy
3. To understand how CAR T-cell therapy differs from other cancer treatments in terms of the resources required to develop and deliver it to patients, and how it will be assessed for reimbursement

Taking part means that:

1. You will participate in one interview either in person, over the phone or through video conferencing.
2. The research coordinator will contact you and schedule the meeting at a convenient time.
3. The interview will be audio recorded for analysis purposes.
4. Anonymized quotations and information provided may be used in an environmental scan report, but no names or identifying information will ever be listed.

TIME COMMITMENT

The interview will be about an hour in length.

RISKS AND/OR DISCOMFORTS

During the interview, you can tell the Research Coordinator about any feeling of discomfort you may have. You will not be forced to answer questions or to continue with the interview if you chose not to.

BENEFITS

You may not receive direct benefit from being in this study. Information learned from this study may help inform decision makers regarding the reimbursement of CAR T-cell therapy.

VOLUNTARY PARTICIPATION

Your participation in this study is strictly **voluntary**. You may refuse to participate in any parts of the study. You may decide to be in the study now, and then change your mind later. You may withdraw from this study at any time.

STUDY WITHDRAWAL

If you decide to withdraw from the study, you have the right to request withdrawal of information collected about you, otherwise the information about you that was/were collected before you left the study will be used. No new information about you will be collected without your permission. If you wish to withdraw from this study please contact the Study Coordinator Stephen Tully at 519-888-4567 ext. 21374.

If you decide to withdraw from the study, would you give permission to use the data collected before the date of withdrawal? ☐ YES ☐ NO

CONFIDENTIALITY

If you agree to join the study, the study team will collect only information needed for the organization of the interview:

- Name
- Address
- Contact information
- Profession

Your identity will be kept confidential. Your name or any other identifying information will never be associated with the research data. The dataset without identifiers may be shared publicly. You will not be named in any reports, publications, or presentations that may come from this study.

When information is transmitted over the internet privacy cannot be guaranteed. There is always a risk your responses may be intercepted by a third party (e.g., government agencies, hackers). University of Waterloo researchers will not collect or use internet protocol (IP) addresses or other information which could link your participation to your computer or electronic device without first informing you.

The sponsor will not be given access to your personal information. All personal information will be destroyed at the end of the study.

COSTS, REIMBURSEMENT, AND COMPENSATION

We anticipate you will not have any extra expenses for taking part in this study.

CONFLICT OF INTEREST:

This study has been funded by BioCanRX. The researchers have no conflict of interest to report. The researchers have an interest in completing this study. Their interests should not influence your decision to participate in this study.

QUESTIONS ABOUT THE STUDY:

This study has been reviewed and received ethics clearance through a University of Waterloo Research Ethics Committee (ORE# 23163). If you have questions for the Committee contact the Office of Research Ethics (ORE), at 1-519-888-4567 ext. 36005 or ore-ceo@uwaterloo.ca.

If you have any questions, concerns or would like to speak to the study team for any reason, please call: Stephen Tully, the study coordinator, by email at stully@uwaterloo.ca, or phone at 519-888-4567 ext. 21374, or the principle-investigator William WL Wong at wwlwong@uwaterloo.ca, or 519-888-4567 ext. 21323.

You will be given a signed copy of this consent form.

CONSENT TO PARTICIPATE IN INTERVIEW

This study has been explained to me and any questions I had have been answered. I know that I may leave the study at any time. I agree to the use of my information as described in this form. I agree to take part in this study.

_____

Printed Name of Participant

_____ _____

Signature of Participant Date

My signature means that I have explained the study to the participant named above. I have answered all questions.

_____

Printed Name of Individual Obtaining Consent

_____ _____

Signature of Individual Obtaining Consent Date

Table A2. Code List for Qualitative Analysis

Category/Theme	Code	Definition
Novel	Novel, personalized therapy, not a drug	It's difficult to classify CAR T-cell therapy. It's not a drug. It's personalized. It doesn't fit into typical classifications.
Novel	Novel development, evolving, cell and gene therapies require innovation in healthcare system	CAR T-cell therapies and others are evolving but the current government and hospitals systems are inflexible, which makes it challenge
Novel	Long-term survival - curative	Novel in ability to cure
Novel	Access, healthcare policy, infrastructure	Novel in the additional resources required
Unmet need	Unmet need	Patients have no other treatment options at the stage they need CAR T-cell therapy
Equity	Ensuring equitable access	Will be difficult to provide equal access across country (e.g., Toronto vs. PEI). Need to have systems to plan for people who are not located near a CAR T-cell site. CAR T won't be offered in all provinces, only specific centres
Future state	Sustainability	If the indications grow, how will it be made more broadly available? It will likely replace some current standards of therapy, but how can provinces afford multiple new breakthrough drugs?
Manufacturing	Manufacturing model	Can be manufactured industrially or in academic setting
Manufacturing	Manufacturing process - lentivirus	How the lentivirus created
Manufacturing	Manufacturing process – patients	Obtaining cell samples from patients
Capacity	General	Doesn't fit into one category, problems with demand
Capacity	Government and regulatory	Governments and regulatory agencies need to be able to review and make decisions about these emerging cell and gene therapies
Capacity	Hospital resources	Need beds (i.e., infusion, ICU). Can be expanded/built in centres who already have capacity for stem cell and bone marrow transplant. Challenge in provinces who won't be able to have this capacity (i.e., PEI).
Capacity	Health human resources	Personnel required to deliver CAR T
Capacity	Manufacturing facilities	Need enough facilities to satisfy demand; facilities that can abide by Good Manufacturing Practices
Capacity	Manufacturing human resources	Who is needed to manufacture CAR T
Problems	Error in manufacturing/quality control	It can happen when making the lentivirus (but quality control catch this), contamination of batch
Problems	Patient health status and cell sample	When patients cannot provide a good sample of T-cells
Problems	Infusion/administration of CAR T-cell	Very unlikely to have a problem or error during infusion. Could be infused as an outpatient and doesn't require inpatient until side effects a few days later.

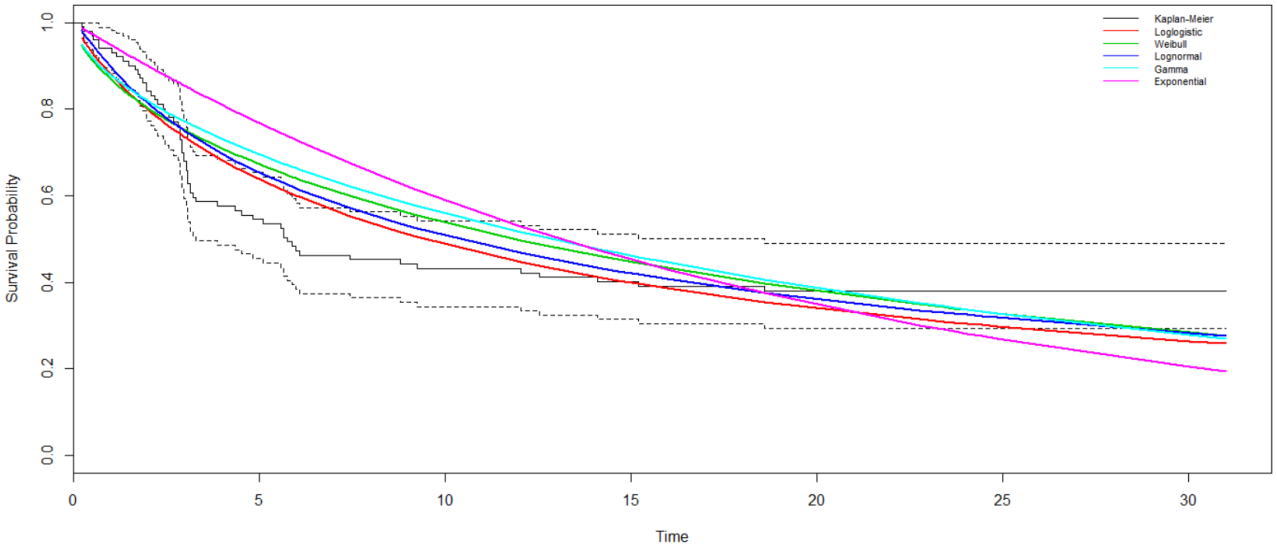
System level planning	Funding	At the moment there is no funding in Canada, which means patients are going to the US to access treatment. Who pays? It's out of scope of the provincial drug program budgets. A budget must be established.
System level planning	Infrastructure-hospital	Ensuring manufacturers/hospitals have sufficient tools to manufacture a product on site. Needs to have redundancy. Includes FACT accreditation and specialized centres-bone marrow transplant
System level planning	Training	Ensuring technicians running machines, clinicians who give treatment, GMP employees have proper training.
System level planning	Hospital care	Ensuring hospitals have capacity to care for patients after infusion. Can rely on past programs that are large and stable—will need to use the same policies. -ICU beds
System level planning	Leadership	Who leads implementation in Canada? Includes CCO, pCPCA mentioned as having experience with these types of therapies and other organizations involved in system level planning
System level planning	Planning - data management (infrastructure needed)	Data needs to be collected, sorted, analyzed, and used to make decisions about future steps and to assess the current systems of reimbursement, cost of treatment delivery, measuring quality, measuring outcomes.
System level planning	Regulatory	Planning through CCO, PCPA, approval process, reviewing cases, relationship between drug companies and government and hospitals
System level planning	Coordination	Logistics, institutions working together (manufacturer, government, hospitals), collaboration
Time	Bedside to bench to bedside	Time for leukapheresis, shipping, manufacturing CAR T in Prodigy machine, shipping, prepping patient, administering to patient, aftercare
Time	Manufacturing	2-3 weeks in manufacturing. Need to move to point of care model where manufacturing happens on site, not industrially.
Time	Patient waiting	Patient knows they are getting CAR T – time when CAR T is being manufactured and they need to remain stable
Time	Reimbursement approval time and price negotiation time	Regulatory – time for assessment if drug will be reimbursed – either for each individual patient or generally by CADTH
Time	In hospital during treatment /monitoring	After infusion, in hospital, adverse events
Cost	To system	Talked about broadly, can't categorize
Cost	CAR T-cell products	Current CAR T cell therapy is unaffordable. Very expensive, cost will limit use.
Cost	Hospital	Need to account for hospital and healthcare provider costs
Cost	Pricing, cost-effectiveness and value	Needs to be negotiated with the manufacturer to bring cost down to be affordable for the healthcare system and cost-effectiveness need to be established before implemented and re-evaluated because of uncertainty in data
Evidence	Limited evidence	Efficacy, effectiveness (mostly these 2 but also limited knowledge about the hospital resources required etc)

		There is uncertainty about the effectiveness of CAR T-cell therapy, which makes it difficult to make decisions (i.e., policy, clinical, etc). Many clinical trials happening now which may point to new indications. Lacking long-term data.
Evidence	Emerging evidence	Place in therapy (moving up to earlier lines), new indications for CAR T, new drugs other than CAR T for cancer Includes: How does the system act on new evidence? Will it be a last resort or the standard of care. Specifically mentions emerging evidence but doesn't use novel
Patient eligibility	Patient eligibility/patient population criteria – current (General characteristics)	Currently, it is for adult and pediatric ALL and DLBCL, when patients have failed bone marrow transplant or cannot receive a BMT, and usually the only other treatment option is palliative. No age limit but patient needs they need to be physically well enough to tolerate it (i.e., no organ failure) and have T-cells that can be harvested.
Patient eligibility	Patient eligibility – Exclusion	Who actually gets treatment. You may not get treatment if you are too old (80-90), cancer is too aggressive, don't have T cells.
Patient eligibility	Patient eligibility – access, healthcare policy	Who determines who has access to and coverage for CAR T-cell therapy, and the timing of when that decision occurs after the request. -Evaluating case by case -Describing # of cases and impact on system -Access in Canada vs U.S.
Patient eligibility	Specific indication for therapy	After 2 failed lines of therapy, refractory/relapsed
Patient experiences	Current burden of treatment process on patient	There is more burden on the patient to access CAR T-cell therapy
Patient experiences	Patient complications/adverse events (collapsed with Process-Adverse events)	Cytokine release syndrome, infection, CNS toxicity (ranges from minor to fatal), late cytopenias. More manageable (less fatal) as time goes on compared to clinical trials.
Patient experiences	Patient trajectory/prognosis	What is the patient's disease course (dismal at this point), how will the treatment alter the disease course. -Describing treatments patients will get and in what order
Process	Storing, shipping, transport	Cell product storage and how/when it is shipped and how it is transported
Process	Preparing the patient	Patients need to have chemotherapy beforehand. Challenge is in keeping patient well enough from leukapheresis to CAR T-cell infusion.
Process	Infusion	Describing how this process works
Process	Monitoring	How patient is infused with CAR T-cells, monitored for side effects as an inpatient and outpatient.
Similar To Transplant		Mention of the similarities to transplant in any way

Table A3. Patient characteristics in ZUMA-1, SCHOLAR-1 and JULIET trials

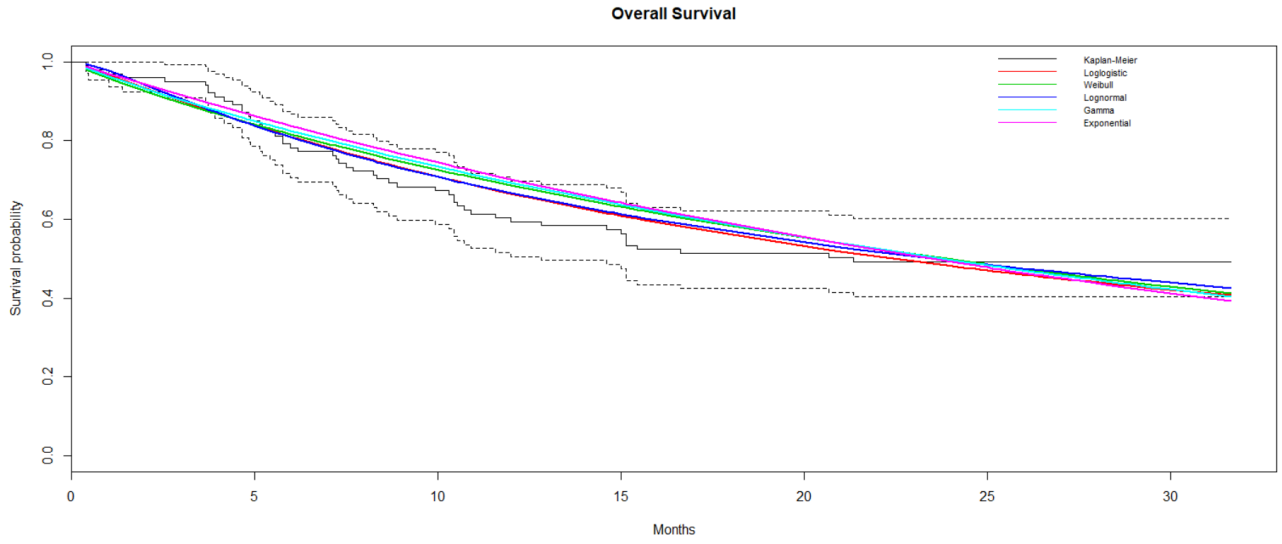
Patient Characteristic	**ZUMA-1**	**SCHOLAR-1**	**JULIET**
Median Age	58 years	55 years	56 years
DLBCL, Primary mediastinal, follicular	76%, 8%, 16%	87%, 2%, 4% (pooled)	79% DLBCL, 19% Transformed follicular lymphoma (primary mediastinal excluded)
Primary refractory disease	26%	28%	Refractory DLBCL: 55%
Received 3 prior therapies	69%	<1% (49% received 2 prior lines)	31%
Disease relapse after transplantation	21%	22% (less than 12 months post transplant)	
Disease resistant to second or late line therapies	77%	50%	
Stage III or IV disease	85%	72%	76%
Previous autologous SCT	21% (ICER)	22% (ICER)	49%
Percentage who received SCT after CAR T	11% (Roth-need to find source)	27%	
Bridging chemotherapy	Systemic bridging chemotherapy was not allowed after leukapheresis and before the administration of axi-cel	N/A	92%
CRS – any	93%	N/A	58%
CRS –Grade 3 or higher	13%	N/A	22%
Neurotoxicity – any	64%	N/A	21%
Neurotoxicity -Grade 3 or higher	28%	N/A	13%

Figure A.3. Axicabtagene ciloleucel – PFS – Parametric distributions



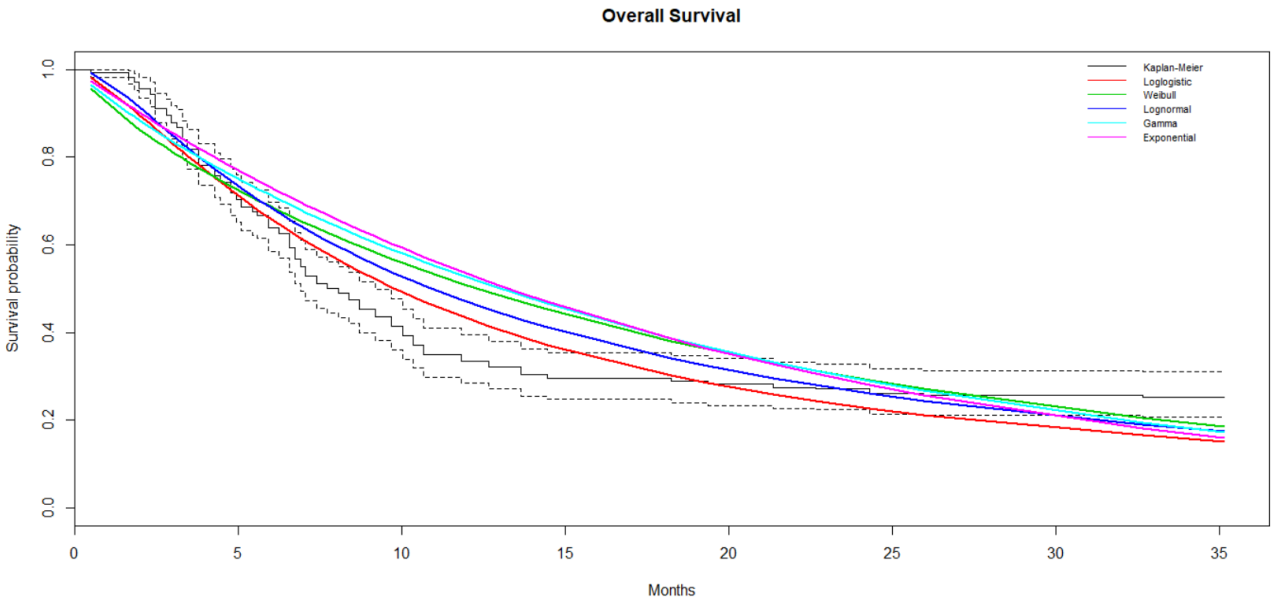
	Loglogistic	Weibull	Lognormal	Gamma	Exponential
AIC	392.779	411.229	**388.534**	416.957	423.254
BIC	398.198	416.648	**393.953**	422.376	425.963

Figure A.4. Tisagenlecleucel – OS – Parametric distributions



	Loglogistic	Weibull	Lognormal	Gamma	Exponential
AIC	404.192	411.229	**388.534**	416.957	423.254
BIC	398.198	416.648	**393.953**	422.376	425.963

Figure A.5 Salvage chemotherapy OS – Parametric distributions – based on 3 years of data using ECOG 1 and 2 patients



	Loglogistic	Weibull	Lognormal	Gamma	Exponential
AIC	1582.236	1646.993	**1578.242**	1654.280	1654.065
BIC	1589.506	1654.262	**1585.512**	1661.550	1657.700

Figure A.6 Validation of extrapolation of axicabtagene ciloleucel PFS curve

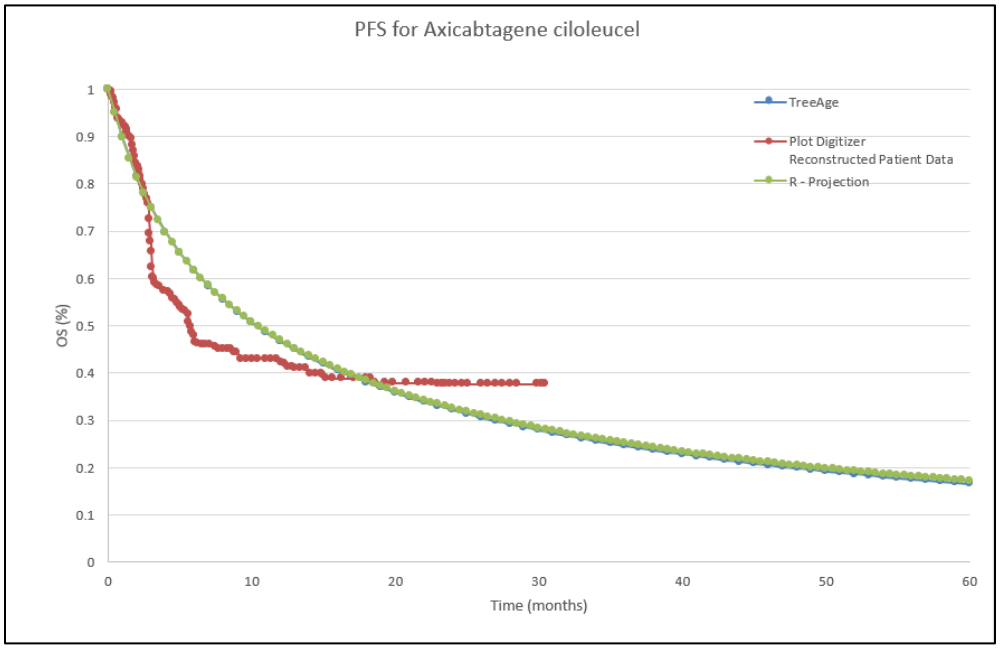


Figure A.7. Validation of extrapolation of axicabtagene ciloleucel OS curve

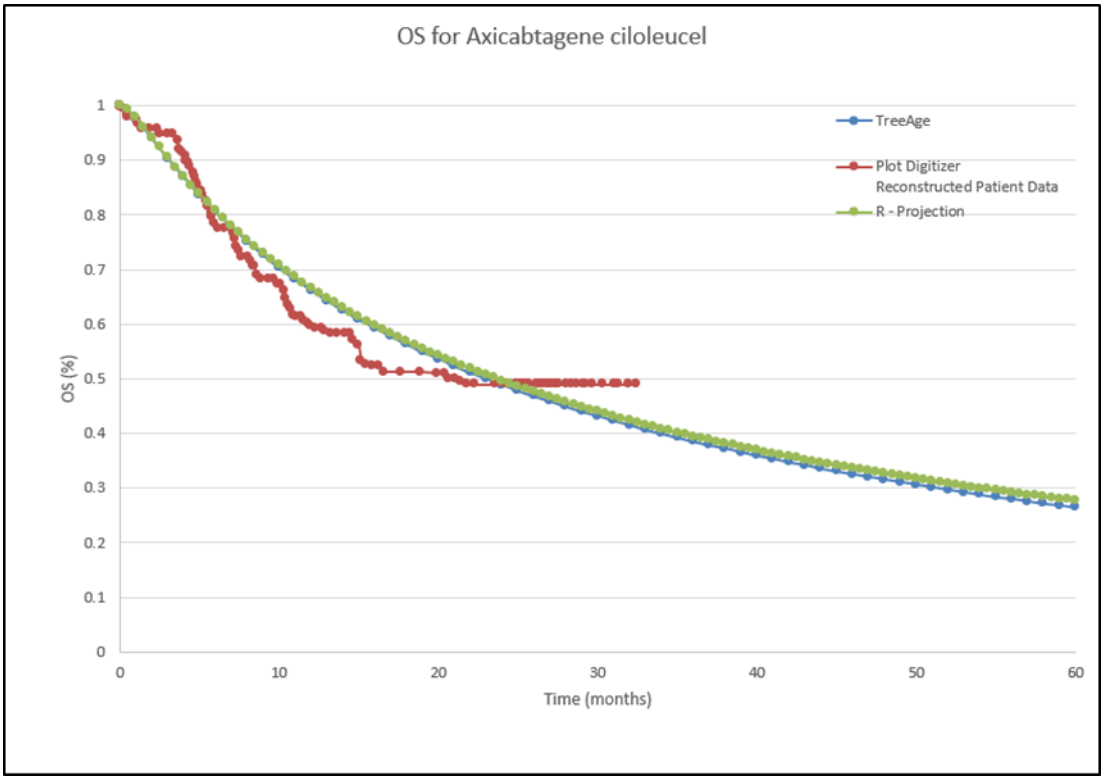


Figure A.8. Validation of extrapolation of salvage chemotherapy OS curve