Pathway to Patient Access to CAR-T Therapies in Canada

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The first two chimeric antigen receptor T-cell (CAR-T) therapies were approved for the Canadian market in September 2018 (Kymriah) and February 2019 (Yescarta). They represent a unique approach to treatment that challenged Canada's standard health technology assessment (HTA) and reimbursement pathways. The innovation they represent demanded reciprocal innovation in how these products were evaluated by HTA bodies and managed by payers.

This article overviews the introduction of CAR-Ts into the Canadian environment and adjustments in HTA processes and closely managed access to these products that may provide lessons for future highly specialized therapies.

CAR-T Assessment and Reimbursement

In April 2018, the **Canadian Agency for Drugs and Technologies in Health (CADTH) announced** that they would assess CAR-Ts through their HTA process for medical devices and clinical interventions, rather than the traditional pan-Canadian Oncology Drug Review (pCODR) process. In addition, the assessment was carried out in parallel with Quebec's HTA process under the auspices of the Institut National d'Excellence en Santé et en Services Sociaux (INESSS). A summary of key events related to patient access to the CAR-T therapies is outlined in Table 1.

Medical device and clinical intervention assessments are led by CADTH's Health Technology Expert Review Panel (HTERP). For the purposes of the CAR-T reviews, HTERP had its membership supplemented with highly specialized clinical experts as well as policy makers leading implementation of CAR T-cell program planning at the provincial level. The Kymriah review focused on Pediatric Acute Lymphoblastic Leukemia as well as Diffuse Large B-Cell Lymphoma, while the Yescarta review focused on Adult Relapsed or Refractory Large B-cell Lymphoma.

The assessment process included the following components: protocol development; a clinical systematic review; an economic review; review of implementation considerations, ethics, and patient and caregiver perspectives and experiences; and a recommendations report. Stakeholder engagement was a key part of the process and included patient groups and registered clinicians as well as the Canadian Association of Provincial Cancer Agencies (CAPCA), to ensure that any operational and implementation issues were addressed.

Metric	Kymriah	Yescarta
Health Canada Notice of Compliance (NOC)	September 2018	February 2019
Indication(s)	• Pediatric Acute Lymphoblastic Leukemia • Diffuse Large B-Cell Lymphoma	• Relapsed or Refractory Large B-cell Lymphoma
Health Technology Expert Review Panel (HTERP) evaluation completed	**January 15, 2019**	**August 15, 2019**
Funding Status	Quebec: **October 2019** Ontario: **December 2019** Alberta: **August 2020**	

Table 1. Summary of key events for CAR-T patient access.

In terms of outcomes, both CAR-T products were recommended for funding with conditions (i.e., criteria for use, etc.) along with a recommended price reduction. Both reviews spoke to the promising patient outcomes delivered by these two products, but also noted the many uncertainties related to both safety and effectiveness due to the limited availability of long-term data.

The reviews also identified a number of challenges and opportunities associated with the use of these agents. Key issues cited include:

- Need for clinical expertise in managing adverse effects associated with CAR-Ts,
- Need to collect long-term data to verify the outcomes expected by using these products,
- Need to set up appropriate oversight of treatment sites,
- Need to set up systems and processes to provide access to CAR-Ts for treatment sites,
- Likely need for patient and caregiver travel due to limited treatment sites across the country, and
- Need for clear and transparent patient eligibility criteria to ensure appropriate use and equitable access to CAR-T therapy.

As cited above, one component of the HTERP recommendations was for a price reduction for both CAR-T agents. It is of note that neither Kymriah nor Yescarta went through negotiations via the pan-Canadian Pharmaceutical Alliance (pCPA), according to the pCPA website. It is assumed that negotiations were limited to the first two provinces to provide access (i.e., Quebec and Ontario). Listing agreements for the CAR-Ts are confidential, as they would be for any product; thus, it is not clear if there were any innovative **outcomes-based agreements** established **such as those suggested in other countries**.

Finally, a summary of the overall timelines to achieve patient access for these two products is outlined in Figure 1. Compared to the traditional six-month single-agent HTA process via pCODR, the timeline for the HTERP review of these CAR-Ts was approximately four months for Kymriah and six months for Yescarta. The overall timeframe for patient access (i.e., regulatory approval, HTA review, negotiations, and funding) was thirteen months in Quebec and longer in other provinces.

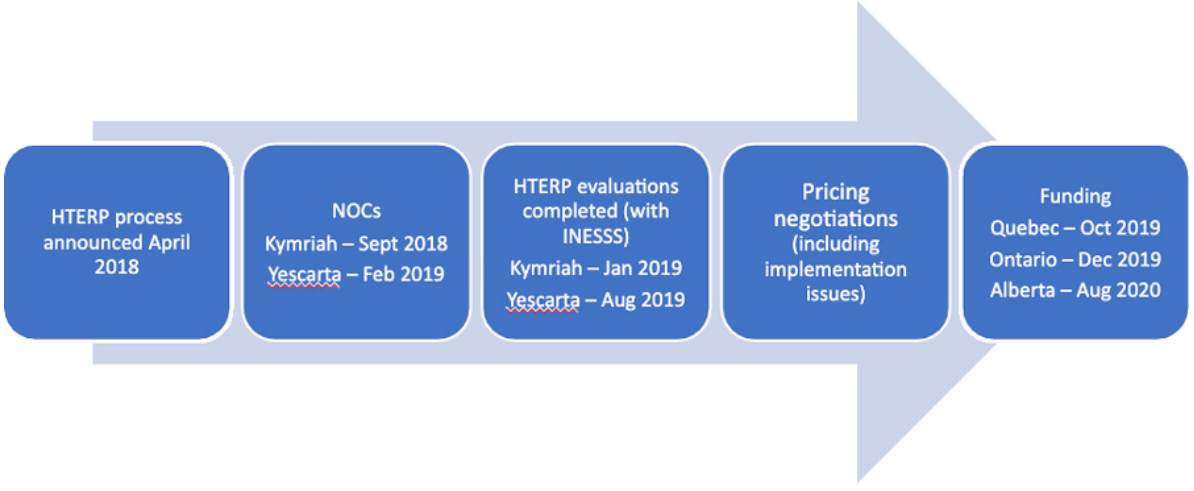

Figure 1. Summary of timeline for CAR-T patient access.

Implementation Case Study

As noted above, only three provinces have implemented funding and treatment sites for CAR-T therapies to date due to the highly specialized nature of and technology underlying the use of these treatments. (Patients who are eligible for CAR-T cell therapy in provinces or territories where it is not yet available may be able to access treatment through provincial out-of-province or out-of-country programs, if applicable.) Public information is available in the Ontario program and provides insights into the **considerations addressed in managing patient access** to these therapies.

Access to CAR-Ts is controlled via **an enrollment process** for both clinicians and patients. Clinicians must complete an application process and be eligible to access a CAR-T therapy. For instance, only an oncologist, hematologist, or CAR-T cell specialist licensed to practice in a Canadian province or territory can enrol patients. In addition, the clinician must have confirmation from the CAR-T cell therapy centre that they will treat the patient within a clinically appropriate timeframe.

To be eligible for access to CAR-T treatment, the patient must first have a valid health card from their Canadian province or territory of residence. In addition, they must meet established clinical eligibility criteria. CAR-T therapy is currently funded in Ontario for pediatric and young adult patients with relapsed/refractory B-cell ALL and for relapsed/refractory lymphoma.

A limited number of hospitals are funded to deliver CAR-T cell therapy to serve Ontarians (population 12 million) and patients from other provinces/territories not offering therapy. Designated CAR-T therapy centres include one pediatric centre (Hospital for Sick Children, Toronto) and two adult centres (Juravinski Cancer Centre, Hamilton and Princess Margaret Cancer Centre, Toronto)

Ongoing Research: Ontario CAR-T RWE Initiative

Recognizing the potential of CAR-Ts to significantly impact care of cancer patients, Ontario is undertaking **a project to evaluate** the real world health outcomes and economic impact of CAR-T cell therapy in the province. The limited comparative clinical data available to evaluate these products as well as the limited Canadian experience and substantial budget impact associated with adopting this emerging technology are key drivers underpinning this initiative.

The project is funded under the auspices of the Ontario Institute for Cancer Research-Cancer Care Ontario Health Services Research Network. Evidence generated by this research will be used to make informed decisions regarding the real world impact of this new technology, and to support development of policies and guidelines to ensure the best evidence-based care.

Key Learnings

Based on the experience gained from assessment of the first two CAR-T products, CADTH established **a specific review process for cell and gene therapies** in January 2020. This new process is intended to leverage the best components of both drug and medical device evaluation processes to address the specific evidence and implementation needs of CAR-Ts. For instance, the new process articulates firm performance targets and well-established processes for conducting reviews and issuing recommendations, similar to that used in HTA

reviews of drugs. In addition, the new process captures the ethical and implementation considerations that are a significant component of the devices HTA review process.

The **first product** to be reviewed under this new process is Luxturna (voretigene neparvovec) which is a gene therapy indicated for inherited retinal dystrophy. The submission is nearing the end of the HTA review process, with a draft recommendation expected in late September 2020.

Conclusions

The CAR-T experience has clearly demonstrated that traditional methods of evidence evaluation and introduction of technologies into the health system need to be adapted if highly innovative new therapies are going to reach patients in a timely manner. In Canada, CAR-Ts have taught us that we need a different HTA approach to evaluate cell and gene therapies; that we need a different approach to managing the introduction of cell and gene therapies into the health system; and that we need different approach to assessing the value of cell and gene therapies through ongoing real world evidence (RWE) generation.

What we have yet to optimize is how all these pillars (i.e., HTA, implementation, and RWE) can be integrated to optimize both access to and the value of CAR-Ts to patients, clinicians, and payers alike. Given the significant future CAR-T pipeline, it is critical for Canada to develop a framework that simultaneously enables access to these products while addressing relevant **clinical and economic uncertainties**.