LYMPHOMA CANADA
LYMPHOME CANADA

2021 UPDATE TO THE 2018 WHITE PAPER

IMPROVING ACCESS TO INNOVATIVE CANCER THERAPIES IN CANADA

Lymphoma Canada is a registered charity and Canada's only national organization focused entirely on lymphoma. Lymphoma Canada connects and empowers the lymphoma community. Together we are promoting early detection, finding new and better treatments, helping patients access those treatments, learning lymphoma's causes, and finding a cure.

Our Mission: Empowering patients and the lymphoma community through education, support, advocacy and research.

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OPINION SUMMARY

Based on 2015 estimates, nearly 1 in 2 Canadians are expected to develop cancer in their lifetime, with a 1 in 4 chance of dying from their cancer[1]. The 2019 and 2020 projected statistics continue to show similar cancer risks, with cancer being the number one cause of mortality in Canada accounting for thirty percent of all deaths[2]. The significant cancer burden in Canada is not slowing down, and yet decisions to approve and access innovative cancer therapies in Canada is not progressing at a rate that addresses patients' needs. Though there are many cancer types, each with their own complex etiology, there are several heterogeneous factors that contribute to the delay in equitable access and affordability of new therapies in both frontline and relapsed/refractory settings. With an aging population, the Canadian healthcare system must address the fast-growing market for, and the development of, new cancer treatments to ensure timely and equitable access. In this Paper, we examine how the Health Technology Assessment (HTA) submission process has changed since the first White Paper was published on this subject in 2018[3] to address today's cancer burden and gaps in access to potentially life-saving treatments for Canadian cancer patients. We further propose new solutions and models for streamlining approval and access to therapies in the form of recommendations.

INTRODUCTION

Cancer continues to significantly impact the Canadian healthcare system and patients, with an estimated 225,800 Canadians newly diagnosed with cancer in 2020[2] and over 2.1 million Canadian patients and cancer survivors based on the 2015 statistics[4]. With the aging Canadian population, the risk of developing cancer increases dramatically. The average number of cancer cases is projected to be 79% higher in 2028-2032 than it was in 2003-2007[2, 5, 6]. As such, the development of and access to innovative therapies to treat cancers will need to increase at a similar rate to keep up with the demand. However, approval and access to cancer therapies follow different pathways and timelines across various countries and continents. For example, public access to therapies to treat age-related diseases like cancer in Canada is delayed compared to the United States, taking on average 674 days longer[7]. It is important to note that this is not applicable to all cancer therapies, as some treatments for specific cancers or indications may be approved just shortly after or even prior to approval in the United States or Europe. There are options available in various countries to circumvent the longer timelines to public reimbursement, such as private coverage or compassionate access programs. However, these options may not be feasible or available long-term to a large percentage of the population. In addition to these timeline constraints and delays, Canada has the highest proportion of patients globally (54%) that wait more than four weeks to see a specialist (international average is 36%), further delaying diagnosis and access to treatment[8].

Few medical fields have seen the same volume and advancement as oncology therapeutics. With continued acceleration of therapeutic development, it falls to the Canadian healthcare system in general, and provincial and territorial ministries of health in particular, to implement a sustainable system for the increasing cancer population that will address quality, equity and patient experience. The White Paper published in 2018 on accessing innovative cancer therapies in Canada yielded valuable insights to the reasons for delayed access to new therapies. Reasons included lack of a timely review process by Health Canada to issue a Notice of Compliance (NOC) or NOC with conditions (NOC/c), negative funding recommendations by the Canadian Agency for Drugs and Technologies in Health (CADTH) based on such factors including non-comparative data or the inability to conduct randomized controlled trials (RCT) in the target population and growing private insurer reliance on public HTA recommendations to inform reimbursement criteria. Further, many barriers exist in the feasibility and applicability of RCTs for cancer patients. The 2018 paper proposed valuable solutions to expedite access to new cancer therapies, including providing conditional approval granted on the premise of the development of real-world evidence (RWE) to address the uncertainty of clinical value thus providing access through temporary funding, and further increasing collaboration and information sharing among stakeholders.

This 2021 White Paper update will analyze what has been achieved since the original 2018 White Paper, including changes to the HTA submission process to facilitate timely and equitable access to innovative therapies, and will propose solutions for improvement to the current systems to address the aging cancer patient population.

BURDEN OF DISEASE AND UNMET PATIENT NEEDS

Chronic disease rates are increasing at 14% each year, impacting 3 of 5 Canadians greater than 20 years of age[9]. These rates are on the rise for all chronic diseases as a result of the increasing Canadian population. Cancer as a chronic disease places a heavy health and financial burden on patients as well as the Canadian healthcare system. In comparison to other health conditions like heart disease and cerebrovascular diseases, cancer kills more people living in Canada (29.6%) compared to these other conditions (19.2% and 5.1%) respectively[2]. Further, cancer is the leading cause of premature death in Canada, with potential years of life lost for all cancers combined equaling 1,411,100 years for Canadians between 2014-2016[2]. There is also an increased burden of disease based on cancer subtypes, with lung cancer mortality for example accounting for 25% of all cancer-related deaths[10]. Cancer survival varies widely by subtype, with a high five-year net survival in thyroid cancer (98%) and testicular cancers (97%), and low survival rates in esophageal (15%) and pancreatic cancers (8%)[2]. The consequential economic impacts of chronic diseases include greater demands for health services, workforce absenteeism, increasing productivity losses, and escalating economic costs[11]. The Public Health Agency of Canada estimates that chronic diseases cost the Canadian economy $122 billion annually in lost productivity[12].

As a result of the progress in treatments, the prevention and survival for chronic illnesses however has greatly improved over the years. Yet, compared to treatments for other chronic illnesses, there are unique challenges in the treatment of cancer which ultimately stem from the categorization of hundreds of diseases under one umbrella. Furthermore, within certain cancers there can be multiple subtypes requiring different treatments, such as lymphoma with over 80 subtypes each with their own clinical course. Cancer can develop from genetic or epigenetic changes to the somatic cells, often causing mutations to proto-oncogenes involved in growth and tumor suppressor functions[13]. This can ultimately result in uncontrolled growth of any type of cell located within the body, affecting organs and systems, which can mutate and worsen over time. This presents a challenge in the development of cancer treatments, as each cancer can have specific histologic and genetic subtypes. There are also some forms of cancer that are curable and respond well to frontline therapy, however there are still many

types of chronic cancers that are incurable and can require multiple treatments over time. In these cases, treatment goals consist of managing the disease to prolong survival and maintain quality of life while patients anxiously wait for new and potentially curable therapies. With chronic diseases such as chronic lymphocytic leukemia (CLL), an incurable type of blood cancer, many treatment options are required as the patient cycles through remission and relapse throughout their clinical course.

It is important to note that there are also many different types of treatment categories, involving systemic or targeted approaches. Many new therapies, such as monoclonal antibodies, which are a type of biologic therapy, target specific features or markers of the cancer cells and as such are only applicable to certain cancers and even within those cancers, only certain subsets of patients. For example, chimeric antigen receptor T-cell therapy (CAR-T) is a novel immunotherapy wherein autologous T-cells have been genetically engineered with the ability to target a specific protein on the cancer cell. Though successful results have been observed in certain lymphoma subtypes and in multiple myeloma, there are difficulties in expanding this therapeutic option to solid tumours due to the challenge in finding suitable antigens or markers on the cancer cells[18]. In scenarios where treatments target specific attributes of the tumor, treatment administration is tailored to mandatory laboratory testing, which could involve complex assays. Some examples include the EGFR (epidermal growth factor receptor) and ALK (anaplastic lymphoma kinase) genetic testing for specific lung cancer treatments, BRAF (v-raf murine sarcoma viral oncogene homolog B1) gene analysis for melanoma, chromosomal and genetic testing for CLL, and estrogen and progesterone receptor status for endocrine therapy[14]. These complementary tests may not be funded at the same time therapies are approved for public reimbursement, or may not be funded at all, requiring out-of-pocket expenses to receive testing to be eligible to access these treatments. Funding can differ depending on the types of tests as well, such as single-gene testing compared to panel sequencing for a number of biomarkers. There may also be a number of tests required for certain cancers, such as for CLL which utilizes FISH (fluorescent in situ hybridization), TP53, and immunoglobulin testing to determine chromosomal and gene mutations that can impact treatment response. As another example, there are many subtypes of lung cancer with specific mutations for which targeted therapies have been developed, including EGFR inhibitors for patients with non-small cell lung cancer (NSCLC) adenocarcinoma that test positive for the EGFR mutation. There are at least five EGFR inhibitor treatments currently approved for use in Canada that require EGFR testing prior to receiving treatment[15]. Though testing is now funded, this was an issue earlier on with EGFR inhibitor treatments receiving Health Canada approval in the early 2000s, yet EGFR mutation testing was not funded by Cancer Care Ontario for example until 2014[16]. Not only can funding play a role in access to treatment, but the timing of molecular and genetic testing can also have a major impact. If testing is not performed at initial consultation, this can delay start to treatment from 13 days (if tested for at diagnosis) to 70 days to receive the result(s) prior to treatment initiation[17].

Another obstacle to consider is that specific cancer cells respond distinctly to certain types of treatments. For example, CD34+ cells, which are the proposed tumor initiating cells in acute myelogenous leukemia (AML), express a specific enzyme that provides resistance to alkylating agents such as the chemotherapy agent cyclophosphamide[13]. Further, cancer cells can progress and mutate over time, and they may not respond to or can become resistant to existing therapies. As such, cancer therapies are not only required in the frontline setting, but new treatment options are also required in the relapsed or refractory settings. Many cancer patients require more than one treatment option, highlighting the need for the continual development and rapid access to therapies specific to cancer subtype and stage of disease.

THE REGULATORY REVIEW PROCESS IN CANADA

Chronic illnesses such as cancer are generally very costly to treat, and the majority of the cost is carried by the public system, mainly at the provincial/territorial levels, with some direct federal responsibility for certain patient populations. There are stringent regulations by these public funders that can limit or delay equitable access to effective and innovative cancer therapies. The entire process from research and development to marketing in Canada can take over ten years[19]. As a consequence, for example, the total overall life-years lost from the time of proof of efficacy to first public funding for eight drugs that treat in Canada for lung and breast cancers was 39,067 years[20]. Thus, it is critical to understand what scientific and clinical evidence is required to obtain Health Canada approval and reimbursement in order to determine where time and resources along this complex pathway can be minimized to increase accessibility for Canadian cancer patients.

To receive market approval in Canada for a new drug, the Health Products and Food Branch (HPFB) of Health Canada, Canada's federal national authority that regulates therapeutic and diagnostic products, must assess the safety, efficacy and quality of the drug[21]. Priority review processes are in place for cancer therapeutics, allowing for faster review. Information included in the New Drug Submission (NDS) consists of results of pre-clinical studies (proof of mechanism, dosing range, pharmacokinetic/dynamics, safety/efficacy)[22] and clinical trials (phase I – III), the location of the research (i.e. Canada or elsewhere), details about how the drug is manufactured, packaged and labelled, and health claims as well as important information about side effects and adverse events[23]. Clinical trial results are the basic information components for a drug review as they provide details on the drugs effectiveness, safety, optimal dosage and adverse reactions. Further, trials can also include valuable comparison data, comparing the new drug against already existing treatments, or against a placebo if no treatment exists, for the same indication. The importance of capturing patient reported outcomes at the clinical trial stage is also becoming more recognized, and more trials are adopting methodology to ensure the impact of a trial intervention is comprehensively assessed. Each phase of a clinical trial has a purpose: **phase I** tests for a safe dose range of a drug by determining the maximum tolerated dose; **phase II** assesses the safety and efficacy of the drug on a smaller patient population; **phase III** confirms the drugs effectiveness and safety and compares against other standard of care (SOC) treatments in a larger patient population; and **phase IV** involves monitoring to gather long-term outcomes including benefits and risks[24]. In 2019, Health Canada initiated a project to strengthen the use of real-world evidence (RWE) for drugs in regulatory submissions, recognizing the importance and use of RWE to assess safety and efficacy in the real-world patient population, which can be collected through observational data outside of an RCT[25].

With the information included in the Health Canada submission, the HPFB, sometimes with external consultants and advisory committees, will determine if the benefits of the drug are greater than the risks, and will further assess if the risks can be reduced[23]. Successful drugs are issued a NOC, i.e. official approval and permission for the pharmaceutical company to market the drug in Canada. The HPFB will not grant a NOC if there is not sufficient evidence to support safety, efficacy or quality claims. In this case, the pharmaceutical company has the ability to either supply additional information, re-submit at a later date with new supportive data, or ask the HPFB to reconsider their decision.

Regulatory Approvals Based on Limited Datasets

Regulatory bodies are addressing the need for drugs to treat diseases, including those for serious conditions. These agencies particularly recognize this need when the treatment is the first available therapy or is advantageous over existing treatments based on safety, efficacy and other relevant criteria. New measures have been adopted to bring promising new drugs to market faster. The Food and Drug Administration (FDA) in the United States has developed for example four distinct and successful review approaches: Priority Review, Breakthrough Therapy, Accelerated Approval, and Fast Track[38]. Priority and fast-track reviews reduce the review time (i.e. from 10 months to 6 months[39]) and increase communication with stakeholders to quickly resolve questions, often leading to earlier drug approvals and access[40]. Accelerated approvals in particular use a surrogate marker that is thought to predict clinical benefit but is not an exact measure of clinical benefit; for example, measuring tumor shrinkage as a predictor of clinical benefit versus waiting months to years to determine the extended survival for cancer patients[38]. The European Medicines Agency (EMA) also has a system in place to grant conditional marketing authorization for drugs with less robust clinical data available where the benefit for immediate availability outweighs the risk and fulfills an unmet need[41]. Health Canada's NOC/c is similar to these other HTA review processes, providing earlier access to drugs for "serious, life-threatening or severely debilitating diseases," such as cancer. The NOC/c expedites the process from market approval to funding recommendations, providing more time to gather clinical outcome data. Health Canada has granted NOC/c's for several innovative cancer therapies where the benefits are promising, but there is limited clinical evidence available to support. Since the last 2018 White Paper, CADTH and INESSS (Institut national d'excellence en santé et en services sociaux), the Quebec equivalent of CADTH, have more recently implemented parallel reviews with Health Canada pre-NOC to facilitate a more rapid review timeline[42]. Manufacturers have been able to apply for priority review with phase I or II non-comparative clinical trial data if infeasible to conduct a RCT, among other reasons. Occasionally, manufacturers submit applications with limited data sets (phase I/II) if the outcome data addresses an unmet need; this can be done while they await phase III trial results, such as seen with olaratumab and doxorubicin for advanced soft tissue sarcoma, or submission can occur without further trials ongoing or planned[43]. Though in this example uncertainty did exist related to overall survival caused by limitations of the phase II trial design, a time-limited reimbursement was provided based on the net clinical benefit and ability to address patient values and needs.

The specific criteria for Health Canada's implementation of NOC/c's are not transparent, as some phase I / II non-comparative trials have received approval while others have not; reasons published for the decision are either nonexistent or limited and vague. Based on a retrospective review of oncology products that received a NOC/c between 1998-2017, 90% of submissions to Health Canada were RCTs of which 73% had active controls, 47% were not blinded, and 57% used surrogate outcomes[44]. Health Canada has improved its transparency over the past years, now making publicly available the clinical study reports within 120 days of a decision, which will be released for all drugs over a four-year phased plan. In the situation where phase II trials provide safety and efficacy data in the trial population while addressing unmet clinical needs, the importance for providing a NOC or NOC/c based on these conditions may avoid the requirement for time-consuming phase III trials when an informed decision could be made based on smaller data sets in order to expedite drug reimbursement and access.

Almost half of all Canadians will develop cancer in their lifetime

1 in 4 Canadians will die of cancer

HEALTH TECHNOLOGY ASSESSMENT (HTA) AND PUBLIC DRUG REIMBURSEMENT ACROSS CANADA

With oncology treatments, many patients may not understand why treatments take longer to become available to Canadians. In Canada's complex public healthcare system, there are multiple steps in the HTA framework to assess the value (safety, efficacy, quality) of novel therapies and integrate them into publicly funded drug plans **(Figure 1)**. The HPFB section of Health Canada reviews the NDS often as the first step however, Health Canada's review can occur concurrently with the CADTH review process. CADTH is a non-for-profit organization responsible for providing an objective review of evidence to make informed recommendations to all provinces, except Quebec, about the value and implementation of cancer drugs into the pan-Canadian public drug reimbursement systems. INESSS is the Quebec equivalent of CADTH. Up until 2020, CADTH employed three review mechanisms: the Common Drug Review (CDR), the pan-Canadian Oncology Drug Review (pCODR), and the Interim Plasma Protein Product Review (PPP). Prior to 2020, all cancer therapies were submitted through the pCODR branch of CADTH. In June 2020, a proposed alignment of these three CADTH drug review processes into one was introduced[26]. Following an extensive internal review, discussions with stakeholders and consideration of input from over 80 organizations and individuals, CADTH made the decision to release a new system on September 30, 2020, that reduced duplication across jurisdictions, maximized the use of limited resources and enhanced the consistency of drug reviews by incorporating the best practices from each program. Highlights of the new alignment process includes the opportunity for drug manufacturers to provide commentary on scientific reports before expert meetings, stratification of reconsideration requests for additional flexibility prior to finalization, and providing patient and clinician groups with the opportunity to provide feedback on all draft recommendations[27]. Though implemented as of October 2020, these reimbursement review procedures are effective for all applications targeting the April 2021 expert committee meetings and onwards[27].

With their submission, some sponsors will submit to CADTH once they have received their NOC or NOC/c, moving through the review process sequentially. However, since 2018, Health Canada and the HTA organizations launched a joint initiative to facilitate information sharing, allowing for parallel reviews for sponsors filing HTA submissions on a pre-NOC basis, thus shortening the review length. Other programs have also been launched to allow for information sharing at the regulatory stage. Project Orbis, an initiative of the FDA Oncology Centre of Excellence that began in September 2019, was developed to provide a framework for concurrent submission and review of oncology therapies amongst international partners[28]. Through teleconferences under confidentiality agreements, the FDA's Office of Hematology and Oncology Products meets with other global regulatory agencies to allow for an exchange of information and collaboration related to drugs under review, with the hope of decreasing timely review processes for earlier access to products. The first Project Orbis action involved a collaboration between the FDA, Health Canada and the Australian Therapeutic Goods Administration for lenvatinib and pembrolizumab for advanced endometrial cancer, resulting in simultaneous decisions for accelerated, conditional and provisional approvals respectively[29].

Following Health Canada's review of preclinical and clinical results, Health Canada will grant a NOC if the benefits outweigh the risks or will grant a NOC/c contingent on the manufacturer carrying out additional research within an agreed upon timeframe to confirm the clinical benefit. The benefits of a NOC/c are two-fold: providing earlier access to the drug and allowing for monitoring of safety and efficacy through enhanced post-market surveillance initiatives[30]. A NOC/c has been granted for several innovative cancer therapies with limited data available, but with promising evidence of clinical effectiveness[30]. The NOC/c takes into account challenges with small patient populations, outcomes such as survival, mortality and morbidity, and measurement of the drug's effect on surrogate markers. This provides manufacturers with more time to accumulate clinical evidence while providing cancer patients with access to drugs of significant clinical benefit[30].

Though a NOC is required for marketing therapies in Canada, CADTH is one of the critical components to paving the path to public access. Once a sponsor submits a request for a drug review to CADTH, the pCODR expert review committee (pERC), a group of expert members including physicians, pharmacists, health economists, other healthcare professionals, patients and an ethicist, will consider a wide range of information including clinical practice guidelines, availability of comparator drugs, economics, clinical trial protocols and results, real-world evidence, and stakeholder input (patient groups, clinical experts, drug programs, expert committee members). CADTH uses a deliberative framework that analyzes clinical input, patient preferences, economic information, and ease of adoption into the present healthcare system. A literature search is often performed to supplement the information provided by the sponsor. Regarding clinical evidence, there is an emphasis on phase III RCT design with primary endpoints of overall survival (OS) and progression free survival (PFS) for positive recommendations[31]. CADTH also reflects on the input from patient and clinician groups, particularly when there is an unmet therapeutic need. Cancer is an intensely personal experience, and as such both clinical outcomes and the patient's experience and quality of life are equally important considerations. The final pERC decision is a non-binding recommendation to public drug reimbursors and can be any of the following: reimburse fully, denial of reimbursement, or reimburse if certain conditions are met. If a negative recommendation is issued by CADTH, this slows down, if not essentially halts the path to public access for new therapies since pan-Canadian Pharmaceutical Alliance (pCPA) will generally not consider negotiations for such a drug.

Following a positive or conditional recommendation by CADTH, the pCPA, an alliance of provincial, territorial and federal governments[32], will then review their recommendation to determine if the therapeutic will enter into the price negotiation phase; if so, participating provinces will choose a lead province for the negotiations[33]. If a decision is made to move forward with the negotiations, the governments will collectively undergo confidential pricing negotiations with the manufacturer. If an agreement is reached, a Letter of Intent (LOI) is signed, and each jurisdiction will subsequently undergo its own review process to determine whether and when the drug will be funded through its public drug plan[32]. The non-transparent nature of the pCPA negotiations, and the fact that it is not bound by any mandatory time frames to complete any aspect of, or all of its negotiations, are of concern to patients and manufacturers as this can lead to delays in equitable access to new drugs in Canada. The specific criteria involved in decision-making, review timelines and the negotiation process are not shared publicly[32].

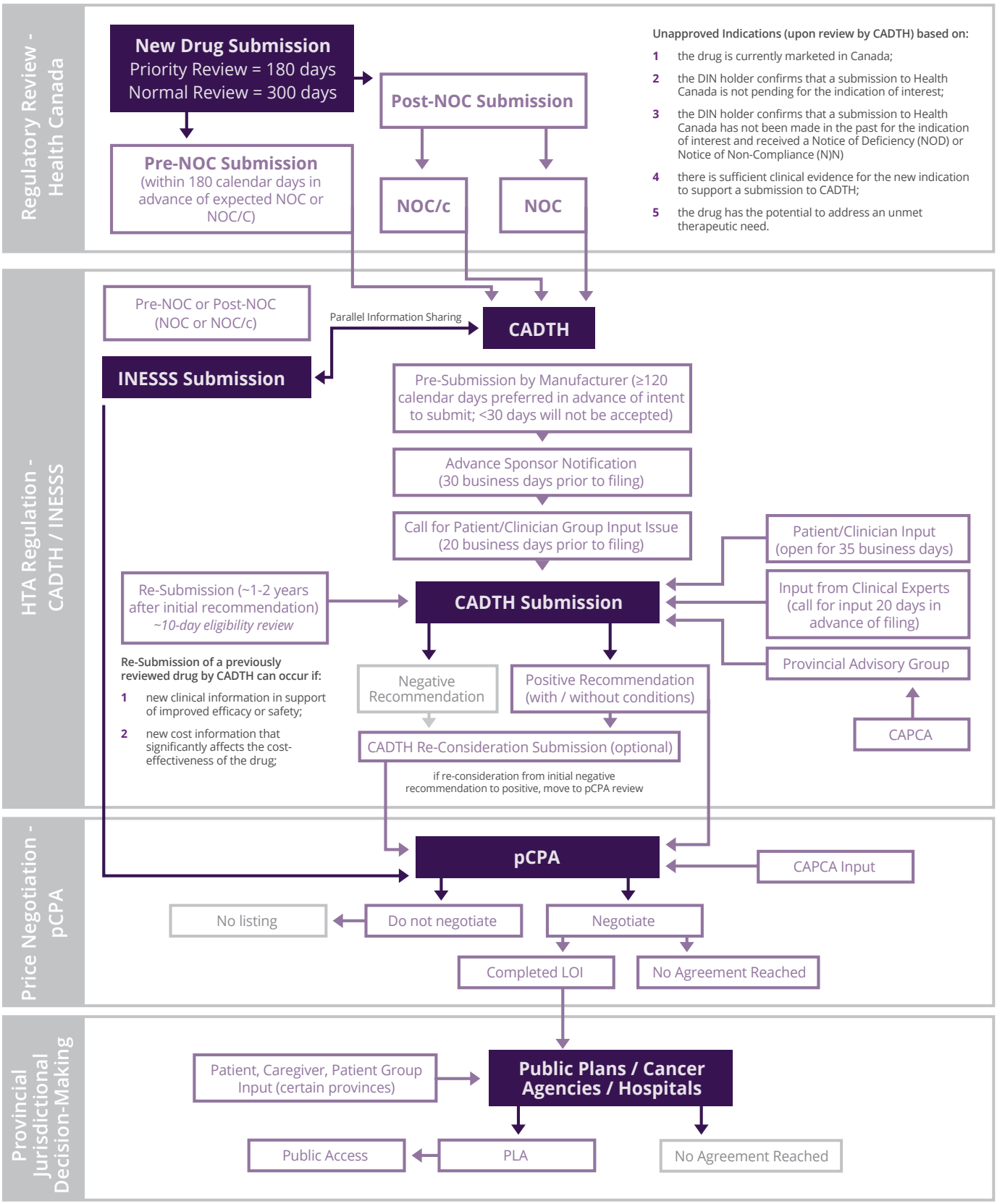
Once successful negotiations are completed, the drug will be considered by each public plan for reimbursement through the provinces or territories drug plans[33]. Each province will develop their own product listing agreement (PLA) with the manufacturer involving the negotiation

of confidential prices which can be achieved through rebates or could be tied to drug expenditures, utilization patterns and/or health outcomes; this can result in otherwise unattainable price discounts[34]. Even after collective negotiation, provinces and territories can refuse to list the drug in their formulary or can have different terms of access. As an example, the breast cancer medication anastrozole is publicly funded for 60/100,000 patients in British Columbia and for only 29/100,000 patients in Alberta[35]. As compliance with the recommendations varies between provinces, this leads to interprovincial inequities in treatments, for example with higher compliance as observed in British Columbia (81%) compared to lower compliance in Prince Edward Island (28%)[36]. Pembrolizumab, an adjuvant treatment for advanced melanoma, received a positive recommendation with conditions based on limitations in cost-effectiveness. As of 2021, it is now funded across all provinces except for PEI, and a 5-month gap can be observed between funding approvals in the first province to the most recent province[37]. This inequity issue is further exacerbated with higher-priced therapies with significant clinical benefit, as observed with CAR T-cell therapy for diffuse large B-cell lymphoma patients, which can cost hundreds of thousands of dollars per patient. Though regulatory review was relatively quick for the two CAR-T therapies (Tisagenlecleucel & Axicabtagene Ciloleucel) via Health Canada approval (September 2018/February 2019) followed by pCODR funding approval (January 2019/August 2019), there has been a significant delay in provincial funding decisions with only local access presently available in Quebec (Oct 2019), Ontario (Dec 2019), and Alberta (Aug 2020) for these manufactured CAR-T therapies. Further restrictions to this therapy have been put in place per province, allowing for only a total of approximately 60 patients to be able to access CAR-T on an annual basis. Ultimately, oncology patients have a risk for triple jeopardy in certain provinces, whereby they face the lack of local access to new cancer drugs that are approved in other provinces/territories, may be unable to access a new drug funded within their province if they do not meet the institutional or provincial eligibility requirements, and may experience a lack of full public coverage for therapies or must consider additional travel or treatment related costs[36].

Triple Jeopardy Impacts to Patients

1	2	3
Lack of local access to new cancer drugs that are approved in other provinces/territories.	May be unable to access a new drug funded within their province if they do not meet the instituitional or provincial eligibility requirements.	May experience a lack of full public coverage for therapies and may need to consider additional travel or treatment related costs.

Figure 1. Overview of HTA and Public Reimbursement Decision Pathway for Innovative Medicines in Canada.



Abbreviations: NOC (notice of compliance), NOC/c (notice of compliance with conditions), INESSS (Institut national d'excellence en santé et en services sociaux), CADTH (Canadian Agency for Drugs and Technologies in Health), pCODR (pan-Canadian Oncology Drug Review), pCPA (pan-Canadian Pharmaceutical Alliance), HTA (Health Technology Assessment), LOI (Letter of Intent), PLA (product listing agreement), CAPCA (Canadian Association of Provincial Cancer Agencies).

CHALLENGES OF PHASE III RANDOMIZED CONTROLLED TRIALS (RCTs)

Phase III trials are large randomized controlled studies that have often been considered the gold standard of medical evidence, providing reliable data and necessary comparisons against SOC that is required for treatment approvals in Canada. However, not only do challenges exist in conducting phase III trials, but more and more RCTs in oncology fail to lead to the registration of new therapies compared to RCTs in other diseases[45]. Early-phase trial failures (phase I/II) are often an expected occurrence, as these are exploratory and provide proof of mechanism and concept in patients[46]. However, it appears there is also a high failure rate (50%) for confirmatory phase III trials, an unexpected finding since early-phase trials should provide the necessary information to proceed with phase III testing, and as such, relatively few RCTs should fail[46]. Reasons for RCT failure can be a result of competitiveness in accelerating the transition from the early phases of drug development into the later phases, without the appropriate demonstration of pre-clinical and early-phase safety and efficacy[45]. Potentially efficacious drugs may fail to demonstrate efficacy as a result of improper study designs and endpoints, and/or safety which may become more evident in larger populations[47]. It is also crucial to identify an appropriate control group in the phase III trial design, especially when a standard therapy does not exist, such as in the case of adjuvant settings after curative resection of a solid tumor. In these scenarios, a strategy may exist by use of a placebo which may be feasible as a control treatment for some trials including biological agents like cytokines or monoclonal antibodies, but is seldom feasible in trials with cytotoxic agents due to side-effect profiles[48]. Further, many patients are concerned about being assigned to a placebo control group and not receiving the active study drug, which could impact recruitment to a trial[47,49]. Phase III trial design is complex, and if not optimized, can lead to reduced success or failure. Another component of phase III trial failure can be related to funding, whereby 22% of phase III trials failed due to lack of resources[50]. It is well-known that phase III trials are lengthy and complex as a result of the larger population enrolled and coordination across many centres, and even countries. Though research in Canada has not been analyzed to determine cost by trial phase[51], the US projections estimate the cost is $42,000 per patient in Phase III trials[47]. If the return on investment is low, there may be lack of interest on the part of industry to continue to develop new therapies or fund clinical trials, especially in more rare disease settings where not as many patients will be accessing the particular treatment once approved.

There are additional patient factors that can be considered as barriers to executing successful RCTs. Inclusion and exclusion criteria for clinical trials are strict and can lead to difficulties in enrolling suitable participants, especially with the larger sample size required for phase III trials. Targeted therapies may require genetic marker testing as part of their inclusion criteria. With certain molecular tests performed at diagnosis, these results may already be available and can prevent delays in accessing treatment, however if not previously tested, patients may need to wait to receive their results. Narrow inclusion criteria in general can also lead to longer recruitment times and

may eventually require amendments to modify protocol design to recruit participants[47]. This is even further exacerbated in trials for rare diseases or distinct cancer subtypes that have small patient populations; 25% of cancer trials fail to enroll enough patients, with 18% of these trials closing as a result[52]. This can have devasting impacts to advanced-stage patients hoping to access new therapies through a trial. Patients at the later stages of their disease where there may not be standard treatment or newer options available are often interested in clinical trials. Unfortunately, however, they may not be eligible based on heavy pre-treatment, either because of receiving therapies that may exclude them from the trial or due to deteriorating health and reduced survival time required for trial outcome assessments. With phase III trials requiring a longer timeline to assess survival endpoints and determine efficacy through OS/PFS, often patients with advanced stage cancer may not live long enough to confirm necessary trial endpoints. Further, there may be multiple trials enrolling patients with the same cancer subtype at the same time, further increasing the difficulty in recruitment. For example, a search of the Canadian Cancer Trials database yielded 51 recruiting trials for multiple myeloma[53]. Since the 2018 White Paper, there are still many similar challenges with conducting phase III RCTs. Novel considerations and adjustments to existing knowledge paradigms must be undertaken, especially in the current landscape with the COVID-19 pandemic effectively halting clinical trial recruitment for indefinite amounts of time and limiting hospital access for ongoing treatment and testing for active participants.

Use of phase II trial data on overall response and outcomes can potentially provide valuable information and should be given appropriate consideration, especially in the setting of targeted therapies that adhere to specific antigens or biomarkers on the cancer cell allowing for tumour response to be a valuable and useful outcome assessment.

In general, as oncology patients eligible for clinical trials are limited, each patient is extremely valuable. We should endeavour to obtain important information on efficacy and safety, as well as patient-reported outcomes, from each participant in all clinical phases of research, beginning with phase I[54]. Though phase III clinical trial designs can be optimized through modeling and simulation, adaptive designs and use of biomarkers[46], **adequate phase II testing with randomization may be a potential data source for regulatory bodies to consider, and agencies are recommended to provide further guidance on assessment criteria in this scenario.**

These structural and clinical barriers to phase III RCTs are evident in recent drug submissions. In the case of ibrutinib for Waldenstrom Macroglobulinemia (WM), a rare and incurable subtype of Non-Hodgkin's lymphoma, encouraging non-comparative trial data was used in the submission as there was no SOC in the relapsed/refractory setting and therefore no single comparator. Though promising results in phase II, supported by a non-randomized companion sub-study within the phase III RCT, revealed a 2-year OS of 95.2% and PFS of 69.1% in a heavily pre-treated population, this therapy did not receive a positive recommendation from pERC, halting the pathway to reimbursement and access to Canadians. This decision was largely based on the fact that the clinical benefit of ibrutinib could not be determined against the appropriate comparators. Since the decision in 2016, there have not been further trials or submissions for ibrutinib as a monotherapy for the WM indication in Canada. Due to the low number of WM patients, approximately 5 cases per million people per year in Canada[55], it is unlikely that further comparative research and submission will occur for Canadians to gain access to this treatment. Currently, there has been no indication for future submissions for this therapy.

Another recent example is enasidenib for relapsed/refractory AML patients. This patient population has a poor prognosis, with only 5-10% of patients surviving after 5 years, and if left untreated OS can be 2-3 months[56]. As acknowledged by pERC, this indicates a dire need for treatment options in this patient setting to improve health outcomes. For patients that achieved a complete or partial remission upon receipt of this therapy, the OS was 19.7 months or 14.4 months respectively with a median OS of 9.7 months[57]; this is compared to phase III trials of salvage regimens with a median overall survival of 3.3 months[58]. Though a notable improvement in OS, pERC noted that the net benefit of enasidenib could not be determined, even with anti-tumor activity, due to lack of direct comparators. With only 12% of patients harbouring the IDH2 (Isocitrate Dehydrogenase (NADP(+)) 2) mutation required to receive this treatment, and due to the poor survival in the relapsed/refractory setting, this further reduces the number of available patients to participate in larger clinical trials. pERC and CADTH's Clinical Guidance Panel (CGP) agreed that results from a phase III trial could provide comparative efficacy data and encouraged the ongoing phase III trial comparing safety and efficacy of enasidinib with conventional care regimens (azacitidine, cytarabine, or best supportive care). In a recent press release in 2020[59], it was announced that the trial did not meet its primary endpoint of OS, with no further information provided. Review of the clinical trial data when released may be able to offer greater insight into whether patient factors contributed to this result.

pCODR REIMBURSEMENT RECOMMENDATIONS FOR PHASE II DATA

Approval for cancer therapeutics in Canada is heavily dependent on clinical trials to rigorously confirm safety, efficacy and quality of the drug for the indication. Preclinical and clinical trial data are reviewed both by Health Canada and HTA regulatory bodies, with the latter performing additional review into economic evidence, patient values and adoption feasibility. Despite Health Canada's decision to provide regulatory approval through a NOC or NOC/c for cancer therapeutics, there has been a trend with NOC/c approvals to not receive reimbursement recommendations through CADTH. Though CADTH's evaluation framework is not transparent with regard to limited datasets, the findings from the 2018 White Paper highlighted trends in negative recommendations. Of the 101 oncology drug funding requests between January 1, 2012 - December 31, 2017, 20 submissions involved non-comparative clinical studies, 40% of which received a positive recommendation[3]. Recurring themes for positive and negative recommendations from this data revealed important components of pCODRs evaluation framework **(Table 1)**.

Table 1. Criteria Listed by CADTH for Positive and Negative Recommendations (2012-2017)

POSITIVE RECOMMENDATION	NEGATIVE RECOMMENDATION
• Significant unmet patient need • Lack of existing safe and effective treatment options • Small patient population • Infeasibility for RCT in target population	• Uncertainty of net clinical benefit due to non-comparative data • Ongoing RCT • Feasibility to conduct RCT in target population

When CADTH issues a negative recommendation, this nearly always prevents access to this treatment through public funding, with pCPA's decision to not negotiate collectively or individually at the provincial-territorial level. Should re-submission occur at a later point as clinical evidence becomes available, this may result in delays of up to 515 days to access innovative therapies if approved the second time around[3]. This delay severely impacts cancer patients as many are often at advanced stage disease, resulting in patients either not receiving treatment or requiring very sick patients to travel outside of Canada to receive therapy, paying out-of-pocket and further increasing their burden.

Therefore, transparency in the CADTH evaluation framework for limited datasets is essential for stakeholders to tailor their applications to meet the appropriate criteria for innovative therapies to become readily and equitably accessible to Canadian patients.

Though delays can happen throughout all stages of the regulatory and reimbursement process, one of the largest bottlenecks is at the pCPA level with provincial negotiations. The pCPA faces many challenges itself. As confirmed by Salek et al. (2019), between 2014 2016, the total time oncology therapies spent in the pCPA negotiation process increased by 180% (from 131 to 371 days) and the time to decision on whether to initiate or decline a negotiation increased 4.5-fold. The growing backlog of products awaiting a decision to negotiate by the pCPA is concerning. The time from pCPA negotiation to listing for oncology products ranges from 45-360 days, a much larger range than for non-oncology products (30-130 days)[32]. Timelines for negotiation are generally found to be shorter in British Columbia, Alberta, Saskatchewan, Manitoba and Ontario, but longer in the Maritime provinces[32]. The more recent pCPA Process Guidelines (April 2019) outlined target completion timelines and expectations to meet these with the hopes of improving and reducing delays: **1)** Initiation – Acknowledgement Letter (<10 business days from HTA recommendation), **2)** Consideration – Engagement/Close/Hold Letter (<40 business days from HTA recommendation), and **3)** Negotiation – Proposal/Counterproposal & 4) Completion (LOI/Close Letter) (<90 days from engagement letter)[60]. The multifactorial impacts to these review delays are uncertain, but it could be due to the inability to meet target timelines, lack of resources or incentives at the provincial level for expeditious review, or due to a lack of standardized negotiation criteria.

Moving from a centralized regulatory process to a decentralized process through public provincial formulary decision makers and payers leads to differences in listing price and implementation timelines observed between the provinces. Public payers do not have target or mandated timelines, nor are the pCPA LOIs binding. Further, pricing is a large challenge, whereby the 2019 PMPRB Annual Report from 2006-2019 showed a steep increase in the cost for oncology therapies based on a 28-day standard treatment from $3,555 to $9,320[61]. Many treatment regimens often use multiple medicines in combination, resulting in even higher costs. Though no general trend could be observed from listing rates due to small numbers in this study, it was found that British Columbia, Ontario, New Brunswick and Nova Scotia all had lower listing rates within an observed time period[32]. Though terms may be jointly negotiated, the LOI may not be uniformly implemented due to budget considerations, willingness to pay, and affordability by their respective provincial formularies. The accelerating oncology market has further shifted to higher-priced medicines alongside utilization and growth rates, thus increasing cost pressures on Canadian payers and beneficiaries[61].

To better understand CADTH's evaluation framework for limited datasets and how it has changed since the 2018 White Paper, funding recommendations from where the last White Paper left off (November 2017 – December 2020) were reviewed. pCODR issued 84 oncology drug funding requests[62] of which 79% (n=66) received a positive recommendation. Submissions with limited data sets were found in 21% (n=18) of applications, further identified by randomized (n=2) and non-randomized (n=16) clinical trials **(Table 2)**. Of these submissions, 55% (n=10/18) received a positive recommendation, with all recommendations conditional on improving the cost-effectiveness of the therapy; other conditions included receipt of more robust clinical data and feasibility of adoption.

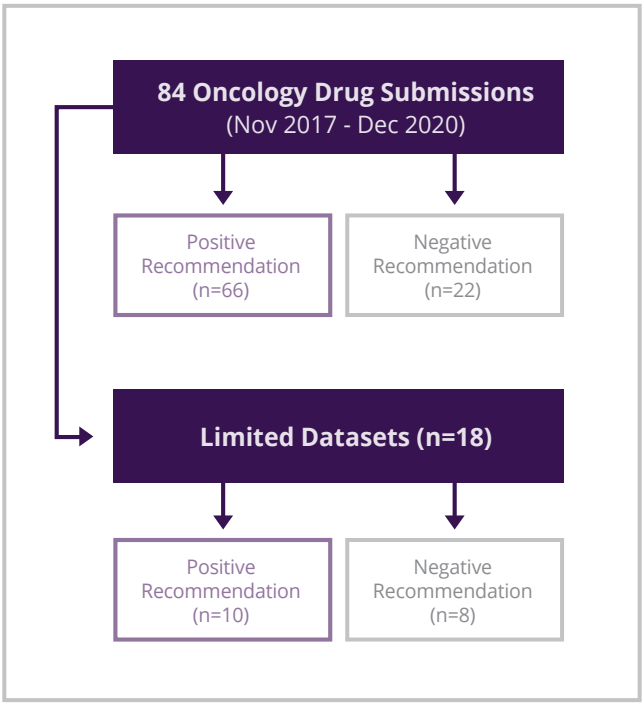


Table 2. pCODR Recommendations for Submissions Supported by Data from Phase II Clinical Trials.

Positive Recommendation Negative Recommendation

DRUG PRODUCT	FUNDING REQUEST	DECISION DATE	RECOMMENDATION	TYPE OF STUDY REVIEWED	REASONS FOR DECISION
Pembrolizumab	Classical Hodgkin lymphoma, relapsed/refractory	2018-01-05	Positive* (*if cost effectiveness is improved)	Two non-randomized, non-comparative trials: phase II, phase Ib	• Considered that there is a net clinical benefit • Substantial need for treatment options in small population • Uncertainty due to limitations in evidence from non-randomized, non-comparative study design
Venetoclax	Chronic lymphocytic leukemia, relapsed/refractory	2018-03-02	Positive* (*if cost effectiveness is improved and more robust clinical data be made available)	Phase II non-randomized, non-comparative trial	• Considered that there is a net clinical benefit • Improvements in PFS and OS • Unmet need for effective treatment options • Uncertainty due to limitations in evidence from non-randomized, non-comparative study design
Avelumab	Metastatic Merkel cell carcinoma	2018-03-21	Positive* (*if cost effectiveness is improved)	Phase II non-randomized, non-comparative	• Satisfied with net clinical benefit • No detrimental effect on QoL • Unmet need for effective treatment options • Manageable toxicities • Uncertainty of cost-effectiveness due to lack of comparative effectiveness data
Olaratumab	Soft tissue sarcoma, advanced	2018-04-18	Positive* (*if cost effectiveness is improved and more robust clinical data be made available)	One phase Ib non-randomized, non-comparative trial, one phase II comparative RCT	• Satisfied with net clinical benefit of olaratumab + doxorubicin • Improvement in OS • Manageable toxicities • Unmet need for effective treatment options • Uncertainty due to limitations in the evidence from available phase II clinical trial

Nivolumab	Classical Hodgkin lymphoma, relapsed/refractory	2018-05-03	Positive* (*if cost effectiveness is improved)	Two non-randomized, non-comparative trials: phase II, phase I	• Satisfied with net clinical benefit • Substantial need for effective treatment options in small populations • Uncertainty regarding comparison to other treatment options due to non-randomized, non-comparative study designs of available clinical trials
Nivolumab	Hepatocellular carcinoma, advanced/metastatic	2018-11-29	Negative	Phase I/II non-comparative, non-randomized trial	• Not confident of net clinical benefit due to limitations in evidence from available non-comparative, non-randomized clinical trial • Unable to determine how it compares with other treatments • Despite significant unmet need, not satisfied that it addresses need for more effective therapies • feasible to conduct phase III RCT
Lenvatinib	Clear-cell renal cell carcinoma, advanced/metastatic	2019-01-04	Negative	Phase Ib/II, comparative RCT	• Not satisfied with net clinical benefit of lenvatinib + everolimus compared to everolimus monotherapy • Uncertainty of clinical benefits due to limitations in evidence from available phase 1b/II RCT
Pralatrexate	Peripheral T-cell lymphoma, relapsed/refractory	2019-04-04	Positive* (*if cost effectiveness is improved and drug plan cost does not exceed drug plan cost of drug)	Phase II, non-comparative, non-randomized trial	• May be a net clinical benefit • Need for effective treatment options in small population
Blinatumomab	B-cell precursor acute lymphoblastic leukemia, Philadelphia Chromosome-positive, relapsed/refractory	2019-04-04	Positive* (*if cost effectiveness is improved)	Phase II, non-comparative, non-randomized trial	• May be net clinical benefit • Need for effective treatment options • Manageable toxicities • Uncertainty of cost-effectiveness due to lack of comparative data
Crizotinib	Non-small cell lung cancer, ROS1-positive, advanced, 1st line	2019-05-23	Positive (*if cost effectiveness is improved and feasibility of adoption is addressed)	Two non-comparative, non-randomized trials: phase I, phase II	• Considered that there is a net clinical benefit • Improvement in PFS, OS • Unmet need for effective treatment options

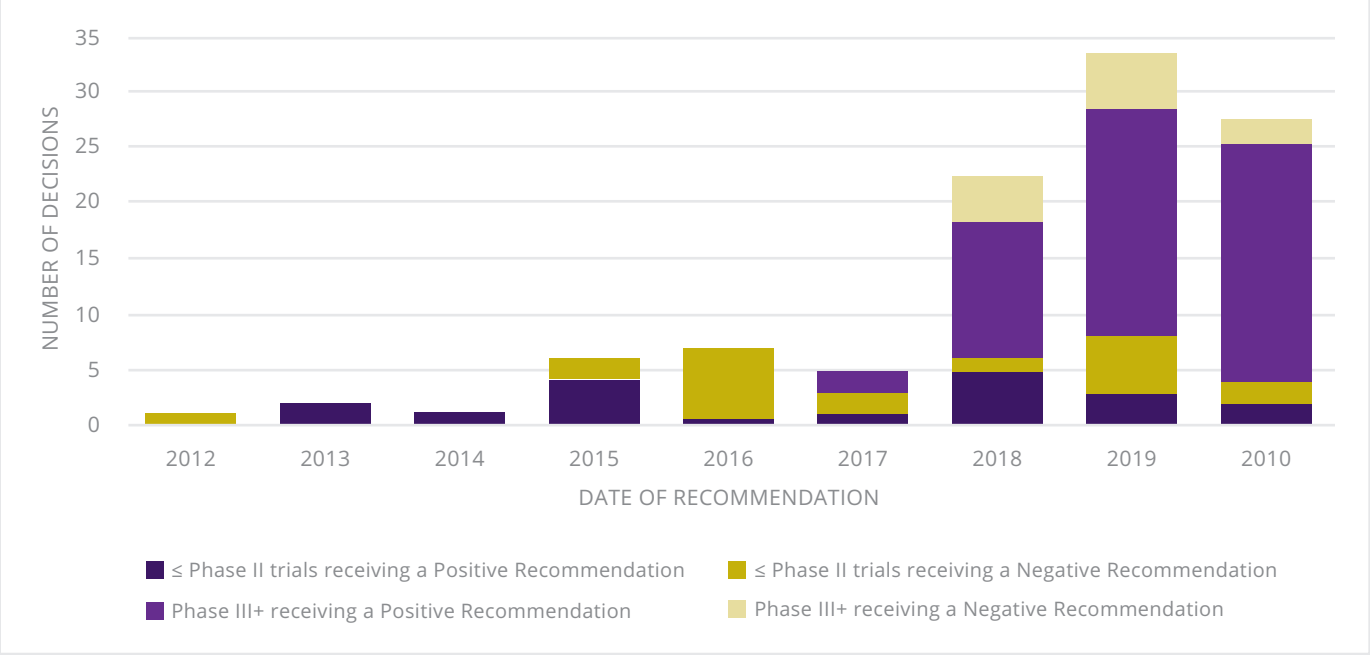
Brigatinib	Non-small cell lung cancer, ALK+, locally advanced/ metastatic	2019-08-01	Negative	Two non-comparative, non-randomized trials: phase II, phase I/II	• Not satisfied with net clinical benefit compared with alectinib, ceritinib or single-agent chemotherapy due to limitations in evidence from available trial. • Unable to determine how it compares with other treatment options due to lack of robust comparative data
Trifluridine and Tipiracil	Colorectal cancer	2019-08-29	Negative	Two non-comparative observational studies	• Significant limitations to evidence (non-comparative, no baseline QoL data prior to treatment) • Observed outcomes cannot be attributed to treatment over BSC • Acknowledges treatment alignment with patient values, benefit of oral administration, manageable toxicities, and modest clinical effect compared to placebo and BSC
Pembrolizumab	Urothelial carcinoma, PD-L1 expression	2019-10-03	Negative	Phase I/II, non-comparative, non-randomized trial	• Not confident of net clinical benefit due to limitations in evidence • Ongoing RCT
Enasidenib	Acute myeloid leukemia, IDH2 mutation, relapsed/ refractory	2019-10-31	Negative	Phase I/II, non-comparative, non-randomized trial	• Unable to conclude net clinical benefit compared to other treatments • Ongoing RCT
Cemiplimab	**Cutaneous squamous cell carcinoma**	**2020-01-22**	**Positive* (*if cost effectiveness is improved)**	**Phase II, non-comparative, non-randomized trial**	• **May be net clinical benefit** • **Substantial need for treatment options in small population**
Lorlatinib	Non-small cell lung cancer, ALK-positive	2020-01-30	Negative	Phase II, non-comparative, non-randomized trial	• Not confident of net clinical benefit due to limitations in evidence • Feasible to conduct RCT
Midostaurin	Aggressive systemic mastocytosis/ systemic mastocytosis with associated hematological neoplasm/ mast cell leukemia	2020-04-02	Negative	Phase II, non-comparative trial	• Not confident of net clinical benefit due to limitations in evidence
Blinatumomab	**Acute lymphoblastic leukemia, Ph -, CD19 +**	**2020-10-29**	**Positive* (*if cost effectiveness is improved)**	**Two phase II, comparative, non-randomized trials**	• **May be a net clinical benefit** • **Maintenance of QoL**

Abbreviations: RCT (randomized control trial), PFS (progression-free survival), OS (overall survival), QoL (quality of life), ROS-1 (ROS Proto-Oncogene 1, Receptor Tyrosine Kinase), ALK (anaplastic lymphoma kinase), PD-L1 (Programmed death-ligand 1), IDH2 (Isocitrate Dehydrogenase (NADP(+)) 2), Ph-CD19+ (B-lymphocyte antigen, Cluster of Differentiation 19), BSC (best supportive care).

Of the 84 submissions, there was one notable re-submission between 2017-2020. Trifluridine and Tipiracil for colorectal cancer patients received dual negative recommendations from pCODR with the review and re-submission process amounting to a total of 661 days. Though three comparative RCTs were provided for support in the first submission showing modest PFS/OS and moderate toxicities compared to best supportive care while aligning with patient values, there were inconsistent results between trials and uncertainty on the impact to quality of life resulting in a negative recommendation. The second submission provided RWE on health-related quality of life. However, this re-submission still received another negative recommendation even while acknowledging that it aligns with patient values, has modest net clinical benefit, and has manageable toxicities. With many methods and designs available to collect quality of life data, the design employed was non-comparative and collected QoL post-treatment following completion of the clinical trial. Lack of appropriate QoL data capture during the intervention was a major reason for the initial negative recommendation, and though QoL data was provided at the time of re-submission, the data was not collected in accordance with pERCs criteria. Therefore, this treatment received a second negative recommendation, denying access to a therapy with clinical benefit that aligns with patient values.

On a more encouraging note, the number of positive recommendations based on limited data sets increased from 2012-2017 (40%) and the 2017-2020 time period (55%) **(Figure 2)**. This could be a result of a more thorough understanding by the sponsor of CADTH's evaluation framework and are thus able to tailor submissions with limited datasets to highlight important findings and themes. Another theory is that CADTH is becoming more aware of the importance of limited data sets that fulfill an unmet patient need for treatment. There are certain circumstances that support the acceptability of Phase II datasets. As previously discussed, Phase III trials may not be feasible to conduct for a variety of reasons including scenarios with smaller patient populations or lack of standard therapy for a comparator arm. Thus, Phase II trial data that provides a net clinical benefit and addresses the infeasibility of Phase III RCTs may be considered. Therapies that align with patient values and address disease burden, involve fewer side effects and improve quality of life, can be exemplified through Phase II data.

Figure 2: Recommendations for Submissions with Evidence from Comparative and Non-Comparative Trials.



Note: The blinatumomab submission was scored as 50% positive, 50% negative, based on the mixed recommendation for this file in 2016. Data from 01-2012 to 11-2017 from the original white paper did not include comparative trial submissions (i.e. Phase III+).

Themes in pCODR's rationale for positive or negative recommendations between 2017-2020 have been summarized **(Table 3)**.

Table 3. Criteria Listed by pCODR for Positive and Negative Recommendations (2017-2020)

POSITIVE RECOMMENDATION	NEGATIVE RECOMMENDATION
• Net clinical benefit of therapy (i.e. improved PFS and OS) • Substantial unmet need for treatment option, often in small patient population • No detrimental effects to QoL, or increased QoL; Manageable toxicities	• Limitations in evidence/minimal confidence in net clinical benefit (non-randomized) • Unable to determine how it compares with other treatments (no comparator); or net clinical benefit cannot be confirmed against comparator arm • Despite significant unmet need, does not address need for more effective therapies • Despite ongoing phase III RCT, received negative recommendation as data was not available at the time of submission for review

The reasons provided for a positive or negative recommendation, included both in **Table 1 and 3** for different time periods, are consistent with more recent research on CADTH's evaluation framework. Andersen et al. (2019) found that no drugs with a NOC/c were given an unconditional recommendation for public reimbursement; conditional recommendations were provided in these scenarios based on required improvements in cost-effectiveness. For therapies that received a negative recommendation, pERC cited insufficient evidence to conclude a significant clinical benefit compared to existing treatments, however response to treatment (i.e. safety issues including toxicity and resultant harm) was felt to outweigh the evidence of clinical outcomes[42]. This concludes that CADTH is less likely to recommend public reimbursement without evidence of both clinically meaningful benefits and safety. Similarly, another review on solid tumors concluded 92% of the positive CADTH recommendations (72/78 positive recommendations; 104 submissions total) received a conditional recommendation, while 8% received a positive recommendation outright[31]. Though statistically significant differences between positive versus negative recommendations could not be concluded based on

tumor type, drug class, treatment setting or line of therapy, there were significant differences dependent on trial characteristics and whether the therapy addresses a significant unmet need[31]. Meyers et al. (2021) revealed that even Phase III trials with primary endpoints of PFS and OS must exhibit substantial clinical benefit according to the European of Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) scores. A final study highlighted uncertainties related to limitations in clinical trials including trial validity (selection bias, reporting bias, performance bias, attrition bias), population (sample is generalizable to clinical practice, power), comparators (lack thereof or comparison with placebo where drug benefit is substantial), outcomes (use of unvalidated endpoints, missing patient-centered outcomes particularly related to OS and health-related QoL), and intervention (duration of treatment, adoption feasibility, administration of drug) which should be addressed in submissions if they exist with appropriate reasons provided[63].

Decisions supporting positive recommendations for limited data sets include compelling Phase II data, small patient populations, lack of alternative/effective treatment options, and lack of feasibility to conduct Phase III trials[64]. This is further corroborated by another review where "overall clinical benefit", unmet patient need, alignment of patient values, and lack of feasibility for RCT were significantly associated with a positive recommendation[65]. pERC does not provide transparency on its deliberation process for the feasibility of Phase III RCTs, but decisions are generally impacted by sample size and the availability of other comparator drugs for the same indication. Negative recommendations have been associated with ongoing RCTs or the feasibility of conducting a RCT according to pERCs evaluation framework.

A full comparison of recommendations based on Phase II data between the 2012-2017 and 2017-2020 review periods can be found in **Table 4.** Many of the themes leading to a positive recommendation compared to a negative recommendation are similar between the two time points and is supported by additional research[42,31,63]. Between 2017-2020, it was noticed that though a treatment addresses a significant unmet need in a patient population, two submissions (Trifluridine+Tipiracil; Nivolumab) received negative recommendations as they did not address the need for more effective treatment options for this patient population. Further clarity by CADTH on the evaluation criteria in these scenarios is welcome.

Our recommendations for submissions to CADTH and INESSS with limited datasets are two-fold: 1) utilize CADTH and Health Canada's new initiative to receive parallel scientific advice to ensure awareness of required evidence for market authorization and reimbursement[66] and 2) based on the information provided in this White Paper and corroborated by other research studies on CADTH's evaluation framework, stakeholders should tailor their submission to ensure uncertainties in the dataset are addressed, while emphasizing the important unmet needs addressed by the therapeutic.

Table 4. Comparison of Metrics for Recommendations on Limited Datasets between 2012-2017 and 2017-2020

METRIC	2012-2017 REVIEW PERIOD	2017-2020 REVIEW PERIOD
Total number of pCODR submissions (oncology products)	101	84
Number of Phase II or non-comparative trials reviewed	20 (20%)	18 (22%)
Positive Recommendation	8 (40%)	10 (56%)
Positive Recommendation Criteria issued by pCODR	• Significant unmet patient need • Lack of existing safe and effective treatment options • Small patient population • Infeasibility for RCT in target population	• Net clinical benefit of therapy (i.e. improved PFS and OS) • Substantial unmet need for treatment option, often in small patient population • No detrimental effects to QoL, or increased QoL; Manageable toxicities
Average Length of time from positive recommendation to first provincial funding	177 days	455 days
Average Length of time between positive recommendation and funding decision within provinces	862 days (2013-2020 follow-up period) * # **Appendix Table 5A**.	148.4 days (2018-2020 follow-up period) * # **Appendix Table 5B**.
Negative Recommendation	12 (60%)	8 (44%)
Negative Recommendation Criteria issued by pCODR	• Uncertainty of net clinical benefit due to non-comparative data • Ongoing RCT • Feasibility to conduct RCT in target population	• Limitations in evidence lowering confidence in net clinical benefit (non-randomized) • Unable to determine how it compares with other treatments (no comparator); net clinical benefit cannot be confirmed against comparator arm • Despite significant unmet need, does not address need for more effective therapies. • Despite ongoing phase III RCT, received negative recommendation as data was not available for review
Re-submissions due to lack of evidence (initial negative recommendation)	7 re-submissions; * # **Appendix Table 5C**	1 * # **Appendix Table 5D**
Positive Recommendation	6; 1 pending	1
Negative Recommendation	0	0
Time Length (initial submission to final approval)	710 days	849 days
Time Length (initial submission to final funding)	952 days	pending

 # Tables 5A-D for review in the appendix.

** all therapies are still not approved for funding in at least one province.*

LEARNINGS, COMPARISONS AND IMPROVEMENTS

HTA Submission Processes in other Countries: Important Learnings for Adoption

It is important to understand how Canada ranks against other countries in its HTA review and submission process to identify barriers and new opportunities to streamline the current system based on global strategies. Canada is comparable to the other countries that make up the Organisation for Economic Co-operation and Development (OECD), a total of 37 countries, in their number of therapeutic launches (124 launches between 2011-2018, compared to OECD20 median of 128)[7]. Canada's reimbursement rate for rare orphan and cancer drugs that treat unmet needs however were significantly lower than OECD countries, reimbursing 74% and 82% of drugs respectively compared to 100% in the OCED20 top and median countries[7]. Generally, for all treatments, Canada ranks 18th out of the 20 OECD countries based on the time from first authorization to public reimbursement[7]. Though Canada's regulatory review for oncology products is on par with the EMA, and longer than the FDA[67], its slow public reimbursement is primarily attributed to longer pCPA timelines as compared between submissions in 2013-2015 to 2016-2017[7]. With Canada's global ranking this can impact pharmaceutical decisions on investment of resources to enable access to innovative therapies in a country with a smaller population and a longer and complex review system. Manufacturers are likely to submit to Europe for market authorization prior to submitting to Australia (on average 81 days later) and Canada (on average 73 days later)[68].

To understand more about the HTA process and evaluation criteria, Canada was compared against other countries. Canada has a similar HTA process compared to Australia with parallel regulatory/HTA review, whereas the United States does not have a standardized HTA process following FDA approval, which allows for more rapid approval times but can potentially prevent population-wide access[7]. The CADTH review process takes into account the quality of evidence (i.e. RCTs) and clinical benefit, while the US has a focus on response rates[31]. Other countries with similar HTA processes and funding models to Canada such as the United Kingdom and New Zealand, do not provide transparency on the type of evidence received in a submission to determine similarities in evaluation criteria[65]. Australia cites preferences for Phase III RCTs but does not exclude non-RCTs from submissions[69]. Though, Canada's multi-layered and sequential drug review and public reimbursement processes provide multiple assessments for quality of a therapy, it can delay access to treatments for serious life-threatening conditions compared to other countries. It is important to note that there are processes that have been developed to help patients gain access to therapies sooner. Certain European countries have developed new approaches and programs such as managed-entry agreements. The Cancer Drug Fund in the UK, operational since 2016, provides access to promising new treatments while further evidence is being collected to address any

clinical uncertainty, providing interim funding for all newly recommended cancer drugs many months earlier[70]. The compassionate use programs in Germany have been available since 2010, wherein medicinal products without market authorization are made free of charge for administration to patients with a seriously debilitating disease or whose disease is life-threatening and who cannot be treated satisfactorily with an authorized medicinal product[71]. There are currently over eight cohort compassionate use programs, mostly in oncology[72]. France has a similar program in place, the Temporary Utilization Program (UTA), with over 205 new medicines available to patients as reported in 2016[72]. Similarly, Canada's Special Access Program (SAP), and even some provincial exceptional access programs (EAP), can provide access to unlicensed medicines. However, this is on a per request basis and is not set-up in a way that enables provision to treat groups of patients or receive automatic re-supply.

It is our recommendation that Canada builds on the strengths displayed in other systems around the world, including adopting parallel review processes, early access programs, and establishing performance criteria and standards to streamline review and ultimately shorten wait times to access innovative therapies.

Importance of Real-World Evidence

Real-World Data (RWD) are the data relating to patient health status and/or care and can be collected from a number of sources such as electronic medical records, product/disease registries, in home-use settings, claims/billings, and mobile devices[73]. **Real-World Evidence (RWE)** is the clinical evidence regarding use and benefits/risks of a medical product or therapy derived from analysis of RWD[73].

RWE is the evidence obtained by the collection of large quantities of data from diversified sources outside of the scope of a RCT, some or all of which may be relevant to the HTA review and price negotiation processes. The limited weight or importance attributed to RWE in a CADTH submission and decision may be due to lack of acceptance of such data as being a source of robust clinical evidence, lack of internal guidance and criteria on whether RWE can be included in a submission, variable analysis and interpretation of RWE, cultural barriers against the use of RWD, and emphasis on the adherence to evidence hierarchies[74,75,76,77]. However, RWD could provide valuable information as patients enrolled in RCTs are highly selective (i.e. meet strict eligibility criteria) and therefore may not be representative of the target population over a long period of time. These populations could potentially differ in comorbidities, co-medications, genetic and molecular profiles, behaviours, perspectives and outcomes[74]. The impact of social determinants of health may also be relevant.

Therefore, clinical evidence from RWD should not only be used to enrich the evidence of support for uncertainties in HTA submissions, but with larger, long-term databases in existence, can provide potential evidence without the possible requirement for further RCTs.

RWD can include observational studies (i.e. cohort, case-control, case-series), electronic health records or medical chart reviews, disease registries, administrative data or surveys, home medical devices or wearable technology, or pragmatic studies (large simple or practical clinical trials)[74]. Sources of RWD in Canada include provincial cancer

agencies such as the Ontario Ministry of Health and Long-term Care (MOHLTC) Evidence Building Program (EBP) for cancer drugs, Alberta Health Services (AHS) and the British Columbia Cancer Agency (BC Cancer), as well as large-scale Electronic Medical Record systems as implemented through Canada Health Infoway. There are also datasets of RWD created by patient organizations and by private companies. It is important to note that each system collects and releases data differently. Some systems involve thorough and lengthy procurement times (i.e. ethics approvals), may lack consistent and standardized data capture, and provide variable delivery options (i.e. tested datasets, data dumps). **Thus, we recommend the development of a national cancer registry that allows for the standardized collection and upload of RWD from each province, thus providing access across Canada.**

With a mandate to gather information about pan-Canadian public datasets, the Canadian Real-world Evidence for Value of Cancer Drugs (CanREValue) multi-stakeholder collaboration of working groups (excluding industry and patient engagement) was set up over a 4-year period[78]. Initial results from the CanREValue initiative, beginning with stakeholders in cancer control, indicated important findings to clarify the intended outcomes for RWE in decision-making:

1) Culture shift to trust RWE and accept its uncertainty (i.e. susceptible to bias, confounding), and shift away from sole reliance on RCT;

- Manage uncertainties through conditional approval, where data capture can continue until the data has matured to provide evidence for a final decision in public funding.

2) Canadian data infrastructure is currently inadequate for decision-making as its collection is not standardized, it is not embedded into clinical workflows, and often is missing key measures (i.e. patient-reported outcomes);

- Key improvements necessary for RWE use include standardization of data collection, creation of a unified pan-Canadian data collection infrastructure, and adaptation of a learning health system approach for use of RWE in public funding decisions.

3) Lack of capacity to financially support generation of RWE and lack of clarity in dividing costs publicly and privately;

- Invest in training programs for RWE analyses; use RWE at smaller provincial levels to work out issues before pan-Canadian adoption.

4) Need for increased collaboration among key stakeholders;

- Determine whether a role for industry exists in the development and ownership of RWE early-on.

These findings can provide valuable insights towards the preparation of a national cancer registry to determine best practices to collect and disseminate RWE.

Research and opinions collected on the importance of using RWE in decision-making is beginning to impact the Canadian system. Health Canada and CADTH recently announced (22-June-2020) the co-development of an action plan to incorporate RWE into regulatory and reimbursement decision-making in Canada[79]. RWE has been successful in providing sufficient quality of evidence to support efficacy and safety outside of oncology in Canada, as with deferiprone for iron transfusion overload due to thalassemia[74]. With high hopes for the future, Health Canada and CADTH will value and weigh the incorporation of RWE into final decisions for cancer therapeutics.

COVID-19 Lessons Learned: Clinical Trials, Vaccines and Approval Processes

An Example of a Modified Model

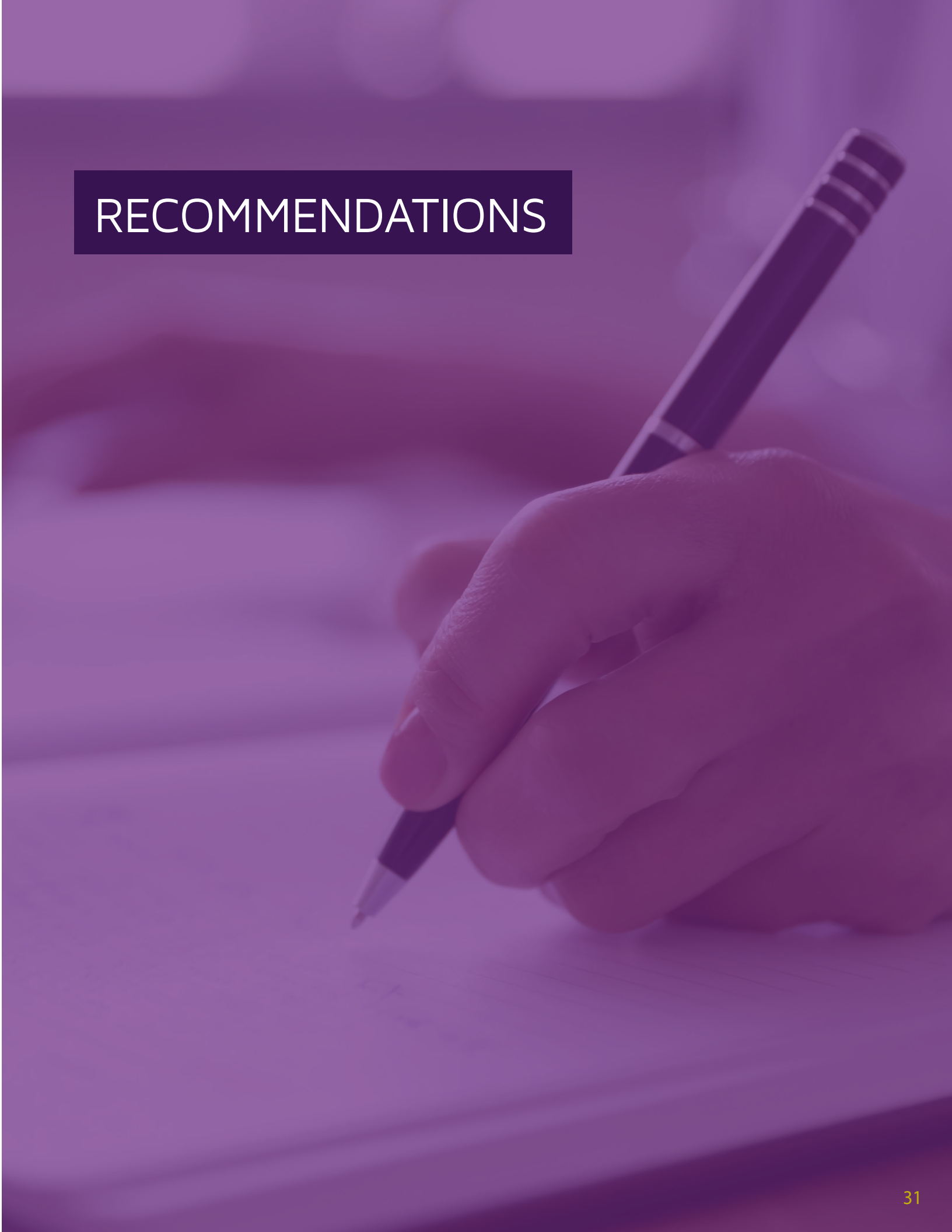
There are many lessons learned about clinical trials and regulatory reviews from the COVID-19 global pandemic. Historically, the clinical trial structure and process in Canada has remained non-adaptive to the needs of the patient and healthcare system, and a number of the processes that delay clinical trial implementation and completion have not been changed or expedited. With the onset of the COVID-19 pandemic, most of this has been modified since March 2020, including:

1. Clinical trial approvals have been expedited through Health Canada for vaccines, shrinking the often lengthy delay of approval to approximately six months;
2. The review of clinical trial results is now being done on a "Rolling Review" basis. Previously, Health Canada would not review trial results until all the data from the trial was available. Now, reviewers are analyzing the data as it becomes available, which significantly decreases review and approval times;
3. Phase II data are sufficient to make the vaccines available under authorization for emergency use regardless of the HTA guidelines that Phase III data is required for sufficient for analysis;
4. Neither head-to-head clinical trials nor systematic or comparative real world data collection and analysis of the vaccines was undertaken prior to access;
5. Phase IV trials have not been mandated as a condition of approval;
6. Little subpopulation analysis has been undertaken or mandated.

We recommend that a full analysis of all of the lessons learned with the COVID-19 vaccine trials regarding implementation and access in Canada, with the hope that these methods (or the learnings therefrom) are considered in standard operation where appropriate to ensure access to life-saving drugs for potentially fatal conditions or conditions that severely impact quality of life.

It is important to note that though there are important lessons learned from the expedited COVID-19 vaccine trials, there are still many unanswered questions as a result of trial design and short length of trials resulting in lack of long-term data and follow-up on trial participants. Generally, cancer patients were not included in the trials and the few that were included did not have population-specific analysis. It is uncertain therefore, what the antibody response rates are in these patient populations, especially in those whose cancer can affect the immune system to different degrees. Thus, it is uncertain whether some or all cancer patients will mount the same antibody response to the COVID-19 vaccine as would healthy individuals included in the trial. Further, the long-term effectiveness and safety of the COVID-19 vaccines remain unknown as clinical trials only examined patient response for less than six months.

RECOMMENDATIONS



FINAL OPINION STATEMENT AND RECOMMENDATIONS

Health Canada, CADTH/INESSS, the pCPA, and provincial funding bodies have individual processes to ensure the safety and efficacy of oncology drugs, and feasibility of implementation. However, these sequential review processes involve time-consuming and burdensome deliberations, resulting in long delays for much-needed medicines. Innovative therapies in oncology hold remarkable potential to transform treatment and increase survival, especially in advanced-stage patient populations. Though the systems in place to increase access to innovative therapies are adapting to optimize and streamline the review processes, especially with limited datasets, there is further action to be taken to increase efficiency, support timely access to therapeutic products, and build better linkages within the healthcare system for ideal implementation. With smaller non-randomized or non-comparative trials, mechanisms to tailor applications to meet evaluation criteria for timely and successful review can be implemented addressing specific components of the disease and setting, patient needs, and feasibility of further trials.

We propose the following recommendations:

- **Phase II data can potentially provide valuable information and should be given appropriate consideration, especially in the setting of targeted therapies that adhere to specific antigens or biomarkers on the cancer cell allowing for tumour response to be a valuable and useful outcome assessment.**

  Recommend agencies to address the possibility to consider phase II testing with randomization as a potential data source, and if so, provide guidance on assessment criteria.

- **Increase transparency of CADTH's and INESSS' evaluation criteria and framework for limited datasets and share publicly, using case studies where required and appropriate.**

  Include information and guidance specific to the alignment of patients needs, unmet needs for the indication, lack of comparative or standard treatment, required primary endpoints, feasibility of RCT Phase III+, implementation feasibility/cost-effectiveness, etc.

  Recommend manufacturers and stakeholders to tailor their submission to ensure uncertainties in the dataset are addressed, while emphasizing the important unmet needs addressed by the therapeutic.

- **Increase use of collaboration with international regulators for joint reviews, or utilize past reviews and foreign decisions, such as through Project Orbis, to increase efficiencies and expertise in the review process and support access to products not otherwise available in Canada.**

- **Develop and strengthen the use and sharing of RWE via a national cancer registry for application in regulatory and HTA submissions to increase evidence for improved decision-making. Establish how to use RWE where there is uncertainty with clinical or pharmacologic evidence to address a significant unmet need.**

  Incorporate findings and collaborate with stakeholders to establish infrastructure for RWE (improve data collection mechanisms, ensure privacy, increase expertise, data-sharing and collaboration, share financial cost, increase sources of evidence, etc.) and determin how RWE can be incorporated (establish criteria frameworks and uncertainty) into decision-making.

- **Adopt and streamline parallel review processes by providing a greater time overlap (>180 days currently) between Health Canada and CADTH reviews, and integrate external feedback throughout review.**

  Provide stakeholder with the opportunity to consent to information-sharing to avoid operational deficiencies and maximize benefits and opportunities during review.

- **Recommend a full analysis of all of lessons learned with the COVID-19 vaccine trials regarding implementation and access to vaccines in Canada, in order to adopt or adapt these methods into as standard operation practices where appropriate, thus ensuring access to other life-saving treatments for potentially fatal conditions or conditions that severely impact quality of life.**

- **Increase patient and clinician feedback opportunities throughout all levels of evaluation and provide adequate timelines.**

  Where no patient organization exists to facilitate submission of patient feedback: 1) create template/ framework for individual submissions that can be available for download; 2) promote to the general population through various outlets that patients frequent including cancer agencies, support groups, social media outlets etc.

  Share available clinical research and data on therapeutic under review with clinicians to assist in preparing feedback.

- **Increase transparency for review procedures and actions by the pCPA and develop a more streamlined process that provides and meets target timelines, detailing criteria required to meet timelines specific to each therapy.**

  Explore the possibility for parallel HTA and pCPA reviews to allow pCPA negotiation information to feed back into the HTA review and recommendation. This would allow the HTA review to re-evaluate cost-effectiveness where therapeutic value is shown, allowing for a HTA recommendation at a cost already negotiated.

- **Where provinces delay access or differ in public funding decisions resulting in inequitable access to therapies, ensure the availability of a provincial funding program by the referring province to provide travel and accommodation support for patients to reduce out-of-pocket costs when referred to another province to receive therapy. This will allow for equitable treatment access, until the time where treatment is locally accessible in all provinces, while limiting the burden to the patient.**

  Further, ensure this provincial support program is available for patients within the province where access to a treatment centre may cause out-of-pocket costs due to living far away from the treatment center.

To implement the many recommendations listed above will require joint leadership between each of the provinces with Health Canada, CADTH and INESSS. The first step would be to understand each province and cancer organizations position on the current processes and their ability and willingness to participate in streamlining and adapting the current systems in place. With this information, collaborations can flourish to coordinate efforts. Further, clinicians, researchers, and patient leaders within each province, along with policy and regulatory specialists, would be necessary collaborators to streamline the processes within each province. With these coordinated efforts throughout every level of the drug review and implementation process, these recommendations can become a reality to achieve more rapid access to innovative cancer therapies in Canada.

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APPENDIX

Sub-Table 5A. Positive Recommendations and Funding Decision Statistics between 2012-2017.

DRUG	INDICATION	DATE OF APPROVAL	1ST FUNDING RECEIVED (PROVINCE/ DATE)	DELAY FROM PCODR APPROVAL TO 1ST FUNDING `	LAST FUNDING RECEIVED (PROVINCE/ DATE)	DELAY FROM PCODR APPROVAL TO LAST FUNDING	DELAYS BETWEEN PROVINCES
Brentuximab Vedotin	Hodgkin lymphoma, 3rd line	29-08-2013	SK (04-02-2014)	159 days	NL (25-06-2018) *Still under provincial consideration (PEI)	1762 days and pending	1603 days and pending
Brentuximab Vedotin	Systemic ALCL, 2nd line	05-12-2013	SK (04-02-2014)	62 days	NL (25-06-2018) *Still under provincial consideration (PEI)	1664 days and pending	1602 days and pending
Vismodegib	Basal cell carcinoma advanced	10-01-2014	ON (16-04-2014)	97 days	NS (29-12-2014) *Still under provincial consideration (PEI)	354 days and pending	257 days and pending
Bosutinib	CML, 2nd-line or more	21-04-2015	SK (28-12-2015)	252 days	BC (01-12-2016) *Still under provincial consideration (PEI)	591 days and pending	339 days and pending
Romidepsin	PTCL, 2nd-line, transplant ineligible	19-05-2015	SK (01-10-2015)	136 days	PEI (01-02-2019) *Still under provincial consideration (NL)	1355 days and pending	1219 days and pending
Aldesleukin	Melanoma, metatstatic	22-06-2015	MB/ON (09-09-2015)	80 days	NB (14-12-2017) *Still under provincial consideration (NL/ PEI)	910 days and pending	830 days and pending
Ponatinib	CML / ALL	01-10-2015	ON (03-08-2016)	308 days	NL (01-07-2018) *Still under provincial consideration (PEI)	1005 days and pending	697 days and pending
Blinatumomab	ALL, Adult, relapsed/ refractory 3rd line	01-04-2016	MB (15-02-2017)	321 days	NS (01-02-2018) *Still under provincial consideration (AB/ NL/PEI)	672 days and pending	351 days and pending
			AVERAGE	176.9 DAYS		1039 DAYS	862 DAYS

Date for last funding checked as of April 8, 2021

Abbreviations: ALCL (Anaplastic Large Cell Lymphoma), CML (Chronic Myelogenous Leukemia), PTCL (Peripheral T-Cell Lymphoma), ALL (Acute Lymphocytic Leukemia), SK (Saskatchewan), ON (Ontario), MB (Manitoba), NL (Newfoundland and Labrador), BC (British Columbia), PEI (Prince Edward Island)

Sub-Table 5B. Positive Recommendations and Funding Decision Statistics between 2012-2017.

DRUG	INDICATION	DATE OF APPROVAL	1ST FUNDING RECEIVED (PROVINCE/ DATE)	DELAY FROM PCODR APPROVAL TO 1ST FUNDING `	LAST FUNDING RECEIVED (PROVINCE/ DATE)	DELAY FROM PCODR APPROVAL TO LAST FUNDING	DELAYS BETWEEN PROVINCES
Pembrolizumab	cHL, relapsed /refractory	05-01-2018	SK/MB/NS (01-05-2020)	848 days	AB (15-09-2020) *Still under provincial consideration (PEI)	985 days and pending	137 days and pending
Venetoclax	CLL, relapsed /refractory	02-03-2018	AB (26-07-2019)	512 days	NB (24-10-2019) *Still under provincial consideration (ON/ PEI)	602 days and pending	90 days and pending
Avelumab	Metastatic Merkel cell carcinoma	21-03-2018	MB (14-02-2019)	331 days	AB (07-10-2019) *Still under provincial consideration (PEI)	566 days and pending	235 days and pending
Olaratumab	Soft tissue sarcoma, advanced	18-04-2018	Not funded (BC, MB, NB, NL) Negotiations closed as agreement could not be reached (AB, SK, ON, NS, PEI)				
Nivolumab	cHL, relapsed /refractory	03-05-2018	ON (29-01-2020)	637 days	AB (10-04-2020) *Still under provincial consideration (ON/PEI)	709 days and pending	72 days and pending
Pralatrexate	PTCL, relapsed /refractory	04-04-2018	BC (01-04-2020)	364 days	AB (15-09-2020) *Still under provincial consideration (NB,N-L,PEI)	531 days and pending	167 days and pending
Blinatumomab	BCP-ALL, Ph+, relapsed /refractory	04-04-2019	SK (03-09-2019)	153 days	BC (01-05-2020) *Still under provincial consideration (AB,N-L,PEI)	394 days and pending	241 days and pending
Crizotinib	NSCLC, ROS1-positive, advanced, 1st line	23-05-2019	NL (01-05-2020)	345 days	SK (01-08-2020) *Still under provincial consideration (MB, ON, NS, PEI)	437 days and pending	92 days and pending
Cemiplimab	Cutaneous squamous cell carcinoma	22-02-2020	Not yet released	Data Not Available			
Blinatumomab	Acute lymphoblastic leukemia, Ph -, CD19 +	29-10-2020	Not yet released	Data Not Available			
			AVERAGE	455 DAYS		603.4 DAYS	148.4 DAYS

Date for last funding checked as of April 8, 2021

Abbreviations: cHL (Classic Hodgkin Lymphoma), CLL (Chronic Lymphocytic Leukemia), PTCL (Peripheral T-Cell Lymphoma), BCP-ALL (B-Cell Pre-Cursor Acute Lymphoblastic Leukemia), Ph+ (Philadelphia Chromosome Positive), Ph- (Philadelphia Chromosome Negative), NSCLC (Non-Small Cell Lung Cancer), SK (Saskatchewan), MB (Manitoba), ON (Ontario), NS (Nova Scotia), PEI (Prince Edward Island), NL (Newfoundland and Labrador), AB (Alberta)

Table 5C. Re-Submission for Initial Negative Recommendations from 2012-2017.

DRUG	INDICATION	INITIAL SUBMISSION DATE AND DATE OF NEGATIVE RECOMMENDATION	RESUBMITTED (Y/N)	IF YES, RE-SUBMISSION STATUS AND APPROVAL DATE	TIME DELAY BETWEEN INITIAL SUBMISSION AND FINAL APPROVAL	DATE OF INITIAL FUNDING	TIME DELAY BETWEEN INITIAL SUBMISSION AND FINAL FUNDING
Crizotinib	NSCLC, ALK positive, advanced	HC NOC: 15-04-2012 Initial: 26-03-2012 Final: 04-10-2012	y	02-05-2013	403 days	01-10-2013	555 days
pertuzumab	breast cancer 1st line	HC NOC: 12-04-2013 Initial: 02-11-2012 Final: 01-08-2013	y	Pending	Data Not Available		
Ceritinib	NSCLC, ALK positive, relapsed/ refractory	HC NOC: 27-03-2015 Initial: 05-06-2015 Final: 03-12-2015	y	21-03-2017	678 days	19-07-2018	1172 days
Blinatumomab	2nd line, ALL	HC NOC: 22-12-2015 Initial: 24-08-2015 Final: 01-04-2016	y	31-08-2017	739 days	01-05-2019	1347 days
Palbociclib	Breast Cancer, ER+/her2-, 1st-line	HC NOC: 16-03-2016 Initial: 11-11-2015 Final: 05-05-2016	y	21-11-2016	377 days	12-02-2018	825 days
Olaparib	BRCA-mutated epithelial ovarian, fallopian tube, primary peritoneal cancer, 2nd line	HC NOC: 29-04-2016 Initial: 01-04-2016 Final: 29-09-2016	N				
Idelalisib	FL, 3rd line+	HC NOC: 27-03-2015 Initial: 12-04-2016 Final: 29-09-2016	N				
Ibrutinib	WM, 2nd line+	HC NOC: 31-03-2016 Initial: 21-04-2016 Final: 03-11-2016	N				
Daratumumab	MM, 4th line+	HC NOC: 29-06-2016 Initial: 21-04-2016 Final: 01-12-2016	N				
Venetoclax	CLL del(17)p, 2nd line	HC NOC: 30-09-2016 Initial: 08-07-2016 Final: 01-12-2016	N				
Alectinib	NSCLC, ALK+, CNS metastasis	HC NOC: 29-09-2016 Initial: 03-10-2016 Final: 04-05-2017	Re-submission for modified indication	29-03-2018	543 days	11-02-2019	862 days
Dabrafenib + trametinib	NSCLC BRAF v600, relapsed /refractory	HC NOC: 16-05-2017 Initial: 31-Mar-2017 Final: 02-11-2017	Re-submission for modified indication	28-05-2021	1520 days	Data Not Available	
				AVERAGE	**710 DAYS**		**952 DAYS**

Date for resubmission status checked as of June 1, 2021

Abbreviations: NSCLC (Non-Small Cell Lung Cancer), ALK (anaplastic lymphoma kinase), ALL (Acute Lymphoblastic Leukemia), BCP-ALL (B-Cell Pre-Cursor Acute Lymphoblastic Leukemia), BRCA (breat cancer gene), FL (Follicular lymphoma), WM (Waldenstrom Macroglobulinemia), MM (Multiple Myeloma), CLL (Chronic Lymphocytic Leukemia), BRAF (v-raf murine sarcoma viral oncogene homolog B1), CNS (Central Nervous System), HC NOC (Health Canada Notice of Compliance).

Table 5D. Re-Submission for Initial Negative Recommendations from 2017-2020.

DRUG	INDICATION	INITIAL SUBMISSION DATE AND DATE OF NEGATIVE RECOMMENDATION	RESUBMITTED (Y/N)	IF YES, RE-SUBMISSION STATUS AND APPROVAL DATE	TIME DELAY BETWEEN INITIAL SUBMISSION AND FINAL APPROVAL	DATE OF INITIAL FUNDING	TIME DELAY BETWEEN INITIAL SUBMISSION AND FINAL FUNDING
Nivolumab	HCC, advanced/ metastatic	HC NOC: 23-03-2018 Initial: 08-05-2018 Final: 29-11-2018	N				
Lenvatinib	RCC, advanced/ metastatic	HC NOC: 13-09-2017 Initial: 08-06-2018 Final: 04-01-2019	N				
Brigatinib	NSCLC, ALK+, locally advanced/ metastatic	HC NOC: 26-07-2018 Initial: 05-12-2018 Final: 01-08-2019	Y	April 1, 2021	849 days	pending	Data Not Available
Trifluridine and Tipiracil	Colorectal cancer	HC NOC: 25-01-2018 Initial: 01-29-2019 Final: 29-08-2019 Re-submission of 2017 submission (2nd negative recommendation)	N				
Pembrolizumab	Urothelial carcinoma, PD-L1 expression	HC NOC: 11-04-2019 Initial: 20-02-2019 Final: 03-10-2019	N				
Enasidenib	AML, IDH2 mutation, relapsed/refractory	HC NOC: 06-02-2019 Initial: 05-04-2019 Final: 31-10-2019	N				
Lorlatinib	NSCLC, ALK+	HC NOC: 22-02-2019 Initial: 11-06-2019 Final: 30-01-2020	Y	Pending	Data Not Available		
Midostaurin	ASM / SM-AHN / MCL	HC NOC: 03-10-2018 Initial: 13-08-2019 Final: 02-04-2020	N				

Date for resubmission status checked as of June 1, 2021

Abbreviations: HCC (Hepatocellular Carcinoma), RCC (Renal Cell Carcinoma), NSCLC (Non-Small Cell Lung Cancer), ALK (anaplastic lymphoma kinase), PD-L1 (programmed death-ligand 1), AML (Acute Myeloid Leukemia), IDH2 (Isocitrate Dehydrogenase (NADP(+)) 2), MCL (Mantle Cell Lymphoma), SM-AHN (Systemic mastocytosis with an associated hematologic neoplasm), HC NOC (Health Canada Notice of Compliance).

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