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WHITE PAPER
**IMPROVING ACCESS TO
INNOVATIVE CANCER
THERAPIES IN CANADA**

Elizabeth Lye, Louise Binder and Martine Elias

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, and research.

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Signatories

The following signatories affirm their support of the values and messages of this position paper



A person is walking away from the camera on a paved road that leads into a hilly, open landscape. The person is wearing a dark jacket, blue jeans, and dark sneakers with white soles. The entire image is overlaid with a semi-transparent purple color. Two text boxes are positioned on the left side of the image.

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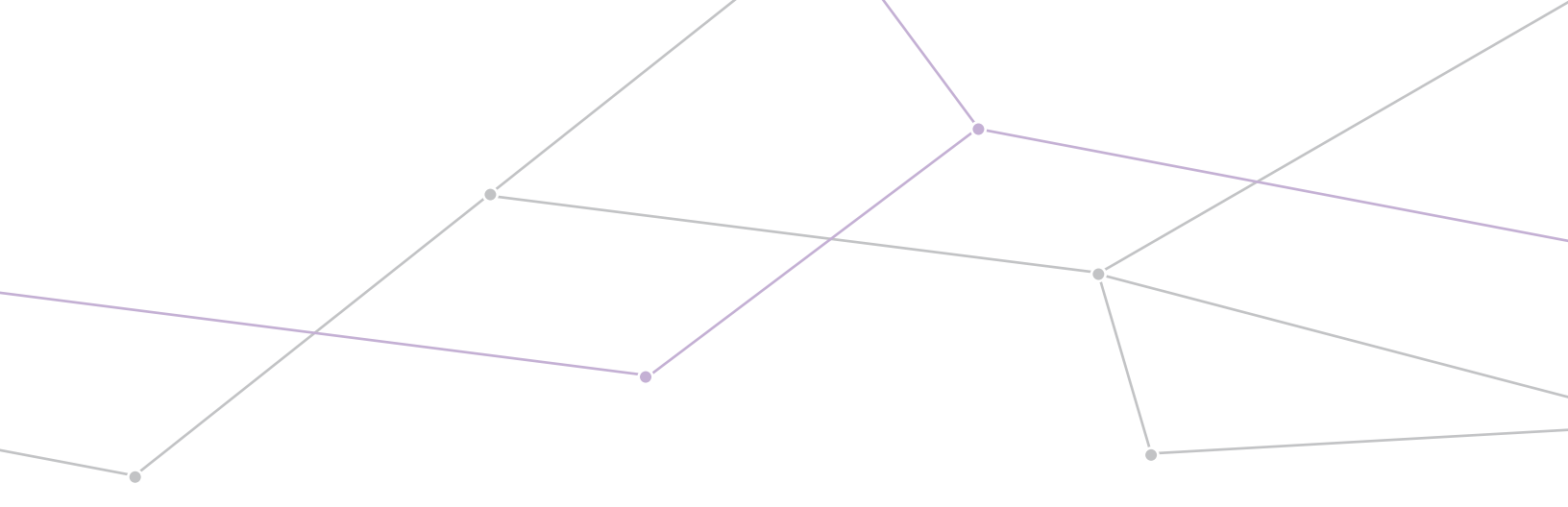


INTRODUCTION

According to 2017 Canadian Cancer Society statistics, almost half of all Canadians will develop cancer in their lifetime. Cancer remains the leading cause of death in Canada, responsible for 30.2% of lives lost nation-wide.[1] Advances in the molecular characterization of many cancers have led to a subdivision of these cancers into several molecular sub-types, resulting in a complex collection of diseases. It has become increasingly clear not only that no two patients' cancer is the same, but even within one person's disease there is a large amount of heterogeneity.

A growing body of research is leading to an ever-greater understanding of how different cancers evolve and how to effectively use treatments to manage them. Likewise, new therapies that provide patients with more effective and often less toxic options than traditional chemotherapy drugs are continuously emerging. Numerous cancer treatments—namely targeted therapies and immunotherapies—are at various stages of development today. Used alone and in combination with conventional chemotherapy, these new treatments have led to improved survival rates for many types of cancer, including melanoma, lung cancer, breast cancer, lymphoma, myeloma and leukemia. [2-7] Nevertheless, despite these improvements, a significant obstacle in combating these diseases is the diverse and evolving molecular signature of each cancer, even within an individual.

Some forms of cancer are curable and respond well to therapy. On the other hand, many types of cancer are presently incurable and treatment goals consist of managing the disease to prolong survival and maintain a good quality of life. Patients and families live with the hope that a new, effective treatment will be available by the time they need it. As the patient moves through the different stages of their disease, challenges often arise, such as drug resistance, decreased efficacy of subsequent courses of treatment, as well as accumulating cancer- and treatment-related symptoms and side-effects. Therefore, many individuals require more than one type of therapy throughout the course of their disease to survive, underscoring the need for multiple, effective treatment options. Given the high price of many cancer drugs, patients in Canada often rely on publicly funded provincial drug programs



for their care. In an environment where the number of new cancer drugs entering the Canadian market is increasing at a rapid pace, there is a great deal of competition for limited public funds to pay for these treatments. In Canada, as in many other jurisdictions, health technology assessment (HTA) frameworks have been developed to assess the value of novel therapies and ultimately facilitate access to cancer drugs through publicly funded drug plans.

To expedite access to promising, new drug treatments, Health Canada can issue a Notice of Compliance with conditions (NOC/c), contingent on the manufacturer carrying out additional clinical trials to verify the anticipated benefit within an agreed upon time frame. Health Canada has granted an NOC/c for several innovative cancer therapies with limited clinical data, but where the clinical benefit is promising. In many of these cases there is no alternative therapy available on the Canadian market; in other instances, the new drug represents a significant improvement in the benefit/risk profile over existing treatments.^[8]

Despite being granted an NOC/c, the pan-Canadian Oncology Drug Review (pCODR)—the Canadian HTA process used to evaluate new cancer drugs—is increasingly recommending that these therapies not be reimbursed. When

a negative pCODR recommendation is issued, the path to public access is greatly limited, if not completely denied. This problem is exacerbated by the trend private insurers are increasingly displaying of relying on public HTA recommendations to inform their reimbursement criteria for innovative, high-priced therapies, many of which are in cancer.

In this paper, we argue that there is a gap in access to innovative new cancer drug therapies, effectively denying or delaying potentially life-saving treatment for many cancer patients in Canada. This is unethical and unnecessary. We recognize that affordability and appropriate prescribing are crucial along with accessibility. They are not mutually exclusive. pCODR in partnership with the pan-Canadian Pharmaceutical Alliance (pCPA) must develop solutions to more effectively deal with uncertainty, beyond a negative recommendation. We propose that new mechanisms that accelerate access to promising new cancer therapies are not only timely but essential—providing seriously ill patients with effective, safe treatment choices in a timely manner to improve quality of life and increase survival.



BACKGROUND

Regulatory approval of cancer drugs: Health Canada

Before a drug can be marketed and sold in Canada, a New Drug Submission (NDS) must be submitted to Health Canada for review. Every NDS undergoes rigorous scrutiny and must fully satisfy all scientific requirements for safety, efficacy and quality under the Food and Drug Regulations to be granted regulatory approval.^[9]

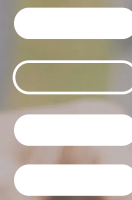
Prior to submission, manufacturers and medical researchers conduct extensive clinical evaluation of the drug. This includes Phase I and II clinical trials to assess optimal dosing, associated toxicity and potential efficacy of the new drug. Typically this is followed by a phase II or III randomized controlled trial (RCT) to assess efficacy and safety in a larger participant population compared to an existing treatment or a placebo. In cancer trials, if no standard of care exists, an existing treatment option is often used as a comparator; a placebo may be used in certain circumstances, for example, when the current standard of care is surveillance or when a new drug is being combined with an existing treatment. After a successful review, Health Canada issues a Notice

of Compliance (NOC) for the product and specific disease setting in which it was evaluated. The regulatory review process can take between one and two years, depending on the nature of the product.^[10]

Priority review can be granted for promising new drug products “intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating diseases or conditions for which there is no alternative therapy available on the Canadian market or where the new product represents a significant improvement in the benefit/risk profile over existing products”.^[11] In such cases, an NOC with conditions (NOC/c) may be issued. An NOC/c is authorization to market a drug with the condition that the manufacturer undertakes additional studies to verify the clinical benefit or other conditions required by Health Canada. ^[8] Manufacturers seeking priority review often submit data from non-comparative phase I and II clinical trials, while awaiting the results of RCTs or other clinical studies.



Almost half of all Canadians will develop cancer in their lifetime



1 in 4 Canadians will die of cancer

Public funding for cancer drugs: Health technology assessment (HTA) and provincial drug plans

Health Canada’s approval of a drug for sale in Canada does not ensure provincial and territorial drug programs will fund the drug. Following issuance of an NOC or NOC/c, a health technology assessment (HTA) is conducted to evaluate the comparative effectiveness, and economic and social impact of the drug. The HTA is used by individual provinces and territories to help them decide if they will fund the drug for eligible recipients of public drug plan coverage. In Canada, HTAs are conducted by independent, not-for-profit organizations: Canadian Agency for Drugs and Technologies in Health (CADTH) [12]—which provides reimbursement recommendations and advice to provincial and territorial public drug plans and cancer agencies for all provinces and territories, except Quebec—and Institut national d’excellence en sante et en services sociaux (INESSS) [13]—which provides the same to the Minister of Health and Social Services in Quebec. Both organizations use similar processes to inform funding recommendations for new drugs.

Once a manufacturer or disease site group submits a request for a drug review, CADTH conducts evidence-based evaluations of clinical benefit, patient values, cost-effectiveness and feasibility of adoption into the Canadian healthcare system.

For assessment of cancer drugs, CADTH uses the pCODR process; the Common Drug Review (CDR) process is used for all other drugs.[14] An expert pCODR review

committee (pERC)—consisting of oncologists, a “non-oncology” physician, health economists, pharmacists, a hematologist, and patient representatives—examines evidence-based reviews of the clinical effectiveness and cost effectiveness of a new cancer drug, conducted by pCODR’s expert guidance panels, as well as input provided by patient advocacy groups, clinicians and pCODR’s Provincial Advisory Group (PAG). The pERC then issues a non-binding recommendation to Canada’s public drug plans to support their drug funding decisions. Province-specific factors such as budgets, priorities and political considerations affect final decisions and can differ markedly across Canada. The pCODR review process typically takes between three to eight months.[15]

Following pCODR’s final recommendation, the pan-Canadian Pharmaceutical Alliance (pCPA) decides whether joint provincial/territorial/federal pricing negotiations will take place for the new drug. If the decision is to move forward, interested provinces, territories and the federal government collectively commence confidential pricing negotiations with the manufacturer. Once an agreement is reached between participating jurisdictions and the manufacturer, it is then up to each provincial/territorial/federal government to make its final decision on funding the drug through its own public drug plan.[16] There are no fixed timelines for pCPA negotiations, nor are the details of agreements made public.



RECENT TRENDS IN

PCODR REIMBURSEMENT

RECOMMENDATIONS

Since the beginning of 2015, many promising cancer drugs have been issued an NOC/c by Health Canada, on the condition that the manufacturer collect additional data verifying the clinical efficacy of the therapeutic. Subsequently, these drugs have been submitted to pCODR with promising non-comparative data to begin the process of achieving public funding and access for patients. Despite being granted regulatory approval, pCODR has issued negative funding recommendations for many of these drugs. To better understand the reasons drug submissions supported by non-comparative data may receive a negative recommendation from pCODR, we analyzed all publicly available funding recommendations issued by pCODR, through December 31, 2017.

Between January 1, 2012 and December 31, 2017, pCODR issued funding recommendations for 101 oncology drug funding requests.^[17] Submissions supported by non-comparative clinical studies made up a minority of

these funding requests (20%; 20 of 101). (*Table 1*) Forty percent (40%; 8 of 20) of submissions supported by data from non-comparative clinical trials received a positive recommendation for the manufacturer's funding request. Recurring themes within pCODR's decision rationale included significant unmet patient need, lack of existing safe and/or effective treatment options, small patient population, and the infeasibility to conduct an RCT in the target population. Of the submissions that received a negative recommendation (55%; 11 of 20), common reasons for pCODR's decision included uncertainty of net clinical benefit due to non-comparative data, and ongoing, or the feasibility to conduct, an RCT in the target population. pCODR issued a mixed recommendation for one submission in 2016, which sought reimbursement of blinatumomab for both 2nd-line and 3rd-line treatment of acute lymphoblastic leukemia (ALL): positive for 3rd-line treatment and negative for 2nd-line treatment.



Table 1: pCODR Recommendations for Submissions Supported by Data from Non-comparative Clinical Trials[17]

DRUG PRODUCT	FUNDING REQUEST	RECOMMEN- DATION DATE	RECOMMEN- DATION	REASONS FOR DECISION
Crizotinib	NSCLC, ALK-positive, advanced	2012-10-04	*Negative	<ul style="list-style-type: none"> • Not confident of net clinical benefit due to limitations of evidence • Ongoing RCTs
Brentuximab vedotin	Hodgkin lymphoma, 3rd line	2013-08-29	Positive	<ul style="list-style-type: none"> • Small population • No other treatment options • Infeasible to conduct RCT
Brentuximab vedotin	Systemic ALCL, 2nd line	2013-12-05	Positive	<ul style="list-style-type: none"> • Aggressive form of the disease • No other effective, non-toxic treatment options • Infeasible to conduct RCT

Vismodegib	Basal cell carcinoma, advanced	2014-01-10	Positive	<ul style="list-style-type: none"> • No standard treatment • Small population • Infeasible to conduct RCT
Bosutinib	CML, 2nd-line or more	2015-04-21	Positive	<ul style="list-style-type: none"> • Less toxic than existing treatments • Decreased risk of exacerbating comorbidities • Infeasible to conduct RCT
Romidepsin	PTCL, 2nd-line, transplant ineligible	2015-05-19	Positive	<ul style="list-style-type: none"> • Aggressive form of the disease • No other effective treatment options • Small population • RCT feasible, but uncertain it would inform clinical value
Aldesleukin	Melanoma, in-transit metastases	2015-06-22	Positive	<ul style="list-style-type: none"> • No standard treatment • Toxicities of existing therapies • Small population
Pertuzumab	Breast Cancer, 1st-line	2015-07-16	Negative	<ul style="list-style-type: none"> • Uncertainty around net clinical benefit due to validity of surrogate endpoint • Ongoing RCT
Ponatinib	CML / Ph+ALL, where other TKI is not appropriate	2015-10-01	Positive	<ul style="list-style-type: none"> • No treatment options for the disease sub-group • Manageable toxicities • Infeasible to conduct RCT
Ceritinib	NSCLC, ALK-positive, relapsed/refractory	2015-12-03	*Negative	<ul style="list-style-type: none"> • Not confident of net clinical benefit due to limitations of evidence • Ongoing RCT
Blinatumomab	ALL, Adult, relapsed/refractory	2016-04-01	*Negative (2nd line)	<ul style="list-style-type: none"> • Not confident of net clinical benefit due to limitations of evidence • Ongoing RCT
			Positive (3rd line)	<ul style="list-style-type: none"> • Small population • Limited treatment options in this setting

Palbociclib	Breast Cancer, ER+/her2-, 1st-line	2016-05-05	*Negative	<ul style="list-style-type: none"> • Not confident of net clinical benefit due to limitations of evidence • Ongoing RCT
Olaparib	Ovarian Cancer, 2nd-line maintenance	2016-09-29	*Negative	<ul style="list-style-type: none"> • Not confident of net clinical benefit due to limitations of evidence • Ongoing RCT
Idelalisib	Follicular Lymphoma, 3rd-line	2016-09-29	Negative	<ul style="list-style-type: none"> • Not confident of net clinical benefit due to limitations of evidence • Feasible to conduct RCT
Ibrutinib	WM lymphoma, 2nd-line	2016-11-03	Negative	<ul style="list-style-type: none"> • Not confident of net clinical benefit due to limitations of evidence • Feasible to conduct RCT
Daratumumab	Multiple myeloma, 4th-line	2016-12-01	Negative	<ul style="list-style-type: none"> • Not confident of net clinical benefit due to limitations of evidence • Feasible to conduct RCT
Venetoclax	CLL, del(17p), 2nd-line	2016-12-01	Negative	<ul style="list-style-type: none"> • Not confident of net clinical benefit due to limitations of evidence • Feasible to conduct RCT
Alectinib	NSCLC, ALK+, CNS, relapsed	2017-03-03	Negative	<ul style="list-style-type: none"> • Not confident of net clinical benefit due to limitations of evidence • Ongoing RCT
Blinatumomab	ALL, pediatric, Ph-, relapsed	2017-08-23	Positive	<ul style="list-style-type: none"> • May be net clinical benefit • Substantial need for treatment options in small population
Dabrafenib + trametinib	NSCLC, relapsed with BRAF V600 mutation	2017-11-17	Negative	<ul style="list-style-type: none"> • Not confident of net clinical benefit due to limitations of evidence • Feasible to conduct RCT

*The funding request received a positive funding recommendation after resubmission with results from a phase III RCT. Abbreviations: ALL: acute lymphoblastic leukemia; ALK: anaplastic lymphoma kinase; CLL: chronic lymphocytic leukemia; CML: chronic myelogenous leukemia; NSCLC: non-small cell lung cancer; PTCL: peripheral T cell lymphoma; RCT: randomized controlled trial; WM: Waldenstrom's macroglobulinemia


Beginning in 2015, the number of pCODR submissions supported by evidence from non-comparative data increased, compared to previous years. (Figure 1) The rate of negative recommendations issued for such submissions also increased: 1 of 4 submissions (25%) received negative recommendations from 2012 through

2014, while negative recommendations were issued for 10 of 16 submissions (63%) from January 2015 to December 31, 2017. Increasingly, the feasibility to conduct an RCT was cited as a reason to reject the funding submission.

Figure 1: Recommendations for Submissions with Evidence from Non-Comparative Trials.

Note: The blinatumomab submission was scored as 50% positive, 50% negative, based on the mixed recommendation for this file in 2016.





FEASIBILITY AND APPLICABILITY OF RANDOMIZED CONTROLLED TRIALS (RCTS)

RCTs have long been considered the “gold standard” of empirical medical knowledge—a source of reliable evidence regarding which treatments will most benefit patients; however, they are not always feasible, appropriate or ethical for the evaluation of new therapeutic interventions. Typically, in oncology RCTs, patients are randomized to receive the experimental treatment or the standard of care for the disease. Where there is no standard of care, an existing treatment option may be chosen as the comparator. RCTs often require many years for patient enrollment, follow-up and analysis. Challenges arise in conducting RCTs for therapies used to treat rare diseases or distinct molecular subsets; small patient numbers and strict eligibility requirements limit the size of the trial-eligible population in such cases. In advanced cancer, a patient’s eligibility for clinical trials may be further reduced due to deterioration of health while, in heavily pre-treated patient populations, finding

trial participants who have not previously received the designated comparator is often difficult. Additionally, the existence of multiple trials for the same patient population limits the number of patients each trial can recruit.

These constraints are exacerbated as cancer treatment continues to evolve towards personalized or precision medicine, where the unique tumour characteristics and other health conditions of individual patients are of increasing importance in treatment selection. As such, it can take many years and the coordination and cooperation of dozens of trial centres across many countries to recruit enough patients for an RCT to assess improvement of meaningful clinical endpoints—namely, progression-free survival (PFS) or overall survival (OS). In cases of rapidly evolving therapeutic areas, such as oncology, RCT results often become outdated before they are published, and conclusions may no longer apply.

Another barrier to conducting RCTs, especially in rare cancers, is the lack of interest on the part of manufacturers when the prospective revenues are relatively small. Over time, RCTs have become large bureaucratic and corporate undertakings, requiring costly investment in research design, patient care, record keeping, ethical review, and statistical analysis. Manufacturers often submit new drugs to Health Canada after receiving regulatory approval in both the United States (US) and the European Union (EU). In instances where a new drug is approved in the US and EU based on evidence solely from non-comparative clinical trials, it is unlikely the manufacturer will initiate an RCT in the approved indication.

These barriers are evident in the case of several recent pCODR drug submissions that were supported by evidence from non-comparative clinical trials. For example, pCODR issued a negative recommendation for ibrutinib in the setting of relapsed Waldenstrom's Macroglobulinemia (WM), a rare and incurable type of non-Hodgkin lymphoma.[18] The pCODR clinical guidance panel (CGP) stated that the two-year PFS of 69% and OS of 95% observed in the non-comparative phase II trial represented excellent disease control in a heavily pre-treated population. Furthermore, they noted that "second-line treatment is frequently given intravenously, is of relatively limited effectiveness in terms of progression-free survival and may have significant toxicity, especially myelosuppression. New treatments with high response and progression free survival rates, especially oral therapies, are highly desirable." [19]

While the pERC noted ibrutinib's ability to control symptoms, with fewer toxic side effects than available therapies, in an easy to take-at-home pill format that is extremely important to patients, it cited the lack of a phase III RCT where it believed such a trial was feasible, as a reason for the negative recommendation. As reported

by pCODR's CGP, WM has an incidence of approximately 5 cases per million people per year in Canada[19], making it difficult to recruit enough patients to evaluate important clinical endpoints in an RCT, even in international trials. The CGP indicated that treatment choice in relapsed WM is largely guided by data from uncontrolled phase II studies and prior treatment history, therefore making comparisons between currently available agents and new therapies challenging. Furthermore, there is no standard treatment for relapsed WM, limiting the feasibility of assessing ibrutinib against a single comparator in this setting.[19]

Daratumumab, given in combination with dexamethasone, is another drug that was recently given a negative pCODR recommendation in the setting of 4th-line treatment of multiple myeloma.[20] The pERC noted that, given the prevalence of patients with multiple myeloma in the treatment setting being evaluated, a phase III RCT would be feasible to determine the efficacy of daratumumab compared with available treatment options or best supportive care. Feedback from clinician and patient stakeholders, supported by pCODR's CGP, indicated that a trial comparing daratumumab to best supportive care was not feasible for pragmatic and ethical reasons, as patients would likely decline participation in a study that may not provide them with an active treatment and opt for a clinical trial that ensures delivery of another potentially efficacious agent.[20] Furthermore, the CGP stated that it would be unethical to enroll patients in a trial comparing daratumumab with best supportive care when the toxicity and effectiveness of the suggested best supportive care had proven detrimental to these patients. [21] The pERC, however, did not change its initial negative recommendation and reiterated that in this treatment setting there is clinical equipoise and therefore an RCT could be justified.[20]



The regulatory review process can take between one and two years



Cancer is the leading cause of death in Canada at 30.2%

IMPACT OF DRUG FUNDING

DENIALS AND DELAYS

ON PATIENTS



A positive funding recommendation from pCODR appears to be a pre-requisite for pCPA to initiate negotiations for drug submissions, as those which received negative recommendations and requested pCPA negotiations resulted in pCPA deciding “not to negotiate collectively or individually at the provincial-territorial level”.[22] As such, drugs receiving negative recommendations from pCODR are very unlikely to receive funding from public drug plans. As of December 31, 2017, only five cancer drug submissions that initially received negative recommendations when only non-comparative data were available, subsequently received positive recommendations following resubmission with RCT data. However, these resubmissions resulted in access delays of up to 515 days.[23-25] Patients will continue to be denied access to drugs where RCTs have not been initiated.

The impact of funding denials or delays on patients is profound. For example, ovarian cancer is the most fatal cancer for Canadian women. Over half of all women diagnosed with ovarian cancer succumb to their disease within five years of diagnosis and new treatments are rare.[1] In fact, over the past five years, only two new drugs for ovarian cancer were submitted for approval and reimbursement in Canada.[17] As a maintenance drug that has positively impacted PFS, olaparib is a welcome drug for women living with ovarian cancer.

Following approval by Health Canada, pCODR issued a negative funding recommendation for olaparib in September 2016, based on the uncertainty of the non-comparative clinical data.[26] In contrast, olaparib was evaluated and listed for public reimbursement in 25 other countries, based on the same data. In September 2017, after resubmission with data from an RCT, olaparib was given a positive recommendation by pCODR. In the year that elapsed, however, many women with ovarian cancer were unable to access this therapy in Canada. PFS and the value of being able to prolong a remission cannot be overstated in this group. Women diagnosed with ovarian cancer know that they will die from their disease and are looking for extra months and years of survival. Further,

by taking an oral, take-home maintenance therapy, the extreme anxiety of a recurrence is reduced, many can go back to work, and others are able to continue aspects of their lives that are meaningful to them. For a disease with such poor prognosis and which has seen so few advances in treatment, the value of this new treatment to these patients is undeniable.

Lung cancer patients have similarly suffered due to negative funding recommendations. In Canada, an estimated 28,600 new cases and 21,100 deaths occurred in 2017 from lung cancer, with a five-year survival rate of only 18%.[1] Much progress is being made in the treatment of this deadly cancer and treatment decision-making in the first-line treatment setting for advanced non-small cell lung cancer (NSCLC) is typically dependent on the driver mutation status of patients. Although targeted therapies are available for some patients, there remains a need to advance treatment options for those who present with other molecular profiles.

Combination treatment with dabrafenib and trametinib was approved by Health Canada in 2017 for BRAF V600-positive metastatic NSCLC after prior systemic therapy. About 1 - 2% of NSCLC patients are BRAF-positive. Despite impressive clinical trial results, this treatment combination received a final negative funding recommendation from pCODR. The pERC’s decision was based on uncertainty of the net clinical benefit of the therapy due to limitations of the evidence, and the feasibility to conduct an RCT. [27] The CGP noted that “the evidence presented in the trial represents the evolution in evidence for precision medicine in lung and other cancers.” and stated that “the current decision disadvantages Canadians in being able to access personalized medicine and potential treatment options that advance outcomes.” Furthermore, the CGP disagreed with the pERC’s conclusion that an RCT is feasible in this small subgroup of patients, noting that there will not be an RCT in this population in the future. [28] As a result, lung cancer patients in Canada may never have access to this therapy.



PROPOSED SOLUTIONS TO

EXPEDITE ACCESS TO PROMISING,

NEW CANCER THERAPIES

There are inherent limitations to estimating the value of a new treatment using non-comparative clinical studies, no matter the approach employed. Small, non-comparative trials, however, are increasingly becoming the final stage of clinical evaluation for new cancer drugs in some disease settings, especially for rare cancers, for tumours with distinct molecular profiles, or where no standard of care exists. Therefore, mechanisms to provide timely access to promising new therapies, while addressing the longterm uncertainty in value, are necessary to help ensure cancer patients in Canada can benefit from potentially successful treatments when they need them.

Funding recommendations conditional on collection of additional evidence

In March 2016, following consultation with numerous stakeholders, CADTH released a new recommendation framework for both CDR and pCODR. [29] Under the current framework, pCODR can issue one of three recommendations following deliberations for a new drug submission:

- Reimburse;
- Reimburse with clinical criteria and/or conditions; or
- Do not reimburse.

In the case of a recommendation to reimburse, the pERC almost always recommends funding the drug conditional on a reduced price. This condition has been equally applied to positive recommendations for drugs submitted with evidence from RCTs and those submitted with non-comparative studies. Additionally, the pERC has begun to issue recommendations that specify clinical criteria and other reimbursement conditions. Within the revised framework, there exists a condition that includes development of real-world evidence for cases where there is uncertain clinical and pharmacoeconomic evidence, but significant unmet need; however, it has not been used to date. A recommendation with this condition could be issued to provide for temporary funding while the drug

manufacturer addresses the perceived uncertainty of the clinical value. Under such circumstances, policies and procedures regarding evidence collection would need to be established by pCODR, pCPA and public payers. Furthermore, changes to pricing negotiations through the pCPA process and alternative pricing and reimbursement strategies would likely need to be adopted.

The National Institute for Health and Care Excellence (NICE) in England recently implemented such a change to its HTA recommendation framework.[30] If a drug has potential to satisfy the criteria for routine use commissioning but significant clinical uncertainty remains, it can now be made available to patients much earlier via the Cancer Drug Fund (CDF). The drug remains available within the CDF while more evidence is gathered to resolve the key areas of clinical uncertainty and show that the drug works in the population in England. Data collection arrangements and commercial agreements during the managed access period are agreed upon between the company and the National Health Service (NHS) England. The data collection period is limited, and the data collected must be able to inform an update of the original NICE recommendation.



On average, 565 Canadians will be diagnosed with cancer every day



It can take years to coordinate trial centers for RTCs

Collection and sharing of real-world evidence

In addition to acquiring more robust or mature trial data, real-world evidence can be collected to resolve value uncertainty. Potential collaborations among relevant stakeholders could be leveraged for this purpose to ensure that pCODR's recommendations, and the data on which they are based, remain sound and relevant over time. Provincial cancer agencies have started to generate real-world evidence from routinely collected health administrative databases and patient registries to be used in this capacity. In 2011, Ontario's Ministry of Health and Long-term Care (MOHLTC) developed the Evidence Building Program (EBP) for cancer drugs. The purpose of the EBP is to resolve uncertainty around clinical and cost-effectiveness data for publicly funded drugs in specific patient populations through the collection and analysis of real-world cancer patient data.^[31] Other provincial cancer agencies, such as Alberta Health Services (AHS) and the British Columbia Cancer Agency (BC Cancer), maintain large databases that include extensive clinical data, which could similarly be used to assess new cancer treatments.^[32, 33] Additionally, some Canadian research networks have initiated the development of disease-specific registries to help support research efforts to improve treatment and management of specific cancers.^[34, 35] With such resources and programs already in place, enhanced information-sharing among provincial cancer agencies and disease networks could facilitate the collection of robust real-world data to address the uncertainty in the value of promising new treatments.

Collaborative stakeholder engagement

As healthcare systems shift toward outcomes-based healthcare models, patients, physicians, researchers, Health Canada, pan-Canadian health bodies, provincial cancer agencies, and drug manufacturers must work together to establish measurements and standards to achieve best outcomes for patients in a sustainable, affordable healthcare system. Engaging all stakeholders in defining important outcomes and establishing systems to collect and share data within and across jurisdictions will ultimately lead to more effective and efficient use of resources and better outcomes for patients.



CONCLUSION

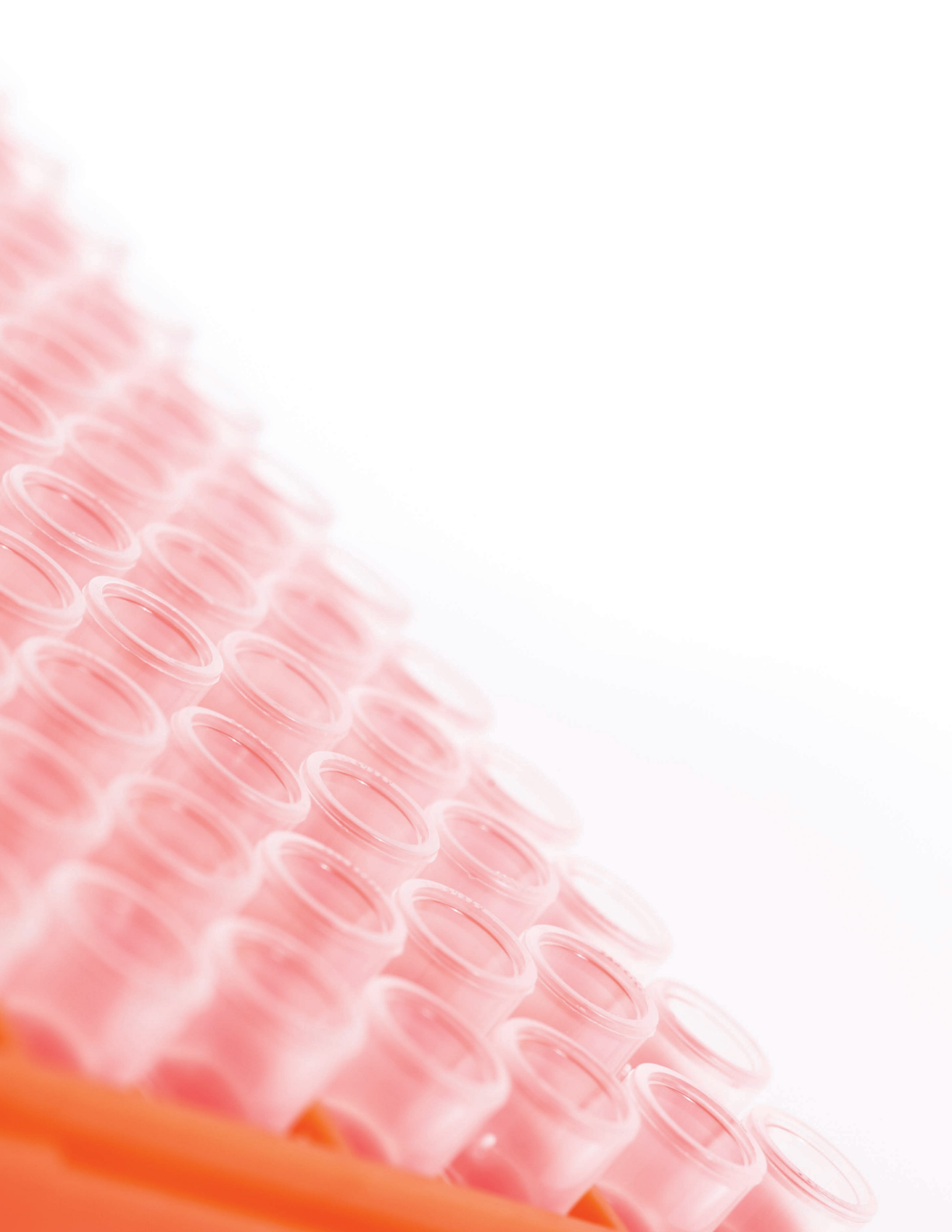


Innovative cancer medicines have led to an increase in patient survival rates, unprecedented improvements in human health, and hold remarkable potential to transform treatment of the disease. A productive oncology-drug pipeline is turning scientific breakthroughs into treatments for many patients who, until recently, had few options; yet, accessing these needed drugs is becoming increasingly difficult for many patients in Canada.

Health Canada has embraced innovation and facilitated accelerated approval of promising new cancer therapies. By contrast, pCODR has issued negative funding recommendations for many of these new medicines, where they conclude there remains uncertainty in the value of the drug. Increased requirements for evidence prior to use, to ensure the clinical- and cost-effectiveness of the drug, may seem reasonable to reduce uncertainty; however, patients cannot wait. It is therefore important not to deny or delay funding of a drug when there is sufficient data available to discern the efficacy and safety of the drug in a vulnerable patient population.

We urge pCODR to adopt a modified approach to its current reimbursement recommendation framework and work with patients, oncologists, manufacturers, and payers to develop mechanisms to improve access to effective treatment options for those living with cancer. Maintaining the status quo will only continue to widen the gap between the number of patients in need of new treatment options and those receiving them, thereby diminishing the quality and longevity of cancer patients' lives.

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