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SHORT COMMUNICATION

Conditional approval of cancer drugs in Canada: accountability and impact on public funding

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ABSTRACT

Background We examined how conditional market approval of cancer pharmaceuticals by Health Canada (HC) affects public funding recommendations by the pan-Canadian Oncology Review (pCODR). We were also interested to see how often HC conditions are enforced.

Methods Health Canada and pCODR databases for 2010–2017 were analyzed for patterns in HC conditional authorization and post-authorization reviews of cancer drugs and for correlation with pCODR reimbursement recommendations.

Results Between 2010 and 2017, pCODR reviewed 105 unique drug–indication pairings; 21% ($n = 22$) had conditional HC authorization. In all cases, conditional authorization was given on the basis of preliminary data in a surrogate endpoint and was contingent on further data showing benefit in more robust outcome measures (for example, overall survival). Of those 22 drugs, 36% did not have updated data, 36% had updated data that met HC conditions, and 27% had data that met some, but not all, conditions. During the period considered, HC never revoked conditional authorization for failure to meet conditions. None of the 22 drugs was given an unconditional positive recommendation for public reimbursement by pCODR. A conditional recommendation was given to 11 of the drugs (50%), and reimbursement was not recommended for 6 drugs (27%) because of insufficient evidence.

Conclusions One fifth of the cancer drugs reviewed for public reimbursement in Canada were conditionally authorized by HC based on preliminary data. Conditional authorization was associated with a recommendation against public funding by pCODR. No drugs had their conditional market authorization revoked for failure to meet conditions, suggesting that a more robust HC reappraisal framework is needed.

Key Words Medical oncology, health policy, health economics, Health Canada, pCODR

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INTRODUCTION

Few medical fields have seen as many therapeutic advances in recent years as oncology. As the development of new pharmaceuticals continues to accelerate, it falls to government regulatory bodies to adjudicate the treatments to approve and to health technology agencies to determine the treatments to recommend for public reimbursement. Regulatory and funding bodies operate under the dual tensions of providing expedient access to novel treatments for life-threatening conditions and of ensuring patient safety and equitable resource allocation[1]. Thus, critical review of the drug reimbursement and approval process is of great economic and social importance.

Drug approval in Canada is undertaken by Health Canada (HC) in a review process that accounts for safety and efficacy data from preclinical and clinical trials[2]. Successful drugs are issued a notice of compliance (NOC) that authorizes the pharmaceutical company to market

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the drug. On occasion, HC instead issues a notice of compliance with conditions (NOC/c), which stipulates that the developer will undertake further studies to confirm benefit; however, those stipulations are not legally binding and do not affect market access[3]. The process is analogous to the "accelerated approval" designation granted by the U.S. Food and Drug Administration[4]. In Canada, the NOC/c policy gives earlier market access to drugs for "serious, life-threatening or severely debilitating diseases," particularly when few treatments are available for such diseases or when the drug demonstrates potential for significant improvement over existing treatment options. Cancer drugs are frequently eligible for these expedited conditional authorizations. Upon review by HC, the NOC/c conditions can subsequently be removed if early efficacy data are borne out in further trials[5].

Once a cancer drug has obtained federal market authorization, each province must independently decide whether to provide public reimbursement for its use. In 2010, the pan-Canadian Oncology Drug Review (pCODR) was established by provincial ministries of health to assess cancer drugs and guide funding decisions[6]. The pCODR process is independent from the Common Drug Review, which assesses all other classes of medications[7]. The pCODR expert review committee (PERC) evaluates clinical evidence, economic evidence, patient values, and adoption feasibility to generate a reimbursement recommendation that can then be used to guide provincial decision-making for all provinces except Quebec. The committee comprises medical oncologists, pharmacists, economists, an ethicist, and patient representatives[6]. The final PERC decision can be to recommend reimbursement, to deny reimbursement, or to consider reimbursement once certain conditions have been met. With assistance from pCODR, funding decisions can be made in a way that is transparent, expert-guided, and timely. In addition, pCODR acts to reduce duplication of the review process and improve standardization between provinces. In 2014, pCODR was incorporated into the Canadian Agency for Drugs and Technologies in Health[8].

A NOC/c issued by HC expedites the progress from market authorization to funding recommendation, which is appealing to patients, providers, and manufacturers. Moreover, pCODR is able to review drugs for funding in parallel with the HC process. However, prior studies of the NOC/c approval process have raised concerns that efforts by HC to expedite access are not routinely followed by critical reappraisal or enforcement of listed conditions[3,9].

Few studies to date have specifically addressed the NOC/c approval process as it relates to oncology and pCODR decisions. Here, we sought to determine whether conditions set by HC affect reimbursement recommendations by pCODR, how often cancer drugs receive early market authorization under the NOC/c policy, and what evidence guides decision-making by HC. We also examined how frequently conditions set by HC are subsequently fulfilled.

METHODS

We used the pCODR database to find all drugs assessed from initiation of the program in 2010 to March 2017. The HC Notice of Compliance database (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/noc-acc/index-eng.php) was searched to determine which of those drugs had received a NOC/c market authorization. Drugs with NOC/c status were reviewed in detail to determine the terms of their conditional approval and whether, subsequently, the stated conditions were met and full NOC status was granted. A literature review and a search of http://ClinicalTrials.gov/ for all relevant drugs were performed to determine whether further studies to address the HC conditions were available. The final pCODR recommendations for NOC/c drugs were further assessed, with particular attention to any correlation with HC conditions. In cases in which one drug was approved for multiple indications, each indication was treated separately.

RESULTS

Between January 2010 and March 2017, pCODR reviewed 105 cancer drugs for consideration of public reimbursement; 16.2% (n = 17) had previously been given NOC/c market authorization by HC. Of those 17 drugs, 4 were given more than one NOC/c for separate indications, for a total of 22 unique marketing indications (Figure 1). One submission was subsequently withdrawn from pCODR consideration.

In all cases, HC provided conditional market approval on the basis of promising preliminary data in a surrogate

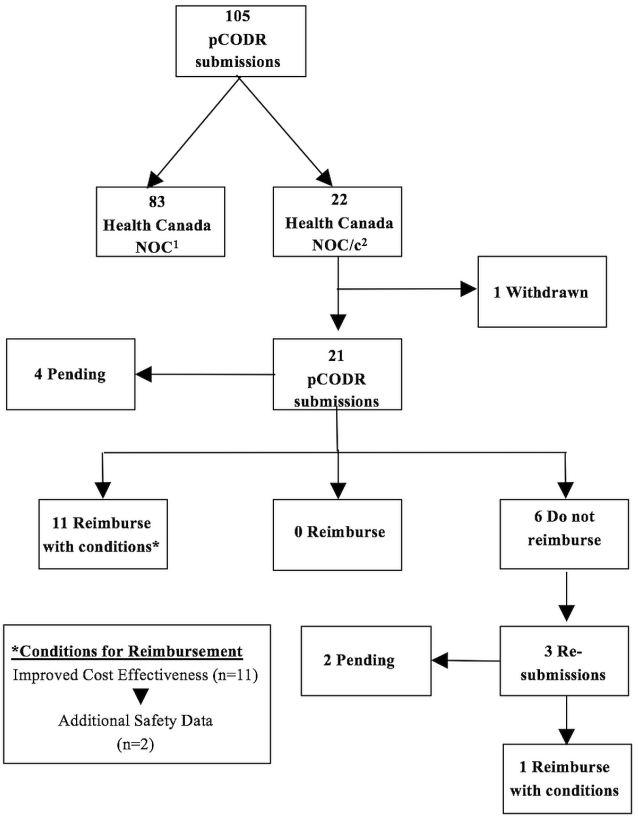

FIGURE 1 Flow chart of the pan-Canadian Oncology Drug Review (pCODR) process. NOC = Notice of Compliance; NOC/c = Notice of Compliance with conditions.

endpoint (such as objective response rate) or in a single-arm study, and post-authorization conditions warranted completion of additional studies—that is, phase II or III clinical trials—to demonstrate benefit in more robust outcome measures such as progression-free survival, overall survival, or quality of life. In some cases, additional safety data were also requested. For 36% of the 22 identified indications, no updated data ($n = 8$) were available; updated data that met the NOC/c conditions were available for another 36% ($n = 8$), and updated data that did not fully meet conditions were available for the remaining 27% ($n = 6$). One drug (crizotinib) and one drug combination (dabrafenib–trametinib) had subsequently received full authorization from HC at the time of our analysis (Table I). During the period under consideration, HC never revoked conditional market authorization for failure to meet conditions (Table I).

No drug with NOC/c status was given an unconditional recommendation for public reimbursement by PERC. Reimbursement recommendations were given for 11 indications (50%) conditional on improvement in cost-effectiveness, and as of March 2017, submissions for 4 indications (18%) were pending. A reimbursement recommendation was not given for 6 NOC/c drugs (27%). In all 6 cases, PERC indicated that the evidence was insufficient to conclude that significant benefit was derived compared with existing treatments. For 2 indications, toxicity was an additional concern, and the resultant harm was felt to outweigh the evidence of benefit. Of the 6 indications not recommended for public reimbursement, 3 were re-submitted by the manufacturer for pCODR review after release of further clinical trial data. Of those 3, 1—crizotinib—was subsequently given a conditional recommendation for funding as second-line treatment for *ALK*-positive advanced or metastatic non-small-cell lung cancer, subject to improvement in cost effectiveness. In all cases, the second pCODR review was triggered by the drug manufacturer and not PERC (supplementary Table I). Figure 2 depicts the post-approval timeline for all drugs reviewed.

DISCUSSION

Several observations about the cancer drug approval and funding process in Canada arise from this study. First, the NOC/c policy permits manufacturers to obtain conditional market authorization for cancer treatments that have not yet demonstrated benefit in overall survival or progression-free survival, arguably the most meaningful clinical outcomes. For at least 6 indications, a NOC/c was granted on the basis of single-arm studies lacking a comparison with a reasonable standard of care. Concerns about surrogate outcomes have been raised by many authors[10–13].

Second, although NOC/c market authorization is conditional, no defined timeline has been attached to the conditions, and no mechanism is in place to trigger reappraisal by HC. As a consequence, manufacturers have little motivation to complete and report additional clinical trials[9]. The absence of rigorous post-authorization evaluation is not unique to Canada; Pease *et al.*[11] recently demonstrated a similar paucity of post-authorization studies after approval by the Food and Drug Administration in the United States.

TABLE I Cancer drugs that were reviewed by the pan-Canadian Oncology Drug Review while they had market authorization under a Notice of Compliance with conditions (NOC/c) issued by Health Canada

Agent[a]	Indications	Date of authorization	Reason for NOC/c authorization	Updated data
Brentuximab vedotin	1. Hodgkin lymphoma 2. Systemic ALCL	1 Feb 2013	■ Promising response rates demonstrated in single-arm trials	1. No 2. No
Alectinib	NSCLC	29 Sep 2016	■ Promising evidence of effectiveness ■ Lack of robust evidence of survival or QOL benefit	No
Blinatumomab	ALL	22 Dec 2015	■ Promising nature of the clinical evidence ■ Awaiting phase III and additional safety data	Partial[b]
Ofatumumab	CLL (in combination with chlorambucil)	2 Oct 2014	■ Durable objective response ■ No evidence of survival or QOL benefit	Yes
Bosutinib	CML	7 Mar 2014	■ Promising nature of the clinical evidence ■ Further safety data requested	Yes
Daratumumab	Multiple myeloma	29 Jun 2016	■ Promising nature of the clinical evidence ■ Awaiting phase III data	Partial[c]
Ponatinib	CML or ALL	2 Apr 2015	■ Promising nature of the clinical evidence ■ Awaiting phase II trial data	No

TABLE I Coontinued

Agent[a]	Indications	Date of authorization	Reason for NOC/c authorization	Updated data
Ibrutinib	1. MCL (relapsed or refractory) 2. Waldenström macroglobulinemia	1. 28 Jul 2015 2. 31 Mar 2016	1 ■ Absence of a comparator arm and uncertainties resulting from cross-study comparisons to other agents ■ Duration of response should be confirmed in a larger population 2	1. Yes 2. No
Romidepsin	Peripheral T cell lymphoma	16 Oct 2013	■ On the basis of the unmet clinical need and clinical effectiveness in patients who have a poor prognosis	No
Pembrolizumab	1. NSCLC (2nd line) 2. NSCLC (1st line) 3. Metastatic melanoma	1. 15 Apr 2016 2. Not found 3. 19 May 2015[d]	1 ■ Improvement in ORR and a manageable safety profile ■ No proven benefit in OS, PFS, or QOL 3 ■ Based on promising efficacy data ■ Awaiting trial data on OS	1. Yes 2. NA 3. Partial[e]
Olaparib	Ovarian cancer	29 Apr 2016	■ Promising nature of the clinical evidence ■ Awaiting phase II/III trial data	Partial[f]
Nivolumab plus ipilimumab	Metastatic melanoma	26 Oct 2016	■ Relative to nivolumab monotherapy, an increase in PFS is established only in patients with low tumour PD-L1 expression (based on the predefined expression level of <5%) ■ An improvement in OS has not yet been established	No
Dabrafenib plus trametinib	Metastatic melanoma	6 Mar 2015	■ Based on improvement in ORR and a trend for improvement in OS	Yes
Osimertinib	NSCLC	5 Jul 2016	■ Promising nature of the clinical evidence ■ Awaiting phase II/III trial data.	Partial[g]
Venetoclax	CLL (with 17p deletion)	30 Sep 2016	■ Clinical effectiveness is based on response rate results from interim analyses of single-arm studies ■ Clinical trial data in patients who do not harbour the 17p deletion are limited	No[h]
Crizotinib	Advanced NSCLC (*ALK*-positive) 1. 1st-line 2. 2nd-line	25 Apr 2012	■ The ORR demonstrates promising evidence of a potential benefit ■ No data demonstrating OS or PFS benefit ■ Based on single-arm studies with no control arm ■ The lack of effective systemic therapies for patients with this rare disease (*ALK*-positive NSCLC) constitutes an unmet medical need ■ Awaiting phase III data in previously treated and treatment-naïve patients	Yes
Idelalisib	Follicular lymphoma	27 Mar 2015	■ Pending the results of studies to verify its clinical benefit ■ Durability of the response could not be estimated because of the immaturity of the data	Partial[i]

[a] Bolded agents subsequently given full authorization.
[b] Additional safety data published January 2017.
[c] Phase III interim analysis available October 2016.
[d] Second-line after ipilimumab. Updated NOC/c 22 June 2016 based on interim report of phase II trial); NOC 6 May 2016 for first-line immunotherapy.
[e] Phase II data on PFS available Aug 2015. Analysis of OS still pending.
[f] Phase II data available November 2016. Phase III results pending.
[g] Phase II data (AURA2) available December 2016.
[h] Subsequently withdrawn from pCODR process.
[i] Phase II data subgroup analysis of PFS available (e-publication December 2016).

ALCL = anaplastic large-cell lymphoma; NSCLC = non-small-cell lung cancer; QOL = quality of life; ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; MCL = mantle cell lymphoma; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; NA = not available.

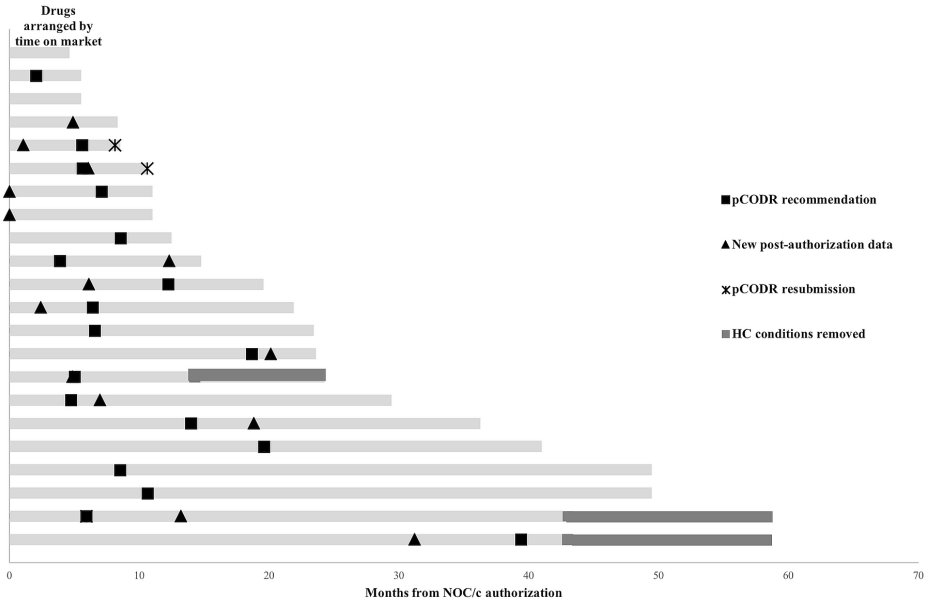

FIGURE 2 Health Canada (HC) market authorization of cancer drugs. pCODR = pan-Canadian Oncology Drug Review; NOC/c = Notice of Compliance with conditions.

Meanwhile, the number of drugs given accelerated approval by the Food and Drug Administration with limited evidence has increased, with downstream implications for funding bodies[12,13]. In contrast, the conditional marketing authorization process in the European Union contains explicit deadlines and requires an annual review and renewal contingent on the stipulated conditions being met[3].

The pCODR process provides a second checkpoint and opportunity for critical appraisal. In the case of NOC/c drugs, the pERC is less likely to recommend drug reimbursement without evidence of meaningful benefit—generally, improvements in overall or progression-free survival. In all cases in which public reimbursement was recommended, those recommendations were conditional on reducing cost to acceptable societal willingness-to-pay thresholds. In the event that pERC recommended against public funding, we note that pCODR reappraisals were triggered by manufacturer resubmissions. As a whole, then, Canadian drug review and funding mechanisms appear to be driven by the pharmaceutical industry. Of course, the decision to publicly fund treatments ultimately rests with individual provinces and territories. Further analysis of pCODR's impact on drug pricing and provincial funding decisions would be of value, although review of the Common Drug Review process for non-cancer drugs suggests that between 60% and 96% of recommendations are adopted by provincial funding agencies[7]. In contrast, funding recommendations by the U.K. National Institute for Health and Clinical Excellence (the equivalent of the Common Drug Review) are legally binding[14].

We recognize that HC, pCODR, and provincial funding bodies have different priorities: ensuring the safety of drugs and making them available in a timely fashion for patients who lack other options on the one hand, and ensuring equitable and rational resource allocation on the other. The burden of proof that that proponents of new treatments must meet is certainly an ongoing debate. It is in no one's interest to fund and treat patients with drugs that provide negligible benefit in the real world. Ideally, then, the regulation and funding of drugs should be a process of continual critical reappraisal. The creation of review bodies such as pCODR is a positive step. However, we argue that stronger HC legislation is needed to ensure the safe and appropriate treatment of cancer patients with novel pharmaceuticals.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: NP, AC, MET, KKWC, and MCC are members of the pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC), a committee that convenes under the auspices of the Canadian Agency for Drugs and Technologies in Health. The Canadian Agency for Drugs and Technologies in Health is an independent, not-for-profit organization established in 1989 by the federal, provincial, and territorial governments.

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