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Benefit of expedited regulatory approval for oncology drugs eliminated by slow reimbursement reviews and price negotiations

Nigel S B Rawson and David J Stewart

ABSTRACT

Summary: In an examination of 92 oncology drugs that received regulatory approval from Health Canada with a Notice of Compliance with conditions (NOC/c) since the policy was introduced in 1998 through to December 1, 2021, the authors concluded the "NOC/c policy has been successful in providing expedited access to promising therapies." We investigated the time required by Canada's Drug Agency (CDA) to complete reimbursement reviews and the pan-Canadian Pharmaceutical Alliance (pCPA) to perform price negotiations with manufacturers for 66 of the 92 drugs that were likely to have been eligible for review and negotiation. Twelve of the 66 drugs had no submission to CDA; potential reasons were identified for six. In the other 54 drugs, 37 (68.5%) had a positive CDA review and 17 (31.5%) a negative review. Only seven reviews (13.0%) took less than CDA's claimed "typical timeline" of 180 days or less, while almost three-quarters were within its 270-day target. The pCPA's targets of 40 business days (60 calendar days) for deciding whether to negotiate and 90 business days (130 calendar days) for completion of negotiations were achieved for only 37% of the recommendations and 41% of the negotiations. The resulting delays led to the time between NOC/c and final pCPA outcome being close to two years for over 50% of the drugs and almost three years for a quarter of them. This delay is compounded by government drug plans taking further lengthy time periods to decide whether to fund the drugs. The potential benefit to patient access of an expedited regulatory review resulting in an NOC/c is eliminated when unnecessarily extensive delays occur in reimbursement review and price negotiation processes established by government drug plans.

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INTRODUCTION

Martin et al recently examined 92 oncology drugs that received regulatory approval from Health Canada by a Notice of Compliance with conditions (NOC/c) since the policy was introduced in 1998 through to December 1, 2021. The objective of the NOC/c policy is to provide patients with earlier access to promising new drugs for serious, life-threatening or severely debilitating conditions for which no therapy is presently marketed in Canada or a significant increase in efficacy or a significant decrease in risk is demonstrated relative to an existing drug marketed in Canada. Martin et al concluded that the "NOC/c policy has been successful in providing expedited access to promising therapies." [1,2]

The regulatory process is only the first step in getting drugs to Canadians. Reimbursement reviews performed by Canada's Drug Agency (CDA) – formerly known as the Canadian Agency for Drugs and Technologies in Health – to provide recommendations for listing of drugs and price negotiations with drug developers carried out by the pan-Canadian Pharmaceutical Alliance (pCPA) are completed after regulatory approval and take time, which can delay access to new medicines. The objective of this work is to investigate the time required by CDA reimbursement reviews and pCPA price negotiations for oncology drugs receiving an NOC/c.

METHODS

CDA began its review process in 2005. In 2007, the review of oncology medicines was transferred to an interim process known as the Joint Oncology Drug Review (JODR). During this process, all drugs for cancer were submitted to Ontario's Drug Benefit Program and reviewed by Ontario's Committee to Evaluate Drugs and Cancer Care Ontario to provide listing recommendations. JODR evolved into the pan-Canadian Oncology Drug Review (pCODR), which began work in 2011. Information on reviews performed by JODR are unavailable. Consequently, this investigation was limited to oncology drugs that received an NOC/c after 2011 and, therefore, likely to have been reviewed by pCODR. The pCPA was established in 2010 and, therefore, most of the drugs were likely to have been eligible for a pCPA negotiation. For these drugs, reimbursement reviews and negotiations were identified from the websites of CDA and the pCPA. [3,4,5,6]

RESULTS

Of the 92 oncology medicines with NOC/c regulatory approval, 66 (71.7%) were eligible for our analysis. Twelve drugs had an NOC/c approval after 2011, but no submission to CDA (TABLE 1). Two of these drugs had submissions to CDA withdrawn, leaving 10 for which no submission was identified. Of these 10, one had its NOC/c withdrawn, one was for an extension to the indication approved in an earlier NOC/c and may not have warranted a new CDA submission, one was withdrawn in the United States, and the other was a vaccine product unlikely to be reviewed by CDA. No alternative explanation for a lack of a CDA submission could be found for the other six drugs.

TABLE 1: 12 oncology drugs with NOC/c regulatory approval and no CDA submission.

Brand name (generic name)	NOC/c date	Indication	
Arzerra (ofatumumab)	09-03-2012	Chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab	
Truseltiq (infigratinib)	27-03-2015	Metastatic cholangiocarcinoma	Drug withdrawn in USA
Ibrance (palbociclib)	16-03-2016	Metastatic HR+ HER2- breast cancer	Withdrawn from CDA
Tepadina (thiotepa)	29-03-2017	Central nervous system lymphoma	
Tecentriq (atezolizumab)	12-04-2017	Metastatic urothelial cancer	NOC/c withdrawn
Imfinzi (durvalumab)	03-11-2017	Metastatic urothelial carcinoma	
Keytruda (pembrolizumab)	21-09-2018	B-cell lymphoma	
Tecentriq (atezolizumab)	21-09-2019	Metastatic triple negative breast cancer	Withdrawn from CDA
Bavencio (avelumab)	06-11-2019	Metastatic Merkel cell carcinoma	Expansion of indication
Keytruda (pembrolizumab)	14-12-2020	Bladder cancer	
Verity-BCG (BCG strain Russian)	24-12-2020	Relapsing urothelial cell carcinoma	Submission to CDA unlikely
Opdivo (nivolumab)	11-02-2021	Colorectal cancer	

In the remaining 54 drugs, erdafitinib (Balversa) is currently under review by CDA and excluded from the analysis. In the other 53 drugs, brentuximab (Adcetris) had an NOC/c for two indications and submissions were made to CDA for each one; these were included separately so that our analysis comprised 54 reimbursement reviews (TABLE 2). Thirty-seven (62.7%) of the 54 CDA reviews were positive and 17 (28.8%) were negative. Summaries of the time taken by CDA to review submissions, the time taken by the pCPA to decide whether to negotiate and, where applicable, the time taken for negotiations are shown in TABLE 3. Only seven reviews (13.0%) took less than CDA's claimed "typical timeline" of 180 days or less, but almost three-quarters were within its 270-day target. The pCPA's targets of 40 business days (60 calendar days) for deciding whether to negotiate and 90 business days (130 calendar days) for completion of negotiations, which the pCPA aims to achieve 90% of the time, were accomplished for only 37% of the decisions about whether to negotiate and 41% of the negotiations. Re-submissions were made for six drugs – brigatinib (Alunbrig) for metastatic ALK+ non-small-cell lung cancer (NSCLC), ceritinib (Zykadia) for metastatic NSCLC, crizotinib (Xalkori) for ALK+ NSCLC, daratumumab (Darzalex) for multiple myeloma, larotrectinib (Vitrakvi) for NTRK solid tumours, and olaparib (Lynparza) for ovarian cancer – that initially received a negative CDA recommendation and not pursued for negotiation by the pCPA. The re-submissions resulted in positive recommendations and successfully completed negotiations. When these re-submissions were taken into account the median time between NOC/c and final pCPA outcome was 710 days (close to two years); a quarter took over 1074 days (almost three years). [7,8]

TABLE 2: 54 oncology drugs with NOC/c regulatory approval and a CDA submission.

Brand name (generic name)	NOC/c date	Indication	CDA outcome	pCPA outcome
Atriance (nelarabine)	22-09-2007	T-cell acute lymphoblastic leukemia	RCC	Not pursued
Vectibix (panitumumab)	03-04-2008	Metastatic colorectal cancer	RCC	LOI
Xalkori (crizotinib)	25-04-2012	ALK+ non-small-cell lung cancer	DNR	LOI
Adcetris (brentuximab)	01-02-2013	Hodgkin's lymphoma	RCC	LOI
Adcetris (brentuximab)	01-02-2013	Anaplastic large-cell lymphoma/mycosis fungoides	RCC	LOI
Istodax (romidepsin)	16-10-2013	Peripheral T-cell lymphoma	RCC	LOI
Blincyto (blinatumomab)	07-03-2014	Acute lymphoblastic leukemia	RCC	LOI
Bosulif (bosutinib)	07-03-2014	Chronic myeloid leukemia	RCC	LOI
Arzerra (ofatumumab)	02-10-2014	Chronic lymphocytic leukemia	DNR	Not pursued
Tafinlar (dabrafenib)/Mekinist (trametinib)	06-03-2015	Metastatic melanoma	RCC	LOI
Zydelig (idelalisib)	27-03-2015	Follicular lymphoma	DNR	Not pursued
Zykadia (ceritinib)	27-03-2015	Metastatic non-small-cell lung cancer	DNR	Not pursued
Iclusig (ponatinib)	02-04-2015	Chronic myeloid/acute lymphoblastic leukemias	RCC	LOI
Keytruda (pembrolizumab)	19-05-2015	Metastatic melanoma	RCC	LOI
Imbruvica (ibrutinib)	28-07-2015	Mantle cell lymphoma	RCC	LOI
Blincyto (blinatumomab)	22-12-2015	Min res dis pos B-cell prec acute lymphoblastic leukemia	RCC	LOI
Keytruda (pembrolizumab)	15-04-2016	Non-small-cell lung cancer	RCC	LOI
Lynparza (olaparib)	29-04-2016	Ovarian cancer	DNR	Not pursued
Darzalex (daratumumab)	29-06-2016	Multiple myeloma	DNR	Not pursued
Tagrisso (osimertinib)	05-07-2016	Non-small-cell lung cancer	RCC	LOI
Alecensaro (alectinib)	29-09-2016	Metastatic ALK+ non-small-cell lung cancer	RCC	LOI
Venclexta (venetoclax)	30-09-2016	Chronic lymphocytic leukemia	RCC	LOI
Opdivo (nivolumab)	26-10-2016	Metastatic melanoma	RCC	LOI
Blincyto (blinatumomab)	28-04-2017	Ph+ precursor acute lymphoblastic leukemia	RCC	LOI
Keytruda (pembrolizumab)	08-09-2017	Hodgkin's lymphoma	RCC	LOI
Opdivo (nivolumab)	10-11-2017	Hodgkin's lymphoma	RCC	LOI
Lartruvo (olaratumab)	23-11-2017	Advanced soft-tissue sarcoma	RCC	No agreement
Bavencio (avelumab)	18-12-2017	Metastatic Merkel cell carcinoma	RCC	LOI
Opdivo (nivolumab)	23-03-2018	Metastatic hepatocellular carcinoma	DNR	Not pursued
Imfinzi (durvalumab)	04-05-2018	Non-small-cell lung cancer	RCC	LOI
Lynparza (olaparib)	04-05-2018	Ovarian cancer	RCC	LOI
Alunbrig (brigatinib)	26-07-2018	Metastatic ALK+ non-small-cell lung cancer	DNR	Not pursued
Folotyn (pralatrexate)	26-10-2018	Peripheral T-cell lymphoma	RCC	LOI
Opdivo (nivolumab)	15-11-2018	Melanoma	RCC	LOI
Idhifa (enasidenib)	06-02-2019	Acute myeloid leukemia	DNR	Not pursued
Lorbrena (lorlatinib)	22-02-2019	Metastatic ALK+ non-small-cell lung cancer	RCC	No agreement
Libtayo (cemiplimab)	10-04-2019	Cutaneous squamous cell carcinoma	RCC	LOI
Keytruda (pembrolizumab)	11-04-2019	Metastatic urothelial carcinoma	DNR	Not pursued
Vitrakvi (larotrectinib)	10-07-2019	NTRK solid tumours	DNR	Not pursued
Keytruda (pembrolizumab)/ Lenvima (lenvatinib)	20-09-2019	Advanced endometrial cancer	RCC	LOI
Rozlytrek (entrectinib)	10-02-2020	NTRK extracranial solid tumours	RCC	LOI
Polivy (polatuzumab)	09-07-2020	Large B-cell lymphoma	RCC	LOI
Bavencio (avelumab)	10-12-2020	Urothelial carcinoma	RCC	LOI
Keytruda (pembrolizumab)	05-02-2021	Hodgkin's lymphoma	RCC	LOI
Keytruda (pembrolizumab)	03-03-2021	Colorectal cancer	RCC	LOI
Abecma (idecabtagene vicleucel)	26-05-2021	Multiple myeloma	DNR	Not pursued
Tepmetko (tepotinib)	27-05-2021	Metastatic non-small-cell lung cancer	DNR	LOI
Retevmo (selpercatinib)	15-06-2021	RET+ non-small-cell lung cancer	RCC	LOI
Gavreto (pralsetinib)	30-06-2021	RET+ non-small-cell lung cancer	RCC	No agreement
Minjuvi (tafasitamab)	19-08-2021	Large B-cell lymphoma	DNR	LOI
Lumakras (sotorasib)	10-09-2021	KRAS non-small-cell lung cancer	DNR	UC
Pemazyre (pemigatinib)	17-09-2021	Metastatic cholangiocarcinoma	DNR	Not pursued
Zepzelca (lurbinectedin)	29-09-2021	Metastatic small-cell lung cancer	DNR	Not pursued
Enhertu (trastuzumab deruxtecan)	15-06-2022	Metastatic HER2-low breast cancer	RCC	LOI

DNR: Do not reimburse; LOI: Letter of intent; RCC: Reimburse with criteria and/or conditions; UC: Under consideration

TABLE 3: Time taken for CDA reviews, pCPA negotiation decisions and negotiations, and time between NOC/c and pCPA outcome.

	CDA reimbursement reviews	pCPA negotiation decisions	pCPA negotiations	Time between NOC/c and pCPA outcome	
				Initial assessments	With resubmissions
No.	54	54	39	54	54
Median	220 days	86 days	149 days	633 days	710 days
Interquartile range	192 – 263 days	45 – 133 days	81 – 252 days	332 – 894 days	438 – 1074 days
% of reviews within 180 days	13.0%				
% of reviews within 270 days	74.1%				
% of decisions within 60 days		37.0%			
% of negotiations within 130 days			41.0%		
% of time between NOC/c and pCPA outcome within 18 months				46.3%	35.2%

DISCUSSION

These results indicate that 82% of the oncology drugs receiving an NOC/c after 2011 and were submitted to CDA. No alternative explanation for a lack of a submission could be found for six drugs.

Less than 50% of the submissions to CDA were made prior to the NOC/c date, although pre-NOC submissions were more likely after 2015. Once submitted, CDA took longer than its commonly stated "typical timeline" of 180 days for 87% of the drugs, but almost 75% were completed within its more realistic nine-month target. The pCPA generally took much longer to decide whether to negotiate with the developer than its target time; only 37% of the oncology drugs had a decision regarding negotiation within 60 days. In addition, just 41% of the negotiations were completed within the pCPA's target of 130 days.

These results are consistent with an analysis of all reimbursement recommendations for oncology medicines issued by CDA between January 2014 and December 2023 and subsequent pCPA price negotiation decisions and outcomes, which found that CDA's "typical timeline" of 180 days was not achieved in any review in 2021, 2022 or 2023. [9] In addition, the pCPA's target of 60 days for deciding whether to negotiate was attained for less than 40% of oncology drugs between 2017 and 2023 and its target of 130 days for negotiations was achieved for only 14.3% of negotiations in 2016, although the rate then gradually increased to 61.5% in 2023.

Delays resulting from reimbursement reviews and price negotiations for oncology drugs with an NOC/c regulatory approval led to the time between NOC/c and final pCPA outcome being close to two years for over 50% of the drugs and almost three years for a quarter of them. These delays are compounded by government drug plans taking further lengthy time periods to decide whether to fund the drugs. The potential benefit to patient access of an expedited regulatory review resulting in an NOC/c is eliminated when extensive delays occur in the reimbursement review and price negotiation processes established by government drug plans.

Many calls have been made for Canada to reduce delays in patient access to new oncology medicines via government drug plans. Canada's governments have established and control CDA and the pCPA and allowed them to develop procedures without accountable performance targets. Even when drugs have passed through these processes, government drug plans do not automatically list the medicine, leading to further delays. Delays in bringing effective new cancer medicines to Canadians, which may lead to thousands of lives being lost, are unacceptable. [10-21]

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