

Pan-Canadian Oncology Drug Review reports in 2019: a positive recommendation rate change?

Nigel S B Rawson, PhD

President, Eastlake Research Group, Oakville, ON
Affiliated Scholar, Canadian Health Policy Institute, Toronto, ON
Senior Fellow, Fraser Institute, Vancouver, BC

Summary

The objective of this work was to examine whether the rate of positive pCODR recommendations changed recently and, if so, to evaluate any potential reasons. All pCODR final recommendations issued in 2019 were reviewed and detailed information recorded, including provincial funding status available from pCODR website. Pan-Canadian Pharmaceutical Alliance (pCPA) pricing negotiation status relating to the pCODR assessments were also recorded.

Seventeen recommendations were issued before July 1, 2019 of which 15 (88.2%) were positive, while only seven (50.0%) of the other 14 recommendations were positive (Fisher's exact test, $p = 0.044$). Little difference was found between positive and negative recommendations in the type of cancer or how the drugs were intended to be used. However, the clinical data included in the submission came from a phase III trial in 90.9% of the positive recommendation reports but only 33.3% of the negative recommendation reports (Fisher's exact test, $p = 0.0026$).

All positive recommendations were qualified by one or more conditions, the most frequent being the need for the drug's cost-effectiveness to be improved to an acceptable level and the second most common being that the impact on drug plan budgets must be addressed. The principal reason for a negative recommendation was uncertainty or concern about the information in the submission regarding the drug's clinical benefit.

The most striking result in this analysis was the difference in the rate of positive recommendations between the first and second halves of 2019. This difference could be due to the type of clinical data included in the submissions or the result of the closer alignment of pCODR with the Common Drug Review. Further analysis of pCODR's positive recommendation rate in 2020 is warranted.

Background

Several barriers exist in Canada between a drug being given marketing approval by Health Canada and being available to patients. One of these hurdles is health technology assessment in which the benefits, risks and costs of the drug are evaluated to provide an assessment of its “value.” This is not an easy task since it is trying to predict the future cost-effectiveness of the drug in the real world of clinical medicine based on balancing experimental data testing the medicine in a highly monitored environment in relatively few patients against a price that is unrepresentative of the cost to public and private insurers.

When it comes to drugs intended for life-threatening diseases or those that cause significant disability, patients want timely access to such products. This is especially the case for cancer therapies. Health technology assessment of oncology drugs is performed for all cancer agencies in Canada, except Quebec’s, by the pan-Canadian Oncology Drug Review (pCODR), which is part of the Canadian Agency for Drugs and Technologies in Health (CADTH). pCODR evaluates oncology drugs based on four criteria: clinical evidence of efficacy, cost-effectiveness, alignment with patient values, and feasibility of adoption into the health system. The effectiveness of pCODR has been evaluated in 2014 and found to provide positive reimbursement recommendations to cancer agencies in around 80% of its reviews.¹

Objective

The aim of this work was to examine whether the rate of positive pCODR recommendations to provinces changed in 2019 and, if so, to evaluate any potential reasons.

Methods

All pCODR final recommendations issued in 2019 were reviewed and the following information abstracted:

- Name of drug.
- Dates of submission to pCODR and issuance of final recommendation, and whether the submission preceded Health Canada’s Notice of Compliance.
- Recommendation and any conditions.
- The indication, i.e. the type of cancer for which the drug is indicated.
- Whether the cancer is a solid tumour or not.
- How the drug is to be used: advanced or metastatic cancer, relapsed or refractory cancer, adjuvant therapy, after prior treatments or surgery, in combination with other therapies. A drug could fit into more than one of these categories.
- The phase of clinical trial(s) whose evidence was reviewed by pCODR.
- Provincial funding status for the drug available from the pCODR website (since pCODR does not review oncology drugs for Quebec, this information excluded the funding status in that province).

Pan-Canadian Pharmaceutical Alliance (pCPA) pricing negotiation status relating to the pCODR assessments were also recorded.

Descriptive analyses of these data were performed.

Results

Thirty-one final recommendations were issued by pCODR in 2019 (the names of the drugs, the conditions to be treated and the recommendation dates are provided in Appendix Tables A and B). Twenty-two (71.0%) were positive and nine (29%) were negative. Selected characteristics of the recommendations are shown in Table 1.

¹ Rawson NSB. Has pCODR improved access to oncology drugs? Timeliness and provincial acceptance of pan-Canadian Oncology Drug Review recommendations. Vancouver: Fraser Institute, 2014.
<https://www.fraserinstitute.org/sites/default/files/has-pCODR-improved-access-to-oncology-drugs-rev.pdf>.

Table 1: Selected characteristics of the pCODR recommendations

	Type of recommendation	
	Positive	Negative
Number of recommendations	22	9
Date of recommendation:		
Before July 1, 2019	15 (68.2%)	2 (22.2%)
On or after July 1, 2019	7 (31.8%)	7 (77.8%)
Date of submission before NOC	12 (54.5%)	3 (33.3%)
Median review time (days)	218	220
Range of review times (days)	97 – 367	192 – 281
Type of cancer:		
Solid tumours	16 (72.7%)	6 (66.7%)
Non-solid tumours	6 (27.3%)	3 (33.3%)
Drug intended for:*		
Advanced or metastatic cancers	10 (45.5%)	5 (55.6%)
Relapsed or refractory cancers	3 (13.6%)	1 (11.1%)
Adjuvant therapy	2 (9.1%)	0 (0.0%)
Use in combination therapy	9 (40.9%)	1 (11.1%)
Use after prior therapy or surgery	10 (45.5%)	4 (44.4%)
Clinical data in submission:		
Phase III trial(s)**	20 (90.9%)	3 (33.3%)
Phase I and/or II	2 (9.1%)	4 (44.4%)
Phase IV trial	0 (0.0%)	1 (11.1%)
Pooled analysis of undefined trials	0 (0.0%)	1 (11.1%)

NOC: Notice of Compliance

* Drugs may be in more than one category

** Some pCODR recommendation reports did not specify the trial's phase but, based on the comments, it was possible to assume phase III

Seventeen recommendations were issued before July 1, 2019 of which 15 (88.2%) were positive, while seven (50.0%) of the other 14 recommendations were positive – a statistically significant difference (Fisher's exact test, $p = 0.044$). Little difference was found between positive and negative recommendations in the type of cancer or how the drugs were intended to be used. However, the clinical data included in the submission came from a phase III trial in 90.9% of the positive recommendation reports but only 33.3% of the negative recommendation reports (Fisher's exact test, $p = 0.0026$). The other two-thirds of the submissions that received a negative recommendation had clinical data from phase I/II trials, a phase IV trial, and a pooled analysis of undefined trials.

All positive recommendations were qualified by one or more conditions, the most frequent being the need for the drug's cost-effectiveness to be improved to an acceptable level (Table 2), although the price reduction required was not specified in any of the recommendations. The second most common condition was that the impact on drug plan budgets must be addressed, although again little guidance was given on how this should be achieved.

Reasons for the negative recommendations are shown in Table 3. All these recommendations specified uncertainty or concern about the information in the submission regarding the drug's clinical benefit and, as a consequence, all but one of the reports stated that the cost-effectiveness was unevaluable.

Table 2: Conditions associated with positive pCODR recommendations

Cost-effectiveness to be improved to acceptable level	20 (90.9%)
Budget impact must be addressed	12 (54.5%)
Cost should not exceed that of a comparable therapy	5 (22.7%)

Table 3: Reasons for negative pCODR recommendations

Uncertainty/concern regarding clinical benefit	9 (100.0%)
Cost-effectiveness unevaluable as a result	8 (88.9%)

Fourteen (63.6%) of the 22 assessments that received a positive recommendation had completed pCPA negotiations, all but one being successful (Table 4). Negotiations for the others were still in progress. Two (22.2%) of the assessments with negative recommendations were had a successful pCPA negotiation, the negotiation for one (11.1%) was ongoing, none was being pursued for five (55.6%), and the status was unknown for the remaining drug (Table 5).

Tables 4 and 5 also list provincial funding status for each assessment at the end of March 2020 provided on the pCODR website (this excludes Quebec as the province does not participate in pCODR). Just over half the drugs with a positive pCODR recommendation and a successful pCPA negotiation completed in the first five months of 2019 are funded in British Columbia, Saskatchewan, Manitoba and Ontario, but the other provinces are slower. A price negotiation was not pursued for more than half the drugs that received a negative pCODR recommendation. Even when one of the negative recommendation drugs did have a successful price negotiation, the likelihood of receiving provincial funding was low.

Discussion

The most striking result in this analysis is the difference in the rate of positive recommendations between the first and second halves of 2019 (88.2% versus 50.0%). The positive rate in the first half of 2019 is similar to the 80% found in a 2014 analysis,² whereas the rate in the second half is consistent with the Common Drug Review's positive recommendation rate.

This difference could be due to the type of clinical data included in the submissions (90.9% of the positive recommendations included at least one phase III clinical trial compared with only 33.3% of the negative recommendations). It could also be a result of the closer alignment of pCODR with the Common Drug Review, which was an objective stated at the fall 2019 CADTH update. A further analysis of the positive recommendation rate in 2020 is warranted.

² Rawson NSB. Has pCODR improved access to oncology drugs? Timeliness and provincial acceptance of pan-Canadian Oncology Drug Review recommendations. Vancouver: Fraser Institute, 2014.
<https://www.fraserinstitute.org/sites/default/files/has-pCODR-improved-access-to-oncology-drugs-rev.pdf>.

Table 4: Pan-Canadian Pharmaceutical Alliance pricing negotiation status and provincial funding status as at March 30, 2019 for positive pCODR recommendations

Brand name	pCPA negotiation status	Province									
		BC	AB	SK	MB	ON	NS	NB	NL	PE	
Tagrisso	Completed	F	UC	F	UC	UC	UC	UC	F	UC	
Cabometyx	Completed	F	UC	F	UC	UC	UC	UC	UC	UC	
Opdivo	Completed	F	UC	F	F	F	UC	UC	UC	UC	
Xtandi	Completed	UN	UN	UN	UN	UN	UN	UN	UN	UN	
Unituxin	Completed	F	UC	F	F	F	UC	UC	UC	UC	
Folotyng	Completed	UC	UC	UC	UC	UC	UC	UC	UC	UC	
Blincyto	Completed	UC	UC	UC	F	UC	UC	F	UC	UC	
Imfinzi	Completed	F	UC	F	F	F	F	UC	UC	UC	
Ibrance	Current	UN	UN	UN	UN	UN	UN	UN	UN	UN	
Tafinlar/Mekinist	Completed	F	UC	F	UC	UC	UC	UC	UC	UC	
Xalkori	Current	UN	UN	UN	UN	UN	UN	UN	UN	UN	
Vizimpro	Closed without agreement	UN	UN	UN	UN	UN	UN	UN	UN	UN	
Keytruda	Current	UN	UN	UN	UN	UN	UN	UN	UN	UN	
Venclexta	Completed	F	UC	F	UC	UC	UC	UC	UC	UC	
Revlimid	Current	UN	UN	UN	UN	UN	UN	UN	UN	UN	
Verzenio	Current	UN	UN	UN	UN	UN	UN	UN	UN	UN	
Lenvima	Completed	UC	UC	F	UC	UC	UC	UC	UC	UC	
Lutathera	Current	UN	UN	UN	UN	UN	UN	NF	UN	UN	
Keytruda	Current	UN	UN	UN	UN	UN	UN	UN	UN	UN	
Darzalex	Current	UN	UN	UN	UN	UN	UN	UN	UN	UN	
Pomalyst	Completed	Provincial listings not available									
Lynparza	Completed	Provincial listings not available									

F: Funded; NF: Not funded; UC: Under consideration; UN: Under negotiation

Table 5: Pan-Canadian Pharmaceutical Alliance pricing negotiation status and provincial funding status as at March 30, 2019 for negative pCODR recommendations

Brand name	pCPA negotiation status	Province									
		BC	AB	SK	MB	ON	NS	NB	NL	PE	
Lenvima	None	UC	UC	NF	NF	UC	UC	UC	NF	NF	
Adcetris	Completed	F	UC	NF	UC	UC	UC	UC	NF	NF	
Ninlaro	None	UC	UC	UC	UC	UC	UC	UC	UC	UC	
Alunbrig	None	NF	UC	NF	NF	UC	UC	NF	UC	UC	
Lonsurf	Completed	NF	UC	NF	NF	UC	UC	NF	UC	NF	
Keytruda	Current	UC	UC	UC	NF	UC	UC	UC	UC	UC	
Idhifa	Unknown	NF	UC	UC	NF	UC	UC	UC	UC	UC	
Vitrakvi	None	NF	UC	UC	NF	UC	UC	UC	UC	UC	
Nerlynx	None	Provincial listings not available									

F: Funded; NF: Not funded; UC: Under consideration

Appendix Table A: Positive pCODR recommendations, 2019

Generic name	Brand name	Recommendation date	Indication
Tagrisso	osimertinib	04-01-19	First-line locally advanced or metastatic NSCLC with EGFR-activating mutations
Cabometyx	cabozantinib	20-02-19	Renal cell carcinoma patients who have had prior therapy
Opdivo	nivolumab	07-03-19	Adjuvant to surgery for melanoma with regional spread or metastases
Xtandi	enzalutamide	26-03-19	Combination with androgen deprivation therapy for non-metastatic castration-resistant prostate cancer
Unituxin	dinutuximab	26-03-19	Combination with GM-CSF, IL-2 and retinoic acid in children with high-risk neuroblastoma who had at least partial response to prior first-line multi-modal therapy
Folotyng	pralatrexate	04-04-19	Relapsed/refractory peripheral t-cell lymphoma
Blincyto	blinatumomab	04-04-19	Philadelphia chromosome positive b-cell precursor acute lymphoblastic leukemia relapsed/refractory to or intolerant of one or more second generation TKI & refractory/intolerant to imatinib
Imfinzi	durvalumab	03-05-19	Locally advanced unresectable NSCLC following platinum-based chemoradiation
Ibrance	palbociclib	03-05-19	Combination with fulvestrant for hormone receptor positive HER-2-negative advanced or metastatic breast cancer that progressed after endocrine therapy
Tafinlar/ Mekinist	dabrafenib/ trametinib	03-05-19	Adjuvant therapy to surgery for BRAF V600 melanoma mutation and lymph node involvement
Xalkori	crizotinib	23-05-19	First-line for ROS-1-positive advanced NSCLC
Vizimpro	dacomitinib	31-05-19	Locally advanced or metastatic NSCLC with epidermal growth factor receptor-activating mutations (first-line)
Keytruda	pembrolizumab	31-05-19	Combination with pemetrexed and platinum chemotherapy for metastatic non-squamous NSCLC with no EGFR or ALK aberrations and no prior systemic chemotherapy
Venclexta	venetoclax	31-05-19	Combination with rituximab for chronic lymphocytic leukemia in adults who had at least one prior therapy, irrespective of 17p deletion status
Revlimid	lenalidomide	19-06-19	Combination with bortezomib and dexamethasone for newly diagnosed multiple myeloma where stem cell transplant is not intended
Verzenio	abemaciclib	05-07-19	Hormone receptor positive HER-2-negative advanced or metastatic breast cancer in combination with other therapies depending on menopausal status
Lenvima	lenvatinib	24-07-19	First-line for unresectable hepatocellular carcinoma
Lutathera	lutetium lu 177 dotatate	01-08-19	Somatostatin-receptor-positive gastroenteropancreatic neuroendocrine tumours
Keytruda	pembrolizumab	01-08-19	Adjuvant therapy to surgery for stage III melanoma or retreatment on loco-regional or distant recurrence more than six months after complete adjuvant course of pembrolizumab
Darzalex	daratumumab	29-08-19	Combination with bortezomib, melphalan and prednisone for newly diagnosed multiple myeloma where stem cell transplant is not suitable
Pomalyst	pomalidomide	18-09-19	Combination with bortezomib and dexamethasone for relapsed/ refractory multiple myeloma who had at least one prior treatment regimen including lenalidomide
Lynparza	olaparib	05-12-19	Monotherapy maintenance for newly diagnosed advanced BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer with at least partial response to first-line platinum-based therapy until disease progression or up to two years if no evidence of disease

NSCLC: Non-small cell lung cancer

Appendix Table B: Negative pCODR recommendations, 2019

Generic name	Brand name	Recommendation date	Indication
Lenvima	lenvatinib	04-01-19	Advanced/metastatic renal cell carcinoma following one prior VEGF treatment
Adcetris	brentuximab	07-03-19	Hodgkin's lymphoma after at least two chemotherapies in non-stem-cell candidates
Ninlaro	ixazomib	05-07-19	Combination with lenalidomide and dexamethasone for multiple myeloma patients who had at least one prior therapy
Alunbrig	brigatinib	01-08-19	Monotherapy for ALK-positive locally advanced or metastatic NSCLC who progressed on or intolerant to crizotinib
Lonsurf	trifluridine/ tipiracil	29-08-19	Metastatic colorectal cancer previously treated with or not considered suitable for available therapies (resubmission)
Keytruda	pembrolizumab	03-10-19	Locally advanced or metastatic urothelial carcinoma not eligible for cisplatin-containing chemotherapy with PD-L1 expression or patients not eligible for any platinum-containing chemotherapy regardless of PD-L1 status
Idhifa	enasidenib	31-10-19	Relapsed or refractory acute myeloid leukemia with IDH-2-mutation
Vitrakvi	larotrectinib	31-10-19	Advanced or metastatic solid tumours with NTRK-gene fusion
Nerlynx	neratinib	05-12-19	Hormone receptor positive HER-2-positive breast cancer patients who have completed adjuvant trastuzumab-based therapy in last 12 months

NSCLC: Non-small cell lung cancer