Lessons Learned from the Dedicated Oncology Drug Review Process (pCODR) in Canada

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INTRODUCTION

- Canada has a universal public healthcare system where healthcare spending is significantly informed by health technology assessments (HTAs).
- National HTAs have been conducted since 2003 by the Common Drug Review (CDR) which functions within the Canadian Agency for Drugs and Technologies in Health (CADTH).
- In 2010, the permanent national oncology-specific drug review process, **pan-Canadian Oncology Drug Review (pCODR)**, was established to assess the clinical evidence and cost-effectiveness of new cancer drugs and provide recommendations to the provinces (except Quebec) and territories to guide their drug funding decisions.
- The review process (**Figure 1**) begins with the pCODR Clinical Guidance Panels consisting of oncologists from across Canada. Clinical Guidance Panels work with either the Program in Evidence-Base Care (PEBC) or CADTH to generate high quality systematic reviews for pCODR cancer drug submissions. In addition, Clinical Guidance Panels generate clinical guidance to be considered with the systematic review, in a report to the pCODR Expert Review Committee (pERC).
- The pERC then utilizes this information during the deliberative process of making a drug funding recommendation. Beginning with the pre-submission planning and concluding with final recommendations to the provincial and territorial Ministries of Health, and provincial cancer agencies, the process takes up to 5-8 months to complete.
  - Public reports are provided including: Final Recommendation, Clinical Guidance Report, Economic Guidance Report, Manufacturers Feedback, Patient Advocacy Declaration and Provincial Advisory Group Feedback.

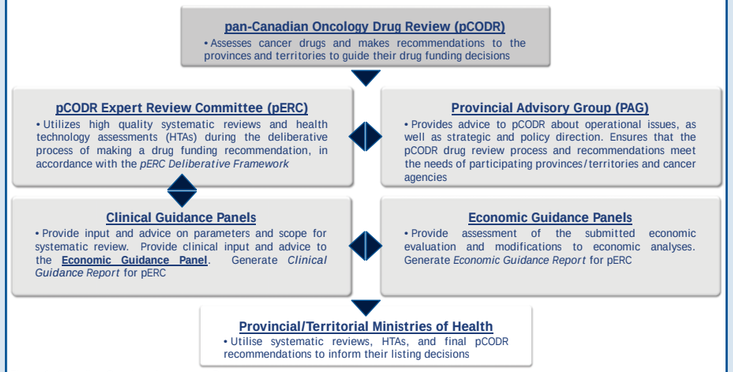

Figure 1: Canadian Oncology Assessment Process

OBJECTIVE

- The objective of this study was to conduct an analysis of the pCODR recommendations to identify trends associated with positive and negative recommendations.

METHODS

- Final recommendations were identified from inception (13 July 2011) to 31 December 2012. Using only publicly available information (accessible at www.pcodr.ca), recommendations were analyzed under the following categories: submission specifics, drug characteristics, clinical factors and economic factors. Descriptive analyses were conducted to identify trends for positive and negative recommendations.

RESULTS

- Twenty cancer drug applications have been submitted through 31 December 2012 since the pCODR began accepting submissions in 2011. Of these, ten had received decisions; three were pending decisions; and seven were under review (**Table 1**).
- From 13 July 2011 through 31 December 2012, ten of twenty applications have received recommendations (**Table 2**).
- In some cases the pCODR Clinical/Economic Guidance Panel included modifications to the manufacturer's submitted model (**Table 3**). The reanalyses often involved:
  - Reducing the time horizon from that modelled by the manufacturer to limit the survival benefit of a therapy post-progression and/or to better align with the duration of trial data.
  - Revising survival post-progression to limit the survival benefit of a therapy post-progression.

SUMMARY TABLES

Table 1: Cancer Drug Submissions to the pCODR, 13 July 2011 to 31 December 2012

Brand (Generic) Name	Indication	pCODR Status
Adcetris (Brentuximab)	Second-line treatment of systemic anaplastic large cell lymphoma (sALCL)	Pending
Adcetris (Brentuximab)	Hodgkin lymphoma (HL) patients after failure of ASCT or ≥ 2 prior chemotherapy regimens in patients who are not ASCT candidates.	Pending
Afinitor (Everolimus)	Patients with well- or moderately differentiated neuroendocrine tumours of pancreatic origin (pNETs) with unresectable, locally advanced or metastatic disease.	Decision
Afinitor (Everolimus)	Treatment of post- menopausal women with hormone receptor-positive advanced breast cancer in combination with exemestane, after progression/recurrence on NSAI therapy.	Under Review[1]
Erivedge (Vismodegib)	Adults with advanced basal cell carcinoma (BCC) for whom surgery is inappropriate.	Pending
Halaven (Eribulin Mesylate)	Patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease (including an anthracycline and a taxane administered in either the adjuvant or metastatic setting).	Decision
Inlyta (Axitinib)	Patients with metastatic renal cell carcinoma (mRCC) of clear histology after failure of prior systemic therapy with either a cytokine or the VEGFR-TKI, sunitinib.	Under Review[1]
Jakavi (Ruxolitinib)	Patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.	Decision
Perjeta-Herceptin Combo Pack	In combination with trastuzumab and a taxane for patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.	Under Review
Sutent (Sunitinib Malate)	Patients with unresectable locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNETs), whose disease is progressive.	Decision
Treanda (Bendamustine Hydrochloride)	Patients with chronic lymphocytic leukemia (CLL) [relapsed/refractory] for whom fludarabine-based therapy is not appropriate.	Decision
Treanda (Bendamustine Hydrochloride)	Patients with chronic lymphocytic leukemia (CLL) [first line] for whom fludarabine-based therapy is not appropriate.	Under Review[1]
Tykerb-Letrozole (Lapatinib)	In combination with letrozole for the treatment of post-menopausal patients with hormone receptor positive metastatic breast cancer, whose tumours overexpress the ErbB2 (HER2) receptor, and who are suitable for endocrine therapy.	Under Review
Velcade (Bortezomib)	Patients with multiple myeloma who are candidates for pre-autologous stem cell transplantation in combination therapy and post-autologous stem cell transplantation as monotherapy.	Under Review[1]
Votrient (Pazopanib Hydrochloride)	First-line therapy in patients with metastatic renal cell [clear cell] carcinoma (mRCC) who have a Memorial Sloan Kettering Prognostic Score of Favourable or Intermediate Risk.	Decision
Votrient (Pazopanib Hydrochloride)	Adult patients with selective subtypes of advanced soft tissue sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo)adjuvant therapy.	Decision
Xalkori (Crizotinib)	Patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).	Decision
Xalkori (Crizotinib)	As monotherapy for use in patients with anaplastic lymphoma kinase (ALK)-positive advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer.	Under Review[1,2]
Yervoy (Ipilimumab)	Treatment of advanced melanoma (unresectable Stage III and IV melanoma) in patients who have received prior systemic therapy.	Decision
Zelboraf (Vemurafenib)	Treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.	Decision

[1] As of 31 December 2012, these submissions were under review by the pCODR. [2] Represents a re-submission. Abbreviations: AE, adverse event; BAT, best available therapy; BSC, best supportive care; CLL, chronic lymphocytic leukemia; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; pNETs, pancreatic neuroendocrine tumours; QoL, quality of life; RCC, renal cell carcinoma; STS soft tissue sarcoma; TPC, treatment of physician's choice.

Table 2: The pCODR Cancer Drug Submission Recommendation Summary, 13 July 2011 to 31 December 2012

Product	Condition	Positive Recommendation		Negative Recommendation	
		Conditional on Improved Cost-Effectiveness	With Limited Population	Clinical Benefit Insufficient or Unclear	Cost-Effectiveness Analysis Insufficient or Unclear
Afinitor	pNETs	X			
Halaven	Breast Cancer (metastatic)	X			
Jakavi	Myelofibrosis	X			
Sutent	pNETs	X			
Treanda	CLL (relapsed/refractory)			X	X
Votrient	RCC (metastatic)		X		
Votrient	STS			X	
Xalkori	NSCLC (advanced)			X	
Yervoy	Melanoma (advanced)	X			
Zelboraf	Melanoma (metastatic)	X			

Abbreviations: CLL, chronic lymphocytic leukemia; NSCLC, non-small cell lung cancer; pNETs, pancreatic neuroendocrine tumours; RCC, renal cell carcinoma; STS soft tissue sarcoma.

Table 3: The pCODR versus Manufacturer Cost-Effectiveness Analyses for Cancer Drug Submissions Receiving Recommendations, 13 July 2011 to 31 Dec. 2012

Product	Manufacturer Submitted ICER ($/QALY)	pCODR Reanalysis ICER ($/QALY)	Components Revised in the pCODR Reanalysis
Positive Recommendations			
Afinitor	$111,805 (everolimus + BSC vs. placebo + BSC)	$165,129 - $273,781	• Time horizon reduced to 3-5 years from 10 years to limit benefit of therapy post-progression.[1]
Halaven	$100,000 – $120,000 (eribulin vs. TPC)	$114,083 – $272,275	• Risk of progression to progressed or terminal state set equal to control group after approximately 24 months.[2] • Added febrile neutropenia as an AE.[2]
Jakavi	$101,207 (ruxolitinib vs. BAT)	$276,191 – $383,686	• Time horizon shortened to 96 or 144 months to remove modeled benefit of ruxolitinib on survival.[3] • Revised model equation to correct possible error.[3]
Sutent	$79,765 (sunitinib + BSC vs. placebo + BSC)	$204,559 – $268,055	• Revised survival assumptions such that risk of death post-progression was equal for both therapies.[4] • In one pCODR analysis the risk of death increased greatly post-progression, in another the risk of death was equal to pre-progression risk of death in the placebo group.[4]
Votrient (RCC)	$57,309 (pazopanib vs. sunitinib)	Dominant – $57,309	• Equal efficacy between therapies in some pCODR re-analyses.[5] • Revised HR for the therapies based on indirect treatment comparison.[5] • Applied price reductions to both therapies.[5]
Yervoy	$103,839 – $166,186 (ipilimumab vs. non-disclosable)	$269,299 - $1,077,198	• Included drug wastage[6] • Shortened time horizon to 5 years to limit extrapolated survival benefits.[6]
Zelboraf	ICER non-disclosable (vemurafenib vs. dacarbazine)	$221,668 – $275,707 (BRAF-mutation testing excluded) to $227,571 – $279,433 (BRAF-mutation testing included)	• Excluded/included BRAF test costs.[7] • Assumed equal post-progression survival for both therapies.[7]
Negative Recommendations			
Treanda	$72,504 (bendamustine + rituximab vs. BSC)	Unable to provide an estimate	• No revisions as concluded "The manufacturer's economic model has major methodological flaws … not able to correct the model to provide meaningful results with respect to cost-effectiveness."[8]
Votrient (STS)	$143,778 - $165,246 (pazopanib vs. placebo)	$146,950 - $167,782	• Reduced time horizon to 5 years from 10 years in all pCODR re-analyses to reduce post-progression survival benefit.[9] • Increased dose intensity in one pCODR re-analysis.[9]
Xalkori	$141,787 (wholesale price) (crizotinib vs. current standard of care)	$240,972 - $255,976 (confidential price) $283,303 - $301,141 (wholesale price)	• Reduced time horizon to 2 years from 6 years, with and without increasing post-progression mortality for crizontinib.[10]

CONCLUSIONS

- The recommendations from pCODR offer new insights into the future of oncology drug reimbursement in Canada.
- The probability of a positive recommendation increased with the availability of data from randomized controlled trials, findings of a net positive overall survival benefit and use of comparators that reflected current care. As such, the new pCODR process highlights the value of strong clinical data and robust cost-effectiveness modeling.
- Almost all the pCODR positive recommendations included the caveat "*conditional on cost-effectiveness being improved to an acceptable level*". This clearly supports a provincial product listing agreement structure that includes negotiations to lower incremental cost-effectiveness of the product through price discounts or other mechanisms.
- Reanalyses by the pCODR of the cost-effectiveness of submitted drugs most often involved reducing the time horizon to reduce post-progression survival benefit of the study drug and/or directly limiting post-progression survival benefit of the study drug. This reflects a recurring preference in the Economic Guidance Reports for survival to be separately modelled pre- and post-progression.
  - Further research is required to determine the implications of this preference by the pCODR economic reviewers and the consistency with common oncology cost-effectiveness modeling methods.
  - Regardless, all submissions to pCODR should include a thorough discussion of the overall survival extrapolation methods, as well as sensitivity analyses to examine the impact of alternative methods that minimize the benefit of a product in terms of post-progression survival.

REFERENCES

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2. pCODR Final Economic Guidance Report - Eribulin (Halaven) for Metastatic Breast Cancer. August 2, 2012, 1-7.
3. pCODR Final Economic Guidance Report - Ruxolitinib (Jakavi) for Myelofibrosis. January 14, 2013, 1-8.
4. pCODR Final Economic Guidance Report - Sunitinib (Sutent) for pNETs. May 3, 2012, 1-10.
5. pCODR Final Economic Guidance Report -Pazopanib Hydrochloride (Votrient) for mRCC. January 5, 2012, 1-8.
6. pCODR Final Economic Guidance Report - Ipilimumab (Yervoy) for Advanced Melanoma. April 18, 2012, 1-11.
7. pCODR Final Economic Guidance Report - Vemurafenib (Zelboraf) for Advanced Melanoma. June 1, 2012, 1-9.
8. pCODR Final Economic Guidance Report - Bendamustine (Treanda) for CLL. November 29, 2012, 1-7.
9. pCODR Final Economic Guidance Report - Pazopanib (Votrient) for STS. November 29, 2012, 1-8.
10. pCODR Final Economic Guidance Report - Crizotinib (Xalkori) for Advanced NSCLC. October 4, 2012, 1-8.

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