

pan-Canadian Oncology Drug Review Initial Economic Guidance Report

Alectinib (Alecensaro) for Non-Small Cell Lung Cancer

March 3, 2017

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Hoffmann-La Roche Limited compared alectinib to pemetrexed ± cisplatin for anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) patients who have progressed on or are intolerant to crizotinib and have central nervous system (CNS) metastases.

Table [1]. Submitted Economic Model

Funding Request/Patient Population Modelled Type of Analysis	The population was modelled based on a subgroup of patients in the NP28761 and the NP28673 trials with ALK-positive, locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib with measurable or unmeasurable CNS metastases at study start. CEA, CUA				
Type of Model	Partitioned-survival model				
Comparator	Pemetrexed with and without cisplatin				
Year of costs	2016				
Time Horizon	years				
Perspective	Government				
Cost of alectinib	 \$42.2 per 150 mg \$318.79 per day (assumed 94.5% dose intensity, base case analysis) \$2,231.5 per week (assumed 94.5% dose intensity, base case analysis) 				
* Price Source: IMSB DeltaPA - current wholesaler unit price in Ontario	Pemetrexed: • \$99.81 per vial (100 mg), \$623.72 per vial (1,000 mg) Cisplatin: • \$225.75 per vial (50 mg) • \$270 per vial (100 mg) Pemetrexed + cisplatin • No vial sharing (assume drug wastage, base case analysis) • \$53.30 per day • \$1,119.4 per 21-day cycle (pemetrexed: \$623.7 + cisplatin: \$495.7) • Perfect vial sharing • \$44.72 per day • \$939.2 per 21-day cycle (pemetrexed: \$569.5 + cisplatin: \$369.8) Pemetrexed monotherapy • No vial sharing (assume drug wastage, base case analysis) • \$29.70 per day				

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o \$623.7 per 21-day cycle			
Perfect vial sharing **T 13 per day			
o \$27.12 per day			
o \$569.5 per 21-day cycle			
The Submitter used a partition survival model			
with three mutually exclusive health states			
including progression-free survival (PFS) or pre-			
progression state, progressed disease (PD) and			
death (Figure 1 in Section 2.1 of the Technical			
Report).			
 PFS and overall survival (OS) associated with alectinib was pooled from a subset of the full clinical populations (60%) in the NP28761 (1) and the NP28673 (2) trials. OS patients receiving pemetrexed ± cisplatin was based on a retrospective analysis of 37 patients who enrolled in the PROFILE 1001 (3) expansion cohort or the PROFILE 1005 (4) and had received systematic therapies following progression on crizotinib. Median PFS for pemetrexed ± cisplatin was assumed to be 			
of the median OS reported in Ou et al (2014)			
• The health utility value for the alectinib pre- progression health state was derived by converting the European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC QLQ) measured in the NP28761 trial ⁽¹⁾ to the EQ- 5D-3L using a published conversion method ⁽⁶⁾ . The health utility value for the PD health state was obtained from a cross-sectional study assessing utility values of patients experience NSCLC in different mutational status in Canada ⁽⁷⁾ .			
 Resource utilization and health care costs were gathered from Canadian data sources, while unit costs were based on a single province, i.e. Ontario. For patients receiving pemetrexed ± cisplatin, pemetrexed was assumed to be discontinued at progression and cisplatin was used for 4 cycles based on Therapeutic Area Experts input. A sensitivity analysis for a situation when all patients received pemetrexed monotherapy was provided by the Submitter. The unit cost of alectinib was provided by Roche Canada, while unit cost of pemetrexed ± cisplatin was obtained from IMSB DeltaPA (as shown in the Submitter report). 			

(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until March 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.)

1.2Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the use of pemetrexed \pm cisplatin is appropriate. If possible, the CGP considered that ceritinib (though not currently publicly funded), whole brain radiation therapy (WBRT) and best supportive care may be also clinically relevant comparators. The Submitter did not include these comparisons in the economic analysis. The CGP noted that there is a lack of efficacy evidence between alectinib and the clinically relevant comparators.

• Relevant concern raised by the CGP included a paucity of randomized clinical trials comparing alectinib to standard chemotherapy in the ALK inhibitor pretreated population.

Summary of registered clinician input relevant to the economic analysis

Registered clinicians recognized alectinib as an efficacious and well-tolerated medication that has potential to improve clinical outcomes and quality of life. Alectinib also has potential to replace WBRT or stereotactic radiation surgery (SRS) as a second line of treatment; it can therefore relieve hospital resources allocating to chemotherapy and radiation services and improve patients health related quality of life.

The effects of alectinib on clinical outcomes including OS, PFS and quality of life were adequately addressed in the economic analysis. However, the effects of WBRT and SRS were considered only in the estimation of the cost of disease progression. The proportion of patients receiving WBRT was assumed to be smaller among patients who progress on alectinib than those receiving a standard chemotherapy. This proportion was based on input from Therapeutic Area Experts. The effects of pemetrexed ± cisplatin were taken into consideration in the estimation of cost, OS and PFS. The impact of these chemotherapy on health utility values should be investigated. The EGP performed the re-analyses by using lower utility values for patients receiving chemotherapy and those experiencing CNS metastases.

Summary of patient input relevant to the economic analysis

Patients considered the following factors important in the review of alectinib: its potential ability to replace/lessen the chance of receiving WBRT, reduction in productivity loss for patients and their caregivers due to oral administration of alectinib, improvement in lung cancer symptoms and survival, improvement in quality of life due to fewer and manageable side effects.

A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

- The submitted economic analysis explicitly considered the effect of alectinib on the chance
 of receiving WBRT by assuming a smaller proportion of patients receiving WBRT in the
 alectinib group than the standard chemotherapy group in the cost estimation. Favourable
 effects of alectinib on survival and quality of life were addressed by applying utility scores
 and measuring outcomes in QALYs.
- The model did not consider patients and caregivers time off work because the analysis adopted the perspective of the publicly funded health care system which is appropriate as per pCODR guidelines.
- The benefits of oral administration were considered in the submitted analysis by replacing the intravenous (IV) administration cost of chemotherapy to zero. However, the impact of switching from IV to oral formulation on quality of life was not included in the submitted model.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for alectinib which are relevant to the economic analysis:

- · Lack of comparative and long-term safety and efficacy data.
- Choice of target population:
 - o patients receiving crizotinib who have developed CNS metastasis,
 - any patients with ALK-positive NSCLC who have CNS metastasis and have previously been treated with crizotinib,
 - patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib but do not have CNS metastasis, or
 - patients with CNS metastasis and have received crizotinib first-line and subsequently treated with chemotherapy or immunotherapy
- Oral route of administration is convenient and does not incur IV administration cost.
 However, the number of pills required (8 capsules) per day may raise concerns of pill burden and cause medication non-adherence.
- Funding recommendation for alectinib would shift a portion of medication expenditures from the government to patients and their families in provinces where oral medications are funded in a different mechanism from intravenous cancer medications.
- Alectinib has potential to be the first-line treatment if an ongoing Phase III trial (ALEX trial) shows better outcomes in patients receiving alectinib than those receiving crizotinib.

The Submitter addressed PAG input by extrapolating long-term efficacy from two Phase II alectinib trials. The lack of comparative safety and efficacy data has not been addressed; this issue should be considered when interpreting the results of the submitted model. In the base case analysis, the Submitter focused on all ALK-positive NSCLC patients who have progressed or are intolerant to crizotinib and who have CNS metastases status at baseline. The benefit of oral route of administration and potential pill burden were adequately addressed in the submitted model given the paucity of evidence.

1.3 Submitted and EGP Reanalysis Estimates

Table [2]. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis
		(Range)
ΔE (LY)	1.967	0.488, 2.730
Progression-free	0.990	0.880, 0.990
Post-progression	0.977	-0.501, 1.740
ΔE (QALY)	1.436	0.416, 1.963
Progression-free	0.762	0.762, 0.762
Post-progression	0.674	-0.346, 1.201
ΔC (\$)	\$156,501	\$162,844, \$144,221
ICER estimate (\$/QALY)	\$108,958	\$82,958, \$346,539

The main assumptions and limitations with the submitted model are:

Lack of comparative safety and efficacy between alectinib and pemetrexed ± cisplatin. The
efficacy of alectinib was based on two phase II single-arm trials, while the efficacy of pemetrexed
± cisplatin was assumed to be equal to the efficacy of systemic therapies reported in a

retrospective analysis of 37 ALK-positive NSCLC patients who discontinued crizotinib for at least 3 weeks ⁽⁵⁾. This retrospective study, however, did not report the type of systemic therapies used, proportion of patients with CNS metastases at baseline and specific time from last dose of crizotinib to first dose of the systemic therapy. The comparative efficacy of alectinib and pemetrexed ± cisplatin estimated by the Submitter may be influenced by difference in population and study characteristics as well as trial designs.

- PFS and OS were extrapolated from short-term trial data. Using trial data the Submitter extrapolated PFS and OS of patients receiving alectinib over a year time horizon. Based on the feedback of the CGP, a 3-year time horizon is deemed more appropriate for this population. (Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until March 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.)
- Efficacy of alectinib was pooled from two single-arm phase II trials with different population characteristics. Because both trials have different study assessment schedules and race distributions, pooling data from both trials are not appropriate. The Submitter provided the results of additional economic evaluation based on each separate trial during the Checkpoint meeting. The economic evaluation results were within ranges of the base case analysis.
- The model estimated utilities for the progression-free (PF) health state for alectinib by mapping responses from the EORTC QLQ-C30 questionnaire reported in the NP28761 trial ⁽¹⁾. However, the Submitter reported only mean utility value () without detailed mapping methods. This utility value was slightly higher than other utility data for NSCLC patients reported in Nafee et al (2008) (PF-stable/no side effect=0.653) ⁽⁸⁾ and Chouaid et al (2013) (PF= 0.70) ⁽⁹⁾). (Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until March 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.) The utility value for progressed disease (PD) was based on Labbe et al (2016) ⁽⁷⁾ but the utility value used by the Submitter was slightly higher than that showed in the most recent Labbe's poster (0.69 vs 0.62) ⁽⁷⁾. Moreover, the Submitter used equal utility values for patients with and without CNS metastases. This assumption was inconsistent with existing evidence cited in the submitted PE report under the Unmet Need Section suggesting that patients with CNS metastases may have shorter life expectancy and poorer quality of life compared to patients who do not develop CNS metastases.

Due to the high uncertainty associated with the utility data, the EGP performed the re-analyses based on a range of different set of utility values reported in Nafee et al (2008)⁽⁸⁾, Chouaid et al (2013) ⁽⁹⁾, the most recent estimates reported in Labbe et a (2016) ⁽⁷⁾, Matza et al (2013) ⁽¹⁰⁾ and Lester-Coll et al (2016) ⁽¹¹⁾.

- The submitter assumed the duration of treatments equal to PFS. This may under- or over-estimate
 the costs of the treatments (including alectinib and standard chemotherapy) and the incremental
 cost-effectiveness ratio (ICER). The EGP conducted the re-analyses by varying treatment duration
 of alectinib and pemetrexed ± cisplatin by 20%.
- The unit costs of pemetrexed and cisplatin used in this study were too high given the availability of their generic versions. This may overestimate the cost of pemetrexed ± cisplatin and the ICER,

causing alectinib more economically attractive. The EGP conducted the re-analyses by varying the unit costs of alectinib, pemetrexed and cisplatin by 25%, 50% and 75% from the base case.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:

The EGP performed reanalyses by taking a shorter time horizon of 3 and 7 years, assuming 80% and 90% of alectinib dose intensity, varying hazard ratio of PFS vs OS by 20%, changing the duration of alectinib and pemetrexed \pm cisplatin by 20%, assuming -/+ 25%, 50%, and 75% of unit cost of pemetrexed \pm cisplatin, replacing utility data for pre- and post-progression health states with data reported in Labbe et al (2016) ⁽⁷⁾, Nafees et al (2008) ⁽⁸⁾ and Chouaid et al (2013)⁽⁹⁾ and replacing a utility value for progression with CNS metastases with a value of 0.40 as reported by Lester-Coll et al (2016) ⁽¹¹⁾. Detailed description of EGP analysis is shown in Table 3. The EGP also varied the unit cost of alectnib by -/+ 25%, 50%, and 75% of the submitted price (Table 4).

Table [3]: Detailed Description of EGP Reanalysis

	ΔC	∆E QALYs	ΔE LYs	ICUR (QALY)	∆ from baseline	
		Q.2.3		,	submitted ICER	
Baseline (Submitter's best case)	\$156,501	1.436	1.967	\$108,958	-	
	P Reanalyses -	- Lower bo	und			
Reducing alectinib dose intensity to 80%	\$134,012	1.436	1.967	\$93,301	(\$15,657)	
Reducing alectinib dose intensity to 90%	\$149,522	1.436	1.967	\$104,099	(\$4,859)	
Increasing a hazard ratio of PFS vs. OS by 20%	\$155,307	1.432	1.967	\$108,455	(\$503)	
Reducing duration of alectinib treatment by 20%	\$127,124	1.436	1.967	\$88,506	(\$20,453)	
Increasing duration of pemetrexed ± cisplatin by 20%	\$155,043	1.436	1.967	\$107,943	(\$1,015)	
Increasing the unit cost of pemetrexed and cisplatin by 25%	\$155,470	1.436	1.967	\$108,241	(\$718)	
Increasing the unit cost of pemetrexed and cisplatin by 50%	\$154,439	1.436	1.967	\$107,523	(\$1,435)	
Increasing the unit cost of pemetrexed and cisplatin by 75%	\$153,408	1.436	1.967	\$106,805	(\$2,153)	
Applying disutility for intravenous chemotherapy (Matza et al, 2013) ⁽¹⁰⁾	\$156,501	1.540	1.967	\$101,607	(\$7,352)	
Extreme case analysis: Upper bound OS for alectinib and Lower bound OS for pemetrexed ± cisplatin	\$162,844	1.963	2.730	\$82,958	(\$26,000)	
EGP Reanalyses-Upper bound						
Reducing a time horizon to 3 years	\$137,150	0.873	1.163	\$157,128	\$48,170	
Reducing a time horizon to 7 years	\$155,074	1.355	1.849	\$114,466	\$5,507	
Reducing a hazard ratio of PFS vs. OS by 20%	\$157,720	1.441	1.967	\$109,475	\$516	
Increasing duration of alectinib treatment by 20%	\$185,878	1.436	1.967	\$129,411	\$20,453	

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Reducing duration of pemetrexed ± cisplatin by 20%	\$157,960	1.436	1.967	\$109,974	\$1,015
Reducing the unit cost of pemetrexed and cisplatin by 25%	\$157,532	1.436	1.967	\$109,676	\$718
Reducing the unit cost of pemetrexed and cisplatin by 50%	\$158,563	1.436	1.967	\$110,394	\$1,435
Reducing the unit cost of pemetrexed and cisplatin by 75%	\$159,594	1.436	1.967	\$111,112	\$2,153
Replacing utility of pre-progression state by Nafees et al (2008) ⁽⁸⁾	\$156,501	1.321	1.967	\$118,512	\$9,553
Replacing utility of pre-progression state by Chouaid et al (2013) ⁽⁹⁾	\$156,501	1.367	1.967	\$114,480	\$5,521
Replacing utility of post-progression by Chouaid et al (2013) ⁽⁹⁾	\$156,501	1.278	1.967	\$119,363	\$10,404
Replacing utility value for CNS metastases and post-progression with Lester-Coll et al (2016) (11)	\$156,501	1.172	1.967	\$133,486	\$24,528
Extreme case analysis: Upper bound OS for alectinib and Upper bound OS for pemetrexed ± cisplatin	\$152,404	1.096	1.474	\$139,054	\$30,096
Extreme case analysis: Lower bound OS for alectinib and Lower bound OS for pemetrexed ± cisplatin	\$154,660	1.283	1.745	\$120,534	\$11,575
Extreme case analysis: Lower bound OS for alectinib and Upper bound OS for pemetrexed ± cisplatin	\$144,221	0.416	0.488	\$346,539	\$237,581
Extreme case analysis: Base case OS for alectinib and Upper bound OS for pemetrexed ± cisplatin	\$148,858	0.801	1.047	\$185,748	\$76,789
Extreme case analysis: Lower OS for alectinib and Base case OS for pemetrexed ± cisplatin	\$151,864	1.051	1.409	\$144,479	\$35,521

Table [4]. Detailed Description of EGP Reanalysis on the unit cost of alectinib

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	∆ from baseline submitted ICER
			Lower bo	und	
Reducing the unit cost of alectinib by 25%	\$119,860	1.436	1.967	\$83,448	(\$25,510)
Reducing the unit cost of alectinib by 50%	\$83,219	1.436	1.967	\$57,938	(\$51,020)
Reducing the unit cost of alectinib by 75%	\$46,577	1.436	1.967	\$32,428	(\$76,531)
	Upper bound				

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	∆ from baseline submitted ICER
Increasing the unit cost of alectinib by 25%	\$193,142	1.436	1.967	\$134,469	\$25,510
Increasing the unit cost of alectinib by 50%	\$229,784	1.436	1.967	\$159,979	\$51,020
Increasing the unit cost of alectinib by 75%	\$266,425	1.436	1.967	\$185,489	\$76,531

1.5 Evaluation of Submitted Budget Impact Analysis

An Ontario-specific budget impact analysis was performed to show the 3-years potential budgetary impact of alectinib, should the medication is recommended for funding for ALK-positive patients with NSCLC who have progressed following crizotinib therapy and who have CNS metastases. Methods used to estimate the budgetary impact, including study design, model, assumptions and input parameters derived from Canadian sources, are appropriate.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for alectinib when compared to usual care consisting of platinum-doublet chemotherapy (cisplatin-pemetrexed) or pemetrexed monotherapy from the perspective of Canadian health care system is between \$82,958/QALY gained (lower bound) and \$346,539/QALY gained (upper bound). Further analysis suggests that the estimated ICERs could be reduced to \$32,428 per QALY gained if the unit cost of alectinib is reduced by 75%.

- The extra cost of alectinib is between \$144,221 and \$162,844. Drug and disease management costs are the main factors that influence ΔC , accounting for 91% and 9%, respectively.
- The extra clinical effect (ΔE) of alectinib is between 0.416 QALYs and 1.963 QALYs. The factors that most influence the incremental QALYs are expected relative efficacy of alectinib vs. pemetrexed ± cisplatin, parametric models used to fit OS and PFS data, time horizon, and utility values associated with disease free and progressed disease health states. Furthermore, given the lack of direct comparative estimates for PFS and OS, there is a high degree of uncertainty in the estimates of extra clinical effect of alectinib. This uncertainty is not reflected in the estimates of incremental effect captured in the model and, therefore, it is also not fully captured in the EGP's range of ICER estimates.

Overall conclusions of the submitted model:

The model structure is adequate and the economic evaluation is well-designed. The model captures patients' preference by incorporating health utility values associated with PFS and PD health states and performing a cost-utility analysis. Consistent with Patient and Provincial Advisory Groups inputs, the Submitter assumed that a smaller proportion of patients who progress after alectinib would receive WBRT. However, the submitted model did not incorporate the impact of having CNS metastases, receiving WBRT, and receiving IV chemotherapy on quality of life or utility values.

More importantly, efficacy data for alectinib and pemetrexed ± cisplatin were derived independently (a pooled analysis of two Phase II studies for alectinib and a retrospective cohort study for a standard chemotherapy). Actual comparative efficacy of alectinib compared to pemetrexed ± cisplatin remains unknown. Lack of head-to-head clinical trial evidence comparing

the efficacy of alectinib and pemetrexed \pm cisplatin may bias the estimated ICERs. Observed differences in costs and outcomes (LY and QALY) may be a result of systematic differences in baseline sociodemographic factors and NSCLC prognosis of patients. The use of data from a small retrospective analysis with limited details of study participants to estimate the OS data of patients receiving pemetrexed \pm cisplatin limit the generalizability of the predicted OS data. PFS data for pemetrexed \pm cisplatin group was approximated from the ratio of PFS and OS data observed in the alectinib group due to paucity of PFS data in this population.

According to the CGP, the use of a year time horizon for the base case analysis is too optimistic given poor prognosis in this patient group. (Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until March 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.)The time horizon should be shortened to 3 years.

Future head-to-head clinical trial is needed to estimate the comparative efficacy of alectinib and pemetrexed \pm cisplatin. The extent to that post ALK-inhibitor immunotherapy affects incremental cost-effectiveness ratios of alectinib requires further investigation.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR [Tumour Group] Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of Alectinib (Alecensaro) for ALK-Positive Non-Small Cell Lung Cancer Patients Previously Treated with Crizotinib Who have Central Nervous System Metastases. A full assessment of the clinical evidence of [drug name and indication] is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Initial Economic Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Economic Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Economic Guidance Report will supersede this Initial Economic Guidance Report.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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