CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Pembrolizumab (Keytruda) for Renal Cell Carcinoma

April 2, 2020

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FUNDING

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List of Abbreviations

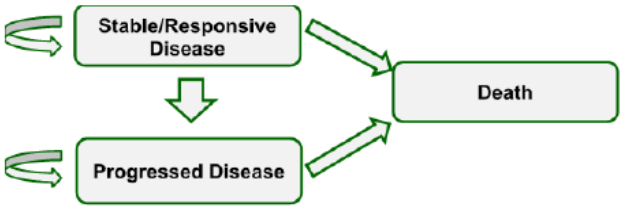
AE(s)	Adverse Events
CI	Confidence interval
CGP	Clinical Guidance Panel
HR	Hazard ratio
ICUR	Incremental cost utility ratio
NMA	Network meta-analysis
OS	Overall survival
PAG	Provincial Advisory Group
pCODR	pan-Canadian Oncology Drug Review
PFS	Progression free survival
QALY	Quality of Life adjusted life year
RCC	Renal Cell Carcinoma
ToT	Time on treatment

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Merck Oncology** compared pembrolizumab in combination with axitinib to alternative treatments for the first-line treatment of advanced renal cell carcinoma (RCC). Three comparators were considered, including sunitinib monotherapy, pazopanib monotherapy, and nivolumab/ipilimumab combination therapy. The target population are patients with previously untreated advanced RCC. An overview of the submitted model is provided in Table 1.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	The submitted funding request is for the treatment of patients with advanced renal cell carcinoma (RCC) in combination with axitinib as first-line treatment Patients were previously untreated advanced RCC and within subgroups defined by IMDC risk (i.e. favourable or intermediate/poor). This aligns with the patient population modelled. The patient population in the model was based on the patient population in KN426 which included patients with previously untreated advanced (Stage IV) clear-cell RCC.
Type of Analysis	CEA, CUA
Type of Model	Partitioned-survival 
Comparator	Sunitinib (clinical data); Pazopanib, nivolumab + ipilimumab (NMA)
Year of costs	2019
Time Horizon	15-year
Perspective	Canadian public healthcare payer
Cost of pembrolizumab plus axitinib	Pembrolizumab costs $4,400 per 100 mg vial, while axitinib costs $97.13 per 5 mg. At the recommended dose of 200 mg intravenously every 3 weeks for pembrolizumab and 5mg twice a day for axitinib for a maximum of 35 cycles (2 years), pembrolizumab + axitinib costs: • $419.05 + $194.26 = $613.31 per day • $17,172.68 per 28-day dose
Cost of sunitinib	Sunitinib costs $257.66 per 50 mg. At the recommended dose of 50 mg once a day orally for 4 weeks and 2 weeks off treatment. • $171.77 per day • $4,809.56 per 28-day course
Cost of pazopanib	Pazopanib costs $35.52 per 200 mg. At the recommended dose of 800 mg once a day orally. • $142.08 per day

	• $3,978.24 per 28-day course
Cost of nivolumab + ipilimumab	Nivolumab costs $782.22 per 40 mg, while ipilimumab costs $5,800 per 50 mg. At the recommended dose of 3 mg/kg intravenously every 3 weeks for nivolumab and 1 mg/kg intravenously every 3 weeks for ipilimumab for up to 4 doses, nivolumab + ipilimumab costs: • $236.90 + $522.00 = $758.90 per day • $21,249.2 per 28-day course Total of 245 mg of nivolumab (6.36 vials) and 82 mg (1.89 vials) of ipilimumab once per 21-day cycle for average body weight of 81.52 kg.
Model Structure	The three health states used in the partitioned survival model were progression free (PF); progressed disease; and Death.
Key Data Sources	*Keynote 426 Trial data for safety and efficacy of pembrolizumab plus axitinib and sunitinib[1]; Sponsor's Network Meta Analysis (NMA) for comparative effectiveness with comparators other than sunitinib; medical literature for safety on comparators other than sunitinib; Keynote 426 for utilities; official sources for costs.*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), at the time the trial was conducted, the standard first line treatment of mRCC was sunitinib or pazopanib, so sunitinib was an appropriate comparator. The most appropriate first line treatment has recently shifted; the combination of two checkpoint inhibitors, ipilimumab and nivolumab, was shown to be superior to sunitinib in intermediate and poor risk patients and is now a funded regimen in intermediate and poor risk patients. While pazopanib is less commonly used for favourable risk compared with sunitinib, it is currently funded for all patient groups and can be used in all scenarios where sunitinib could be used.

- Relevant issues identified of the clinical trial comparing pembrolizumab and axitinib with sunitinib included:
    - The median overall survival (OS) was not reached in either group after a median follow-up of 12.8 months, the data from KN426 is immature, *hence further increasing the uncertainty on the extrapolation of relative effectiveness in the economics model*.
    - The incidence of grade 3 or 4 elevations in liver-enzyme levels in the pembrolizumab/axitinib group was higher than seen when each agent was used as monotherapy, but no death related to hepatic AE was observed. *The cost and disutility of AEs were addressed in the economic model.*
    - Discontinuation of any treatment because of adverse events occurred more frequently in the pembrolizumab/axitinib group than in the sunitinib group. *This was modelled in the economic submission through the time on treatment (ToT) curve*.

Summary of registered clinician input relevant to the economic analysis

- The benefits of pembrolizumab/axitinib compared with sunitinib in overall survival and progression-free survival were observed in all patient subgroups examined, including all IMDC risk and PD-L1 expression categories, and is clinically and statistically significant. This distinguished pembrolizumab/axitinib from ipilimumab/nivolumab, as the latter showed a benefit over sunitinib only in the poor and intermediate risk groups. *The*

economic evaluation included all subgroups of patients, including analyses considering either favourable or intermediate/high risk subgroups.

- The results of KN426 trial are not generalizable to the second-line setting. *This is accounted for in the economic submission as no patients receive pembrolizumab as a subsequent treatment.*

Summary of patient input relevant to the economic analysis

- Respondents indicated a general need for more effective therapies with manageable side effects. *The economic evaluation addressed this through incorporation of the frequency of and disutility associated with adverse events experienced in the KN426 trial.*
- Respondents also found the short administration times, a monthly visit for the infusion and taking tablets at home was minimally disruptive to lead a normal life. *The economic evaluation did not address implications of administration and appropriately used of the payer's perspective.*

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 pembrolizumab/axitinib which are relevant to the economic analysis:

- PAG is seeking clarity of dosing schedule and treatment duration. The CGP agreed with alternative dosing schedule of up to a flat dose cap of 400mg every 6 weeks. *The model assumed 200mg every 3 weeks up to a maximum of 35 cycles. Using alternate dosing of 400mg every 6 weeks resulted an ICUR of $124,807/QALY.*
- PAG has concerns with drug wastage, as vial sharing may not be feasible in smaller outpatient cancer centres. *The model assumed that vial wastage for intravenous drugs with weight-based dosing would happen 50% of the time, while vial sharing would occur in the other 50%.*

1.3 Submitted and EGP Base Case Estimates

Table 2. Submitted and EGP Estimates (deterministic for disaggregated results) for pembrolizumab / axinitib vs. sunitinib (overall RCC population)

Estimates (range/point)	Submitted	EGP Base Case
ΔE (LY)	2.218	1.080
Progression-free*	0.454	0.391
Post-progression*	1.765	0.690
ΔE (QALY)	1.839	0.847
Time to death 0-29 days*¥	-0.004	-
Time to death 30-89 days*	-0.011	-
Time to death 90 to 179 days*	-0.017	-
Time to death 180 to 359 days*	-0.021	-
Time to death ≥360 days*	1.892	-
Progression-free*	-	0.313
Post-progression*	-	0.532
ΔC ($)	225,239	213,875
ICER estimate ($/QALY)	122,487	252,636

*Deterministic value only available

¥Submitted base case used QALY based on time to death.

The main assumptions and limitations with the submitted economic evaluation were:

- The model was based on a median follow-up of 12.8 months from the KN426 trial and extrapolated the treatment effect of pembrolizumab/axitinib over a 15-year time horizon and assumed the relative treatment effect would continue indefinitely over the entire time horizon.
    - There is uncertainty in long term post-trial relative efficacy. Continued relative efficacy over a lifetime is an optimistic assumption.
    - The median OS was not reached in either arm of the KN426 trial, as such the OS data was immature and further increased the uncertainty on the extrapolation, especially on OS.
    - The parametric function used to estimate long term relative effectiveness in sunitinib (which was not the best fit option) favoured pembrolizumab/axitinib but CGP agreed it was more clinically feasible.
    - Furthermore, while the CGP agreed that a 15-year horizon was reasonable as most patients shall be dead by that time, in the model, 15% of the pembrolizumab/axitinib were still alive at 15 years, suggesting an optimistic extrapolation.
- Trial data (KN426) was only available for the comparison between pembrolizumab/axitinib and sunitinib. The relative effectiveness of relevant comparators (pazopanib and nivolumab/ipilimumab) were derived from network meta-analysis (NMA) that included bevacizumab, which is not used in Canada[2].
    - However, the HRs estimated with or without bevacizumab in sensitivity analysis provided by the sponsor (requested by the pCODR Review Team) were very similar. As such, the overall HRs were used in the EGP reanalysis.
    - In addition, the constant HR NMA estimates were used in the EGP base case given the significant uncertainty (large variance) in the time-varying HR NMA results as suggested by the CGP.
    - The results from the NMA should be interpreted with caution because of the limitations of NMA, including a mix of different types of clinical trials (open-label vs double-blind), inconsistencies in outcome measurements (investigator assessed vs independently assessed), and uncontrolled clinical factors (e.g. dropouts).
    - Pazopanib is indicated for patients with good performance status (although sunitinib is more commonly used) while nivolumab/ipilimumab is indicated for intermediate/poor IMDC risk subgroup. The estimated HRs in the base case from the NMA which extrapolated its effects to the entire patient population were underestimated, as such, subgroup analyses should be used to evaluate the cost-effectiveness of pazopanib or nivolumab/ipilimumab.

1.4 Detailed Highlights of the EGP Reanalysis

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

- **Attenuating relative treatment effect:** The sponsor assumed the relative treatment effect of pembrolizumab/axitinib would continue indefinitely for the entire 15-year time horizon. Given the short follow up period and the immaturity of the data, a decline in the treatment effect beyond the end of the trial period (duration ~12 months) was felt to be more reasonable. In addition, as 50% of the patients on pembrolizumab/axitinib were given subsequent treatments in the KN426 trial, the durable effect of pembrolizumab/axitinib and likely attenuates over time. For the EGP reanalysis, the treatment effect for pembrolizumab/axitinib was assumed to wane from the end of the treatment (2 years) up to 3 to 10 years, with no incremental benefit after 5 years used in the EGP base case (i.e., HR of both PFS and OS linearly converge towards those of sunitinib over a 3-year period,

starting at 2 years and ends at 5 years). This approach used in previous review of nivolumab/ipilimumab was agreed by the CGP as a valid approach in this situation.

- **Parametric assumption of sunitinib OS:** The sponsor used the exponential parametric function to estimate sunitinib OS, however the best fit was observed with the log-normal function. The log-normal function was tried for sunitinib in the EGP reanalysis. Nevertheless, CGP agreed that the OS was too high at 15 years using the log-normal function, as such it was not included in the EGP base case.
- **Utility values:** The utility values in the base case analysis were based on number of days to death, which allowed for different utility values by treatment and health state. Although time-to-death health states is not an unreasonable approach to use in a model, it is currently not transparently modeled; more details are needed to determine the appropriateness of this approach and should be transparent to align with CADTH guidelines. The sponsor provided a deterministic scenario analysis using utility values anchored by health state, which was determined to be more transparent and consistent with previous reviews in RCC.
- **Cost of subsequent therapies:** Subsequent therapies were selected based on initial therapy, and only cost difference was modelled, not changes in effectiveness. The nature and distribution of subsequent therapies were taken from KN426 trial for pembrolizumab/axitinib and sunitinib. Subsequent treatments following nivolumab/ipilimumab were assumed to be the same as for pembrolizumab/axitinib, while those following pazopanib were assumed to be the same as tivozanib as published in 2013[3]. It is possible that the cost difference of the subsequent therapies might confound the cost-effectiveness of the comparators (comparison of a sequence of therapies rather than initial therapy and consideration of only cost). For the EGP reanalysis, the average cost of subsequent therapies was assumed to occur for both treatment arms.

In their feedback on the pERC initial recommendation, the sponsor stated that the 5-year treatment waning period in the EGP reanalysis is inappropriate as there is no clinical support for a limited period of treatment. The sponsor noted that a treatment waning effect at 5 years shows minimal survival benefit of pembrolizumab in combination with axitinib versus sunitinib and that a treatment waning at 10 years yields more plausible results. The EGP, however, maintains their reanalysis estimates for the following reasons:

- There were no data submitted during the review that demonstrated the benefit of pembrolizumab plus axitinib beyond the trial period. Due to the uncertainty in the benefit of pembrolizumab plus axitinib beyond the trial period and the short duration of follow-up, the clinical guidance panel stated that allowing treatment benefit to accrue until 10 years is uncertain, specifically in light of immature overall survival data. Given the uncertainty in the data, the EGP reiterated that the selection of the treatment waning to begin at the end of treatment up to 3 to 10 years, with no incremental benefit at 5 years between pembrolizumab/axitinib and comparators was appropriate.

- The EGP also noted that by implementing a treatment waning period of 3 to 10 years, with no incremental benefit at 5 years the treatment effect of pembrolizumab/axitinib is not negated. Given the short term follow-up in the Keynote-426 trial which leads to uncertainty in the OS data and to align with previous CADTH reviews in addressing uncertainty in long term incremental treatment effect, the EGP reiterated that a treatment waning effect which demonstrates no incremental benefit at 5 years is a reasonable approach.

Table 3: Detailed Description of EGP Reanalysis of Pembrolizumab/axitinib vs. Sunitinib (overall RCC population – probabilistic analysis)

One-way and multi-way sensitivity analyses by submitter				
Description of Reanalysis	ΔC ($)	ΔE QALYs	ICUR ($/QALY)	Δ from baseline submitted ICER
NMA sensitivity analysis without Bevacizumab	225,437	1.846	122,123	-93
Health State utilities	225,608	1.734	130,098	7,882
EGP's Reanalysis for the Best Case Estimate				
Description of Reanalysis	ΔC	ΔE	ICUR	Δ from baseline submitted ICER
Baseline (Submitter's best case)	225,608	1.846	122,216	-
1) Waning treatment effect				
*1a) Waning treatment effect: reduced from 15 years to 5 years**	214,804	0.938	228,993	106,777
1b) Waning treatment effect: declines from 15 years to 3 years	211,971	0.728	291,122	168,906
1c) Waning treatment effect: declines from 15 years to 10 years	219,519	1.291	170,046	47,830
*2) Lognormal OS for sunitinib**	210,503	0.554	380,126	257,910
3) Average cost of subsequent treatment	241,193	1.846	130,659	8,443
*4) Utility anchored on health state (same as submitter's SA)**	225,608	1.734	130,098	7,882
Best case estimate				
EGP Base case (1a+4)*	**214,118**	**0.84**	**255,001**	**132,785**
Scenario analysis of EGP base case using 3) Average subsequent treatment costs	229,699	0.84	273,557	151,341

* indicates re-analysis used in the EGP Base Case

In the EGP base case (treatment effects wane at 2 years and end after 5 years and using utilities anchored in health states) the ICUR of pembrolizumab/axitinib was $255,001/QALY when compared to sunitinib. A scenario analysis of the EGP base case using average subsequent treatment costs in both arms increased the ICUR to $273,557/QALY.

Table 4. EGP base case (waning and health state utilities) with additional comparators using time constant HRs from NMA, Pembrolizumab/axitinib vs. Sunitinib, overall RCC population – probabilistic analysis

Regimen	Total Costs	Total QALYs	Δ Costs	Δ QALYs	ICUR vs. least expensive treatment (vs. pazopanib)	Sequential ICUR (vs. pazopanib)
Pazopanib	144,954	3.237	-	-	-	-
Sunitinib	195,484	3.191	50,530	-0.046	Dominated	Dominated
Nivolumab/ ipilimumab	323,431	3.628	178,476	0.391	456,535	Extended dominated
Pembrolizumab /axitinib	409,602	4.03	264,648	0.793	333,528	333,528

In the sequential analysis of additional comparators of pazopanib and nivolumab/ipilimumab in the overall RCC population, the sequential ICUR of pembrolizumab/axitinib is $333,528/QALY when compared to the least expensive treatment (pazopanib). Sunitinib was dominated by pazopanib (i.e., less effective and more expensive than pazopanib). Nivolumab/ipilimumab were extendedly dominated by pembrolizumab/axitinib. Extended dominance rules out an intervention (i.e., nivolumab/ipilimumab) that has an ICUR higher (i.e., $456,535 compared to $333,528) than a more expensive intervention (i.e., pembrolizumab plus axitinib).

When comparing pembrolizumab/axitinib to nivolumab/ipilimumab in the EGP base case, the incremental cost is $86,171, with an incremental benefit of 0.402 QALYs, resulting an ICUR of $214,356/QALY. However, pazopanib and nivolumab/ipilimumab are currently listed for different patient populations (pazopanib is listed for patients with good performance status, while nivolumab/ipilimumab are indicated for intermediate/poor risk subgroup). When comparing pembrolizumab/axitinib to nivolumab/ipilimumab in the *immediate/poor IMDC risk group* for the EGP base case (using HR from the NMA in this specific patient population), the incremental cost is $74,999, with an incremental benefit of 0.316 QALYs, resulting an ICUR of $237,339/QALY. A 25% price reduction is required to achieve an ICUR around $100,000/QALY (Table 5b).

When considering only the favourable IMDC risk subgroup, the ICUR of pembrolizumab/axitinib to sunitinib was $462,171/QALY. While pazopanib is less frequently used, the ICUR of pembrolizumab/ axitinib to this comparator was $585,372/QALY. Price reductions of 85% is needed to achieve an ICUR of around $100,000/QALY compared to sunitinib (Table 5a). Compared to pazopanib, a 99% reduction is needed to achieve an ICUR of around $200,000/QALY (Table 5a).

Table 5. Cost-effectiveness of pembrolizumab/axitinib versus sunitinib assuming discounts on drug price

Pembrolizumab Drug Price Reduction	Estimate of cost-effectiveness ($/QALY)
EGP base case	255,001
25%	204,010

Pembrolizumab Drug Price Reduction	Estimate of cost-effectiveness ($/QALY)
50%	151,286
75%	102,028

Table 5a. Cost-effectiveness of pembrolizumab/axitinib versus pazopanib and sunitinib assuming discounts on drug price (favourable IMDC risk subgroup)

Pembrolizumab Drug Price Reduction	Estimate of cost-effectiveness ($/QALY) vs pazopanib	Estimate of cost-effectiveness ($/QALY) vs sunitinib
EGP base case	585,372	462,171
25%	486,967	354,602
50%	388,562	247,031
75%	290,157	139,462
85%	250,795	96,433
99%	195,688	36,193

Table 5b. Cost-effectiveness of pembrolizumab/axitinib versus sunitinib and nivolumab/ipilimumab assuming discounts on drug price (immediate/poor IMDC risk subgroup)

Pembrolizumab Drug Price Reduction	Estimate of cost-effectiveness ($/QALY) vs sunitinib	Estimate of cost-effectiveness ($/QALY) vs nivolumab/ipilimumab
EGP base case	251,935	237,337
25%	202,884	104,377
50%	153,834	Dominant

In the entire patient population, compared with sunitinib a price reduction of 75% is required to achieve an ICUR of approximately $100,000/QALY (Table 5).

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include the peak share of pembrolizumab combination, time to peak for pembrolizumab combination, shape of pembrolizumab combination uptake curve, and nivolumab/ipilumumab share at pembrolizumab's peak. In the EGP reanalysis, considering only first-line treatment and increase the number of relapsed patients also increased the budget impact.

Limitations of the BIA model include lack of data on the market share assumptions and possible overestimation of the assumption of relative dose intensity for nivolumab/ipilimumab. Both inputs were able to be modified and explored by the EGP.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for pembrolizumab/axitinib when compared to sunitinib is:

- Between $130,659/QALY and $273,557/QALY. Within this range, the best estimate would likely be: $255,001/QALY using the assumptions of treatment effect waning over time, and utility anchored by health states.

- The extra cost of pembrolizumab/axitinib is between $210,503 and $241,193 (ΔC). The main factor that influences the incremental costs is pembrolizumab/axitinib drug and administration costs.
- The extra clinical effect of pembrolizumab/axitinib is between 0.554 and 1.846 QALYs (ΔE). The main factor that influences the incremental effects are estimates of long term treatment effect, including selection of the parametric function to estimate sunitinib OS.
- According to the EGP base case, a 75% price reduction is needed to achieve an ICUR around $100,000/QALY.
- When comparing pembrolizumab/axitinib to nivolumab/ipilimumab in the immediate/poor IMDC risk group for the EGP base case (using HR from the NMA in this specific patient population), the incremental cost is $74,999, with an incremental benefit of 0.316 QALYs, resulting an ICUR of $237,339/QALY. A 25% price reduction is required to achieve an ICUR around $100,000/QALY. However, in view of the limitations to the NMA identified by the CGP, these results should be viewed with caution.
- In the favourable IMDC risk group in the EGP base case (using HR from the NMA for this subgroup) the pembrolizumab/ axitinib has an incremental cost of $194,112, incremental benefit of 0.42 QALY, with an ICUR of $462,171/QALY compared with sunitinib, an 85% price reduction is required to achieve an ICUR around $100,000/QALY. However, in view of the limitations to the NMA identified by the CGP, these results should be viewed with caution.

Overall conclusions of the submitted model:

- Overall, the approach taken and most of the assumptions made in the submitted economic evaluation were reasonable and appropriate, except where otherwise noted.
- Using a more appropriate estimate of long-term comparative effectiveness where the relative treatment effect of pembrolizumab/axitinib compared to sunitinib wanes over time, and utility that is anchored by health state, the ICUR would be $255,001/QALY. A 75% price reduction is needed to achieve an ICUR around $100,000/QALY in the entire population; price reductions of 25% and 85% are needed for the favourable and intermediate/high risk subgroup, respectively.

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. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Genitourinary 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 pembrolizumab plus axitinib vs suntinib for renal cell carcinoma. A full assessment of the clinical evidence of pembrolizumab plus axitinib vs suntinib for renal cell carcinoma 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*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the 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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