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pan-Canadian Oncology Drug Review
Initial Economic Guidance Report

Pembrolizumab (Keytruda) for Metastatic Urothelial Carcinoma

August 1, 2019

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR** by **Merck Canada Inc.** evaluated pembrolizumab in patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin therapy. The economic analysis included two base case analyses based on patient characteristics: 1) patients that are cisplatin-ineligible and PD-L1 positive (CPS>=10) and 2) patients that are ineligible for platinum therapy, irrespective of their PD-L1 expression level. For the PD-L1 positive population pembrolizumab was compared to both gemcitabine plus carboplatin and gemcitabine monotherapy. For the platinum ineligible population pembrolizumab was compared to gemcitabine monotherapy.

Table 1: Submitted Economic Model	
The funding request is for pembrolizumab for patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin and either: a) are PD-L1 positive (CPS>=10) b) ineligible for platinum therapy These target populations are based on the inclusion/exclusion criteria for the PD-L1 positive (CGP≥10) and platinum-ineligible subgroups within the Keynote-052 trial.	The clinical data for the model is based on 2 main sources. For pembrolizumab, clinical input data were based on the Keynote 052 study, a single arm trial that included cisplatin ineligible patients. For comparators, a simulated treatment comparison was used to derive relative rates of clinical outcomes (e.g. overall survival, progression free survival). The economic model presented two base cases for the two subpopulations from Keynote 052 that meet the reimbursement request: a) are PD-L1 positive (CPS>=10) b) ineligible for platinum therapy as well as a scenario analysis for the overall Keynote 052 trial population (which includes patients that do not meet the reimbursement request criteria).
Type of Analysis	Cost utility analysis and Cost-effectiveness analysis
Type of Model	Three state partitioned-survival model
Comparator	*a) PD-L1 positive (CPS>=10)* • *gemcitabine plus carboplatin* • *gemcitabine monotherapy* *a) Ineligible for platinum therapy* • *gemcitabine monotherapy* *b) Overall Keynote052 population* • *gemcitabine plus carboplatin* • *gemcitabine monotherapy*
Year of costs	*2018*
Time Horizon	*10 years*
Perspective	*Government*
Cost of pembrolizumab*	• Unit cost $2200.00 per 50 mg vial, $4400.00 per 100 mg vial. • Based on recommended fixed dosing of 200 mg every 3 weeks the cost of pembrolizumab is:

	• $8,800.00 per 3-week cycle • $11,733.00 per 28 days • $419.00 per day
Cost of gemcitabine monotherapy*	• Unit cost $6.00 per 200 mg vial, $30.00 per 1000mg vial. • Based on recommended dosing of 1200 mg/m^2 for 3 times every 4 weeks the cost of gemcitabine alone is: • $216.00 per 4-week cycle • $216.00 per 28 days • $7.71 per day *assumes bsa=1.88 m^2, 100% drug wastage

Cost of gemcitabine plus carboplatin*	• Unit cost:
	  ○ gemcitabine $6.00 per 200 mg vial, $30.00 per 1000mg vial.
	  ○ carboplatin $18.80 per 150 mg vial, $56.39 per 450 mg vial
	• Based on recommended dosing of 1000mg/m^2 for gemcitabine, once every 3 weeks, and AUC 5, once every 3 weeks for carboplatin, the cost of gemcitabine plus carboplatin is:
	
	• $326.39 per 4-week cycle
	• $326.39 per 28 days
	• $11.66 per day
	*assumes bsa=1.88 m2, 100% drug wastage

Model Structure	A proportion of patients is in one of 3 health states during each weekly cycle of the model: 1) alive and progression free; 2) alive with progressed disease; 3) dead. The proportion in each health state is determined by overall survival estimates and progression free survival estimates over time.
Key Data Sources	Keynote 052, a phase 2 single arm trial which evaluated first line treatment of pembrolizumab in patients with locally advanced or metastatic urothelial cancer who were ineligible for cisplatin. Data from this trial was used to derive the following for pembrolizumab: • Overall survival • Progression free survival • Utility values (also applied to comparators) • Subsequent treatments (also applied to comparators) • Adverse events Simulated treatment comparison: an indirect comparison using data from Keynote 052 and from studies that included the treatment comparators of

	interest. This data was used to derive the following for the treatment comparators: • Relative overall survival to pembrolizumab • Relative progression free survival to pembrolizumab • Adverse events (from individual studies)
** Drug costs in this table are based on costing information provided by the submitter, Merck Canada Inc, and used in the economic model.*	

1.2 Clinical considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison of pembrolizumab to chemotherapy are appropriate in cisplatin-ineligible patients with PD-L1 ≥10 disease (gemcitabine plus carboplatin or gemcitabine monotherapy) and platinum-ineligible patients (gemcitabine monotherapy)

Relevant issues identified included:

- The CGP agree that there may be a net clinical benefit to pembrolizumab, compared to chemotherapy in cisplatin-ineligible patients with PD-L1 ≥10 disease, or in platinum-ineligible patients irrespective of their PD-L1 expression status.
- There is a pressing unmet need for effective and tolerable treatment options for patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy. The need is even more urgent in patients who are ineligible for platinum-based regimens with no effective treatment options available.
- The non-comparative phase II KEYNOTE 052 clinical trial showed:
  - a clinically meaningful overall response rate, prolonged durability of responses and encouraging early overall survival in cisplatin-ineligible patients with PD-L1 ≥10 disease.
  - a clinically meaningful overall response rate and prolonged durability of responses in platinum-ineligible patients irrespective of their PD-L1 expression status.
- The CGP agreed that pembrolizumab has a favourable toxicity profile compared to chemotherapy. Adverse events were considered in the model and applied as a once-off cost at model start.
- The data supporting this conclusion are from non-randomized studies. Hence there is no reliable estimate of the comparative efficacy or effectiveness of pembrolizumab to chemotherapy. The CGP noted that two randomised phase III trials (KEYNOTE 361 and MK 7902 PN 011) may provide additional data on ORR, PFS and OS outcomes and toxicities for pembrolizumab compared to alternative treatment options in patients belonging to the two subgroups included in the reimbursement request. However, it was noted that the comparator in the MK 7902 PN 011 trial (lenvatinib) is currently not funded.
- The follow up of the clinical trials informing the comparative efficacy is relatively short and additional data on longer term toxicities and PFS outcomes are awaited.

Summary of registered clinician input relevant to the economic analysis
Clinicians providing input indicated that advanced UC is an area of clear unmet need owing to suboptimal treatment options. Many patients have comorbidities that preclude the use of toxic

chemotherapy. In contrast, pembrolizumab is less toxic and can provide significant and durable benefits. There is general agreement that pembrolizumab should be the preferred first-line treatment for the target population. Next in line would be chemotherapy should the patient become eligible. Contraindications for pembrolizumab are not as numerous as for chemotherapy, but autoimmune disorders should be considered and managed. Some clinicians mentioned that PD-L1 testing is not standard in all settings and should be made more broadly available.

- Progression-free survival and adverse events were incorporated into the model. The impact on PD-L1 testing costs is included as part of the budget impact analysis. The cost of PD-L1 testing is also included for the CPS>=10 population in the cost-effectiveness analysis.

Summary of patient input relevant to the economic analysis

From a patient's perspective, blood in urine was the most commonly reported symptom related to UC, followed by fatigue and urination problems. Almost all patients surveyed by BCC had experience with some form of chemotherapy that led to additional fatigue, nausea, constipation and other well-known side effects, some of which were difficult to tolerate. By comparison, pembrolizumab gave rise to milder side effects, an aspect that was strongly appreciated by patients. The net effect was a subjective improvement in disease control, symptoms, and general quality of life in patients switching to pembrolizumab therapy. These benefits were in line with patients' expectations for alternative treatment options, which focused on achieving disease control, extending life expectancy and maintaining quality of life.

- PFS, OS, adverse events and quality of life were incorporated into the 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 pembrolizumab which are relevant to the economic analysis:

- The dose is 200mg for urothelial cancer in the funding request and the KEYNOTE-052 trial. PAG noted trials suggest that weight-based dose of 2mg/kg and 200mg fixed dose are similar. Although fixed dose would minimize drug wastage, PAG is seeking guidance on weight-based dose for urothelial cancer (i.e., 2mg/kg up to 200mg) given the high cost of fixed dose compared to weight-based dose for patients weighing less than 100kg. PAG also identified emerging data of dosing pembrolizumab at 400mg every 6 weeks, PAG is seeking guidance on the appropriateness of alternate dosing/schedule (i.e., 400mg or 4mg/kg up to a flat dose cap of 400mg every 6 weeks). PAG was concerned that vial sharing might not be possible in smaller cancer centers.
    - *The CGP stated that the fixed dose used in the trial reflects the standard dose schedule used in Canada and has been approved by Health Canada. The CGP noted that there is currently insufficient evidence to guide the decision on a weight-based dose schedule or alternative fixed dosing schedule of 400 mg every 6 weeks schedule.*
    - *The economic analysis does not address this issue. All analyses were based on fixed dosing as per the Keynote 052 trial.*
- PAG noted that pembrolizumab requires monitoring and treating of immune-mediated reactions. There was concern that smaller centres may not have the resources to administer pembrolizumab or monitor for and treat serious adverse events.
    - *The CGP noted that immunotherapy is now commonly used across many cancers, and experience in managing side effects is growing. Only centers appropriately*

trained to give these drugs are using these drugs. Standard monitoring for these drugs, as with other drugs needs to be implemented

- *This is not addressed in the economic analysis.*

- PAG noted that there would be an increase volume for PD-L1 testing and PAG would like this accounted for in the economic analysis.
  - *The impact of reimbursing pembrolizumab for the manufacturers requested indication on PD-L1 testing costs is included as part of the budget impact analysis. The cost of PD-L1 testing is also included for the CPS>=10 population in the cost-effectiveness analysis.*

1.3 Submitted and EGP Reanalysis results

The main cost drivers of the manufacturers' model were drug acquisition costs, time on treatment, and drug administration costs. The main drivers of the clinical outcomes of the model (QALYs, Life Years) were: 1) overall survival estimates; 2) progression free survival estimates; 3) the time horizon used in the model, and 4) the utility values assigned to patients over the duration of the model time horizon. Overall the approach taken in the economic evaluation was reasonable and appropriate.

CPS>=10 Population

Table 2: Submitted and EGP Estimates: CPS>=10 population: Pembrolizumab vs Carboplatin plus Gemcitabine

Estimates	Submitted	EGP Reanalysis	
		Best Case Scenario	Worst Case Scenario
ICER estimate ($/QALY)	$69,948	$124,028	unknown
ΔE (QALY)	1.44	0.87	unknown
ΔE (LY)	1.95	1.18	unknown
ΔC ($)	$100,632	$108,468	unknown

Table 3: Submitted and EGP Estimates: CPS>=10 population: Pembrolizumab vs Gemcitabine monotherapy

Estimates	Submitted	EGP Reanalysis	
		Best Case Scenario	Worst Case Scenario
ICER estimate ($/QALY)	$70,300	$122,734	unknown
ΔE (QALY)	1.48	0.90	unknown
ΔE (LY)	2.01	1.22	unknown
ΔC ($)	$103,925	$110,701	unknown

Platinum ineligible Population

Table 4: Submitted and EGP Estimates: Platinum ineligible population: Pembrolizumab vs Gemcitabine

Estimates	Submitted	EGP Reanalysis	
		Best Case Scenario	Worst Case Scenario
ICER estimate ($/QALY)	$160,863	$236,610	unknown
ΔE (QALY)	0.42	0.32	unknown
ΔE (LY)	0.69	0.52	unknown
ΔC ($)	$68,179	$76,010	unknown

Scenario Analysis: Overall Keynote 052 population

Table 5: Submitted and EGP Estimates: Overall Keynote 052 population: Pembrolizumab vs Carboplatin plus Gemcitabine

Estimates	Submitted	EGP Reanalysis	
		Best Case Scenario	Worst Case Scenario
ICER estimate ($/QALY)	$97,016	$160,324	unknown
ΔE (QALY)	0.78	0.53	unknown
ΔE (LY)	1.09	0.74	unknown
ΔC ($)	$75,799	$84,546	unknown

Table 6: Submitted and EGP Estimates: Overall Keynote 052 population: Pembrolizumab vs Gemcitabine monotherapy

Estimates	Submitted	EGP Reanalysis	
		Best Case Scenario	Worst Case Scenario
ICER estimate ($/QALY)	$89,341	$142,481	unknown
ΔE (QALY)	0.9	0.61	unknown
ΔE (LY)	1.25	0.86	unknown
ΔC ($)	$79,983	$87,397	unknown

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

- Clinical Data: There is uncertainty around the cost-effectiveness analysis due to the clinical data that was used for the main clinical inputs in the data (e.g. overall survival, progression free survival, time on treatment). The clinical data for pembrolizumab was based a single arm phase II trial. The trial was an estimation study and no hypothesis testing was performed. Furthermore, clinical data for pembrolizumab were based on subgroup analyses from this phase II trial. The subgroup efficacy data are considered to be exploratory.

- Lack of comparative data: Direct comparative evidence was not used to estimate and project differences in overall survival or progression free survival between pembrolizumab and its comparators. Instead, an indirect treatment comparison (ITC) was used to estimate relative OS and PFS of comparators to pembrolizumab. The pCODR Methods Team identified serious limitations with the ITC (e.g., unanchored comparisons, missing baseline values) and concluded that the estimates may over-or underestimate the true treatment effect associated with pembrolizumab. Overall survival and progression free survival projections are a big driver when estimating relative QALYs and cost-effectiveness between comparative treatments. The lack of direct evidence of comparative overall survival and progression free

survival creates high uncertainty around the cost-effectiveness of pembrolizumab compared to carboplatin plus gemcitabine and gemcitabine alone.

- Time Horizon: The submitted model uses a 10-year time horizon. Based on Keynote 052 median survival with pembrolizumab was approximately 1 year for all patients, 2 years for patients with CPS>=10 and 10 months for platinum ineligible patients. Using such a long-time horizon can lead to erroneous predictions of long-term overall survival and progression free survival based on extrapolation of trial data with limited follow-up. Considering expected survival duration in this population of patients, the CGP felt that a 5-year time horizon was more appropriate.

- Adverse Event unit costs: The submitted model assumed that all grade 3+ adverse events would be assigned the cost of a hospital admission. However, the CGP noted that most of the adverse events would be treated on an outpatient basis. The CGP noted that a proportion of febrile neutropenia adverse events would likely require hospitalization. The CGP suggested assuming 10% of febrile neutropenia grade 3+ adverse events would require a hospitalization.

1.4 Detailed Highlights of the EGP Reanalysis

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

- Time Horizon: As part of their re-analysis, the EGP assumed a 5-year time horizon.

- Adverse Event unit costs: In the EGP re-analysis the adverse event unit costs were changed from the cost of a hospitalization to a medical oncologist consultation fee ($157. Ontario schedule of benefits). For febrile neutropenia, it was assumed that 10% were applied the cost of a hospitalization ($7,599) while the remaining 90% were assigned a consultation fee ($157).

- No Upper Bound of ICER calculated: Because of the large amount of uncertainty around the clinical data that drives the model (relying on efficacy results from subgroup analyses of a single arm phase II study along with no direct comparative data), the upper bound of the ICER in the EGP re-analysis is not calculated and reported as unknown.

Table 7 provides a summary of ICERs for the various populations and comparators using pairwise analysis. Table 8 presents a summary of ICERs by population using sequential analysis.

Detailed Description of EGP Reanalysis

ICER summary by population-Pairwise Comparisons

Table 7: Summary of Submitted and EGP Estimates of ICER ($/QALY) by population and comparator-Pairwise analysis:

Estimates	Submitted	EGP Reanalysis	
		Best Case Scenario	Worst Case Scenario
CPS>=10			
vs. carboplatin plus gemcitabine	$69,948	$124,028	unknown
vs. gemcitabine alone	$70,300	$122,734	unknown
Platinum ineligible			
vs. gemcitabine alone	$160,863	$236,610	unknown
Overall Keynote 052 population			unknown
vs. carboplatin plus gemcitabine	$97,016	$160,324	unknown
vs. gemcitabine alone	$89,341	$142,481	unknown

ICER summary by population-Sequential Analysis

Table 8: Summary of Submitted and EGP Estimates of ICER ($/QALY) by population and comparator-Sequential analysis:

Estimates	Submitted	EGP Reanalysis	
		Best Case Scenario	Worst Case Scenario
CPS>=10			
Pembrolizumab	$70,300	$124,028	unknown
Carboplatin plus gemcitabine	extendedly dominated	$81,441	unknown
Gemcitabine monotherapy	reference	reference	unknown
Platinum ineligible			
Pembrolizumab	$160,863	$236,610	unknown
Gemcitabine monotherapy	reference	reference	unknown
Overall Keynote 052 population			
Pembrolizumab	$97,016	$160,324	unknown
Carboplatin plus gemcitabine	$34,860	$70,469	unknown
Gemcitabine monotherapy	reference	reference	unknown

Detailed cost-effectiveness results from the EGP re-analysis is provided is Tables 9 to 13.

CPS>=10 Population

Table 9: Cost-effectiveness results from EGP reanalysis: CPS>=10 Pembrolizumab vs Gemcitabine plus Carboplatin

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
1.Basecase	$100,632	1.44	$69,948	
2. Change time horizon from 10 years to 5 years	$99,688	0.87	$114,015	$44,067
3. Alternate assumptions on adverse event costs.	$109,955	1.46	$75,239	$5,291
Low range of best Estimate of cost effectiveness (includes changes in 2 and 3)	$108,468	0.87	$124,028	$54,080
High range of best estimate of cost effectiveness)	unknown	unknown	unknown	unknown

Table 10: Cost-effectiveness results from EGP reanalysis: CPS>=10 Pembrolizumab vs Gemcitabine monotherapy

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
1.Basecase	$103,925	1.48	$70,300	
2. Change time horizon from 10 years to 5 years	$102,578	0.90	$113,700	$43,400
3. Alternate assumptions on adverse event costs.	$112,666	1.51	$74,617	$4,317
Low range of best Estimate of cost effectiveness (includes changes in 2 and 3)	$110,701	0.90	$122,734	$52,434
High range of best estimate of cost effectiveness	unknown	unknown	unknown	unknown

Platinum ineligible population

Table 11: Cost-effectiveness results from EGP reanalysis: Platinum Ineligible Pembrolizumab vs Gemcitabine monotherapy

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
1. Basecase	$68,179	0.42	$160,863	
2. Change time horizon from 10 years to 5 years	$67,622	0.33	$205,512	$44,649
3. Have pembrolizumab patients who have not progressed continue treatment for 3 years instead of 2 years	$76,443	0.42	$182,088	$26,098
Low range of best Estimate of cost effectiveness (includes changes in 2 and 3)	$76,010	0.32	$236,610	$54,522
High range of best estimate of cost effectiveness	unknown	unknown	unknown	Unknown

Scenario Analysis: Pooled Keynote 052 Population

Table 12: Cost-effectiveness results from EGP reanalysis: Overall Keynote 052 population Pembrolizumab vs Gemcitabine plus Carboplatin

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
1.Basecase	$75,799	0.78	$97,016	
2. Change time horizon from 10 years to 5 years	$75,605	0.53	$143,141	$46,125
3. Alternate assumptions on adverse event costs.	$84,535	0.78	$108,507	$11,492
Low range of best Estimate of cost effectiveness (includes changes in 2 and 3)	$84,546	0.53	$160,324	$63,308
High range of best estimate of cost effectiveness	unknown	unknown	unknown	unknown

Table 13 Cost-effectiveness results from EGP reanalysis: Overall Keynote 052 population Pembrolizumab vs Gemcitabine monotherapy

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
1.Basecase	$79,983	0.90	$89,341	
2. Change time horizon from 10 years to 5 years	$78,891	0.61	$128,382	$39,041
3. Alternate assumptions on adverse event costs.	$88,287	0.89	$98,753	$9,412
Low range of best Estimate of cost effectiveness (includes changes in 2)	$87,397	0.61	$142,481	$53,140
High range of best estimate of cost effectiveness (includes changes in 2 and 3)	unknown	unknown	unknown	unknown

1.5 Evaluation of Submitted Budget Impact Analysis

The overall approach of the BIA appears to be reasonable and appropriate. The factors that had the biggest impact on the BIA were the estimates of the number of people that would be eligible for pembrolizumab under the current reimbursement request and the medication costs. There were a couple of assumptions which may have resulted in an underestimate in the submitters BIA. These assumptions included that only 83% with locally advanced or metastatic urothelial cancer would be referred to a medical oncologist and that only 73% of platinum eligible patients would be tested for PD-L1. The BIA was taken from a Canada wide perspective.

1.6 Conclusions

CPS >=10 population

Pembrolizumab vs. Gemcitabine plus Carboplatin

- The EGP's best estimate of the incremental cost per QALY of pembrolizumab compared to gemcitabine plus carboplatin ranges between $124,028 and unknown.
- The EGP's best estimate of the incremental cost of pembrolizumab compared to gemcitabine plus carboplatin ranges between $108,468 and unknown. Incremental costs were most impacted by drug acquisition costs, and adverse event costs.
- The EGP's best estimate of the incremental QALY's gained of pembrolizumab compared to gemcitabine plus carboplatin ranges between 0.87 and unknown. Incremental QALYs were most impacted by overall survival estimates and time horizon.

Pembrolizumab vs. Gemcitabine monotherapy

- The EGP's best estimate of the incremental cost per QALY of pembrolizumab compared to gemcitabine monotherapy ranges between $122,734 and unknown.
- The EGP's best estimate of the incremental cost of pembrolizumab compared to gemcitabine monotherapy ranges between $110,701 and unknown. Incremental costs were most impacted by drug acquisition costs and adverse event costs.

- The EGP's best estimate of the incremental QALY's gained of pembrolizumab compared to gemcitabine monotherapy ranges between 0.90 and unknown. Incremental QALYs were most impacted by overall survival estimates and time horizon.

Platinum ineligible population

Pembrolizumab vs. Gemcitabine monotherapy

- The EGP's best estimate of the incremental cost per QALY of pembrolizumab compared to gemcitabine monotherapy ranges between $236,610 and unknown.

- The EGP's best estimate of the incremental cost of pembrolizumab compared to gemcitabine monotherapy ranges between $76,010 and unknown. Incremental costs were most impacted by drug acquisition costs and adverse event costs.

- The EGP's best estimate of the incremental QALY's gained of pembrolizumab compared to gemcitabine monotherapy ranges between 0.33 and unknown. Incremental QALYs were most impacted by overall survival estimates and time horizon.

Scenario Analysis: Overall Keynote 052 population

Pembrolizumab vs. Gemcitabine plus Carboplatin

- The EGP's best estimate of the incremental cost per QALY of pembrolizumab compared to gemcitabine plus carboplatin ranges between $160,324 and unknown.

- The EGP's best estimate of the incremental cost of pembrolizumab compared to gemcitabine plus carboplatin ranges between $84,546 and unknown. Incremental costs were most impacted by drug acquisition costs and adverse event costs.

- The EGP's best estimate of the incremental QALY's gained of pembrolizumab compared to gemcitabine plus carboplatin ranges between 0.53 and unknown. Incremental QALYs were most impacted by overall survival estimates and time horizon.

Pembrolizumab vs. Gemcitabine monotherapy

- The EGP's best estimate of the incremental cost per QALY of pembrolizumab compared to gemcitabine monotherapy ranges between $142,162 and unknown.

- The EGP's best estimate of the incremental cost of pembrolizumab compared to gemcitabine monotherapy ranges between $87,397 and unknown. Incremental costs were most impacted by drug acquisition costs and adverse event costs.

- The EGP's best estimate of the incremental QALY's gained of pembrolizumab compared to gemcitabine monotherapy ranges between 0.61 and unknown. Incremental QALYs were most impacted by overall survival estimates and time horizon.

Overall conclusions of the submitted model:

- The overall structure and most assumptions in the model were appropriate.
- A major limitation of the cost-effectiveness analysis was the reliance on a single arm phase II trial and the use of non-comparative data in order to derive relative overall and progression free survival over time between pembrolizumab and its comparators. This leads to high uncertainty around the incremental cost-effectiveness findings. Extrapolating these findings to a 10 year time horizon increases this uncertainty.

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

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 information redacted from this publicly available Guidance Report.

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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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