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PAN-CANADIAN  
ONCOLOGY DRUG REVIEW

## pan-Canadian Oncology Drug Review Final Economic Guidance Report

### Pembrolizumab (Keytruda) for Non-Small Cell Lung Cancer

November 3, 2016

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## **FUNDING**

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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# 1 ECONOMIC GUIDANCE IN BRIEF

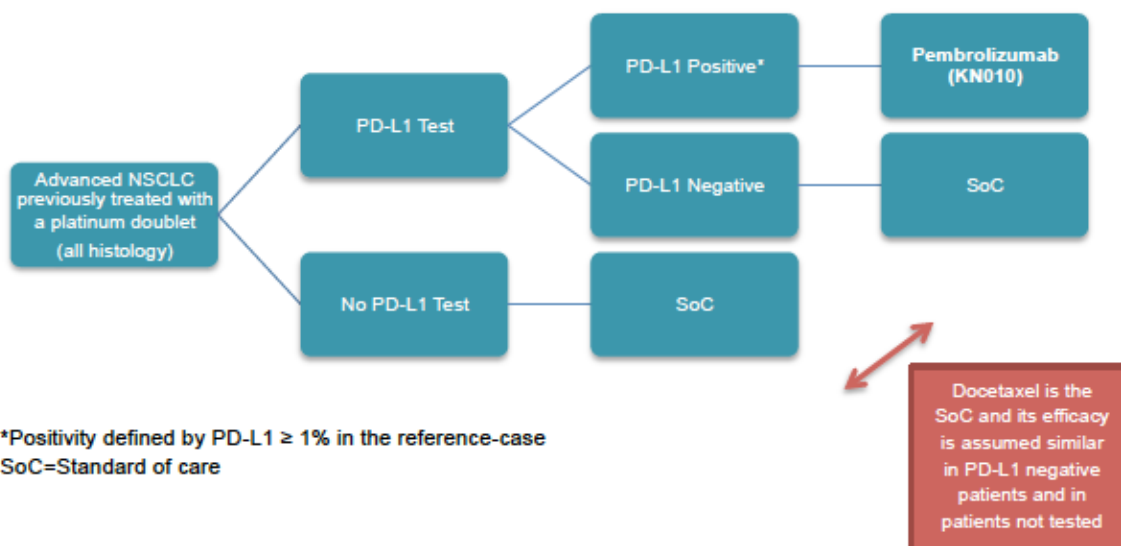
## 1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Merck Canada compared pembrolizumab to docetaxel for patients with metastatic non-small cell lung carcinoma (NSCLC) whose tumors express PD-L1 via validated test and who have progressed on or after a platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on authorized therapy for these aberrations prior to receiving pembrolizumab. Funding is being requested specifically for patients with a tumor proportion score of PD-L1  $\geq 1\%$ .

**Table 1. Submitted Economic Model**

Funding Request/Patient Population Modelled	Yes
Type of Analysis	<i>CUA &amp; CEA</i>
Type of Model	<i>Partitioned-survival</i>
Comparator	<i>Docetaxel</i>
Year of costs	<i>2015</i>
Time Horizon	<i>10 years</i>
Perspective	<i>Government</i>
Cost of pembrolizumab:	<ul style="list-style-type: none"> <li>• \$44.00 per mg</li> <li>• \$294.18 per day or \$8,237 per 28-day course at 2 mg/kg every three weeks (assuming average weight and body surface area from Keynote 010 (KN010) and no wastage)</li> </ul>
Cost of docetaxel * Price Source: IMS Brogan accessed February 24, 2016	<ul style="list-style-type: none"> <li>• \$11.42 per mg</li> </ul> <p>At the recommended dose of 75 mg/m<sup>2</sup> every 3 weeks, docetaxel costs:</p> <ul style="list-style-type: none"> <li>• \$69.36 per day</li> <li>• \$1,942.00 per 28-day course (assuming body surface area from Keynote 010 and no wastage)</li> </ul>
Model Structure	The model was comprised of 3 mutually exclusive health states: progression-free, progressive disease and death. <i>See Figure 1 for model flow.</i>
Key Data Sources	<i>KN010 clinical trial<sup>1</sup> (final analysis, Sept 2015)—2 mg/kg every 3 week dosing used</i>
Key Assumptions	<i>All patients tested for PD-L1 in intervention arm; no one tested in comparator arm. Docetaxel is assumed to be similar in PD-L1 negative and not-tested patients.</i>

Figure 1. Decision problem model structure, as taken from pCODR submission



## 1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. The Clinical Guidance Panel considered that nivolumab may be a relevant comparator (though not any more relevant than docetaxel). The Submitter did not include the comparison to nivolumab in modifications to the main economic analysis due to lack of head-to-head clinical trial evidence, and differences in trial design and dose scheduling precluded a relevant and appropriate indirect treatment comparison.

- Relevant issues identified by the CGP included:
  - There is a net clinical benefit to pembrolizumab in the treatment of patients with advanced or metastatic NSCLC following platinum doublet combination chemotherapy based on the KN010 clinical trial.
  - All eligible patients require a biomarker test. The CGP noted that the optimal test has yet to be determined, however, both archival and fresh tumor biopsies are acceptable for PD-L1 testing.

### Summary of registered clinician input relevant to the economic analysis

Registered clinicians considered that pembrolizumab is better tolerated than chemotherapy, with a shorter infusion time and less frequent dosing than nivolumab, for patients who have disease progression and whose tumors express PD-L1. They identified that testing for PD-L1 expression is important, but that the turnaround time for test results would delay initiation of treatment.

### Summary of patient input relevant to the economic analysis

Patients considered response to therapy, including complete response, side effects, and quality of life as important with treatment for NSCLC. These factors were adequately considered in the economic analysis.

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.

**Enablers**

- Frequency of administration for pembrolizumab is similar to docetaxel.

**Barriers**

- Timing of conducting the PD-L1 test, and the turnaround time for the results given that there are six centralized facilities set up to conduct the tests.
- Incremental costs due to drug wastage. The submitted base case analysis did not take into account any vial sharing.
- Potential for another tissue sample for biopsy for PD-L1 testing. The submitted base case includes an estimate that a small estimate of patients will need to be re-biopsied.
- High cost of the drug.

Other factors that PAG considered relevant was the requirement of the PD-L1 test prior to treatment and sequencing of treatment.

**1.3 Submitted and EGP Reanalysis Estimates**

Table 2. Submitted and EGP reanalysis estimates

Estimates (Range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ICER estimate (\$/QALY)	\$143,730	\$149,342	\$254,945
ΔE (QALY)	0.53	0.48	0.27
Progression-free	0.15	Not available*	Not available*
Post-progression	0.38	Not available*	Not available*
ΔE (LY)	0.75	0.58	0.34
Progression-free	0.19	0.18	0.18
Post-progression	0.56	0.40	0.15
ΔC (\$)	\$76,742	\$71,649	\$68,441

\* When utility is defined by time to death, as the EGP has done in the lower and upper bound, the utility value given to a patient is dependent on the time remaining before the models assumes death. In order to estimate the distribution of utilities by pre and post-progression state, the submitter would need to make assumptions on the death rate in the PF and PD state for each time point, which they are unable to do.

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

- The trial on which the inputs in the model are based had a median follow-up of 57 weeks, which is relatively short compared to the submitted time horizon of 10 years.
- The submitted base case assumed that patients could only receive one line of subsequent treatment. This does not reflect the clinical trial on which the model is based where patients were able to get more than one subsequent treatment. Including all treatments could impact both the incremental cost and effects, though the magnitude on the impact on the ICER is unknown. In their feedback, the Submitter stated that less than 10% of patients in KEYNOTE 010 received more than one line of subsequent therapy. The Submitter claimed that the impact of modeling more than one line of subsequent therapy would likely

be minimal and any further modeling would not result in a significant change in ICER. The CGP supported the Submitter's claim that less than 10% of patients would receive more than one line of subsequent therapy; though the impact on the magnitude of the ICER is likely to be small, the direction on the ICER remains unknown if all subsequent treatment lines were to be accounted for.

- In the submitted model, there is incremental benefit seen in the pembrolizumab group in the post-progression period. Though the CGP identified that patients may continue to derive benefit after coming off the drug, given the evidence available, the magnitude of benefit between the two treatments in the post-progression period is unknown.

#### 1.4 Detailed Highlights of the EGP Reanalysis

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

- Time horizon of 5 years instead of 10 years, based on input from the clinical guidance panel that patients in this population realistically do not live beyond 5 years. This is further confirmed by visual interpretation of the survival curves presented by the submitter of NSCLC patients in the SEER database, that overall survival of patients beyond five years is less than 10% (further impacted by stage of the disease).
- Utilities by time to death approach instead of progression status approach. This may be more appropriate as sometimes patients do not have a response in the progression-free state, and if/when they do have a response, they can have a response for a long duration.
- Overall survival benefit capped at trial end date. The EGP explored, as an upper bound, no survival benefit beyond the trial period given the uncertainty in the survival estimates due to the heavy reliance on extrapolation.
- PAG provided feedback and noted that the survival benefit in the pembrolizumab treated patients was greater in the TPS >50% group than the TPS >1% group. PAG asked if pERC would note the differences in the ICERs in the final report. The EGP would like to reiterate that a one-way scenario analysis was conducted by the EGP using TPS $\geq$ 50% as opposed to TPS $\geq$ 1%; the magnitude of difference in the overall ICER was minimal (difference of \$185/QALY). This is because there are increased costs, but there are also increased benefits when looking only at the TPS $\geq$ 50% subgroup. During the course of the review of pembrolizumab, the EGP discussed TPS group cutoffs with the CGP and confirmed that TPS $\geq$ 50% was a sub-group population of the trial and does not represent the funding request (TPS $\geq$ 1%). Given the above, the EGP felt that it was unwarranted to include a TPS $\geq$ 50% subgroup as part of the EGP's reanalysis for the best case estimate.
- The Submitter provided feedback and stated that they disagree with pERC that the true ICER is likely towards the upper bound of their reanalysis due to the application of a 100 week treatment effect cap and no more than one subsequent line of therapy. The EGP would like to reiterate that the statement has a qualifier in it that, if you believe that the duration of benefit for overall survival does not extend beyond the trial period, then the ICER is likely towards the upper range estimate \$254,945/QALY.
- In their feedback, the Submitter provided a graph and commentary of the overall survival used by the Submitter compared to the EGP, disagreeing with the EGP's upper bound reanalysis stating that capping treatment effect at 100 weeks underestimates the clinical value of pembrolizumab and results in less appropriate extrapolation of overall survival. The EGP respectfully disagrees with the Submitter's claim that the extrapolation of overall survival in the base case displays a more natural curve than what the EGP has selected as a curve for the upper bound only of the best estimate. The EGP would like to emphasize that, at 52 weeks-- where the Submitter has stopped using KM data and moved to extrapolation in the submitted base case-- there is a



noticeable turn in the curve, and not a natural curve shape. Therefore, their claim that the submitted base case overall survival curve is more “natural” than the EGP upper bound overall survival curve, is unfounded.

Table 3. EGP reanalysis estimates

Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ From Baseline Submitted ICER
Submitted base case	\$76,472	0.53	\$143,730	----
<b>EGP’s Reanalysis for the Best Case Estimate</b>				
LOWER BOUND				
Time horizon - 5 years	\$71,649	0.42	\$172,635	\$28,905
Utilities by time to death	\$76,472	0.61	\$125,350	-\$18,380
<i>Best case estimate of above two parameters</i>	\$71,649	0.48	\$149,342	\$5,612
UPPER BOUND				
Overall survival benefit capped at trial end	\$68,550	0.25	\$275,812	\$135,265
<i>Best case estimate of above three parameters</i>	\$68,441	0.27	\$254,945	\$111,215

## 1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include: inclusion of funding of nivolumab, treatment duration of pembrolizumab, inclusion of administration costs, change in PD-L1 testing uptake and change in vial size of pembrolizumab (Note: changes in vial size could result in a cost savings).

A key limitation of the BIA model is the assumption around the funding of nivolumab, both in the setting where it is funded (market share) and if it is not funded (a much larger incremental cost of pembrolizumab). These two alternatives were able to be explored by the EGP.

## 1.6 Conclusions

The EGP’s best estimate of ΔC and ΔE for pembrolizumab when compared to docetaxel is:

- Between \$149,342/QALY and \$254,945/QALY
- Within this range, it is difficult to estimate where the best estimate would likely be, as it depends on the overall survival benefit beyond the trial data.
- The extra cost of pembrolizumab is between \$68,441 and \$71,649 (ΔC). The factors that most influence ΔC include the duration of benefit for overall survival beyond the trial data, histology (squamous only), and the percentage of patients requiring a PD-L1 test re-biopsy.
- The extra clinical effect of pembrolizumab is between 0.27 and 0.48 (ΔE). The factors that most influence ΔE include the time horizon, the duration of overall survival benefit beyond the trial data, and the histology (squamous only).

**Overall conclusions of the submitted model:**

- Based on the data available, the assumptions in the economic model are reasonable. A limitation of the data is the heavy reliance on extrapolation, which introduces uncertainty.
- If you believe that the duration of benefit for overall survival does not extend beyond the trial period, then the ICER is likely towards the upper range estimate \$254,945/QALY.

## 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 Lung 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 for non-small cell lung. 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](http://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. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

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](http://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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