



pan-Canadian Oncology Drug Review Final Economic Guidance Report

Pembrolizumab (Keytruda) for Metastatic Urothelial Carcinoma

February 15, 2018

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FUNDING

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Merck, compared KEYTRUDA® (pembrolizumab), a high affinity antibody against programmed-death-receptor-1 (PD-1) that inhibits the PD-1 receptor and modulates anti-tumour immunity, to monotherapy with investigator's choice of chemotherapy with paclitaxel, docetaxel, or vinflunine for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.

Table 1.1. Submitted Economic Model

Funding Request	Merck is requesting pembrolizumab to be listed for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy. The funding request and modelled population are in alignment.
Type of Analysis	Cost effectiveness analysis and cost utility analysis
Type of Model	Partitioned-survival model
Comparator	The base-case analysis was performed for combined docetaxel and paclitaxel as standard of care (SOC).
Time Horizon	10 years
Perspective	Publicly funded health care system in Canada
Cost of pembrolizumab	At the list price, pembrolizumab costs \$44.00 per mg; \$4,400 per 100mg and \$2,200 per 50mg vial. At the recommended dose of 200 mg IV every 3 weeks, pembrolizumab costs \$419.05 per day and \$11,733.33 per 28-day cycle.
Cost of docetaxel and paclitaxel	At the list price, docetaxel costs \$1.52 per mg. At the recommended dose of 75 mg/m ² IV every 3 weeks, docetaxel costs \$9.20 per day and \$257.72 per 28-day cycle. At the list price, paclitaxel costs \$2.00 per mg. At the recommended dose of 175 mg/m ² IV every 3 weeks, paclitaxel costs \$12.14 per day and \$340.00 per 28-day cycle.
Model Structure	The model was comprised of 3 health states: pre-progression, progression (or post-progression), and death. Transitions between these health states were driven by the KeyNote-45 (KN-045); Kaplan-Meier (KM) data were used directly for the first 15 weeks of the model time horizon and parametric functions were fitted onwards.
Key Data Sources	The efficacy and safety parameters were based on the KeyNote-045 trial. In all treatment arms, time-on-treatment (ToT), PFS and OS were extrapolated using parametric functions fitted to the patient-level trial data.

1.2 Clinical Considerations

Summary of patient input relevant to the economic analysis

For respondents who have not experience the drug under review expect that it would improve their physical condition, such as decreasing the size or stabilizing of the tumor, reducing pain, and improving breathing. In addition, it is also expected that the new drug would improve the quality of life and provide long-term stability or reduction of disease. Over half of these respondents reported that they would be willing to tolerate moderate side-effects if the new drug is proven to be effective. Of the three patient respondents that had experience with pembrolizumab, all indicated that pembrolizumab was effective at controlling the bladder cancer with two respondents mentioning decreased severity of side-effects compared to other therapies. The side effects that were experienced included fatigue, skin rash, itchiness and diarrhea. For those who had experience with other therapies, they also reported that the infusion period for pembrolizumab was shorter than other therapies.

Summary of registered clinician input relevant to the economic analysis

The clinicians providing input noted that a modest proportion of patients with muscle-invasive urothelial cancer might develop disease progression after first-line chemotherapy. In these patients, second-line therapy with pembrolizumab has been shown to offer an improvement in overall survival and quality of life, as well as better tolerability. Pembrolizumab will be used after cisplatin-based chemotherapy or in patients who are not eligible to receive cisplatin. The drug may also be used as a third-line therapy after taxane chemotherapy in a relatively small group of patients. The drug will likely replace or displace second-line chemotherapy with taxanes (paclitaxel or docetaxel). The clinicians providing input indicated that retreatments with and restarts of pembrolizumab should be performed in a fashion similar to other immunotherapy agents (e.g. nivolumab). Although pharmacokinetic evidence suggests no advantage to either fixed dose (200 mg) or weight-based (2 mg/kg) regimens, a number of patients may experience overdoses with a 200 mg fixed dosing schedule. However, from a clinical point of view, the clinicians providing input support the 200mg fixed dose suggested by the evidence.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

Input was obtained from five provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact implementation:

Clinical factors:

- Unmet need for second line treatment of urothelial cancer
- Sequencing of treatments for urothelial cancer

Economic factors:

- Treatment until progression

PAG also noted the following:

- The comparators in the KEYNOTE-045 trial were investigator's choice of paclitaxel, docetaxel or vinflunine. PAG noted that if the patient is fit enough for chemotherapy, paclitaxel or docetaxel would be used. Vinflunine is not available in Canada. The economic model submitted reflects the clinical practice in Canada, and so, the vinflunine was excluded from the analysis.
- PAG is also seeking guidance on re-treatment with pembrolizumab in patients who have disease progression while on a treatment break. The economic model took into account

the actual treatment with pembrolizumab as observed in KN045, with pembrolizumab duration beyond the progression and for a maximum of 2-year period.

- PAG is seeking guidance on weight based dose for urothelial cancer given the high cost of fixed dose compared to weight based dose for patients weighing less than 100kg. The economic model was based on a fixed dose of 200 mg without any possibility of conducted reanalysis on a weight-based dosing.

1.3 Submitted and EGP Reanalysis Estimates

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

The key assumption that has the most impact on the results of the economic evaluation is the difference in OS adjusted for post-progression treatments. In the KN-045 trial, there was no planned crossover at disease progression. However, subjects assigned to the standard chemotherapy arm could be administered an anti-PD1/PD-L1 as subsequent therapy following confirmation of disease progression. The OS treatment effect estimated in the docetaxel or paclitaxel arm was adjusted to correct for the potential bias induced by anti-PD1/PD-L1 treatment (pembrolizumab) as subsequent therapy after discontinuation. The EGP acknowledged the feedback by the Submitter on the pCODR Expert Review Committee's (pERC's) Initial Recommendation that pembrolizumab is currently not reimbursed as a treatment option for UC in Canada and therefore should not be available as a subsequent treatment for the comparator arm. Therefore, the OS of the comparator arm should be adjusted for the crossover of patients. However, the EGP noted that with respect to OS without adjustment for crossover, in KN-045 there was no planned crossover at disease progression. The OS treatment effect estimated in the docetaxel or paclitaxel arm was adjusted in the economic model to correct for the potential bias induced by anti-PD1/PD-L1 treatment (pembrolizumab) as subsequent therapy after discontinuation. Overall survival had the greatest impact on the ICUR. The different methods for adjusting for survival after disease progression all assumed a survival benefit for pembrolizumab that was maintained after the trial period and over the entire time horizon. Various methods for extrapolating overall survival were considered which reduced the impact of the assumption of survival benefit with pembrolizumab after disease progression. As there is uncertainty in the true overall survival of patients in the economic model, considering a different extrapolation method (OS without adjustment for crossover) was considered in the upper bound of the EGP's reanalysis in order to estimate the impact the extrapolation methods had on the ICUR. The different methods for adjusting for survival at the time of disease progression were explored as the assumption of survival benefit with pembrolizumab after disease progression favoured pembrolizumab and reduced the ICUR. The use of these methods to adjust for the difference in survival resulting from crossover at the time of disease progression has the potential to reduce the ICUR. The EGP was, however, able to modify this input in the model. The submitted model provides one non-adjusted scenario as well as two additional scenarios using different adjustment methods.

A second key factor influencing the output of the submitted model was the time-horizon of 10 years, which was considered by CGP and EGP to be too long in duration, as patients with this condition have a median survival of less than 10 months. The submitted model allowed EGP to evaluate the impact of different time horizons. The model allowed the EGP to perform several re-analyses. Time-horizon had a large impact on ICER. Following review of feedback by the Submitter on the pCODR pERC Initial Recommendation, the EGP noted that the updated CADTH guideline¹¹ recommends that "the time horizon of the analysis should be conceptually driven, based on the natural history of the condition or anticipated impact of the intervention", the guideline also states that justifying the plausibility of the extrapolation may involve reference to external data sources, biology or clinical expert judgment. Further, in justifying the percentage of the

estimated effect that occurs beyond the observed data, it is important to consider whether it is clinically reasonable which will help researchers to assess the suitability of the extrapolation methods. "Expert judgment may be helpful in this regard." The EGP discussed and agreed with the CGP with using a 5 year time horizon because it was more clinically plausible in this patient population. The EGP are unaware of any studies that report a maximum overall survival of 10 years for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy. The time horizon of ten years also resulted in greater extrapolation results that are subject to high uncertainty. The CGP and EGP felt the time horizon of 10 years was too long in duration. When several sensitivity analyses were explored with time horizon, the ICUR became quite large under a shorter time horizon.

The CGP and EGP agreed that the utilities by time to death used by the submitter in the base-case scenario were appropriate. This is in accordance with other prior pCODR recommendations seen in similar immunotherapy treatments.

The greatest model uncertainty related to the extrapolation of OS beyond the trial period over the specific time horizon. The impact on the ICUR of the many alternative OS extrapolation methods that were tested was moderate, but when applied over a shorter time horizon, the ICUR became quite large. Although different extrapolation methods have been used, all assumed a survival benefit for pembrolizumab that was maintained after the trial period and over the entire time-horizon modelled.

Finally, the EGP noted that a flat dose of 200 mg was used in this economic model for pembrolizumab, and no re-analysis was possible for this input.

The following re-analyses have been performed by varying components of the model that were significant drivers of either the incremental effect or the incremental cost, including time-horizon and survival extrapolation method.

1. The EGP noted that the time horizon of 10 years in the submitted model was considered too long in duration for a patient population with a median survival of less than 10 months. In addition, as a main assumption in this model is that the survival benefit for pembrolizumab is maintained after the trial period, a shorter time horizon decreases the impact of this assumption.
2. Several re-analyses were performed to assess the impact of the OS extrapolation methods. This included different adjustment methods for cross-over.
3. For OS extrapolation parametric curves, the reference case fitted a parametric function distribution over the entire time horizon period with a reference case cut-off point of 32 weeks. A re-analysis utilized Kaplan-Meier data up to a 40 week cut-off (longest available) to take into account the maximum data from the trial and extrapolation over a shorter period of time. The updated trial analysis had a median follow-up of 80 weeks (18.5 months).
4. As KN-045 trial did not provide a clinical rationale for PD-L1 testing in patients with locally advanced or metastatic UC who have received platinum-containing chemotherapy (since the survival benefit observed with pembrolizumab in this indication was independent of PD-L1 expression), there was no re-analysis conducted by EGP incorporating PD-L1 testing.

Table 1.2. Submitted and EGP Reanalysis Estimates

Estimates	Submitted	EGP Reanalysis: lower and upper bounds
ICER estimate (\$/QALY), range/point	\$126,150/QALY range: \$92,887/QALY to \$207,232/QALY	\$217,954/QALY to \$285,514/QALY
ΔE (QALY), range/point	0.75 QALY; range: NA	0.30 QALY to 0.41 QALY
ΔE (LY), range/point	0.93 LY; range: NA	0.36 LY to 0.50 LY
ΔC (\$), range/point	\$94,317; range: NA	\$84,631 to \$89,225

Table 1.3: Detailed Description of EGP Reanalysis

	ΔC	ΔE	ICUR	Δ from baseline submitted ICER
Baseline (Submitter's best case)	\$94,317	0.75	\$126,150/QALY	--
LOWER BOUND				
Time-horizon 5y	\$90,013	0.46	\$193,771/QALY	\$67,621
Utilities by time to death	\$94,317	0.75	\$126,150/QALY	0
OS cut-off 40 weeks	\$90,960	0.60	\$151,083/QALY	\$24,933
Best case estimate of above 3 parameters	\$89,225	0.41	\$217,954/QALY	\$91,804
UPPER BOUND				
Time-horizon 5y	\$90,013	0.46	\$193,771/QALY	\$67,621
OS without adjustment for crossover	\$88,022	0.58	\$150,780/QALY	\$24,630
OS cut-off 40 weeks	\$90,960	0.60	\$151,083/QALY	\$24,933
Best case estimate of above 3 parameters	\$84,631	0.30	\$285,514/QALY	\$159,364

1.4 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include: the number of patients eligible to be treated with pembrolizumab and market expansion.

The submitter's BIA included several one-way sensitivity analyses. These demonstrated that the results were most sensitive to the market expansion assumption followed by the percentage of patients treated with second-line pembrolizumab (market penetration), the second-line UC treatment rate, the percentage of patients receiving platinum-containing chemotherapy in first-line, the referral rate to medical oncologists and the first-line treatment rate. These parameters all influence the number of patients projected to be treated with pembrolizumab. The EGP noted a limitation of BIA is that the estimated patient population was based on expert opinion and that it would have been useful if BIA were based on real-world data sets.

1.5 Conclusions

The EGP's best estimate of ICUR for pembrolizumab when compared to paclitaxel/docetaxel is:

- between \$217,954/QALY and \$285,514/QALY. The EGP further notes that this range is due to the uncertainty in the magnitude of long term benefit.
- The extra cost of pembrolizumab is between \$84,631 and \$89,225. The factor that most influences the costs is duration of treatment.

- The extra clinical effect of pembrolizumab is between 0.30 QALY to 0.41 QALY. The factors that most influence the incremental clinical benefit are the time horizon, the survival extrapolation methods used and the OS cutoff.

Overall conclusions of the submitted model:

The submitted model included many appropriate assumptions and an extensive set of sensitivity analysis. An important driver in this economic evaluation was the time-horizon which was considered to be too long by both the CGP and EGP, as patients with locally advanced or metastatic urothelial cancer previously treated with platinum-based chemotherapy have a median survival of less than 10 months. The long-term benefit of pembrolizumab relative to the comparator group is uncertain and cannot reasonably be estimated. However, the submitted model allowed the EGP to evaluate the impact of the factors contributing to long term benefit. Finally, pembrolizumab was evaluated at a flat dose of 200mg. The flat dose might favour reduced drug wastage but at the increased cost of medication for patients with low body weight. The submitted model did not allow the EGP to explore the impact of different dosing schedules and no vial wastage was considered for pembrolizumab.

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 Lymphoma/Myeloma 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-utility of Pembrolizumab for patients with recurrent or metastatic, squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum therapy. A full assessment of the clinical evidence of pembrolizumab compared with alternative treatments 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. 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). 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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