CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Pembrolizumab (Keytruda) for Melanoma Adjuvant Therapy

August 1, 2019

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

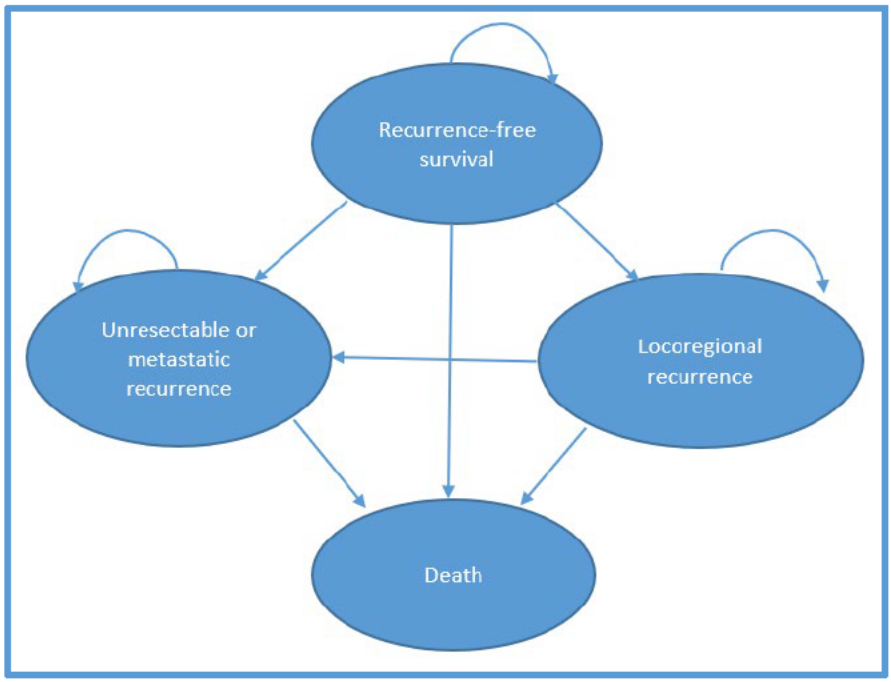
The economic analysis submitted to pCODR by Merck Canada compared pembrolizumab (KEYTRUDA), a high affinity antibody against programmed-death-receptor-1 (PD-1) that inhibits the PD-1 receptor and modulates antitumour immunity, with placebo (standard of care [SOC]). Pembrolizumab has been approved by Health Canada for the treatment of multiple oncology conditions, including unresectable or metastatic melanoma. On April 2, 2019 Health Canada issued a Notice of Compliance for pembrolizumab for the following indication: the adjuvant treatment of patients with melanoma with lymph node involvement who have undergone complete resection.

Table 1: Submitted Economic Model

Funding Request/Patient Population Modelled	Merck Canada is requesting reimbursement of pembrolizumab in patients who have melanoma: (1) with lymph node involvement who have undergone complete resection; and (2) for the retreatment of patients upon locoregional or distant recurrence more than six months following a completed adjuvant course of pembrolizumab. The first part of the funding request (1) aligns with the patient population informing the economic model; however, the patient population specified in (2) did not inform the economic model.
Type of Analysis	Cost-effective analysis and cost-utility analysis
Type of Model	Markov cohort, partitioned-survival
Comparator	Pembrolizumab versus two comparators: • SOC (placebo) — the term "observation" was used in this economic evaluation to define SOC, placebo, and "watchful waiting." • Interferon (IFN) as an alternative adjuvant treatment strategy (scenario analysis).
Year of Costs	2018
Time Horizon	Lifetime (46 years)
Perspective	Canadian public payer
Cost of Pembrolizumab	• 50 mg vial at $2,200 • 100 mg vial at $4,400 • Recommended fix dose of 200 mg q.3.w: $8,800
Cost of Standard of Care (SOC) i.e., observation	• $0
Model Structure	The model consists of four mutually exclusive health states (i.e., recurrence-free, locoregional recurrence, distant metastases, and death).

	(Figure 1)
Key Data Sources	• KEYNOTE-054 trial data • Canadian life tables • Flatiron database[a] of real-world evidence and published literature were used to estimate transition probabilities from the locoregional recurrence health state and from the distant metastases health state.
Source: Merck Canada (pembrolizumab) and Saskatchewan online Formulary (IFN) (1). [a]The Flatiron database collects real-world clinical data from electronic health records used by cancer care providers in the US.	

Figure 1: Schematic Model



1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison of pembrolizumab with observation, which is the most common treatment strategy used in Canadian clinical practice, is an appropriate comparator for adjuvant systemic therapy. However, the CGP considered that nivolumab may be a more clinically relevant comparator. The submitter did not include nivolumab as a comparator in the economic analysis. According to the CGP, it is unlikely that a phase III trial will be conducted that directly compares pembrolizumab with nivolumab in stage III patients as presented in the KEYNOTE-054 trial. The submitter did provide a comparison with IFN; however, because of its minimal use (due to modest clinical benefit and toxic side effects), the CGP noted that it is rarely used. Based on this input from the CGP, the Economic Guidance Panel (EGP) has only presented analyses for the comparison between pembrolizumab and observation. However, the EGP performed several reanalyses in order to make results of the pembrolizumab economic evaluation as comparable as possible with the recent pCODR economic evaluation of nivolumab for adjuvant melanoma (2).

The relevant issues identified included the following:

- Outcome: Recurrence-free survival (RFS) is considered an appropriate surrogate end point from which to infer a net clinical benefit for effectiveness in stage III melanoma (3).
    - The economic evaluation was based on RFS data from the KEYNOTE-054 trial and other external sources. The direct evidence from KEYNOTE-054 was not used to estimate overall survival (OS) because the trial survival data were immature with very few patient deaths occurring during the trial period (i.e., two in the pembrolizumab group and one in the observation group).
- Retreatment — The KEYNOTE-054 trial has two parts. In part 2 of the trial, the efficacy of retreatment with pembrolizumab is assessed. Specifically, patients who were initially treated with pembrolizumab and recurred could be retreated with pembrolizumab after completing a completed course of adjuvant treatment; the eligibility criteria for retreatment were a time frame of greater than six months post-completion of adjuvant pembrolizumab. Patients assigned to placebo who experienced a recurrence could crossover and receive pembrolizumab. Part 2 of the trial is ongoing and results are not currently available (expected in 2023) yet the submitter has included retreatment as part of their funding request. The submitter provided evidence for retreatment (as proof of concept) from a separate trial in advanced melanoma patients; however, the CGP considered these data not applicable to the target patient population of this review and indicated guidance on retreatment should await the results of part 2. Part 2 will enhance the knowledge of these drugs in recurrent disease; however, it makes interpretation of OS slightly more difficult.
    - The economic evaluation did not include specific analyses for pembrolizumab retreatment. The EGP agrees that no economic guidance on retreatment can be made without the results of part 2 of the trial.
- **Degree of metastatic lymph node involvement** — The KEYNOTE-054 trial eligibility criteria specified that patients with completely resected stage IIIA (AJCC 7th edition) disease were required to have lymph node metastasis measuring > 1 mm to be enrolled in the trial. The CGP indicated that since only sentinel lymph node biopsy is currently being done in clinical practice (versus completion lymphadenectomy), clinicians do not have as much information with respect to true nodal involvement and therefore would not want to apply a requirement with respect to degree of involvement in one solitary lymph node. They also noted that this aligns with Health Canada's Notice of Compliances for adjuvant pembrolizumab, nivolumab and dabrafenib-trametinib, which do not exclude patients with nodal metastases measuring < 1 mm. Therefore, the CCP recommended all stage III patients (A through D AJCC 8th edition) be eligible for adjuvant pembrolizumab.
    - The economic evaluation did not include all stage III melanoma patients; only stage III patients as per the KEYNOTE-054 trial eligibility criteria were included (stage IIIA with nodal metastases measuring >1 mm).
- **Options for Treatment** - With the Health Canada approval of pembrolizumab, nivolumab, and dabrafenib-trametinib, the CGP noted clinicians will potentially have three options to present to patients. Dabrafenib-trametinib combination would be only available to those patients with BRAF mutated melanomas; a significant but minority of patients with melanoma. With respect to pembrolizumab and nivolumab, the individual randomized controlled trials (RCTs) evaluating these drugs (KEYNOTE-054, Checkmate 238 of

nivolumab) were not directly comparable and therefore, one has to be careful about cross trial comparisons. The major differences between the two trials were:

- Comparators: pembrolizumab was compared with placebo, nivolumab was compared with ipilimumab.
- Included patient populations: stage IV patients with resected metastatic disease to no evidence of disease were allowed in the nivolumab trial and were excluded from the pembrolizumab trial.
- Dosing frequency: pembrolizumab every three weeks, nivolumab every two weeks.
- Dosing type: pembrolizumab is one standard dose (i.e., capped dose) and nivolumab is weight-based dosing.
    - The EGP conducted several reanalyses in order to facilitate a comparison between the pembrolizumab and nivolumab pCODR economic evaluations. However, the comparison between economic models was limited by different model structures, different subsequent therapies distributions, and other relevant assumptions. The EGP noted that in the pembrolizumab economic evaluation no reanalysis was possible for patients with resected stage IV disease, and chair time for pembrolizumab and other treatments for advanced melanoma were considered in the economic model.

- **Sequencing currently available adjuvant therapy —** Patients previously treated with IFN as adjuvant to surgery were permitted enrolment into the KEYNOTE-054 trial; specifically, eligible patients had been previously treated with IFN for thick primary melanomas without evidence of lymph node involvement. The CGP indicated that as there are very few to any patients receiving adjuvant IFN in Canada the number of individuals that would be potentially eligible to switch to a PD-1 inhibitor would be minimal and have minimal financial impact.
- **Reinitiating of pembrolizumab as adjuvant treatment after interruption for toxicity —** Dose modifications for treatment-related adverse events (AEs) were permitted in the KEYNOTE-054 trial, and were managed according to a dose adjustment scheme specified in the trial protocol. The CGP felt adjustment schemes to manage toxicity and clinical judgment should be used in clinical practice when deciding to reinitiate adjuvant treatment with pembrolizumab.
    - The economic model took into account the actual dose and the actual time on treatment.
- **Impact of the utilization of pembrolizumab as adjuvant treatment to surgery on subsequent treatment decision-making in the metastatic relapse setting -** The CGP indicated that part 2 of KEYNOTE-054 trial will provide some information with respect to sequencing of treatments in the metastatic relapse setting, however, currently, there are no data upon which to base appropriate sequencing. Patients in the KEYNOTE-054 trial received a variety of post-study treatments that included anti-CTLA4, anti-PD-1/PD-L1, and targeted agents.
    - The economic model included treatments for advanced melanoma, including pembrolizumab retreatment. The CGP considered the treatments distribution in the submitted model not representative of Canadian clinical practice. Accordingly, the EGP conducted some reanalyses using alternative treatment distributions.

- **PD-L1 status** — The CGP indicated that PD-L1 is not performed on melanoma specimens in Canadian clinical practice; therefore, the degree of PDL-1 positivity would not change clinicians' recommendations with respect to treatment for melanoma.
    - The economic evaluation did not include PD-L1 testing and associated costs, as the clinical trial demonstrated similar results independent of PD-L1 status.

Summary of registered clinician input relevant to the economic analysis
Two clinician inputs were received by pCODR: one submission on behalf of a single oncologist in Ontario, and a joint submission from clinicians from Cancer Care Ontario capturing the perspectives of four oncologists. In total, input was provided by five oncologists.

- Registered clinicians considered nivolumab the main adjuvant treatment option.
    - The EGP conducted several reanalyses in order to compare the economic evaluation of pembrolizumab with the prior pCODR evaluation of nivolumab.
- While some clinicians may consider nivolumab and pembrolizumab equivalent, the input suggested that clinicians may prefer to use pembrolizumab over nivolumab for its less frequent administration schedule (every three weeks versus every two weeks, respectively). Administering adjuvant pembrolizumab at a weight-based dosing schedule up to a cap was supported by the clinicians. Use of pembrolizumab for adjuvant treatment for greater than one year was stated to potentially benefit some patients. However, it was suggested that eligibility criteria for reimbursement specify treatment by number of doses and not by time period.
    - The economic model was based on a 200 mg fixed dose; as such, no reanalyses were possible to account for a weight-based dose. The EGP reanalyses suggest comparable incremental cost-effectiveness ratios (ICERs) for pembrolizumab and nivolumab.
- The joint clinician input stated that pembrolizumab would most likely replace IFN and observation, and could be used for high- and low-risk patients regardless of BRAF status.
- Both clinician inputs indicated that diagnostic testing should not be a consideration in treatment algorithms, and that testing is not required for pembrolizumab.
- The clinician input stated that there are data supporting the use of RFS as a surrogate end point for OS in melanoma.

Summary of patient input relevant to the economic analysis
Two patient advocacy groups, the Melanoma Network of Canada (MNC) and the Save Your Skin Foundation (SYSF), provided input on pembrolizumab as adjuvant treatment for melanoma patients.

- Patients reported experiencing high stress when they are told there is a high risk of recurrence after surgery, with no optimal systemic treatment options available to them afterward.
- Patients indicated wanting therapies with fewer side effects than IFN, with improved outcomes to reduce recurrence rates and spread of disease. It was noted that while IFN may have previously been provided to patients in the adjuvant setting, most hospitals no longer prescribe it due to the ineffectiveness and side effects.
    - The EGP did not conduct any additional reanalyses for the comparison with IFN.
- Among patients having experience with pembrolizumab, they commented that side effects of pembrolizumab were very limited and manageable with over the counter medications, such as Advil, Tylenol, or Gravol. Fatigue was the most commonly reported side effect

from patients according to both patient inputs. Other common side effects mentioned included, skin rash, gastrointestinal issues, headaches, loss/gain of appetite, fever, and rapid heartbeat. All of the patients who experienced side effects stated that the benefits of pembrolizumab outweighed the experience of the side effects. Compared with IFN, patients reported side effects as being less severe, easily manageable, and allowing them to maintain quality of life. Patients and caregivers stated they would appreciate access to therapies with improved survival and reasonable quality of life. For survival and/or prevention of disease, patients and caregivers stated they are willing to accept some side effects related to treatment.

    - All indicated factors were adequately considered in the economic analysis, and patient health-related quality of life was one of the main outcomes in the economic evaluation.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
Input was obtained from all nine provinces (ministries of health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of pembrolizumab:

- Currently funded treatments — PAG noted that the comparator in the KEYNOTE-054 trial was placebo, and is seeking information on data comparing pembrolizumab with IFN.
    - As previously noted, the economic evaluation included IFN as a comparator; however, based on CGP input, the EGP did not perform additional reanalyses using this comparator.
- Eligible patient population — PAG is seeking guidance on whether patients currently being treated with IFN or observation would be eligible for adjuvant pembrolizumab.
- Implementation factors — PAG is seeking guidance on weight-based dosing up to a cap of 200 mg for adjuvant melanoma; clarification on a dosing schedule of every six weeks with pembrolizumab; the appropriateness of re-initiation with pembrolizumab after toxicity resolution or treatment interruption for other reasons, and if this occurs, clarification on the total duration of therapy. PAG also noted pembrolizumab requires increased chair time and resources for drug administration, as well as additional nursing and pharmacy resources for monitoring and treating side effects (e.g., immune-mediated side effects of pneumonitis, ulcerative colitis, and Crohn's disease).
    - The economic evaluation included resources and costs associated with the administration, monitoring, and treatment of immune-mediated side effects. In addition, the cost of pembrolizumab was estimated by the Kaplan-Meier curve of the data observed in the trial; as such, this took into account the actual treatment duration, including interruptions and re-initiations after toxicity management. The model was based on a 200 mg fixed dose; therefore no reanalyses were possible to account for a weight-based dose. As well, the economic evaluation did not account for every six weeks versus every three weeks dosing of pembrolizumab.
- Sequencing with current therapies — PAG is seeking guidance on the appropriate treatment options in the metastatic setting as well as treatment-free interval following adjuvant therapy
    - As previously noted, the economic evaluation included subsequent treatments for advanced melanoma. The distributions of these treatments, however, were not derived from the KEYNOTE-054 trial. The EGP considered alternative distributions yet these had a minimal impact on the ICER, as both survival benefits and costs were impacted simultaneously. The model also took into account possible re-challenge with pembrolizumab in advanced stage melanoma.

- Companion diagnostic testing — PAG is seeking clarity on whether PD-L1 testing would be required in this setting
    - As previously noted, PD-L1 testing and associated costs were not included into the model, as the clinical trial demonstrated similar results independent on the PD-L1 status.

1.3 Submitted and EGP Reanalysis Estimates

The submitted economic evaluation was conducted using observation as the comparator group, as per the KEYNOTE-054 trial. The primary end point of the trial was RFS. Secondary end points included distant metastasis-free survival (DMFS) and OS. One sensitivity analysis was submitted with an additional comparator: IFN as an alternative adjuvant treatment strategy. As there is no head-to-head clinical trial comparing pembrolizumab with IFN, a systematic literature review and network meta-analysis (NMA) were conducted to indirectly compare these two adjuvant therapies with respect to RFS. The NMA did not include other relevant comparators (nivolumab, dabrafenib-trametinib). As IFN is rarely used in Canadian clinical practice due to high toxicity and modest clinical benefit, the CGP and EGP agreed to exclude this comparator from further reanalyses. In addition, the CGP and registered clinicians considered nivolumab a relevant and important comparator. However, the submitter declined pCODR's request of including nivolumab in this economic evaluation. The EGP conducted some reanalyses in order to account for differences observed between the current economic evaluation of pembrolizumab and the recent pCODR economic evaluation of nivolumab (2).

Overall, the submitted model was very complex and considered extensive sensitivity analyses. One-way sensitivity analyses and probabilistic analyses were described and conducted by the submitter to evaluate important elements and assumptions used in the model. In general, the assumptions made in the model and related input variables caused little variation of the ICER. The EGP considered the model structure appropriate, despite its complexity, and agreed with most of the choices made in the base-case. Nevertheless, the model did not allow alterations related to the transition probabilities from locoregional recurrence or distant metastases. Most importantly, no alteration of the clinical benefit after the two-year trial period was possible; as such, all the base-case and sensitivity analyses considered the maintenance of the clinical benefit over the entire time horizon.

There were several concerns and limitations of the model identified by the EGP, which are listed below:

Model structure and assumptions: The greatest source of model uncertainty is the extrapolation of outcomes beyond the trial period over a lifetime horizon. The base-case considered a 46-year time horizon. As the trial duration was only two years (median follow-up of 15 months), the direct evidence from the KEYNOTE-054 trial was not used to estimate OS because the trial survival data were immature and only a very few patients died during the trial period (i.e., two in the pembrolizumab group and one in the observation group).

The EGP performed two additional reanalyses: One using an alternative approach (time-constant hazard ratio), and the other using alternative parametric models (Gompertz and Weibull) for OS extrapolation. The first approach was performed in order to address comparability with the pCODR economic evaluation of nivolumab, while the second was chosen by the EGP as producing plausible OS estimates at 20 and 30 years.

Modelling the survival benefits using the Gompertz and Weibull model, as well as the time-constant hazard-ratio approach, produced a moderate to high impact on the ICER.

Time horizon: The submitted economic evaluation was based on a 46-year time horizon with the only direct evidence derived from the two-year KEYNOTE-054 trial. Both CGP and EGP considered the time horizon excessive, especially considering uncertainties related to OS extrapolation. The EGP reduced the time horizon to 25 years to represent a more realistic scenario. The impact of a time horizon of 10 years was also explored by the EGP in a reanalysis. These time horizons align with previous pCODR reviews for adjuvant therapy in the same population; nivolumab over a 10-year time horizon and dabrafenib-trametinib over a 25-year time horizon. Other time horizons (five and 20 years) were also tested by the EGP for comparison with the nivolumab economic evaluation. Time horizon reanalyses had a moderate to high impact on the ICER.

Subsequent therapies for advanced melanoma: The choice of subsequent therapies in the model was not derived from the KEYNOTE-054 trial. Instead, the market shares were estimated as follows: in the observation group, base-case market shares of first-line treatments for advanced melanoma were obtained from Canadian market research data (4); in the adjuvant pembrolizumab group, market shares of immunotherapies in the advanced setting were assumed to be 0% in the base-case, while market shares for the remaining advanced treatment regimens were proportionately increased, subject to the constraint that the total market share of BRAF inhibitors (i.e., vemurafenib, dabrafenib, vemurafenib-cobimetinib, and dabrafenib-trametinib) did not exceed the proportion of patients who were BRAF-positive in the KEYNOTE-054 trial (i.e., 49.8%)(5). In addition to these first-line therapies, second-line therapies were also considered.

The CGP considered the distributions of treatments non-representative, as it is expected that more patients (approximatively 80%) would receive single-agent therapies (i.e., pembrolizumab or nivolumab). The EGP noted that the KEYNOTE-054 trial was too short to capture the actual treatments distribution.

The submitted model allowed alteration of the treatment distributions and lines of treatments. The EGP conducted reanalyses using different distributions of treatments and using one line of treatment or two lines of treatment. Because the treatment distribution concomitantly has an impact on OS and costs, the impact on the ICER was minimal.

The EGP noted a high discrepancy between the costs of subsequent treatments estimated in the current submission versus those estimated in the prior submission of nivolumab. For example, over a time horizon of 10 years, the costs of subsequent treatments were estimated at: $141,821 and $207,186 for the pembrolizumab and observation groups, respectively; versus $41,058 and $60,173 for nivolumab and observation, respectively. The EGP explored this discrepancy and noted that this was due to the distribution of subsequent treatments considered in each economic evaluation. This produced a costs difference for pembrolizumab (-$65,365) that exceeds the costs difference for nivolumab (-$19,115), and this can partially explain a systematically reduced ICUR for pembrolizumab compared with nivolumab. Unfortunately, the level of detail reported in the nivolumab evaluation was insufficient to conduct further reanalyses.

Utilities: The utilities for the recurrence-free, locoregional recurrence, and distant metastases pre-progression health states for the base-case analysis were derived from repeated EQ-5D-3L measures in the KEYNOTE-54 trial, and from external sources for the distant metastases post-progression health state.

Alternative utilities values were used by the submitter in sensitivity analyses. These had a minimal impact on the ICER. No additional reanalyses were made by the EGP.

The EGP noted that the utility values for the recurrence-free state were similar between the pembrolizumab and nivolumab pCODR economic evaluations, but were smaller for all the other states: locoregional recurrence, distant metastases pre- and post-progression. This might partially

explain the lower quality-adjusted life-year (QALY) estimates in the pembrolizumab economic evaluation compared with the nivolumab evaluation. The EGP conducted a reanalysis using utilities as per the nivolumab evaluation and the impact on the ICER was minimal.

Costs and resource use:
Ongoing disease management including physician services, diagnostic tests, outpatient prescription drugs, hospital services for the surveillance of cancer recurrence is standard practice for patients in the recurrence-free state. In the locoregional recurrence state, the disease management costs included the costs of salvage surgeries for disease recurrence as well as ongoing disease management/surveillance costs as reported for the recurrence-free state.

Costs of intravenous administration of systemic melanoma therapies in the metastatic health state were estimated from the duration of infusion and the hourly infusion cost. Oral therapies were assumed to require a pharmacy dispensing cost once every four weeks. However, this cost was considered negligible and hence was not included in the model. No additional reanalyses were made by the EGP.

Re-challenge with pembrolizumab in locoregional recurrence state: The submitted model provided a scenario analysis in which patients in the adjuvant pembrolizumab group were allowed to be retreated (i.e., re-challenged) with pembrolizumab after they transitioned from recurrence-free state to locoregional recurrence state as per the KEYNOTE-054-trial protocol. Pembrolizumab acquisition, administration and AEs management costs, as well as AE-associated disutility were considered for patients who received this re-challenge. However, due to lack of data, these scenarios did not account for any improvements in DMFS and/or OS as a result of the re-challenge. No additional reanalyses were made by the EGP.

Table 2: Submitted and EGP Reanalysis Estimates (Deterministic)

Estimates (range/point)	Submitted	EGP Reanalysis Lower bound	EGP Reanalysis Upper bound
ΔE (LY)	4.68	2.64	1.04
Progression-free	5.61	3.0	1.66
Post-progression	-0.93	-0.37	-0.62
ΔE (QALY)	4.34	2.39	0.93
Progression-free	4.95	2.65	1.46
Post-progression	-0.61	-0.26	-0.53
ΔC ($)	$68,371	$108,581	$74,824
ICER estimate ($/QALY)	$15,755	$45,437	$80,872

EGP = Economic Guidance Panel; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

1.4 Detailed Highlights of the EGP Reanalysis

Many of the comments made by the CGP, and inputs from registered clinicians, patient advocacy group groups, and PAG were addressed in the submitted model, and were therefore not revisited in reanalyses by the EGP, which included the following factors:

- Resources and costs associated with the administration, monitoring and treatment of immune-mediated side effects.
- Reinitiating of pembrolizumab as adjuvant treatment after interruption for toxicity.
- Chair time in chemotherapy suites.
- Whether PD-L1 testing would be required in this setting.
- Quality of life.

As noted previously, the greatest source of model uncertainty in the submitted model is the extrapolation of outcomes beyond the trial period over a lifetime horizon. As such, the EGP performed a reanalysis using alternative parametric models (Gompertz and Weibull) for OS extrapolation, which produced plausible OS estimates at 20 and 30 years.

As well, issues related to the comparison of pembrolizumab with nivolumab were not addressed in the model, as the submitter declined pCODR's request for its inclusion. Although a comparison of pembrolizumab with IFN was also provided in the submitted model, the CGP noted that IFN is sparingly used because of the toxic side effects and modest clinical benefit associated with it. Based on this input from the CGP, the EGP only presented detailed analysis for the comparison between pembrolizumab and observation. In addition, the EGP conducted several reanalyses in order to make a reasonable comparison between pembrolizumab and nivolumab.

The EGP made the following changes to the economic model:

- Time horizon was set to five, 10, and 25 years. The nivolumab economic evaluation considered a 10-year time horizon in the base case and a five-year in EGP reanalyses.
- Parametric models combination of Gompertz and Weibull (11th combination).
- Time-constant hazard-ratio approach used to estimate OS benefits to allow comparability to the nivolumab economic evaluation.
- Same market share for subsequent therapies for advanced melanoma.
- Utility values as per the nivolumab economic evaluation.

Table 3: Detailed Description of EGP Reanalysis

One-way And Multi-way Sensitivity Analyses					
Description of Reanalysis	**ΔC**	**ΔE QALYs**	**ΔE LYs**	**ICUR (QALY)**	**Δ From Baseline Submitted ICER**
Parameter 1.1: time horizon of 25 years	$64,240	3.46	3.67	$18,568	$2,813
Parameter 1.2: time horizon of 10 years	$55,656	1.26	1.18	$44,261	$28,506
Parameter 1.3: time horizon of 5 years	$56,407	0.4	0.29	$139,912	$124,157
Parameter 2: parametric models: Gompertz and Weibull (11th combination)	$110,084	2.31	2.49	$47,631	$31,876
Parameter 3: time-constant hazard-ratio approach	$93,487	2.95	3.19	$31,696	$15,941
Parameter 4: same mix of treatments for advanced stage	$66,885	4.42	4.82	$15,142	($613)
Parameter 5: utility values as per nivolumab submission	$68,371	4.15	4.68	16,467	$712
EGP's Reanalysis for the Best Case Estimate (Deterministic)					
Description of Reanalysis	**ΔC**	**ΔE**		**ICUR**	**Δ From Baseline Submitted ICER**

One-way And Multi-way Sensitivity Analyses					
Description of Reanalysis	**ΔC**	**ΔE QALYs**	**ΔE LYs**	**ICUR (QALY)**	**Δ From Baseline Submitted ICER**
Baseline (submitter's best case) (Deterministic)	$68,371	4.34		$15,755	--
[LOWER BOUND]					
Best case estimate of above 2 and *4* parameters					
Parameters 1.1, 2 and 4 (parametric models Gompertz and Weibull, same mix of treatments for advanced stage, and 25-year time horizon)	$108,581	2.39	2.63	$45,437	$29,682
[UPPER BOUND]					
Best case estimate of above *1.2, 3, 4 and 5* parameters					
Parameters 1.2, 3, 4 and 5 (same as in nivolumab submission)	$74,824	0.93	1.04	$80,872	$65,117
Baseline (submitter's best case)	$68,371	4.34		$15,755	—
EGP's Reanalysis for the Best Case Estimate (Probabilistic)					
Description of Reanalysis	**ΔC**	**ΔE QALYs**	**ΔE LYs**	**ICUR**	**Δ from Baseline Submitted ICER**
Baseline (submitter's best case) (Probabilistic)	$67,907	4.17	NA	$16,293	—
[LOWER BOUND]					
Best case estimate of above 1.1, 2 and 4 parameters					
Parameters 1.1, 2 and 4 (parametric models Gompertz and Weibull and same mix of treatments for advanced stage , and 25-year time horizon)	$105,210	2.05	NA	$51,289	$34,996
[UPPER BOUND]					
Best case estimate of above *1.2, 3, 4 and 5* parameters					
Parameters 1.2, 3, 4 and 5 (same as in nivolumab submission)	$80,657	0.7	NA	$114,584	$98,291

EGP = pCODR Economic Guidance Panel; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; LY = life-year; NA = not available; pCODR = CADTH pan-Canadian Oncology Drug Review; QALY = quality-adjusted life-year.

1.5 Evaluation of Submitted Budget Impact Analysis

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

The submitted budget impact analysis (BIA) was based on the projected number of patients in Canada who would be expected to start pembrolizumab for the adjuvant treatment of stage III melanoma who have undergone a complete lymph node resection. The submitter considered that the addition of pembrolizumab in the adjuvant setting will offset some of these costs through the decreased use of anti-PD-1 and other targeted therapies in the advanced and metastatic stage of melanoma.

The EGP considered the BIA assumptions and estimations to be valid. The submitter conducted several one-way sensitivity analyses and these demonstrated that the results were most sensitive to the exclusion of subsequent therapies costs after recurrence. Other sources of important uncertainties having a significant impact on the BIA estimates were the proportion of patients with stage III melanoma, the percentage of patients referred to medical oncologists, the treatment rate of medical oncologists, the time to peak share of pembrolizumab, and the scenario where treatments of patients who have recurred to distant metastases is done with only immunotherapy eligible patients. These parameters all influence the number of patients projected to be treated with adjuvant pembrolizumab. No additional reanalyses were conducted by the EGP.

1.6 Conclusions

The EGP's best estimate (probabilistic) of ΔC and ΔE for pembrolizumab when compared with observation is:

- Between $51,289/QALY and $114,584/QALY. The EGP further notes that this range is due to the uncertainty in the magnitude of long-term benefit.
- Within this range of the ICUR, the best estimate would likely be $51,289/QALY (lower bound), corresponding to the scenario over a 25-year time horizon.
- The EGP anticipates that the ICER is likely to be lower if the flat dose of 200 mg is not adopted for the entire population as it represents an excessive dose for patients who are underweight.
- The extra cost of pembrolizumab is between $80,657 and $105,210. The factor that most influences extra cost is the cost of subsequent therapies for advanced melanoma, survival extrapolation method, and the considered time horizon.
- The extra clinical effect of pembrolizumab is between 0.70 QALY and 2.05 QALY. The factors that most influence the incremental clinical benefit are the time horizon and the survival extrapolation methods used.
- EGP's deterministic ICERs are lower than probabilistic ICERs. These are between $45,437/QALY and $80,872/QALY.
- The EGP noted that upper bound estimates are similar to the EGP's upper bound estimated in the nivolumab economic evaluation (2).

Table 4: Comparison of the Results of Pembrolizumab pCODR Economic Evaluation Versus Nivolumab pCODR Economic Evaluation (upper bound estimates):

Drug Evaluation	ΔC ($)	ΔE (LY)	ΔE (QALY)	ICER ($/QALY)
Pembrolizumab (probabilistic)	$80,657	NA	0.70 QALY	$114,584/QALY
Nivolumab (probabilistic)	$87,191	0.92 LY	0.98 QALY	$94,846/QALY
Pembrolizumab (deterministic)	$74,824	1.04 LY	0.93 QALY	$80,872/QALY
Nivolumab (deterministic)	$87,293	1.00 LY	0.93 QALY	$93,493/QALY

LY = life-year; NA = not available; QALY = quality-adjusted life-year.

Overall conclusions of the submitted model:

The submitted model included many appropriate assumptions and an extensive set of sensitivity analyses. An important driver in this economic evaluation was the time horizon, which was considered to be too long by both the CGP and EGP considering the uncertainty related to the clinical benefit beyond the two-year clinical trial. The long-term benefit of pembrolizumab relative to the observation group is uncertain and cannot reasonably be estimated. However, the submitted model allowed the EGP to evaluate the impact of some factors contributing to long-term benefit. The EGP noted that upper bound estimates are similar to the EGP's upper bound estimated for the pCODR economic evaluation of nivolumab. Finally, pembrolizumab was evaluated at a flat dose of 200 mg. 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 Melanoma 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 as adjuvant treatment for melanoma. A full assessment of the clinical evidence on pembrolizumab as adjuvant treatment for melanoma 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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