pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation

This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug:

Pembrolizumab (Keytruda)

Submitted Funding Request:

For the treatment of patients with metastatic non-small cell lung carcinoma whose tumours express PD-L1 (as determined by a validated test) and who have disease progression on or after platinum-containing chemotherapy. Patients with epidermal growth factor receptor or anaplastic lymphoma kinase genomic tumour aberrations should have disease progression on authorized therapy for these aberrations prior to receiving pembrolizumab. Funding is being requested for patients with a Tumour Proportion Score of PD-L1 ≥ 1%.

Submitted By:	Manufactured By:
Merck Canada Inc.	Merck Canada Inc.
NOC Date:	**Submission Date:**
April 15, 2016	April 21, 2016
Initial Recommendation:	**Final Recommendation:**
September 1, 2016	November 3, 2016

pERC RECOMMENDATION

pERC recommends reimbursement of pembrolizumab (Keytruda) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours express PD-L1 (as determined by a validated test) and who have disease progression on or after cytotoxic chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations should have disease progression on authorized therapy for these aberrations and cytotoxic chemotherapy prior to receiving pembrolizumab. Patients could receive up to 12 months of pembrolizumab if they experienced an investigator-determined confirmed radiographic disease progression, according to immune-related response criteria after stopping their initial treatment with pembrolizumab due to achievement of a confirmed complete response or having experienced 35 administrations of pembrolizumab. Funding should be for patients with a Tumour Proportion Score (TPS) of PD-L1 ≥ 1% and who have good performance status. Treatment should continue until confirmed disease progression or unacceptable toxicity, or to a maximum

	of two years, whichever comes first. pERC made this recommendation because it was satisfied that there is a net overall clinical benefit with pembrolizumab compared with docetaxel, based on the statistically significant and clinically meaningful improvements in overall survival, durable response, a meaningful improvement in the toxicity profile, and no detriment in quality of life. The Committee was satisfied that pembrolizumab aligned with patient values. pERC concluded that pembrolizumab, compared with docetaxel, could not be considered cost-effective in patients with metastatic NSCLC whose tumours express PD-L1 (as determined by a validated test) and who have disease progression on or after cytotoxic chemotherapy.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given that there is a net clinical benefit of pembrolizumab, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of pembrolizumab to an acceptable level. **Accessibility and Feasibility of Companion Diagnostic Test** pERC recognized the uncertainty that exists concerning the specificity and sensitivity and the lack of a gold standard in PD-L1 testing. Until such a reference standard becomes available, pERC agreed that PD-L1 testing using a validated test authorized by Health Canada, or one that is equivalent to that used in the KEYNOTE-010 trial (KN010), is reasonable. The Committee noted that it would be desirable for jurisdictions to have validated, reliable, and available PD-L1 testing across Canada to manage the prevalent patient population and the budget impact of a funding recommendation, which may require evidence generation from jurisdictions. pERC agreed that the results of the KN010 trial cannot be generalized to patients in whom tissue biopsy is not feasible or where the tissue specimen is inadequate to determine PD-L1 status; therefore, the Committee concluded that the recommendation does not include this group of patients. **Factors Affecting Budget Impact and Adoption Feasibility** pERC noted that the duration of treatment with pembrolizumab continues until confirmed disease progression, unacceptable toxicity, or a maximum of two years (in the case of KN010), whichever comes first. In considering the high cost of pembrolizumab, the large new and prevalent population, the potential for drug wastage, and the unknown but potentially long duration of treatment, pERC concluded that a substantial reduction in drug price would be required to improve affordability. **Optimal Sequencing of Pembrolizumab and Other Therapies Unknown** pERC concluded that the optimal sequencing of pembrolizumab and other treatments now available for the treatment of advanced or metastatic NSCLC is currently unknown. pERC was, therefore, unable to make an evidence-informed recommendation on sequencing following pembrolizumab. pERC also noted that there is no direct evidence to inform the comparative efficacy of pembrolizumab with other PD-1 inhibitors. Thus, with their overlapping indications, there is no evidence to inform the choice of pembrolizumab over nivolumab, or vice versa.

There is also no evidence to support using PD-1 inhibitors in sequence (e.g., pembrolizumab then nivolumab, or vice versa). However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of pembrolizumab and noted that collaboration among provinces to develop a common approach would be of value, as would the development and implementation of an evidence-based clinical practice guideline.

Common Approach to Defining Confirmed Disease Progression

pERC noted the unique mechanism of action of immunotherapeutic agents and acknowledged that, in a small percentage of patients, standard Response Evaluation Criteria in Solid Tumours (RECIST)-defined radiologic disease progression may be due to immune-related inflammation and may not be reflective of true disease progression (i.e., it is pseudoprogression). pERC noted that there is no consistently accepted definition for pseudoprogression in the clinical community. pERC agreed that until such a definition becomes available, it is reasonable to use the criteria in KN010: patients who progressed according to investigator-assessed immune-related response criteria could remain on treatment until a confirmatory scan was done four to six weeks later. The Committee noted that jurisdictions may want to reach agreement on the appropriate interval (for confirmatory scans) that is consistent for PD-1 inhibitor use.

Time-Limited Need for Pembrolizumab

At the time of implementing a funding recommendation for pembrolizumab, jurisdictions may consider addressing the time-limited need for pembrolizumab in patients who are currently receiving treatment with single-agent cytotoxic chemotherapy, or who have recently completed treatment with single-agent cytotoxic chemotherapy. pERC noted that this time-limited access should be for patients who have a good Eastern Cooperative Oncology Group Performance Status (ECOG PS) and would otherwise meet the eligibility criteria of KN010.

Evidence Generation to Understand Optimal Duration of Therapy and Criteria for Re-Treatment

pERC noted that pembrolizumab is approved at a dose of 2 mg/kg administered intravenously over 30 minutes every three weeks until confirmed disease progression, unacceptable toxicity, or a maximum of two years (in the case of KN010), whichever comes first. There is currently no evidence to identify an optimal set or fixed duration of treatment with pembrolizumab, and pERC agreed that it is important to prospectively collect such data. The Committee also agreed that jurisdictions should reassess the duration of treatment in the event that new evidence emerges on an optimal duration of treatment. pERC noted that the KN010 trial allowed for re-treatment with pembrolizumab for up to 12 months; however, data for this subgroup of patients were not available to pERC. The Committee agreed that jurisdictions should consider evidence generation to define appropriate criteria for re-treatment. In the absence of evidence, jurisdictions may want to consider a national approach to develop appropriate criteria for re-treatment that are consistent across jurisdictions.

Fixed Dose Is Forthcoming

pERC is aware that a fixed 200 mg dose of pembrolizumab is forthcoming. However, pERC recognized that the fixed dose of pembrolizumab was not included as part of the submission, therefore, it was not discussed by the Committee.

SUMMARY OF pERC DELIBERATIONS

Lung cancer is the most common type of cancer in Canada. In 2015, an estimated 26,600 new cases and 20,900 deaths occurred in Canada from lung cancer, with a five-year survival rate of < 5%. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers. Treatment decisions for advanced or metastatic NSCLC are typically dependent on the presence or absence and type of driver mutation status of patients in the first-line setting. In patients without a driver mutation, treatments in the second-line setting include single-agent chemotherapy with docetaxel or pemetrexed. Patients who have driver mutations (i.e., ALK or EGFR) typically receive targeted therapy upfront, then platinum-doublet chemotherapy for second-line treatment, and then single-agent chemotherapy for third-line treatment for those who maintain a good performance status. Given that most patients have advanced age and stage of disease, a greater number have a poor performance status, as well as a higher likelihood of significant comorbidities that affect their ability to tolerate conventional chemotherapy regimens. Therefore, pERC agreed that there is a need for alternative treatment options that reduce toxicity and prolong survival in this patient population.

pERC's *Deliberative Framework* for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of one open-label, randomized phase 2/3 trial (KN010) that compared two doses (2 mg/kg versus 10 mg/kg) of pembrolizumab to docetaxel in previously treated, PD-L1-positive, advanced NSCLC patients who have progressed on or after platinum-doublet chemotherapy (KN010, Herbst et al. 2015). pERC noted that the Health Canada-approved indication was based on a phase 1 trial (KEYNOTE-001, Garon et al. 2015) that considered a TPS of ≥ 50%, whereas KN010 had stratified results by ≥ 1% and ≥ 50% and, thus, pERC had different information (on the comparative effectiveness of pembrolizumab) than Health Canada for the indication. Based on KN010 results, the Committee noted the greater magnitude of survival benefit seen in patients who stained strongly for PD-L1 (≥ 50%) compared with PD-L1 TPS ≥ 1%, and considered a reimbursement recommendation for the TPS ≥ 50% group distinctly from the ≥ 1% group. However, pERC agreed that both TPS cut-offs (≥ 1% and ≥ 50%) demonstrated statistically significant and clinically meaningful improvements in overall survival (OS) compared with docetaxel. pERC also agreed that pembrolizumab offered a durable response compared with docetaxel regardless of TPS cut-offs. Therefore, the Committee concluded that there is a clinically meaningful and statistically significant improvement in OS and durable response, regardless of the level of PD-L1 expression (≥ 1% or ≥ 50%).

Upon reconsideration, pERC noted that platinum-containing chemotherapy is the standard treatment option for patients prior to qualifying for pembrolizumab; however, there may be instances where patients cannot tolerate the platinum portion of their treatment. In these instances, where cytotoxic chemotherapy has been administered, pERC agreed that it would be reasonable to treat patients with pembrolizumab, providing that they meet all other criteria within this Recommendation.

As well, upon reconsideration, pERC also noted that in patients in whom tissue biopsy is not feasible or where the tissue specimen is inadequate to determine PD-L1 status, there is a lack of evidence to support or refute the use of pembrolizumab. For this reason, the recommendation remains for patients with a TPS of PD-L1 ≥ 1%, and does not include patients for whom tissue biopsy is not feasible or where the tissue specimen is inadequate for determining PD-L1 status.

pERC discussed the quality of life (QoL) data from KN010 and noted the absence of a clear signal indicating an improvement in QoL; however, neither was there a decline in QoL. pERC agreed with the pCODR Methods Team that data were incomplete and the Committee was cautious regarding the potential

for selective reporting. pERC discussed the safety data from KN010 and noted meaningful improvements in toxicities with pembrolizumab compared with docetaxel. Overall, pERC concluded that there is a net overall clinical benefit with pembrolizumab in this patient population, based upon statistically significant and clinically meaningful improvements in OS, durable response, a meaningful improvement in the toxicity profile, and no apparent detriment in QoL compared with docetaxel.

pERC noted that KN010 was restricted to patients with ECOG PS 0 to 1 and specifically excluded patients with ECOG PS ≥ 2. pERC discussed the fact that many patients seen in clinical practice generally have a poorer performance status than patients included in KN010, due to advanced age (if with comorbidities) and stage of disease, and that such patients would have a reduced ability to tolerate conventional chemotherapy regimens. pERC noted the Clinical Guidance Panel (CGP)'s justification (i.e., real-world experience) for using clinical judgment when offering pembrolizumab to patients with an ECOG PS of 2. The Committee agreed that patients with a good performance status, beyond ECOG PS 1, who can tolerate this treatment, may derive benefit.

Upon reconsideration, pERC discussed the registered clinicians' feedback requesting an amendment to allow retreatment with pembrolizumab in the trial protocol; that is, patients could receive up to 12 months of pembrolizumab if they experienced an investigator-determined confirmed radiographic disease progression, according to immune-related response criteria after stopping their initial treatment with pembrolizumab due to achievement of a confirmed complete response or having experienced 35 administrations of pembrolizumab. pERC noted the CGP's response to the feedback that it would be reasonable to re-treat (for up to 12 months) patients who progressed after pembrolizumab was stopped, either due to a complete response or after two years, as per trial protocol. The Committee agreed with the CGP that it would be reasonable to re-treat patients (for up to 12 months) as per trial protocol and felt that the number of patients who would qualify for re-treatment after 35 administrations of pembrolizumab would be low. The Committee also agreed that it would be desirable for jurisdictions to collect data to determine the appropriate approach for determining the criteria for re-treatment and that a national approach to criteria for re-treatment would be of value.

pERC deliberated upon input from patient advocacy groups concerning pembrolizumab and noted that tolerable treatment side effects, control of symptoms, and control of disease progression were most important to patients. The Committee recognized the emotional burden from the stigma associated with smoking that patients with lung cancer and their caregivers face and noted that patients with lung cancer are often emotionally burdened with the stigma associated with smoking as the leading cause of their cancer. The patient advocacy group input included patients who had experience with pembrolizumab who reported improved symptom burden, better QoL, ability to return to normal activities, and fewer side effects with pembrolizumab. The results of KN010 demonstrated statistically significant and clinically meaningful improvements in OS, a meaningful improvement in toxicity profile, and no difference in QoL compared with docetaxel. pERC noted the difference in QoL described in the patient advocacy group input compared with the QoL data from the KN010 trial. The Committee discussed that although no deterioration in QoL was demonstrated in the trial, patients treated with pembrolizumab were responding and living longer than patients treated with docetaxel. Thus, the Committee felt that the QoL was sustained over a longer period of time, given the longer survival benefit compared with docetaxel. The Committee also agreed that pembrolizumab was well tolerated and led to fewer side effects and shorter infusion times compared with docetaxel. Therefore, pERC considered pembrolizumab to align with patient values.

In its feedback on the Initial Recommendation, the patient advocacy group clarified the total number of patients with experience with pembrolizumab in its submission. pERC acknowledged this clarification and confirmed that it did not have an impact on pERC's conclusion that pembrolizumab aligned with patient values.

pERC deliberated upon the cost-effectiveness of pembrolizumab and concluded that, at the submitted price, it is not cost-effective. pERC considered estimates provided by the submitter and reanalysis estimates provided by the pCODR Economic Guidance Panel (EGP) and noted uncertainty regarding the approach to evaluate utilities; extrapolation for OS and progression-free survival (PFS) over a 10-year time horizon; and uncertainty regarding the magnitude of benefit in the post-progression period. pERC

noted that the factors that most influence incremental cost included duration of benefit for OS beyond the trial data, histology (squamous only), and the percentage of patients requiring a PD-L1 test re-biopsy. The factors that most influenced the incremental effectiveness were time horizon, duration of OS benefit beyond the trial data, and histology (squamous only). pERC noted that the cost of PD-L1 testing was not considered in the docetaxel group and debated the merits of including its cost in the model. Although the Committee concluded that it would have little impact on the incremental cost-effectiveness ratio (ICER), the cost of the test would have a large budget impact. pERC noted that the cost of docetaxel used in the model was significantly higher than the true cost of docetaxel. The Committee noted that the reanalysis done by the EGP demonstrated that the cost of docetaxel was a small factor in the overall costs calculated in the docetaxel arm, but agreed that the reduced cost used by the EGP was still high compared with its true value. Nonetheless, pERC acknowledged that the higher cost of docetaxel had little impact on the ICER compared with the factors that most influence cost and effect. Moreover, the Committee agreed with the EGP that the inclusion of only one subsequent treatment in the economic model was not reflective of the trial, nor clinical practice, and noted that the EGP was unable to model additional subsequent lines of therapy. Overall, pERC concluded that the true ICER is likely near the upper end of the EGP's reanalysis estimate, and could possibly be even higher, given that the model did not account for more than one line of subsequent therapy. Upon reconsideration, pERC discussed the submitter's feedback related to the EGP's reanalysis estimates and reiterated that if one believes that the duration of benefit for OS does not extend beyond the trial period, then the ICER is likely toward the upper range of the EGP's estimates (i.e., $254,945 per quality-adjusted life-year [QALY]). pERC also acknowledged the CGP's confirmation that less than 10% of patients would receive more than one line of subsequent therapy. Notwithstanding, the Committee maintained that the true ICER is likely near the upper end of the EGP's reanalysis estimates.

In addition, upon reconsideration, pERC discussed pCODR's Provincial Advisory Group's (PAG's) request to note the differences in the ICERs for patients with a TPS ≥ 1% compared with ≥ 50%. pERC noted that the EGP felt that it was unwarranted to include a TPS ≥ 50% subgroup as part of the EGP's reanalysis for the best-case estimate as the funding request was for patients with TPS ≥ 1%. pERC also noted that the EGP conducted a scenario analysis using TPS ≥ 50% as opposed to TPS ≥ 1%; the magnitude of difference in the overall ICER was minimal (difference of $185/QALY). pERC agreed with the EGP that, while there are increased clinical benefits in this subgroup of patients, there are also increased costs, as treatment continues until disease progression, which resulted in a minimal difference in the incremental cost-effectiveness ratio for patients with TPS ≥ 50% compared with patients with TPS ≥ 1%.

pERC also considered factors affecting the feasibility of implementing a positive funding recommendation for pembrolizumab for previously treated, PD-L1 TPS ≥ 1%, advanced NSCLC patients. pERC noted that the number of prevalent and new cases of advanced or metastatic NSCLC in patients who have progressed on or after cytotoxic chemotherapy may be large. Therefore, pERC considered that the budget impact of pembrolizumab could be substantial and that provinces may want to take steps to limit the budget impact. pERC noted that the submitter's budget impact analysis is sensitive to the 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. pERC also noted that jurisdictions will need to consider the uncertainty in these factors during implementation. The Committee considered that enablers of reimbursement of pembrolizumab include a decline in the administrative cost due to the reduced chemotherapy chair time associated with the shorter infusion time and less frequent dosing of pembrolizumab versus nivolumab; pERC reiterated these enablers upon reconsideration. However, pERC noted that the potential for drug wastage and impact on pharmacy resources (given the short stability of the final product, single-use vials requiring reconstitution, and weight-based dosing), together with the high cost of pembrolizumab, would have a substantial impact on the cost-effectiveness and affordability of pembrolizumab, and that jurisdictions may need to consider alternative pricing arrangements and/or cost structures to improve the cost-effectiveness and affordability to an acceptable level.

The Committee noted the input from the PAG requesting information and clarity on the appropriate dose and benefit of pembrolizumab in all subgroup analyses. pERC discussed the higher dose of pembrolizumab (10 mg/kg) and pERC agreed with the CGP that the 2 mg/kg dose of pembrolizumab was most

appropriate. Upon reconsideration, the Committee discussed PAG's feedback regarding the availability of a fixed dose of pembrolizumab at 200 mg instead of a 2 mg/kg weight-based dose in the future. However, pERC recognized that the fixed dose of pembrolizumab was not included as part of the submission, therefore, it was not discussed by the Committee.

pERC also discussed the subgroup analyses results, particularly the uncertainty of benefit in EGFR mutation–positive patients. pERC agreed that due to the absence of a powered subgroup analysis in the study design, conclusions and funding recommendations excluding this subgroup or other pre-specified or post-hoc subgroups (e.g., histology) could not be made. pERC was cautious regarding the type I and II errors associated with unpowered subgroup analysis results.

pERC noted that there is no direct evidence to inform the comparative efficacy of pembrolizumab with other PD-1 inhibitors. Thus, with their overlapping indications, there is no evidence to inform the choice of pembrolizumab over nivolumab, or vice versa. Additionally, pERC noted that there is also no evidence to support using PD-1 inhibitors in sequence (e.g., pembrolizumab then nivolumab, or vice versa). However, pERC recognized that provinces would need to address this issue upon implementation of pembrolizumab funding, and noted that collaboration among provinces to develop a common approach would be of value.

KN010 included only patients with TPS ≥ 1%, and specifically excluded patients with TPS < 1%. The Committee agreed that there is a lack of comparative evidence to support the efficacy or harm of pembrolizumab compared with docetaxel or nivolumab in patients with a TPS < 1%. pERC recognized the uncertainty that exists concerning the specificity and sensitivity and the lack of a gold standard in PD-L1 testing, and until such a reference standard becomes available, pERC agreed that PD-L1 testing should be conducted with a validated test authorized by Health Canada, or one that is equivalent to that used in KN010. The Committee noted that it would be desirable for jurisdictions to have validated, reliable, and available PD-L1 testing across Canada in order to manage the prevalent patient population and the budget impact of a funding recommendation, which may require evidence generation from jurisdictions. pERC also stated that it would be appropriate for jurisdictions to reassess the duration of treatment once evidence is available on the optimal duration of treatment. Upon reconsideration, pERC discussed feedback from registered clinicians that indicated a need to reassess the recommendation when data become available regarding the duration of treatment. pERC discussed different potential mechanisms for the reassessment of the recommendations. The Committee agreed that jurisdictions should reassess the duration of treatment once new evidence becomes available on the optimal duration of treatment.

pERC also recognized that provinces would need to have a common approach to defining true disease progression and ensure that patients who experience pseudoprogression may continue treatment with pembrolizumab until true disease progression occurs, as defined in KN010 (progression demonstrated through a confirmatory scan conducted four to six weeks after initial progression). Lastly, pERC acknowledged a time-limited need for pembrolizumab in patients who are currently receiving treatment with single-agent cytotoxic chemotherapy, or who have recently completed treatment with single-agent cytotoxic chemotherapy. This time-limited need would be for patients who would otherwise meet the eligibility criteria of KN010.

EVIDENCE IN BRIEF

The pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the submitter's economic model and budget impact analysis
- Guidance from pCODR clinical and economic review panels
- Input from three patient advocacy groups: Lung Cancer Canada (LCC), and in a joint submission British Columbia Lung Association and Ontario Lung Association
- Two input submissions from registered clinicians: one from an individual oncologist and one joint submission
- Input from pCODR's Provincial Advisory Group (PAG)

Feedback on the pERC Initial Recommendation was also provided by:

- PAG
- One patient advocacy group (LCC)
- Registered clinicians
- The submitter (Merck Canada Inc.)

The pERC Initial Recommendation was to fund pembrolizumab (Keytruda) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of patients with metastatic non–small cell lung cancer (NSCLC) whose tumours express PD-L1 (as determined by a validated test) and who have disease progression on or after platinum-containing chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations should have disease progression on authorized therapy for these aberrations and platinum-doublet chemotherapy prior to receiving pembrolizumab. Funding should be for patients with a Tumour Proportion Score (TPS) of PD-L1 ≥ 1% and who have good performance status. Treatment should continue until confirmed disease progression, unacceptable toxicity, or to a maximum of two years, whichever comes first.

Feedback on the pERC Initial Recommendation indicated that the submitter, patient advocacy group, registered clinicians, and PAG agreed in part with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of pembrolizumab compared with standard therapy in previously treated patients with advanced or metastatic NSCLC whose tumours express PD-L1 and who have progressed on or after platinum-doublet chemotherapy and an appropriate tyrosine kinase inhibitor (TKI) for patients with EGFR mutations or ALK rearrangements.

Studies included: One open-label, phase 2/3 randomized controlled trial

The pCODR systematic review included KEYNOTE-010 (KN010), an open-label, randomized phase 2/3 trial comparing two doses of pembrolizumab to docetaxel in previously treated, PD-L1 TPS ≥ 1%, advanced NSCLC patients who have progressed on or after platinum-based doublet chemotherapy.

Key inclusion criteria were as follows: Age at least 18 years; with progression as per Response Evaluation Criteria in Solid Tumours (RECIST) (version 1.1) after two or more cycles of platinum-doublet chemotherapy, as well as an appropriate TKI for those with an EGFR-sensitizing mutation or ALK gene rearrangement; measurable disease as per investigator-assessed RECIST; an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1; provision of a tumour sample; and PD-L1 expression on at

least 1% of tumour cells. pERC noted the following key exclusion criteria: previous treatment with PD-1 checkpoint inhibitors or docetaxel; known active brain metastases or carcinomatous meningitis; active autoimmune disease requiring systemic steroids; and interstitial lung disease or history of pneumonitis requiring systemic steroids.

Four primary end points were assessed at two doses (2 mg/kg and 10 mg/kg). The primary end points were overall survival (OS) and progression-free survival (PFS) both in the total population (PD-L1 TPS ≥ 1%) and in patients with PD-L1 expression on at least 50% of tumour cells. A threshold for significance of $P < 0.00825$ (one-way) for the OS analysis and a threshold of $P < 0.001$ for the PFS analysis were used to compare pembrolizumab 2 mg/kg to docetaxel and pembrolizumab 10 mg/kg to docetaxel. Secondary end points were safety, response rate, and duration of response. Exploratory end points included patient-reported outcomes (using the European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [QLQ]-C30, the QLQ-Lung Cancer Module [LC-13], and the EuroQoL 5-Dimensions questionnaire [EQ-5D]).

The pCODR review also provided contextual information on PD-L1 testing and data on non-comparative trials including previously treated, PD-L1 TPS < 1%, advanced NSCLC patients. pERC noted the uncertainty that exists concerning the specificity and sensitivity and the lack of a gold standard in PD-L1 testing. The Committee acknowledged the OS benefit of nivolumab in patients with squamous NSCLC and uncertainty of benefit in the non-squamous subgroup. pERC agreed that there is a lack of direct comparative evidence to support the efficacy or harm of pembrolizumab compared with docetaxel or nivolumab in patients with a TPS < 1%.

Patient populations: Previously treated, PD-L1 TPS ≥ 1%, advanced NSCLC patients

Patients (n = 1,034) were randomly assigned (1:1:1) and stratified by PD-L1 tumour expression (≥ 1%, ≥ 50%), ECOG PS (0, 1), and geographic site (East Asia, non–East Asia) to receive pembrolizumab 2 mg/kg over 30 minutes, pembrolizumab 10 mg/kg over 30 minutes, or docetaxel 75 mg/m² over one hour every three weeks. Treatment continued for 24 months or until disease progression, intolerable side effects, withdrawal from study, or death. Crossover was not permitted.

pERC noted the mechanism of action of immunotherapies and the possibility that some patients may experience pseudoprogression — whereby some patients technically meet RECIST criteria for disease progression, but do not have true disease progression — and, therefore, may be treated beyond RECIST-defined disease progression and continue to receive treatment until true disease progression. pERC noted that there is no consistently accepted definition for pseudoprogression in the clinical community. Until such a definition becomes available, pERC agreed that it is reasonable to use the definition in KN010 (progression demonstrated through a confirmatory scan conducted four to six weeks after initial progression). The Committee noted that jurisdictions may want to reach agreement on the appropriate interval (for confirmatory scans) that is consistent for PD-1 inhibitor use.

The median age of patients was approximately 63 years. Most patients were Caucasian (72%) and former or current smokers (80%); had non-squamous histology (70%) and an ECOG PS of 1 (66%); and had received one line of previous systemic treatment (69%). PD-L1 testing was performed on archived tumour samples in 455 patients (44%) and new tumour samples in 578 patients (56%). The Committee also noted that 57% of patients had TPS 1 to 49% and 43% had TPS ≥ 50%.

pERC noted that after discontinuation of study treatment, 41% of patients received subsequent anticancer therapy. These patients could have received more than one type of subsequent therapy.

Key efficacy results: Clinically meaningful improvement in overall survival and durable response

The key efficacy outcome deliberated on by pERC included OS and PFS (co-primary outcomes), response (secondary outcome), and QoL (exploratory outcome) of the trial.

Among patients with TPS ≥ 1%, the median OS for the 2 mg/kg pembrolizumab, 10 mg/kg pembrolizumab, and docetaxel groups was 10.4 months, 12.7 months, and 8.5 months, respectively (hazard ratio [HR] for 2 mg/kg pembrolizumab versus docetaxel = 0.71; 95% confidence interval [CI], 0.58 to 0.88; *P* = 0.0008; HR for 10 mg/kg pembrolizumab versus docetaxel = 0.61; 95% CI, 0.49 to 0.75; *P* < 0.0001). Compared with docetaxel, the survival benefit associated with pembrolizumab was 1.9 months at a dose of 2 mg/kg and 4.2 months at a dose of 10 mg/kg. Among the TPS ≥ 50% patient subgroup, the median OS for the 2 mg/kg pembrolizumab, 10 mg/kg pembrolizumab, and docetaxel groups were 14.9 months, 17.3 months, and 8.2 months, respectively (HR for 2 mg/kg pembrolizumab versus docetaxel = 0.54; 95% CI, 0.38 to 0.77; *P* = 0.0002; HR for 10 mg/kg pembrolizumab versus docetaxel = 0.50; 95% CI, 0.36 to 0.70; *P* < 0.0001). Compared with docetaxel, the survival benefit associated with pembrolizumab was approximately 6.7 months at a dose of 2 mg/kg and 9.1 months at a dose of 10 mg/kg. In terms of pre-specified or post-hoc subgroup analysis, the difference between treatment groups did not reach statistical significance in the following subgroups: Those with squamous cell histology, mutant EGFR status, age ≥ 70 years, and an ECOG status of 0. The subgroups analysis was pre-specified for ECOG PS, EGFR status, and age of tumour sample. For tumour histology, it was a post-hoc exploratory subgroup analysis. However, pERC agreed that because of the absence of a powered subgroup analysis in the study design, conclusions and funding recommendations excluding this subgroup or other pre-specified or post-hoc subgroups (e.g., histology) could not be made. pERC noted that the results of the subgroup analyses should be interpreted with caution because of the risk of type I and II errors.

The Committee agreed that overall, compared with docetaxel, pembrolizumab significantly prolonged OS, regardless of dose, among all patients (TPS ≥ 1%) but the magnitude of benefit was greater in the TPS ≥ 50% patient subgroup. pERC discussed the higher dose of pembrolizumab and pERC agreed with the Clinical Guidance Panel (CGP) that the 2 mg/kg dose of pembrolizumab was most appropriate.

The response rate was higher in both pembrolizumab treatment groups compared with docetaxel for all patients (18% in both pembrolizumab groups, versus 9%) and the TPS ≥ 50% patient subgroup (30% versus 29% versus 8%). The Committee noted that all observed responses were partial response. The duration of responses was longer with pembrolizumab, regardless of dose compared with docetaxel. The median duration of response was not reached for either pembrolizumab treatment group and was six months and eight months in the docetaxel group for all patients and the TPS ≥ 50% patient subgroup, respectively. pERC agreed that pembrolizumab offered a durable response compared with docetaxel.

pERC noted that among all patients (TPS ≥ 1%), no statistically significant difference in PFS was found; however, for patients with PD-L1 expression on ≥ 50% of tumour cells, a statistically significant difference in PFS, in favour of pembrolizumab, was found. The Committee also noted the CGP's justification (i.e., real-world experience) for using clinical judgment when offering pembrolizumab to patients with an ECOG PS of 2.

Quality of life: No difference between groups and no detriment in quality of life

Patient-reported quality of life (QoL) was assessed using the EORTC QLQ-C30, the QLQ-LC-13, and the EQ-5D. For the QLQ-C30, a mean change from baseline of 10% or greater was considered the minimal clinically important difference (MCID), with lower scores indicative of improvement in symptoms and side effects. For the EQ-5D, possible scores range from –0.594 to 1.0, with a change in score of ≥ 0.06 deemed the MCID.

In all patients (TPS ≥ 1%) at week 12, differences in the mean change from baseline on the EORTC QLQ-C30 showed numerical improvements (i.e., less deterioration) of the Global Health Status score in patients treated with either dose of pembrolizumab compared with docetaxel, although these differences did not reach the MCID of > 10%. Among patients in the TPS ≥ 50% subgroup, the difference in mean change did reach statistical significance in the 2 mg/kg pembrolizumab group. For the majority of lung cancer symptoms, patients treated with pembrolizumab showed numerical improvements from baseline, while patients treated with docetaxel showed numerical worsening from baseline. Specifically, in all

patients (TPS ≥ 1%) at week 12, alopecia, peripheral neuropathy, and sore mouth were statistically significantly improved with pembrolizumab 2 mg/kg versus docetaxel. In the TPS ≥ 50% patient subgroup, dyspnea, hemoptysis, alopecia, and sore mouth were statistically significantly improved with pembrolizumab 2 mg/kg versus docetaxel.

Considering all treatment groups, EQ-5D scores generally increased over time, with similar scores observed among the treatment groups at weeks 3 and 6, and lower scores observed in the docetaxel group at weeks 12, 24, and 36. At most assessment periods, the mean differences in index scores between pembrolizumab groups versus docetaxel were small (< 0.04), except at week 36, when at both doses the difference exceeded the MCID of 0.06 (difference versus docetaxel for both doses = 0.18, *P* = 0.01). The Committee noted, however, that the number of patients in the analysis at week 36 included only 14% of trial patients, which limited interpretation of the findings.

pERC noted the absence of a clear signal indicating an improvement in QoL; however, neither was there a decline in QoL, and therefore, the Committee concluded that there is no detriment in QoL compared with docetaxel. pERC agreed with the pCODR Methods Team that data were incomplete and was cautious over the potential risk of selective reporting.

Safety: Meaningful improvement in toxicities

pERC discussed the toxicity profile of pembrolizumab as observed in KN010. Compared with docetaxel, pembrolizumab was associated with fewer treatment-related adverse events (TRAEs) of any grade (63% to 66% versus 81%), grade 3 to 5 TRAEs (13% to 16% versus 35%), and withdrawals due to TRAEs (4% to 5% versus 10%). Deaths attributed to study treatment occurred in < 1% of patients treated with pembrolizumab (2 mg/kg or 10 mg/kg) and in 2% of patients treated with docetaxel.

A higher percentage of patients receiving docetaxel required dose modifications due to TRAEs: 42% versus 29% and 30% in the 2 mg/kg and 10 mg/kg pembrolizumab treatment groups, respectively. Treatment discontinuations due to TRAEs were also higher among patients treated with docetaxel: 10% versus 4% and 5% of patients in the 2 mg/kg and 10 mg/kg groups, respectively. Treatment interruptions were similar among the treatment groups (22% and 24% in the 2 mg/kg and 10 mg/kg pembrolizumab groups, respectively, versus 24% in the docetaxel group).

Immune-related events of special interest occurred in 20% of patients receiving pembrolizumab at a dose of 2 mg/kg, and 19% of patients at a dose of 10 mg/kg. The most frequent type of events, any grade (2 mg/kg, 10 mg/kg dose), included hypothyroidism (8% at both doses), pneumonitis (5%, 4%), and hyperthyroidism (4%, 6%). Of these events, only pneumonitis and severe skin reactions occurred at a severity of grade 3 or higher in greater than 1% of patients.

Overall, pERC agreed that pembrolizumab demonstrated meaningful improvement in toxicities compared with docetaxel.

Limitations: Open-label design, selective reporting on QoL data, underpowered subgroup analyses, OS confounded by subsequent therapy, no comparative data to inform TPS < 1%.

The trial was open label, which can introduce bias and threaten the internal validity of the trial. pERC recognized, however, that the potential for bias was minimized given the independent central review of key efficacy outcomes, the blinding of parties to the PD-L1 status of patients, and the use of blinded data-analysts. The OS results of the trial (co-primary end point) are likely confounded by subsequent anticancer therapy, as 41% of patients received such therapy after discontinuing study treatment. KN010 included patients with PD-L1 TPS ≥ 1%, and specifically excluded patients with TPS < 1%. The Committee agreed there is a lack of comparative evidence to support the efficacy or harm of pembrolizumab compared with docetaxel or nivolumab in patients with a TPS < 1%. QoL data were assessed in the KN010 trial but have not been published in the public domain and undergone peer review. The Committee recognized that the QoL data reviewed for the pCODR submission is incomplete, and was cautious about

the potential risk of selective reporting. As well, the open-label design of KN010 may have introduced bias to the patient-reported QoL outcomes.

Need: Treatment with reduced toxicity, improved quality of life and survival

Lung cancer is the most common type of cancer in Canada. In 2015, an estimated 26,600 new cases and 20,900 deaths occurred in Canada from lung cancer, with a five-year survival rate of < 5%. NSCLC accounts for 85% of all lung cancers. In patients without a driver mutation and who have received cytotoxic chemotherapy in the first-line setting, second-line treatment includes single-agent chemotherapy with docetaxel or pemetrexed. This is based on modest improvements in survival and QoL. For those who received driver mutation–specific therapy in the first line, second-line treatment consists of platinum-doublet and third-line therapy is generally single-agent chemotherapy, for those who maintain a good performance status.

pERC noted that the goals of treatment for patients with advanced-stage NSCLC are primarily palliative; namely, to prolong life while maintaining or improving QoL. Given that most patients are of advanced age and have an advanced stage of disease, pERC noted that a disproportionately greater number of patients at this stage of disease have a poor performance status, as well as a higher likelihood of significant comorbidities that affect their ability to tolerate conventional chemotherapy regimens. Given the toxicity associated with available single-agent chemotherapy in patients who progressed on or after a platinum-based doublet, pERC agreed that there is a need for alternative options that reduce toxicity and prolong survival.

Registered clinician input: Effective, better tolerated, shorter infusion, less frequent dose, but concerned over PD-L1 testing turnaround time

pERC agreed with the clinician input: Pembrolizumab is more effective and better tolerated than chemotherapy, and pembrolizumab would provide another immunotherapy treatment option, with a shorter infusion time and less frequent dosing schedule than nivolumab. The registered clinicians identified that testing for PD-L1 expression is important but that the turnaround time for test results would delay initiation of treatment. pERC acknowledged this concern and noted that it would be desirable for jurisdictions to have validated, reliable, and available PD-L1 testing across Canada to manage the prevalent patient population and the budget impact of a funding recommendation.

In their feedback, registered clinicians noted that in a Second Course Phase of the KN010 trial, patients could receive up to 12 months of pembrolizumab if they experienced an investigator-determined confirmed radiographic disease progression, according to immune-related response criteria after stopping their initial treatment with pembrolizumab due to achievement of a confirmed complete response or having experienced 35 administrations of pembrolizumab. According to the KN010 trial protocol, patients could receive up to 12 months of pembrolizumab in the Second Course Phase of the KN010 trial, if they:

- stopped their initial treatment with pembrolizumab after attaining an investigator determined confirmed complete response (CR) according to immune-related response criteria (irRC), was treated for at least six months with pembrolizumab, and received at least two treatments with pembrolizumab beyond the date when the initial CR was declared. A CR by irRC means that all index lesions have resolved (none have bidimensional measurements), all non-index lesions have disappeared, and no new lesions have been identified. These findings must be confirmed on subsequent imaging at least 4 weeks later for the call of CR by irRC to be appropriate. So the patient will have no evidence of metastatic cancer in order for the subject and his/her physician to consider the subject's participation in this Second Course Phase.
- experienced an investigator-determined confirmed radiographic disease progression according to irRC after stopping their initial treatment with pembrolizumab due to achievement of a confirmed CR or have experienced 35 administrations of pembrolizumab
- did not receive any anti-cancer treatment since the last dose of pembrolizumab.
- continues to meet KN010 inclusion criteria 3, 6, 7, 11, 12 and 13.
- does not meet KN010 exclusion criteria 3, 4, 9 to 18 and/or 20.

The Committee agreed with the CGP that it would be reasonable to re-treat patients (for up to 12 months) as per trial protocol and felt that the number of patients who would qualify for re-treatment after 35 administrations of pembrolizumab would be low. The Committee also agreed that it would be desirable for jurisdictions to collect data to determine the appropriate approach for determining the criteria for re-treatment and that a national approach to criteria for re-treatment would be of value.

PATIENT-BASED VALUES

Values of patients with non-small cell lung cancer: Control of symptoms, treatment-related toxicity, and disease progression

pERC deliberated upon patient advocacy group input for pembrolizumab for NSCLC and discussed the values of patients with NSCLC. Lung cancer affects many aspects of day-to-day life for people living with NSCLC. The Committee noted that NSCLC has an impact on the respondents' ability to work, travel, socialize, and participate in leisure and physical activities. It also affects their relationships with family and friends and emotional well-being, and may cause financial hardship. Both patient and caregiver respondents reported that the high symptom burden of lung cancer is difficult to manage. These symptoms include fatigue (100%), loss of appetite (97%), shortness of breath (95%), cough (93%), and pain (92%). Other symptoms include anxiety, depression, and dependence on others. For the vast majority of this patient population, the current standard of care is chemotherapy or radiation.

pERC noted that the control of symptoms, the control of disease progression, and reduced treatment-related toxicity would be valued. pERC also noted that patients with lung cancer are often burdened with the stigma associated with smoking as the leading cause of their cancer.

The Committee also discussed patients' comments that stable disease may be an important outcome of treatment and they expressed a need for more education to help patients and families understand this.

Patient values on treatment: Improved efficacy, safety, and quality of life with new therapy

Chemotherapy is viewed as a necessary, but feared, treatment. According to patients, the burden of chemotherapy was felt during all stages of treatment and extended beyond the treatment. Caregivers are also affected by the side effects of chemotherapy. pERC noted that the key concerns of patients with current treatment are acute side effects of chemotherapy, recovery time after each infusion, susceptibility to infection, and lasting effects of chemotherapy. Patients would also like their treatment to provide improved independence and they desire fewer medical appointments and less financial cost burden.

In its feedback, LCC clarified that phone interviews were conducted with four patients and one caregiver who had experience with pembrolizumab. However, the environmental scans of online blogs and forums included only feedback from those who have had experience with pembrolizumab; from this source, the comments from 13 patient and nine caregiver respondents, all of whom had experience with pembrolizumab, were included. Therefore, in total, 17 patients and 10 caregivers who have had experience with pembrolizumab were included in the LCC submission.

Patients and caregivers expected that pembrolizumab would offer reduced symptom burden, good quality of life, more tolerable and easily managed side effects, return to some normal daily activities, ability to live the remaining days of life, stable or tumour shrinkage, and shorter infusion time. Patients with experience with pembrolizumab reported relieved symptom burden; tolerable and well-managed side effects; feeling better, not worse, from treatment; and the return to some normal activities. pERC noted the difference in QoL reported by the patient advocacy group compared with the trial. The Committee discussed that although there was no deterioration in QoL demonstrated in the trial, patients treated with pembrolizumab were responding and living longer compared with patients treated with docetaxel. Thus,

the Committee felt that the QoL was sustained over a longer period of time, given the longer survival benefit compared with docetaxel. The Committee also agreed that pembrolizumab was better tolerated, with fewer side effects and a shorter infusion time compared with docetaxel. Therefore, pERC concluded that pembrolizumab aligned with patient values.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed cost-effectiveness and cost-utility analyses comparing pembrolizumab to docetaxel for patients with metastatic NSCLC whose tumours express PD-L1 via validated test and who have progressed on or after a platinum-doublet chemotherapy.

Basis of the economic model: Partitioned survival analysis, 10-year time horizon

Costs included in the model were cost of PD-L1 testing (pembrolizumab group only), cost of treatment, cost of adverse event management, resource cost for administration and disease follow-up, and one line of subsequent therapy. pERC noted that the cost estimates for pembrolizumab were based on KN010.

Key clinical effects considered in the analysis included OS, PFS, and health state utilities. pERC noted that OS data were extrapolated over 10 years in the base case and agreed with the truncation of the time horizon to five years, to better reflect survival of patients at this advanced stage of disease and given the median follow-up of KN010 was 57 weeks. pERC also noted the approach used to evaluate utilities and agreed with using the time to death approach, given that sometimes patients do not have a response in the progression-free state and if or when they do have a response, patients can have a response for a long duration. Given the high uncertainty in the survival estimates, the Committee agreed with capping the OS benefit at the trial end date. pERC noted that the EGP was unable to model additional subsequent lines of therapy and agreed with the EGP that one subsequent treatment modelled was not reflective of the trial.

pERC agreed with the CGP that either archival or fresh tumour biopsies are acceptable for PD-L1 testing. The Committee noted that the model assumed a small estimate of patients will require a fresh biopsy for the test and acknowledged the CGP's confirmation that archival samples are sufficient.

Drug costs: High cost of drug

Pembrolizumab costs $44.00 per mg. At a recommended dose of 2 mg/kg every three weeks, pembrolizumab costs $294.18 per day and $8,237 per 28-day cycle (assuming the average patient weight from KN010 and no wastage).

Brand-name docetaxel costs $11.42 per mg. At the recommended dose of 75 mg/per m^2 every three weeks, docetaxel costs $69.36 per day and $1,942.00 per 28-day cycle (assuming the average body surface area from KN010 and no wastage).

pERC noted that the cost of docetaxel used in the model was significantly higher than the true cost of docetaxel. The Committee noted that the reanalysis done by the EGP demonstrated that the cost of docetaxel was a small factor in the overall costs calculated in the docetaxel arm, but agreed that the reduced cost used by the EGP was still high compared with its true value. Nonetheless, pERC acknowledged that the higher cost of docetaxel had little impact on the incremental cost-effectiveness ratio (ICER) compared with the factors that most influence cost and effect.

Cost-effectiveness estimates: Utilities, overall survival, and time horizon

pERC discussed the submitter's and the EGP's best estimate of the ICER of pembrolizumab in patients with metastatic NSCLC whose tumours express PD-L1 via validated test and who have progressed on or after platinum-doublet chemotherapy.

pERC noted uncertainty regarding the approach to evaluate utilities; extrapolation for OS and PFS over a 10-year time horizon; and uncertainty regarding the magnitude of benefit in the post-progression period. The factors that most influence the incremental cost were duration of benefit for OS beyond the trial data, histology (squamous only), and percentage of patients requiring a PD-L1 test re-biopsy. Additional factors that influenced incremental cost included the incorporation of drug wastage, unknown median treatment duration, and cost of subsequent therapies. The factors that most influenced the incremental effectiveness were time horizon, duration of OS benefit beyond the trial data, and histology (squamous only).

pERC noted that the cost of PD-L1 testing was not considered in the docetaxel group and the cost of docetaxel used in the model was significantly higher than the true cost of docetaxel. The Committee noted that the reanalysis done by the EGP accounted for this, but agreed that the reduced cost by the EGP was still high compared with its true value. Nonetheless, pERC acknowledged that the exclusion of the cost of PD-L1 testing in the docetaxel group and the higher cost of docetaxel had little impact on the ICER compared with the other factors described above. pERC noted that only one subsequent treatment was modelled, which was not reflective of the trial.

The Committee concluded that the true ICER is likely near the upper end of the EGP's reanalysis estimate, and could possibly be even higher, given that the model did not account for more than one line of subsequent therapy. Upon reconsideration, pERC discussed the submitter's feedback related to the EGP's reanalysis estimates and reiterated that if one believes that the duration of benefit for OS does not extend beyond the trial period, then the ICER is likely toward the upper range of the EGP's estimates (i.e., $254,945 per quality-adjusted life-year [QALY]). pERC also acknowledged the CGP's confirmation that less than 10% of patients would receive more than one line of subsequent therapy. Notwithstanding, the Committee maintained that the true ICER is likely near the upper end of the EGP's reanalysis estimates.

As well, upon reconsideration, pERC discussed PAG's request to note the differences in the ICERs for patients with a TPS ≥ 1% compared with ≥ 50%. pERC noted that the EGP felt it was unwarranted to include a TPS ≥ 50% subgroup as part of the EGP's reanalysis for the best-case estimate as the funding request was for patients with TPS ≥ 1%. pERC also noted that a scenario analysis was conducted by the EGP using TPS ≥ 50% as opposed to TPS ≥ 1%; the magnitude of difference in the overall ICER was minimal (difference of $185/QALY). pERC agreed with the EGP that, while there are increased clinical benefits in this subgroup of patients, there are also increased costs, as treatment continues until disease progression, which resulted in a minimal difference in the incremental cost-effectiveness ratio for patients with TPS ≥ 50% compared with patients with TPS ≥ 1%.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: High drug costs, PD-L1 testing, unknown duration of treatment, and large budget impact

pERC considered the feasibility of implementing a funding recommendation for pembrolizumab. pERC acknowledged that drug wastage is an important concern for PAG and noted that although vial sharing was assumed to not occur in the model, the number of vials used in the base-case analysis was based on the average number of vials based on the distribution of patient weight. pERC also recognized the impact on pharmacy resources, given the short stability of the final product, single-use vials requiring reconstitution, and weight-based dosing, but also considered the decline in administrative cost, given the reduced chair time associated with shorter infusion time and less frequent dosing with pembrolizumab.

Overall, due to the large new and prevalent population of patients with advanced or metastatic NSCLC, the high cost of pembrolizumab, and the unknown but potentially long duration of treatment, pERC concluded that a substantial reduction in drug price would be required to improve cost-effectiveness and

affordability to an acceptable level. pERC noted that the submitted budget impact analysis was sensitive to the 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. pERC noted that jurisdictions will need to consider the uncertainty in these factors during implementation.

pERC noted the CGP's statement that patients can be treated beyond initial evidence of progression, given the possibility of pseudoprogression (whereby some patients technically meet RECIST criteria for disease progression but do not have true disease progression) on immunotherapy, although this phenomenon appears less common in lung cancer (approximately 5%) than in other diseases such as melanoma. pERC recognized that provinces would need to have a common approach to define true disease progression and ensure that patients who experience pseudoprogression may continue treatment with pembrolizumab until true disease progression is confirmed. The Committee agreed that until such a definition becomes available, it is reasonable to use the criteria from within the KN010 study: Patients who progressed according to investigator-assessed immune-related response criteria could remain on treatment until a confirmatory scan was done four to six weeks later. pERC noted that jurisdictions may want to reach agreement on the appropriate interval (for confirmatory scans) that is consistent for PD-1 inhibitor use.

pERC considered the contextual information on PD-L1 testing and noted the uncertainty that exists regarding the specificity and sensitivity and lack of gold standard in PD-L1 testing. Until such a reference standard becomes available, pERC agreed that PD-L1 testing using a validated test authorized by Health Canada, or one that is equivalent to that used in KN010, is reasonable. The Committee noted that it would be desirable for jurisdictions to have validated, reliable, and available PD-L1 testing across Canada to manage the prevalent patient population and the budget impact of a funding recommendation, which may require evidence generation from jurisdictions.

The Committee also considered the data on non-comparative trials including previously treated, PD-L1 TPS < 1%, advanced NSCLC patients and acknowledged the OS benefit of nivolumab in patients with squamous NSCLC and uncertainty of benefit in the non-squamous subgroup, but agreed that there is a lack of direct comparative evidence to support the efficacy or harm of pembrolizumab (versus docetaxel or versus nivolumab) in patients with a TPS < 1%. Therefore, pERC noted that there is no direct evidence to inform the comparative efficacy of pembrolizumab with other PD-1 inhibitors and with their overlapping indications, there is no evidence to inform the choice of pembrolizumab over nivolumab, or vice versa. Additionally, pERC noted that there is also no evidence to support using PD-1 inhibitors in sequence (e.g., pembrolizumab then nivolumab, or vice versa). However, pERC recognized that provinces would need to address this issue upon implementation of pembrolizumab funding, and noted that collaboration among provinces to develop a common approach would be of value.

pERC also acknowledged a time-limited need for pembrolizumab in patients who are currently receiving treatment with single-agent cytotoxic chemotherapy, or who have recently completed treatment with single-agent cytotoxic chemotherapy, and who would otherwise meet the eligibility criteria of KN010.

DRUG AND CONDITION INFORMATION

Drug Information	• Immunotherapy anti-PD-L1 • 50 mg lyophilized single-use vial • Recommended dosage of 2 mg/kg administered intravenously over 30 minutes every three weeks
Cancer Treated	• Metastatic non-small cell lung carcinoma
Burden of Illness	• Large prevalent and new population • Patients generally have advanced age, advanced stage of disease, poor performance status, and a higher likelihood of significant comorbidities
Current Standard Treatment	• Docetaxel • Pemetrexed
Limitations of Current Therapy	• Modest improvements in survival with current therapies • Poor performance status of patients makes it difficult for many patients to tolerate toxicities of chemotherapy

ABOUT THIS RECOMMENDATION

pERC Membership During Deliberation of the Initial Recommendation

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy Thompson, Pharmacist
Valerie McDonald, Patient Member Alternate
Carole McMahon, Patient Member
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Danica Wasney, Pharmacist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Kelvin Chan and Matthew Cheung, who were not present for the meeting
- Anil Abraham Joy, who was excluded from deliberations and voting due to a conflict of interest
- Jo Nanson, who was the designated non-voting patient member alternate for this meeting.

pERC Membership During Deliberation of the Final Recommendation

Recommendations are made by pERC following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Paul Hoskins, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Carole McMahon, Patient Member
Valerie McDonald, Patient Member Alternate
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Dr. Marianne Taylor, Oncologist
Karen MacCurdy Thompson, Pharmacist
Danica Wasney, Pharmacist

All members participated in deliberations and voting on the Final Recommendation except:

- Allan Grill, who was not present for the meeting
- Anil Abraham Joy, who was excluded from deliberations and voting due to a conflict of interest
- Valerie McDonald, who did not vote due to her role as a patient member alternate.

Avoidance of conflicts of interest

All members of pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of pembrolizumab NSCLC, through their declarations, six members had a real, potential or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this Recommendation document.

Use of this Recommendation

This Recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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