pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH 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
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Pembrolizumab (Keytruda) **Submitted Funding Request:** For previously untreated patients with metastatic NSCLC whose tumours express PD-L1 and who do not harbor a sensitizing EGFR mutation or ALK translocation. Funding is being requested for patients with a TPS (Tumour Proportion Score) of PD-L1 ≥50%.	
Submitted By: Merck Canada Inc.	**Manufactured By:** Merck Canada Inc.
NOC Date: July 12, 2017	**Submission Date:** December 12, 2016
Initial Recommendation: August 3, 2017	**Final Recommendation:** August 23, 2017

Approximate per Patient Drug Costs, per Month (28 Days) Submitted list price of $2,200.00 per 50mg vial Note: Costs are calculated based on an average weight of 70kg and BSA = 1.7m^2	Pembrolizumab regimen costs: $11,733.33 per 28-day course

pERC RECOMMENDATION

pERC recommends reimbursement of pembrolizumab (Keytruda) conditional on the cost-effectiveness being substantially improved to an acceptable level. Funding should be for the treatment of locally advanced or previously untreated metastatic non-small cell lung cancer (NSCLC) in patients whose tumours express PD-L1 (Tumour Proportion Score [TPS] ≥ 50%) as determined by a validated test and who do not harbour a sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation. Patients with locally advanced disease (stage IIIB) should be eligible for funding if they are not eligible for potentially curative concurrent chemoradiotherapy. Funding should be for patients who have good performance status.

Treatment should be administered at a dose of 2 mg/kg up to a total dose amount of 200 mg (dose capped at 200 mg). Treatment should continue until confirmed disease progression or unacceptable toxicity or to a maximum of two years (35 cycles), whichever comes first.

pERC made this recommendation because it was satisfied that there is a net overall clinical benefit with pembrolizumab compared with platinum-doublet chemotherapy, based on the statistically and clinically meaningful improvements in progression-free survival, improved overall survival, durable response, meaningful reductions in the toxicity profile, and delay in deterioration in quality of life. The Committee was satisfied that pembrolizumab aligned with patient values of symptom control, control of

	disease progression, and reduced treatment-related toxicity. pERC concluded that pembrolizumab, at the submitted price and compared with platinum-doublet chemotherapy, could not be considered cost-effective in patients with previously untreated metastatic NSCLC whose tumours express PD-L1 (TPS ≥50%) and who do not harbour a sensitizing EGFR mutation or ALK translocation. pERC also highlighted that the submitted potential budget impact of pembrolizumab was underestimated and would be substantial.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given that pembrolizumab has a net overall clinical benefit, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of pembrolizumab to an acceptable level. **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 KEYNOTE-024), whichever comes first. pERC also discussed an amendment in the KEYNOTE-024 trial that allowed re-treatment with pembrolizumab in the trial protocol. In the trial patients could receive re-treatment for up to 17 cycles if patients stopped receiving pembrolizumab after receiving 35 cycles for reasons other than disease progression or intolerability, or if patients attained a complete response and stopped treatment with pembrolizumab, they may be eligible for re-treatment with pembrolizumab upon experiencing disease progression. In considering the high cost of pembrolizumab, the large incidence and prevalent population, the unknown number of patients that would receive the full 35 cycles or re-treatment, pERC concluded that a substantial reduction in drug price would be required to improve affordability. **Pembrolizumab Dosing of 2 mg/kg up to a Flat Dose of 200 mg** The Committee acknowledged that, although KEYNOTE-024 assessed pembrolizumab at a dose of 200 mg every three weeks up to 35 cycles, there is no evidence to suggest that the dosing amount of 200 mg is superior to 2 mg/kg (the dose used in initial pembrolizumab trials). For many patients, the flat dose results in a larger dose and greater cost. Therefore, pERC felt it would be reasonable that pembrolizumab be administered at 2 mg/kg up to a total dose of 200 mg (dose capped at 200 mg). **Available Vial Sizes** pERC noted the high cost and potential for drug wastage associated with pembrolizumab. The continued availability of a 50 mg vial and consideration of the development of a smaller vial would reduce implementation barriers such as drug wastage associated with pembrolizumab. **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-024 trial, is reasonable. The Committee noted that it would be desirable for jurisdictions to have validated, reliable PD-L1 testing available in Canada to identify both the relevant patient population and manage the budget impact. Evidence generation from jurisdictions would be of value in regard to actual numbers of eligible patients and the true budget impact. pERC agreed that the

results of the KEYNOTE-024 trial cannot be generalized to patients for whom tissue biopsy is not feasible or where the tissue specimen is inadequate to determine PD-L1 status; therefore, the Committee does not recommend reimbursement for patients whose PD-L1 status cannot be determined.

SUMMARY OF pERC DELIBERATIONS

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

In 2015, an estimated 26,600 new cases were diagnosed and 20,900 deaths occurred in Canada from lung cancer. The five-year survival rate for lung cancer is 15% to 18%. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers. Treatment decisions for locally advanced or metastatic NSCLC are typically dependent on the presence (or absence) and type of driver mutation in the first-line setting. In patients whose disease does not have a driver mutation, treatments in the first-line setting include platinum-doublet chemotherapy. Platinum agents (cisplatin or carboplatin) are paired with cytotoxic agents such as vinorelbine, gemcitabine, pemetrexed, paclitaxel, and docetaxel. Patients whose disease has driver mutations (e.g., epidermal growth factor receptor [EGFR] mutation or anaplastic lymphoma kinase [ALK] translocation) typically receive targeted therapy up-front, then platinum-doublet chemotherapy for second-line treatment, and then single-agent chemotherapy for third-line if they maintain a good performance status. Patients whose disease does not have driver mutations typically receive single-agent chemotherapy for second- and third-line treatment. Newer treatments in the second-line NSCLC setting, irrespective of driver mutation presence, include immunotherapy such as nivolumab and pembrolizumab. The majority of patients have disease without driver mutations. Given that the majority of patients at this stage of disease are older, typically have poorer performance status, and a higher likelihood of significant comorbidities that affect their ability to tolerate conventional chemotherapy regimens, pERC concluded there is a need for alternative treatment options that reduce toxicity, improve quality of life, and prolong survival in this patient population.

pERC deliberated on the results of one open-label, randomized phase III trial (KEYNOTE-024) that compared pembrolizumab with platinum-doublet chemotherapy in patients who had previously untreated stage IV NSCLC with PD-L1 expression (TPS ≥50%) and with no EGFR mutation or ALK translocation. pERC agreed that pembrolizumab demonstrated statistically significant and clinically meaningful improvements in progression-free survival (PFS) compared with chemotherapy. While treatment benefit was evident in the intent-to-treat population and in all patient subgroups examined, statistical significance was not reached in the following subgroups: female patients, patients who are current smokers, patients who were smokers, and patients with brain metastases at baseline. However, pERC noted that the subgroups were not powered to detect a difference in the treatment groups; therefore, conclusions and funding recommendations regarding subgroups or other pre-specified or post-hoc subgroups could not be made. The Committee noted that, even with the cross-over of patients from chemotherapy to pembrolizumab, which would confound the observed treatment effect in favour of chemotherapy, there was a statistically significant and clinically meaningful overall survival (OS) advantage observed with pembrolizumab. pERC also noted that the response rate and the duration of response were higher in the pembrolizumab group compared with the chemotherapy group. Therefore, pERC concluded that pembrolizumab offered improved PFS, OS, and response, compared with chemotherapy.

pERC discussed the quality of life (QoL) data from KEYNOTE-024 and noted the absence of a clear signal indicating an improvement in QoL; however, there was a delay in time-to-true deterioration with pembrolizumab. pERC discussed the safety data from KEYNOTE-024 and noted meaningful reductions in toxicities with pembrolizumab compared with chemotherapy. Overall, pERC concluded there is a net overall clinical benefit with pembrolizumab in this patient population, based upon statistically significant and clinically meaningful improvements in PFS, improved OS (even with cross-over), durable response, a meaningful reduction in toxicities, and a delay in time to deterioration in QoL compared with chemotherapy.

pERC noted that KEYNOTE-024 was restricted to patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1, and specifically excluded patients with an ECOG ≥ 2. pERC discussed the fact that many patients seen in clinical practice generally have poorer performance status than patients included in KEYNOTE-024, due to advanced age (if coupled with comorbidities) and stage of

disease, and that such patients would have a reduced ability to tolerate conventional chemotherapy regimens, which was the standard treatment group in KEYNOTE-024. pERC discussed the pCODR Clinical Guidance Panel's (CGP) justification for using clinical judgment when offering pembrolizumab to patients with an ECOG PS of 2. The Committee agreed with the CGP that patients with a good performance status (including those above an ECOG PS of 1), who can tolerate this treatment, may derive benefit. pERC also noted that KEYNOTE-024 was restricted to patients with a histologically or cytologically confirmed diagnosis of stage IV NSCLC. pERC discussed and agreed with the CGP that patients with locally advanced (stage IIIB) disease who are not eligible for potentially curative concurrent chemoradiotherapy may derive benefit from pembrolizumab. pERC noted there was no age restriction in KEYNOTE-024 and that pembrolizumab appears to be tolerated in older patients, and therefore concluded that pembrolizumab should not be restricted according to age.

pERC noted that the input from registered clinicians was consistent with the Committee's interpretation of the results of KEYNOTE-024 that pembrolizumab was more effective and better tolerated than chemotherapy. pERC also acknowledged that for the vast majority of this patient population, testing for EGFR mutation and ALK translocation would have already been completed, and PD-L1 testing would add only one additional test to the reflex panel. pERC also acknowledged that pembrolizumab would provide an immunotherapy treatment option in the first-line setting for locally advanced and metastatic NSCLC.

pERC deliberated on input from patient advocacy groups concerning pembrolizumab and noted that control of symptoms, control of disease progression, and reduced treatment-related toxicity were important to patients. The patient advocacy group input included patients who had experience with pembrolizumab and who reported relieved symptom burden, tolerable and well-managed side effects, less interference with day-to-day activities, and higher QoL. The results of KEYNOTE-024 demonstrated statistically significant and clinically meaningful improvements in PFS, improved OS, a meaningful improvement in the toxicity profile, and delay in deterioration in QoL compared with chemotherapy. pERC noted the difference in improved QoL reported by the patient advocacy group compared with the absence of a clear signal in the trial. The Committee discussed that, although there was no deterioration in QoL demonstrated in the trial, patients treated with pembrolizumab were experiencing disease responses and living longer compared with patients treated with chemotherapy. Thus, the Committee felt that the sustained QoL was maintained over a longer period of time, given the longer survival benefit compared with chemotherapy. The Committee also agreed that pembrolizumab was well tolerated and led to fewer side effects compared with chemotherapy. Therefore, pERC concluded that pembrolizumab aligns with patient values.

pERC deliberated on the cost-effectiveness of pembrolizumab and concluded that, at the submitted price, it was not cost-effective. pERC considered the estimates provided by the submitter and the reanalysis estimates provided by the pCODR Economic Guidance Panel (EGP) and noted uncertainty regarding the extrapolation of PFS and OS over a 10-year time horizon and the magnitude of benefit in the post-progression period. pERC noted that the factors that most influenced incremental cost included the cost of pembrolizumab, the adjustment method for crossover, and subsequent treatment with pemetrexed. The factors that most influenced the incremental effectiveness included the duration of treatment effect of pembrolizumab, the time horizon, and the adjustment method for crossover. The EGP was unable to evaluate the use of pembrolizumab at 2 mg/kg for this patient population as the base case used a flat dose of 200 mg per patient. The opinion of pERC was that although the use of a 2 mg/kg dose amount would likely not impact the effectiveness of pembrolizumab, there was still uncertainty on how it would impact cost estimates; for many patients, the use of the flat dose would results in a larger dose and greater cost. Moreover, the Committee noted that the proportion of patients who received subsequent treatments after treatment discontinuation varied between treatment groups. Overall, pERC concluded that the true incremental cost-effectiveness ratio (ICER) is likely near the upper end of the EGP's reanalysis estimate, and could possibly be even higher, given the uncertainty with respect to the long-term treatment effect of pembrolizumab and the duration of pembrolizumab and cost of pembrolizumab.

pERC also considered factors affecting the feasibility of implementing a positive funding recommendation for pembrolizumab for locally advanced or previously untreated metastatic NSCLC in patients whose tumours express PD-L1 (TPS of ≥50%) and who do not harbour a sensitizing EGFR mutation or ALK translocation. The Committee noted that, currently, some patients are not able to tolerate chemotherapy due to toxicities, and thus do not receive treatment; however, since the toxicity profile of pembrolizumab is more manageable than chemotherapy, more patients may be eligible for treatment with pembrolizumab. Therefore, the eligible population of patients for pembrolizumab may be greater than estimated in the budget impact analysis. The number of prevalent and new cases of locally advanced

or metastatic NSCLC may be large. pERC considered that the budget impact of pembrolizumab would be substantial and that provinces may want to take steps to limit the budget impact. pERC noted that the submitter's budget impact analysis was sensitive to increases in the treatment rate and treatment duration of pembrolizumab and increases in the rate of PD-L1 testing as well as in the funding of a second-line anti PD-L1 checkpoint inhibitor. pERC noted that jurisdictions will need to consider the uncertainty in these factors during implementation.

The Committee noted the input from the pCODR Provincial Advisory Group (PAG), which requested information and clarification on treatment criteria for pembrolizumab. pERC noted that in KEYNOTE-024, the maximum number of cycles of pembrolizumab that patients received was 26 cycles, but patients were permitted up to 35 cycles. pERC recognized that the actual treatment duration of pembrolizumab is unknown as no patients received the full 35 cycles and that provinces would need to address this issue upon implementation of pembrolizumab funding. pERC also discussed an amendment in the KEYNOTE-024 trial that allowed re-treatment with pembrolizumab in the trial protocol. In the trial patients could receive re-treatment for up to 17 cycles if patients stopped receiving pembrolizumab after receiving 35 cycles for reasons other than disease progression or intolerability, or if patients attained a complete response and stopped treatment with pembrolizumab, they may be eligible for re-treatment with pembrolizumab upon experiencing disease progression. pERC noted that in the trial, if pembrolizumab was withheld for toxicity, patients were able to resume pembrolizumab if appropriate and when toxicity had improved. pERC felt that these criteria for re-treatment with pembrolizumab following a progression-free time period and toxicity interruption were reasonable.

pERC also discussed that the possibility of pseudoprogression (where some patients technically meet Response Evaluation Criteria in Solid Tumors [RECIST] guideline for disease progression, but do not have true progression) for patients on immunotherapy appears less common in lung cancer (approximately 5%) than in other diseases such as melanoma. pERC also noted that the results of the KEYNOTE-024 trial cannot be generalized to patients for whom tissue biopsy is not feasible, or where the tissue specimen is inadequate to determine PD-L1 status; therefore, the Committee does not recommend reimbursement for patients whose PD-L1 status cannot be determined.

pERC considered 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 with the CGP that PD-L1 testing using a validated test authorized by Health Canada, or one that is equivalent to that used in KEYNOTE-024, 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 CGP's statement that there is no evidence to suggest superiority or inferiority of a 200 mg flat dose of pembrolizumab versus the dose of 2 mg/kg dose administered in initial pembrolizumab trials. pERC noted that the flat dose will result in greater doses and costs for some patients without evidence of improved effectiveness. pERC agreed with the CGP and felt it was reasonable that pembrolizumab be administered at a dose of 2 mg/kg up to a total dose amount of 200 mg (dose capped at 200 mg).

EVIDENCE IN BRIEF

The CADTH 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 manufacturer's economic model and budget impact analysis
- Guidance from the pCODR clinical and economic review panels
- Input from three patient advocacy groups (Lung Cancer Canada, British Columbia Lung Association and Ontario Lung Association)
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- The PAG
- The submitter [Merck Canada Inc.]

The pERC Initial Recommendation was to recommend reimbursement of pembrolizumab (Keytruda) conditional on cost-effectiveness being substantially improved to an acceptable level. Feedback on the pERC Initial Recommendation indicated that PAG and the submitter agreed with the Initial Recommendation.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of pembrolizumab (Keytruda) compared with an appropriate comparator for previously untreated patients with metastatic non-small lung cancer (NSCLC) whose tumours express PD-L1 (tumour proportion score [TPS] ≥50%) and who do not harbour a sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation.

Studies included: One randomized controlled trial

The pCODR systematic review included one randomized controlled trial, KEYNOTE-024, which evaluated the efficacy and safety of pembrolizumab compared with investigator's choice of platinum-based chemotherapy for patients who had previously untreated stage IV NSCLC with PD-L1 expression (TPS ≥50%) and without an EGFR mutation or ALK translocation. Patients were randomized in a 1:1 ratio to pembrolizumab (n = 154) or to one of five platinum-based chemotherapy regimens based on investigator's choice (n = 151).

Pembrolizumab was administered at a fixed dose of 200 mg every three weeks up to 35 cycles. The five platinum-based chemotherapy regimens used in the study were carboplatin plus pemetrexed; cisplatin plus pemetrexed; carboplatin plus gemcitabine; cisplatin plus gemcitabine; and carboplatin plus paclitaxel. pERC noted that the comparator of platinum-based chemotherapy used in the trial was applicable to the Canadian treatment landscape.

Key inclusion criteria were as follows: ≥18 years of age; measurable disease using the Response Evaluation Criteria in Solid Tumours (RECIST) (version 1.1) guideline as determined by the treating site; histologic or cytologic confirmation of stage IV NSCLC; absence of an EGFR-sensitizing (-activating) mutation or ALK translocation; no prior systemic chemotherapy for metastatic NSCLC; an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1; tumour strongly expressing PD-L1 defined as PD-L1 expression on at least 50% of tumour cells, referred to as a TPS of ≥50%, as measured by central laboratory. pERC noted the following key exclusion criteria: patient has an EGFR-sensitizing mutation or ALK translocation; patient received systemic therapy for the treatment of their stage IV NSCLC; patient had previously been treated with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti-CD137, or anti–CTLA-4

antibody; or patient had untreated central nervous system metastases, carcinomatous meningitis, active autoimmune disease, interstitial lung disease or a history of pneumonitis requiring oral or intravenous steroids. Patients whose tumour specimen was not evaluable for PD-L1 expression were also excluded.

The primary endpoint of the study was progression-free survival (PFS). The secondary endpoints were overall survival (OS) and objective response rate (complete and partial). Exploratory endpoints 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], the EuroQoL 5-Dimensions questionnaire (EQ-5D), and duration of response.

The pCODR review also provided contextual information on the clinical utility of PD-L1 testing, the effectiveness of PD-1 and PD-L1 checkpoint inhibitors for treatment of patients with NSCLC with different levels of PD-L1 expression, and the accuracy of PD-L1 diagnostic antibody assays. pERC noted that evidence to inform the question of the clinical utility of PD-L1 testing compared with no testing was not identified. Given the absence of evidence on the clinical utility and accuracy of PD-L1 testing, combining trial data on clinical outcomes by PD-L1 expression may not be appropriate or yield accurate, reliable findings on effectiveness. pERC also noted and acknowledged the limited evidence to inform the accuracy of PD-L1 diagnostic antibody assays and to identify the preferred PD-L1 diagnostic antibody assay.

Patient populations: Previously untreated, PD-L1 TPS ≥ 50%, advanced NSCLC patients

Patients (n = 305) were randomly assigned and stratified by ECOG PS (0, 1), tumour histologic type (squamous, nonsquamous), and region of enrollment (East Asia, non-East Asia) to receive pembrolizumab or chemotherapy. Treatment was continued for the specified number of cycles or until the patient had radiologic disease progression, treatment-related adverse events (TRAEs) of unacceptable toxicity, or withdrew consent, or until the investigator decided to withdraw the patient (whichever occurred first). Patients in the chemotherapy group who had disease progression were permitted to crossover and receive pembrolizumab, if safety criteria were met. After disease progression, 43.7% of patients in the chemotherapy group crossed over to receive pembrolizumab.

The median age of patients in the pembrolizumab group was 64.5 years and 66.0 years in the chemotherapy group. pERC noted there was no age restriction in KEYNOTE-024 and agreed with the pCODR Clinical Guidance Panel (CGP) that pembrolizumab appears to be tolerated in older patients. Most patients were white (82%), former or current smokers (92%), had non-squamous histology (82%), and an ECOG PS of 1 (65%). pERC noted the CGP's justification 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. pERC also noted that KEYNOTE-024 was restricted to patients with a histologically or cytologically confirmed diagnosis of stage IV NSCLC. pERC discussed and agreed with the CGP that patients with locally advanced (stage IIIB) disease who are not eligible for potentially curative concurrent chemoradiotherapy may derive benefit from pembrolizumab.

Key efficacy results: Clinically meaningful improvement in PFS, OS, and response

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

After a median follow-up of 11.2 months, the median PFS in the pembrolizumab group was 10.3 months and 6.0 months in the chemotherapy group. pERC noted that the PFS gain of 4.3 months with pembrolizumab was statistically significant and clinically meaningful. Treatment benefit was evident in all patient subgroups examined. However, the difference between treatment groups did not reach statistical significance in the following subgroups: female patients, patients who are current smokers, patients who were smokers, and patients with brain metastases at baseline. pERC agreed that because of the absence of powered subgroup analyses in the study design, conclusions and funding recommendations excluding subgroups or other pre-specified or post-hoc subgroups 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.

At an updated data cut-off, the median OS was not reached in the pembrolizumab group and was 14.5 months in the chemotherapy group. pERC acknowledged that even with crossover of patients from chemotherapy to pembrolizumab, an OS benefit was observed for pembrolizumab. The response rate was higher in the pembrolizumab group compared with chemotherapy group. pERC noted that the median

duration of response was not reached in the pembrolizumab group and was 6.3 months in the chemotherapy group.

pERC agreed that pembrolizumab offered improved PFS, response, and OS compared with chemotherapy.

Patient-reported outcomes: No difference between groups, delayed time to deterioration

Patient-reported QoL was assessed using EORTC QLQ-C30, EORTC QLQ-LC-13, and EQ-5D. For the QLQ-C30, a mean change from baseline of 10 points or greater was considered the minimum clinically important difference (MCID), with lower scores indicative of improvement in symptoms and side effects.

At week 15, differences in the mean change from baseline on the QLQ-C30 showed numerical improvements (i.e., less deterioration) of the Global Health Status Score in patients treated with pembrolizumab compared with chemotherapy. Although the difference in mean change in QLQ-C30 between treatment groups reached statistical significance, the difference did not reach the MCID of 10-points or greater. For the majority of lung cancer symptoms (i.e., cough, chest pain, and dyspnea), patients treated with pembrolizumab compared with chemotherapy showed a statistically significant improvement in time-to-true deterioration.

EQ-5D scores generally increased over time for patients in the pembrolizumab group and not the chemotherapy group. The difference in mean change from baseline to week 15 reached statistical significance in the pembrolizumab group compared with the chemotherapy group.

pERC noted the absence of a clear signal indicating an improvement in QoL; however, there was a delay in time-to-true deterioration, and therefore, the Committee concluded there was a delay in time to deterioration in QoL compared with chemotherapy. pERC agreed with the pCODR Methods Team that the open-label design of the study increases the risk of bias in the interpretation of the QoL data.

Limitations: Open-label design, underpowered subgroup analyses, OS confounded by cross-over

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. However, pERC noted that for treatment-level results, external unblinded data-analysts were utilized in KEYNOTE-024. The OS results (secondary endpoint) of the trial are likely confounded by the crossing over of patients in the chemotherapy group to the pembrolizumab group. However, pERC recognized that the OS results remained statistically significant although one would expect crossover would confound the observed treatment effect in favour of chemotherapy.

Safety: Meaningful reductions in toxicities

pERC discussed the toxicity profile of pembrolizumab as observed in KEYNOTE-024. Compared with chemotherapy, pembrolizumab was associated with fewer TRAEs of any grade (73.4% versus 90.0%), fewer grade 3 to 5 adverse events (26.6% versus 53.3%), and fewer withdrawals due to adverse events (7.1% versus 10.7%). Deaths attributed to study treatment occurred in less than 1% of patients treated with pembrolizumab and in 2% of patients treated with chemotherapy.

Treatment discontinuations due to TRAEs were also higher among patients treated with chemotherapy; 10.7% versus 7.1% of patients in the chemotherapy and pembrolizumab groups, respectively.

Immune-related events of special interest occurred in 29.2% of patients receiving pembrolizumab and 4.7% of patients receiving chemotherapy. The most frequent type of events of any grade (pembrolizumab versus chemotherapy), were hypothyroidism (9.1% versus 1.3%), hyperthyroidism (7.8% versus 1.3%), pneumonitis (5.8% versus 0.7%), infusion reaction (4.5% versus 1.3%), severe skin reaction (3.9% versus 0%), thyroiditis (2.6% versus 0%), colitis (1.9% versus 0%), and myositis (1.9% versus 0%). Of these events, only pneumonitis, severe skin reactions, and colitis occurred at a severity of grade 3 or higher in more than 1% of patients in the pembrolizumab treatment group. All infusion reactions were graded as 1 or 2.

Overall, pERC agreed that pembrolizumab demonstrated meaningful reductions in toxicities compared with chemotherapy.

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

In 2015, an estimated 26,600 new cases were diagnosed and 20,900 deaths occurred in Canada from lung cancer, with a five-year survival rate of 15% to 18%. NSCLC accounts for 85% of all lung cancers. Patients with disease without a driver mutation are treated with platinum-based doublet chemotherapy combinations in the first-line setting. Platinum agents are paired with third generation cytotoxic agents such as vinorelbine, gemcitabine, pemetrexed, paclitaxel, and docetaxel. This is based on modest improvements in survival and QoL.

pERC noted that the goals of treatment for patients with advanced-staged 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 platinum-based doublet chemotherapy, pERC agreed there is a need for alternative options that reduce toxicity and prolong survival.

Registered clinician input: Effective and better tolerated than chemotherapy, need for up-front PD-L1 testing

The Committee deliberated on input from a joint submission from seven clinicians on behalf of the Lung Cancer Canada Medical Advisory Committee. Based on this input, current standard options in the Canadian setting were platinum-doublet chemotherapy (cisplatin or carboplatin plus gemcitabine, paclitaxel, docetaxel, vinorelbine, or pemetrexed). pERC noted and agreed with the clinician input that the comparators in KEYNOTE-024 were reflective of current Canadian standards of care. pERC also agreed with the clinician input that pembrolizumab was more effective and better tolerated than chemotherapy. pERC noted pembrolizumab would provide an immunotherapy treatment option in the first-line setting for metastatic NSCLC. Clinician input also acknowledged that pembrolizumab would not replace a line of therapy but would shift the use of platinum-doublet chemotherapy to after the use of first-line pembrolizumab. Clinician input recommended that reflex testing for all instances of locally advanced and metastatic NSCLC be conducted. The input noted that EGFR mutation and ALK translocation testing is already done for the vast majority of this patient population and would add only one additional immunohistochemical test to the reflex panel. pERC noted that it would be desirable for jurisdictions to have validated and reliable PD-L1 testing available across Canada and conducted at the same time as the diagnosis of metastatic NSCLC.

PATIENT-BASED VALUES

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

pERC deliberated on 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. Both patient and caregiver respondents reported that the high symptom burden of lung cancer is difficult to manage. These symptoms included loss of appetite, cough, pain, shortness of breath, fatigue, and lack of energy. Patient advocacy group input indicated that symptoms are not fixed or consistent, but rather change frequently, which can also be difficult to manage. pERC noted that the control of symptoms, control of disease progression, and reduced treatment-related toxicity would be valued.

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

Chemotherapy is viewed as a necessary, but feared, treatment. pERC noted that the key concerns of patients with current treatment are side effects of chemotherapy and the significant recovery time needed after each infusion. Patients would also like their treatment to provide improved independence, and they desire fewer medical appointments and less financial cost burden.

A total of six patients and four caregivers had experience with first-line pembrolizumab. Patients with experience with pembrolizumab reported no side effects to mild side effects that are easily managed.

pERC acknowledged patient advocacy group input that patients who are not PD-L1-positive may still benefit from immunotherapy, and that additional wait times may occur for patients who need to undergo a biopsy that is then tested for PD-L1 expression. pERC noted that based on the current evidence, patients who would benefit from pembrolizumab are those whose tumours express PD-L1 (TPS ≥50%). pERC also discussed patient advocacy group input that indicated that there needs to be more education for health professionals and patients as pembrolizumab is a new type of treatment for NSCLC.

Patients with experience with pembrolizumab reported relieved symptom burden; tolerable and well-managed side effects; less interference with day-to-day activities; and higher QoL. pERC noted the difference in improved QoL reported by the patient advocacy group compared with the absence of a clear signal in the trial. The Committee noted 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 chemotherapy. Thus, the Committee felt the sustained QoL was maintained over a longer period of time, given the longer survival benefit compared with chemotherapy. The Committee also agreed that pembrolizumab was better tolerated, with fewer side effects and a shorter infusion time compared with chemotherapy. Therefore, pERC concluded that pembrolizumab aligned with patient values.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis, partitioned survival analysis,

The pCODR Economic Guidance Panel (EGP) assessed a cost-utility analysis comparing pembrolizumab to platinum-based doublet chemotherapy for patients with previously untreated NSCLC whose tumours expressed PD-L1 (TPS ≥50%). Currently available treatments for patients with previously untreated NSCLC whose tumours expressed PD-L1 (TPS ≥50%) include carboplatin plus paclitaxel, carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, and cisplatin plus gemcitabine. The submitted model was a three-state partitioned-survival model.

Basis of the economic model: 10-year time horizon, crossover adjustment

Costs included in the model were cost of PD-L1 testing (pembrolizumab group only), cost of treatment, cost of managing adverse events, resource costs for administration and disease follow-up, subsequent therapy (second- and third-line), and end-of-life care. pERC noted that the cost estimates were based on KEYNOTE-024 and published literature.

Key clinical effects considered in the analysis included PFS, OS, and health state utilities. pERC noted that KEYNOTE-024 had a short median follow-up of 11.2 months, extrapolated to a 10-year time horizon. Crossover was not adjusted for in the base-case analysis; however, it was adjusted for in a submitted scenario analysis.

Drug costs: High cost of drug

Pembrolizumab costs $44.00 per mg. At a recommended dose of 200 mg every three weeks, pembrolizumab costs $419.05 per day and $11,733.33 per 28-day course.

Cisplatin costs $2.70 per mg and carboplatin costs $1.33 per mg. Pemetrexed costs $0.83 per mg, gemcitabine costs $0.22 per mg, and paclitaxel costs $0.19 per mg. At the recommended dose for cisplatin of 75 mg/m^2 every 21 days and a pemetrexed dose of 500 mg/m^2 every 21 days, cisplatin plus pemetrexed costs $50.06 per day and $1,401.67 per 28-day course. At the recommended dose for carboplatin of area under the curve (AUC) of 5 or 6 every 21 days and a pemetrexed dose of 500 mg/m^2 every 28 days, carboplatin plus pemetrexed costs $65.33 per day and $1,829.32 per 28-day-course. At the recommended dose of cisplatin 75 mg/m^2 every 21 days and a gemcitabine dose of 1,250 mg/m^2 on days 1 and 8 every 28 days, cisplatin plus gemcitabine costs $60.65 per day and $1,698.31 per 28-day course. At the recommended dose of carboplatin AUC 5 or 6 every 21 days and a gemcitabine dose of 1,250 mg/m^2 on days 1 and 8 every 28 days, carboplatin plus gemcitabine costs $75.93 per day and $2,125.97 per 28-day course. At the recommended dose of carboplatin AUC 5 or 6 every 21 days and a paclitaxel dose of 200 mg/m^2 every 21 days, carboplatin plus paclitaxel costs $34.81 per day and $974.71 per 28-day course.

Cost-effectiveness estimates: Drug costs, duration of treatment effect

pERC discussed the submitter's and the EGP's best estimate of the ICER of pembrolizumab compared with chemotherapy for patients with metastatic NSCLC whose tumours express PD-L1 (TPS ≥50%).

pERC considered estimates provided by the submitter and reanalysis estimates provided by the EGP and noted uncertainty regarding the extrapolation for OS and PFS over a 10-year time horizon and the magnitude of benefit in the post-progression period. The factors that most influenced the incremental cost were the cost of pembrolizumab, adjustment method for crossover, and subsequent treatment with pemetrexed. The factors that most influenced the incremental effectiveness were duration of treatment effect of pembrolizumab, time horizon, and adjustment method for crossover.

pERC noted that the EGP was unable to evaluate the use of a 2 mg/kg dose of pembrolizumab. Although the use of a 2 mg/kg dose amount would likely not impact the effectiveness of pembrolizumab, there was uncertainty on how it would impact cost estimates; for many patients, the use of the flat dose would results in a larger dose and greater cost. Furthermore, the proportion of patients who received subsequent treatments after treatment discontinuation varied between treatment groups.

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 the uncertainty with respect to the long-term treatment effect of pembrolizumab, and the duration of pembrolizumab and cost of pembrolizumab.

ADOPTION FEASIBILITY

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

pERC considered the feasibility of implementing a funding recommendation for pembrolizumab.

The Committee noted that, as some patients are not able to tolerate chemotherapy due to toxicities, the eligible population of patients for pembrolizumab may be greater than estimated in the budget impact analysis. Furthermore, the eligible population including patients with locally advanced disease who are not eligible for potentially curative concurrent chemoradiotherapy would further increase the budget impact of pembrolizumab reimbursement. The number of prevalent and new cases of locally advanced or metastatic NSCLC may be large. pERC noted that the budget impact analysis was sensitive to increases in the treatment rate, treatment duration, and PD-L1 testing rate, as well as to funding of a second-line anti-PD-1. pERC noted that jurisdictions will need to consider the uncertainty in these factors during implementation. Overall, due to the large incidence and prevalent population of patient with metastatic NSCLC, the high cost of pembrolizumab, and the unknown number of patients that would receive the full 35 cycles or re-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 in KEYNOTE-024, the maximum number of cycles of pembrolizumab that patients received was 26 cycles and were permitted up to 35 cycles. pERC recognized that the actual treatment duration of pembrolizumab is unknown as no patients received the full 35 cycles and that provinces would need to address this issue upon implementation of pembrolizumab funding. pERC also discussed that the possibility of pseudoprogression (whereby some patients technically meet RECIST criteria for disease progression but do not have true progression) on immunotherapy appears less common in lung cancer (approximately 5%) than in other diseases such as melanoma. pERC also agreed that the results of the KEYNOTE-024 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 does not recommend reimbursement for patients whose PD-L1 status cannot be determined. pERC also discussed an amendment in the KEYNOTE-024 trial that allowed re-treatment with pembrolizumab in the trial protocol. In the trial patients could receive re-treatment for up to 17 cycles if patients stopped receiving pembrolizumab after receiving 35 cycles for reasons other than disease progression or intolerability, or if patients attained a complete response and stopped treatment with pembrolizumab, they may be eligible for re-treatment with pembrolizumab upon experiencing disease progression. pERC noted that in the trial, if pembrolizumab was withheld for toxicity, patients were able to resume pembrolizumab if appropriate and when toxicity had improved. pERC felt that these criteria for re-treatment with pembrolizumab following a progression-free time period and toxicity interruption were reasonable.

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 with the CGP that PD-L1 testing using a validated test authorized by Health Canada, or one equivalent to that used in KEYNOTE-024, is reasonable.

The Committee also considered the CGP's statement that there is no evidence to suggest the superiority or inferiority of a 200 mg flat dose of pembrolizumab versus the dose of 2 mg/kg based on body weight that was previously administered in initial pembrolizumab trials. pERC noted that the flat dose will result in larger doses and greater costs for some patients without evidence of improved effectiveness of pembrolizumab. pERC acknowledged and agreed with the CGP that it is reasonable that pembrolizumab be administered at a dose of 2 mg/kg up to a total dose amount of 200 mg (dose capped at 200 mg).

DRUG AND CONDITION INFORMATION

Drug Information	• Immunotherapy anti-PD-1 • 50 mg solution for infusion 100 mg/4mL vial • Recommended dose of 2 mg/kg up to a cap of 200 mg every 3 weeks up to 35 cycles
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	• Platinum-based doublet chemotherapy
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

The pCODR Expert Review Committee

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. 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
Karen MacCurdy Thompson, Pharmacist
Valerie McDonald, Patient Member Alternate
Carole McMahon, Patient Member
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Dr. Marianne Taylor, Oncologist
Danica Wasney, Pharmacist

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

- Dr. Scott Berry, Dr. Allan Grill, and Don Husereau who were not present for the meeting
- Dr. Anil Abraham Joy, who was excluded from deliberations and voting due to a conflict of interest
- Carole McMahon, who did not vote due to her role as a patient member alternate.

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee 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 for NSCLC (first-line), through their declarations, one member had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, one of these members were 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 base its recommendations on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee 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 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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