pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

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
This 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 Reimbursement Request:** In combination with pemetrexed and platinum chemotherapy, for the treatment of metastatic non-squamous NSCLC, in adults with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.	
Submitted By: Merck Canada	**Manufactured By:** Merck Canada
NOC Date: March 13, 2019	**Submission Date:** September 14, 2019
Initial Recommendation: April 4, 2019	**Final Recommendation:** May 31, 2019

Approximate per Patient Drug Costs	• Submitted list price of $4,400.00 per 100 mg vial • Cost per dose $8,800.00

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends the reimbursement of pembrolizumab (Keytruda) in combination with pemetrexed and platinum chemotherapy, for the treatment of metastatic non-squamous, non-small cell lung cancer (NSCLC), in adults with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC if the following conditions are met:

- Cost-effectiveness being improved to an acceptable level.
- Feasibility of adoption (budget impact) being addressed.

Eligible patients include those with good performance status. Treatment should continue until confirmed disease progression or unacceptable toxicity 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 in combination with pemetrexed and platinum chemotherapy compared with pemetrexed and platinum chemotherapy alone, based on the statistically significant and clinically meaningful improvements in progression-free survival (PFS) and overall survival (OS), quality of life (QoL), and manageable toxicities.

pERC agreed that pembrolizumab aligns with patient values in that it offers control of disease progression and improvements in OS and QoL, with manageable toxicities.

pERC concluded that pembrolizumab in combination with pemetrexed and platinum chemotherapy, at the submitted price and compared with pemetrexed and platinum chemotherapy alone, could not be considered

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	cost-effective in patients with previously untreated non-squamous NSCLC and who do not harbour an EGFR or ALK genomic tumour aberrations. pERC also highlighted that the potential budget impact of pembrolizumab in combination with pemetrexed and platinum chemotherapy may be underestimated and will be substantial.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness and Budget Impact** Given that pembrolizumab in combination with pemetrexed and platinum chemotherapy 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 and improve affordability (budget impact). pERC noted that the budget impact of pembrolizumab in combination with pemetrexed and platinum chemotherapy results from the high cost of pembrolizumab, the potentially large number of eligible patients, the duration of treatment, and the potential for retreatment. pERC concluded that a substantial reduction in drug price would be required to improve the cost-effectiveness and affordability. **Pembrolizumab Flat Dosing of 200 mg** pERC noted that the KEYNOTE-189 trial assessed pembrolizumab at a dose of 200 mg every three weeks up to 35 cycles. Additionally, pERC recognized that the initial trials investigating pembrolizumab utilized weight-based dosing at 2 mg/kg and that there are pERC recommendations of pembrolizumab in other indications with weight-based dosing. pERC considered that there is no direct evidence to suggest that flat dosing is superior to weight-based dosing. However, for many patients, the flat dose results in a larger dose and greater cost. Upon implementation of reimbursement of pembrolizumab for patients with metastatic non-squamous NSCLC, pERC recognized that jurisdictions will need to choose between administering pembrolizumab as a flat dose of 200 mg, as in the KEYNOTE-189 trial, or at a dose of 2 mg/kg up to a total dose of 200 mg (dose capped at 200 mg), as is used in clinical practice for other indications. **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, particularly if jurisdictions consider weight-based dosing (2 mg/kg up to 200 mg). **Time-Limited Need for Pembrolizumab for Patients who are Currently Receiving Pemetrexed and Platinum Chemotherapy as First-Line Treatment** At the time of implementing a reimbursement recommendation for pembrolizumab in combination with pemetrexed and platinum chemotherapy, jurisdictions may consider addressing the time-limited need of pembrolizumab for patients who recently initiated treatment with platinum chemotherapy. However, pERC noted that this would not apply to patients who have already commenced maintenance pemetrexed or for patients who are not candidates for platinum chemotherapy. **Please note:** Provincial Advisory Group questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

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SUMMARY OF pERC DELIBERATIONS

In 2016, there were approximately 28,400 new cases of lung cancer and 20,800 deaths from lung cancer. Approximately 85% of these cases are classified as non-small cell lung cancer (NSCLC) and of these, 75% present with locally advanced or metastatic disease. Approximately 75% of these cases are non-squamous histology. Treatment decisions for locally advanced or metastatic NSCLC are dependent on the presence or absence of a driver mutation in the first-line setting. In patients whose disease does not have a driver mutation, platinum chemotherapy would be offered as a first-line treatment; however, most patients experience disease progression, with only 18% of patients alive at five years. The majority of patients have disease without driver mutations. Newer treatments in the second-line NSCLC setting, irrespective of driver mutation presence, include immunotherapy such as nivolumab or pembrolizumab. Currently, pembrolizumab is offered as first-line treatment for patients with high PD-L1 expression (≥ 50%), which represents about 30% of the patient population with metastatic NSCLC. pERC considered input from registered clinicians that emphasized the need for treatment with immunotherapy independent of PD-L1 expression. Therefore, pERC concluded that there is a need for treatment options that reduce toxicity, improve quality of life and prolong survival.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated on the results of two randomized controlled trials, KEYNOTE-189 and KEYNOTE-021, that compared pembrolizumab in combination with pemetrexed and platinum chemotherapy (herein, referred to as pembrolizumab plus chemotherapy) and the combination of placebo and pemetrexed and platinum chemotherapy (herein, referred to as placebo plus chemotherapy) as first-line therapy in patients with metastatic non-squamous (NSQ) NSCLC with any level of PD-L1 expression and with no EGFR or ALK mutations. Overall, the Committee noted that the results from the KEYNOTE-021 trial were confirmed in the KEYNOTE-189 trial. The Committee primarily focused the deliberations on the KEYNOTE-189 trial, the phase III confirmatory, international, multicentre, double-blind, placebo-controlled trial that provided evidence on the use of pembrolizumab plus chemotherapy in patients with metastatic NSQ NSCLC. pERC noted that the KEYNOTE-189 trial demonstrated a clinically meaningful and statistically significant improvement in PFS in favour of pembrolizumab plus chemotherapy compared with chemotherapy alone. The Committee noted that although the median overall survival (OS) was not reached in the pembrolizumab plus chemotherapy group, and even with the crossover of patients in the chemotherapy group upon disease progression to open-label pembrolizumab monotherapy, there was a clinically meaningful and statistically significant improvement in OS. pERC also noted that the response rate and duration of response were higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy alone group.

The Committee also discussed the Clinical Guidance Panel's (CGP)'s conclusions regarding the generalizability of treatment with pembrolizumab plus chemotherapy to particular subgroups of patients. pERC agreed with the CGP's expert opinion that it would be reasonable to extend treatment with pembrolizumab plus chemotherapy to patients with ECOG performance status 2 and concluded that eligible patients would be those with a good performance status. Furthermore, pERC agreed with the CGP that patients with stable brain metastases, who are off treatment with steroids, could derive benefit from pembrolizumab plus chemotherapy. The Committee noted that the results from the KEYNOTE-189 trial are not generalizable to patients with molecular abnormalities (e.g., *EGFR*, *ALK*, *ROS1* mutations), patients with squamous NSCLC (a separate review of this patient population is currently ongoing at pCODR), and patients who have been previously treated in the advanced/metastatic setting. However, pERC noted that patients who received adjuvant or neoadjuvant therapy would be eligible for treatment if the adjuvant/neoadjuvant therapy was completed at least 12 months before the development of metastatic disease.

pERC discussed that patients with high PD-L1 expression (≥ 50%) were included in the trials and a subgroup analysis of these patients demonstrated a treatment benefit in favour of pembrolizumab plus chemotherapy. Currently, patients with tumours with high PD-L1 expression would receive pembrolizumab

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monotherapy in the first-line setting. The Committee noted that the submitted indirect treatment comparison (ITC) compared pembrolizumab alone versus pembrolizumab plus chemotherapy suggested the combination of pembrolizumab plus chemotherapy was superior to pembrolizumab alone, however, the corresponding confidence intervals for the hazard ratios for PFS and OS crossed the null hypothesis value, indicating statistical non-significance. The Committee noted that the efficacy of the addition of chemotherapy to pembrolizumab for patients with high PD-L1 expression is uncertain, as neither trial investigated this. However, pERC also considered the CGP's and the registered clinicians' expert opinions that both treatments are superior to chemotherapy alone and should be available to clinicians to choose based on individual patient need and preferences.

pERC deliberated on the safety profile of pembrolizumab plus chemotherapy. The most common grade 3 to grade 4 adverse events (AEs) reported among patients receiving pembrolizumab plus chemotherapy were anemia and neutropenia. pERC discussed that a higher proportion of immune-mediated AEs occurred in the pembrolizumab plus chemotherapy group, but that immune-mediated AEs could be managed with appropriate monitoring. Additionally, pERC discussed the quality of life (QoL) data from the KEYNOTE-189 trial. pERC noted that at week 12 there was no statistically significant difference in QoL between the two treatment groups. However, at week 21, a statistically significant improvement in QoL was observed in the pembrolizumab plus chemotherapy group. Overall, pERC concluded that there is a net clinical benefit of pembrolizumab plus chemotherapy compared with placebo plus chemotherapy for patients with metastatic NSQ NSCLC based on a statistically significant and clinically meaningful improvement in PFS, OS, QoL, and a manageable toxicity profile.

pERC deliberated on patient input from three patient advocacy groups. Patient input indicated that patients value treatment that slows disease progression, reduces or eliminates side effects, and improves quality of life. The Committee also discussed that patients reported that they were willing to tolerate aggressive treatment and the potential side effects of treatment if the outcomes are favourable. Additionally, pERC discussed that patients prefer a treatment option that can be taken at home and that has less cost burden. pERC noted that patients would have to travel to a treatment centre to receive the combination of pembrolizumab plus chemotherapy by infusion. However, the Committee noted that this therapy could be offered at treatment centres that may be closer to a patient's home. Overall, pERC concluded that pembrolizumab plus chemotherapy aligns with patient values in that it is an effective treatment option that delays disease progression, improves survival and QoL, and has a manageable toxicity profile.

pERC deliberated on the cost-effectiveness of pembrolizumab plus chemotherapy compared with placebo plus chemotherapy based on the submitted economic evaluation and the reanalysis provided by the pCODR Economic Guidance Panel (EGP). pERC noted uncertainty regarding the extrapolation of PFS and OS over a 10-year time horizon. The Committee noted that the factor that most influenced the incremental cost is the duration of treatment, and the factors that most influenced the incremental clinical effect are the time horizon and the clinical benefit after two years. pERC discussed the fact that the duration of treatment benefit of pembrolizumab plus chemotherapy is uncertain because of the short trial follow-up. Furthermore, the EGP was unable to evaluate the use of pembrolizumab weight-based dosing at 2 mg/kg for this patient population as the base case used a flat dose of 200 mg. pERC noted that there is uncertainty on how weight-based dosing would impact the cost estimates. Overall, pERC agreed with the EGP's reanalysis estimates and concluded that at the submitted price, pembrolizumab plus chemotherapy cannot be considered cost-effective and that a substantial price reduction would be required. The Committee acknowledged the uncertainty in the long-term treatment effect and the duration of treatment with pembrolizumab plus chemotherapy will impact the true incremental cost-effectiveness ratio (ICER).

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the submitter, who disagreed with the EGP's reanalysis of using the two-stage adjustment for crossover for OS in the lower-bound estimate and the use of a five-year time horizon in the upper-bound ICER estimate.

pERC discussed that the EGP explored a crossover adjustment in the lower-bound ICER estimate and a five-year time horizon in the upper-bound estimate to account for the uncertainty of the long-term benefits of pembrolizumab due to the short trial follow-up in the KEYNOTE-189 trial and the uncertainty related to the long-term benefit of pembrolizumab beyond the trial specifically for the submitted pharmacoeconomic model and economic analysis provided for this review. pERC noted that the submitter's base-case analysis included a 10-year time horizon and that the two-stage adjustment for

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crossover for OS was not utilized. Overall, the Committee agreed that the EGP's reanalysis was appropriate and reiterated that the submitter's best estimate, and the EGP's lower-bound and upper-bound ICER estimates, cannot be considered cost-effective.

pERC discussed the feasibility of implementing a reimbursement recommendation for pembrolizumab plus chemotherapy. Overall, pERC noted that the submitted budget impact was likely underestimated and will be substantially higher based on the CGP's estimates of eligible patients. pERC also noted that the submitted budget impact accounts for the displacement of the use of second-line pembrolizumab. pERC expressed serious concern about the affordability of pembrolizumab plus chemotherapy and the capacity for jurisdictions to implement reimbursement of pembrolizumab plus chemotherapy in this setting. pERC discussed that increasing the market share uptake, the number of patients eligible to receive pembrolizumab plus chemotherapy and the duration of treatment as well as retreatment will increase the budget impact. pERC recognized that jurisdictions will need to consider the uncertainty in these factors during implementation.

pERC noted input from the pCODR Provincial Advisory Group (PAG), which requested information and clarification on the treatment criteria for pembrolizumab plus chemotherapy. pERC discussed that patients would be eligible for pembrolizumab plus chemotherapy in this setting irrespective of PD-L1 TPS. In addition, the Committee noted that retreatment with pembrolizumab for 12 months was permitted in the trial if a patient responded to treatment with pembrolizumab and had disease progression at any time during the two-year follow-up period. pERC considered the CGP's expert opinion that patients who complete two years of pembrolizumab and discontinue therapy without progression should have the option for treatment with pembrolizumab if there are at least six months between completion of therapy and documented disease progression. As well, pERC discussed the time-limited need of pembrolizumab for patients who recently initiated treatment with platinum chemotherapy. However, pERC noted that this would not apply to patients who already commenced maintenance pemetrexed or for patients who are not candidates for platinum chemotherapy.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed PAG's request for clarity on the rationale for the six-month time interval between disease progression and re-treatment with pembrolizumab.

pERC discussed that the KEYNOTE-189 trial did not report data on re-treatment with pembrolizumab upon disease progression after the completion of therapy. In the absence of evidence, the Committee discussed the CGP's opinion that it would be clinically reasonable to re-treat with pembrolizumab if there are at least six months between the completion of therapy and documented disease progression. Upon implementation of a reimbursement recommendation for pembrolizumab plus chemotherapy, jurisdictions may want to consider a national approach to develop appropriate criteria for re-treatment that is consistent across jurisdictions.

Additionally, PAG requested guidance on weight-based dosing of 2 mg/kg up to a flat dose cap of 200 mg in this setting as well as other alternative dosing of pembrolizumab based on emerging data. The Committee noted that the KEYNOTE-189 trial assessed pembrolizumab at a dose of 200 mg every three weeks up to 35 cycles and recognized that previous pERC recommendations for other indications supported the use of weight-based dosing up to a flat dose cap of 200 mg. pERC noted that the CGP supported the dosing of pembrolizumab as administered in the KEYNOTE-189 trial, flat dosing of 200 mg every three weeks. pERC considered that there is no direct evidence to suggest that flat dosing is superior to weight-based dosing. However, for many patients, the flat dose results in a larger dose and greater cost. Upon implementation of the reimbursement of pembrolizumab plus chemotherapy for metastatic NSQ NSCLC patients, pERC recognized that jurisdictions will need to choose between administering pembrolizumab at a flat dose of 200 mg or at 2 mg/kg up to a total dose of 200 mg (dose capped at 200 mg) for metastatic NSQ NSCLC patients.

Finally, pERC noted PAG's request for clarification and guidance on whether patients with mutations *(*e.g., *EGFR, ALK, or ROS-1*) should be treated with targeted treatment first and whether it would be reasonable to subsequently treat with pembrolizumab. pERC noted that patients with mutations should have disease progression on targeted treatment for the mutations and chemotherapy prior to receiving pembrolizumab. In addition, pERC noted that patients who receive pembrolizumab in the first-line setting would not be eligible to receive subsequent PD-1 (e.g., nivolumab) or PD-L1 (e.g., atezolizumab) inhibitors in the second-line setting. Furthermore, PAG requested guidance on whether pembrolizumab or

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other PD-1/PD-L1 inhibitors would be used for treating metastatic disease after progression on durvalumab, as well as guidance on the appropriate time frame between treatments.

Upon consideration of the pERC Initial Recommendation, the Committee discussed feedback from the registered clinicians from the Cancer Care Ontario Lung Drug Advisory Committee, which stated that some clinicians feel that patients who have received durvalumab in the curative intent setting who then progress should not need to have a minimum of a year between progression and stopping durvalumab. The registered clinicians stated that it is reasonable to have pembrolizumab plus chemotherapy available even for patients who progress while on durvalumab (or at any time after) as it is unclear whether durvalumab and pembrolizumab are equivalent.

pERC considered the CGP's expert opinion and agreed with the CGP that for patients who received prior adjuvant or consolidation durvalumab and remain candidates for platinum-pemetrexed chemotherapy, it would be reasonable to consider treatment with platinum-pemetrexed plus pembrolizumab. In general, patients should be more than 12 months since they last received platinum-based therapy. For patients progressing during adjuvant or consolidation immune checkpoint inhibitor therapy, there is limited data at this time to support further immune checkpoint inhibitor therapy.

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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 two patient advocacy groups (Lung Cancer Canada [LCC] and Ontario Lung Association [OLA])
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- one clinician group, Cancer Care Ontario Lung Drug Advisory Committee
- PAG
- the submitter, Merck Canada.

The pERC Initial Recommendation was to recommend reimbursement of pembrolizumab (Keytruda) in combination with pemetrexed and platinum chemotherapy compared with pemetrexed and platinum chemotherapy alone for the treatment of metastatic non-squamous NSCLC in adults with no EGFR or ALK genomic tumour aberrations and no prior systemic chemotherapy treatment for metastatic NSCLC. Feedback on the pERC Initial Recommendation indicated that PAG agreed with the pERC Initial Recommendation. The submitter and registered clinicians agreed in part with the pERC Initial Recommendation. Patient feedback was not provided on the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of pembrolizumab in combination with pemetrexed and platinum chemotherapy compared with pemetrexed and platinum chemotherapy alone for the treatment of metastatic non-squamous NSCLC in adults with no EGFR or ALK genomic tumour aberrations and no prior systemic chemotherapy treatment for metastatic NSCLC.

Studies included: Two Randomized Controlled Trials

The pCODR systematic review included two randomized controlled trials KEYNOTE-189 (N = 616) and KEYNOTE-021 (N = 123).

KEYNOTE-021 is an ongoing phase I/II, multicentre, multi-cohort randomized controlled trial that compared the safety and efficacy of pemetrexed-platinum chemotherapy with and without pembrolizumab as first-line therapy in patients with metastatic non-squamous (NSQ) non-small cell lung cancer (NSCLC) in whom there were no EGFR or ALK mutations. KEYNOTE-021 included multiple cohorts. Cohort G (N = 123) is the cohort relevant to the pCODR submission (i.e., chemotherapy naive patients who received pembrolizumab plus chemotherapy or chemotherapy alone). Eligible patients were randomized (1:1 ratio) to receive pembrolizumab plus pemetrexed-carboplatin chemotherapy (pembrolizumab combination arm; n = 60) or pemetrexed-carboplatin chemotherapy alone (chemotherapy arm; n = 63). Treatment was to be continued until disease progression or protocol-defined unacceptable toxicities. In the chemotherapy arm, patients who experienced documented disease progression could crossover to pembrolizumab monotherapy.

KEYNOTE-189 is an ongoing phase III, international, multicentre, randomized, double-blind, placebo-controlled trial of combination therapy with pembrolizumab plus pemetrexed and a platinum-based drug as first-line therapy in patients with metastatic non-squamous (NSQ) NSCLC in whom there were no EGFR or ALK mutations. This trial was performed to confirm the results of KEYNOTE-21G. Eligible patients were randomized (2:1 ratio) to receive pembrolizumab in combination with pemetrexed-platinum chemotherapy (pembrolizumab combination arm; n = 410) or placebo plus pemetrexed-platinum chemotherapy per investigator's choice (placebo combination arm; n = 206) on day 1 of each three-week dosing cycle. Treatment was continued until the completion of 35 cycles with pembrolizumab (or placebo), radiographic disease progression, unacceptable toxicities, investigator's decision to stop the

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treatment, or patient withdrawal of consent. Patients who attained a complete response could consider stopping trial treatment. In the pembrolizumab arm, initial responders with a disease progression at any time during the two-year follow-up period were eligible to receive up to 12 months of pembrolizumab monotherapy in the second course phase. In the placebo arm, patients who experienced documented disease progression during the treatment phase could continue on open-label pembrolizumab monotherapy in the crossover phase.

The pCODR review also provided contextual information on a manufacturer submitted indirect treatment comparison of pembrolizumab in combination with chemotherapy versus pembrolizumab monotherapy for patients with metastatic, NSQ NSCLC with strong PD-L1 (TPS $\geq$ 50%) as well as a manufacturer submitted network meta-analysis (NMA) of pembrolizumab plus platinum plus pemetrexed for the first-line treatment of metastatic NSQ NSCLC patients whose tumours are sensitizing EGFR mutation and ALK translocation negative.

Patient populations: Previously untreated, non-squamous NSCLC patients

The majority of study participants in KEYNOTE-189 were white (94%) and current or former smokers (88%). A PD-L1 tumour proportion score of ≥1% was reported in 63.4% of the patients in the pembrolizumab combination arm and in 62.1% of those in the placebo combination arm. Carboplatin was selected as the platinum-based chemotherapy drug in 72.4% of the patients in the pembrolizumab combination arm and 71.8% of patients in the placebo combination arm. Overall, the baseline characteristics were generally well balanced between the two study arms; except, in the placebo combination arm there was a higher proportion of patients who were female (47.1% versus 38.0% in the pembrolizumab combination arm; P = 0.04). The median age was 65 years in the pembrolizumab combination arm and 63.5 years in the chemotherapy arm. In KEYNOTE-021G, the baseline characteristics were generally well balanced between the two study arms. Overall, the majority of patients were female (63% versus 59%) in the chemotherapy arm, white (82% versus 92% in the chemotherapy arm), current or former smokers (75% versus 86% in the chemotherapy arm), with adenocarcinoma histology (97% versus 87% in the chemotherapy arm). The median age was 62.5 years in the pembrolizumab combination arm and 63.2 years in the chemotherapy arm.

In the placebo arm, patients with verified disease progression (by independent central imaging review) were permitted to crossover to pembrolizumab monotherapy. A total of 67 (32.5%) patients in the placebo combination arm crossed over during the trial to receive pembrolizumab monotherapy after disease progression.

Key efficacy results: Clinically Meaningful Improvements in PFS, OS, and Response Rates

The key efficacy outcome deliberated on by pERC included PFS, OS, and response rates from the KEYNOTE-189 trial.

As of the November 8, 2017 data cut-off date, after a median follow-up duration of 10.5 months, a total of 235 deaths were reported in the KEYNOTE-189 trial (127 [31.0%] in the pembrolizumab combination arm and 108 [52.4%] in the placebo combination arm). The median OS was not reached in the pembrolizumab combination arm, and was 11.3 months (95% CI, 8.7 to 15.1) for the placebo combination arm (HR = 0.49; 95% CI, 0.38 to 0.64; P < 0.00001). The OS rate at 12 months was 69.2% (95% CI, 64.1 to 73.8) in the pembrolizumab combination arm and 49.4% (95% CI, 42.1 to 56.2) in the placebo combination arm. The OS subgroup analyses results were consistent with those of the original OS analysis.

A total of 410 PFS events were reported in the KEYNOTE-189 trial (244 [59.5%] in the pembrolizumab combination arm and 166 [80.6%] in the placebo combination arm). The median PFS was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab combination arm, and was 4.9 months (95% CI, 4.7 to 5.5) in the placebo combination arm (HR = 0.52; 95% CI, 0.43 to 0.64; P < 0.00001). PFS rate at 12 months was 34.1% (95% CI, 28.8 to 39.5) in the pembrolizumab combination arm and 17.3% (95% CI, 12.0 to 23.5) in the placebo combination arm. The PFS subgroup analyses results were generally consistent with those of the original PFS analysis.

The blinded independent central radiology review assessed ORR was 47.6% (95% CI, 42.6 to 52.5) in the pembrolizumab combination arm and 18.9% (95% CI, 13.8 to 25.0) in the placebo combination arm (estimated treatment difference = 28.5%; 95% CI, 21.1 to 35.5; P < 0.0001) The median DOR was 11.2 months (range 1.1 to 18.0) in the pembrolizumab combination arm and 7.8 months (range 2.1 to 16.4) in the placebo combination arm.

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Results from the KEYNOTE-021 trial from the longest term follow-up of December 1, 2017, with a median follow-up of 23.9 months are as follows: ORR assessed BICR was 56.7% in the pembrolizumab combination arm and 30.2% in the chemotherapy arm (estimated treatment difference = 26.4%; 95% CI, 8.9 to 42.4; *P* = 0.0016). The median DOR was 11.2 months (range 1.1 to 18.0) in the pembrolizumab combination arm and 7.8 months (range 2.1 to 16.4) in the placebo combination arm.

A total of 71 PFS events were reported (28 [47%] in the pembrolizumab combination arm and 43 [68%] in the chemotherapy arm). The median PFS was 24.0 months (95% CI, 8.5 to not estimable) with the pembrolizumab combination and 9.3 months (95% CI, 6.2 to 14.9) with chemotherapy alone. The PFS benefit was statistically higher in the pembrolizumab combination arm than that in the chemotherapy arm (HR = 0.53; 95% CI, 0.33 to 0.86; *P* = 0.0049)

After a median follow-up duration of approximately 24 months, 22 (37%) patients in the pembrolizumab combination group and 35 (56%) patients in the chemotherapy arm had died. The OS benefit with the pembrolizumab plus chemotherapy was statistically higher than with chemotherapy alone (HR = 0.56; 95% CI, 0.32 to 0.95; *P* = 0.0151). The median OS was not reached in the pembrolizumab combination arm (95% CI, 24.5 months to not estimable) and 21.1 months (95% CI, 14.9 to not estimable) in the chemotherapy arm.

Patient-reported outcomes: Statistically significant improvement in quality of life (QoL) for patients in the pembrolizumab plus chemotherapy group at Week 21

At the time of data cut-off, more than 99% of the patients (in either of the study arms) had completed ≥ 1 patient-reported outcome assessment. At week 12, no statistically significant differences were found in EORTC QLQ-C30 global health status/QoL change from baseline between the pembrolizumab and the placebo combination arms (mean difference = 3.58 points; 95% CI, -0.05 to 7.22; *P* = 0.053). At week 21, a statistically significant improvement was observed with the pembrolizumab combination (mean difference = 5.27 points; 95% CI, 1.07 to 9.74; *P* = 0.014). At both week 12 and week 21, statistically significant changes from the baseline in the EQ-5D visual analogue (VAS) scores were observed between the two study arms, favouring the pembrolizumab combination.

Limitations: No direct comparison between pembrolizumab monotherapy and pembrolizumab plus chemotherapy for patients with high PD-L1 expression (≥ 50%)

Indirect treatment comparisons (ITCs) were performed using Bucher method after weighted adjustment of the treatment arms from the KEYNOTE-189 and KEYNOTE-024 trials. Point estimates of the effect from the ITC suggested that pembrolizumab plus chemotherapy was superior to pembrolizumab monotherapy, in terms of PFS (HR = 0.69, 95% CI, 0.40 to 1.19) and OS (HR = 0.65, 95% CI, 0.33 to 1.28) in patients with metastatic, NSQ NSCLC with strong PD-L1 (TPS ≥ 50%). However, the corresponding confidence intervals crossed the null hypothesis value, indicating a statistical non-significance. Therefore, the relative efficacy of pembrolizumab plus chemotherapy over pembrolizumab monotherapy remains uncertain.

The submitter also conducted a systematic review of literature and NMA to provide indirect comparisons between pembrolizumab plus platinum-pemetrexed chemotherapy and competing interventions for the first-line treatment of metastatic NSCLC in patients with non-squamous histology who are EGFR mutation and ALK translocation negative. The submitted NMAs concluded that in the patient population of interest, pembrolizumab plus chemotherapy could be superior to most competing interventions in terms of OS and PFS except for atezolizumab regimen and other pembrolizumab regimens. There were some levels of heterogeneity in effect modifiers between trials. However, these results should be interpreted with caution due to limitations that may arise from between-study differences in some covariates; and lack of sufficient evidence to minimize heterogeneity and inconsistency (e.g., by performing meta-regression analysis).

Safety: Manageable toxicity profile; increased immune-mediated AEs with pembrolizumab plus chemotherapy

AEs of any grade were reported in 93.2% of patients in the pembrolizumab combination arm and 91.9% of patients in the chemotherapy arm. The most common AEs reported in both groups included fatigue, nausea, anemia, vomiting, rash, and diarrhea. In addition, grade 3+ AEs were reported in 41% of patients treated in the pembrolizumab combination arm and 27% of those treated with chemotherapy alone. Anemia was the most common grade 3 or 4 AEs that was reported in 12% of patients in the pembrolizumab combination arm and 13% of those in the chemotherapy arm. Immune-mediated AEs occurred in 17

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(28.8%) patients in the pembrolizumab combination arm and in seven (11.3%) of the patients in the chemotherapy arm.

Treatment-related AEs that led to discontinuation of any component of study medication were reported in 16.9% of patients in the pembrolizumab combination arm and 12.9% of those in the chemotherapy arm. Treatment-related fatal AEs occurred in one (1.7%) patient in the pembrolizumab combination arm (due to sepsis) and two (3.2%) patients in chemotherapy arm (due to pancytopenia and sepsis).

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

In 2016, there were approximately 28,400 new cases of lung cancer and 20,800 deaths from lung cancer. Approximately 85% of these cases are classified as NSCLC and of these, 75% present with locally advanced or metastatic disease. Approximately 75% of these cases present with non-squamous histology. Treatment decisions for locally advanced or metastatic NSCLC are dependent on the presence or absence of a driver mutation in first-line setting. In patients whose disease does not have a driver mutation, platinum doublet chemotherapy would be offered as a first-line treatment; however, most patients experience disease progression, with only 18% of patients who are alive at five years. The majority of patients have disease without driver mutations. Approximately 30% of patients who are PD-L1 strongly positive (≥ 50%) would be eligible to receive first-line pembrolizumab monotherapy. There is a need for treatment options that reduce toxicity, improve quality of life, and prolong survival in this patient population.

Registered clinician input: Combination of pembrolizumab and platinum-based chemotherapy as a suitable first-line option for all non-squamous NSCLC patients with low and high PD-L1

The clinicians providing input noted that the combination of pembrolizumab and pemetrexed-platinum-based chemotherapy would be a suitable first-line option for all non-squamous NSCLC patients with low expression of PD-L1, as well as for those with high expression of PD-L1 who are eligible for pembrolizumab monotherapy but may benefit from a rapid therapeutic response. According to the clinicians, the combined use of chemotherapy and immunotherapy addresses a therapeutic gap whereby one would usually have to risk a worsening condition after progression on one therapy before trying the other. The availability of first-line immunotherapy independent of PD-L1 expression increases equity in patients who have no PD-L1 results and those unfit for second-line therapy. Safety and tolerability were not seen as major issues by clinicians. They noted that both combination and monotherapy options should remain available for NSQ NSCLC patients but agreed that the sequence of therapies should favour first-line pembrolizumab therapy (alone or combined with chemotherapy, as determined by PD-L1 status and patient preference) moving forward.

PATIENT-BASED VALUES

Experience of patients with non-squamous NSCLC: High symptom burden; current treatment has significant side effects

From a patient perspective, lung cancer affects many aspects of day-to-day life. Specifically, it affects the patient's ability to work, travel, socialize, and participate in leisure and physical activities. It also affects their relationships with family and friends, emotional well-being, and may cause financial hardship. It was reported by both patient and caregiver respondents that the high symptom burden of lung cancer is difficult to manage. Patient input reported symptoms including loss of appetite, cough, pain, and shortness of breath. Moreover, one of the most common symptom burdens for patients with lung cancer is fatigue or lack of energy. In addition, patient input noted that patients want better communication about the disease and the range of treatment options available.

Patient input reported that although treatment with chemotherapy is needed, it is a persistent psychological and physical burden, with significant side effects that limit personal independence and quality of life. Patients who have experience with immunotherapy reported much milder side effects that did not significantly interfere with daily life. Pneumonitis, a less frequent but severe side effect, was noted in one patient who required hospitalization.

Patient values on treatment: Stop or slow disease progression, reduce side effects, and improve appetite and energy

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Three patient groups, Ontario Lung Association, Lung Cancer Canada and, British Columbia Lung Association provided input on the drug under review. Patient input reported that, from their perspective, the following key treatment outcomes were the most important areas to be addressed by the combination of pembrolizumab and chemotherapy: to stop or slow the progression of the disease, to reduce or eliminate side effects (e.g., reduce pain, fatigue, cough, and shortness of breath), and to improve appetite and energy. Respondents additionally indicated that they would value improved independence and requiring less assistance from others. Patients also expressed the need for lower or no cost burden associated with new treatments. A total of two patient respondents had direct experience with the drug under review. Patients reported that they had a better sense of well-being, tumour shrinkage, reduced symptoms, and increased independence on the combination therapy. The patients with direct experience with the combination therapy reported fatigue, nausea, thyroiditis, pneumonitis, and itchy skin as side effects of treatment. Patient input suggested that patients were willing to tolerate significant side effects if the outcomes of treatment are favourable.

ECONOMIC EVALUATION

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

The pCODR Economic Guidance Panel (EGP) assessed the cost-effectiveness and cost-utility analysis comparing pembrolizumab plus chemotherapy (cisplatin or carboplatin and pemetrexed) and chemotherapy alone (cisplatin or carboplatin and pemetrexed). The submitted model was a three-state partitioned-survival model. The submitter provided analyses for the overall trial population in the base case as well as for the PD-L1 TPS ≥ 50% and < 50% subgroups in scenario analyses.

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

Costs considered included PD-L1 testing, drug acquisition costs, treatment costs for managing adverse events, resource costs for drug administration and disease follow-up, subsequent therapies, and end of life care.

Key clinical effect estimates considered in the analysis included OS, PFS, time on treatment, and health state utilities from the KEYNOTE-189 trial.

A sensitivity analysis was also submitted for the comparison of pembrolizumab plus chemotherapy with pembrolizumab monotherapy (from KEYNOTE-024). These estimations of PFS and OS were obtained by conducting an indirect treatment comparison. The submitted model did not make it possible to alter the hazard ratios calculated using the ITC, which was used to estimate the clinical benefits between pembrolizumab plus chemotherapy and pembrolizumab monotherapy. This was considered an important limitation of the submitted model and the EGP concluded that there was too much uncertainty with the methodology to consider this economic analysis further in its review. As a result, the EGP did not undertake reanalysis estimates for the comparison of pembrolizumab plus chemotherapy with pembrolizumab monotherapy.

Drug costs: High drug cost

The cost of pembrolizumab is $4,400.00 per 100 mg vial or $8,800.00 per dose.

The cost of cisplatin is $19.00 per 100 mg vial. The cost of carboplatin is $18.80 per 150 mg vial. The cost of pemetrexed is $0.83 per mg.

Clinical effect estimates: Uncertainty in the long-term benefit of pembrolizumab

The key inputs that have the most impact on the results of the main economic evaluation include the difference in OS between groups (adjusted or not for post-progression treatment crossover), the clinical benefits after the trial period (maintained or declined after the two-year trial period), and the time horizon. A decline of the clinical benefit of pembrolizumab after the two-year trial period and up to five years was explored. Furthermore, the CGP and EGP considered that a time horizon of 10 years was appropriate. However, the EGP noted that the median follow-up of this trial was 13 months, and there is uncertainty related to the maintenance of the clinical benefit after the two-year trial period. In addition, the EGP was unable to evaluate the use of weight-based dosing of 2 mg/kg of pembrolizumab.

Cost-effectiveness estimates: Not cost-effective at the submitted price

The EGP's ICER estimate (lower bound: $194,242 per quality-adjusted life-year (QALY) and upper bound: $196,477/QALY) was higher than the submitter's estimate ($132,760 per QALY). The EGP's best estimate

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lower bound ICER was based on OS with two-stage adjustment for crossover and clinical benefit decline after two years. The EGP's best estimate upper bound ICER was based on a five-year time horizon, pembrolizumab discontinued at disease progression, and utilities value by progression status. The magnitude of the long-term benefit of pembrolizumab plus chemotherapy is unknown given the lack of long-term survival data from the KEYNOTE-189 trial.

The submitter provided feedback on the pERC Initial Recommendation, disagreeing with the EGP's reanalysis. Specifically, the submitter did not agree with the use of two-stage adjustment for crossover for OS in the lower-bound ICER estimate and the use of a five-year time horizon in the upper-bound ICER estimate. The EGP, however, maintains its reanalysis estimates for the lower-bound and upper-bound ICER estimates. The EGP has clarified that the submitted base-case was based on a time horizon of 10 years and the EGP's lower-bound ICER estimate maintained the 10-year time horizon. The CGP and EGP considered that a time horizon of 10 years was appropriate. However, the EGP reiterated that the median follow-up of the KEYNOTE-189 trial was only 13 months, and there is uncertainty related to the maintenance of the clinical benefit over the two-year trial period. The submitted model allowed the EGP to evaluate the impact of different time horizons by performing several reanalyses. To explore uncertainty related to the maintenance of the clinical benefit over the two-year trial period in the submitted model provided for this review, a five-year time horizon and the crossover adjustment for OS were included in the EGP's reanalysis estimates to account for the uncertainty in the long-term benefits of pembrolizumab. pERC concluded that the submitter's best estimate and the EGP's lower-bound and upper-bound cost-effectiveness estimates were all considered not cost-effective.

ADOPTION FEASIBILITY

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

Increasing the market share uptake, the number of patients eligible to receive pembrolizumab and the duration of treatment as well as retreatment will increase the budget impact. The submitted budget impact accounts for the displacement of the use of second-line pembrolizumab. The submitted budget impact estimate was likely underestimated and will be substantially higher based on the CGP's estimates of eligible patients.

Treatment with pembrolizumab continues until confirmed disease progression, unacceptable toxicity, or a maximum of two years, whichever comes first. In the KEYNOTE-189 trial, the mean duration of therapy was 7.4 months in the pembrolizumab combination group. Patients were eligible for retreatment with pembrolizumab for 12 months if they were initial responders (complete response, partial response, or stable disease) during treatment with pembrolizumab, and had a disease progression at any time during the two-year follow-up period; however, there were no patients in the trial who received retreatment with pembrolizumab. The CGP noted that patients who complete two years of pembrolizumab and discontinue therapy without progression, should have the option for retreatment with pembrolizumab, if there is at least six months between completion of therapy and documented disease progression.

The KEYNOTE-189 trial assessed pembrolizumab at a dose of 200 mg every three weeks up to 35 cycles. However, it is noted that initial pembrolizumab trials assessed pembrolizumab with weight-based dosing at 2 mg/kg. The CGP supports the dosing of pembrolizumab as administered in the KEYNOTE-189 trial, flat dosing of 200 mg every three weeks up to 35 cycles. There is no direct evidence to suggest that flat dosing is superior to weight-based dosing. However, for many patients, the flat dose results in a larger dose and greater cost.

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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. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

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

- Dr. Kelvin Chan and Dr. Marianne Taylor who were not present for the meeting.
- Dr. Anil Abraham Joy who was excluded from voting due to a conflict of interest.
- Daryl Bell who did not vote due to his role as a patient member alternate.

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

- Dr. Kelvin Chan and Dr. Anil Abraham Joy, who were not present for the meeting
- Daryl Bell, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of the 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 (Keytruda) for non-squamous NSCLC, through their declarations, six members had a real, potential, or perceived conflict and based on the application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting. For the Final Recommendation for the review of pembrolizumab (Keytruda) for non-squamous NSCLC, through their declarations, six members had a real, potential, or perceived conflict and based on the application of the *pCODR Conflict of Interest Guidelines*, none 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 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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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG is seeking confirmation that eligibility for pembrolizumab in this setting would not include patients with EGFR, ALK, or ROS-1 mutations. • With respect to treatment sequencing, PAG is seeking guidance on whether patients with mutations (*EGFR, ALK, or ROS-1*) should be treated with targeted treatment first and if it would be reasonable to subsequently treat with pembrolizumab.	• pERC noted that the results from the KEYNOTE-189 trial are not generalizable to patients with molecular abnormalities (e.g., *EGFR, ALK, and ROS1*). • Patients with these mutations should have disease progression on targeted treatment and chemotherapy prior to receiving pembrolizumab.
• PAG is seeking clarity that patients would be eligible for pembrolizumab in this setting irrespective of PD-L1 TPS. • PAG is seeking confirmation that PD-L1 testing is not required for pembrolizumab in this setting.	• Patients would be eligible for pembrolizumab in this setting irrespective of PD-L1 TPS. However, the CGP noted, and pERC agreed, that patients with strong PD-L1 (greater than 50%) would require PD-L1 testing to facilitate treatment decisions using pembrolizumab plus chemotherapy and pembrolizumab alone.
• Although out of scope of the review, PAG is seeking information on the use of pembrolizumab in combination with other chemotherapy regimen (e.g., non-platinum-based regimens).	• There is insufficient evidence to generalize the results from the KEYNOTE-189 trial to non-platinum-based chemotherapy regimens.
• PAG is seeking guidance on weight-based dosing of 2 mg/kg up to a flat dose cap of 200 mg in this setting. • PAG also identified emerging data of dosing pembrolizumab at 400 mg every 6 weeks, PAG is seeking guidance on the appropriateness of alternate dosing/schedule (i.e., 400 mg or 4 mg/kg up to a flat dose cap of 400 mg every 6 weeks).	• pERC noted that the KEYNOTE-189 trial assessed pembrolizumab at a dose of 200 mg every 3 weeks up to 35 cycles and recognized that initial pembrolizumab trials assessed pembrolizumab with weight-based dosing at 2 mg/kg. pERC noted that the CGP supported the dosing of pembrolizumab as administered in the KEYNOTE-189 trial; flat dosing of 200 mg every 3 weeks up to 35 cycles. pERC considered that there is no direct evidence to suggest that flat dosing is superior or inferior to weight-based dosing. However, for many patients, the flat dose results in a larger dose and greater cost than for a weight-based dose. Upon implementation of the reimbursement of pembrolizumab for non-squamous NSCLC patients, pERC recognized that jurisdictions will need to choose to administer pembrolizumab as a flat dose of 200 mg, as in the KEYNOTE-189 trial or at 2 mg/kg up to a total dose of 200 mg (dose capped at 200 mg), as used in clinical practice for other indications.
• PAG is seeking confirmation that patients would not receive subsequent PD-1 or PD-L1 inhibitors (e.g., nivolumab) in the second-line setting.	• pERC noted that patients receiving pembrolizumab plus chemotherapy in the first-line setting would not receive subsequent PD-1 (e.g., nivolumab) or PD-LI inhibitors (e.g., atezolizumab) in the second-line setting.

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• For patients who are unable to tolerate pemetrexed, whether single agent pembrolizumab would be appropriate to continue up to 35 cycles.	• Patients who are unable to tolerate pemetrexed would likely not be administered pembrolizumab. However, in this unlikely setting, it would be reasonable to continue single agent pembrolizumab.
• Following completion of 35 cycles of treatment, appropriateness of retreatment with pembrolizumab and the time interval between end of treatment and relapse. • Appropriateness of retreatment with single agent pembrolizumab (i.e., after 35 cycles or earlier) or pemetrexed maintenance therapy.	• pERC noted that treatment with pembrolizumab continues until confirmed disease progression, unacceptable toxicity, or a maximum of 2 years, whichever comes first. In the KEYNOTE-189 trial, the mean duration of therapy was 7.4 months in the pembrolizumab combination group. pERC also discussed that patients were eligible for retreatment with pembrolizumab for 12 months if they were initial responders (complete response, partial response, or stable disease) during treatment with pembrolizumab, and had a disease progression at any time during the 2-year follow-up period; however, there were no patients in the trial that received retreatment with pembrolizumab. In the absence of evidence from the KEYNOTE-189 trial, pERC felt it is reasonable that patients who complete two years of pembrolizumab and discontinue therapy without progression, should have the option for retreatment with pembrolizumab, if there is at least six months between completion of therapy and documented disease progression. • pERC noted that in the KEYNOTE-189 trial, pembrolizumab dose reductions were not permitted; however, pembrolizumab and chemotherapy treatment could be interrupted or discontinued due to toxicity. If chemotherapy was withheld for toxicity, patients could discontinue chemotherapy and continue on single-agent pembrolizumab. Similarly, they could discontinue pembrolizumab and continue on chemotherapy alone, if appropriate. Chemotherapy could be interrupted for a maximum of 6 weeks; pembrolizumab could be interrupted for a maximum of 12 weeks.
• At the time of this PAG input, durvalumab for locally advanced, unresectable NSCLC in patients whose disease has not progressed following platinum-based chemoradiation therapy is being reviewed by pCODR. PAG is seeking data on whether pembrolizumab or other PD-1/PD-L1 inhibitors would be used for treating metastatic disease after progression on durvalumab as well as the appropriate time frame between treatments.	• pERC considered the CGP's expert opinion and agreed that for patients who received prior adjuvant or consolidation durvalumab and remain candidates for platinum-pemetrexed chemotherapy, it would be reasonable to consider treatment with platinum-pemetrexed plus pembrolizumab. In general, for such patients, it should be more than 12 months since they last received platinum-based therapy. For patients progressing during adjuvant or consolidation immune checkpoint inhibitor therapy there is limited data at this time to support further immune checkpoint inhibitor therapy.

• PAG noted the following groups of patients would need to be addressed on a time-limited basis:
  • Patients recently treated or currently treated with a platinum-based drug plus pemetrexed.
  • Patients currently treated with pemetrexed.
	• At the time of implementing a reimbursement recommendation for pembrolizumab plus chemotherapy, jurisdictions may consider addressing the time-limited need of pembrolizumab for patients who recently initiated treatment with platinum chemotherapy. However, pERC noted that this would not apply to patients who already commenced maintenance pemetrexed or for patients who are not candidates for platinum chemotherapy.

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• For patients with PD-L1 ≥ 50%, single-agent pembrolizumab is available in jurisdictions; PAG is seeking clarity whether these patients should receive single agent pembrolizumab or the combination of pembrolizumab with pemetrexed and platinum chemotherapy.	• pERC noted that single agent pembrolizumab for patients with PD-L1 ≥ 50% is available in jurisdictions. Pembrolizumab in combination with pemetrexed and platinum chemotherapy provides another option for the treatment of these patients. However, there are no randomized trials evaluating the effectiveness of pembrolizumab alone versus pembrolizumab plus chemotherapy in this patient group. pERC agreed with the CGP that both treatments are superior to pemetrexed and platinum chemotherapy alone and should be available to clinicians to choose based on individual patient needs and preferences. pERC noted that routine testing for PD-L1 expression will still be required to facilitate treatment decisions between pembrolizumab plus pemetrexed and platinum chemotherapy or pembrolizumab alone in patients with strong PD-L1 positive tumours.

PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.

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