pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL 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.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this initial recommendation.

Drug: Pembrolizumab (Keytruda)

Submitted Reimbursement Request: For the treatment of patients with metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel, in adults with no prior systemic chemotherapy treatment for metastatic NSCLC.

Submitted by: Merck Canada

Manufactured by: Merck Canada

NOC Date: July 4, 2019

Submission Date: February 8, 2019

Initial Recommendation Issued: October 31, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Cost of Pembrolizumab • $4,400 per 100 mg vial • Cost per dose: $8,800.00 • Cost per 28 days: $11,733

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 does not recommend the reimbursement of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel for the treatment of patients with metastatic squamous NSCLC, in adults with no prior systemic chemotherapy treatment for metastatic NSCLC.

pERC made this recommendation because, despite the observed short-term benefit: overall survival (OS) and, progression-free survival (PFS) with pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel, the long-term benefit of the combination of pembrolizumab with carboplatin and either paclitaxel or nab-paclitaxel could be not established due to the short duration of follow-up from the submitted data from the clinical trial.

pERC agreed that pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel aligns with patient values in that it offers an improvement in short-term OS, no detriment in quality of life, and provides another treatment option.

As a result of the long-term extrapolation due to the short-term follow-up (median follow-up 7.8 months) in the available clinical trial, there is a high degree of uncertainty in the long-term benefit of pembrolizumab in combination with chemotherapy. pERC noted that there were scenarios where pembrolizumab in combination with carboplatin and paclitaxel was less effective and more costly (i.e., dominated) than carboplatin and paclitaxel or pembrolizumab alone (for patients with programmed death

	ligand 1 [PD-L1] tumor proportion score [TPS] ≥50%) and that no possible price reduction would make the pembrolizumab combination cost-effective. Overall, pERC concluded that there was a high level of uncertainty in the comparative estimates and therefore a high level of uncertainty in the cost-effectiveness estimates.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility for Resubmission to Support Reimbursement** pERC considered that the duration of follow-up for the submitted data (Keynote 407) for pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel was short and that long-term data (e.g., OS, PFS and quality of life) are needed to confirm that the results observed are maintained during a longer period of time. pERC acknowledged that Keynote 407 was based on the second interim analysis results and that a third interim analysis will be performed after approximately 415 PFS events are observed, and final analysis will be performed after approximately 361 deaths are observed. As well, pERC noted that the submitted indirect treatment comparison (ITC) (for patients with PD-L1 TPS ≥ 50%) did not include the Keynote 024 trial. Furthermore, pERC agreed with the Economic Guidance Panel (EGP)'s request for the sponsor to provide an economic model in which pembrolizumab in combination with carboplatin and paclitaxel for all patients is compared with pembrolizumab monotherapy for patients with PD-L1 TPS ≥ 50% and with carboplatin and paclitaxel for patients with PD-L1 TPS < 50%. As a result, pERC noted that updated long-term data from Keynote 407, the inclusion of Keynote 024 in the ITC (for PD-L1 TPS ≥ 50%), and a revised economic model to include these data could form the basis of a resubmission to CADTH. In addition, a second economic model where the comparator is divided into two subgroups; pembrolizumab monotherapy for patients with PD-L1 TPS ≥ 50% and carboplatin and paclitaxel for patients with PD-L1 TPS < 50% would be helpful.

SUMMARY OF pERC DELIBERATIONS

pERC noted that there are approximately 29,000 new cases of lung cancer in Canada and 85% of these lung cancers are classified as NSCLC. Of these, 25% to 30% are squamous cell carcinoma. Moreover, pERC acknowledged that of the patients presenting with lung cancer, an estimated 17% will be alive in five years. pERC noted that platinum doublet chemotherapies are standard of care for first-line treatment of advanced squamous NSCLC and that pembrolizumab monotherapy is reimbursed in most jurisdictions for the first-line treatment of patients with PD-L1 TPS ≥ 50% while nab-paclitaxel is not funded in any jurisdiction for advanced NSCLC. pERC considered that there is a need for effective treatment that reduces toxicity, improves quality of life, and prolongs survival irrespective of PD-L1 expression.

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 one double-blind, phase III, superiority randomized controlled trial (Keynote 407) of pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel versus placebo with carboplatin and paclitaxel or nab-paclitaxel for the first-line treatment of patients with metastatic squamous NSCLC, irrespective of PD-L1 TPS. pERC felt there was a clear short-term benefit of pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel, which was observed in the OS gain, modest PFS benefit, and no worsening of quality of life in favour of pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel compared with placebo with carboplatin and paclitaxel or nab-paclitaxel. With respect to OS, pERC noted that crossover from the placebo combination arm to pembrolizumab was allowed, which may have confounded the OS results. pERC acknowledged that despite the high crossover rate in the trial, there was a statistically significant improvement in OS. pERC also discussed whether benefit after progression is a result of the subsequent therapy and not of the initial therapy. Overall, pERC agreed that the short-term OS benefit was clinically meaningful. In terms of PFS, pERC noted that the results were modest. As well, pERC noted the response rates were higher for patients in the pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel group than for the placebo with carboplatin and paclitaxel or nab-paclitaxel group and that the median duration of treatment aligned with the PFS results of both groups. pERC also discussed that there was no worsening of quality of life. In terms of safety, pERC acknowledged that the observed adverse events were expected for immunotherapies and were considered manageable. Any grade infusion reactions, hypothyroidism, hyperthyroidism, and pneumonitis were noted and expected of immunotherapies. pERC also noted that discontinuation rates for grade ≥ 3 adverse events were similar between groups.

pERC acknowledged the Clinical Guidance Panel (CGP)'s conclusion that there is a net clinical benefit from the addition of pembrolizumab to carboplatin/paclitaxel or nab-paclitaxel in patients with no prior systemic chemotherapy treatment for metastatic NSCLC. Based on a robust discussion of the evidence where various strong opinions were expressed, the majority of pERC members agreed that despite the short-term benefits noted above, there was a high degree of uncertainty in the long-term benefit of pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel. As a result, pERC felt that long-term benefit could not be established given the short-term follow-up from Keynote 407 with interim analysis results. pERC discussed that the submitted data were based on second interim analysis results with 349 events of blinded independent central review assessed progressive disease or death (and 205 events of death), and that a third interim analysis will be performed after approximately 415 progression-free survival (PFS) events are observed, and final analysis will be performed after approximately 361 deaths are observed. pERC felt that updated data would provide clarity on the long-term benefit of pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel.

pERC also discussed the sponsor's ITC which estimated the treatment difference in OS and PFS between pembrolizumab in combination with chemotherapy versus pembrolizumab monotherapy in squamous NSCLC patients with PD-L1 TPS ≥ 50%. pERC noted that this ITC was used to inform the cost-effectiveness analysis that compared pembrolizumab in combination with chemotherapy (carboplatin and paclitaxel) to pembrolizumab monotherapy in patients with a PD-L1 TPS ≥ 50%. pERC deliberated on the results of the comparison which found no statistically significant difference in OS and PFS between pembrolizumab and

chemotherapy and pembrolizumab monotherapy in both unadjusted and adjusted models. pERC noted the limitations highlighted by the review team, specifically the exclusion of Keynote 024: a phase III study of pembrolizumab monotherapy versus platinum-based chemotherapy in patients with previously untreated advanced NSCLC with PD-L1 TPS ≥ 50% without epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation. pERC noted that the methods team requested that the sponsor repeat the ITC analysis using patients included in Keynote 024 and that the sponsor was unable to comply. pERC felt that the inclusion of Keynote 024 could reduce the uncertainty in the analysis results. Overall, pERC agreed with the review team's conclusion that the relative efficacy of pembrolizumab in combination with carboplatin and paclitaxel versus pembrolizumab monotherapy remains uncertain in the patient population of interest.

pERC discussed the registered clinician input which indicated that for patients with PD-L1 ≥ 50% who wish to delay or avoid chemotherapy, pembrolizumab may be provided as a monotherapy. pERC also acknowledged that clinicians felt that pembrolizumab with chemotherapy would replace other treatments offered in the first-line setting, especially for patients with PD-L1 < 50%. Lastly, pERC noted that the clinicians indicated that pembrolizumab should be limited to a combination with any platinum doublet and noted that the CGP indicated that pembrolizumab in combination with carboplatin and paclitaxel should be the preferred regimen, but it may be reasonable to use other platinum-based therapies (e.g., for patients who are intolerant to taxanes).

pERC deliberated on patient group input which indicated that patients with NSCLC value symptom control and reduction of adverse events, therapeutic options, avoidance of out-of-pocket costs to patients, and improved survival and quality of life. pERC noted that the patient respondents who had experience with pembrolizumab in combination with chemotherapy were diagnosed with non-squamous, and not squamous, NSCLC. pERC noted that Lung Cancer Canada (LCC) did not believe there was any reason that the experiences of patients with non-squamous NSCLC would be any different from patients with squamous NSCLC. pERC acknowledged that based on these patient experiences, patient respondents found that the pembrolizumab combination was effective at controlling disease, reducing tumour size and stabilizing metastases, side effects were tolerable, and patient respondents reported being able to return to work and engage in social activities with friends and families. pERC also acknowledged that the pembrolizumab combination would provide patients (and clinicians) with the option to treat first-line squamous NSCLC. Overall, pERC agreed that pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel aligns with patient values since it offers another treatment option and improves short-term OS, with no detriment to quality of life.

Of note, the initial recommendation was deferred during the first deliberation because pERC required additional economic data from the review team. Following the deferral of the initial recommendation, the EGP provided additional economic information.

pERC deliberated upon the cost-effectiveness of pembrolizumab in combination with carboplatin and paclitaxel compared to carboplatin and paclitaxel, and ii) pembrolizumab monotherapy (for PD-L1 TPS ≥ 50%) based on the submitted economic evaluation and the reanalysis provided by the EGP. pERC noted the changes that EGP made to address the limitations of the economic evaluation subsequent therapies, modelling of overall survival (OS) for pembrolizumab in combination with carboplatin and paclitaxel, and extrapolation of efficacy data. Firstly, pERC noted that reimbursement of nivolumab as a second-line therapy following first-line treatment with pembrolizumab may not be permitted in jurisdictions and therefore agreed with a change to exclude nivolumab as an option from the possible second-line therapies. As well, pERC acknowledged that SEER data were used for the extrapolation beyond one year and agreed with the EGP's description of the limitations regarding the use of SEER data. pERC supported the EGP's choice to use the OS estimates that were based on extrapolations of Keynote 407 OS data. Moreover, pERC noted the uncertainty regarding the extrapolation of PFS and OS during a 10-year time horizon and discussed that the duration of treatment benefit of pembrolizumab in combination with carboplatin and paclitaxel is uncertain because of the short trial follow-up. As a result, pERC noted the significant uncertainty in the incremental cost-effectiveness ratio (ICER) due to the uncertainty in the clinical effectiveness of pembrolizumab in combination with carboplatin and paclitaxel compared with carboplatin and paclitaxel. Furthermore, in addition to the two changes noted above, pERC discussed the choice of parametric fitting curves in great detail, noting that the choices used to guide the derivation of lower and upper bound estimates could lead to different conclusions about the cost-effectiveness of pembrolizumab plus carboplatin and paclitaxel compared with carboplatin and paclitaxel. The effect of this reanalysis was observed in the EGP's best-case lower bound estimate ($216,280/quality-adjusted life-year [QALY] and upper bound estimate where pembrolizumab in combination with carboplatin and

paclitaxel was less effective and more costly than carboplatin and paclitaxel. Although the EGP concluded that the ICER will likely be closer to the lower estimate, pERC noted that in the EGP's probabilistic analysis results of the upper bound estimate, more than half of the ICER estimates showed that pembrolizumab plus carboplatin and paclitaxel was less effective and more costly than carboplatin and paclitaxel (i.e., dominated). As a result, pERC felt that this scenario was possible. pERC felt that this difference in conclusion in the cost-effectiveness of pembrolizumab plus carboplatin and paclitaxel compared with carboplatin and paclitaxel reflected the high-level of uncertainty about the long-term benefit of pembrolizumab in combination with carboplatin and paclitaxel compared with carboplatin and paclitaxel. pCODR noted that the uncertainty in the long-term treatment effect will impact the true ICER.

When comparing pembrolizumab in combination with carboplatin and paclitaxel to pembrolizumab alone for patients with PD-L1 TPS ≥ 50%, pERC noted that the EGP's best-case estimate of the ICER indicated that pembrolizumab in combination with carboplatin and paclitaxel was less effective and more costly than pembrolizumab alone (i.e., dominated). pERC noted that the EGP requested that the sponsor provide an economic model in which pembrolizumab in combination with carboplatin and paclitaxel for all patients is compared with pembrolizumab monotherapy for patients with PD-L1 TPS ≥ 50% and with carboplatin and paclitaxel for patients with PD-L1 TPS < 50% in order to better understand differences in effectiveness and to consider the treatment most relevant to the Canadian context. However, pERC noted that the sponsor was unable to comply. pERC agreed with the EGP and felt that a secondary analysis dividing the comparator into two subgroups pembrolizumab monotherapy for patients with PD-L1 TPS ≥ 50% and carboplatin and paclitaxel for patients with PD-L1 TPS < 50%, would have been of value.

pERC discussed in great detail the short-term trial results (median follow-up 7.8 months), the extrapolation of data (approximately nine years of extrapolation in a 10-year time horizon model), the choice of parametric fitting curve, the limitations of the economic model and the EGP's best-case estimates (in particular the scenarios that resulted in pembrolizumab in combination with carboplatin and paclitaxel being less effective and more costly than the comparator). As a result of the long-term extrapolation due to the short-term follow-up (median follow-up of 7.8 months) in the available clinical trial, there is a high degree of uncertainty in the long-term benefit of pembrolizumab in combination with chemotherapy. pERC noted that there were scenarios where pembrolizumab in combination with carboplatin and paclitaxel was less effective and more costly (i.e., dominated) than in scenarios with carboplatin and paclitaxel or pembrolizumab alone (for patients with programmed death ligand 1 [PD-L1] tumor proportion score [TPS] ≥50%) and that no possible price reduction would make the pembrolizumab combination cost-effective. Overall, pERC concluded that there was a high level of uncertainty in the comparative estimates and therefore a high level of uncertainty in the cost-effectiveness estimates.

Therefore, given the high uncertainty in the long-term benefit and limitations noted above, pERC felt that the following components could form the basis of a resubmission to CADTH: updated data from Keynote 407, the inclusion of Keynote 024 in the indirect comparison (for PD-L1 TPS ≥50%), and a revised economic model to include these data, in addition to a second economic model where the comparator is divided into two subgroups: pembrolizumab monotherapy for patients with PD-L1 TPS ≥ 50% and carboplatin and paclitaxel for patients with PD-L1 TPS < 50%.

Lastly, pERC considered the feasibility of implementing a positive reimbursement recommendation for pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel. pERC noted that most jurisdictions currently fund pembrolizumab for patients with NSCLC with PD-L1 TPS ≥50% patients in the first-line setting and that nab-paclitaxel is not funded in any jurisdiction for advanced NSCLC. In terms of eligible population, it was noted that patients with active central nervous system metastases, Eastern Cooperative Oncology Group (ECOG) performance status of two or greater or if they had prior treatment with any PD-1/PD-L1 drug were excluded from the KEYNOTE 407 trial. With regard to implementation factors, weight-based dosing and flat dosing was discussed along with the costs and budget impact of pembrolizumab in combination with carboplatin and paclitaxel.

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, the Ontario Lung Association, and the British Columbia Lung Association
- Input from two joint registered clinicians: total of 15 registered clinicians; two from Cancer Care Ontario and thirteen from LCC
- Input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel, for the treatment of metastatic, squamous NSCLC in adult patients with no prior systemic chemotherapy.

Studies included: Phase III trial, second interim analysis

The pCODR systematic review included one randomized controlled trial (RCT), KEYNOTE-407 (KN-407). KN-407 was an international, multi-centre, double-blind, phase III, superiority RCT of pembrolizumab in combination with chemotherapy (carboplatin and paclitaxel or nab-paclitaxel) versus placebo with chemotherapy (carboplatin and paclitaxel or nab-paclitaxel) for the first-line treatment of patients with metastatic squamous NSCLC, irrespective of PD-L1 tumour proportion score (TPS). Eligible patients were randomized in a 1:1 ratio to receive either 200 mg of pembrolizumab or saline placebo for up to 35 cycles, in combination with carboplatin (at a dose to produce an area under the curve of 6 mg per millilitre per minute) and paclitaxel (200 mg per square metre of body-surface area) or nab-paclitaxel (100 mg per square metre of body-surface area) for four cycles. Assignment to the chemotherapy arm was determined prior to randomization. Treatments were administered intravenously in three-week cycles.

A total of 559 patients underwent randomization, with 278 randomized to the pembrolizumab + chemotherapy arm and 281 to the placebo + chemotherapy arm. All patients randomized received at least one dose of the assigned treatment, except for one patient in the placebo + chemotherapy arm. Participants continued treatment until radiographically confirmed progressive disease (PD), occurrence of unacceptable toxic effects, investigator's decision to discontinue the treatment, or withdrawal of consent.

The dual primary end points of KN-407 were OS and PFS, and secondary outcomes included objective response rate (ORR) and duration of response (DOR). Exploratory endpoints included OS, PFS, and ORR, by PD-L1 subgroup, taxane therapy, and PFS, ORR, DOR were assessed by the investigator as per irRECIST and RECIST 1.1. Health-related quality of life (HRQoL) was also explored and assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core 30 (EORTC-QLQ-C30) and the EORTC-QLQ-Lung Cancer 13 (EORTC-QLQ-LC13), as well as the EQ-5D questionnaire for economic evaluation. Safety was monitored regularly throughout the study and included all patients who received at least one dose of the assigned combination treatment.

The submitted data were based on second interim analysis results with 349 events of BICR-assessed PD or death (and 205 events of death), and a third interim analysis will be performed after approximately 415 PFS events are observed, and final analysis will be performed after approximately 361 deaths are observed.

Patient populations: Stage IV squamous NSCLC patients with no prior systemic therapy

Key eligibility criteria included ≥ 18 years of age, stage IV squamous NSCLC (mixed histology accepted if squamous component), no prior systemic therapy, measurable disease based on RECIST 1.1, tumour tissue

sample for PD-L1 assessment, ECOG PS 0 or 1, adequate organ function, and life expectancy of ≥ 3 months.

Overall, 54.6% (n = 305) of participants were ≥ 65 years of age, 81.4% (n = 455) were male, 81.0% (n = 453) were from non-East Asia countries, 92.7% (n = 518) were current or former smokers, 97.7% (n = 546) had predominant squamous histology, and 63.1% (n = 353) had a PD-L1 TPS of ≥ 1%. Baseline characteristics were generally balanced between treatment arms, except for a higher proportion of males (n = 235; 83.6%) in the placebo combination arm compared with the pembrolizumab combination arm (n=220; 79.1%) and a higher proportion of patients with ECOG PS 1 in the pembrolizumab combination arm (n = 205; 73.7%) compared with the placebo combination arm (n = 191; 68.0%).

The treatment crossover rate including all participants receiving a PD-1 or PD-L1 inhibitor internal and external to the trial in the intent-to-treat (ITT) population was 31.7%, and 42.8% among those who discontinued their assigned treatment for any reason. It was acknowledged by the methods team that crossover from the placebo combination arm to pembrolizumab monotherapy was allowed, which may confound the results of the analysis of OS. Given the results showed a statistically significant reduction in the risk of death despite the potential for confounding due to crossover (HR: 0.64; 95% CI, 0.49 to 0.85; *P* < 0.001), the treatment effect when adjusted for crossover was larger than reported in the trial (HR: 0.54; 95% CI, 0.44 to 0.68; P < 0.0001).

Key efficacy results: Short duration of follow-up, short-term OS benefit, and modest PFS benefit

Efficacy analyses were performed using the ITT population, which included a total of 559 patients. As of the second interim analysis data cut-off date, the median duration of follow-up, defined as the time from randomization to death or date of data cut-off (for those who were still alive), was 7.8 months (range, 0.1 to 19.1 months).

The key efficacy outcomes deliberated on by pERC included OS and PFS.

Overall survival: The median OS was 15.9 months (95% CI, 13.2 to not reached [NR]) in the pembrolizumab combination arm (85 deaths) and 11.3 months (95% CI, 9.5 to 14.8) in the placebo combination arm (120 deaths). There was a significant reduction in the risk of death by 36% in the pembrolizumab combination arm compared with the placebo combination arm (HR: 0.64, 95% CI, 0.49 to 0.85; *P* < 0.0001). Exploratory subgroup analyses of OS were consistent with overall trial results, with a clinically meaningful reduction in risk of death observed across all subgroups, however there was no statistically significant difference between treatment arms for patients with PD-L1 TPS ≥ 50% or patients ≥ 65 years of age.

Progression-free survival: The median PFS was 6.4 months (95% CI, 6.2 to 8.3) in the pembrolizumab combination arm (152 events) compared with 4.8 months (95% CI, 4.3 to 5.7) in the placebo combination arm (197 events). There was a 44% reduction in the risk of BICR-assessed PD or death in the pembrolizumab combination arm compared with the placebo combination arm (HR: 0.56; 95% CI, 0.45 to 0.70; *P* < 0.0001). Exploratory subgroup analyses of PFS were consistent with the overall trial results, with a statistically and clinically significant reduction in the risk of PD or death seen across all subgroups.

pERC also discussed ORR and duration of response.

Objective response rate: The ORR was higher in the pembrolizumab combination arm (57.9%, 95% CI, 51.9 to 63.8) than in the placebo combination arm (38.4%, 95% CI, 32.7 to 44.4), representing a treatment difference of patients experiencing a complete response (CR) or partial response (PR) of 19.5% (95% CI, 11.2 to 27.5). Few patients in both treatment arms achieved a best overall response of CR (six patients in the placebo combination arm and four patients in the pembrolizumab combination arm). The ORR treatment difference was consistent across all subgroups showing a marked benefit in achieving a CR or PR response with pembrolizumab combination therapy when compared with placebo combination therapy, however the ORR treatment difference was not statistically significant for patients with ECOG PS 0.

Duration of response: The median time to response was 1.4 months in both groups, and median DOR was 7.7 months (95% CI, 1.1 to 14.7) in the BICR-assessed pembrolizumab combination group compared with 4.8 months (95% CI, 1.3 to 15.8) in the placebo combination group, with participants experiencing ongoing response in both treatment arms.

Patient-reported outcomes: No worsening of quality of life, statistical improvement in quality of life at certain time points.

Study compliance was high at baseline (> 90%) and at both weeks 9 and 18 (> 80%); however, patient numbers decreased at each time point as more participants discontinued from the trial. Mean EORTC QLQ-C30 global health status (GHS)/quality of life (QoL) score at baseline was similar between the two treatment arms (63.9 versus 62.7 in the pembrolizumab combination and placebo combination arms, respectively). There was a statistically significant difference between treatment arms in the mean global health score based on the EORTC-QLQ-C30 at both week 9 (LS mean difference: 3.6; 95% CI, 0.3 to 6.9) and 18 (LS mean difference: 4.9; 95% CI, 1.4 to 8.3). As noted by the methods team, based on evidence-based guidelines, the clinical relevance of this finding is small. There was no statistically significant difference between treatment arms in the EQ-5D-3L visual analogue scale score at week 9, however there was a statistically significant difference between treatment arms at week 18.

Limitations: Short duration of follow-up, long-term data required

The key limitations of the KN-407 trial included:

- Investigator and respondent bias may still have existed, despite a double-blinded study, as specific immune-related adverse events (AEs) commonly associated with pembrolizumab may have made treatment assignment predictable. This may have influenced outcomes such as PFS, specifically in terms of delaying or expediting a scan to confirm PD based on suspected treatment regimen.
- Crossover from the placebo combination arm to pembrolizumab monotherapy was allowed, which may confound the results of the analysis of OS. Given the results showed a statistically significant reduction in the risk of death despite the potential for confounding due to crossover, the actual treatment effect, when adjusting for crossover, was larger than reported in the trial.
- There was a higher proportion of patients with ECOG PS 1 and fewer male patients in the pembrolizumab combination group compared with the placebo combination group. The combination of these factors may have biased results in favour of the placebo combination group.
- The duration of follow-up in KN-407 was short. Long-term OS, PFS, and HRQoL data are required to ensure the results observed in this study are consistent and maintained during a longer period. Additionally, there is the possibility for toxic, delayed immune-related AEs to develop over time with drugs such as pembrolizumab, and the duration of the trial was inadequate to capture these events. Long-term safety data are also required.

In the absence of a RCT comparing pembrolizumab + chemotherapy with pembrolizumab monotherapy for patients with squamous NSCLC with PD-L1 TPS ≥ 50%, the sponsor submitted an ITC that estimated the treatment difference in OS and PFS between pembrolizumab in combination with chemotherapy versus pembrolizumab monotherapy in squamous NSCLC patients with PD-L1 TPS ≥ 50%. This ITC was used to inform the cost-effectiveness analysis that compared pembrolizumab in combination with chemotherapy (carboplatin and paclitaxel) to pembrolizumab monotherapy in patients with a PD-L1 TPS ≥ 50%.

Overall the review team concluded that a head-to-head trial would be required to definitively confirm the results reported in the ITC, and the relative efficacy of pembrolizumab plus chemotherapy versus pembrolizumab monotherapy remains uncertain in the patient population of interest. The following limitations were noted:

- The exclusion of Keynote 024; as the inclusion of these patients in the indirect treatment comparison may have provided a more realistic estimate of the comparative efficacy of pembrolizumab plus chemotherapy versus pembrolizumab monotherapy.
- The small sample size may also contribute to instability of the estimates, as CIs for reported HRs were wide, and as such, the results should be interpreted with caution.
- The proportional hazards assumption was not met for OS and PFS for the KN-042 study, suggesting results should be interpreted with caution.

Of note, the methods team requested that the sponsor repeat the ITC analysis using patients included in Keynote 024; the sponsor was unable to comply.

Safety: Manageable toxicity profile and typical outcomes for immunotherapies

AEs of any grade occurred in 98.2% and 97.9% of patients in the pembrolizumab combination arm and placebo combination arm, respectively. AEs of grade ≥ 3 occurred in 69.8% and 68.2% of participants in

the pembrolizumab combination group and placebo combination arms, respectively. There was a higher proportion of patients in the pembrolizumab combination arm (95.3%) with treatment-emergent AEs (TEAEs) compared with the placebo combination arm (88.9%). Participants with serious AEs (SAEs) were comparable between treatment arms (40.6% versus 38.2% in the pembrolizumab combination group and placebo combination group, respectively); however, a higher proportion of patients in the pembrolizumab combination arm experienced a serious TEAE (25.2% versus 18.2%). Participants with grade ≥ 3 TEAEs were comparable between treatment arms (54.7% versus 55.0% in the pembrolizumab combination arm and placebo combination group, respectively).

Any grade AEs of interest, defined as events of interest that are infusion reactions and events with an immune-related cause, were higher in the pembrolizumab combination arm (28.8% versus 8.6% in the placebo combination arm). Hypothyroidism (7.9%), hyperthyroidism (7.2%), and pneumonitis (6.5%) were higher in the pembrolizumab combination arm than the placebo combination arm (1.8%, 0.7%, and 2.1% for hypothyroidism, hyperthyroidism, and pneumonitis, respectively). Grade ≥ 3 AEs of interest were higher in the pembrolizumab combination arm (10.8% versus 3.2% in the placebo combination group), with pneumonitis being the most common (2.5% versus 1.1%, respectively).

A higher proportion of participants in the pembrolizumab combination group discontinued all treatment components (13.3% versus 6.4% in the placebo combination arm) and any treatment components (23.4% versus 11.8% in the placebo combination group) due to any grade AEs. Discontinuation rates were similar for grade ≥ 3 AEs.

Rates of AEs resulting in death were 8.3% for participants in the pembrolizumab combination arm and 6.4% in the placebo combination group. As per investigator assessment, 10 deaths in the pembrolizumab combination group were treatment-related compared with six deaths in the placebo combination arm. One patient in each group died from an immune-related adverse event (pneumonitis in both patients).

Need and burden of illness: Platinum doublet therapies are standard of care, pembrolizumab monotherapy available for patients with PD-L1 TPS ≥ 50%

There are close to 29,000 new cases of lung cancer in Canada and NSCLC comprises approximately 85% of lung cancer diagnosis with squamous cell carcinoma representing 20% to 30% of NSCLC cases. Of the patients presenting with lung cancer, an estimated 17% will be alive in five years. Platinum doublet therapies are standard of care for first-line treatment of advanced squamous NSCLC and pembrolizumab monotherapy is reimbursed in most jurisdictions for patients with PD-L1 TPS ≥ 50%, while nab-paclitaxel is not funded in any jurisdiction for advanced NSCLC.

Registered clinician input: platinum doublet chemotherapy appropriate comparator for patients with PD-L1 TPS <50% and pembrolizumab monotherapy appropriate comparator for patients with PD-L1 TPS ≥50%

Registered clinicians suggested that the most appropriate comparators were pembrolizumab monotherapy for patients with PD-L1 TPS ≥ 50% and platinum doublet chemotherapy for patients with PD-L1 TPS < 50%. Clinicians agreed that inclusion and exclusion criteria from the Keynote 407 trial were generalizable to and were reflective of Canadian patients in clinical practice. Clinicians noted that while pembrolizumab will not be introduced as a new treatment for patients with squamous NSCLC, it would replace other treatments (e.g. immunotherapy and chemotherapy), offered in the first-line setting. For patients with PD-L1 ≥50% who wish to delay or avoid chemotherapy, pembrolizumab may be provided as a monotherapy. However, the treatment regimen for the patient will ultimately depend on disease characteristics in addition to patient preference. With regard to whether pembrolizumab should be provided to patients with a single-drug chemotherapy or platinum doublet chemotherapy, both clinicians agreed that pembrolizumab should be limited to a combination with any platinum doublet; current evidence does not support the use of pembrolizumab in combination with single-drug chemotherapy.

PATIENT-BASED VALUES

Values of patients with NSCLC: Symptom control and reduction of AEs, therapeutic options, no patient/caregiver cost for treatment and improved survival and QoL

From a patient's perspective, lung cancer can limit a patient's ability to engage in activities with friends and family, work and engage in tasks of day-to-day living. Patients can feel isolated and experience a loss

of independence due to their condition, which can lead to depression. Current treatments for patients with squamous NSCLC include chemotherapy and immunotherapy. Both chemotherapy and immunotherapy were stated to help with disease control, however side effects of immunotherapy were generally described as more tolerable compared with chemotherapy. A concern was raised regarding the use of chemotherapy and immunotherapy as single drugs, as patients with squamous NSCLC may progress while on treatment and subsequently may not be able to receive systemic treatment due to the aggressive nature of their disease. Patient groups value having symptom control and reduction of AEs, therapeutic options, avoidance of out-of-pocket costs to patients, and improved survival and QoL.

Patient values on treatment: No squamous NSCLC patient respondents with pembrolizumab and chemotherapy experience

The combination of pembrolizumab with chemotherapy would provide patients with the option of the most effective treatment up front. Only input from LCC provided information regarding the combination of pembrolizumab and chemotherapy, however none of the patients providing input had a diagnosis of squamous NSCLC. LCC stated that they did not believe there was any reason that the experiences of patients with non-squamous NSCLC would be any different from patients with squamous NSCLC. A total of seven patients with non-squamous NSCLC provided input regarding treatment with the combination of pembrolizumab and chemotherapy. Patients found that chemotherapy combined with pembrolizumab was effective at controlling disease, reducing tumour size, and stabilizing metastases. Side effects were described as tolerable, and patients reported being able to return to work and engage in social activities with friends and families. However, one patient did report having to stop treatment due to having developed diverticulitis, and two other patients reported progression of their disease. Overall, pembrolizumab and chemotherapy was described as an effective treatment with tolerable side effects.

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 in combination with carboplatin and paclitaxel to carboplatin and paclitaxel. The sponsor also included an additional comparison among PD-L1 ≥ 50% patients only which compared pembrolizumab in combination with carboplatin and paclitaxel to pembrolizumab monotherapy. The submitted model was a three-state partitioned-survival model. The EGP requested that the sponsor provide a model in which pembrolizumab + chemotherapy for all patients is compared against the status quo in Canada, in which patients with TPS ≥ 50% receive pembrolizumab monotherapy and patients with TPS < 50% receive chemotherapy. The sponsor was unable to comply.

Basis of the economic model: Partitioned-survival model

The submitted model was a partitioned-survival model. Model effectiveness parameters (for the primary comparison pembrolizumab in combination with carboplatin and paclitaxel compared to carboplatin and paclitaxel) were estimated from KN407 patient-level data for time on treatment (ToT), PFS based on blinded independent review and OS up to year 1, and SEER data were used for OS extrapolation beyond one year.

For the additional comparison among PD-L1 ≥ 50% patients only, data were derived from an ITC of KN407 with KN042.

Drug costs: High drug cost compared with carboplatin and paclitaxel and compared with pembrolizumab monotherapy

Cost of Pembrolizumab *Price source: Merck Canada Inc.*	• $4,400 per 100 mg vial • Cost per dose: $8,800.00 • Cost per 28 days: $11,733
Cost of chemotherapy * *Price Source:* *Carboplatin: INESSS Avis au ministre, Giotrif (June 2014)* *Paclitaxel: INESSS Avis au ministre, Avastin (June 2016)*	Carboplatin: • $18.80 per 150 mg vial • $56.39 per 450 mg vial • Cost per dose (645 mg): $87.41 • Cost per 28 days: $116.55 Paclitaxel: • $5.27 per 30 mg vial

	• $17.56 per 100 mg vial • Cost per dose (200 mg/m^2): $64.36 • Cost per 28 days: $85.81

INESSS = Institut national d'excellence en santé et en services sociaux.

Clinical effect estimates: Extrapolation in OS estimate is main factor influencing cost, shortened estimated overall survival obtained when an extrapolation model is used for OS is main factor influencing clinical effect

The sponsor's estimate of the ΔC for pembrolizumab in combination with carboplatin and paclitaxel versus carboplatin and paclitaxel is $99,499. The main factor that influences the difference in ΔC is the extrapolated OS estimate, which predicts a shorter expected time during which patients receive pembrolizumab and hence lower drug acquisition costs. Specifically, under the sponsor's base case estimated OS, the difference in expected time in the progression-free state is 10.21 months. In the EGP's reanalysis, this difference was revised down to between 6.88 and 7.75 months.

The sponsor's estimate of the extra clinical effect of pembrolizumab in combination with carboplatin and paclitaxel versus carboplatin and paclitaxel is between 0.63 and 1.15 QALYs greater than the EGP's estimate. The main factor causing this difference is the shortened estimated overall survival that is obtained when an extrapolation model is used for the OS.

- The sponsor's estimate of the ΔC for pembrolizumab in combination with carboplatin and paclitaxel versus pembrolizumab monotherapy is $11,180. The main factor that influences the difference in ΔC is the extrapolated OS estimate, which predicts a shorter expected time during which patients receive pembrolizumab and hence lower drug acquisition costs. Specifically, under the sponsor's base case estimated OS, the difference in expected time in the progression-free state is 7.83 months. In the EGP's reanalysis, this difference was revised down to between 7.06 and 7.83 months.
- The sponsor's estimate of the extra clinical effect of pembrolizumab in combination with carboplatin and paclitaxel versus pembrolizumab monotherapy is between 0.08 and 0.09 QALYs greater than the EGP's estimate. The main factor causing this difference is the shortened estimated overall survival that is obtained when an extrapolation model is used for the OS.

Cost-effectiveness estimates: Scenarios where pembrolizumab in combination with carboplatin and paclitaxel is more costly and less effective than comparators highlight the uncertainty in the long-term clinical benefit

The EGP's best estimate of ΔC and ΔE for pembrolizumab in combination with carboplatin and paclitaxel when compared with carboplatin and paclitaxel is:

- Lower bound ΔC = $106,271
- Upper bound ΔC = $98,981
- Lower bound ΔE = 0.49
- Upper bound ΔE = -0.03
    - These ranges produced a lower bound on the ICER of $216,280/QALY and an upper bound in which pembrolizumab in combination with carboplatin and paclitaxel is dominated (more costly, less effective). Given that the CGP agreed that the chemotherapy alone OS is unlikely to be greater than pembrolizumab + chemotherapy OS, EGP believe that the ICER will be likely closer to the lower bound of the reanalysis.

The EGP judged that the extrapolation of OS during a nine-year period from a 7.8-month median follow-up study is highly uncertain. Therefore, to derive the upper bound of the reanalysis, the EGP conducted sensitivity analyses using log-logistic extrapolation curves. This class of curve was identified by the sponsor as the next best fitting parametric function "based on AIC and BIC criteria with visual inspection."

It was found that by only changing the chemotherapy OS extrapolation from the best (exponential) extrapolation to the second best (log-logistic) extrapolation, and keeping the best fitting (exponential) curve for the pembrolizumab + chemotherapy OS, the conclusion of the analysis would change. Specifically, based on a deterministic reanalysis of the economic model, the expected OS in the chemotherapy arm is 1.29 life-years (LY) using the exponential extrapolation, and 1.94 LYs using the log-logistic extrapolation. The expected overall survival in the pembrolizumab + chemotherapy arm using the

exponential OS extrapolation is 1.92 LY. Therefore, under this reanalysis, an expected LY estimate of -0.02 LY is obtained. With respect to the sponsor's model, this reanalysis projects that chemotherapy OS would overtake pembrolizumab + chemotherapy OS around week 182, which shows the KM trial data and the modelled long-term OS curves that yielded the upper bound ICER. In the cost-effectiveness scatter plot resulting from the PSA carried out for the upper bound estimate, negative QALYs were estimated for 55% (2,745 of 5,000) of probabilistic iterations of the model. Based on the PSA, this reanalysis predicts that pembrolizumab + chemotherapy treatment is more costly and less effective (therefore, is dominated).

The EGP's best estimate of ΔC and ΔE for pembrolizumab in combination with carboplatin and paclitaxel when compared with pembrolizumab monotherapy (among PD-L1 ≥ 50% patients) is:

- Lower bound ΔC = $9,010
- Upper bound ΔC = $8,252
- Lower bound ΔE = -0.07
- Upper bound ΔE = -0.08
    - Pembrolizumab in combination with carboplatin and paclitaxel is dominated under both the lower bound and upper bound scenarios.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: feasibility of implementing a positive funding recommendation discussed

The budget impact is that of the Canadian public health care system and the estimated overall three-year Canadian budgetary impact of reimbursing pembrolizumab for the first-line treatment of patients with metastatic squamous non-small cell lung cancer in combination with carboplatin and paclitaxel or nab-paclitaxel.

The EGP stated that the factors that most influence the budget impact analysis are the shape of the pembrolizumab combination uptake curve (which determines the rate at which the pembrolizumab combination captures market share with respect to competing treatments), the inclusion of patients at stage IIIb, the percentage of patients referred to medical oncologists, the percentage of patients treated by medical oncologists, the time to peak share of pembrolizumab in combination with carboplatin and paclitaxel, and a modification of the dose intensity.

pERC considered the feasibility of implementing a positive funding recommendation for pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel. In terms of the patient population, most jurisdictions currently fund pembrolizumab for patients with NSCLC with PD-L1 TPS ≥ 50% patients in the first-line setting and nab-paclitaxel is not funded in any jurisdiction for advanced NSCLC. In terms of eligible population, it was noted that patients with active central nervous system metastases, ECOG performance status of two or greater or had prior treatment with any PD-1/PD-L1 drug were excluded from KEYNOTE 407. With regard to implementation factors, weight-based dosing and flat dosing was discussed along with the costs and budget impact.

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. Michael Crump, 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. Maureen Trudeau, Dr. Kelvin Chan, and Dr. Winson Cheung 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.

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 squamous NSCLC, through their declarations, four members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and PAG 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*.

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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