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

Drug: Pembrolizumab (Keytruda)

Submitted Reimbursement Request:
First-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) as monotherapy, in adult patients whose tumours have programmed death-ligand 1 (PD-L1) expression (Combined Positive Score [CPS] ≥ 1) as determined by a validated test.
First-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in combination with platinum and fluorouracil (FU) chemotherapy, in adult patients.

Submitted By: Merck Canada	**Manufactured By:** Merck Canada
NOC Date: October 9, 2020	**Submission Date:** May 1, 2020
Initial Recommendation: December 3, 2020	**Final Recommendation:** December 22, 2020

Approximate per Patient Drug Costs, per Month (28 Days)	Pembrolizumab costs $4,400 for a 100 mg/4 mL vial. At the recommended dose of 200 mg administered as intravenous infusion over 30 minutes every three weeks, pembrolizumab costs $8,800 per 21-day cycle. Pembrolizumab in combination with platinum chemotherapy plus 5-fluorouracil (FU) costs $9,701 to $9,982 per 21-day cycle.

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 reimbursement of pembrolizumab for the first-line treatment of metastatic or unresectable recurrent HNSCC as monotherapy for patients whose tumours have PD-L1 expression CPS ≥ 1, or in combination with platinum and 5-FU chemotherapy regardless of PD-L1 expression level, if the following conditions are met:

- cost-effectiveness being improved to an acceptable level
- feasibility of adoption (budget impact) is addressed.

Pembrolizumab treatment should continue until confirmed disease progression or unacceptable toxicity to a maximum of 35 cycles (approximately two years), whichever occurs first.

pERC made this recommendation because it was satisfied that compared with cetuximab in combination with platinum and 5-FU chemotherapy, there is a net clinical benefit of pembrolizumab monotherapy for patients with metastatic or unresectable recurrent HNSCC whose tumours have PD-L1 expression CPS ≥ 1 or in combination with chemotherapy regardless of PD-L1 expression level, based on a statistically significant and clinically meaningful improvement in overall survival (OS), an acceptable toxicity profile, and a need for improved treatment options. As well,

	pembrolizumab monotherapy or in combination with chemotherapy appears to maintain quality of life (QoL) compared with cetuximab in combination with platinum and 5-FU chemotherapy. Furthermore, the Committee noted that cetuximab in combination with chemotherapy is not available for most Canadian patients. pERC agreed with the CGP that it would be reasonable to generalize the treatment effect of pembrolizumab monotherapy or in combination with chemotherapy from the KEYNOTE-048 trial to patients receiving standard care with first-line platinum doublet chemotherapy. pERC acknowledged that HNSCC has a major negative impact on patients' quality of life. pERC concluded that pembrolizumab monotherapy or in combination with chemotherapy aligns with the following patient values: improves OS, has manageable toxicities, appears to maintain QoL, and offers an additional treatment option. pERC concluded that pembrolizumab, either as monotherapy or in combination with platinum chemotherapy plus 5-FU, was not cost-effective at the submitted price versus platinum plus 5-FU. This is driven largely by the high cost of pembrolizumab relative to current standard of care. CADTH's reanalysis of the sponsor's budget impact analysis suggests that the budget impact of introducing pembrolizumab to the market is substantial and underestimated.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing arrangements to improve cost-effectiveness and decrease budget impact** Given that pERC was satisfied that there is a net clinical benefit of pembrolizumab monotherapy or in combination with chemotherapy, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of pembrolizumab monotherapy or in combination with chemotherapy. pERC noted that a reduction in the price of pembrolizumab would be required to improve the cost-effectiveness to an acceptable level and to decrease the predicted budget impact. **Companion diagnostic test (PD-L1 CPS test)** pERC considered that determination of PD-L1 expression level by a validated test is required prior to initiation of treatment with pembrolizumab monotherapy. pERC noted that some jurisdictions may not have CPS-validated testing in place and may be required to send tissue samples out of province. The Committee noted that it would be ideal for jurisdictions to have PD-L1 CPS testing results at the time of diagnosis to manage both the patient population and the budget impact of a reimbursement recommendation. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

In Canada, an estimated 5,400 people are diagnosed with head and neck cancers every year and an estimated 1,500 Canadians will die from these in 2020. Approximately 90% to 95% of head and neck cancers are squamous cell carcinomas. The majority of patients will present with metastatic disease (regional nodal involvement in 43% and distant metastasis in 10%). The most commonly used therapies in Canada for first-line treatment of recurrent or HNSCCs are typically platinum doublet chemotherapy (cisplatin plus 5-FU, carboplatin plus 5-FU or carboplatin plus paclitaxel), which have been the standard of care in Canada for several decades. The median OS with platinum-based combination regimens ranges from 5.0 months to 8.7 months across trials. Cetuximab in combination with platinum plus 5-FU is not currently approved by Health Canada and not funded in most provinces. pERC noted that recurrent or metastatic HNSCC is associated with significant morbidity and poses a treatment challenge due to the limited therapeutic options. pERC agreed with the CADTH CGP and the registered clinicians who provided input to this submission that there is a need for more effective and tolerable treatments in this patient population.

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

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated the results of one randomized, multi-national, open-label, phase III trial (KEYNOTE-048) that evaluated the efficacy and safety of pembrolizumab monotherapy (PEMB-mono) or pembrolizumab in combination with platinum and 5-FU (PEMB-chemo) compared with cetuximab in combination with platinum plus 5-FU (CET-chemo) as a first-line treatment in patients with recurrent or metastatic HNSCC that was considered incurable by local therapies. pERC discussed that the KEYNOTE-048 trial was generally well-conducted. Overall, the KEYNOTE-048 trial had 14 hypotheses for the primary efficacy analysis, which were evaluated by comparing PEMB-mono or PEMB-chemo with CET-chemo for the co-primary outcomes OS and PFS in the intention-to-treat (ITT) population and patients with PD-L1 expression levels of CPS ≥ 1 or CPS ≥ 20. pERC noted that the reimbursement request for PEMB-mono was for the CPS ≥ 1 subgroup; for PEMB-chemo, it was for the ITT population (all patients regardless of PD-L1 expression level). pERC noted that when compared to CET-chemo, OS results were statistically significant and clinically meaningful in favour of PEMB-mono and PEMB-chemo for the CPS ≥ 1 subgroup and ITT population, respectively. pERC also considered long-term exploratory analyses at four-years follow-up that suggested that the OS benefit was maintained across the overall trial population and subpopulations (i.e., CPS ≥ 1 and CPS ≥ 20). The Committee agreed with the CGP and the registered clinicians that the improvements in OS observed in the KEYNOTE-048 trial are of clinical importance in this incurable disease setting, in which current median OS ranges from 5.0 months to 8.7 months with platinum-based combination chemotherapies, which have been the standard of care in Canada for several decades. pERC noted that the proportional hazard assumption was not met regarding OS analyses, which introduced some uncertainty, but that this phenomenon has been observed frequently in cancer immunotherapy trials due to delayed clinical effects, which is likely due to the mechanism of action of immunotherapies. pERC discussed that neither PFS, the co-primary outcome, nor objective response rate (ORR), a secondary outcome, showed statistically significant or clinically meaningful benefits compared with CET-chemo for either PEMB-mono or PEMB-chemo. pERC agreed with the CGP that PFS and ORR have not been validated as surrogate end points for OS in immunotherapy trials in solid tumours.

pERC deliberated the safety data from the KEYNOTE-048 trial and noted that almost all patients in each of the three groups (PEMB-mono, PEMB-chemo, and CET-chemo) experienced at least one all-grade treatment-emergent adverse event (TEAE). Patients receiving PEMB-mono generally had a favourable safety profile compared with patients receiving PEMB-chemo and CET-chemo, with lower proportions of TEAEs of grade 3 to 5, serious TEAEs, and drug-related adverse events (AEs). Although the incidence and severity of AEs in the PEMB-chemo and CET-chemo groups were broadly similar, PEMB-chemo had a higher proportion of serious TEAEs and serious drug-related AEs. The most commonly reported TEAEs of any grade in the PEMB-mono group included fatigue, hypothyroidism, rash, and pruritis; whereas, in the PEMB-chemo and CET-chemo groups, the most commonly reported TEAEs of any grade included anemia, nausea, neutropenia, and fatigue. Markedly fewer patients had dose modifications (dose was reduced, drug was interrupted, or drug was withdrawn) due to AEs in the PEMB-mono group compared with the PEMB-chemo

and CET-chemo groups. Overall, pERC agreed with the CGP and the registered clinicians providing input to this submission and concluded that both pembrolizumab regimens (PEMB-mono and PEM-chemo) had manageable safety profiles compared to CET-chemo, with no new safety concerns.

pERC discussed the available patient-reported outcomes data from the KEYNOTE-048 trial and noted that the overall QoL scores — European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) global health status/QoL score and EORTC QLQ Head and Neck Module (H&N35) pain and swallowing score — showed no clinically meaningful changes from baseline to week 15 and no meaningful differences between the study groups (PEMB-mono versus CET-chemo, and PEMB-chemo versus CET-chemo). Overall, the Committee agreed that PEMB-mono and PEMB-chemo may not have a detrimental impact on QoL in this patient population and considered that AEs of PEMB- chemo did not significantly impact overall QoL. However, because patient-reported outcomes data were not adjusted for multiple testing and were considered exploratory in nature, pERC noted these results must be interpreted with caution.

Furthermore, pERC noted that the KEYNOTE-048 trial compared PEMB-mono or PEMB-chemo with CET-chemo, a regimen that does not currently have Health Canada approval in this population and is not funded in most provinces. pERC agreed with the CGP and the registered clinicians that platinum doublet chemotherapies (e.g., cisplatin plus 5-FU, carboplatin plus 5-FU, or carboplatin plus paclitaxel), are currently the standard first-line treatments in patients with recurrent or metastatic HNSCC in Canada. pERC agreed with the CGP that most clinicians would consider platinum plus 5-FU and carboplatin plus paclitaxel as interchangeable in the management of HNSCC. In the absence of a direct comparison of PEMB-mono or PEMB-chemo with platinum doublet chemotherapy, pERC considered the results of a sponsor-submitted network meta-analysis (NMA) that included a comparison of PEMB-mono and PEMB-chemo to platinum double chemotherapy. pERC acknowledged the limitations noted by the CADTH Methods Team and agreed with key concerns regarding heterogeneity across study populations and immature OS data in some trials. pERC agreed with the CGP and the CADTH Methods Team and cautioned against drawing conclusions from the NMA on the magnitude of effect of PEMB-mono or PEMB-chemo compared with platinum doublet chemotherapy. However, pERC agreed with the CGP that it would be reasonable to broadly generalize the treatment effect of PEMB-mono or in combination with chemotherapy from the KEYNOTE-048 trial to patients receiving standard care with platinum doublet chemotherapy given that cetuximab plus chemotherapy has demonstrated superior efficacy compared with platinum doublet chemotherapy in a phase III trial.

In summary, pERC concluded that compared with cetuximab in combination with platinum and 5-FU, there is a net clinical benefit of PEMB-mono or PEMB-chemo based on a statistically significant and clinically meaningful improvement in OS, an acceptable toxicity profile, and a need for improved treatment options. As well, pembrolizumab monotherapy or in combination with chemotherapy appears to maintain QoL compared with cetuximab in combination with platinum and 5-FU chemotherapy. pERC also considered that an unmet need exists for HNSCC patients in Canada due to limited therapeutic options. pERC noted that it would be reasonable to generalize the treatment effect of PEMB-mono or PEMB-chemo from the KEYNOTE-048 trial to patients receiving standard care with first-line platinum doublet chemotherapy.

pERC deliberated the patient advocacy group input from Life Saving Therapies Network (LSTN). According to patients, key symptoms of concern with HNSCC included pain and discomfort in the head and neck region, difficulty breathing, excessive coughing, and difficulty chewing and swallowing meals. Patients reported that HNSCC has a major negative emotional impact (i.e. anxiety, depression, panic attacks, and fear of recurrence) and negative impact on quality of life, day-to-day life, social and family life and imposes an immense burden on caregivers. Patients who had direct experience using pembrolizumab reported that pembrolizumab was effective in controlling their cancer with high QoL and no side effects. pERC concluded that the use of PEMB-mono or PEMB-chemo aligned with the following patient values: improves OS, has manageable toxicities, appears to maintains QoL, and offers an additional treatment option.

pERC deliberated the cost-effectiveness of PEMB-mono or PEMB-chemo compared with platinum plus 5-FU. pERC noted that the extrapolation of OS had the largest impact on the results. Pembrolizumab is only given for two years; therefore, cost estimates did not vary considerably based on the OS extrapolation method chosen but quality-adjusted life-year (QALY) estimates changed significantly. pERC was

concerned about the lack of model transparency and the uncertainty this creates around the cost-effectiveness results. Therefore, pERC felt the results should be considered with caution because they might overestimate the benefits associated with pembrolizumab. pERC concluded it is highly unlikely that pembrolizumab would be considered cost-effective at a willingness to pay of $50,000 per QALY and substantial price reductions would be required.

pERC also discussed the budget impact analysis. pERC considered the estimated budget impact to be substantial and noted that the lack of funding for cetuximab would mean that pembrolizumab would be replacing therapies with far lower costs to the health system.

The Committee deliberated the input from PAG about factors related to currently funded treatments, the eligible population, implementation factors, and sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

EVIDENCE IN BRIEF

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

- a CADTH systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the sponsor's economic model and budget impact analysis
- guidance from the CADTH clinical and economic review panels
- input from one patient advocacy group: Life Saving Therapies Network (LSTN)
- input from registered clinicians: two individual inputs from a clinician from Cross Cancer Institute, a clinician from Princess Margaret Cancer Center (PMCC), and one joint input from Cancer Care Ontario comprised of two clinicians
- input from CADTH's PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- One clinician group, Cancer Care Ontario
- The PAG
- The sponsor, Merck

The pERC Initial Recommendation was to recommend reimbursement of pembrolizumab for the first-line treatment of metastatic or unresectable recurrent HNSCC as monotherapy for patients whose tumours have PD-L1 expression CPS ≥ 1, or in combination with platinum and 5-FU chemotherapy regardless of PD-L1 expression level, if the following conditions are met: cost-effectiveness being improved to an acceptable level and feasibility of adoption (budget impact) is addressed.

Feedback on the pERC Initial Recommendation indicated that the sponsor, the registered clinician group (Cancer Care Ontario) and PAG agreed with the Initial Recommendation. No feedback on the pERC Initial Recommendation was received from the patient advocacy group.

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

OVERALL CLINICAL BENEFIT

pCODR Review Scope

The purpose of the CADTH review was to evaluate the efficacy and safety of pembrolizumab for the first-line treatment of metastatic or unresectable recurrent HNSCC both in combination with platinum and 5-FU chemotherapy for all patients regardless of PD-L1 status, and as monotherapy for patients whose tumours have PD-L1 expression CPS ≥ 1.

Studies Included: Multi-National, Open-Label, Ongoing Phase III Trial (KEYNOTE-048)

The CADTH systematic review included one multi-national, open-label, phase III trial (KEYNOTE-048) of the efficacy and safety of PEMB-mono or PEMB-chemo compared with CET-chemo in patients with metastatic or unresectable recurrent HNSCC that was considered incurable by local therapies, and who had received no prior chemotherapy for metastatic disease. The primary objectives of the trial were to compare PEMB-mono with CET-chemo and PEMB-chemo with CET-chemo for OS and PFS in all patients. Additional primary objectives were to make the same comparisons for the subsets of patients with PD-L1 CPS ≥ 1 and CPS ≥ 20.

A total of 882 patients were randomized in a 1:1:1 ratio to receive either PEMB-mono (n = 301), PEMB-chemo (n = 281), or CET-chemo (n = 300). For patients randomized to received PEMB-chemo or CET-chemo, platinum chemotherapy was either carboplatin or cisplatin as selected by the investigator prior to randomization. Patients who were randomized to the PEMB-mono or PEMB-chemo groups received pembrolizumab 200 mg IV every three weeks until disease progression, intolerable toxicity, physician or patient decision, or completion of 35 cycles (24 months), whichever occurred first. Clinically stable

patients with unconfirmed disease status could remain on pembrolizumab until disease status was ascertained. Patients who were randomized to chemotherapy (PEMB-chemo and CET-chemo) received carboplatin (AUC 5 mg/m^2) or cisplatin (100 mg/m^2) every three weeks for six cycles. Investigators determined whether patients received carboplatin or cisplatin. The initial determination preceded randomization, but patients who had started the study on cisplatin were allowed to cross over to carboplatin.

The median duration of study treatments at the second interim analysis was 3.5 months, 5.78 months, and 4.86 months in the PEMB-mono, PEMB-chemo, and CET-chemo groups, respectively.

Eligible patients included adults (18 years or older) with pathologically confirmed squamous cell carcinoma of the oropharynx, oral cavity, hypopharynx, or larynx that was recurrent or metastatic and was not considered curable by local therapies. Patients with primary tumours in the nasopharynx were not eligible. Patients could not have received prior systemic therapy for recurrent or metastatic disease, although systemic therapy for locally advanced disease was allowed if it had been completed more than six months prior to screening. Patients had to have at least one tumour that was evaluable for Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and have tumour tissue available for PD-L1 testing. Eligibility did not depend on PD-L1 expression. Those with oropharyngeal cancers had to have results of testing for p16 expression available. Patients were to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1.

Patient Populations: Median Age = 61 Years, Baseline Characteristics Balanced

PEMB-Mono

Baseline demographics and characteristics were generally balanced between the three populations (ITT, PD-L1 CPS ≥ 1, and PD-L1 CPS ≥ 20) for the comparison between PEMB-mono and CET-chemo.

In the ITT population, the majority of patients were male (85.0%) and White or Asian (73.7% and 18.6%, respectively). The median age of patients was 61 years, most patients were current or former smokers (15.6% and 63.1%, respectively), and had an ECOG PS score of 1 (60.9%). Most patients had metastatic disease (69.7%). Most patients had tumours with PD-L1 expression, with PD-L1 Tumor Proportion Score (TPS) strongly positive (≥ 50%) in 22.1%, PD-L1 CPS ≥ 1 in 85.2%, and PD-L1 CPS ≥ 20 in 42.2%. Human papilloma virus (HPV) status was negative in 78.4%. Approximately half had received prior systemic therapy, with most receiving platinum and a small proportion receiving cetuximab.

In the ITT population, compared with the CET-chemo group, the PEMB-mono group had a lower proportion of males (83.1% versus 87.0%) and a higher proportion of patients with PD-L1 CPS ≥ 20 (44.2% versus 40.7%) and metastatic disease (71.8% versus 67.7%). These differences were unlikely to have an impact on the treatment difference observed.

The PD-L1 CPS ≥ 1 subgroup had similar characteristics to the ITT population. Compared with the CET-chemo group, the PEMB-mono group had a lower proportion of males (83.1% versus 86.3%) and a higher proportion of patients with PD-L1 CPS ≥ 20 (51.8% versus 47.8%) and metastatic disease (69.6% versus 65.9%). These differences were unlikely to have an impact on the treatment difference observed.

In the PD-L1 CPS ≥ 20 subgroup, the difference in the proportion of males between groups was greater (78.2% for PEMB-mono versus 88.5% for CET-chemo). In the PEMB-mono group, the patients were younger (< 65 years, 60.2% versus 69.7%), and a lower proportion were HPV positive (18.0% versus 23.0%). The proportion with metastatic disease was similar (66.2% versus 64.8%). These differences were unlikely to have an impact on the treatment difference observed.

PEMB-Chemo

Baseline demographics and characteristics were generally balanced between the three populations (ITT, PD-L1 CPS ≥ 1, and PD-L1 CPS ≥ 20) for the comparison between PEMB-chemo and CET-chemo.

In the ITT population, the majority of patients were male (83.4%) and White or Asian (73.3% and 19.5%, respectively). The median age was 61 years, most patients were current or former smokers (16.5% and 62.1%, respectively) and had an ECOG PS score of 1 (61.0%). Most had metastatic disease (69.4%). Most patients had tumours with PD-L1 expression, with PD-L1 TPS strongly positive (≥ 50%) in 22.9%, PD-L1 CPS ≥ 1 in 83.5%, and PD-L1 CPS ≥ 20 in 42.4%. HPV status was negative in 78.4%. Approximately half had received prior systemic therapy, with most receiving platinum and a small proportion receiving cetuximab (approximately 6%).

In the ITT population, compared with the CET-chemo group, the PEMB-chemo group had a lower proportion of males (79.7% versus 87.1%), a higher proportion of patients with PD-L1 CPS ≥ 20 (44.8% versus 39.6%), and metastatic disease (71.8% versus 67.3%). These differences were unlikely to have an impact on the treatment difference observed.

The PD-L1 CPS ≥ 1 group had similar characteristics to the ITT population. Compared with the CET-chemo group, the PEMB-chemo group had a lower proportion of males (77.7% versus 86.4%), a higher proportion of patients with PD-L1 CPS ≥ 20 (52.1% versus 46.8%) and metastatic disease (71.5% versus 65.5%). These differences were unlikely to have an impact on the treatment difference observed.

In the PD-L1 CPS ≥ 20 group, the difference in proportion of males between groups was greater (71.4% for PEMB-chemo versus 87.3% for CET-chemo). In the PEMB-chemo group, the patients were younger (< 65 years, 61.1% versus 70.0%). The proportion with metastatic disease was higher (69.0% versus 62.7%). These differences were unlikely to have an impact on the treatment difference observed.

Key Efficacy Results: Statistically Significant and Clinically Meaningful Improvements in OS for PEMB-Mono and PEMB-Chemo

The co-primary end points were OS and PFS. Secondary end points were the proportion of patients who were progression-free at six and 12 months and ORR (defined as proportion of patients with overall response, complete response, or partial response according to RECIST 1.1 criteria). ORR was not hypothesis tested or adjusted for multiplicity. Duration of response was an exploratory end point. Overall, the KEYNOTE-048 trial had 14 hypotheses for the primary efficacy analysis, which were evaluated by comparing PEMB-mono or PEMB-chemo with CET-chemo for the co-primary outcomes OS and PFS in the ITT population and patients with PD-L1 expression levels of CPS ≥ 1 or CPS ≥ 20. The alpha spending was controlled by a testing scheme that involved parallel testing of six hypotheses and hierarchical testing of the remainder.

PEMB-Mono

For OS in the ITT population, PEMB-mono was noninferior (hazard ratio [HR] = 0.85; 95% confidence interval [CI], 0.71 to 1.03; P = 0.0456) but not statistically significantly superior to CET-chemo for survival at the second interim analysis. For OS in both the PD-L1 CPS ≥ 1 and CPS ≥ 20 populations, PEMB-mono was statistically significantly superior to CET-chemo at the second interim analysis. In the PD-L1 CPS ≥ 1 population, the OS HR was 0.78 (95% CI, 0.64 to 0.96; P value = 0.00855) and the median OS was 12.3 months (95% CI, 10.8 to 14.9) for PEMB-mono compared with 10.3 months (95% CI, 9.0 to 11.5) for CET-chemo. In the PD-L1 CPS ≥ 20 population, the OS HR was 0.61 (95% CI, 0.45 to 0.83; P value = 0.00074) and median OS was 14.9 months (95% CI, 11.6 to 21.5) for PEMB-mono compared with 10.7 months (95% CI, 8.8 to 12.8) for CET-chemo.

There was no statistically significant difference between the two treatments for PFS in any of the three populations (ITT, PD-L1 CPS ≥ 1, and PD-L1 CPS ≥ 20). For the PD-L1 CPS ≥ 1 population, median PFS was 3.2 months (95% CI, 2.2 to 3.4) for PEMB-mono and 5.0 months (95% CI, 4.8 to 4.8) for CET-chemo (HR = 1.16; 95% CI, 0.96 to 1.39) in the final analysis.

For the ITT population in the final analysis, the ORR was 16.9% (95% CI, 12.9 to 21.7) for PEMB-mono compared with 36.0% (95% CI, 30.6 to 41.7) for CET-chemo. ORR in the PD-L1 CPS ≥ 1 population was 19.1% (95% CI, 14.5 to 24.4) for PEMB-mono compared with 34.9% (95% CI, 29.2 to 41.1) for CET-chemo. ORR in the PD-L1 CPS ≥ 20 was 23.3% (95% CI, 16.4 to 31.4) for PEMB-mono compared with 36.1% (95% CI, 27.6 to 45.3) for CET-chemo.

Median duration of response in the final analysis for patients in the PD-L1 CPS ≥ 1 population who received PEMB-mono and had complete response or partial response was 23 months compared with 5.2 months for those who received CET-chemo.

PEMB-Chemo

For OS, PEMB-chemo was statistically significantly superior to CET-chemo in all three populations (ITT, PD-L1 CPS ≥ 1, and PD-L1 CPS ≥ 20). For the ITT population, in the second interim analysis, the difference in OS HR was 0.77 (95% CI, 0.63 to 0.93; P value = 0.0034), favouring PEMB-chemo. Median OS was 13.0 months (95% CI, 10.9 to 14.7) for PEMB-chemo compared with 10.7 months (95% CI, 9.3 to 11.7) for CET-chemo. For the PD-L1 CPS ≥ 1 population, in the final analysis, the OS HR was 0.65 (95% CI, 0.53 to 0.80; P value = 0.0002) favouring PEMB-chemo. The median OS was 13.6 months (95% CI, 10.7 to 15.5) for PEMB-chemo and 10.4 months (95% CI, 9.1 to 11.7) for CET-chemo. For the PD-L1 CPS ≥ 20 population, in the final analysis, the OS HR was 0.60 (95% CI, 0.45 to 0.82; P value 0.00044) favouring PEMB-chemo . The median OS was 14.7 months (95% CI, 10.3 to 19.3) for PEMB-chemo and 11.0 months (95% CI, 9.2 to 13.0) for CET-chemo.

There was no statistically significant difference between the two treatments for PFS in any of the three populations (ITT, PD-L1 CPS ≥ 1, and PD-L1 CPS ≥ 20). For the ITT population, in the final analysis, the median PFS was 4.9 months for PEMB-mono and 5.1 months for CET-chemo.

For the ITT population, the ORR was 35.6% (95% CI, 30.0% to 41.5%) for PEMB-chemo compared with 36.3% (95% CI, 30.7% to 42.3%) for CET-chemo. The ORR in the PD-L1 CPS ≥ 1 population was 36.4% for PEMB-chemo compared with 35.7% for CET-chemo. The ORR in the PD-L1 CPS ≥ 20 was 42.9% for PEMB-chemo compared with 38.2% for CET-chemo.

Median duration of response in patients in the ITT population who received PEMB-chemo and had complete or partial response was 6.7 months compared with 4.3 months in those who received CET-chemo.

Patient-Reported Outcomes: Overall No Significant Differences Between Treatment Groups

In the KEYNOTE-048 trial, patient-reported outcomes were pre-specified secondary end points and included change from baseline to week 15 in the EORTC QLQ-C30 global health status/QoL score and time to deterioration (TTD) in EORTC QLQ-C30 Global health status/QoL score and TTD in EORTC QLQ-H&N35 pain and swallowing score. Multiplicity was not controlled for the analyses of the secondary efficacy and health-related QoL outcomes. Pre-specified exploratory end points were additional analyses of the EORTC QLQ-C30 and EORTC QLQ-H&N35 domains.

The EORTC scales were collected at treatment cycles 1 through 4, 6 (week 15), and every two cycles until 30 days post-treatment. Results were summarized for baseline and week 15, the expected final cycle of chemotherapy. A decline of 10 points or greater on a 100-point scale represented clinically significant deterioration. Overall, health-related QoL measures showed minimal difference between groups in the comparisons for any of the groups.

PEMB-Mono

Measured QoL and symptoms did not notably differ between groups over time and remained relatively stable. The mean EOTRC QLQ-30 global health status score at baseline was 61.3 (SD 21.60) on a 100-point scale for patients who received PEMB-mono and 59.7 (SD 21.48) for those who received CET-chemo. At week 15, the means were 64.7 (SD 20.55) and 62.6 (SD 18.80), and the least square (LS) mean changes from baseline to week 15 were 0.85 (95% CI, -1.90 to 3.59) and 0.60 (95% CI, -2.19 to 3.40) for the PEMB-mono and CET-chemo groups, respectively.

The HR for TTD in the EORTC QLQ-C30 global health status/QoL score was 1.38 (95% CI, 0.95 to 2.00) for the comparison of PEMB-mono with CET-chemo. The HR for time to deterioration in EORTC QLQ-H&N35 pain subscale was 0.80 (95% CI, 0.53 to 1.21) and for EORTC QLQ-H&N35 swallowing subscale was 1.26 (95% CI, 0.85 to 1.88).

PEMB-Chemo

QoL and symptoms did not notably differ between groups over time and remained relatively stable. At baseline, the mean EOTRC QLQ-30 global health status score was 62.2 (SD 21.18) on a 100-point scale for patients who received PEMB-chemo and 60.0 (SD 21.86) for those who received CET-chemo. At week 15, the means were 64.6 (SD 21.10) and 63.3 (SD 18.27), and the LS mean changes from baseline to week 15

were 1.17 (95% CI, –1.79 to 4.12) and 0.77 (95% CI, –2.22 to 3.76) for the PEMB-chemo and CET-chemo groups, respectively.

The HR for TTD in the EORTC QLQ-C30 global health status/QoL was 1.37 (95% CI, 0.94 to 2.00) for the comparison of PEMB-chemo with CET-chemo. The HR for TDD for the EORTC QLQ-H&N35 pain subscale was 1.37 (95% CI, 0.93 to 2.02) and for EORTC QLQ-H&N35 swallowing subscale was 1.05 (95% CI, 0.69 to 1.59).

Safety: Manageable Toxicities

Almost all patients in each of the three groups (PEMB-mono, PEMB-chemo, and CET-chemo) experienced at least one all-grade TEAE. Patients receiving PEMB-mono generally had a favourable safety profile compared with those receiving PEMB-chemo and CET-chemo, with lower proportions of TEAEs of grades 3 to 5, serious TEAEs, and drug-related AEs. Although the incident and severity of AEs in the PEMB-chemo and CET-chemo groups were broadly similar, the PEMB-chemo group had a higher proportion of serious TEAEs and serious treatment-related AEs. A smaller proportion of patients discontinued pembrolizumab if they received it as monotherapy (12.0%) rather than in combination with chemotherapy (17.0%). Likewise, a smaller proportion of those receiving PEMB-mono required pembrolizumab dose modification due to an AE than those receiving PEMB-chemo (38.7% versus 57.6%); dose modifications involved reduction, interruption, or discontinuation of a drug. Dose discontinuations in the CET-chemo arm occurred in 27.5% of patients and 83.6% of patients had dose modification due to an AE in patients receiving CET-chemo.

PEMB-Mono

The most reported TEAEs of any grade were fatigue (27.7% of patients), anemia (21.0%), constipation (19.7%), and hypothyroidism (18.0%). The most reported treatment-related AEs were fatigue (14.3% of patients), hypothyroid (13.0%), rash (8.3%), and pruritis (7.0%). In the PEMB-mono group, 54% of patients had at least one grade 3 to 5 AE. The most reported grade 3 to 5 AEs were anemia (4.7%), hyponatremia (5.7%), pneumonia (5.3%), and fatigue (3.0%). The most common serious AEs (SAEs) were pneumonia (5.7%) and tumour hemorrhage (3.0%).

Twenty-five patients (8.3%) experienced one or more AEs leading to death. Infections were the most common cause of death (nine patients, 3.0%), followed by respiratory, thoracic and mediastinal disorders (four patients, 1.3%) and cardiac disorders (3 patients, 1.0%).

PEMB-Chemo

The most reported TEAEs of any grade were anemia (57.6% of patients), nausea (50.7%), constipation (37.0%), and fatigue (34.4%). The most reported treatment-related AEs were anemia (48.2% of patients), nausea (44.9%), neutropenia (33.0%), and fatigue (30.4%). In this group, 84.8% of patients had at least one grade 3 to 5 AE compared with 83.6% in the CET-chemo group. The most reported grade 3 to 5 AEs were anemia (24.6%), neutropenia (18.1%), decreased neutrophil counts (11.2%), and mucosal inflammation (9.8%). The most common SAEs were febrile neutropenia (5.8%s), pneumonia (5.4%), and anemia (5.1%).

Thirty-two patients (11.6%) experienced one or more AEs leading to death. Infections were the most common cause of death in 12 (4.3%) patients, followed by respiratory, thoracic, and mediastinal disorders in six (2.2%) patients, and cardiac disorders in four (1.4%) patients.

CET-Chemo

The most reported TEAEs were nausea (51.2% of patients), anemia (46.0%), hypomagnesemia (40.4%), and rash (38.7%). The most reported treatment-related AEs were nausea (41.1% of patients), nausea (45.6%), rash (35.2%), and hypomagnesemia (33.1%). The most reported treatment-related AEs were neutropenia (21.6%), anemia (16.4%), decreased neutrophil count (12.9%), and decreased white blood cells and thrombocytopenia (both 9.1%). The most reported SAEs were pneumonia (6.3%), febrile neutropenia (4.9% of patients), and anemia (3.1%).

Twenty-seven patients (9.4%) experienced one or more AEs leading to death. Infections were the most common cause of death (13 patients, 4.5%), followed by respiratory, thoracic, and mediastinal disorders in six (2.1%) patients and cardiac disorders in three (1.0%) patients.

Limitations: No Direct Comparative Data to Platinum Doublet Chemotherapy

The KEYNOTE-048 trial compared PEMB-mono or PEMB-chemo with CET-chemo, which currently does not have an approved Health Canada indication for this population and is not funded in most provinces. The CGP noted that platinum doublet chemotherapies (cisplatin plus 5-FU, carboplatin plus 5-FU, or carboplatin plus paclitaxel), are currently the most common first-line treatments for patients with metastatic or unresectable recurrent HNSCC in Canada. The CADTH Methods Team summarized and critically appraised a sponsor-provided NMA that compared PEMB-mono and PEMB-chemo with other treatments, including platinum doublet chemotherapy. Two sets of analyses were conducted, using the ITT populations for all trials and the PD-L1 CPS ≥ 1 population of the KEYNOTE-048 trial with the ITT populations of all other trials because a PD-L1 selected population was not available.

The results suggested that for the analysis using the KEYNOTE-048 PD-L1 CPS ≥ 1 population, estimates of OS HR favoured PEMB-mono over platinum plus 5-FU and cisplatin plus paclitaxel for most time-points from 6 months on, although the difference was lost for cisplatin plus paclitaxel at later time-points. Estimates of OS HR favoured PEMB-chemo over platinum plus 5-FU in the ITT population for most time-points from 6 months on. PEMB-chemo was favoured over cisplatin plus paclitaxel at the early (before 18 months) but not the later time-points.

The CADTH Methods Team identified several limitations with the NMA, including concerns regarding heterogeneity across study populations, immature OS data in some trials, and that data representing the PD-L1 CPS ≥ 1 population were only available for the KEYNOTE-048 trial. The CADTH Methods Team noted that the results of the NMA should be interpreted with consideration of these limitations and should be interpreted with caution. The CGP noted that it would be reasonable to broadly generalize the treatment effect of pembrolizumab monotherapy or in combination with chemotherapy from the KEYNOTE-048 trial to patients receiving standard care with platinum doublet chemotherapy given that cetuximab plus chemotherapy has demonstrated superior efficacy compared with platinum doublet chemotherapy in a phase III trial.

Need and Burden of Illness: Need for More Effective and Tolerable Treatments

In Canada, an estimated 5,400 people are diagnosed with head and neck cancers every year, and an estimated 1,500 Canadians died from it in 2020. Approximately 90% to 95% of head and neck cancers are squamous cell carcinomas. The majority of patients will present with metastatic disease (regional nodal involvement in 43% and distant metastasis in 10%). The standard of care therapies in Canada for first-line treatment of metastatic or unresectable recurrent HNSCC are platinum doublet chemotherapy (cisplatin plus 5-FU, carboplatin plus 5-FU, or carboplatin plus paclitaxel). The median OS with platinum-based combination regimens ranges from 5.0 to 8.7 months across trials. Metastatic or unresectable recurrent HNSCC is associated with significant morbidity and poses a treatment challenge due to the limited therapeutic options.

Registered Clinician Input: PEMB-Mono and PEMB-Chemo Important Treatment Options, Funding for PD-L1 Testing Necessary

A total of three registered clinician inputs were provided for the review of pembrolizumab (Keytruda) for the first-line treatment of patients with metastatic or unresectable recurrent HNSCC as monotherapy or in combination with platinum plus 5-FU chemotherapy: two individual inputs from a clinician from Cross Cancer Institute, a clinician from PMCC, and one joint input from Cancer Care Ontario comprising two clinicians. All clinicians agreed that pembrolizumab, with or without chemotherapy, should be made available for first-line treatment for all patients with metastatic or unresectable recurrent HNSCC. Patient populations of particular interest are patients with a PD-L1 CPS < 1 or patients with PD-L1 CPS > 20. The clinicians stated that the decision to add chemotherapy to pembrolizumab depends on the patients' PD-L1 CPS status; patients with PD-L1 CPS > 1 could be treated with PEMB-mono, whereas patients with PD-L1 CPS <1 could be treated with PEMB-chemo. However, the clinicians noted that patient factors such as comorbidities and age should also be taken into consideration when deciding between PEMB-mono and PEMB-chemo. All clinicians emphasized the importance of funding for PD-L1 testing because it can identify patients who are eligible for PEMB-mono, which could minimize toxicity from chemotherapy. Contraindications to pembrolizumab identified by clinicians were patients with severe active autoimmune disorders and those with solid organ transplants. Clinicians described possible sequencing options: if PEMB-mono is prescribed in the first-line setting, then the second-line option would be platinum-based chemotherapy. If PEMB-chemo is prescribed in the first-line, then the second-line option would be non-platinum-based chemotherapy. Patients who are ineligible or intolerant to platinum-based therapy may receive either pembrolizumab or nivolumab because there is no evidence to suggest the use of one drug over the other. Clinicians noted that re-treatment with pembrolizumab after reaching the two-year time-period can be considered; however, they noted that there is limited evidence on re-

treatment with pembrolizumab. Although there is currently no evidence to inform the discontinuation of pembrolizumab earlier than the two-year time-period, the clinicians noted that treatment may be discontinued earlier due to reasons such as toxicity or as per the clinical judgment. Clinicians commented that alternative dosing can be considered but it is preferable to use the same dosing as in the clinical trial.

PATIENT-BASED VALUES

Experience of Patients With HNSCC: Symptoms Include Pain and Discomfort in the Head and Neck Region, Difficulty Breathing, Excessive Coughing, Difficulty Chewing and Swallowing, and Negative Impact on Social Life and Emotional Well-Being

One patient group, LSTN, provided input for pembrolizumab for HNSCC. Patient respondents noted common symptoms of HNSCC, including pain and discomfort in the head and neck region, difficulty breathing, excessive coughing, and difficulty chewing and swallowing meals. Additionally, concerns about the ability to perform day-to-day tasks, a negative impact on patients' social interactions, and reduced emotional well-being (i.e., anxiety, depression, panic attacks, and fear of recurrence) were highlighted. LSTN emphasized that an unmet need exists for HNSCC patients in Canada due to limited therapeutic options and lack of community supports. It was reported that current treatments available for patients include nivolumab, methotrexate, hydroxyurea, and docetaxel in combination with cisplatin and 5-FU, which are often associated with significant side effects that can affect patients' QoL.

Patient Values and Experience on or Expectations for Treatment: Increased Effectiveness, Improved Side Effect Profile, and Improved QoL

Three patients reported having experience with pembrolizumab. The respondents rated the drug as extremely effective in controlling the cancer and they reported a high QoL and experienced normal living while on the treatment. The patients reported no side effects while undergoing treatment and considered pembrolizumab to have an acceptable side effect profile. Patients also noted that they were better able to perform their daily tasks and continue normal living following treatment with pembrolizumab. It was highlighted that treatment with pembrolizumab is less intensive and exhausting than other currently available treatments for HNSCC because it enables patients to return to day-to-day activities while undergoing treatment. Since the drug was accessed through a clinical trial, patients emphasized that pembrolizumab should be widely accessible for HNSCC patients so that more patients can benefit from the treatment. Overall, patients value new HNSCC treatments that will result in increased effectiveness, improved side effect profile, improved QoL, and additional treatment options.

ECONOMIC EVALUATION

Pembrolizumab is given in up to 35 three-week cycles of 200 mg doses. Administration of pembrolizumab requires 30 minutes of IV infusion per cycle. Each 100 mg vial costs $4,400, for a total cost of $8,800 per cycle. As combination therapy, pembrolizumab is given in combination with up to six three-week cycles of either 100 mg/m^2 cisplatin or 500 mg carboplatin plus up to six three-week cycles of 4,000 mg/m^2 5-FU for a total cost of $9,701 to $9,982 per 21-day cycle.

The sponsor submitted a cost-utility analysis comparing pembrolizumab as either monotherapy or combination therapy for the first-line treatment of recurrent or metastatic HNSCC, to platinum plus 5-FU and CET-chemo. The sponsor submitted a three-state partitioned survival model that used a piecewise approach based on Kaplan–Meier data and parametric survival curves. The three mutually exclusive states were "progression-free," "progressed disease," and "death." Time spent in each state was based on direct modelling of OS and PFS curves, which the sponsor extrapolated over the time horizon of the analysis using parametric methods. In the model, the patient may also discontinue treatment, at which point the cost of treatment is no longer incurred. The KEYNOTE-048 trial is the primary source of efficacy data in the model. Since platinum plus 5-FU was not considered in the KEYNOTE-048 trial, and because there are no other head-to-head comparisons, the sponsor used a fractional polynomial NMA to model the relative efficacy of pembrolizumab to platinum plus 5-FU. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer over a 15-year time horizon.

The following key limitations were identified:

- CET-chemo is not a relevant comparator from a Canadian public health payer perspective because cetuximab is not funded for this indication by participating plans.
- The sponsor's preferred approach for extrapolating OS beyond the KEYNOTE-048 study resulted in an unrealistic number of patients alive beyond 10 years.
- The sponsor's base-case analysis included no treatment effect waning.
- The sponsor overestimated the number of patients receiving subsequent treatment.
- The sponsor assumed that some patients would receive cetuximab as subsequent treatment following pembrolizumab. Because cetuximab is not funded in most jurisdictions for this indication, other (less expensive) subsequent treatments would be provided in Canadian clinical practice.
- The sponsor's submitted Excel model was excessively complex. This reduced model transparency made the task of validation difficult. Therefore, CADTH could not guarantee the model was free from error.

CADTH's reanalysis included the following changes: CET-chemo was removed as a comparator, an exponential function was used to extrapolate OS, a five-year treatment effect waning was applied, the number of patients receiving subsequent treatment was reduced by 30%, and subsequent treatment with cetuximab was reallocated to platinum + 5-FU following treatment with pembrolizumab.

According to CADTH's reanalyses, the incremental cost-effectiveness ratio (ICER) for pembrolizumab monotherapy versus platinum + 5-FU in adult patients with recurrent or metastatic HNSCC whose tumours have PD-L1 expression (CPS ≥ 1) is $131,260 per QALY, whereas the ICER for pembrolizumab combination therapy versus platinum plus 5-FU in all adult patients with recurrent or metastatic HNSCC is $162,165 per QALY. As CADTH was unable to fully validate the model, due to excessive complexities with the model design, the resulting ICER may overestimate the cost effectiveness of pembrolizumab and therefore the following price reductions may be underestimated. At a willingness-to-pay threshold of $50,000 per QALY, a price reduction of at least 49% is required for PEMB-mono to be cost-effective, while a price reduction of at least 67% is required for PEMB-chemo to be cost-effective. At a $100,000 per QALY threshold, a price reduction of at least 19% is required for PEMB-mono to be cost-effective, while a price reduction of at least 37% is required for PEMB-chemo to be cost-effective.

ADOPTION FEASIBILITY

Considerations for Implementation and Budget Impact: Budget Impact Substantial and Underestimated

CADTH reanalysis suggests that the sponsor-submitted budget impact of introducing pembrolizumab to the market is underestimated, with the three-year budget impact from the CADTH reanalysis estimated at $151,370,606.

Factors related to currently funded treatments, the eligible patient population, implementation, and sequencing and priority of treatments are described in Appendix 1.

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
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Michael Crump, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Cameron Lane, Patient Member
Dr. Christopher Longo, Health Economist
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, who did not vote due to her role as pERC Chair.

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

Avoidance of conflicts of interest

All members of the pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the CADTH website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of pembrolizumab (Keytruda) for HNSCC, through their declarations, no members had a real, potential or perceived conflict and based on 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 CADTH website. Please refer to the pCODR Guidance Reports for more detail on their content.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
Currently funded treatments	
Initial treatments for recurrent or metastatic HNSCC include single-agent chemotherapy or combination chemotherapy. The more commonly used therapies in Canada for first-line treatment of recurrent or metastatic HNSCC are platinum agents plus 5-FU or docetaxel, or carboplatin plus paclitaxel. Cetuximab with or without platinum-fluorouracil chemotherapy or radiation therapy is another option for these patients. Non-platinum-based chemotherapies and nivolumab are available to patients with significant intolerance or contraindication to platinum-based chemotherapies. • PAG noted that the KEYNOTE-048 trial compared pembrolizumab monotherapy to pembrolizumab + platinum doublet + 5-FU and to cetuximab + platinum doublet + 5-FU. PAG is also seeking comparative information of pembrolizumab versus platinum-based chemotherapies.	• Only indirect comparisons can be made between pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy and platinum-based chemotherapies because no trial to date has directly compared these drugs in recurrent or metastatic HNSCC. The results of a sponsor-provided NMA suggested that for the analysis using the KEYNOTE-048 PD-L1 CPS ≥ 1 population, estimates of OS HR favoured pembrolizumab monotherapy over platinum plus 5-FU and cisplatin plus paclitaxel for most time-points from 6 months on, although the difference was lost for cisplatin plus paclitaxel at later time-points. Estimates of OS HR favoured pembrolizumab plus chemotherapy over platinum plus 5-FU in the ITT population for most time-points from 6 months on. Pembrolizumab plus chemotherapy was favoured over cisplatin plus paclitaxel at the early time-points (before 18 months) but not the later. pERC agreed with the CGP and the CADTH Methods Team that, due to limitations identified in the NMA, caution must be used in interpreting the comparative efficacy estimates. However, pERC agreed with the CGP that because the EXTREME regimen provides improved survival and tumour response compared to platinum plus 5-FU chemotherapy, it would be expected that the survival benefits of pembrolizumab-based treatment could be generalized to Canadian patients with recurrent or metastatic HNSCC receiving standard care with platinum-based chemotherapy.
Eligible patient population	
PAG is seeking guidance on whether the following patients would be eligible for treatment with pembrolizumab monotherapy and pembrolizumab in combination with chemotherapy: • Patients with an ECOG PS > 2	• The KEYNOTE-048 trial included patients with ECOG PS score of 0 or 1. Most patients in the trial had an ECOG PS score of 1. The CGP noted that approximately half the patients seen in

	clinical practice have worse performance status than patients included in the KEYNOTE-048 trial (ECOG PS ≥ 2). pERC noted that it would be reasonable to offer pembrolizumab monotherapy to patients with ECOG PS of 2 or greater in patients whose ECOG PS may be related to the underlying disease or tumour symptoms.
• Patients with CNS metastases	• The KEYNOTE-048 trial excluded patients with known active CNS metastases and/or carcinomatous meningitis. The CGP noted that patients with active CNS disease and carcinomatous meningitis were excluded due to the poor prognosis associated with these conditions. Patients with effectively treated CNS metastases were eligible for the trial. pERC agreed with the CGP that it would be reasonable to generalize the KEYNOTE-048 trial results to patients with asymptomatic CNS disease because small lesions may not require immediate treatment with stereotactic radiosurgery or radiotherapy, particularly if the burden of systemic disease is prominent and needs to be addressed.
• Patients with squamous cell cancer of the sinus cavity.	• The KEYNOTE-048 trial excluded patients with squamous cancer of the sinus cavity. The curative and metastatic treatment of squamous cell cancer of the nasal cavity and paranasal sinuses as well as non–EBER-expressing nasopharyngeal cancer aligns with the treatment of HNSCC in general. pERC agreed with the CGP that generalizing to this population seems appropriate.
PAG is seeking guidance on whether patients with recurrent or metastatic HNSCC patients who are not amenable to local therapy and who have started first-line non-curative chemotherapies, or who are unable to tolerate treatment, could switch to pembrolizumab as their first-line treatment. Should switching be acceptable, PAG would like clarity on the types of first-line therapies that would be applicable and whether these include cetuximab + platinum + 5-FU.	pERC agreed with the CGP that it would be reasonable to add pembrolizumab monotherapy to combination chemotherapy in patients who are not amendable to local therapy and who have initiated first-line chemotherapy prior to funded access to pembrolizumab. Combination chemotherapy should be platinum-based. In rare cases in which patients have started on cetuximab plus platinum plus 5-FU, a switch to pembrolizumab plus chemotherapy would be reasonable. pERC noted that patients with recurrent or metastatic HNSCC who are intolerant or do not respond to first-line platinum-based chemotherapy should be offered nivolumab.
PAG noted that HNSCC patients having recurred within 6 months of potentially curative neoadjuvant or adjuvant platinum-based therapy for locally advanced malignancies are eligible to receive nivolumab (another PD-1 inhibitor) and is seeking guidance on whether pembrolizumab could be used in the same fashion despite the exclusion of such patients from the trial. PAG is unsure if this population would be eligible as per the wording of the reimbursement request.	The KEYNOTE-48 trial excluded patients who have recurred within 6 months of potentially curative neoadjuvant or adjuvant platinum-based therapy or had prior systemic treatment for advanced or metastatic disease. The CGP noted that nivolumab is available in most jurisdictions for this patient population. Therefore, nivolumab would be the preferred option in this setting.
PAG is also concerned about potential indication creep to:	
• Patients who experienced prior non-curative chemotherapy or immunotherapy	• pERC noted that the KEYNOTE-048 trial results are in the first-line recurrent or metastatic setting and agreed with the CGP that there is insufficient evidence to extrapolate to the second-line or greater setting if previously treated with chemotherapy or immunotherapy.

• Patients in the locally or regionally advanced setting (as neoadjuvant or adjuvant therapy).	• The KEYNOTE-048 trial included patients with recurrent or metastatic disease and treatment was with palliative intent. pERC agreed with the CGP that the KEYNOTE-048 trial results are not generalizable to patients with locally or regionally advanced disease in the curative intent setting.
Implementation factors	
The proposed dose of pembrolizumab for HNSCC is 200 mg. Although fixed dose would minimize drug wastage, PAG is seeking guidance on a weight-based dose for HNSCC (i.e., 2 mg/kg up to 200 mg) given the high cost of fixed dose compared with a weight-based dose for patients weighing less than 100 kg. PAG also identified emerging data of dosing pembrolizumab at 400 mg every 6 weeks. PAG noted that a CADTH Technology Review suggests that weight-based doses of pembrolizumab and corresponding flat doses have similar effects. PAG is seeking guidance on the appropriateness of alternate dosing (i.e., 400 mg or 4 mg/kg up to a maximum of 400 mg every 6 weeks).	The Committee acknowledged that, although the KEYNOTE-048 trial assessed pembrolizumab at a dosage of 200 mg every 3 weeks up to 2 years (maximum of 35 cycles), there is no evidence to suggest that the dosing amount of 200 mg is superior to 2 mg/kg (the dose used in initial pembrolizumab trials). For many patients, the flat dose results in a larger dose and greater cost. Therefore, pERC agreed with the CGP that it would be reasonable that pembrolizumab be administered at 2 mg/kg up to a total dose of 200 mg (a flat dose cap of 200 mg). Furthermore, pERC agreed with the CGP that there is emerging evidence in support of an alternate dosing scheduling for pembrolizumab based on 400 mg every 6 weeks; however, pERC noted that there is currently insufficient evidence to inform a recommendation on the use of a weight-based dosing schedule of 4 mg/kg up to a flat dose cap of 400 mg every 6 weeks in the present target population.
PAG is seeking guidance on treatment discontinuation as per the KEYNOTE-048 trial treatment of "once every 3 weeks until disease progression, intolerable toxicity, physician or participant decision, or 35 cycles, whichever occurred first."	In the KEYNOTE-048 trial, treatment after initial radiographic progression was possible until a repeat tumour assessment 4 weeks later confirmed progressive disease. Patients who were awaiting radiologic confirmation of progression were able to continue treatment at the investigator's discretion if they were clinically stable. pERC agreed with the CGP that the trial parameters in the KEYNOTE-048 trial set for treatment discontinuation are reasonable and reflective of clinical practice.
For patients who do not tolerate the pembrolizumab plus chemotherapy combination, PAG is seeking guidance on whether pembrolizumab monotherapy can be attempted before electing to discontinue therapy.	pERC agreed with the CGP that pembrolizumab monotherapy could be continued if chemotherapy would need to be discontinued due to intolerance while a patient is benefiting from treatment and would be considered likely to continue to benefit. In the KEYNOTE-048 trial reduction or holding of one agent and not the other agents was appropriate if the toxicity was clearly related to one of the study drugs as determined by the investigator.
PAG is also seeking confirmation whether the evidence is generalizable: • to any chemotherapy backbone • concurrent use with radiation.	 • Although the KEYNOTE-048 trial did not evaluate pembrolizumab in combination with carboplatin plus paclitaxel, pERC agreed with the CGP that the results of the trial can be generalized to pembrolizumab in combination with carboplatin plus paclitaxel or other platinum doublet agents (carboplatin plus 5-FU, paclitaxel plus cisplatin) commonly used in HNSCC. Most clinicians would consider platinum plus 5-FU and carboplatin plus paclitaxel as interchangeable in the management of HNSCC. • As concurrent use of radiation was not allowed in the KEYNOTE-048 trial, pERC agreed with the CGP that there are no data to support the generalizability of treatment benefit in patients with concurrent use of radiation.
Is there evidence to inform and recommendations for which patients are most	pERC agreed with the CGP that beyond trends to greater benefit with pembrolizumab monotherapy with increasing CPS score,

likely to benefit from pembrolizumab plus chemotherapy in recurrent or metastatic HNSCC?	there is no robust evidence to inform which patients are most likely to benefit from pembrolizumab monotherapy versus pembrolizumab chemotherapy.
How frequently should patients on pembrolizumab for recurrent or metastatic HNSCC be monitored for disease progression, and with which tests?	pERC agreed with the CGP that response to treatment is ideally monitored by evaluating changes in clinical symptoms, signs, and imaging. Symptoms and signs are monitored regularly in the course of clinical care, usually at each visit for treatment (every 3 weeks to 4 weeks). Imaging should be done at a minimum of every 12 weeks. In the KEYNOTE-048 trial, tumour imaging and measurement was conducted at baseline, week 9, and every 6 weeks through year 1, then every 9 weeks through year 2, until radiographic disease progression. Computed tomography imaging was preferred, but magnetic resonance imaging could also be used.
Is there evidence to inform if there are any groups of patients that could discontinue pembrolizumab earlier than 2 years (35 cycles), such as any that achieve a complete response?	pERC noted that there is lack of evidence to define a clinical situation in which patients may discontinue pembrolizumab earlier than 2 years. However, despite insufficient evidence, pERC agreed with the CGP that it would be reasonable to discontinue pembrolizumab earlier than 2 years in patients who have achieved a complete response as is commonly being done in clinical practice and was allowed in the KEYNOTE-048 trial. However, these patients should be considered for pembrolizumab re-challenge if they experience tumour progression because they have not demonstrated the development of drug resistance.
Sequencing and priority of treatment	
PAG is seeking guidance on circumstances that would justify preferred use of pembrolizumab monotherapy vs. pembrolizumab chemotherapy vs. other standard of care therapies, including patient factors driving the decision to combine chemotherapy with pembrolizumab.	The Health Canada indication for pembrolizumab monotherapy is for first-line treatment of metastatic or unresectable recurrent HNSCC in adult patients whose tumours have PD-L1 expression CPS ≥ 1 as determined by a validated test. pERC agreed with the CGP that pembrolizumab monotherapy would be the preferred choice for most patients. Clinical circumstances in which pembrolizumab in combination with chemotherapy would be preferred would be organ-critical or symptomatic metastatic disease requiring high probability of tumour response to therapy. Other circumstances in which pembrolizumab in combination with chemotherapy would be indicated is in patients whose tumours have CPS score < 1 or lack CPS data. Patients who have contraindications to pembrolizumab immunotherapy would be treated with platinum doublet chemotherapy.
Are there clinical situations where it would be appropriate to continue pembrolizumab beyond the 2-year (35 cycle) time duration?	pERC noted that there are currently no data from the KEYNOTE-048 trial supporting treatment with to pembrolizumab beyond the 2-year time (35-cycle) duration. However, pERC agreed with the CGP that in rare clinical situations with an ongoing very delayed clinical response the treating clinician may consider taking this approach.
PAG is seeking guidance on the choice of downstream platinum and non-platinum-based chemotherapies.	pERC was unable to make an informed recommendation on the optimal sequencing of available treatments following progression on first-line treatment with pembrolizumab monotherapy or in combination with chemotherapy. pERC noted that it did not review evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of pembrolizumab monotherapy or in combination with chemotherapy and noted that a national approach to developing clinical practice guidelines addressing sequencing of treatments would be of value.
Companion diagnostic testing	
PAG seeks clarity on any requirement for p16	pERC noted that immunohistochemical testing of HNSCC tumours

testing for pembrolizumab eligibility.	for p16 expression is of value in the diagnosis and prognostic staging of localized oropharyngeal cancer being considered for curative treatment; however, it is not currently validated as a prognostic or predictive biomarker for recurrent or metastatic HNSCC. Therefore, there is no requirement for testing in this population.

5-FU = 5-fluorouracil; CGP = Clinical Guidance Panel; CNS = central nervous system; CPS = combined positive score; EBER = Epstein–Barr virus-encoded small RNAs; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HNSCC = head and neck squamous cell carcinoma; HR = hazard ratio; ITT = intention to treat; NMA = network meta-analysis; OS = overall survival; PAG = Provincial Advisory Group; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; pERC = pCODR Expert Review Committee; vs. = versus.