pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

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

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

Drug: Pembrolizumab (Keytruda)

Submitted Reimbursement Request:
Pembrolizumab as monotherapy is indicated for the treatment of adult patients with refractory or relapsed classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) or who are not ASCT candidates and have failed BV.

Submitted By: Merck Canada Inc.	**Manufactured By:** Merck Canada Inc.
NOC/c Date: September 8, 2017	**Submission Date:** July 7, 2017
Initial Recommendation: November 2, 2017	**Final Recommendation:** January 5, 2018

Approximate per Patient Drug Costs, per Month (28 Days) Submitted list price Pembrolizumab: $4,400.00 per 100 mg Note: Costs are calculated based on 200 mg every three weeks (fixed dose)	Pembrolizumab costs: $11,733.33 per 28-day course

pERC RECOMMENDATION

pERC recommends reimbursement of pembrolizumab (Keytruda) as monotherapy in adult patients with refractory or relapsed classical Hodgkin lymphoma (cHL) who

- have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or
- are not candidates for ASCT and have failed BV,

conditional on the cost-effectiveness being improved to an acceptable level. Treatment should continue until confirmed disease progression or unacceptable toxicity, or to a maximum of two years, whichever comes first.

pERC made this recommendation because the Committee considered that there is a net clinical benefit of pembrolizumab based on the rates of complete remission in a heavily pre-treated population, a favourable toxicity profile, the potential to improve quality of life and a substantial need for treatment options in this small population of patients who have multiply relapsed disease. However, pERC acknowledged that, because of the non-randomized, non-comparative study designs of the available clinical trials, there was considerable uncertainty in the magnitude of clinical benefit of pembrolizumab.

pERC was also satisfied that pembrolizumab aligns with patient values, because patients value treatments that provide disease control and an opportunity to achieve disease remission, manage disease-related

symptoms, have the potential for improvement in quality of life, and have tolerable side effects.

The Committee concluded that pembrolizumab, at the submitted price, was not cost-effective compared with available treatment options. The Committee noted that there was considerable uncertainty in the cost-effectiveness estimates because of a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given that pERC was satisfied that pembrolizumab has a net clinical benefit in adult patients with refractory or relapsed cHL who have failed ASCT and BV or who are not ASCT candidates and have failed BV, jurisdictions may want to consider pricing arrangements that would improve the cost-effectiveness of pembrolizumab to an acceptable level. pERC noted that the cost of pembrolizumab was high and that drug price was a key driver of the incremental cost-effectiveness estimates. Therefore, to offset the considerable uncertainty in the clinical effect estimates, pERC concluded that a substantial reduction in drug price would be required to improve cost-effectiveness to an acceptable level.

Resource Use and Adoption Feasibility
pERC discussed that pembrolizumab may have the potential for indication creep because of the lack of effective treatment options for patients who (1) are ineligible for ASCT and do not have access to BV therapy or (2) are not eligible for BV due to contraindications. pERC noted that reimbursement of BV for patients who are not candidates for ASCT because of age, comorbidities, or refractoriness to salvage therapy is not uniform across Canada and results in a significant treatment gap for this subgroup of patients in most provinces. However, pERC recognized that the use of pembrolizumab in BV-naive patients was beyond the scope of this review. Therefore, the Committee noted that a separate submission to pCODR for pembrolizumab in patients who are ineligible for ASCT and are BV-naive would be required.

Factors Affecting Budget Impact and Adoption Feasibility
pERC noted that the budget impact of pembrolizumab resulted from the high cost of pembrolizumab, the relatively small number of eligible patients, and a large market share expected for the pembrolizumab indication. pERC also agreed with the Economic Guidance Panel (EGP) that the submitted budget impact analysis was underestimated because pembrolizumab will likely take the full market share in this reimbursement scenario.

Optimal Dosage of Pembrolizumab
pERC noted the Provincial Advisory Group's (PAG) concern with pembrolizumab's fixed dosing schedule as opposed to a weight-based dosing schedule. Although a fixed dose would minimize drug wastage, PAG noted the high cost of using a fixed dose compared with a weight-based dose for patients weighing less than 100 kg. In addition, as pembrolizumab is currently used in a number of other indications, drug wastage could be minimized with vial sharing. pERC acknowledged that a weight-based dose of 2 mg/kg every three weeks has been approved for other indications; however, there is currently no evidence for the 2 mg/kg dose for the current indication. pERC noted that jurisdictions may want to further discuss the dosing concern and agree on a common approach that is feasible for all.

Ensuring long-term optimal use
pERC noted that Health Canada issued a Notice of Compliance with conditions, pending results of clinical trials to verify the anticipated benefit of pembrolizumab in this patient population. Jurisdictions may want to consider a time-limited reimbursement of pembrolizumab, with a reassessment of the safety, efficacy, and cost-effectiveness of pembrolizumab for the treatment of cHL when the results of these studies are available from the submitter. pERC noted that this strategy would help ensure the greatest value for money for the health care system and the continued use of evidence in associated reimbursement decisions.

Changing need for pembrolizumab
pERC noted that BV is not currently reimbursed in Canada for consolidation therapy post-ASCT for patients at high risk of relapse, but may be in the future; this may decrease the number of patients who would receive pembrolizumab after BV for relapse following ASCT.

SUMMARY OF pERC DELIBERATIONS

Classical Hodgkin lymphoma (cHL) is an uncommon but distinct lymphoma subtype that has a bimodal age distribution. It is seen in both children and adolescents and in adults more than 60 years of age. cHL is characterized by rare malignant Reed-Sternberg cells, which are positive for CD30 and negative for the B cell antigens CD20 and CD79a. PDL-1 is strongly expressed by Reed-Sternberg cells and by infiltrating cells of the microenvironment but is less strongly expressed on the malignant cell population of nodular lymphocyte predominant Hodgkin lymphoma (HL); this latter subgroup comprises only about 5% of all patients with HL. There are approximately 900 new cases of HL in Canada each year, and approximately 160 Canadians will die annually from this disease. Out of 900 new cases, approximately 20% (n = 180) will become candidates for second-line treatment including autologous stem cell transplant (ASCT), which cures approximately 50% of patients. Patients who fail ASCT receive brentuximab vedotin (BV) as standard of care. However, at least 90% of patients will relapse after BV and, therefore, will be candidates for pembrolizumab. The Clinical Guidance Panel (CGP) estimated that the total annual number of pembrolizumab-eligible patients in Canada nears 100 to 110 and will probably be at least 10% to 20% lower because of contraindications to the use of a checkpoint inhibitor. Currently there is no standard of therapy for this multiply relapsed patient population (after ASCT and BV). Current treatment options include chemotherapy and radiotherapy with palliative intent, best supportive care, and clinical trials. pERC agreed with CGP that chemotherapy in this patient population is associated with significant toxicities, low response rates, and short progression-free survival (PFS) of only three to four months. Due to the significant potential for severe toxic effects with chemotherapy, some patients may not be eligible for chemotherapy treatment. pERC acknowledged that there is a lack of effective therapy options with the potential for long-term remission or to delay or avoid systemic therapy. pERC concluded that there is a pressing need for more effective treatments in this heavily pre-treated patient population, who relapse after both ASCT and BV, or who have disease that is resistant to salvage chemotherapy, or who are otherwise not candidates for ASCT and have failed on BV.

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 two single-arm, non-randomized studies (KEYNOTE-087 [KN-087], a phase II trial, and KEYNOTE-013 [KN-013], a phase Ib trial) that investigated treatment with pembrolizumab in patients with refractory or relapsed cHL. pERC noted that the phase II KN-087 trial (N = 210) provided the main evidence for the submission and was supplemented by the much smaller phase Ib KN-013 trial (N = 31). pERC noted that the KN-087 trial had three cohorts; however, only cohort 1 (failed both ASCT and BV) and cohort 2 (received salvage chemotherapy and BV, ineligible for ASCT) were included in this appraisal, as cohort 3 (failed ASCT and BV-naive) was beyond the scope of this review as it was not part of the reimbursement request. pERC agreed with CGP that both studies demonstrated very impressive and highly clinically relevant objective response rates (KN-087, 73% and 64.2% for cohorts 1 and 2, respectively; KN-013, 58%) and complete response rates (KN-087, 21.7% and 24.7% for cohorts 1 and 2, respectively; KN-013, 10.4%) in this heavily pre-treated patient population. pERC noted the prolonged durability of responses, as the median duration of response had not been reached in either study.

pERC noted that the robustness of the preliminary overall survival (OS) and PFS results are limited due to the short follow-up of the study populations and the lack of randomized comparison treatment groups in KN-087 and KN-013. pERC discussed that the conclusions that can be drawn from non-randomized studies with short follow-up are not as robust as those that can be drawn from randomized controlled trials. pERC considered that, there are currently no randomized controlled trials under way in this heavily pre-treated, multiply relapsed or refractory population. pERC agreed with CGP that, despite the significant unmet need in this patient population, conducting a randomized controlled trial in this setting with pembrolizumab compared with palliative chemotherapy would likely not be feasible. pERC noted that, based on the available evidence, it was not possible to conclude whether the antitumour activity expressed as complete response rate and duration of response will translate into clinical benefit in terms of PFS and OS. However, pERC discussed that in earlier lines of therapy it has been shown that tumour response rates expressed as complete response rates and duration of response translate into survival benefits. Further, pERC noted that, despite the uncertainty and immaturity of the survival results, it may

be reasonable to assume that the tumour responses expressed as complete response are clinically meaningful because they could potentially delay tumour progression and result in a prolonged survival benefit for this patient population.

pERC discussed the quality-of-life (QoL) data from the KN-087 study and noted a net improvement in QoL at week 12 as compared against baseline among all patients using either QoL instrument (the European Organization for Research and Treatment of Cancer [EORTC] QoL questionnaire C30; or the European Quality of Life Five Dimensions questionnaire [EQ-5D]). The Committee further discussed that, without a comparator group, there is considerable uncertainty in the QoL of patients who receive pembrolizumab compared with other available therapies. pERC noted that the improvement in QoL from baseline was in line with the patient group submission, which indicated that a majority of patients felt that pembrolizumab was able to manage all their disease symptoms as well as dramatically improve their health and well-being similar to their pre-disease state. pERC noted that an improvement in QoL was likely, given the high rate of tumour responses and excellent safety profile observed with pembrolizumab.

pERC considered the excellent safety profile observed with pembrolizumab. pERC noted that the single-arm, non-randomized design of KN-087 makes interpreting the safety events attributable to pembrolizumab challenging, since all patients with relapsed or refractory cHL received the same treatment. However, pERC noted that, nonetheless, the incidence of adverse events was very low and all events seemed tolerable and manageable. pERC acknowledged patient advocacy group input stating that the majority of patients treated with pembrolizumab reported that pembrolizumab had a positive impact on their health and well-being, with very few adverse events, all of which were tolerable.

pERC discussed that there is a pressing need for more effective treatments for this heavily pre-treated patient population (after ASCT and brentuximab). Currently, there is no standard of therapy. Current treatment options include chemotherapy and radiotherapy with palliative intent, best supportive care, and clinical trials. pERC agreed with CGP that chemotherapy in this patient population is associated with significant toxicities, low response rates, and short PFS of only three to four months. pERC noted that, due to the significant potential for severe toxic effects with chemotherapy, some patients may not be eligible for chemotherapy treatment. pERC concluded that pembrolizumab is a treatment with minimal toxicity that could offer patients an effective treatment option with the potential to enjoy long-term durable remission or to delay or avoid systemic therapy The Committee was in agreement that there is a substantial need for the indicated patient population, since there are currently no alternative treatment options, and conducting a randomized controlled trial in this setting would likely not be feasible.

pERC concluded that there is a net clinical benefit to pembrolizumab, compared with chemotherapy, in the treatment of patients with relapsed cHL with disease progression after both ASCT and BV or who are not eligible for ASCT and have disease progression after BV. In making this conclusion, pERC considered the high response rates and encouraging early PFS in a heavily pre-treated population, a favourable toxicity profile, the potential to improve QoL, and a substantial need for treatment options in this small population of patients who have multiply relapsed disease.

pERC reviewed patient advocacy group input and concluded that pembrolizumab aligns with patient values. pERC noted that according to patients, relapsed or refractory cHL disease manifests stressful disease symptoms such as drenching night sweats, itching, persistent cough, fatigue or lack of energy, enlarged lymph nodes, and mental or emotional problems such as anxiety and difficulties with concentrating. Patients reported that pembrolizumab had a positive impact on their QoL with minimal and manageable side effects. pERC considered that patients value treatments that will provide disease and symptom control. pERC agreed that pembrolizumab may provide an opportunity for a patient to achieve disease remission, stop disease progression, manage disease-related symptoms, attain better QoL, and experience few and well-tolerated side effects. Hence, the Committee concluded that pembrolizumab aligned with patient values.

Upon reconsideration of the initial recommendation, pERC noted the patient group feedback indicating that BV-naive patients who are ineligible for ASCT should be included in the recommendation. pERC recognized that the use of pembrolizumab in BV-naive patients was beyond the scope of this review. Therefore, the Committee noted that a separate submission to pCODR for pembrolizumab in patients who are ineligible for ASCT and BV-naive would be required.

pERC deliberated upon the cost-effectiveness of pembrolizumab in patients with relapsed or refractory cHL and concluded that pembrolizumab is not cost-effective when compared with gemcitabine at the submitted price. pERC noted that the pCODR Economic Guidance Panel (EGP) reanalysis of cost-effectiveness presented an incremental cost-effectiveness ratio (ICER) as the lower bound with no upper bound, given the uncertainty of non-comparative data. pERC also noted that the submitted base-case ICER was lower than EGP's lower bound ICER estimate. The Committee noted several limitations in the submitted analysis, particularly the lack of comparative effectiveness data and the resulting uncertainty in relative efficacy between pembrolizumab and gemcitabine. pERC noted that in the absence of comparative efficacy data, the submitter provided an indirect treatment comparison (ITC) to compare pembrolizumab with conventional chemotherapy (gemcitabine). Although the ITC suggested that pembrolizumab is associated with improved efficacy and safety as compared with gemcitabine, these results should be interpreted with caution. There were considerable differences in inclusion criteria across trials and a lack of adjustment for relevant baseline patient or study characteristics that impact the treatment effects. pERC concluded that given these limitations, the comparative efficacy of pembrolizumab versus gemcitabine is highly uncertain. pERC noted that according to EGP's sensitivity analyses, the factors that most influence the incremental cost of pembrolizumab are treatment duration, cost of pembrolizumab, and selection of cohort 1 or 2 (not combined). The key effect drivers of the incremental effect are the time horizon, utility values, and selection of cohort 1 or 2 (not combined). Overall, pERC agreed with EGP's reanalyses and the limitations identified in the submitted economic model. Therefore, pERC accepted EGP's best ICER estimates, which were between a minimum of $197,055/quality-adjusted life-year (QALY) and no upper bound when pembrolizumab was compared with gemcitabine. Consequently, pERC concluded that pembrolizumab was not cost-effective at the submitted price compared with gemcitabine.

Upon reconsideration of the Initial Recommendation, pERC noted the submitter's feedback indicating that the time horizon should be longer than the 10 years used in EGP's reanalyses. The submitter suggested a time horizon between 10 and 20 years, referring to a previous pCODR recommendation for BV in HL, which used a 15-year time horizon. pERC noted CGP's feedback that it seems reasonable to expect that patients receiving pembrolizumab for cHL in this current review would have shorter survival than patients receiving BV for HL in the setting of the previous pCODR recommendation for BV in HL, since patients who receive pembrolizumab would have shorter OS because they would have an additional treatment due to an additional progression. Further, CGP noted that while there is a lack of data to inform OS for cHL patients, data from a retrospective study reviewed by the pCODR Methods Team (Cheah et al.) show that more than 70% of patients died within five years of cHL that progressed after ASCT and subsequent BV. pERC concluded that since patients progressing after pembrolizumab are expected to have shorter OS than patients progressing after ASCT and BV, a 10-year time horizon seemed optimistic for this patient population.

Upon reconsideration of the Initial Recommendation, pERC noted PAG's feedback stating that without an upper bound for an ICER, pricing discussions may be challenging, as it may be difficult to determine a cost-effective price. pERC acknowledged and agreed with EGP's feedback maintaining that it was not possible to place an upper bound on the ICER given the lack of comparative effectiveness estimates and the poor quality of the indirect treatment comparison.

pERC considered the feasibility of implementing a reimbursement recommendation for pembrolizumab in patients with relapsed or refractory cHL. pERC discussed that pembrolizumab may have the potential for indication creep because of the lack of effective treatment options for patients who (1) are ineligible for ASCT and do not have access to BV therapy or (2) are not eligible for BV because of contraindications. pERC noted that reimbursement of BV for those who are not candidates for ASCT because of age, comorbidities, or refractoriness to salvage therapy is not uniform across Canada and results in a significant treatment gap for this subgroup of patients in most provinces. However, pERC recognized that the use of pembrolizumab in BV-naive patients was beyond the scope of this review. Therefore, the Committee noted that a separate submission to pCODR for pembrolizumab in patients who are ineligible for ASCT and are BV-naive would be required.

Upon reconsideration of the Initial Recommendation, pERC noted feedback from PAG regarding the recommendation to use pembrolizumab in patients who are ASCT ineligible and who have failed BV. PAG noted that since pERC did not recommend reimbursement of BV for patients who are ASCT ineligible, it is inconsistent to recommend pembrolizumab for patients who are ASCT ineligible and who have failed BV. pERC agreed with the CGP's response to PAG's feedback that despite pERC's negative recommendation, there currently is a population of ASCT-ineligible patients who have subsequently received BV in Canada.

The Committee agreed with CGP that there is a high need for treatment options in this small population of patients who are likely to relapse again after BV and could benefit from pembrolizumab because it is effective and well-tolerated and can induce quite durable responses.

pERC noted CGP's opinion that PDL-1 testing is not necessary. PDL-1 is highly expressed on Reed–Sternberg cells that characterize cHL. pERC also noted that CGP's opinion that the efficacy results of pembrolizumab could not easily be extended to nodular lymphocyte predominant HL, as PDL-1 is expressed less frequently in nodular lymphocyte predominant HL than in cHL.

pERC noted PAG's concern with pembrolizumab's fixed dosing schedule as opposed to a weight-based dosing schedule. pERC acknowledged that a weight-based dose of 2 mg/kg every three weeks has been approved for other indications; however, there is currently no evidence for the 2 mg/kg dose for patients with relapsed cHL with disease progression after both ASCT and BV or who are not eligible for ASCT and have disease progression after BV.

pERC also accepted EGP's conclusion that the submitted budget impact analysis was underestimated because pembrolizumab will likely achieve the full market share in this funded scenario. pERC noted that the budget impact of pembrolizumab resulted from the high cost of pembrolizumab, the relatively small number of eligible patients, and a large market share expected for the pembrolizumab indication. pERC also noted that it is possible that a minority of patients would be on pembrolizumab for an extended time, beyond two years.

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 pCODR clinical and economic review panels
- input from one patient advocacy group: Lymphoma Canada
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- one patient advocacy group: Lymphoma Canada
- one clinician group
- PAG
- the submitter: Merck Canada Inc.

The pERC Initial Recommendation was to recommend reimbursement of pembrolizumab (Keytruda) as monotherapy in adult patients with refractory or relapsed classical Hodgkin lymphoma (cHL) who

- have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or
- are not candidates for ASCT and have failed BV,

conditional on the cost-effectiveness being improved to an acceptable level.

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

OVERALL CLINICAL BENEFIT

pCODR review scope

The objective of this review is to evaluate the effectiveness and safety of pembrolizumab (Keytruda) for the treatment of patients with cHL who (1) failed to achieve a response or progressed after ASCT and have relapsed after treatment with or failed to respond to BV post-ASCT, or who (2) did not receive an ASCT and have relapsed after treatment with or failed to respond to BV.

Studies included: Two non-comparative studies, a phase II and phase Ib trial

The pCODR systematic review included two non-randomized trials: KN-087, a phase II trial (N = 210) and KN-013, a phase Ib trial (N = 31) which met the inclusion criteria for this review. While the KN-087 trial had three cohorts, only cohorts 1 and 2 were included in the pCODR systematic review, as cohort 3 was beyond the scope of this review. Cohort 1 patients failed on both ASCT and BV, cohort 2 patients received salvage chemotherapy and BV and were ineligible for ASCT due to chemoresistance, and cohort 3 patients failed on ASCT and were BV-naive.

KN-087 was a phase II, single-arm trial that assessed the effect of pembrolizumab in three patient cohorts with relapsed or refractory cHL (N = 210). Adult patients were included in the KN-087 trial if they met the following criteria: relapsed or refractory cHL, measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function. All the included patients in the trial received pembrolizumab at 200 mg every three weeks for up to two years or until documented confirmed disease progression, intolerable toxicity, or investigator decision. Treatment beyond first assessment of progressive disease was allowed for patients who were clinically stable.

KN-013 trial was a single-arm, multi-cohort, open-label phase Ib trial that assessed the effect of pembrolizumab in patients with relapsed or refractory cHL who had disease progression during or after treatment with BV (N = 31). Patients were included in KN-013 if they had confirmed diagnosis of relapsed or refractory cHL; relapsed after, were ineligible for, or refused ASCT; received treatment with BV; had an ECOG performance status of < 2; and had adequate organ function. All patients in the trial received pembrolizumab at 10 mg/kg every two weeks for a maximum of 24 months or until confirmed disease

progression or intolerable toxicity. Clinically stable patients with radiologic progressive disease at week 12 could remain on therapy if they were experiencing a clinical benefit or until disease progression was confirmed by a follow-up scan.

Patient populations: Majority young adults and in multiple relapse

Study KN-087 enrolled 210 patients with relapsed or refractory cHL. The median age of the patient population was 35 years (range 18 to 76), 53.8% were male, 51.0% had an ECOG performance status of 1, 88.1% were white, 16.7% had not received treatment with BV, and 36.2% had prior radiation therapy. The most common subtype of cHL was nodular sclerosing Hodgkin lymphoma (HL) (80.5%) followed by mixed cellularity HL (11.4%). All patients had refractory disease or had relapsed after more than three lines of therapy (100%). The majority of patients (83.3%) had previously failed or relapsed after treatment with BV (cohort 1, 100%; cohort 2, 100%; and cohort 3, 41.7%). Patients in cohorts 1 and 3 were all post-ASCT while none of the patients in cohort 2 had received ASCT. Patients received a median of four previous lines of systemic therapy (range 1 to 12).

Study KN-013 enrolled 31 patients with relapsed or refractory cHL. The median age of the patient population was 32 years (range 20 to 67), 58.1% were male, 54.8% had an ECOG performance status of 1, 93.5% were white and 41.9% had prior radiation therapy. Most patients had nodular sclerosing HL (96.8%). All patients in the trial had refractory disease or had relapsed after more than three lines of therapy (100%) and had failed or relapsed after BV treatment (100%). The majority of patients (74.2%) had previously failed or relapsed after ASCT, and 25.8% were ineligible for ASCT. Patients received a median of five previous lines of systemic therapy (range 2 to 15).

Key efficacy results: Meaningful but uncertain response rates

In the KN-087 trial the key efficacy outcomes deliberated on by pERC were objective response rate (ORR) as assessed by a blinded review committee, the primary outcome, as well as ORR as assessed by the study investigator, duration of response, complete response rate, progression-free survival (PFS), overall survival (OS), safety, and health-related quality of life (HRQoL). The ORR for cohort 1 was 73.9% (95% confidence interval [CI], 61.9% to 83.7%) and for cohort 2 was 64.2% (95% CI, 52.8% to 74.6%). In addition, the complete response rate for cohort 1 was 21.7% (95% CI, 12.7% to 33.3%) and for cohort 2 was 24.7% (95% CI, 15.8% to 35.5%). pERC noted that in spite of the uncertainties in the magnitude of benefit given the lack of a comparator, the tumour responses were impressive and clinically meaningful in this heavily pre-treated patient population. pERC noted that there were prolonged durability of responses, as the median duration of response had not been reached for any of the cohorts.

The six-month and nine-month PFS rates for all patients were 72.4% and 63.4%, respectively. Survival estimates were pooled across the three cohorts in KN-087; hence, they may not be directly applicable to cohort 1 and cohort 2 and might limit the conclusions that can be drawn for cohorts 1 and 2. Only four patients had died and median OS had not been reached. pERC noted that the robustness of the preliminary OS and PFS results is limited due to the short follow-up of the study populations and the lack of randomized comparison treatment groups in KN-087. However, pERC noted that despite the uncertainty and immaturity of the survival results, it may be reasonable to assume that the tumour responses expressed as complete response are meaningful because they could potentially delay tumour progression and result in a prolonged survival benefit for this patient population.

In the KN-013 study the key efficacy outcomes were complete response rate as assessed by blinded review committee, the primary outcome, as well as ORR as assessed by the blinded review committee, duration of response, and PFS and OS assessed as exploratory outcomes. At the time of analysis the complete response rate was 19% (95% CI, 8 to 38). The ORR for all patients was 58% (90% CI, 39 to 76; N = 31). The median time to response was 2.8 months (range 2.4 to 8.6). The median duration of response had not been reached (range 0.0 to 26.1+ months). The median PFS was 11.4 months (95% CI, 4.9 to 27.8). The six-month and 12-month PFS rates were 66% and 48%, respectively. The median OS had not been reached at a median 20 months' follow-up time. The six-month and 12-month OS rates were 100% and 87%, respectively. pERC noted that the robustness of the efficacy results is limited due to the small patient population, the non-comparative study design, and the short follow-up of the study. pERC noted that it is not possible to draw robust conclusions from phase Ib trials that are classified as hypothesis-generating research rather than hypothesis-testing research. However, pERC noted that in spite of the uncertainties, the tumour response rates achieved with pembrolizumab in this heavily pre-treated population are impressive and in line with the results observed in the larger phase II KN-087 trial.

Patient-reported outcomes: The potential for improvement in quality of life

HRQoL data were collected in the KN-087 study but not in the KN-013 trial. HRQoL was measured using two instruments: the EORTC (European Organization for Research and Treatment of Cancer) QoL questionnaire C30 and the EQ-5D (European Quality of Life Five Dimensions). HRQoL estimates were pooled across the three cohorts in KN-087; hence, they may not be directly applicable to cohort 1 and cohort 2 and might limit the conclusion that can be drawn for cohorts 1 and 2. HRQoL was documented using a change from baseline at week 12. At week 12, there was a net improvement in QoL as compared with baseline among all patients using either QoL instrument. pERC considered that although no comparator group is available to provide a reference point for these changes, the Committee noted that the improvement in QoL was in line with patient group input indicating that a majority of patients felt that pembrolizumab was able to manage all their disease symptoms as well as dramatically improve their health and well-being similar to their pre-disease state.

Limitations: No direct comparative data with current treatment options

pERC discussed that KN-087 and KN-013 were non-comparative studies. The single-arm, non-randomized design makes interpreting the efficacy and safety events attributable to pembrolizumab relative to current treatment options challenging. pERC considered that the robustness of the preliminary OS and PFS results are limited due to short follow-up and small sample sizes in KN-087 and KN-013. pERC discussed that the conclusions that can be drawn from non-randomized studies with short follow-up are not as robust as those that can be drawn from randomized controlled trials. pERC considered that there are currently no randomized controlled trials under way in this heavily pre-treated, multiply relapsed or refractory population. pERC agreed with the Clinical Guidance Panel (CGP) that conducting a randomized controlled trial in this setting with pembrolizumab compared with palliative chemotherapy would likely not be feasible.

pERC noted that in the absence of comparative efficacy data, the submitter provided an indirect treatment comparison (ITC) to compare pembrolizumab with conventional chemotherapy (gemcitabine). Although the ITC suggested that pembrolizumab is associated with improved efficacy and safety as compared with gemcitabine, these results should be interpreted with caution. There were considerable differences in inclusion criteria across trials and a lack of adjustment for relevant baseline patient or study characteristics that impact the treatment effects. pERC concluded that given these limitations, the comparative efficacy of pembrolizumab versus gemcitabine is highly uncertain.

Safety: Excellent toxicity profile

pERC reviewed information of adverse events from the KN-087 study, noting that the spectrum of toxicities in the KN-013 trial was similar to the larger phase II study. The most common grade 1 or grade 2 treatment-related adverse events that occurred in ≥ 5% of the safety population were hypothyroidism (12.4%) and pyrexia (10.5%). The most common grade 3 treatment-related adverse events were neutropenia (2.4%), diarrhea (1%), and dyspnea (1%). No grade 4 adverse events occurred during the trial, and there were no treatment-related deaths. Sixty patients experienced an immune-mediated adverse event (IMAE) or infusion-related reaction. The most common grade 1 or grade 2 IMAEs were hypothyroidism (13.3%) and infusion-related reactions (4.8%). No grade 4 IMAEs occurred. pERC noted that the single-arm, non-randomized design makes interpreting the safety events attributable to pembrolizumab relative to current treatment options challenging. However, pERC noted that, overall, the incidence of adverse events was low and all events seemed tolerable and manageable. pERC acknowledged patient advocacy group input stating that the majority of patients treated with pembrolizumab reported that pembrolizumab had a positive impact on their health and well-being, with very few adverse events, which were all tolerable.

Need and burden of illness: More effective therapies required

There are approximately 900 new cases of HL in Canada each year, and approximately 160 Canadians will die annually from this disease. It is estimated that the annual number of candidates for this use of pembrolizumab in Canada is not likely to exceed 100 to 110 patients. Currently, there is no standard of therapy for this multiply relapsed patient population (after ASCT and BV). Current treatment options include chemotherapy and radiotherapy with palliative intent, best supportive care, and clinical trials. pERC agreed with CGP that chemotherapy in this patient population is associated with significant toxicities, low response rates, and short PFS of only three to four months. Due to the significant potential for severe toxic effects with chemotherapy, some patients may not be eligible for chemotherapy treatment. pERC acknowledged that there is a lack of effective therapy options with the potential for long-term remission or to delay or avoid systemic therapy. pERC concluded that there is a pressing need

for more effective treatments in this heavily pre-treated patient population who relapse after both ASCT and BV, or who have disease that is resistant to salvage chemotherapy, or who are otherwise not candidates for ASCT and have failed on BV.

Registered clinician input: Need for effective treatment for small population

The Committee deliberated on input from two clinician groups. pERC agreed with the clinicians' input that this indication and reimbursement will affect only a very small number of patients and that there is currently no standard of care in relapsed or refractory patients with cHL. Two of the key benefits identified by both clinician groups was the encouraging response rate and good safety profile of pembrolizumab. An unmet need was identified by both groups. Pembrolizumab could be used in patients with refractory or relapsed cHL post-ASCT and BV or patients who are ineligible for transplant and have no access to BV. In patients who are eligible for allogeneic stem cell transplant**,** pembrolizumab may replace conventional chemotherapy to provide a bridge to transplant. In patients who have chemo-refractory cHL but who are BV-naive, PD-1 inhibitors may replace BV in patients who would not be able to tolerate BV (e.g., baseline neutropenia or neuropathy). The clinicians also noted that PDL-1 testing would not be required.

PATIENT-BASED VALUES

Values of patients with cHL: Disease control and treatment side effect management

One patient advocacy group, Lymphoma Canada (LC), provided input on pembrolizumab for the treatment of patients with cHL.

From a patient's perspective, there are a number of symptoms associated with cHL that impact QoL, including fatigue or lack of energy, enlarged lymph nodes, drenching night sweats, itching, persistent cough, and mental or emotional problems such as anxiety and difficulties with concentrating. Respondents also reported that cHL negatively affected their ability to work, personal image, family obligations, intimate relations, friendships, and ability to attend school. Most respondents indicated that current treatment options (e.g., ABVD [adriamycin, bleomycin, vinblastine, dacarbazine], GDP [gemcitabine, dexamethasone, cisplatin], BEACOPP [bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, prednisone], MOPP/COPP [mustargen or cyclophosphamide, oncovin, procarbazine, prednisone], radiation, stem cell transplant, BV, and surgery) work well in managing their cHL symptoms. LC noted that toxicities associated with their previous treatments were of great concern to many respondents; specifically, fatigue, "chemo-brain," peripheral neuropathy, loss of menstrual periods, thyroid dysfunction, sterility, and lung damage were most commonly reported. LC indicated that respondents also experienced one or more late or long-term treatment-related side effects (lasting longer than two years or appearing later than two years after the end of treatment). LC noted that 93% of respondents had been treated with at least one line of conventional therapy and 16% of respondents had received three or more lines of therapy. Respondents' expectations about the new drug under review were most importantly effectiveness, minimal side effects, and fewer side effects than current treatments.

Patient values on treatment: Remission, fewer side effects, effectiveness, disease control

Respondents who have experience with pembrolizumab reported few side effects, and these were tolerable. Some of the side effects reported with pembrolizumab included fatigue, cough, shortness of breath, nausea, itching, rash, and joint pain. The majority of patients responded that pembrolizumab had positively impacted their health and well-being and that there were no negative impacts on work or school, family obligations, friendships, intimate relations, activities, or travel. Some patients reported that they were able to begin working for the first time since they began treatments for cHL.

pERC noted that patients value treatments that will provide disease and symptom control. pERC agreed that pembrolizumab may provide an opportunity for a patient to achieve disease remission, stop disease progression, manage disease-related symptoms, attain better QoL, and experience few and well-tolerated side effects. Therefore, the Committee concluded that pembrolizumab aligned with patient values.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility (QALY) and cost-effectiveness (life-years) analyses

The pCODR Economic Guidance Panel (EGP) assessed one cost-utility analysis (clinical effects measured by QALYs gained) and one cost-effectiveness analysis (clinical effects measured by life-years gained) of pembrolizumab compared with gemcitabine in patients with relapsed or refractory cHL who (1) failed to achieve a response or progressed after ASCT and had relapsed after treatment with or failed to respond to BV post-ASCT, or who (2) did not receive an ASCT and had relapsed after treatment with or failed to respond to BV. The submitter provided two model structures: a Markov model and a partitioned survival model (scenario analysis).

EGP elected to use the Markov model because (1) it was the model chosen as the base case by the submitter, (2) it provided a more conservative estimate of the incremental cost-effectiveness ratio (ICER), and (3) it addressed some of the structural issues identified with the partitioned survival model. An assessment and critique of the partitioned survival model was therefore out of scope for this review.

Basis of the economic model: Clinical and economic inputs

Costs considered in the analyses included drug acquisition cost, drug administration cost, disease management (progression-free and progressed disease) cost, terminal care cost, subsequent treatment cost, the cost of stem cell transplantation, and the cost of managing adverse events. The key clinical outcomes considered in the cost-utility analysis were OS and PFS. Non-comparative data from a retrospective cohort study were used to inform the comparison of pembrolizumab with gemcitabine.

Drug costs: Pembrolizumab more expensive than comparator

The unit cost of pembrolizumab is $4,400.00 per 100 mg. At the recommended dose of 200 mg every three weeks, the cost of pembrolizumab is $419.05 per day and $11,733.33 per 28-day course.

At the generic list price, gemcitabine costs $270.00 per 1,000 mg, $49.18 per day, and $1,377.00 per 28-day course.

Cost-effectiveness estimate: Not cost-effective compared with chemotherapy, uncertainty due to non-comparative data

pERC deliberated on the cost-effectiveness of pembrolizumab compared with gemcitabine in patients with relapsed or refractory cHL. pERC noted that the cost-effectiveness estimates provided by EGP were higher than the manufacturer's estimates. This was primarily due to (1) the use of PFS curves to model pembrolizumab treatment duration, (2) a shorter time horizon (10 years instead of 20 years), and (3) EGP's choice to use the lower 95% CI for the PFS hazard rate for gemcitabine versus pembrolizumab. pERC noted that according to EGP's sensitivity analyses, the factors that most influence the incremental cost of pembrolizumab are treatment duration, cost of pembrolizumab, and selection of cohort 1 or 2 (not combined). The key effect drivers of the incremental effect are the time horizon, utility values, and selection of cohort 1 or 2 (not combined). Further, the Committee noted the following key limitations of the submitted economic analyses: (1) non-comparative effectiveness data and use of a naive treatment comparison, (2) gemcitabine used as a proxy for all chemotherapies in the comparator arm, and (3) assumption that patients in the progression-free state are at the same risk of death from other causes as the general population. Overall, pERC agreed with EGP's best estimates of the ICER when pembrolizumab was compared with gemcitabine. Consequently, pERC concluded that pembrolizumab was not cost-effective at the submitted price.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: High drug cost, potentially substantial budget impact, and uncertain duration of treatment

pERC discussed the feasibility of implementing a reimbursement recommendation for pembrolizumab in patients with relapsed or refractory cHL.

pERC noted PAG's concern with pembrolizumab's fixed dosing schedule as opposed to a weight-based dosing schedule. Although a fixed dose would minimize drug wastage, PAG noted the high cost of using a fixed dose compared with a weight-based dose for patients weighing less than 100 kg. In addition, as

pembrolizumab is currently used in a number of other indications, drug wastage could be minimized with vial sharing. pERC acknowledged that a weight-based dose of 2 mg/kg every three weeks has been approved for other indications; however, there is currently no evidence for the 2 mg/kg dose for the current indication. pERC noted that jurisdictions may want to further discuss the dosing concern and agree on a common approach that is feasible for all.

pERC acknowledged PAG's input that pembrolizumab would require additional chair time as a result of it being an additional line of therapy.

pERC discussed that pembrolizumab may have the potential for indication creep because of the lack of effective treatment options for patients who (1) are ineligible for ASCT and do not have access to BV therapy or (2) are not eligible for BV because of contraindications. pERC noted that reimbursement of BV for those who are not candidates for ASCT because of age, comorbidities, or refractoriness to salvage therapy is not uniform across Canada and results in a significant treatment gap for this subgroup of patients in most provinces. However, pERC recognized that the use of pembrolizumab in BV-naive patients was beyond the scope of this review. Therefore, the Committee noted that a separate submission to pCODR for pembrolizumab in patients who are ineligible for ASCT and are BV-naive would be required.

pERC noted that the budget impact of pembrolizumab resulted from the high cost of pembrolizumab, the relatively small number of eligible patients, and a large market share expected for the pembrolizumab indication. pERC also agreed with EGP that the submitted budget impact analysis was underestimated because pembrolizumab will likely take the full market share in this funded scenario.

DRUG AND CONDITION INFORMATION

Drug Information	• Monoclonal antibody • 100 mg/4 mL vial • 200 mg administered intravenously over 30 minutes every three weeks
Cancer Treated	• Classical Hodgkin lymphoma
Burden of Illness	• There are approximately 900 new cases of HL in Canada each year and approximately 160 Canadians will die annually from this disease. It is estimated that the annual number of candidates for this use of pembrolizumab in Canada is not likely to exceed 100 to 110 patients.
Current Standard Treatment	• Current treatment options include chemotherapy with palliative intent, best supportive care, and enrolment in clinical trials.
Limitations of Current Therapy	• Significant toxicities and low response rates

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)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Mike Doyle, Health Economist
Dr. Craig Earle, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

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

- Kelvin Chan and Lauren Flay Charbonneau, who were not present for the meeting
- Cameron Lane, who did not vote due to his role as a patient member alternate.

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

- Dr. Avram Denburg and Dr. Craig Earle, who were not present for the meeting
- Cameron Lane, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of pembrolizumab in cHL, through their declarations, two members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were excluded from voting. For the Final Recommendation, two members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of interest Guidelines*, two members were excluded from voting.

Information sources used

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

Consulting publicly disclosed information

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

Use of this Recommendation

This Recommendation from 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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