pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

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

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

Drug:
Nivolumab (Opdivo)

Submitted Funding Request:
Nivolumab is indicated for the treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous stem cell transplantation (ASCT) and brentuximab vedotin (BV) or three or more lines of systemic therapy including ASCT.

Submitted by:
Bristol-Myers Squibb

Manufactured by:
Bristol-Myers Squibb

NOC/c Date:
November 10, 2017

Submission Date:
September 29, 2017

Initial Recommendation Issued:
March 2, 2018

Approximate per Patient Drug Costs, per Month (28 Days)	Nivolumab costs:
Submitted list price Nivolumab: $782.22 per 40 mg vial or $1,955.56 for 100 mg vial. * Note: Costs are calculated based on an average weight of 70 kg and body surface area of 1.7 m^2.	• $8,213.35 per 28-day course

pERC RECOMMENDATION

pERC conditionally recommends reimbursement of nivolumab (Opdivo) for patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous stem cell transplantation (ASCT) and brentuximab vedotin (BV) only if the following condition is met:

- cost-effectiveness being improved to an acceptable level.

If the aforementioned condition cannot be met, pERC does not recommend reimbursement of nivolumab. Treatment should continue until confirmed disease progression or unacceptable toxicity.

The Committee made this recommendation because it was satisfied that there is a net clinical benefit of nivolumab in patients who have relapsed or progressed after ASCT followed by BV, based on the rates of complete remission in a heavily pre-treated population, a favourable toxicity profile, the potential to improve quality of life (QoL), 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 about the magnitude of clinical benefit of nivolumab compared with relevant treatment options.

pERC does not recommend funding nivolumab for patients with cHL that has relapsed or progressed after three or more lines of systemic therapy, one of which was ASCT.

The Committee made this recommendation because it was not satisfied that there is a net clinical benefit of nivolumab in patients with cHL that has relapsed or progressed after three or more lines of systemic therapy, one of which included ASCT. While pERC was confident that nivolumab produces a tumour response, pERC was unable to determine how nivolumab compares with other treatment options (such as BV) given the lack of comparative data and long-term outcomes important to patients, such as overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and QoL. Given the availability of BV, pERC was uncertain whether nivolumab addressed an unmet need and noted ongoing phase III trials in this setting.

pERC was satisfied that nivolumab aligns with patient values for patients who relapse or progress after (1) ASCT followed by BV or (2) ASCT and did not receive BV, as there is a need for more effective treatment options with tolerable side effects.

The Committee concluded that nivolumab, 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 nivolumab has a net clinical benefit in patients with cHL that has relapsed or progressed after ASCT and subsequent BV, jurisdictions may want to consider pricing arrangements that would improve the cost-effectiveness of nivolumab to an acceptable level. pERC noted that the cost of nivolumab 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 nivolumab may have the potential for indication creep because of the lack of effective treatment options for patients who are ineligible for ASCT and who do not have access to BV therapy. 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 noted that the use of nivolumab in ASCT ineligible and BV-naive patients was beyond the scope of this review. Therefore, the Committee noted that a separate submission to pCODR for nivolumab in patients who are ineligible for ASCT and who are BV-naive would be required.

Generalizability of Results to Patients Who Have Relapsed or Progressed After ASCT and Who Are Not Candidates to Receive BV
pERC noted that the generalization of CHECKMATE-205 results to patients who have cHL that has relapsed or progressed after three or more lines of systemic therapy including ASCT and who are not eligible to receive BV was likely reasonable. pERC noted that there is a clear need for more effective treatment options and it is unlikely that there will be trials specifically designed for this small group of patients.

Wastage and Factors Affecting Budget Impact
pERC noted that drug wastage with the weight-based dose would be minimized with the two different vial sizes (40 mL and 100 mL) and with vial sharing, given that nivolumab is currently used for many other indications. pERC noted that the submitted budget impact analysis (BIA) was most sensitive to changes in the number of cHL patients assumed to relapse or progress after ASCT and subsequent BV treatment. pERC discussed that the estimated high market uptake of nivolumab seemed reasonable given the need for effective treatment options in this setting.

Optimal Dosage of Nivolumab
pERC noted the Provincial Advisory Group's (PAG) request for information on the appropriateness of using cost-saving dosing strategies of 3 mg/kg up to a dose cap of 240 mg every two weeks and 6 mg/kg up to a dose cap of 480 mg every four weeks. pERC acknowledged that while flat dosing is widely used in solid tumour treatment, there is currently insufficient evidence available to recommend using cost-saving dosing strategies of 3 mg/kg up to a dose cap of 240 mg every two weeks and 6 mg/kg up to a dose cap of 480 mg every four weeks. pERC noted that jurisdictions may want to assess new dosing strategies as they become available 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 nivolumab in this patient population. Jurisdictions may want to consider a time-limited reimbursement of nivolumab, with a reassessment of the efficacy, safety, and cost-effectiveness of nivolumab for the treatment of patients with cHL that has relapsed or progressed after ASCT followed by BV 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.

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

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

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

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. There are approximately 900 new cases of cHL in Canada each year, and approximately 160 Canadians will die annually from this disease. Out of 900 new cases, approximately 20% will become candidates for second-line treatment including autologous stem cell transplant (ASCT), which cures approximately 50% of patients. Currently, most patients who relapse after ASCT are treated with Brentuximab vedotin (BV). However, at least 90% of patients will relapse after BV, and there is no standard of care therapy for this multiply relapsed patient population (i.e., relapse after ASCT followed by BV). Current treatment options include chemotherapy and radiotherapy with palliative intent, best supportive care, and clinical trials. pERC agreed with the Clinical Guidance Panel (CGP) that chemotherapy in this patient population is associated with significant toxicities, low response rates, and median progression-free survival (PFS) of only three to four months. pERC acknowledged that there is a lack of effective treatment 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 have relapsed after both ASCT and subsequent BV treatment. The Committee noted a recent conditional pERC recommendation for pembrolizumab for patients with refractory or relapsed cHL who have failed ASCT followed by BV or who are not candidates for ASCT and have failed BV. pERC recognized that as of yet no funding decisions have been made for pembrolizumab in this setting.

pERC deliberated on two single-arm, non-randomized studies CHECKMATE-205 [CM-205], a phase II trial, and CHECKMATE-039 [CM-039], a phase I trial) that evaluated the efficacy and safety of nivolumab in patients with refractory or relapsed cHL. pERC noted that the phase II CM-205 trial provided the main evidence for the submission, which was supplemented by evidence from the much smaller phase I CM-039 trial. pERC noted that the CM-205 trial had four cohorts, however, only cohort A (patients who failed ASCT and were BV-naive) and cohort B (patients who failed ASCT and subsequent BV) were deliberated on. Cohort C included patients who received BV before ASCT, after ASCT, or both before and after ASCT. pERC noted that the inclusion criteria for cohort B (patients who received BV after ASCT) are a subset of the inclusion criteria for cohort C. pERC felt that cohort B represents the outcomes of patients who receive BV after ASCT better than cohort C, as results for cohort C were pooled across three subsets of patients with varying inclusion criteria. pERC further noted that the other two subsets in cohort C (patients who receive BV before ASCT or both before and after ASCT) are not applicable to current Canadian clinical practice. Cohort D included patients with newly diagnosed and untreated advanced stage cHL and was beyond the scope of this review. pERC agreed with the CGP that both studies demonstrated very impressive and highly clinically relevant objective response rates (ORR; defined as the percentage of patients with a complete or partial response) and complete response rates in a heavily pre-treated patient population. pERC also noted the prolonged durability of the tumour responses.

However, pERC noted that the robustness of the exploratory overall survival (OS) and PFS results are limited due to the short follow-up of the study population and the lack of randomized comparator treatment groups in CM-205 and CM-039. pERC acknowledged 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 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 a clinical benefit in terms of PFS and OS. However, pERC agreed with the CGP that, despite the uncertainty and immaturity of the survival results, it may be reasonable to assume that the tumour responses, expressed as complete responses, are clinically meaningful because they could potentially delay tumour progression and have the potential to result in a prolonged survival benefit for this patient population.

pERC agreed with the CGP that the tumour responses observed in the two non-comparative phase I and II studies compare favourably to currently available palliative chemotherapy options in patients who have relapsed or progressed on ASCT followed by BV. Further, the Committee agreed that, despite the significant unmet need in patients who failed on both ASCT and subsequent BV treatment, conducting a randomized controlled trial in this setting with nivolumab compared with palliative chemotherapy would likely not be feasible. pERC agreed with the CGP that equipoise between nivolumab and a palliative chemotherapy agent does not exist.

However, pERC was unable to determine how nivolumab compares with other treatment options (such as BV) given the lack of comparative data and long-term outcomes important to patients, such as OS, PFS, ORR, and QoL. Given the availability of BV for patients who have relapsed or progressed after ASCT and who are BV-naive, pERC was uncertain whether nivolumab addressed an unmet need in this patient population and noted ongoing phase III trials comparing BV against a PD-1 inhibitor and BV plus nivolumab against BV in this setting.

pERC considered the generally mild and manageable toxicity profile observed with nivolumab. pERC noted that the single-arm, non-randomized designs of CM-205 and CM-039 make interpreting the safety events attributable to nivolumab challenging, since all patients with relapsed or refractory cHL received the same treatment. However, pERC agreed with the CGP that the side effects observed in the two trials (CM-205 and CM-039) are as expected for PD-1 inhibitors. Less than 5% of patients experienced grade 3/4 adverse events (AEs), which are manageable by clinicians who are used to dealing with immune-related AEs. pERC acknowledged patient advocacy group input stating that the majority of patients treated with nivolumab reported that nivolumab had a positive impact on their health and well-being, with very few AEs, all of which were tolerable.

pERC noted the available quality-of-life (QoL) data for nivolumab. When the data for cohorts A, B, and C of the CM-205 trial were pooled, nivolumab treatment resulted in a clinically meaningful and statistically significant improvement in general and cancer-specific patient-related outcomes. However, the Committee discussed that, without a comparator group, there is considerable uncertainty in the QoL of patients who receive nivolumab compared with other available therapies. pERC noted that the improvement in QoL from baseline was consistent with the input received from patient groups, which indicated that a majority of patients felt that nivolumab was able to manage their disease symptoms with minimal side effects and effectively improve their health and well-being. pERC noted that an improvement in QoL was likely, given the high rate of tumour responses and excellent safety profile observed with nivolumab.

pERC concluded that there is a net clinical benefit to nivolumab compared with chemotherapy in the treatment of patients with relapsed or progressed cHL after both ASCT and subsequent BV treatment. 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 concluded that there is no net clinical benefit to nivolumab compared with BV in the treatment of patients who have relapsed or progressed after ASCT and who are BV-naive. While pERC was confident that nivolumab produces a tumour response, pERC was unable to determine how nivolumab compares with other treatment options (such as BV) given the lack of comparative data and long-term outcomes important to patients, such as OS, PFS, overall response rate (ORR), and QoL. Given the availability of BV, pERC was uncertain whether nivolumab addressed an unmet need and noted ongoing phase III trials comparing BV against a PD-1 inhibitor in this setting.

pERC deliberated upon patient advocacy group input and concluded that nivolumab aligns with patient values. pERC noted that, according to patients, relapsed or refractory cHL manifests stressful disease symptoms such as 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. pERC considered that patients value effective treatment options with reduced toxicity. Hence, the Committee concluded that nivolumab aligned with patient values in both treatment settings (ASCT followed by BV or ASCT without BV).

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. The clinicians providing input indicated that nivolumab would be an additional line of therapy for patients who have relapsed disease following ASCT and BV and who have no other effective options. They noted that nivolumab offers patients hope of long-term cure, given the high response rates and remissions. The magnitude of benefits allows patients, who are typically 20 to 30 years old, to return to work and enjoy

an excellent QoL. The side effects are as expected for immunotherapies and are manageable by clinicians who are used to dealing with immune-related AEs.

pERC deliberated on the cost-effectiveness of nivolumab in patients with relapsed or refractory cHL and concluded that nivolumab, at the submitted price, is not cost-effective when compared with (1) BV in patients who failed ASCT and are BV-naive or (2) chemotherapy (weighted average of mix of chemotherapies) in patients who failed ASCT and subsequent BV treatment. pERC noted that the pCODR Economic Guidance Panel (EGP) reanalyses of cost-effectiveness presented incremental cost-effectiveness ratios (ICERs) as lower bounds with no upper bounds, given the uncertainty in the non-comparative data. pERC also noted that the submitted base-case ICERs were lower than the EGP's lower bound ICER estimates. The Committee noted several limitations in the submitted analysis, particularly the lack of comparative effectiveness data and the resulting uncertainty in relative efficacy between nivolumab and chemotherapy or BV. pERC noted that, in the absence of comparative efficacy data, the submitter provided an indirect treatment comparison (ITC) to compare nivolumab with BV. Although the ITC suggested that nivolumab is associated with improved OS as compared with BV, these results should be interpreted with caution. There was insufficient follow-up data for nivolumab, lack of adjustment for differences in patient and disease characteristics (especially treatment-effect modifiers), differences in trial design, and inability to control for unknown confounders. pERC noted EGP's opinion that, due to the poor quality of the ITC, the ITC did not reduce the uncertainty in the non-comparative data. pERC concluded that given these limitations, the comparative efficacy of nivolumab versus BV or chemotherapy is highly uncertain. Furthermore, the Committee noted that the EGP made the following changes to the model to address some of its limitations: (1) a shorter time horizon to address the uncertainty in survival estimates based on extrapolation of short-term trial data, (2) lower utility values as the CGP indicated that those observed in the CM-205 trial seemed high, and (3) a shorter treatment duration for BV, as according to the CGP, few patients complete all cycles of BV treatment. Overall, pERC agreed with the EGP's reanalyses and the limitations identified in the submitted economic model. pERC noted that the EGP's estimates of the ICERs for nivolumab compared with chemotherapy and compared with BV included lower bounds but no upper bounds due to the uncertainty in the available data. pERC therefore accepted the EGP's estimates of the ICERs. Consequently, pERC concluded that nivolumab was not cost-effective at the submitted price compared with chemotherapy or BV. pERC considered the feasibility of implementing a reimbursement recommendation for nivolumab in patients who relapsed or progressed after ASCT and subsequent BV treatment. pERC discussed that, if nivolumab were implemented, the estimated high market uptake of nivolumab seemed reasonable given the need for effective treatment options in this setting. pERC noted that the budget impact of nivolumab resulted from the high cost of nivolumab, the relatively small number of eligible patients, and a large market share expected for the nivolumab indication after ASCT and subsequent BV failure.

pERC noted that drug wastage with the weight-based dose would be minimized with the two different vial sizes (40 mL and 100 mL) and with vial sharing, given that nivolumab is currently used for many other indications.

pERC discussed that nivolumab may have the potential for indication creep because of the lack of effective treatment options for patients who are ineligible for ASCT and who do not have access to BV therapy. 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 noted that the use of nivolumab in ASCT ineligible and BV-naive patients was beyond the scope of this review. Therefore, the Committee noted that a separate submission to pCODR for nivolumab in patients who are ineligible for ASCT and are BV-naive would be required.

pERC noted that the generalization of CHECKMATE-205 results to patients who have cHL that has relapsed or progressed after three or more lines of systemic therapy including ASCT and who are not eligible to receive BV was likely reasonable. pERC noted that there is a clear need for more effective treatment options, and it is unlikely that there will be trials specifically designed for this small group of patients.

pERC agreed that PDL-1 testing would not be necessary. PDL-1 is highly expressed on Reed–Sternberg cells that characterize cHL. pERC noted that the efficacy results of nivolumab could not necessarily be extended to nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), as PDL-1 is expressed less strongly on the malignant cell population of NLPHL, which affects only about 5% of all patients with Hodgkin lymphoma and these patients were not included in the pivotal studies reviewed.

pERC noted the PAG request for information on the appropriateness of using cost-saving dosing strategies of 3 mg/kg up to a dose cap of 240 mg every two weeks and 6 mg/kg up to a dose cap of 480 mg every

four weeks. pERC acknowledged that while flat dosing is widely used in solid tumours, there is currently insufficient evidence to recommend using cost-saving dosing strategies of 3 mg/kg up to a dose cap of 240 mg every two weeks and 6 mg/kg up to a dose cap of 480 mg every four weeks in this group of patients. pERC noted that jurisdictions may want to assess new dosing strategies as they become available and agree on a common approach that is feasible for all.

EVIDENCE IN BRIEF

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

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from the pCODR clinical and economic review panels
- Input from one patient advocacy group: Lymphoma Canada
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The objective of this review is to evaluate the effectiveness and safety of nivolumab (Opdivo) for classical Hodgkin lymphoma (cHL) that has relapsed or progressed after (1) autologous stem cell transplantation (ASCT) and brentuximab vedotin (BV) or (2) three or more lines of systemic therapy including ASCT.

Studies included: Two Non-comparative Studies, a Phase II and Phase I trial

The pCODR systematic review included two non-randomized trials: CHECKMATE-205 (CM-205), a phase II trial (N = 243), and CHECKMATE-039 (CM-039), a phase I trial (N = 23), which met the inclusion criteria for this review. While the CM-205 trial had four cohorts, only cohorts A and B were deliberated on as cohort C was considered not applicable to current Canadian clinical practice and cohort D was beyond the scope of this review. Cohort A patients failed both ASCT and subsequent BV treatment, cohort B patients failed ASCT and were BV-naive, cohort C patients received BV before ASCT, after ASCT, or both before and after ASCT, and cohort D patients had newly diagnosed and untreated advanced stage cHL.

CM-205 was a phase II, non-comparative, multi-cohort, single-arm, open-label trial that assessed the effect of nivolumab in four patient cohorts with relapsed or refractory cHL (N = 243). Adult patients were included in the CM-205 trial if they met the following criteria: failed or progressed after ASCT, an Eastern Cooperative Oncology Group performance (ECOG) status score of 0 or 1, previous high-dose conditioning chemotherapy followed by ASCT as part of salvage therapy, and either documented failure to achieve at least partial remission after the most recent treatment or documented relapse or disease progression. Patients in the trial were treated with nivolumab 3 mg/kg, intravenously, every two weeks until unacceptable toxicity or disease progression or progressive disease according to the International Working Group criteria for malignant lymphoma (2007 IWG).

CM-039 was a phase I, open-label, multi-centre, dose-escalation, multi-dose study to assess the tolerability of nivolumab and the combination of nivolumab and daratumumab, with or without immunomodulatory drugs (pomalidomide and dexamethasone), in patients with relapsed and refractory hematological malignancies, including a cohort of 23 patients with Hodgkin lymphoma. The trial included adult patients who had histologically confirmed evidence of relapsed or refractory Hodgkin lymphoma with at least one lesion measuring more than 1.5 cm, an ECOG performance status score of 0 or 1, previous treatment with at least one chemotherapy regimen, and no ASCT within the previous 100 days. The expansion cohort (23 cHL patients) was treated at the maximum tolerated dose (3 mg/kg), determined during the dose escalation phase. A response assessment following administration of the first dose was obtained, and the treatment was administered every two weeks thereafter. Patients continued to receive the study drug for up to two years or until confirmed complete remission (CR), confirmed progressive disease, or unacceptable toxicity.

Patient populations: Median Age of 34 with Refractory or Relapsed Disease After Median of Four Prior Lines of Systemic Cancer Regimens

Study CM-205 included 243 patients with relapsed or refractory cHL. The median age of the patient population was 34 years (range, 18 to 72), 77.0% of patients had stage III or IV disease at study entry, 58.0% were male, and 46% had an ECOG performance status of 1. Patients had received a median of four prior systemic cancer regimens (range, 2 to 15), and 67.1% had prior radiation therapy. The main

differences between the study cohorts were related to the lower proportion of patients with stage IV disease (at the study entry) in cohort A (38.0%) when compared with cohort B (68.0%) and cohort C (56.0%), the longer median time from initial diagnosis to the first dose of nivolumab in cohort B (6.2 years) when compared with cohort A (3.1 years) and cohort C (3.5 years), and the longer median time from the most recent transplant to the first dose of nivolumab in cohort B (3.4 years) when compared with cohort A (1.0 years) and cohort C (1.7 years).

Study CM-039 included an expansion cohort of 23 cHL patients. Among the 23 study participants, 15 patients had a history of prior BV treatment as a salvage therapy after failure of ASCT. Of the remaining eight patients, five were ASCT-naive, two had failed on ASCT but were BV-naive, and one had failed on BV followed by ASCT. The median age was 35 years (range, 20 to 54 years). The majority of all cHL patients were white 20 (87%) and had a baseline ECOG performance status score of 1 (74%). There were 12 (52%) males and 11 (48%) females included in the study. All the patients had been heavily pre-treated, and 65% of them had received four or more previous systemic treatments. Of the 23 patients, 78% had undergone ASCT, 78% had a history of treatment with BV therapy, and 83% had received radiation therapy. Extra-nodal disease involving bone, lung, pelvis, peritoneum, or pleura was reported in 17% of the patients. The most common first-line chemotherapy was ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), which was administered in 20 out of 23 patients (87%).

Key efficacy results: Clinically Meaningful but Uncertain Response Rates

In the CM-205 trial the key efficacy outcomes deliberated on by pERC were objective response rate (ORR) as assessed by the independent radiologic review committee (IRRC) (the primary outcome), as well as duration of objective response (DOR), CR rate, duration of CR, partial remission (PR) rate, duration of PR, progression-free survival (PFS) based on IRRC assessments; ORR, DOR, and PFS based on investigator assessments; and overall survival (OS), safety, and quality of life (QoL). ORR was achieved in 65% (95% confidence interval [CI], 52 to 77) of patients in cohort A, 68% (95% CI, 56 to 78) of patients in cohort B, and 73% (95% CI, 63 to 81) of patients in cohort C, with corresponding complete remission rates of 29%, 13%, and 12%, respectively. 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 support for the tumour responses was observed in the prolonged durability of responses. The median duration of IRRC-assessed objective response reached 20 months (95% CI, 13 to 20) in cohort A, 16 months (95% CI, 8 to 20) in cohort B, and 15 months (95% CI, 9 to 17) in cohort C. Overall, the durations of response were 20 months (95% CI, 16 to not available) in patients with a CR and 13 months (95% CI, 9 to 17) in patients with a PR. The median IRRC-assessed PFS rates were 18 months (95% CI, 11 to 22) in cohort A (22.24 months in patients with a CR, and 18.83 months in patients with a PR), 15 months (95% CI, 11 to 20) in cohort B (22.11 months in patients with a CR, and 14.65 months in patients with a PR), and 11.93 months (95% CI, 11.07 to 18.40) in cohort C (16.59 months in patients with a CR, and 15.05 months in patients with a PR). The PFS rate was 54.8% in cohort A (at 12 months), 47.4% in cohort B (at 18 months), and 49.1% in cohort C (at 12 months).

The median OS was not reached in any of the study cohorts. After a minimum follow-up of 15 months (median follow-up, 19.12 months), the OS rate was 93.4% in cohort A. After a minimum follow-up of 20 months (median follow-up, 22.70 months), the OS rate was 89.2% in cohort B. After a minimum follow-up of 14 months (median follow-up, 16.16 months), the OS rate was 88.7% in cohort C. 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 CM-205. 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 CR are meaningful because they could potentially delay tumour progression and result in a prolonged survival benefit for this patient population.

In the CM-039 study, the key efficacy outcomes were the safety and side-effect profile of nivolumab, the primary outcome, as well as characterizing the efficacy of nivolumab based on best overall response (BOR), DOR, ORR, PFS, and OS, and assessing PD-1 ligand loci integrity and expression of the encoded ligands. After a median follow-up of 86 weeks, ORR was reported in 20 out of 23 (87%) of the patients; among those, 22% had a CR and 65% had a PR. However, the median DOR had not been reached. The investigator-assessed median time to response was 1.7 (range, 0.7 to 8.9) months for all cHL patients, with time to CR being 5.3 (range, 1.6 to 19.9) months, and time to PR 1.7 months (range, 0.7 to 8.9). The PFS rate at 24 weeks was 86% (95% CI, 62 to 95). The OS rates at one year and 1.5 years were 91% (95% CI, 69.5 to 97.8) and 83% (95% CI, 60.1 to 93.1), respectively. After a median follow-up of 86 weeks, the median PFS and OS had not been reached. 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 I 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 nivolumab in this heavily pre-treated population are impressive and in line with the results observed in the larger phase II CM-205 trial.

Patient-reported outcomes: The Potential for Improvement in Quality of Life

Health-related QoL data were collected in the CM-205 study but not in the CM-039 trial. Health-related QoL was measured using two instruments: the EuroQoL 5-Dimensions questionnaire (EQ-5D) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 36 (EORTC QLQ-C30). QoL assessment in cohort B (58% of patients) revealed least squares mean score change from baseline at week 33 of 19.1 (± 3.1) for the EQ-5D visual analogue scale and 7.6 (± 2.3) for the EORTC QLQ-C30.When the data were pooled for cohorts A, B, and C, nivolumab treatment resulted in a clinically meaningful and statistically significant improvement in general and cancer-specific patient-related outcomes. Improvement started early (week 9) and persisted to week 93. pERC noted that although no comparator group was available to provide a reference point for these changes, the improvement in QoL was in line with patient group input indicating that a majority of patients felt that nivolumab was able to manage their disease symptoms as well as improve their health and well-being.

Limitations: No direct comparative data with current treatment options

pERC discussed that CM-205 and CM-039 were non-comparative studies. The single-arm, non-randomized design makes interpreting the efficacy and safety events attributable to nivolumab 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 CM-205 and CM-039. pERC noted 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 patients with multiply relapsed or refractory cHL who have failed on ASCT and subsequent BV treatment. pERC agreed with the Clinical Guidance Panel (CGP) that conducting a randomized controlled trial in this setting with nivolumab compared with palliative chemotherapy would likely not be feasible.

Given the lack of comparative effectiveness data, pERC was unable to determine how nivolumab compares with other treatment options (such as BV) with regard to outcomes important to patients, such as OS, PFS, ORR, and QoL. In the absence of comparative efficacy data, the submitter provided a naive indirect treatment comparison (ITC) and a matched adjusted indirect comparison to compare nivolumab with BV. Although the naive ITC and matched adjusted comparison suggested that nivolumab is associated with longer OS compared with BV, these results should be interpreted with caution. There were insufficient follow-up data for nivolumab, lack of adjustment for baseline differences in patient and disease characteristics (especially treatment effect modifiers), differences in trial designs, and an inability to control for unknown confounders. pERC concluded that given these limitations, the comparative efficacy of nivolumab versus BV is highly uncertain. pERC noted ongoing phase III trials comparing BV against a PD-1 inhibitor in this setting.

Safety: Favourable toxicity profile

pERC reviewed information about adverse events (AEs) from the CM-205 study. The most common drug-related AEs in 243 nivolumab-treated patients (cohorts A, B, and C) were fatigue (23%), diarrhea (15%), and infusion reactions (14%). The most common drug-related serious AEs were infusion reactions (2%) and pneumonitis (1%). Serious AEs also included fatigue (1%), diarrhea (1%), rash (1%), infusion reactions (< 1%), and autoimmune hepatitis (1%). The most common drug-related AEs that led to discontinuation of the study treatment were pneumonitis (2%) and autoimmune hepatitis (1%). One patient (1%) died from multi-organ failure that was deemed to be unrelated to the study treatment. pERC agreed with the CGP that, in general, these side effects are as expected for PD-1 inhibitors, with less than 5% having grade 3/4 AEs and these being manageable by clinicians who are used to dealing with immune-related AEs.

pERC also reviewed information about AEs from the CM-039 study. At a median follow-up of 40 weeks (range, 0 to 75), the incidence of drug-related AEs of any grade that occurred in at least 5% of the patients was 78%. Grade 3 AEs were reported in 22% of patients. Overall, drug-related AEs were reported in 18 patients (78%). The most common AEs included rash (22%) and a decreased platelet count (17%). Drug-related grade 3 AEs were reported in five patients (22%) and included the myelodysplastic syndrome,

pancreatitis, pneumonitis, stomatitis, colitis, gastrointestinal inflammation, thrombocytopenia, an increased lipase level, a decreased lymphocyte level, and leukopenia. No drug-related grade 4 or 5 AEs were reported. No treatment-related deaths were reported. Twelve patients (52%) discontinued treatment; of those, two patients (9%) had toxic events (the myelodysplastic syndrome and thrombocytopenia).

Need and Burden of Illness: More Effective Therapies Required in Patients who Fail ASCT and Subsequent BV; Uncertain Unmet Need in Patients who Fail ASCT and are BV-naive

There are approximately 900 new cases of Hodgkin lymphoma 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 nivolumab in Canada is not likely to exceed 100 to 110 patients.

Currently, there is no standard of therapy for multiply relapsed patients who fail after ASCT and subsequent 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 median 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.

pERC noted that given the availability of BV, there was uncertainty if nivolumab addressed an unmet need in patients who fail after ASCT and are BV-naive. Given lack of comparative effectiveness data, pERC was unable to determine how nivolumab compares with other treatment options (such as BV) with regard to outcomes important to patients, such as OS, PFS, ORR, and QoL. pERC noted ongoing phase III trials comparing BV against a PD-1 inhibitor in this setting.

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. The clinicians providing input indicated that nivolumab would be an additional line of therapy for patients who have relapsed disease following ASCT and BV and who have no other effective options. They noted that nivolumab offers patients hope of long-term cure, given the high response rates and remissions. The magnitude of benefits may allow patients, who are typically 20 to 30 years old, to return to work and enjoy an excellent QoL. The side effects are as expected for immunotherapies and are manageable by clinicians who are used to dealing with immune-related AEs.

PATIENT-BASED VALUES

Values of Patients with Classical Hodgkin Lymphoma: Disease Control and Treatment Side Effect Management

One patient advocacy group, Lymphoma Canada, provided input on nivolumab 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 and emotional problems such as anxiety and difficulties with concentrating. Respondents also reported on aspects of their life negatively impacted by cHL, including 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, GDP [gemcitabine, dexamethasone, cisplatin], BEACOPP [bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, dexamethasone], MOPP/COPP [mechlorethamine, vincristine, procarbazine, prednisone/cyclophosphamide, vincristine, procarbazine, prednisone], radiation, stem cell transplant, BV, and surgery) work well in managing their cHL symptoms. Lymphoma Canada noted that toxicity associated with 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 the most commonly reported. Lymphoma Canada also indicated that respondents 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). In the current sample, Lymphoma Canada 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 who had not experienced nivolumab expected that it would demonstrate effectiveness (i.e., offer disease control and remission) followed by minimal side effects or fewer side effects than current treatments.

Patient Values on Treatment: Remission, Fewer Side Effects, Effectiveness, Disease Control

Respondents who had experience with nivolumab reported few side effects, and said that these were tolerable. Some of the side effects reported with nivolumab included fatigue, muscle or joint pain, diarrhea, constipation, headache, shortness of breath, rash, and back pain. The most common reason for choosing treatment with nivolumab was that there were no other treatment options available. At the time of the survey, Lymphoma Canada reported that 11 of 15 respondents were still receiving treatment with nivolumab, four respondents were no longer being treated with nivolumab (two had completed their full course of treatment, one respondent did not respond to the drug, and one respondent proceeded to allogeneic transplant after achieving a complete response with nivolumab). The majority responded that nivolumab had positively impacted their health and well-being; notably, no negative impacts on school, work and family obligation had been experienced. Respondents also reported that nivolumab had positive impacts on their ability to work, attend school, travel, and participate in activities and on their personal relationships.

pERC noted that patients value effective treatment options with reduced toxicity.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility and Cost-effectiveness Analyses

The pCODR Economic Guidance Panel (EGP) assessed one cost-utility analysis (clinical effects measured by quality-adjusted life-years gained) and one cost-effectiveness analysis (clinical effects measured by life-years gained) of nivolumab compared with (1) BV in patients who failed ASCT and were BV-naive, and (2) chemotherapy (weighted average of chemotherapies) in patients who had failed ASCT and subsequent BV treatment.

Basis of the economic model: Clinical and Economic Inputs

Costs considered in the analyses included drug cost, disease management cost, palliative care cost, and AEs cost. The key clinical outcomes considered in the cost-utility analysis were PFS and OS. Non-comparative data were used to inform the comparison of nivolumab against BV or chemotherapy.

Costs considered in the analyses included drug acquisition cost, drug administration cost, disease management cost (progression-free and progressed disease), terminal care cost, subsequent treatment cost, the cost of stem cell transplantation, and the cost of managing AEs. The key clinical outcomes considered in the cost-utility analysis were OS and PFS.

Drug costs: Nivolumab more Expensive than Chemotherapy, Cheaper than BV

The unit cost of nivolumab is $782.22 for a 40 mg vial, $1,955.56 for a 100 mg vial, or $19.556 per mg. At the recommended dose of 3 mg/kg every two weeks, the cost of nivolumab is $293.34 per day and $8,213.35 per 28-day course. Calculations assume no wastage.

Nivolumab treatment should continue until confirmed disease progression or unacceptable toxicity. The median number of nivolumab doses received was 17 in in the CM-205 trial for cohort B.

The cost of BV is $4,840 per 50 mg vial, $691.43 per day, and $19,360 per 28-day course. A total of 126 mg are used (three vials) once per 21-day cycle for an average body weight of 70 kg.

The submitter indicated that the combination of chemotherapies produced an average weighted cost of $3,095 per 28-day model cycle. The cost of chemotherapy was a weighted average of approximately 30 chemotherapy regimens and agents based on frequency of usage.

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

pERC deliberated on the cost-effectiveness of nivolumab compared with (1) BV in patients who failed ASCT and are BV-naive, and (2) chemotherapy (weighted average of mix of chemotherapies) in patients who failed ASCT and subsequent BV treatment. pERC noted that the cost-effectiveness estimates provided

by EGP were higher than the manufacturer's estimates. This was primarily due to three factors: (1) A shorter time horizon (10 years instead of 15 years) was used to address the uncertainty in survival estimates based on extrapolation of short-term trial data (median OS was not reached in both trials: CM-205 with median follow-up of 19.12 months in cohort A and 22.70 months in cohort B; CM-039 with median follow-up of 86 weeks). Given the lack of data to inform OS in patients with multiply relapsed cHL, the time horizon was aligned with the previous review for pembrolizumab in patients with multiply relapsed cHL. (2) Lower utility values were used, as the CGP indicated that those observed in the CM-205 seemed high, notably the relatively high utilities in the post-progression period. To align with previous cHL reviews and other reviews of nivolumab in the cHL population (notably that of the Scottish Medicines Consortium), the EGP elected to use utility values sourced from the literature. (3) A shorter treatment duration for BV (9 instead of 12 months) was used, as according to the CGP, few patients complete all 16 cycles of BV treatment due to progression or peripheral neuropathy.

pERC noted that according to EGP's one-way scenario analyses, the factors that most influence the incremental cost of nivolumab compared with BV (in patients who have failed ASCT and are BV-naive) are the source of utilities, the population under consideration (naive indirect comparison versus matched adjusted indirect comparison), and the assessment of PFS outcomes for nivolumab (independent versus investigator assessment). The factors that most influence the incremental cost of nivolumab compared with chemotherapy (in patients who have failed ASCT and subsequent BV treatment) are the source of utilities, the cost of nivolumab, and the time horizon. The key effect drivers of the incremental effect for nivolumab compared with BV (in patients who failed ASCT and are BV-naive) are the time horizon, the parametric curve used to extrapolate OS, and the source of utilities. The key cost drivers of the incremental effect are the assessment of PFS outcomes for nivolumab (independent versus investigator assessment), the population under consideration (naive indirect comparison versus matched adjusted indirect comparison), and the comparator (BV versus chemotherapy). The key effect drivers of nivolumab compared with chemotherapy (in patients who failed ASCT and subsequent BV) are the time horizon, the source of survival data for the comparator for PFS, and the source of utilities. The key cost drivers are the time horizon (15 years versus shorter time), the assessment of PFS outcomes for nivolumab (independent versus investigator assessment), and vial sharing. Further, the Committee noted the following main limitations of the submitted economic analyses: (1) lack of direct comparative effectiveness data, and (2) extrapolation of OS using short-term data. Overall, pERC agreed with EGP's best estimates of the ICER when nivolumab was compared with BV or chemotherapy. Consequently, pERC concluded that nivolumab was not cost-effective at the submitted price.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: High market share; wastage minimized with vial sharing

pERC considered the feasibility of implementing a reimbursement recommendation for nivolumab in patients who relapsed or progressed after ASCT and subsequent BV treatment. pERC discussed the fact that, if nivolumab were implemented, the estimated high market uptake of nivolumab seemed reasonable given the need for effective treatment options in this setting. pERC noted that the budget impact of nivolumab resulted from the high cost of nivolumab, the relatively small number of eligible patients, and a large market share expected for the nivolumab indication after ASCT and subsequent BV failure.

pERC noted that drug wastage with the weight-based dose would be minimized with the two different vial sizes (40 mL and 100 mL) and with vial sharing, given that nivolumab is currently used for many other indications.

pERC discussed that nivolumab may have the potential for indication creep because of the lack of effective treatment options for patients who are ineligible for ASCT and who do not have access to BV therapy. 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 noted that the use of nivolumab in ASCT ineligible and in BV-naive patients was beyond the scope of this review. Therefore, the Committee noted that a separate submission to pCODR for nivolumab in patients who are ineligible for ASCT and are BV-naive would be required.

pERC noted that the generalization of CHECKMATE-205 results to patients who have cHL that has relapsed or progressed after three or more lines of systemic therapy including ASCT and are not eligible to receive

BV was likely reasonable. pERC also noted that there is a clear need for more effective treatment options and that it is unlikely that there will be trials specifically designed for this small group of patients.

pERC agreed that PDL-1 testing would not be necessary. PDL-1 is highly expressed on the Reed–Sternberg cells that characterize cHL. pERC noted that the efficacy results of nivolumab could not necessarily be extended to nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), as PDL-1 is expressed less strongly on the malignant cell population of NLPHL, which affects only about 5% of all patients with Hodgkin lymphoma and these patients were not included in the pivotal studies reviewed.

pERC noted PAG's request for information on the appropriateness of using cost-saving dosing strategies of 3 mg/kg up to a dose cap of 240 mg every two weeks and 6 mg/kg up to a dose cap of 480 mg every four weeks. pERC acknowledged that while flat dosing is widely used in solid tumours, there is currently insufficient evidence available to recommend using cost-saving dosing strategies of 3 mg/kg up to a dose cap of 240 mg every two weeks and 6 mg/kg up to a dose cap of 480 mg every four weeks. pERC noted that jurisdictions may want to assess new dosing strategies as they become available and agree on a common approach that is feasible for all.

DRUG AND CONDITION INFORMATION

Drug Information	• Immunotherapy (monoclonal antibody) • Solution for injection at a nominal concentration of 10 mg/mL in either 40 mg or 100 mg single use vial • Nivolumab is administered intravenously at a dose of 3 mg/kg over 60 minutes every 2 weeks until progression or unacceptable toxicity.
Cancer Treated	• Classical Hodgkin lymphoma (cHL)
Burden of Illness	• There are approximately 900 new cases of cHL 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 nivolumab in Canada is not likely to exceed 100 patients.
Current Standard Treatment	• For patients who fail after autologous stem cell transplant (ASCT) and subsequent brentuximab vedotin (BV), current treatment options include chemotherapy with palliative intent, best supportive care, and enrolment in clinical trials. • For patients who fail after ASCT and are BV-naive, current treatment options include BV.
Limitations of Current Therapy	• Palliative chemotherapy: 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
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:

- Dr. Anil Abraham Joy who was not present for the meeting.
- Cam Lane who did not vote due to his role as a patient member alternate

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website,

and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of nivolumab for classical Hodgkin lymphoma, 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.

Information sources used

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

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

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.

Disclaimer

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APPENDIX 1: pERC RESPONSES TO PAG IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG is seeking clarity on whether trial data could be generalized to other subtypes of Hodgkin lymphoma or whether nivolumab is indicated only for the classical subtype.	• pERC agreed that PDL-1 testing would not be necessary. PDL-1 is highly expressed on the Reed-Sternberg cells that characterize cHL. pERC noted that the efficacy results of nivolumab could not necessarily be extended to nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), as PDL-1 is expressed less strongly on the malignant cell population of NLPHL, which affects only about 5% of all patients with Hodgkin lymphoma and these patients were not included in the pivotal studies reviewed.
• PAG is seeking information on the appropriateness of using cost-saving dosing strategies of 3 mg/kg up to a dose cap of 240 mg every two weeks and 6 mg/kg up to a dose cap of 480 mg every four weeks.	• pERC acknowledged that while flat dosing is widely used in solid tumours, there is currently insufficient evidence available to recommend using cost-saving dosing strategies of 3 mg/kg up to a dose cap of 240 mg every two weeks and 6 mg/kg up to a dose cap of 480 mg every four weeks. pERC noted that jurisdictions may want to assess new dosing strategies as they become available and agree on a common approach that is feasible for all.
• PAG is seeking guidance on whether results could be generalized to patients who are ineligible for an autologous stem cell transplant (ASCT).	• pERC discussed that nivolumab may have the potential for indication creep because of the lack of effective treatment options for patients who are ineligible for ASCT and do not have access to brentuximab vedotin (BV) therapy. 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, which results in a significant treatment gap for this subgroup of patients in most provinces. However, pERC noted that the use of nivolumab in ASCT ineligible and BV-naive patients was beyond the scope of this review. Therefore, the Committee noted that a separate submission to pCODR for nivolumab in patients who are ineligible for ASCT and are BV-naive would be required.
• PAG noted that drug wastage is minimized as vial sharing is possible, given that nivolumab is presently indicated for a number of other cancers.	• pERC agreed and noted that drug wastage with the weight-based dose would be minimized with the two different vial sizes (40 mL and 100 mL) and with vial sharing, given that nivolumab is currently used for a number of other indications.
• PAG is seeking information on the comparison of nivolumab and pembrolizumab.	• pCODR asked the submitter to provide both clinical and cost-effectiveness data addressing a comparison of nivolumab to pembrolizumab in patients who receive ASCT and subsequent BV. The submitter stated that treatment comparisons are not possible due to lack of access to important clinical outcomes data for pembrolizumab.