pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

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

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Pembrolizumab (Keytruda)	
Submitted Reimbursement Request: For adjuvant treatment of stage III melanoma patients following resection; for retreatment of patients upon loco-regional or distant recurrence more than six months following a completed adjuvant course of pembrolizumab.	
Submitted By: Merck Canada	**Manufactured By:** Merck Canada
NOC Date: April 2, 2019	**Submission Date:** December 13, 2018
Initial Recommendation: May 31, 2019	**Final Recommendation:** August 1, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	• Pembrolizumab costs $2,200 and $4,400 per 50 mg* and 100 mg vial, respectively. • At the recommended dose of 200 mg administered intravenously over 30 minutes every three weeks for a total of 18 administrations (approximately one year), pembrolizumab costs $8,800 per monthly treatment cycle. *Vial size available until mid-2019

pERC RECOMMENDATION

☐ **Reimburse**

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

☐ **Do not reimburse**

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

pERC conditionally recommends the reimbursement of pembrolizumab (Keytruda) for the adjuvant treatment of patients with stage IIIA (limited to lymph node metastases of > 1 mm) to stage IIID (8th edition of the American Joint Committee on Cancer [AJCC] staging system) cutaneous melanoma. Disease must be completely resected; however, presence of regional lymph nodes with micrometastases after sentinel lymph node biopsy alone is allowed. Patients must have good performance status. Reimbursement is only recommended if the following conditions are met:

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

Treatment with pembrolizumab should continue up to a maximum of 18 administrations or until unacceptable toxicity or disease recurrence, at which point the intent of further therapy (adjuvant or metastatic) should be re-evaluated based on extent of recurrence.

pERC made this recommendation because it was confident that there is a net clinical benefit of pembrolizumab based on a statistically significant and clinically meaningful improvement in relapse-free survival compared with placebo (observation), and a manageable but not insignificant toxicity profile with no detriment to quality of life. pERC agreed that pembrolizumab aligns with patient values because it fulfills a need for effective treatment options that prevent recurrence with manageable side effects and maintain quality of life.

	pERC concluded that considering the uncertainty related to the overall survival benefit, pembrolizumab is not cost-effective compared with observation at the submitted price. pERC also had concerns about the capacity of jurisdictions to implement pembrolizumab due to the magnitude (high cost per patient) of the budget impact.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-effectiveness and Budget Impact** Given that pERC was satisfied that there is a net clinical benefit of pembrolizumab for the adjuvant treatment of patients with stage IIIA-D cutaneous melanoma (8th edition AJCC), jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness and budget impact of pembrolizumab to an acceptable level. **Retreatment with Pembrolizumab** pERC noted that part 2 of the KEYNOTE-054 trial allowed for retreatment with pembrolizumab for up to two years in trial patients with documented disease recurrence after at least six months of a completed course of adjuvant pembrolizumab. Data for this subgroup of patients are not yet available since part 2 of the trial is ongoing. pERC concluded that they would be open to reviewing the evidence and make a recommendation on retreatment when the data are available. **Weight-Based Dosing with a Cap** pERC acknowledged that, although the KEYNOTE-054 trial assessed pembrolizumab at a dose of 200 mg every three weeks up to a total of 18 administrations, there is no evidence to suggest that the dosing amount of 200 mg is superior to 2 mg/kg (the dose used in the initial pembrolizumab trials). For many patients the flat dose results in a larger dose and greater cost. Therefore, pERC felt either dosing approach is reasonable and provincial jurisdictions will have to choose between implementing flat- versus weight-based dosing. **Available Vial Sizes** pERC noted the high cost and potential for drug wastage associated with pembrolizumab. The continued availability of a 50 mg vial and consideration of the development of a smaller vial would reduce implementation barriers such as drug wastage associated with pembrolizumab, particularly if jurisdictions consider weight-based dosing (2 mg/kg up to 200 mg). **No Evidence for Optimal Sequencing** pERC acknowledged that there is no direct comparative evidence investigating the efficacy and safety or the appropriate sequence of adjuvant therapies for patients with stage IIIA-D cutaneous melanoma. Further, the optimal sequencing of subsequent therapies for patients with metastatic melanoma after disease progression with adjuvant pembrolizumab is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognizes that provinces will need to address this issue upon implementation of a reimbursement recommendation for pembrolizumab and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value. **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

Malignant melanoma is a relatively uncommon but aggressive skin cancer with an estimated incidence in Canada of 7,200 cases per year. The incidence of melanoma in Canada continues to rise and it is the most commonly diagnosed cancer in individuals between the ages of 20 and 29 years. A proportion of patients will present with locally advanced cancers that, while amenable to surgery, signify a high risk of relapse and death, with a five- and 10-year disease-specific survival rate of 32% and 24%, respectively, for patients with high-risk disease (stage IIID according to the 8th edition of the American Joint Committee on Cancer [AJCC] staging system). In Canada, high-dose interferon (IFN)-alpha is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but are at high-risk for systemic recurrence. In practice, however, IFN is infrequently prescribed due to its substantial toxicity profile and uncertain efficacy, with most patients declining IFN treatment, and instead choosing observation alone (also referred to as watchful waiting). Although a number of immunotherapies and targeted agents are being studied in this setting, for patients presenting with resected stage III melanoma, adjuvant treatment options are currently limited, particularly with respect to systemic therapy. pERC acknowledged that there is a significant need for effective curative treatment options in the adjuvant setting for patients with resected stage III melanoma.

pERC deliberated on the results of one phase III, double-blind, international randomized controlled trial (RCT), KEYNOTE-054, which evaluated the safety and efficacy of pembrolizumab compared with matched placebo (observation) in the adjuvant treatment of patients with completely resected stage III (AJCC 7th edition) cutaneous melanoma. The trial demonstrated a statistically significant and clinically meaningful improvement in relapse-free survival (RFS) in favour of pembrolizumab compared with placebo that was observed regardless of BRAF mutation status and PD-L1 tumour expression. pERC noted that the median follow-up of the trial was short with a median of 15.1 months, and that this was shorter than the follow-up in other adjuvant trials (COMBI-AD [dabrafenib-trametinib], median 34 months; Checkmate 238 [nivolumab], median 19 months). Data on key secondary end points, including overall survival (OS) and distant metastasis-free survival (DMFS) are immature and therefore were not available to pERC. pERC also deliberated on the toxicity profile of pembrolizumab and noted that grades ≥ 3 adverse events (AEs; any and treatment-related), serious adverse events (SAEs), and AEs leading to dose discontinuation were all increased in the pembrolizumab group compared with placebo. pERC highlighted that although manageable to most patients, the toxicity profile of pembrolizumab may not be insignificant to some patients. However, pERC also acknowledged that clinicians have experience managing the specific toxicities associated with pembrolizumab. Further, the analysis of trial health-related quality of life (QoL) data, which was limited to the time period (week 48) before treatment crossover, demonstrated that despite greater toxicity global health status/QoL was not significantly different between the two treatment groups. Based on the evidence from KEYNOTE-054, pERC concluded that there is a net clinical benefit of pembrolizumab based on the clinically meaningful result in RFS, no observed detriment to QoL, a manageable but not insignificant toxicity profile, and the need for more effective and tolerable treatment options.

pERC discussed the Clinical Guidance Panel (CGP)'s assessments regarding the generalizability of evidence to particular subgroups of patients who were not included in the KEYNOTE-054 trial. pERC agreed that patients should be eligible for adjuvant pembrolizumab based on the criteria used in the KEYNOTE-054 trial which included patients with cutaneous melanoma who were staged IIIA-C based on the 7th edition of the AJCC (which is equivalent to stages IIIA-D in the AJCC 8th edition) with no in-transit metastases and good performance status (Eastern Cooperative Oncology Group [ECOG] 0 or 1). pERC considered the CGP's conclusion to offer adjuvant pembrolizumab to all stage IIIA patients regardless of the extent of nodal metastases; however, pERC agreed treatment should be offered based on the requirement in the trial which specified stage IIIA patients have lymph node metastases measuring > 1 mm. pERC based this decision on the low risk of recurrence among patients with stage IIIA disease (10-year survival rate of 88% according to AJCC 8th edition). pERC also discussed that the KEYNOTE-054 trial required completion

lymphadenectomy for all patients with lymph node involvement detected on a sentinel lymph node biopsy. However, recognizing that recent evidence has changed this practice and established observation as an acceptable alternative to complete lymph node dissection, pERC agreed with the CGP that the results of the trial are generalizable to patients who do not have complete lymph node dissection.

During the reconsideration of the Initial Recommendation, pERC discussed the feedback received from the submitter and clinicians on additional subgroups of patients who should be considered for adjuvant pembrolizumab. The submitter requested that, similar to pERC's recommendation for adjuvant nivolumab, pediatric patients and patients with pre-existing autoimmune disorders should be eligible for adjuvant pembrolizumab on an individual basis at the discretion of the treating oncologist. pERC noted that the CGP also considered the evidence from the KEYNOTE-054 trial to be generalizable to these groups of patients. pERC therefore concluded that adjuvant pembrolizumab could be offered on an individual basis to pediatric patients and patients with pre-existing autoimmune disorders who otherwise meet the eligibility criteria of the KEYNOTE-054 trial. Additionally, pERC agreed with the clinician feedback that the recommendation for adjuvant pembrolizumab should apply to patients with acral melanoma, given that it is a subtype of cutaneous melanoma. Clinician feedback also requested pERC consider alignment of the adjuvant pembrolizumab recommendation with the adjuvant nivolumab recommendation (based on perceived therapeutic equivalence) and make resected stage IV patients also eligible to receive adjuvant pembrolizumab; however, pERC agreed with the CGP that adjuvant pembrolizumab after surgery should not be used in these patients in the absence of clinical trial data.

pERC discussed that the requested reimbursement criteria for pembrolizumab includes retreatment of patients upon loco-regional or distant recurrence more than six months following a completed adjuvant course of pembrolizumab. However, pERC noted that part 2 of the KEYNOTE-054 trial which evaluates retreatment with pembrolizumab is ongoing and therefore no data are currently available to inform a recommendation. pERC agreed with the CGP's conclusion that in the absence of evidence a recommendation on retreatment cannot currently be made.

During the reconsideration of the Initial Recommendation, pERC discussed the submitter's feedback to allow retreatment with pembrolizumab in the adjuvant setting in order to align with the wording in the product monograph and other recommendations on pembrolizumab in non-small cell lung cancer, where positive recommendations for retreatment were issued in the absence of evidence. pERC discussed that the non-small cell lung cancer recommendations referenced by the submitter were in the metastatic setting and they noted that the expected benefit of retreatment in the metastatic setting should not be extrapolated to the adjuvant setting. pERC therefore agreed that a recommendation on retreatment should await the trial evidence from part 2 of the KEYNOTE-054 trial.

pERC deliberated on input received from two patient advocacy groups and noted that patients with stage III melanoma value access to a variety of effective treatment options that prevent recurrence of disease and prolong survival, have manageable side effects, and are affordable. The patient input indicated that lack of effective treatment options after surgery is a source of extreme stress and anxiety for patients and their caregivers. Patients previously treated with IFN indicated they experienced significant side effects that they considered unmanageable, which led to treatment discontinuation. pERC noted that patients who had experience with pembrolizumab indicated the drug was associated with different, fewer, and milder AEs compared with IFN, and overall was well tolerated. Based on the results of the KEYNOTE-054 trial, which demonstrated a statistically significant improvement in RFS, a manageable toxicity profile, and no detriment to HRQoL, pERC concluded that pembrolizumab aligns with patient values.

pERC deliberated on the cost-effectiveness of pembrolizumab compared with placebo (observation), which was based on the submitted economic evaluation and reanalysis provided by the pCODR Economic Guidance Panel (EGP). The Committee discussed the main limitation of the submitted model that was identified by the EGP, which was extrapolation of the clinical benefit beyond the trial period (median follow-up time of 15.1 months) over a lifetime horizon (46 years). The EGP noted that the submitted model did not permit alterations to the transition probabilities from the loco-regional and distant metastases health states, and therefore, all base case and sensitivity analyses performed assumed maintenance of the clinical benefit over the entire time horizon. pERC noted the EGP considered the extrapolation of outcomes over such a long time horizon the greatest source of model uncertainty. Additional sources of uncertainty included assumptions regarding the subsequent therapies for advanced melanoma, the method of extrapolation of survival outcomes and the choice of utility values. The

Committee concluded that, given the uncertainty in the OS benefit, pembrolizumab could not be considered cost-effective at the submitted price.

During the reconsideration of the Initial Recommendation, pERC discussed the submitter's feedback that adjuvant pembrolizumab is cost-effective at the list price, citing that the EGP's best estimate of the incremental cost-utility ratio (lower bound) was $51,289 per quality-adjusted life-years (QALY), and that the use of a lifetime horizon was appropriate considering the relatively young age of the patient population and curative intent of the adjuvant setting. pERC reiterated that the use of a lifetime horizon was unanimously agreed to be inappropriate by the CGP and the EGP, given the length of follow-up in the trial, and this is supported by the shorter time horizons used in the other adjuvant melanoma pCODR reviews. pERC also highlighted that the EGP's best-case estimate upper bound was $114,584 per QALY; it noted that the large range in the incremental cost-utility ratio reflects the uncertainty in the magnitude of long-term benefit of adjuvant pembrolizumab. Therefore, pERC maintained its conclusion that pembrolizumab could not be considered cost-effective at the submitted price.

pERC considered the feasibility of implementing a reimbursement recommendation for pembrolizumab for the adjuvant treatment of resected stage IIIA (limited to lymph node metastases of >1 mm) to stage IIID cutaneous melanoma (AJCC 8th edition). pERC noted that the budget impact may be underestimated due to potential underestimation of the market share of therapies and the market expansion of pembrolizumab, and the proportion of patients with stage III disease. Given the potentially substantial budget impact of pembrolizumab, the provinces should consider taking steps to limit the budget impact by way of pricing arrangements and/or cost structures. pERC acknowledged that there are a number of immunotherapies being evaluated in the adjuvant setting. pERC agreed with the CGP's assessment that there is no direct evidence from RCTs to inform the choice of adjuvant immunotherapies or BRAF-mutated targeted therapies in patients with melanoma who have undergone resection. In the absence of direct evidence, pERC commented that treatment choice will likely be influenced by toxicity profiles, patient preference for treatment administration (oral versus intravenous), schedules (frequency), bulk of disease, time interval before recurrence (time-to-progression or disease-free interval), comorbidities, and what is provincially funded.

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

EVIDENCE IN BRIEF

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

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and BIA
- guidance from the pCODR clinical and economic review panels
- input from two patient advocacy groups (Melanoma Network Canada [MNC] and Save Your Skin Foundation [SYSF])
- input from registered clinicians
- input from pCODR's PAG.

Feedback on the pERC Initial Recommendation was also provided by:

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

The pERC Initial Recommendation was to recommend reimbursement of pembrolizumab, conditional on cost-effectiveness being improved to an acceptable level and feasibility of adoption being addressed (budget impact). Feedback on the pERC Initial Recommendation indicated that the submitter, the registered clinician group, and PAG agreed in part with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of pembrolizumab (Keytruda) as adjuvant treatment for patients with stage III melanoma with regional lymph node involvement who have undergone resection; and in the retreatment of patients upon loco-regional or distant recurrence more than six months following a completed adjuvant course of pembrolizumab.

Studies included: One randomized phase III placebo-controlled trial – KEYNOTE-054

The pCODR systematic review included one randomized, double-blind, international (123 centres in 23 countries), placebo-controlled, phase III trial that assessed the effect of adjuvant pembrolizumab as compared with placebo in patients with high-risk, resected stage III melanoma. KEYNOTE-054 has two parts. In part 1, a total of 1,019 patients were randomly assigned to receive pembrolizumab at 200 mg every three weeks for 18 doses (approximately one year; n = 514) or saline placebo (n = 505). Patients who had documented disease recurrence in part 1 were eligible to enter part 2 of the trial. In part 2, patients who were randomized to receive pembrolizumab could be retreated (re-challenged) with pembrolizumab (if more than six months after completed adjuvant treatment) while those randomized to placebo could crossover and receive pembrolizumab. The results of part 2 are expected in 2023.

Patient population: Stage III A-C (AJCC 7th edition) completely resected cutaneous melanoma

Key eligibility criteria included patients who were at least 18 years of age, had histologically confirmed cutaneous melanoma with metastasis to regional lymph nodes, and either stage IIIA melanoma (with at least one micrometastasis measuring > 1 mm in greatest diameter), stage IIIB, or stage IIIC disease with no in-transit metastases according to the AJCC classification system 7th edition. All patients had a complete regional lymphadenectomy within 13 weeks before the start of treatment and an ECOG performance status of 0 or 1. Patients were excluded from the trial if they had autoimmune disease, uncontrolled infections, used systemic glucocorticoids or had previous systemic therapy for melanoma.

The median age of patients in the trial was 54 years (range, 19 to 88 years). The majority of patients were male (62%), stage IIIB (46%), had one positive lymph node on pathologic testing (46%), macroscopic lymph node involvement (66%), and were positive for BRAF mutations (50%) and PD-L1 expression (84%). Approximately 40% of patients had tumour ulceration.

Key efficacy results: Statistically significant improvement in RFS based on short median follow-up

The key efficacy outcome deliberated on by pERC was RFS. Key secondary outcomes included DMFS and OS, and HRQoL was an exploratory end point. At the primary efficacy analysis data cut-off date of October 2, 2017, the median patient follow-up time was 15.1 months. An updated (unplanned) analysis of RFS was performed on May 2, 2018, which provided an additional seven months (median of 21.6 months) of follow-up time. Trial data on OS and DMFS were not available at either data cut-off date.

At the October 2, 2017 data cut-off date, 135 patients (26%) in the pembrolizumab group had first recurrence of disease or died as compared with 216 patients (43%) in the placebo group. The median RFS in the pembrolizumab group was not reached (not reached [NR], 95% CI, NR to NR) and was 20.4 months (95% CI, 16.2 to NR) in the placebo group. Treatment with pembrolizumab was associated with statistically significant prolonged RFS compared with placebo (hazard ratio [HR]: 0.57, 98.4% CI, 0.43 to 0.74; P = 0.0001). A pre-specified subgroup analysis performed by PD-L1 positive tumour expression (defined as a score of 2 or higher [i.e., staining on > 1% of cells]) demonstrated a similar treatment benefit with pembrolizumab compared with placebo (HR: 0.54, 95% CI, 0.42 to 0.69; P < 0.001). Similar results were reported for those with a negative PD-L1 tumour (HR: 0.47, 95% CI, 0.26 to 0.85; P = 0.01) but there was no significant difference among those with an indeterminate PD-L1 tumour (HR: 0.88, 95% CI, 0.29 to 2.72, P = 0.7709).

At the updated analysis, which was based on 404 events (30.7% in the pembrolizumab group and 48.7% in the placebo group), the treatment benefit observed with pembrolizumab was consistent with the primary efficacy analysis (HR: 0.56, 98.4% CI, 0.44 to 0.72; P < 0.0001).

Patient-reported outcomes: No meaningful differences in HRQoL between pembrolizumab and placebo as assessed by the EORTC QLQ-C30 and EQ-5D-3L

HRQoL was measured using the EORTC QLQ-C30 and EQ-5D-3L questionnaires. The QLQ-C30 includes five functional scales (i.e., physical, role, emotional, social, and cognitive), three symptom scales (i.e., fatigue, nausea and vomiting, and pain), one global health status scale and six single items (i.e., dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). The EQ-5D-3L, which encompasses a utility score and visual analogue scale (VAS), assesses general health status and health utility measures; and includes five dimensions of health state: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

HRQoL was assessed at baseline, every 12 weeks after randomization for two years, and then every six months thereafter. The data cut-off for the HRQoL analysis was October 2, 2017. Compliance rates for completing questionnaires decreased over time as a result of patient crossover to receive pembrolizumab in part 2 of the trial; consequently, pCODR focused on HRQoL outcomes at week 48, which was the last assessment prior to crossover. The primary HRQoL end point was the change from baseline to week 48 in the QLQ-C30 global health status/QoL scale score; a ≥ 10-point decrease between the two treatment groups was considered the minimally important difference (MID). Patients were included in the analysis if they received ≥ 1 dose of study treatment and completed ≥ 1 HRQoL questionnaire.

Compliance rates for completing EORTC QLQ-C30 questionnaires were 96.5% in the pembrolizumab group and 97.0% in the placebo group at baseline; and 81.8% and 82.4% at week 48, respectively. Baseline global health status/QoL scores were reported as similar for patients in both the pembrolizumab and placebo groups and remained stable over time. There were no significant differences between the two treatment groups in the global health status/QoL scale score at week 48 and the MID was not reported. Similar results were observed for the EQ-5D 3L questionnaire for both the index and VAS.

Limitations: No direct comparative data to relevant comparators nivolumab and dabrafenib-trametinib

There is no direct evidence from RCTs comparing contemporary adjuvant treatments in stage III melanoma. The submitter provided an unpublished network meta-analysis (NMA) which indirectly compared pembrolizumab to observation and different preparations of IFN but did not include the more relevant comparators of nivolumab and dabrafenib-trametinib, which are approved by Health Canada but not currently reimbursed in Canada. The submitter stated they were unable to compare pembrolizumab to nivolumab and dabrafenib-trametinib in the NMA due to significant differences between the pivotal trials with respect to drug administration and patient populations. Although the economic analysis also did not include nivolumab or dabrafenib-trametinib as comparators, the EGP performed several reanalyses to allow

for comparability between the current economic evaluation of pembrolizumab and the previous pCODR economic evaluation of nivolumab.

Safety: Higher frequency of grade ≥ 3 adverse events, serious adverse events, and dose discontinuations with pembrolizumab

At the October 2, 2017 data cut-off, patients had received a median of 18 doses (interquartile range [IQR]: 9 to 18) of pembrolizumab and a median of 18 doses (IQR: 8 to 18) of placebo; and the median number of days on therapy for those in the pembrolizumab group was 357 days (range: 1 to 478) and 357 days (range: 1 to 424) in the placebo group.

AEs of any grade occurred at the same frequency among those treated with pembrolizumab or placebo (93.3% versus 90.2%), while treatment-related AEs (TRAEs) of any grade were higher in the pembrolizumab group (77.8% versus 66.1%). The most common TRAEs in both the pembrolizumab and placebo groups, respectively, were fatigue (37.1% versus 33.3%), skin reactions (28.3% versus 18.3%), diarrhea (19.1% versus 16.7%), arthralgia (12.0% versus 11.0%) and nausea (11.4% and 8.6%). Compared with placebo, more immune-related AEs of any grade (37.3% vs. 9.0%; the majority of which were endocrine-related) occurred in the pembrolizumab group. The incidence of grade 3 or greater AEs (31.6% versus 18.5%), grade 3 or greater TRAEs (14.7% versus 3.4%), SAEs (25.1% versus 16.3%), and treatment-related SAEs (13% versus 1.2%) were all higher in the pembrolizumab group relative to the placebo group, respectively. Dose discontinuations due to AEs were also higher in patients treated with pembrolizumab (13.8 %) compared to patients receiving placebo (3.6%); as were discontinuations due to TRAEs (12.2% versus 1.6%).

Two patient deaths occurred in the pembrolizumab group; one patient died from treatment-related autoimmune myositis involving respiratory muscles, and one patient death was attributed to a drug reaction with eosinophilia and systemic symptoms from the initiation of vemurafenib and cobimetinib. There were no deaths in the placebo group.

Need and burden of illness: Unmet need for stage III patients at high-risk of relapse after surgery

Malignant melanoma is a relatively uncommon but aggressive skin cancer with an estimated incidence in Canada of 7,200 cases per year. The incidence of melanoma in Canada continues to rise and it is the most commonly diagnosed cancer in individuals between the ages of 20 and 29 years. A proportion of patients will present with locally advanced cancers that, while amenable to surgery, signify a high risk of relapse and death, with a five- and 10-year disease-specific survival rate of 32% and 24%, respectively, for patients with high-risk disease (stage IIID according to the 8th edition of the AJCC staging system). In Canada, high-dose IFN is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but are at high-risk for systemic recurrence. In practice, however, IFN is infrequently prescribed due to its substantial toxicity profile, with most patients declining IFN treatment, and instead choosing observation alone (also referred to as watchful waiting). Although a number of immunotherapies and targeted agents are being studied in this setting, for patients presenting with resected stage III melanoma, adjuvant treatment options are currently limited, particularly with respect to systemic therapy. Therefore, there is a significant need for effective curative treatment options in the adjuvant setting for patients with resected stage III melanoma.

Registered clinician input: Unmet need for adjuvant treatment options

Input from a total of five registered clinicians was received, one joint submission comprising input from four oncologists and one individual oncologist submission. The clinicians providing input unanimously agreed that there is an unmet need for additional treatment options in the adjuvant treatment setting; and stated that the KEYNOTE-054 trial demonstrated a clinically significant RFS benefit in favour of pembrolizumab with reasonable toxicity. Clinicians commented pembrolizumab is very safe and tolerable to patients. Nivolumab, although not currently funded, was considered by the clinicians to be the most relevant treatment comparator for adjuvant therapy in melanoma, as well as dabrafenib-trametinib for BRAF-positive patients. The clinicians highlighted that the patient populations differ between the pembrolizumab and nivolumab pivotal trials, and reimbursement of pembrolizumab would increase access to immunotherapy for all stage III patients as the nivolumab trial only included stage IIIB-C and stage IV patients but not stage IIIA. Further, the clinicians also requested resected stage IV patients be considered in the funding request, similar to the pCODR review for adjuvant nivolumab in melanoma. The rationale for the inclusion was based on potential discrepancies in eligibility criteria for immunotherapy in the adjuvant setting. The clinicians stated pembrolizumab would most likely replace IFN or observation and

could be used for high- and low-risk patients regardless of BRAF mutation status. Clinicians cited the importance of having access to both immunotherapy options in order to offer an alternative agent to patients who develop resistance (i.e., BRAF-positive patients) and intolerance. Clinicians indicated that choice of immunotherapy would be dependent on clinician and patient preferences with consideration of comorbidities, but also noted that pembrolizumab may be preferred over nivolumab as its schedule is less frequent at every three weeks compared with every two weeks. Clinicians agreed that six months or greater was a reasonable treatment-free interval after completion of adjuvant treatment; but they noted, however, that the time frame would be dependent on a number of factors that included location of relapse, aggressiveness of disease, time to relapse, and BRAF status. For patients who relapse later than six months, the clinicians commented they would like the option to retreat patients with pembrolizumab.

PATIENT-BASED VALUES

Values of patients with stage III melanoma: fear and anxiety about lack of effective treatments

Patient input was received from two patient advocacy groups: MNC and SYSF. Patients in the sample cited a significant need for effective treatment options that prevent recurrence of disease and prolong survival with manageable side effects and affordable costs. Patients noted that newer therapies have improved quality of life relative to IFN, which is no longer being offered to most patients. All patients in the sample who had experience with IFN indicated the side effects (severe fatigue, nausea, vomiting, hair loss, depression) could not be managed, which resulted in discontinuation of treatment for the majority of these patients. The patient input indicated that lack of effective treatment options after surgery is a source of extreme stress, anxiety and depression for patients and their caregivers. Other common side effects associated with the disease included fatigue, scarring and disfigurement. These impairments had an impact on patients' daily functioning and ability to work, with many patients commenting on job loss and other financial impacts. A proportion of patients in the sample (~14%) indicated they were dealing with the melanoma diagnosis and treatment on their own with no caregiver support.

Patient values on treatment: Willingness to tolerate side effects for clinical benefit

Patients with melanoma expressed a strong desire for a variety of effective and affordable adjuvant treatment options that can address the mental strain the disease and a lack of available options impose on patients and their families. Patients who had experience with pembrolizumab indicated it was well-tolerated; and relative to IFN, it was associated with different side effects that were overall milder and less toxic. Reported side effects included fatigue, gastrointestinal issues (diarrhea), skin reactions and headache while other patients reported no side effects. The majority of patients said the benefits of treatment outweighed the side effects.

ECONOMIC EVALUATION

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

The submitted economic model assessed the cost-effectiveness (clinical effects measured as life-years gained) and cost-utility (clinical effects measured by QALYs gained) of pembrolizumab compared with observation (placebo) in patients with resected stage III melanoma. The submitter also provided a comparison of pembrolizumab to IFN; however, due to its substantial toxicity and modest clinical benefit, which limits its use in clinical practice, the EGP only presented reanalysis estimates for the comparison between pembrolizumab and observation.

Basis of the economic model: Markov cohort partitioned survival

The submitted partitioned survival model comprised of four mutually exclusive health states: recurrence-free, loco-regional recurrence, distant metastases, and death. The economic evaluation was based on RFS and safety data from the KEYNOTE-054 trial. Direct evidence from the KEYNOTE-054 trial was not used to estimate OS because the trial survival data were immature with very few patient deaths occurring during the trial period (i.e., two in the pembrolizumab group and one in the observation group). However, RFS is considered an appropriate surrogate end point from which to infer a net clinical benefit for effectiveness in stage III melanoma. Transition probabilities were derived based on primary analyses of patient level data from the KEYTNOTE trial for the recurrence-free health state, and from external resources for the loco-regional and distant metastases health states. Parametric models were used to estimate the cause-specific

hazards of each transition over time within the adjuvant pembrolizumab and observation groups. Utility data were collected directly from the KEYNOTE-054 trial.

Costs considered in the economic evaluation included those for drugs and drug administration (in the adjuvant and advanced melanoma setting), ongoing disease management (physician services, diagnostic tests, outpatient prescription drugs, hospital services for the surveillance of recurrence, and salvage surgery for recurrence), AEs and AE management, and terminal care.

Drug costs: High drug cost

Pembrolizumab costs $2,200 and $4,400 per 50 mg and 100 mg vial, respectively. At the recommended fixed dose of 200 mg every three weeks, pembrolizumab costs $8,800 per monthly treatment cycle.

There were no costs associated with observation as an adjuvant treatment strategy.

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

Overall, the EGP considered the submitted model complex but appropriate in terms of structure and most assumptions and agreed with the majority of choices made for the base case. However, the submitted model did not permit alterations to the transition probabilities from the loco-regional and distant metastases health states, and therefore, all base case and sensitivity analyses performed considered maintenance of the clinical benefit over the entire time horizon. As such, the EGP considered extrapolation of outcomes beyond the trial period (median follow-up time of 15.1 months) over a lifetime horizon (46 years) the greatest source of model uncertainty. The EGP made changes to the model to address the uncertainty in the clinical benefit extrapolation, as well as some other identified limitations; the changes that had the most impact on the incremental cost-effectiveness ratio (ICER) included the following:

- A shorter time horizon (5, 10, and 25 years) to represent a more clinically realistic scenario and to align with the time horizons used in previous pCODR reviews of adjuvant treatments for melanoma (nivolumab, dabrafenib-trametinib);
- Use of an alternative parametric model combination for OS extrapolation (Gompertz and Weibull) to produce more plausible survival estimates at 20 and 30 years;
- Use of a time-constant HR approach to estimate OS benefits to enable comparability to the pCODR economic evaluation of nivolumab; and
- Use of a different distribution of subsequent treatments for the advanced melanoma setting that was more representative of Canadian clinical practice.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: substantial budget impact

The PAG identified the following factors that could impact the implementation of pembrolizumab: the higher cost of fixed dosing, increased chair time and resources for drug administration, additional clinic visits and bloodwork, and additional nursing and pharmacy resources for monitoring and treating side effects. PAG also requested clarity on implementation-related issues that included the eligibility criteria for patients who would and would not be eligible for pembrolizumab (other histologic sub-types, patients with resected stage IIB-C with T4 lesions, resected stage IV disease, and resected in-transit metastases), priority of treatments in the adjuvant setting (including appropriate treatment-free interval following adjuvant therapy), and sequencing of treatments in the advanced/metastatic disease setting.

The submitter provided a Canada-wide budget impact analysis (BIA) to assess the feasibility of implementing a reimbursement recommendation for adjuvant pembrolizumab for patients with resected stage III melanoma. The EGP considered the assumptions and estimations used in the submitter's BIA to be valid; based on the submitted results the budget impact of pembrolizumab is substantial. The key factors that were identified to most influence the budget impact over a three-year time period were the number of patients eligible to be treated with pembrolizumab and the extent of market expansion. The EGP noted that the results of the BIA were most sensitive to the exclusion of subsequent therapy costs after recurrence, as well as the proportion of patients with stage III melanoma, the proportion of patients referred to medical oncologists, treatment rate of medical oncologists, time to peak share of pembrolizumab, and the scenario where the treatments of patients who have recurred to distant metastases is only with immunotherapy eligible patients.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

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

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

- Dr. Anil Abraham Joy who was not present for the meeting.
- Dr. Winson Cheung and Cameron Lane, who were excluded from voting due to a conflict of interest.

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

- Dr. Kelvin Chan, who was not present for the meeting
- Dr. Winson Cheung and Cameron Lane, who were excluded from voting due to a conflict of interest.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the pCODR Conflict of Interest Guidelines; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of pembrolizumab for melanoma adjuvant therapy, through their declarations, seven members had a real, potential or perceived conflict and based on application of the pCODR Conflict of Interest Guidelines, two 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*. 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.

Disclaimer

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

PAG Implementation Questions	pERC Recommendation
• PAG is seeking information on data comparing pembrolizumab with IFN • PAG is seeking guidance on whether adjuvant pembrolizumab would be limited to the following patients: o Patients with an ECOG performance status of 0 to 1 o Patients with cutaneous melanoma (e.g., not mucosal or ocular)	• The comparator used in the KEYNOTE-054 trial was placebo (observation). pERC agreed with the CGP that the choice of comparator was appropriate considering the minimal use of IFN in Canadian clinical practice. • pERC noted that the KEYNOTE-054 trial only enrolled patients with an ECOG performance status of 0 to 1 and agreed that adjuvant treatment with pembrolizumab should be offered to patients with a good performance status. • pERC agreed with the CGP that the data from the KEYNOTE-054 trial could not reliably be generalized to patients with non-cutaneous melanoma because the trial specifically excluded patients with non-cutaneous melanoma. • Upon reconsideration of the Initial Recommendation, pERC agreed with the clinician feedback and the CGP that adjuvant pembrolizumab should also be offered to patients with acral melanoma, given that it is a subtype of cutaneous melanoma.
• PAG is seeking guidance on whether adjuvant pembrolizumab would be offered to the following patients: o Patients with completely resected stage IV disease as well as resected stage IIB/C disease with T4 lesions (high-risk node negative) who are fit and motivated for treatment o Patients who would have been eligible at the time of diagnosis, but are currently being treated with IFN or on observation o Patients who have received adjuvant ipilimumab and have not progressed o Patients who are BRAF mutation positive and received one year of dabrafenib-trametinib therapy and have not progressed, whether they should be eligible upon relapse if their disease was completely resectable o Neoadjuvant treatment for patients with borderline resectable lymphadenopathy	• pERC agreed with the CGP's judgment that the decision to use adjuvant pembrolizumab after resection in patients with stage IIB/C disease and T4 lesions should await the results of ongoing clinical trials. pERC acknowledged that this group of patients may have a worse prognosis than some stage III patients; however, patients with stage IIB/C disease and T4 lesions were excluded from the KEYNOTE-054 trial. The trial also did not enrol patients with resected stage IV disease, and as such, pERC agreed with the CGP that adjuvant pembrolizumab after surgery should not be used in these patients in the absence of clinical trial data. • pERC agreed that there may be rare circumstances when clinicians may wish to transition a patient from receiving adjuvant IFN to treatment with pembrolizumab as adjuvant treatment to surgery. Patients previously treated with IFN as adjuvant to surgery were permitted enrolment in the KEYNOTE-054 trial, specifically, eligible patients who had been previously treated with IFN for thick primary melanomas without evidence of lymph node involvement. pERC agreed with the CGP that in practice the decision may be reasonable. For patients currently receiving adjuvant IFN who wish to transition to adjuvant pembrolizumab, the CGP advised that clinicians may want to consider the KEYNOTE-054 eligibility criteria as guidance when contemplating a change in adjuvant systemic therapy. The CGP also indicated factors such as duration of IFN therapy and tolerance to IFN therapy, as well as patient factors such as time from diagnosis, age, and performance status are also relevant when considering a change in adjuvant systemic therapy. • pERC agreed with the CGP that, for patients who have previously completed an adjuvant course of ipilimumab and have not progressed, there would be no indication for a second adjuvant treatment. pERC also agreed with the CGP that, for patients who

○ Patients who are disease-free following treatment of in-transit metastases, and are node negative	are already on ipilimumab with a planned duration of three years, in the absence of evidence it is unclear what the best duration of ipilimumab would be with respect to positive outcomes. Lastly, pERC noted the CGP's opinion that, in patients who have been on ipilimumab for less than one year and who wish to stop the regimen due to toxicity, it may be reasonable, on a case-by-case basis, to discuss with patients the use of pembrolizumab to complete a total of one year of adjuvant treatment. pERC highlighted that this guidance is based on clinical opinion and not evidence. • pERC agreed with the CGP's opinion that, in patients with BRAF-mutated melanoma who have completed one year of adjuvant dabrafenib-trametinib and have recurred, whether or not their disease has been resected to no evidence of disease, they would be eligible for retreatment with BRAF MEK inhibitors, PD-1 inhibitors or dual immunotherapy. The regimen chosen for each patient would be dependent upon a discussion between the clinician and the patient with respect to bulk of disease, tolerance of treatment, time interval before recurrence (time-to-progression or disease-free interval), and comorbidities. • pERC noted the CGP's opinion that there are no available phase III trial data on the use of neoadjuvant pembrolizumab for patients with borderline resectable lymphadenopathy. In clinical practice, locally advanced melanomas that are not amenable to curative intent due to morbidity of the surgery are treated as advanced disease, and that in cases where there is dramatic response of the primary lesion, thus rendering the lesion surgically resectable, then surgery may be discussed with the patient as a treatment option. • pERC noted that patients with past or current in-transit metastases or satellites were excluded from the KEYNOTE-054 trial. pERC also considered that in previous reviews of nivolumab and of dabrafenib-trametinib, the key trials (Checkmate 238 and COMBI-AD, respectively) included patients with resectable in-transit metastases. Due to a lack of available evidence, pERC was unable to draw a conclusion on the adjuvant use of pembrolizumab in patients who are disease free following treatment for in-transit metastases, and who are node negative.
• PAG is seeking guidance on weight-based dosing up to a cap of 200 mg for adjuvant melanoma; given the use of this dosing schedule in the metastatic melanoma setting and the high cost of fixed dose compared with weight-based dose for patients weighing less than 100 kg. • PAG is seeking clarification on a dosing schedule of every 6 weeks with pembrolizumab.	• pERC noted that the dose schedule of pembrolizumab in the KEYNOTE-054 trial was 200 mg over 30 minutes every three weeks up to a total of 18 administrations. This schedule requires less chemotherapy suite chair time in comparison to nivolumab (Checkmate trial) where dosing was weight based (3 mg per kilogram) every two weeks. However, pERC acknowledged for many patients the flat dose results in a larger dose and greater cost. Considering there is no evidence to suggest that the dosing amount of 200 mg is superior to 2 mg/kg, pERC felt it would be reasonable for pembrolizumab to be administered at 2 mg/kg up to a total dose of 200 mg (dose capped at 200 mg). • Upon reconsideration of the Initial Recommendation, pERC discussed the issue of dosing and ultimately agreed with the CGP's response to stakeholder feedback that either dosing approach is reasonable. The CGP noted that given the efficacy of a flat dose of 200 mg has been established with pembrolizumab in the KEYNOTE-054 trial and considering previous studies (in the

	metastatic setting) that have shown therapeutic equivalence of the two dosing approaches (flat- versus weight-based) and various doses per kg (2-10 mg/kg), under-treatment with weight-based dosing is not of appreciable concern. Therefore, pERC maintained its conclusion that either dosing approach is reasonable and noted that provincial jurisdictions will have to choose between implementing flat- versus weight-based dosing. Further, pERC also agreed with clinician feedback and the CGP that clarification in the definition of recurrence was needed to distinguish the different management approaches required; the CGP suggested pembrolizumab be administered up to a total of 18 administrations, unacceptable toxicity, or until disease recurrence, at which point the intent of further therapy (adjuvant or metastatic) should be re-evaluated based on the extent of recurrence. • pERC noted that, currently, there are no data from the adjuvant setting to inform dosing pembrolizumab every six weeks versus three weeks. pERC agreed that there may be rare instances where a 6-week dose interval may be required (e.g., long travel distance for patients), otherwise pERC reiterated that adherence to the trial dosing schedule is advised.
• PAG is seeking guidance on the appropriateness of re-initiation with pembrolizumab after toxicity resolution or treatment interruption for other reasons and, if this occurs, clarification on the total duration of therapy.	• pERC noted that dose modifications for treatment-related AEs were permitted in the KEYNOTE-054 trial and were managed according to a dose adjustment scheme specified in the trial protocol. Patients in the trial received 18 doses of pembrolizumab over approximately one year or until disease recurrence or unacceptable toxic effects. After interruption for toxicity, patients were required to be placed back on therapy within three weeks of the scheduled interruption unless otherwise specified by the treating investigator. pERC noted that it is reasonable to re-start treatment, at the discretion of the treating oncologist, in select patients who have had a treatment break due to toxicity; in this situation patients should receive up to a total of 18 doses of pembrolizumab.
• For patients who have received pembrolizumab in the adjuvant setting and then develop metastatic disease: o What would be the first-line treatment options in the metastatic setting? Currently, ipilimumab, nivolumab and pembrolizumab are funded for first-line treatment and BRAF targeted therapies are available for BRAF mutation positive disease. Nivolumab plus ipilimumab combination therapy is not yet funded at the time of this PAG input but should also be considered as a potential option. o What would be an appropriate time frame from completion of	• pERC agreed that there are no data to inform optimal sequencing of treatments in the metastatic setting; however, patients in the KEYNOTE-054 trial received a variety of post-study treatments that included anti-CTLA4, anti-PD-1/PD-L1, and targeted agents. As previously noted, part 2 of the trial, which is evaluating the efficacy of retreatment with pembrolizumab at recurrence, will provide some information with respect to sequencing; however, data from part 2 are not yet available. pERC noted the lack of available evidence to confirm or refute the activity of pembrolizumab in the metastatic setting following progression as adjuvant treatment. • pERC noted that the criterion used for retreatment in Part 2 of the KEYNOTE-054 trial was greater than six months post completion of adjuvant pembrolizumab. This time frame is in keeping with clinical practice in other tumour sites. However, pERC noted that, at this time, there is no available evidence to determine the appropriate time frame from progression on adjuvant therapy to initiation of treatment in the metastatic setting.

adjuvant pembrolizumab therapy and initiation of immunotherapy options for metastatic disease? Would single agent nivolumab or pembrolizumab immunotherapy be viewed differently than combination ipilimumab and nivolumab? ○ Patients in the trial were BRAF mutation positive or negative. PAG noted that adjuvant treatment with dabrafenib and trametinib may be available. What would be the best treatment for BRAF mutation positive patients in the adjuvant setting?	• pERC noted that patients in the KEYNOTE-054 trial with both BRAF-wild type and BRAF-mutated stage III melanoma benefited from treatment with adjuvant pembrolizumab. The Committee noted that, at present, there are no data to guide treatment with respect to optimal systemic therapy (i.e., PD-1 inhibitor [nivolumab or pembrolizumab] or BRAF-mutated targeted therapy [dabrafenib-trametinib]) for patients with completely resected BRAF-mutated melanoma other than treatment and patient characteristics such as mode of administration, tolerance of medications, expected side effects, lifestyle issues, and distance from treatment centres. Upon reconsideration of the Initial Recommendation, pERC agreed with the CGP that in the absence of evidence for retreatment and optimal sequencing, the choice of subsequent treatment should be at the discretion of the treating oncologist and be made on an individual basis that considers a patient's tumour mutation status as well as other factors such as time to relapse, location of relapse, and comorbidities.
• PAG is seeking clarity on whether PD-L1 testing would be required in this setting.	• pERC noted the CGP's opinion that, in clinical practice, PD-L1 is not performed on melanoma specimens and degree of positivity would not change clinicians' recommendations with respect to treatment for this particular disease site (as it was not predictive of a differential response to therapy). Therefore, pERC agreed that PD-L1 testing is unlikely required in this setting.

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