pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

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

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

Drug: Nivolumab (Opdivo) **Submitted Reimbursement Request:** For the adjuvant treatment of adult patients after complete resection of melanoma with regional lymph node involvement, in transit metastases/satellites without metastatic nodes, or distant metastases.	
Submitted By: Bristol-Myers Squibb Canada	**Manufactured By:** Bristol-Myers Squibb Canada
NOC Date: November 15, 2018	**Submission Date:** August 27, 2018
Initial Recommendation: January 04, 2019	**Final Recommendation:** March 07, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Nivolumab costs $1,956.00 per 100 mg/10 mL vial. At the recommended dose, nivolumab costs $263.00 per day and $7,369 per 28-day course.

pERC RECOMMENDATION

pERC recommends to reimburse nivolumab (Opdivo) only if the following conditions are met:

- Cost-effectiveness is improved to an acceptable level
- Feasibility of adoption is addressed (budget impact).

If the aforementioned conditions are not met, pERC does not recommend reimbursement. Reimbursement should be for the adjuvant treatment of patients with completely resected stage IIIB/C/D and stage IV disease (8th edition of the American Joint Committee on Cancer (AJCC) melanoma staging system). Disease must be completely resected including in-transit metastases; however, presence of regional lymph nodes with micrometastases after sentinel lymph node biopsy alone is allowed. Eligible patients should continue treatment until disease progression or a maximum of one year, whichever comes first.

pERC made this recommendation because it was confident that there is a net clinical benefit of nivolumab based on a clinically meaningful improvement in recurrence-free survival and a manageable toxicity profile. pERC was also satisfied that nivolumab aligns with patient values of a need for effective treatment options that have minimal side effects, stop disease progression and maintain quality of life (QoL).

pERC concluded that nivolumab may be cost-effective compared with observation and pERC had concerns about the capacity for jurisdictions to implement nivolumab due to the underestimated budget impact.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Optimal Sequencing of Available Therapies After Progression on Nivolumab

pERC concluded that the optimal sequencing of therapies for patients with metastatic melanoma after adjuvant treatment with nivolumab 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 nivolumab, and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.

Pricing Arrangements to Improve Budget Impact

Given that pERC was satisfied that there is a net clinical benefit of nivolumab for the adjuvant treatment of patients with stage IIIB/C/D or IV disease (based on the AJCC 8th edition staging system), jurisdictions may want to consider pricing arrangements and/or cost structures that would improve affordability.

Use of Staging System for Eligibility of Patients

pERC noted that the CheckMate 238 trial included patients with stage IIIB/C or IV melanoma based on the 7th edition of the AJCC staging system while clinical practice has since shifted to using the 8th edition of the AJCC staging system. pERC recognized that the update to the AJCC staging system will result in the inclusion of patients who were not eligible in the CheckMate 238 trial based on the 7th edition while other patients who were eligible for the trial would now be deemed ineligible. pERC further recognized that the greater clarity provided in the 8th edition of the AJCC staging system aligns with the intent of the CheckMate 238 trial, which was designed to include patients at higher risk for relapse and exclude those with earlier stages of disease. pERC noted that patients with earlier stages of disease (stage IIIA) are unlikely to require adjuvant treatment. Based on this, pERC agreed that the results of the CheckMate 238 trial are generalizable to patients who would have stage IIIB/C/D or IV melanoma using the 8th edition of the staging system. Following the posting of the pERC initial recommendation, pERC noted feedback received from the submitter indicating that stage IIIa patients should be eligible for treatment with nivolumab. pERC reviewed further feedback received from the CGP and agreed that the current evidence from CheckMate238 supports the use of nivolumab in patients with stage IIIB/C/D or IV melanoma using the 8th edition of the staging system. Although there is some complexity in the patient population with the revision to the 7th and 8th edition of the AJCC staging system, pERC reiterated that the intent of the CheckMate 238 trial was to include patients at higher risk for relapse and exclude those in earlier stages of disease. pERC also clarified the wording of the reimbursement recommendation to indicate that the eligible patient population should include patients with completely resected stage IIIB/C/D and stage IV disease (8th edition of the AJCC melanoma staging system). pERC outlined that the presence. Disease must be completely resected including in-transit metastases; however, presence of regional lymph nodes with micrometastases after sentinel lymph node biopsy alone is allowed.

Weight-Based Doses with a Cap

Although less frequent treatment dosage schedules have been adopted in other indications, pERC noted that clinicians may choose to adhere to the trial protocol of biweekly dosages given that treatment with nivolumab in this setting is for curative intent. Following the posting of the pERC initial recommendation, pERC noted feedback received from stakeholders on the dosing of nivolumab. Furthermore, feedback from the CGP indicated that treatment should adhere to the best available evidence. pERC therefore

agreed that dosing should generally follow the clinical trial.

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. 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 ten-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 interferon-alpha (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 at high risk for systemic recurrence. In practice, however, IFN is infrequently prescribed due to its toxicity profile. Most patients decline IFN treatment, instead choosing observation alone. Although a number of immunotherapies and targeted agents are being studied in this setting, for patients presenting with resected stage III or IV melanoma, adjuvant treatment options are currently limited, particularly with respect to systemic therapy. pERC acknowledged that there is a need for effective treatment options in the adjuvant setting for patients with resected melanoma.

pERC deliberated on the results of one randomized controlled trial, CheckMate 238, which evaluated the efficacy and safety of nivolumab compared with ipilimumab in the adjuvant treatment of patients with resected stage IIIB/C or IV melanoma. The CheckMate 238 trial demonstrated a clinically meaningful and statistically significant improvement in recurrence-free survival (RFS) in favour of nivolumab compared with ipilimumab. Overall survival (OS) data was not mature. pERC deliberated on the toxicity profile of nivolumab compared with ipilimumab and noted that serious adverse events, grades 3 or 4 adverse events (AE), grade 3 or 4 treatment-related AEs, any grades 3 or 4 AEs leading to discontinuation, and treatment-related grades 3 or 4 AEs leading to discontinuation were all increased in the ipilimumab group. Overall, pERC agreed that nivolumab had a manageable toxicity profile compared with ipilimumab. pERC discussed the available patient-reported outcomes data from the CheckMate 238 trial. The Committee noted that although there was no clinically meaningful difference in QoL for patients in the two treatment groups, the number of patients contributing to the QoL questionnaires in the ipilimumab group were low due to treatment discontinuation (under 30% on the last assessment). pERC therefore concluded that there may have been a detriment in QoL with ipilimumab if the missing data were accounted for. Overall, pERC concluded that there is a net clinical benefit of nivolumab compared with ipilimumab, based on the clinically meaningful results in RFS, no observed detriment in QoL, a manageable toxicity profile, and the need for more effective and tolerable treatment options.

pERC discussed the use of ipilimumab as the comparator group in the CheckMate238 trial, noting that ipilimumab is not available in the adjuvant setting for melanoma in Canada. The Committee, however, acknowledged that currently available treatment options such as interferon (IFN) do not generally provide meaningful benefit and are associated with substantial toxicity. pERC further considered the results of an indirect treatment comparison and network meta-analysis provided by the submitter that compared nivolumab with observation and IFN. The results of these analyses reported that adjuvant treatment with nivolumab was associated with a reduction in the risk of cancer recurrence or death as compared with IFN or observation/placebo. Nivolumab had a similar safety profile as placebo, but a statistically significantly lower risk of grade 3 or 4 AEs and discontinuation due to AEs, as compared with IFN. Between-group differences in QoL were not statistically significant, suggesting comparable QoL for patients who received nivolumab and placebo. OS was not assessed in the comparisons between nivolumab and other active treatments due to the unavailability of data.

pERC considered the generalizability of the trial results in a number of patient populations. pERC noted that the trial was restricted to patients with stage IIIB/C or IV melanoma based on the 7th edition of the AJCC staging system, while clinical practice has since shifted to using the 8th edition of the AJCC staging

system. pERC recognized that the update to the AJCC staging system will result in the inclusion of patients who were not eligible based on the 7th edition, while other patients who were eligible for the trial would now be deemed ineligible. pERC further recognized that the greater clarity provided in the 8th edition of the AJCC staging system aligns with the intent of the CheckMate 238 trial, which was designed to include patients at higher risk for relapse and exclude those in earlier stages of disease. pERC agreed that patients with earlier stages of disease (stage IIIA or earlier) are unlikely to require adjuvant treatment. Based on this, pERC agreed that the results of the CheckMate 238 trial are generalizable to patients who would have stage IIIB/C/D or IV melanoma using the 8th edition of the staging system. Following the posting of the pERC initial recommendation, pERC noted that feedback received from the submitter indicated that stage IIIa patients should be eligible for treatment with nivolumab. pERC reviewed further feedback received from the CGP and agreed that the current evidence from CheckMate238 supports the use of nivolumab in patients with stage IIIB/C/D or IV melanoma using the 8th edition of the staging system. Although there is some complexity in the patient population with the revision of the 7th edition to the 8th edition of the AJCC staging system, pERC reiterated that the intent of the CheckMate 238 trial was to include patients at higher risk for relapse and exclude those in earlier stages of disease. pERC further noted that clinical trials are underway to evaluate the efficacy and safety of adjuvant treatment in patients with stage IIC melanoma, and agreed that the decision to use nivolumab in this subset of patients should await trial results. pERC also noted that patients included in the trial had to have complete lymph node dissection for patients with micrometastatic lymph node involvement detected on a sentinel lymph node biopsy. However, recent evidence has established that observation within this patient population is a viable treatment strategy, as survival was not improved with complete lymph node dissection. Based on this, pERC agreed with the pCODR Clinical Guidance Panel that the results of the CheckMate 238 trial are generalizable to patients who do not have complete lymph node dissection for micrometastatic nodal involvement. pERC also considered that the CheckMate 238 trial allowed the enrolment of patients above the age of 15 years, although the youngest patient on the trial was 18 years old. pERC noted that the use of nivolumab in the pediatric population who otherwise met the CheckMate 238 inclusion criteria could be considered on an individual patient basis and should be at the discretion of the treating oncologist. pERC suggested that treatment with nivolumab as adjuvant therapy should not be restricted based on programmed death-ligand 1 (PD-L1) status as there was no evidence to suggest a difference in the efficacy of nivolumab based on PD-L1 expression levels. pERC also noted that patients with pre-existing autoimmune disorders were excluded from the trial. Based on the pCODR Clinical Guidance Panel's opinion, pERC acknowledged that patients with pre-existing immune-mediated illnesses who otherwise met the CheckMate 238 inclusion criteria should be considered for treatment with nivolumab as adjuvant therapy to surgery on an individual patient basis and in consultation with the treating oncologist.

pERC deliberated upon input from patient advocacy groups and noted that patients value having new treatment options that prolong survival, have minimal side effects, stop disease progression, and improve or maintain QoL. Patients experience significant side effects with IFN, which were considered unmanageable. Based on the results of the CheckMate 238 trial, which demonstrated a statistically significant improvement in RFS, manageable toxicity profile, and maintenance of QoL, pERC concluded that nivolumab aligned with patient values. pERC acknowledged that OS was immature in the trial, while results of an indirect treatment comparison and network meta-analysis suggested superiority in OS of nivolumab compared with observation.

pERC deliberated the cost-effectiveness of nivolumab compared with observation, and concluded that, at the submitted price and based on the submitted economic analysis, nivolumab may be cost-effective. pERC reached this conclusion noting some uncertainty regarding the incremental cost-effectiveness ratio (ICER) due to the uncertainty in the clinical effectiveness of nivolumab compared with observation. In the absence of direct head-to-head comparison and immature survival data from the CheckMate 238 trial, indirect evidence informed the comparative effectiveness estimates for RFS of nivolumab and observation and furthermore, RFS was then used to predict for OS. pERC noted that there is published evidence supporting the predictive ability of RFS for OS in this setting; however, the pCODR Economic Guidance Panel noted a large variation in the predictive formula used to map the relationship between RFS and OS. When this variation was explored in the model, it had the most substantial impact on the ICER. Furthermore, assumptions on the time horizon and the proportion of patients receiving the full dose of nivolumab had an impact on the cost-effectiveness estimates. pERC noted that the majority of the OS benefit was captured in the first five years and therefore, shortening the time horizon did not have a substantial impact on the ICER. Although changes to various model inputs were explored, pERC noted that the model was not sensitive to most other changes. Following the posting of the pERC initial recommendation, pERC noted feedback received from PAG on the uncertainty associated with the clinical

effect estimates and subsequently on the cost-effectiveness of nivolumab. pERC acknowledged that the CheckMate 238 trial only has two years of follow-up data and that there remains uncertainty on the validity of the long-term OS estimates predicted by the model. Given that the estimates for the comparative OS had the biggest impact on the ICER, pERC agreed that the ICER would be significantly affected if long-term data demonstrated smaller incremental gains in OS. Overall, pERC accepted the pCODR Economic Guidance Panel's reanalysis estimates but noted that longer-term follow up data on OS will help clarify the true ICER. Incorporating this uncertainty, pERC concluded that nivolumab may be cost-effective.

pERC considered the feasibility of implementing a reimbursement recommendation for nivolumab for the adjuvant treatment of resected stage IIIB/C/D and IV melanoma (using the 8th edition of the AJCC melanoma staging system). pERC noted that the budget impact analysis (BIA) substantially underestimated the market share for nivolumab and overestimated the use of IFN, a treatment option that is infrequently used due to its toxicity. pERC anticipates that the majority of patients will receive nivolumab in the adjuvant setting. Therefore, the population of patients eligible for nivolumab may be substantially greater than estimated in the submitter's BIA. Given the potentially substantial budget impact of nivolumab, the provinces should consider taking steps to limit the budget impact. pERC further noted that the submitted BIA was sensitive to average patient weight, market share multiplier, Canadian population, and the number of new cases diagnosed at ages 15 and older.

pERC acknowledged that there are a number of other immunotherapies and targeted agents being studied in this setting. However, until the evidence is reviewed for reimbursement, pERC agreed that there is no evidence to determine the sequencing of nivolumab relative to other adjuvant therapies in patients who are still candidates for surgery. Following the posting of the initial recommendation, feedback was received from stakeholders on the sequencing of agents. pERC re-iterated that there is no evidence to guide sequencing of agents in this setting. pERC noted feedback from the CGP indicating that subsequent treatment decisions will be based on multiple factors. pERC acknowledged that the trial did not allow dose delays or interruptions. However, in select patients who have had a treatment break due to toxicity, pERC noted that it is reasonable to re-start treatment, at the discretion of the treating oncologist. While acknowledging that there may be instances where patients are prevented from starting adjuvant therapy at the appropriate time frame, pERC agreed that the initiation of adjuvant therapy following surgery should generally follow the CheckMate 238 trial criteria (surgically rendered free of macroscopic disease within 12 weeks). Following the posting of the initial recommendation, feedback was received from PAG on the total duration of therapy. pERC noted that the decision to restart treatment and the duration of treatment thereafter will likely be based on a case by case assessment and should be left to the discretion of the treating clinician.

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 (BIA)
- guidance from the pCODR clinical and economic review panels
- input from two patient advocacy groups (Melanoma Network of Canada [MNC] and the Save Your Skin Foundation [SYSF])
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- one patient advocacy group, (Melanoma Network of Canada)
- one clinician group, (Cancer Care Ontario Skin DAC)
- the PAG
- the submitter (Bristol Myers-Squibb)

The pERC Initial Recommendation was to recommend reimbursement of nivolumab (Opdivo) conditional on the feasibility of adoption being addressed (budget impact). Feedback on the pERC Initial Recommendation indicated that the manufacturer, PAG, the patient advocacy group, and registered clinician group agreed in part with the Initial Recommendation.

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of nivolumab (Opdivo) for the adjuvant treatment of patients with completely resected stage III and IV melanoma.

Studies included: Randomized phase III trial comparing with non-standard treatment

The pCODR systematic review included one double-blind, multi-centre, phase III randomized controlled trial, CheckMate238, which assessed the efficacy and safety of nivolumab compared with ipilimumab on recurrence free survival (RFS) in 906 patients with resected stage III or IV melanoma.

The pCODR review also provided contextual information on an appraisal of a manufacturer-submitted network meta-analysis on the relative efficacy and safety of nivolumab as adjuvant therapy compared with other therapies in adult patients with resected advanced-stage melanoma. pERC considered the results of the indirect treatment comparison and network meta-analysis and noted that adjuvant treatment with nivolumab was associated with a reduction in the risk of cancer recurrence or death as compared with IFN or watchful observation/placebo. Nivolumab had a similar safety profile as placebo, but a statistically significantly lower risk of grade 3 or 4 adverse events (AEs) and discontinuation due to AEs, as compared with IFN. Between-group differences in quality of life (QoL) were not statistically significant, suggesting comparable QoL for patients who received nivolumab and placebo. Overall survival (OS) was not assessed in the comparisons between nivolumab and other active treatments due to the unavailability of data.

Patient populations: Stage IIIB/C and IV based on AJCC 7th edition

Key eligibility criteria included patients 15 years and older, except where local regulations and/or institutional policies do not allow subjects under 18 years of age (pediatric population) to participate. For those sites, the eligible subject population is 18 years of age and older. pERC noted that the use of nivolumab in the pediatric population who otherwise met the CheckMate 238 inclusion criteria could be considered on an individual patient basis and should be at the discretion of the treating oncologist. Key inclusion criteria were complete regional lymphadenectomy or resection within 12 weeks before randomization, stage IIIB/C or stage IV melanoma before complete regional lymphadenectomy or resection, no previous anti-cancer treatment and, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. pERC noted that recent evidence has established that survival was not improved with complete lymph node dissection and observation within the group with micrometastatic involvement is a viable treatment strategy. Based on this, pERC agreed with the pCODR Clinical Guidance Panel that the results of the CheckMate 238 trial are generalizable to patients who do not have complete lymph node dissection. Patients with resected brain metastases were allowed to enroll in the trial.

Patients enrolled in the trial all had resected stage IIIB, IIIC, or IV melanoma, the majority were male (57% to 59%), and had ECOG performance status of 0 (90.3%) and 1 (9.7%). pERC agreed that nivolumab should be used in patients with a good performance status. pERC further agreed that patients with pre-existing immune-mediated illnesses who otherwise met the CheckMate 238 inclusion criteria should be considered for treatment with nivolumab as adjuvant therapy to surgery on an individual patient basis and in consultation with the treating oncologist.

pERC noted that the trial was restricted to patients with stage IIIB/C and IV melanoma based on the 7th edition of the American Joint Committee on Cancer (AJCC) staging system while clinical practice has since shifted to using the 8th edition of the AJCC staging system. pERC recognized that the update to the AJCC staging system will result in the inclusion of patients who were not eligible based on the 7th edition, while other patients who were eligible for the trial would now be deemed ineligible. pERC further recognized that the greater clarity provided in the 8th edition of the AJCC staging system aligns with the intent of the CheckMate 238 trial, which was designed to include patients at higher risk for relapse and exclude those with earlier stages of disease. pERC agreed that patients with earlier stages of disease (stage IIIA or earlier) are unlikely to require adjuvant treatment. Based on this, pERC agreed that the results of the CheckMate 238 trial are generalizable to patients who would have stage IIIB/C or IV melanoma using the 8th edition of the staging system. Following the posting of the pERC initial recommendation, pERC noted feedback received from the submitter indicating that stage IIIa patients should be eligible for treatment with nivolumab. pERC reviewed further feedback received from the CGP and agreed that the current evidence from CheckMate238 supports the use of nivolumab in patients with stage IIIB/C/D or IV melanoma using the 8th edition of the staging system. Although there is some complexity in the patient population with the revision of the 7th edition to the 8th edition of the AJCC staging system, pERC reiterated that the intent of the CheckMate 238 trial was to include patients at higher risk for relapse and exclude those in the earlier stages of disease.

The recommended dosage of nivolumab is 3 mg/kg administered intravenously over 60 minutes every two weeks until progression or unacceptable toxicity. Patients continued to be treated with their assigned therapies until they had documented disease progression, developed unacceptable toxic events, or withdrew consent.

Key efficacy results: Significant improvement in recurrence-free survival

The key efficacy outcome deliberated on by pERC included RFS. Key secondary efficacy end points included OS, health-related quality of life (HRQoL), and safety. At the time of the interim analysis for RFS (data cut-off on May 15, 2017, minimum follow-up of 18 months), the median RFS had not been reached in either treatment group. The rates of RFS were 66.4% and 52.7% for nivolumab and ipilimumab, respectively. Adjuvant therapy with nivolumab was associated with a prolonged RFS compared with ipilimumab in patients with resected stage IIIB/C or IV melanoma (hazard ratio: 0.65; 97.56% confidence interval, 0.51 to 0.83; $P < 0.001$). pERC agreed that the CheckMate 238 trial demonstrated a clinically meaningful and statistically significant improvement in RFS in favour of nivolumab compared with ipilimumab. At the time of the interim analysis, the OS data were not mature.

Patient-reported outcomes: Missing data may contribute to lack of difference between groups

HRQoL was measured using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire – Core 30 Global Health status, European Quality of Life–5 Dimensions (EQ-5D) utility index, and EQ-5D visual analogue scale (VAS). The mean changes from baseline were reported for global health status, EQ-5D, and VAS scores from baseline to week 49. There were no clinically meaningful changes with respect to the scores observed on any of the HRQoL instruments. Individual functional and symptom scales were not available. pERC discussed that the number of patients contributing to the QoL questionnaires in the ipilimumab group were low due to treatment discontinuation (under 30% on the last assessment). pERC therefore concluded that there may have been a detriment in QoL with ipilimumab if the missing data were accounted for.

Safety: Nivolumab toxicity profile is manageable compared with ipilimumab

pERC deliberated the toxicity profile of nivolumab compared with ipilimumab and noted that serious adverse events (17.5% versus 40.4%), grades 3 or 4 AEs (25.4% versus 55.2%), grade 3 or 4 treatment-related AEs (14.4% versus 45.9%), any grades 3 or 4 AEs leading to discontinuation (9.7% versus 42.6%), and treatment-related grades 3 or 4 AEs leading to discontinuation (3.5% versus 30.0%) were all less in the

nivolumab versus ipilimumab group, respectively. Two deaths were reported for the ipilimumab group, both occurring more than 100 days after the last dose of ipilimumab. Both cases were considered to be treatment related. Overall pERC agreed that nivolumab had a manageable toxicity profile compared with ipilimumab.

Need and burden of illness: High risk of relapse for high-risk disease

Malignant melanoma is a relatively uncommon but aggressive skin cancer with an estimated incidence in Canada of 7,200 cases per year. Melanoma is, however, the most commonly diagnosed cancer in individuals between the ages of 20 and 29, creating a disproportionate societal impact. Despite efforts of patient advocacy groups and public awareness campaigns to educate the public regarding risk factors, the incidence of melanoma in Canada continues to rise. Most diagnoses of melanoma represent early stage disease and are cured with surgery alone; however, a proportion of patients will present with locally advanced cancers that, while also amenable to surgery, signify a high risk of relapse and death with a five- and ten-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 melanoma staging system).
With improvements in patient survival in the metastatic setting, attempts have been made to reduce the risk of relapse and death in patients with locally advanced, non-metastatic melanoma in the adjuvant setting. In Canada, high-dose interferon-alpha (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 at high risk for systemic recurrence, within 56 days of surgery (product monograph). In practice, however, IFN is infrequently prescribed as most patients decline this treatment option, instead choosing observation alone. Although a number of immunotherapies and targeted agents are being studied in this setting, for patients presenting with resected stage III or IV melanoma, adjuvant treatment options are currently limited, particularly with respect to systemic therapy. pERC acknowledged that there is a need for effective treatment options in the adjuvant setting for patients with resected melanoma.

Registered clinician input: High unmet need for a treatment option

Registered clinicians noted that the only currently available reimbursed adjuvant treatment option for patients with resected high-risk stage II and stage III melanoma, as well as resected stage IV melanoma, is high-dose IFN, a treatment option that has little benefit for survival or disease metastasis but is associated with significant toxicities including fever, flu-like symptoms, myelosuppression, liver toxicity, and depression. Based on this, registered clinicians noted that IFN is rarely used globally as patients opt to be under observation. Registered clinicians agreed that there is a high unmet need for the treatment of melanoma.

Although direct comparative trials are unavailable, registered clinicians indicated that nivolumab has a more favourable efficacy and safety profile when compared with IFN. Nivolumab would replace the currently available treatment of IFN or observation alone. Clinicians also indicated that treatment with adjuvant therapy should not have an impact on the treatment options for metastatic disease with patients being eligible for subsequent oral targeted therapy, pembrolizumab, or a combination of ipilimumab plus nivolumab. pERC, however, agreed that there is no evidence to help guide the sequencing of agents in the metastatic setting. Registered clinicians agreed with the pCODR Clinical Guidance Panel and pERC in that complete lymph node dissection should not be a requirement to receive treatment with nivolumab as is supported by recent evidence by Faries MB et al.

One registered clinician noted that the risk of metastatic relapse is higher for stage IIC patients than for stage IIIA patients and that there exists a strong possibility of indication creep to include the higher risk group, such as patients with stage IIC disease. pERC noted that clinical trials are underway to evaluate the efficacy and safety of adjuvant treatment in patients with stage IIC melanoma, and agreed that the decision to use nivolumab in this subset of patients should await trial results.

PATIENT-BASED VALUES

Values of patients with melanoma: Fear and anxiety, quality of life impact

pERC deliberated input received from two patient advocacy groups, MNC and SYSF. A total of 381 responses from patients and caregivers were obtained from both MNC and SYSF, with 37 patients receiving nivolumab in the adjuvant setting for the treatment of melanoma.

Fear and/or anxiety, scarring and disfigurement, fatigue, pain, and depression and were reported by at least half of patients as issues experienced with melanoma. Patients also voiced distress related to their condition, how it has impacted their lives, including their work and relationships with both family and friends, and how it has resulted in a general sense of anxiety. Patients' experience with IFN included severe fatigue and flu-like symptoms. Nearly all respondents indicated experiencing weight loss (95%), some form of depression (90%), hair loss or hair thinning (90%), and nausea and vomiting (90%). All respondents receiving IFN described their symptoms as unmanageable, and 95% reported that the side effects were not worth the result as they all experienced disease recurrence in stage IV melanoma. Patients on "watch and wait" express regret about the lack of treatment options as they felt that if they had another treatment option their condition might not have worsened.

Caregivers described experiencing extreme levels of stress and anxiety related to a lack of available treatment options for patients in the adjuvant setting after surgery. They also mentioned feeling fatigue due to increased responsibilities of care, having to take time off work for appointments and home care, the financial impact on their household due to lost income and increased medical costs, uncertainty regarding the future, and fear of losing their loved ones. Most caregivers indicated a negative impact on their families due to greater feelings of stress on their children.

Patient values on treatment: Improved survival, side effects profile, quality of life

Patient input highlighted that patients value having new treatment options that prolong survival, have minimal side effects, stop disease progression, and improve QoL. Among the 28 out of 37 patients who had experience with nivolumab in the adjuvant therapy for stage III melanoma, side effects experienced with nivolumab were reported as fewer and different than IFN, contributing to the improvement of patient's QoL. Fatigue and weakness (53%, n = 25), skin rash (35%, n = 16), and muscle and joint pain (30%, n = 14) were side effects reported by metastatic patients receiving nivolumab through a clinical trial. Other side effects were also reported, but in far fewer numbers. Of 47 adjuvant and metastatic patients, 46 stated the side effects experienced while on nivolumab were worth it. Patients indicated that frequent hospital visits to receive infusions of nivolumab created issues for work and impacted them financially; however, regardless of these limitations, patients were willing to participate in the trial.

Patient input reiterated the comparative tolerability of immunotherapies and targeted therapies to IFN, which they mentioned as being mostly intolerable, with approximately 70% of patients ending treatment before they completed a year-long regimen with interferon. Input further described that IFN does not provide patients with a net benefit in terms of OS, and that IFN is no longer offered in most centres. Finally, the patient input emphasized the need for therapies with greater effectiveness, the availability of a greater variety of therapies, better accessibility of therapies, and cost coverage by either the Canadian government or private insurance. pERC agreed that the improvement in RFS, manageable toxicity profile, and maintenance of QoL in favour of nivolumab reported in the CheckMate 238 trial aligns with patient values.

ECONOMIC EVALUATION

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

The pCODR Economic Guidance Panel (EGP) assessed cost-effectiveness and cost-utility analyses comparing nivolumab with observation for the adjuvant treatment of patients with stage III to IV melanoma. The submitter also provided a comparison of nivolumab with high-dose IFN; however, due to its associated toxic side effects, which limit its clinical use, the EGP has only presented analysis for the comparison between nivolumab and observation.

Basis of the economic model: Indirect treatment comparison and mapping of recurrence-free survival to estimate overall survival

Costs included were drug acquisition costs, drug administration costs, disease-related monitoring cost, subsequent treatment costs, and cost of treatment-related AEs.

Key clinical effect estimates considered in the analysis include RFS, OS, utilities, and disutilities. In the absence of direct head-to-head comparison and immature survival data from the CheckMate 238 trial, indirect evidence informed the comparative effectiveness estimates for RFS of nivolumab and observation and furthermore, RFS was then used to predict for OS. pERC noted that there is published evidence

supporting the predictive ability of RFS for OS in this setting; however, the EGP noted a large variation in the predictive formula used to map the relationship between RFS and OS.

Drug costs: New incremental cost

Nivolumab costs $782.22 per 40 mg vial, or equivalently $1,955.56 per 100 mg vial. At the recommended dosage of 3 mg/kg intravenous every two weeks for up to one year, the annual cost of nivolumab is $96,062 (based on average CheckMate238 patient weight and rate of discontinuation) was calculated. The daily cost of nivolumab is $263, making it $7,369 per 28-day course.

There were no costs modelled in relation to observation.

IFN costs $218.76 for 15 million units (MU), $364.60 for 25 MU, or $729.19 for 50 MU. At the recommended dosage of 20 MU/m^2 five days per week for four weeks, 10 MU/m^2 three days per week for 48 weeks, the average annual cost of high-dose IFN is $31,889.65 (based on the average CheckMate238 patient surface area and rate of discontinuation). The daily cost of IFN is $87, making it $2,446 per 28-day course.

Cost-effectiveness estimates: Mapping of overall survival using recurrence-free survival

pERC deliberated the cost-effectiveness of nivolumab compared with observation, and concluded that at the submitted price and based on the submitted economic analysis, nivolumab may be cost-effective. pERC reached this conclusion noting some uncertainty regarding the incremental cost-effectiveness ratio (ICER) due to the uncertainty in the clinical effectiveness of nivolumab compared with observation. pERC noted that indirect evidence informed the comparative effectiveness estimates for RFS of nivolumab and observation and furthermore, RFS was then used to predict for OS. Given the large variation in the predictive formula used to map the relationship between RFS and OS, the EGP explored this input in the model and noted that it had the most substantial impact on the ICER. Furthermore, assumptions on the time horizon and the proportion of patients receiving the full dose of nivolumab had an impact on the cost-effectiveness estimates. pERC noted that the majority of the OS benefit was captured in the first five years and therefore, shortening the time horizon did not have a substantial impact on the ICER. Although changes to various model inputs were explored, pERC noted that the model was not sensitive to most other changes. Following the posting of the pERC initial recommendation, pERC noted feedback received from PAG on the uncertainty associated with the clinical effect estimates and subsequently on the cost-effectiveness of nivolumab. pERC acknowledged that the CheckMate 238 trial only has two years of follow up data and that there remains uncertainty on the validity of the long term OS estimates predicted by the model. Given that the estimates for the comparative OS had the biggest impact on the ICER, pERC agreed that the ICER would be significantly impacted if long-term data demonstrated smaller incremental gains in OS. Overall, pERC accepted the pCODR Economic Guidance Panel's reanalysis estimates but noted that longer-term follow up data on OS will help clarify the true ICER. Based on this, pERC concluded that nivolumab may be cost-effective.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Underestimated budget impact

pERC considered the feasibility of implementing a reimbursement recommendation for nivolumab in the adjuvant treatment of patients with resected stage IIIB/C/D and IV melanoma (using the 8th edition of the AJCC melanoma staging system). pERC noted that the BIA substantially underestimated the market share for nivolumab and overestimated the use of IFN, a treatment option that is infrequently used due to its toxicity. pERC anticipates that the majority of patients will receive nivolumab in the adjuvant setting. Therefore, the population of patients eligible for nivolumab may be substantially greater than estimated in the submitter's BIA. Given the potentially substantial budget impact of nivolumab, the provinces should consider taking steps to limit the budget impact. pERC further noted that the submitted BIA was sensitive to average patient weight, market share multiplier, Canadian population, and the number of new cases diagnosed at ages 15 and older.

pERC acknowledged that there are a number of other immunotherapies and targeted agents being studied in this setting. However, until the evidence is reviewed for reimbursement, pERC agreed that there is no evidence to determine the sequencing of nivolumab relative to other adjuvant therapies in patients who are still candidates for surgery. Following the posting of the initial recommendation, feedback was received from registered clinicians and PAG on the sequencing of agents. pERC re-iterated that there is no evidence to guide sequencing of agents in this setting. pERC noted feedback from the CGP indicating that subsequent treatment decisions will be based on multiple factors, including, but not limited to time-to-

relapse, extent of disease, patient clinical status. Furthermore, although there is some data demonstrating the efficacy of using anti-PD-1 agents in sequence (all treatments given in the metastatic setting), pERC agreed it would be difficult to generalize to the current setting. pERC acknowledged that the trial did not allow dose delays or interruptions. However, in select patients who have had a treatment break due to toxicity, pERC noted that it is reasonable to re-start treatment, at the discretion of the treating oncologist. Following the posting of the initial recommendation, feedback was received from PAG on the total duration of therapy. pERC noted that the decision to restart treatment and the duration of treatment thereafter will likely be based on a case-by-case assessment and should be left to the discretion of the treating clinician. While acknowledging that there may be instances where patients are prevented from starting adjuvant therapy at the appropriate time frame, pERC agreed that the initiation of adjuvant therapy following surgery should generally follow the CheckMate 238 trial criteria (surgically rendered free of macroscopic disease within 12 weeks).

pERC identified a number of populations in which the current evidence should not be generalized. These populations included patients with resected ocular melanoma and patients with earlier stages of melanoma (e.g., stage IIIA and earlier) as there is no evidence to support the use of nivolumab as adjuvant treatment in these populations. pERC, however, agreed that the results of the CheckMate 238 trial are generalizable to patients who would have stage IIIB/C/D or IV melanoma using the 8th edition of the staging system.

DRUG AND CONDITION INFORMATION

Drug Information	• Immunotherapy (monoclonal antibody) • Solution for injection at a concentration of 10 mg/mL in either 40 mg or 100 mg single-use vials • Nivolumab is administered intravenously at a dosage of 3 mg/kg over 60 minutes every two weeks until disease progression or unacceptable drug toxicity or a maximum of 1 year
Cancer Treated	• Resected stage III or IV melanoma
Burden of Illness	• 7,200 cases per year in Canada • Most commonly diagnosed cancer in individuals between the ages of 20 and 29 • Incidence continues to rise in Canada • Five- and ten-year disease-specific survival rate of 32% and 24%, respectively for stage IIID patients (using the 8th edition of the AJCC melanoma staging system)
Current Standard Treatment	• High-dose interferon-alpha (IFN) • Observation
Limitations of Current Therapy	• High toxicity profile of IFN • Stress and anxiety of watch and wait approach

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
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. Dominika Wranik, Health Economist

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

- Cameron Lane, Dr. Henry Conter, and Dr. Winson Cheung were excluded from voting due to a conflict of interest.

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

- Cameron Lane, Dr. Henry Conter, Dr. Winson Cheung, and Dr. Anil Abraham Joy were excluded from voting due to a conflict of interest.

Avoidance of conflicts of interest

All members of pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of nivolumab (Opdivo) for adjuvant melanoma, through their declarations, eight members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, four of these members was excluded from voting.

Information sources used

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

Consulting publicly disclosed information

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

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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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 clarity on whether patients with BRAF mutation positive disease who are receiving or have been treated with dabrafenib plus trametinib in the adjuvant setting would be eligible for treatment with nivolumab. • PAG is seeking confirmation that nivolumab would be limited to patients with cutaneous melanoma (e.g., not ocular melanoma).	• pERC agreed that the use of nivolumab as adjuvant therapy to surgery could be considered in the subset of patients who had received IFN but pERC noted that there is no evidence for the use of nivolumab after other agents in the adjuvant setting. • pERC agreed that extrapolating the data to include treatment of patients with resected ocular melanoma was lacking, and nivolumab should not be used in this population.
• PAG is seeking guidance for use of adjuvant nivolumab for patients who would have been eligible at the time of diagnosis, but who are currently being treated with interferon alfa or on observation. • PAG is seeking guidance on, if recommended these patients transition to nivolumab therapy, what would be considered a maximum time frame since surgical resection to initiate nivolumab.	• pERC agreed that it is reasonable to switch patients currently on interferon alpha and who have not experienced disease progression to nivolumab. Following the posting of the initial recommendation, feedback was received from PAG on the appropriate time frame of switching patients currently on interferon to nivolumab. pERC noted that instances of switching from interferon to nivolumab will be few as interferon is rarely prescribed. pERC agreed that patients can be switched at any time as long as adjuvant treatment started within 12 weeks of surgery. Based on feedback from the CGP, pERC agreed that it is reasonable to treat patients, who have been switched from interferon to nivolumab, for a full 1-year course of nivolumab. • While acknowledging that there may be instances where patients are prevented from starting adjuvant therapy at the appropriate time frame, pERC agreed that the initiation of adjuvant therapy following surgery should generally follow the trial criteria (12 weeks).
• PAG noted that there is potential for indication creep to use nivolumab in earlier stages (e.g., stage IIIA and earlier). • PAG wanted to note that adjuvant interferon alfa is sometimes offered to resected stage IIC patients with T4 lesions (high-risk node negative) who are fit and motivated for treatment.	• There is no evidence to support the use of nivolumab as adjuvant treatment in earlier stages of melanoma (e.g., Stage IIIA and earlier).
• PAG is seeking clarity on dosages, specifically the appropriate dose interval (i.e., every 2 weeks or 4 weeks), weight-based dosages (i.e., 3 mg/kg or 6 mg/kg), weight-based dosages up to a cap (i.e., 240 mg every 2 weeks or 480 mg every 4 weeks), or flat dosages (i.e., 240 mg every 2 weeks or 480 mg every 4 weeks). It would be an enabler to implementation to align the dosages of nivolumab used for other indications with a weight-based dosage up to a cap. In addition, clarification for use of the faster infusion time of 30 minutes would also be an enabler to implementation.	• Although less frequent treatment dosage schedules have been adopted in other indications, pERC noted that clinicians may choose to adhere to the trial protocol of biweekly dosages given that treatment with nivolumab in this setting is for curative intent. Following the posting of the pERC initial recommendation, pERC noted feedback received from stakeholders on the appropriateness of dose capping with nivolumab in this setting. Feedback from the CGP also indicated that treatment should generally adhere to the best available evidence as the intent is curative. pERC therefore agreed that until there is evidence to confirm the efficacy at the capped dose (240 mg), the dose of nivolumab should generally adhere to the trial data. pERC also agreed that there may be rare instances where 4 week dose intervals 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 nivolumab after toxicity resolution or treatment interruption for other reasons and, if this occurs, clarification on the total duration of therapy.	• 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. Following the posting of the initial recommendation, feedback was received from PAG on the total duration of therapy. pERC noted that the decision to restart treatment and the duration of treatment thereafter will likely be based on a case-by-case assessment and should be left to the discretion of the treating clinician.
For patients who have received nivolumab in the adjuvant setting and then develop metastatic disease: • 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. • What would be an appropriate time frame from completion of adjuvant nivolumab 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 agreed that there is no data to guide treatment sequencing in the metastatic setting after progression on treatment with adjuvant nivolumab or progression following completion of treatment with adjuvant nivolumab. A review of post-protocol treatments in the CheckMate 238 trial indicates that patients received subsequent BRAF-targeted agents (in the case of patients with BRAF-mutated melanoma), immune checkpoint inhibitors (anti-CTLA-4 and anti-PD-1), and chemotherapy or experimental agents upon relapse. pERC noted the CGP comments indicating that single agent nivolumab would not be viewed differently in the metastatic setting following progression on adjuvant nivolumab. pERC noted the lack of evidence to confirm or refute the activity of nivolumab in the metastatic setting following progression as adjuvant treatment. Following the posting of the initial recommendation, feedback was received from stakeholders on the sequencing of agents. pERC re-iterated that there is no evidence to guide sequencing of agents in this setting. pERC noted feedback from the CGP indicating that subsequent treatment decisions will be based on multiple factors, including but not limited to, time-to-relapse, extent of disease, and patient clinical status. Furthermore, although there is some data demonstrating the efficacy of using anti-PD-1 agents in sequence (all treatments given in the metastatic setting), pERC agreed it would be difficult to generalize that data to the current setting. • pERC further noted that there is no evidence to determine the appropriate time frame from progression on adjuvant therapy to initiation of treatment in the metastatic setting. • The CGP agreed that patients with completely resected BRAF-mutated melanoma who otherwise met the CheckMate 238 inclusion criteria should be offered treatment with nivolumab as adjuvant therapy to surgery. Notably, the CGP acknowledged that there is evidence evaluating the efficacy and safety of dabrafenib plus trametinib and pembrolizumab in the adjuvant setting but the data are yet to be evaluated and approved for reimbursement.
• PAG is seeking information on data comparing nivolumab with interferon alfa.	• pERC noted that high-dose interferon-alpha is seldom used due to its toxicity. The only comparative evidence available was through a network meta-analysis that reported that adjuvant treatment with nivolumab was associated with a reduction in the risk of cancer recurrence, distant metastasis, or death as compared with interferon.

CGP = pCODR Clinical Guidance Panel; CTLA-4 = cytotoxic T-lymphocyte-associated protein-4; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; PD-1 = programmed death-ligand 1.