pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The 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-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

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

Drug:
Nivolumab (Opdivo)

Submitted Funding Request:

For the treatment of patients with unresectable or metastatic melanoma, regardless of BRAF status

Submitted By:
Bristol-Myers Squibb Canada

Manufactured By:
Bristol-Myers Squibb Canada

NOC Date:
September 25, 2015

Submission Date:
August 13, 2015

Initial Recommendation Issued:
February 4, 2016

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding nivolumab (Opdivo) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of patients with unresectable or metastatic BRAF wild-type melanoma who are previously untreated, with good performance status and who have stable brain metastases (if present). Treatment should continue until unacceptable toxicity or disease progression. However, pERC does not recommend funding nivolumab for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

pERC made this recommendation because it was satisfied that there is a net clinical benefit with nivolumab in patients with previously untreated unresectable or metastatic BRAF wild-type melanoma, based on a favourable toxicity profile, a clinically meaningful improvement in progression-free survival, and stable quality of life compared with ipilimumab.

pERC does not recommend funding nivolumab for the treatment of patients with unresectable or metastatic melanoma who have previously received treatment with ipilimumab.

pERC made this recommendation because the Committee was not satisfied that there is a net clinical benefit of nivolumab in patients with unresectable or metastatic melanoma who have previously received treatment with ipilimumab due to limitations in the evidence from the available clinical trial. Due to the immaturity of the data, pERC was unable to determine how nivolumab compares with chemotherapy with regard to important outcomes such as overall survival and progression-free survival.

	The Committee was satisfied that nivolumab aligned with patient values in both the untreated and previously treated population as there is a need for more effective treatment options with more favourable toxicity profiles in metastatic melanoma. pERC concluded that nivolumab compared with ipilimumab could not be considered cost-effective in patients with unresectable or metastatic melanoma.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given that pERC was satisfied that there is a net clinical benefit of nivolumab in previously untreated patients with BRAF wild-type unresectable or metastatic melanoma, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of nivolumab to an acceptable level. **Wastage and Budget Impact Likely Impact Adoption Feasibility** pERC noted the unknown duration of treatment with nivolumab, as it continues until disease progression or unacceptable toxicity, whichever comes first. In considering the high cost of nivolumab, the potential for drug wastage and the unknown but potentially long duration of treatment, pERC concluded that a substantial reduction in drug price would be required to improve cost-effectiveness and affordability. **Evidence Generation to Understand Optimal Duration of Therapy** pERC noted that nivolumab is approved at a dose of 3 mg/kg every two weeks until disease progression or unacceptable toxicity, whichever comes first. pERC acknowledged that there is currently no evidence to identify an optimal duration of treatment with nivolumab and agreed that it is important to prospectively collect such data. **Optimal Sequencing of Ipilimumab and Other Therapies Unknown** pERC concluded that the optimal sequencing of nivolumab and other treatments now available for the treatment of metastatic melanoma is currently unknown. pERC was therefore unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces would need to address this issue upon implementation of nivolumab funding and noted that collaboration among provinces to develop a common approach would be of value.

SUMMARY OF pERC DELIBERATIONS

pERC noted that unresectable stage III or stage IV melanoma carries a poor prognosis with a median survival of approximately 6 months and only 25% of patients with late-stage disease surviving to one year. Ipilimumab is commonly used in the first- and second-line settings for patients with BRAF mutation-negative (i.e., BRAF wild-type) or BRAF V600 mutation-positive metastatic melanoma. While a proportion of patients (approximately 20%) have prolonged clinical benefit to ipilimumab, the majority of patients experience disease progression. Adverse events with ipilimumab are also significant and potentially life threatening. Treatment options are limited for patients who have progressed on ipilimumab and generally include dacarbazine or best supportive care (BSC). pERC noted that dacarbazine has not shown an advantage in survival or quality of life in randomized trials. pERC agreed that there is a need for more effective and tolerable treatment options in previously untreated patients and in patients who have previously received ipilimumab.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC discussed the evidence on the efficacy of nivolumab and concluded that there is a net clinical benefit with nivolumab in patients who have previously untreated unresectable or metastatic BRAF wild-type melanoma. The Committee based this conclusion on evidence from the CheckMate 067 trial that demonstrated a clinically meaningful difference in progression-free survival in favour of nivolumab compared with ipilimumab in patients with previously untreated unresectable or metastatic melanoma. pERC explicitly made their recommendation for patients with BRAF wild-type melanoma because the Committee noted that a subgroup analysis by BRAF mutation status in the CheckMate 067 trial demonstrated a clear advantage in progression-free survival in favour of nivolumab in patients with BRAF wild-type disease; however, no such advantage was demonstrated in the BRAF V600 mutation-positive subgroup. Furthermore, the Committee noted that the CheckMate 066 trial, which enrolled patients with previously untreated BRAF wild-type advanced melanoma, demonstrated clinically meaningful differences in overall survival and progression-free survival in favour of nivolumab compared with dacarbazine. pERC also noted that while the most relevant comparator for this patient population in the Canadian setting, based on input from the Clinical Guidance Panel and pCODR's Provincial Advisory Group, is ipilimumab, the CheckMate 066 trial provides supporting evidence of the clinical benefit of nivolumab. Therefore, pERC could not conclude that there is a net clinical benefit with nivolumab in patients with BRAF V600 mutation-positive previously untreated unresectable or metastatic melanoma. Additionally, the Committee discussed the toxicity profile of nivolumab, and concluded that it is favourable compared to ipilimumab. In particular, the lower incidence of immune-related adverse events in the nivolumab arm compared with the ipilimumab arm was noted as a clinically meaningful advantage. Finally, pERC noted that while the health-related quality of life data from the CheckMate 067 trial suggest that patients' health-related quality of life is more stable over time with nivolumab and with ipilimumab, no comparison was made between treatment arms.

pERC could not conclude that there is a net clinical benefit of nivolumab in patients with unresectable or metastatic melanoma who have previously received ipilimumab because of the limitations in the evidence available from the CheckMate 037 trial which compared nivolumab with investigator's choice of chemotherapy in patients who were previously treated with ipilimumab. pERC noted that despite the reported objective response rates, no statistical comparison of those rates was completed. Furthermore, the progression-free survival and overall survival data were not statistically significant and were immature; therefore, pERC was unable to determine how nivolumab compares with chemotherapy with regard to these outcomes in this patient population. The Committee discussed the toxicity profile of nivolumab in this setting and concluded that it is more favourable than chemotherapy. The Committee also noted that no quality of life data are yet available from the CheckMate 037 trial.

pERC reviewed patient advocacy group input that indicated that patients value effective treatment options with reduced toxicity, improved quality of life, and improved survival. Given this input, pERC considered that nivolumab, in both treatment settings, aligned with patient values.

pERC discussed the cost-effectiveness of nivolumab and concluded that it is not cost-effective when compared to ipilimumab in patients with previously untreated disease, and when compared to chemotherapy in patients previously treated with ipilimumab. pERC accepted the Economic Guidance Panel's (EGP) re-analysis estimates and noted several limitations in the Submitter's base case analysis. The largest impact on the cost-effectiveness estimates was due to differences in the choice of data to inform the duration of treatment of nivolumab. pERC noted that patients continued receiving nivolumab beyond RECIST-defined disease progression and agreed with the EGP's approach that time-to-treatment discontinuation would better reflect the treatment duration for patients who receive nivolumab and should, therefore, be used to inform the cost estimates for nivolumab. Furthermore, pERC noted that the short-term survival data for CheckMate 067 trial (in the previously untreated model) and for the CheckMate 037 trial (in the previously untreated with ipilimumab model) were immature and created a lot of uncertainty in the estimate of clinical effect for nivolumab. pERC discussed the Submitter's assumption that the short-term survival data from the KEYNOTE-006 trial of pembrolizumab compared with ipilimumab would be similar for the comparison of nivolumab with ipilimumab. pERC noted that, while nivolumab and pembrolizumab have similar mechanisms of action, there are no comparative trial data that demonstrate the equivalence of these two agents. Similarly, pERC also discussed the Submitter's assumption that the short-term survival data from the CheckMate 066 trial, comparing nivolumab with dacarbazine in previously untreated patients, would be similar for nivolumab compared with chemotherapy in patients previously treated with ipilimumab (i.e., CheckMate 037). pERC noted that no data are currently available to support or refute the Submitter's assumption. pERC therefore agreed with the EGP's conclusion that there is no evidence to support either assumption and accepted the EGP's re-analyses that used the CheckMate 067 and CheckMate 037 trial data to model the short-term survival in the previously untreated and previously treated with ipilimumab settings, respectively. pERC also noted the short duration of follow-up from the trials and discussed the Submitter's assumption that long-term survival for nivolumab in both settings could be estimated using long-term data for ipilimumab and that the effect would plateau over a long follow-up period. In the absence of long-term follow-up data for nivolumab demonstrating such an effect, pERC accepted the EGP's re-analysis using an alternative distribution with a decreasing pattern of survival. In addition, pERC noted that assumptions around the time horizon, utility estimates, and a potential price reduction of ipilimumab and/or nivolumab, impacted the cost-effectiveness estimates significantly. pERC considered that nivolumab has a high cost and would need a substantial price reduction in order for it to be considered cost-effective. Overall, pERC accepted the EGP's re-analysis estimates and concluded that nivolumab is not cost effective compared either with ipilimumab in previously untreated patients or with investigator's choice of chemotherapy in patients who were previously treated with ipilimumab.

pERC considered the feasibility of implementing a funding recommendation for nivolumab. pERC considered that the optimal sequencing of agents in this setting is currently unknown. pERC also noted the absence of evidence on the comparative efficacy and safety of nivolumab and pembrolizumab. However, pERC recognized that provinces may need to address this issue upon implementation of funding and noted that the development and implementation of an evidence-informed provincial guideline would help guide consistency in drug funding. pERC noted that the Submitter's budget impact analysis is sensitive to nivolumab's market share, treatment duration, and number of cases of advanced melanoma and agreed that jurisdictions will need to consider the uncertainty in these factors during implementation. While pERC acknowledged that the number of eligible patients in both settings is small, the introduction of nivolumab as an additional treatment option, and not as an alternative treatment, is likely to have a significant impact on budgets. Furthermore, pERC noted that the potential for drug wastage, given the short stability and weight-based dosing, together with the high cost of nivolumab, would have a substantial impact on the cost-effectiveness and affordability of nivolumab.

EVIDENCE IN BRIEF

pERC deliberated upon a pCODR systematic review, other literature in the Clinical Guidance Report providing clinical context, an evaluation of the manufacturer's economic model and budget impact analysis, guidance from pCODR clinical and economic review panels, input from one patient advocacy group [Melanoma Network of Canada (MNC)] and input from pCODR's Provincial Advisory Group.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of nivolumab for the treatment of adult patients with unresectable or metastatic (stage III or IV) melanoma that was:

- Previously untreated.
- Previously treated with ipilimumab.

Studies included

The pCODR systematic review included three fully published randomized controlled trials:

- CheckMate 067 which randomized patients with previously untreated unresectable or metastatic melanoma to one of the following:
  - 3 mg/kg nivolumab once every 2 weeks plus placebo (n=316)
  - 3 mg/kg nivolumab once every 3 weeks plus 3 mg/kg ipilimumab every 3 weeks for 4 doses, followed by 3 mg/kg nivolumab every 2 weeks for cycle 3 and beyond (n=314)
  - 3 mg/kg ipilimumab every 3 weeks for 4 doses plus placebo (n=315).
- CheckMate 066 which randomized patients with previously untreated unresectable or metastatic melanoma to 3 mg/kg nivolumab once every 2 weeks plus dacarbazine (n=210) or to dacarbazine plus placebo (n=208).
- CheckMate 037 which randomized patients who were previously treated with ipilimumab 2:1 to 3 mg/kg nivolumab every 2 weeks (n=272) or to investigator's choice of chemotherapy (dacarbazine or the combination of paclitaxel and carboplatin) every 3 weeks (n=133).

In all three studies, patients received treatment until RECIST-defined disease progression, unacceptable toxicity or withdrawal of consent. In the CheckMate 067 and 037 trials, treatment beyond RECIST-defined disease progression was permitted for patients who had a clinical benefit (assessed by the investigator) and did not have substantial burden of adverse events.

Patient populations: patients previously untreated with ipilimumab or previously treated with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

Previously Untreated Patients

Baseline characteristics were, generally, well balanced between the treatment arms in both studies.

In CheckMate 067 the mean age ranged from 59 to 61 across the three treatment arms and approximately 65% were men. The trial included patients with ECOG PS 0 (73%) or 1 (26%). The trial included patients with unresectable or metastatic melanoma, regardless of BRAF status. Approximately 32% of patients were BRAF V600 mutation-positive. Patients could not have received prior therapy with an immune checkpoint inhibitor (e.g., anti-PD-1, anti-CTLA-4, etc.). Patients with active brain metastases and ocular melanoma were also excluded.

In CheckMate 066 the median age of patients was 62 years and 59% were men. pERC noted that the trial included patients with an ECOG PS of 0 or 1; however, more patients in the nivolumab arm had an ECOG PS of 0 at baseline than in the dacarbazine arm (70.5% and 58.2%, respectively), therefore, it is possible that the results of the trial were biased in favour of nivolumab by this baseline imbalance. The trial only included patients with BRAF wild-type unresectable or metastatic melanoma and excluded patients with active brain metastases or ocular melanoma. Patients could not have received prior therapy with an immune checkpoint inhibitor (e.g., anti-PD-1, anti-CTLA-4, etc.).

Patients Previously Treated with Ipilimumab

In CheckMate 037 the median age of patients was 59 years and a 64.4% of patients were men. The trial included patients with ECOG PS 0 (60.7%) or 1 (39.0%). The trial included patients with unresectable or

metastatic melanoma, regardless of BRAF status, who had previously received an anti-CTLA-4 (e.g., ipilimumab) and, in those with BRAF V600 mutation-positive disease, a BRAF inhibitor. Patients with active brain metastases and ocular melanoma were excluded.

Key efficacy results: clinically meaningful improvements for previously untreated patients; uncertainty in outcomes for patients previously treated with ipilimumab

Previously Untreated Patients

pERC noted that the CheckMate 067 trial demonstrated a statistically significant and clinically meaningful improvement in PFS in favour of nivolumab compared with ipilimumab. Median PFS was 6.9 months for nivolumab compared with 2.9 months for ipilimumab (HR 0.57; 99.5% CI 0.43 to 0.76; p<0.001). Additionally, the objective response rate demonstrated a statistically significant improvement in favour of nivolumab (43.7%) compared with ipilimumab (19.0%; odds ratio 6.11, 95% CI 3.59 to 10.38). In a subgroup analysis by BRAF mutation status, pERC noted a statistically significant and clinical meaningful difference in progression-free survival in favour of nivolumab (median 7.89 months) compared with ipilimumab (median 2.83 months; HR 0.50, 95% CI 0.39 to 0.63) in patients with BRAF wild-type disease. However, in patients with BRAF V600 mutation-positive disease, no statistically significant difference was demonstrated (HR 0.77, 95% CI 0.54 to 1.09 in favour of nivolumab). Furthermore, pERC noted that the results in the BRAF wild-type subgroup were consistent with the results of the CheckMate 066 trial that demonstrated a statistically significant and clinically meaningful improvement in 1-year OS and PFS in favour of nivolumab compared with dacarbazine in previously untreated patients with BRAF wild-type unresectable or metastatic melanoma. One year OS was 72.9% for nivolumab and 42.1% for dacarbazine (HR 0.42; 95% CI 0.25 to 0.73). Median PFS was 5.1 months for nivolumab and 2.2 months for dacarbazine (HR 0.43; 95% CI 0.34 to 0.56).

Patients Previously Treated with Ipilimumab

pERC noted that the CheckMate 037 trial included objective response and OS as primary study endpoints. An interim analysis of the objective response data indicated that patients who received nivolumab had a higher rate of objective response rate than patients who received chemotherapy (31.7% and 10.6%, respectively); however, the trial was not designed to compare objective response rates between arms. Therefore, the statistical relevance of this result is uncertain. pERC also noted the availability of a descriptive analysis of PFS in the European Public Assessment Report (EPAR) for nivolumab. Median PFS was 4.7 months in the nivolumab arm and 4.2 months in the chemotherapy, with a statistically non-significant HR of 0.74 (95% CI 0.68 to 1.26); however, the PFS data were immature at the time of analysis. The interim analysis of OS demonstrated that median OS was 15.5 months for nivolumab compared with 13.7 months for chemotherapy, with a statistically non-significant HR of 0.93 (95% CI 0.68 to 1.26); however, pERC noted that the trial is ongoing and that the final analysis of OS is expected in late 2016.

Quality of life: stable HRQoL or less decline in HRQoL with nivolumab in previously untreated patients; no HRQoL data for patients previously treated with ipilimumab

In all three studies, HRQoL was measured using the EORTC QLQ-C30, which is not yet validated in melanoma, but has been validated in several other types of cancer.

Previously Untreated Patients

In Checkmate 067, completion rates at baseline and at least one post-baseline visit were 85.1% in the nivolumab arm and 88.2% in the ipilimumab arm. HRQoL was maintained over time for both the nivolumab arm and the ipilimumab arm as the mean change in the EORTC QLQ-C30 global health status scores did not reach or exceed the minimal important difference of 10 or more points.

In CheckMate 066, completion rates at baseline or at baseline and at least one post-baseline study visit were not reported, which makes it difficult to critically appraise the data on HRQoL. The minimal important difference for the EORTC QLQ-C30 was defined as ≥10 points. pERC noted that a cross-sectional analysis indicated that HRQoL appeared stable over time in both treatment arms. pERC also noted that patients who received nivolumab experienced a statistically significantly longer time to first decline in global health status than patients who received dacarbazine (median 276 days versus 179 days, respectively; HR 0.66, 95% CI 0.47 to 0.94; p=0.021).

Patients Previously Treated with Ipilimumab
pERC noted that no HRQoL data are yet available from the CheckMate 037 trial in patients previously treated with ipilimumab.

Safety: not insignificant but manageable toxicity

pERC discussed the safety profile of nivolumab in both settings and agreed that the toxicity associated with nivolumab was manageable compared to either ipilimumab or chemotherapy. In CheckMate 067, the rate of grade 3 or 4 treatment-related adverse events was lower in those who received nivolumab (16.3%) than in those who received ipilimumab (27.3%). The rate of discontinuation due to treatment-related adverse events was 7.7% for nivolumab and 14.8% for ipilimumab. The rates of grade 3 or 4 diarrhea and colitis in the nivolumab arm were 2.2% and 0.6%, respectively, and in the ipilimumab arm were 6.1% and 8.7%. Two deaths were attributed to study drug toxicity: one death (neutropenia) in a patient treated with nivolumab and one death (cardiac arrest) in a patient treated with ipilimumab.

In CheckMate 066, rates of grade 3-4 adverse events were lower for the nivolumab arm (11.7%) than in the dacarbazine arm (17.6%). The rate of discontinuation due to adverse events was 6.8% for the nivolumab arm and 11.7% for the dacarbazine arm. The rate of grade 3 or 4 diarrhea was 1.0% in the nivolumab arm and 0.5% in the dacarbazine arm and the rate of grade 3 or 4 colitis was 0.5% in the nivolumab arm and 0% in the dacarbazine arm.

In CheckMate 037, the rate of grade 3 or 4 treatment-related adverse events was 9% in the nivolumab arm and 31.4% in the chemotherapy arm. Increased lipase and alanine aminotransferase, fatigue, and anemia were the most commonly reported grade 3 or 4 treatment-related adverse events for patients who received nivolumab. The rate of grade 3 or 4 diarrhea was 0.4% in the nivolumab arm and 2.0% in the chemotherapy arm. The rate of grade 3 or 4 colitis was not reported. The rate of withdrawal due to study drug toxicity was 2.6% for patients who received nivolumab and 6.9% for patients who receive chemotherapy. No deaths were attributed to study drug toxicity in either arm.

Burden and Need: more effective treatment options required that improve survival and with more favourable toxicity profiles

It is estimated that 6,500 Canadians will be diagnosed with melanoma in 2014, and approximately 1,050 patients will die of melanoma in 2015. Unresectable stage III or stage IV melanoma carries a poor prognosis with a median survival of approximately 6 months and only about 25% of patients with late stage disease surviving to one year.

The emergence of BRAF inhibitors that target the V600 mutation has led to improvements in response rate, PFS, and OS; however, resistance to these therapies ultimately develops and patients experience rapid and unrelenting disease progression. The immune checkpoint inhibitor, ipilimumab, has shown improved outcomes, independent of BRAF status, when used to treat patients with unresectable or metastatic melanoma, with approximately 20% of patients experiencing prolonged disease control lasting many years. However, approximately 80% of advanced melanoma patients do not have such a response. Treatment options for ipilimumab-refractory patients are very limited and patients typically have short survival. Adverse events with ipilimumab are also significant and potentially life threatening, with approximately 15% of patients experiencing grade 3 or 4 immune mediated side effects that require management and monitoring, including risks for severe and fatal events (in particular, colitis). The most common grade 3 or 4 toxicities are diarrhea and colitis, which generally occur in 3% to 10% of patients.

pERC noted that historically there was no effective standard treatment for metastatic melanoma in patients previously treated with ipilimumab. It was discussed that commonly used systemic therapies include dacarbazine, temozolomide and interleukin-2 but there is limited evidence that these treatments improve overall survival. pERC noted that pembrolizumab is Health Canada-approved for the treatment of patients with advanced or metastatic melanoma who have previously received ipilimumab, but it has not yet received funding in any provinces that participate in the pCODR process. pERC also noted that patients with metastatic melanoma are often younger than those affected by other types of cancer and while this cancer may affect a small patient population, incidence is increasing and it cannot be considered a rare disease. Overall, pERC considered that there is a need for new and effective therapies for patients with unresectable stage III or stage IV metastatic melanoma that provide durable improvements in patient survival, have more favourable toxicity profiles and improve quality of life.

PATIENT-BASED VALUES

Values of patients with metastatic melanoma: QoL, improved survival and manageable toxicity

Patient advocacy group input indicated that there are limited therapies available for patients with advanced melanoma. Patients expressed the importance of having new effective therapies that extend life expectancy, have reduced toxicity and provide improvements in quality of life. Patients indicated that current therapies for advanced melanoma are limited and have significant side effects that have a negative impact on the quality of life for both the patient and the caregiver. Patients commonly experience pain, scarring, fatigue, disrupted sleep, fear, depression and anxiety as a result of their disease. As related to current treatments, patients experience a myriad of symptoms attributed to treatments including fatigue, irritability, flu-like symptoms (chills, sweats), headaches, weight loss, diarrhea (including colitis), and nausea and vomiting. In some patients, significant and devastating side effects result in patients deciding not to use the available treatments.

Patient values on treatment: less decline in QoL, manageable toxicity profile

Patients indicated that they expected nivolumab to offer a longer life, less frequent and more manageable side effects, a good quality of life and potential lasting response. pERC noted that input from 22 patients who had experience with nivolumab was included and recognized that this represents an impressive sample size for a new agent that would have required a substantial amount of effort on the part of the patient advocacy group to identify and include these patients. The majority of patients who had experience with nivolumab indicated the drug was well tolerated with few side effects. These side-effects included skin rash, shortness of breath, fatigue, diarrhea and colitis, constipation, headaches, weight loss, liver problems, and muscle or joint problems. Approximately 28% of 22 patients reported having no side effects. Overall, side-effects with nivolumab were reported to be manageable, and treatment improved patients' quality of life, with all patients indicating that the side effects associated with nivolumab were worth the benefits of the treatment. pERC noted that input from patients aligned with the results of the studies included in the pCODR systematic review.

pERC noted that nivolumab, compared with ipilimumab, demonstrated improvements in progression-free survival in previously untreated patients, and was associated with a manageable toxicity profile, including minimal immune related side effects. pERC agreed this aligned with the patient value of having access to effective treatments with a durable survival advantage and manageable toxicity profile. pERC noted that QoL was a patient-expressed value and that it did not meet or exceed the minimal important difference in either the nivolumab arm or ipilimumab arm in the CheckMate 067 trial.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel assessed cost-effectiveness and cost-utility analyses comparing nivolumab to ipilimumab in patients with unresectable or metastatic melanoma who are naive to ipilimumab treatment and nivolumab to chemotherapy (dacarbazine alone or paclitaxel plus carboplatin) in patients with unresectable or metastatic melanoma who were previously treated with ipilimumab.

Basis of the economic model: uncertainties due to immaturity of OS data and treatment duration for nivolumab

Costs included were cost of treatment, adverse events management costs, and resource costs for disease follow-up. pERC noted that the cost estimates for nivolumab were based on progression-free survival data from the CheckMate 067 trial in previously untreated patients and from the CheckMate 037 trial in patients previously treated with ipilimumab. pERC considered the appropriateness of PFS to inform this input as a significant proportion of patients in both studies continued to receive nivolumab after disease progression based on the investigator's assessment of whether a patient would derive clinical benefit from continuing treatment. pERC accepted the EGP's approach to use time-to-treatment discontinuation as an alternative data source that would more accurately reflect the treatment duration of patients who received nivolumab.

Key clinical effects considered in the analysis included PFS, OS and utilities. pERC noted that the OS data for the key studies (CheckMate 067 and 037) were not mature and that the submitter assumed that; 1) the OS for nivolumab compared with ipilimumab for previously untreated patients could be estimated by the

KEYNOTE-006 trial that compared pembrolizumab with ipilimumab, and that; 2) the OS for nivolumab compared with chemotherapy for patients previously treated with ipilimumab could be estimated by the CheckMate 066 trial that compared nivolumab with dacarbazine in previously untreated patients. pERC considered the appropriateness of these data sources for short-term OS and noted that; 1) while pembrolizumab and nivolumab have similar mechanisms of action, there are currently no data available to support or refute the equivalence of these agents, and; 2) there are no data to support or refute the assumption that the effect of nivolumab is similar in previously untreated patients and patients previously treated with ipilimumab. Therefore, pERC accepted the EGP's use of alternative sources to model short-term OS.

Additionally, pERC noted that the long-term estimates for OS in the submitted models were based on extrapolation using long-term OS data from previous ipilimumab studies. pERC considered the appropriateness of this data source and noted that there is uncertainty in the assumption that a proportion of patients will experience a sustained benefit, as was observed with ipilimumab. pERC, therefore, accepted the EGP's use of an alternative distribution with a declining pattern of survival to model long-term survival and to explore the uncertainty in the data that currently has a short follow-up period.

Drug costs: high cost of both nivolumab and ipilimumab

Nivolumab costs $1,955.56 per 100 mg vial or $782.22 per 40 mg vial; at the recommended dose of 3 mg/kg once every 14 days, the average cost per day in a 28-day course of nivolumab is $293.33 and the average cost per 28-day course is $8,213.31. pERC also discussed that the submitted analysis and EGP's re-analysis estimates reflect an incremental cost-effectiveness ratio of one high cost drug compared to another high cost treatment, and may artificially give the impression of a reasonable incremental cost-effectiveness ration when compared to other lower cost and/or historical treatments.

Ipilimumab costs $5,800 and $23,200.00 per 50 mg and 200 mg vial, respectively. At the recommended dose of 3 mg/kg every 3 weeks for a 28-day cycle, the cost of ipilimumab is $1160.00 per day and $32,480.00 per 28-day cycle. Ipilimumab is administered for a maximum of 4 cycles.

Dacarbazine costs $200.20 per 600 mg per vial. At the recommended dose of 200–250 mg/m² IV days 1-5 every 21-28 days, the cost of dacarbazine is $20.26 – $33.76 per day and $567.230 – $945.39 per 28-day cycle. Paclitaxel costs $0.33 per 1 mg and carboplatin costs $0.10 per mg^2. At the recommended dose of paclitaxel of 175 mg/m^2 IV every 21 days and carboplatin of AUC 5-6 mg*min/mL IV every 21 days, the cost of the combination is $10.77 to $11.99 per day and $301.69 to $335.69 per 28-day cycle.

Cost-effectiveness estimates: alternate assumptions on OS benefit and treatment duration

pERC discussed the EGP's best estimate of the incremental cost-effectiveness ratio in previously untreated patients and in patients previously treated with ipilimumab. In both settings, pERC accepted the EGP's re-analysis estimates and concluded that nivolumab is not cost-effective.

pERC discussed the uncertainty in the long-term survival effects for nivolumab in both settings. pERC noted the short duration of follow-up available for the CheckMate 067 and 037 trials and discussed the Submitter's assumption of a lasting benefit with nivolumab in a proportion of patients, similar to the benefit observed with previous immunotherapies. In the absence of longer term data, pERC was unable to accept this assumption of prolonged benefit and agreed with the EGP's use of alternative data sources to extrapolate survival in both settings and acknowledged that there is a large amount of uncertainty in the survival effects which have a substantial impact on the ICER. Furthermore, pERC discussed the uncertainty in the short-term survival effects for nivolumab in both settings and agreed with the EGP's conclusion that there exists substantial uncertainty in the estimates of short-term survival. pERC noted that the EGP's reanalysis estimates are based on the best available data; however, both the CheckMate 067 and 037 trials are ongoing and collecting overall survival data. When those data become available, they may have a substantial impact on the EGP's range of estimated ICER's.

pERC also discussed that the factor with the largest impact on the ICERs for both settings was the use of PFS to inform the treatment duration of nivolumab. pERC agreed with the EGP's conclusion that the time-to-treatment discontinuation from CheckMate 067 (previously untreated patients) and CheckMate 037 (patients previously treated with ipilimumab) would best reflect the duration of treatment with nivolumab. pERC made this conclusion due to the mechanism of action of immunotherapies and the possibility that some patients may experience pseudoprogression—whereby some patients technically meet RECIST criteria for disease progression, but do not have true disease progression—and, therefore,

may be treated beyond RECIST-defined disease progression and continue to receive treatment until true disease progression.

In addition, pERC also noted re-analysis altering assumptions around the time horizon, the use of utility estimates standardized to Canadian patients, and potential price reduction of ipilimumab and nivolumab all impacted the cost-effectiveness estimates. Overall, the range of estimates provided by the EGP was wide. Considering the uncertainty in both the short-term and long-term benefit of nivolumab coupled with the high cost and unknown duration of treatment (until disease progression or unacceptable toxicity), pERC agreed that a substantial price reduction would be needed for nivolumab to be considered cost-effective. Overall, pERC accepted the EGP's re-analysis estimates and concluded that, at the submitted price, nivolumab is not cost effective relative to ipilimumab for previously untreated patients, or compared with investigator's choice of chemotherapy for patients previously treated with ipilimumab.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: treatment duration, sequencing of available therapies

pERC considered the feasibility of implementing a funding recommendation for nivolumab. pERC noted PAG's concern about the long duration of therapy with nivolumab as compared to other immunotherapies with shorter treatment cycles. pERC noted that the mechanism of action of immunotherapies suggest it is reasonable to investigate whether a shorter treatment exposure period could provide an optimal response to patients while minimizing exposure to potential side effects. pERC acknowledged that there is currently no evidence to suggest an optimal duration of treatment with nivolumab but agreed that it is important for jurisdictions to prospectively collect this data to manage the budget impact of a funding recommendation. pERC considered that the optimal sequencing of agents in this setting is currently unknown. However, pERC recognized that provinces may need to address this issue upon implementation of a funding recommendation and noted that the development and implementation of an evidence-informed provincial guideline would help to ensure consistency in drug funding. pERC acknowledged that drug wastage is an important concern for PAG. pERC noted that the EGP included wastage in the model and it is reflected in the ICER in both settings. Overall, due to the high cost of nivolumab and the unknown but potentially long duration of treatment, pERC concluded that a substantial reduction in drug price would be required to improve cost-effectiveness to an acceptable level. pERC noted that the submitted budget impact analysis was sensitive to the duration of treatment for both nivolumab and ipilimumab in the previously untreated setting and the duration of treatment of nivolumab in the previously treated with ipilimumab setting. The budget impact analysis was also sensitive to the number of patients eligible for nivolumab and the estimated market share for nivolumab. pERC discussed that jurisdictions will need to consider the uncertainty in these factors during implementation.

DRUG AND CONDITION INFORMATION

Drug Information	• Immunomodulatory agent • 40mg and 100mg vials submitted for review • Recommended dose of 3mg/kg every 2 weeks
Cancer Treated	• Unresectable stage III or stage IV Metastatic Melanoma
Burden of Illness	• 6,500 Canadians diagnosed and ~1050 died of melanoma in 2015 • Unresectable stage III or stage IV melanoma carries a poor prognosis. Median survival of approximately 6 months with about 25% of patients surviving to one year.
Current Standard Treatment	• Ipilimumab • Vemurafenib • Dabrafenib • Trametinib • Dacarbazine • Best supportive care (BSC)
Limitations of Current Therapy	• Limited efficacy with ipilimumab, sustained response in approximately 20% of patients • Immune-related toxicity with ipilimumab • Rapid progression following BRAF inhibitors • Toxicity and limited efficacy of dacarbazine

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy-Thompson, Pharmacist
Valerie MacDonald, Patient Member-in-Training
Carole McMahon, Patient Member Alternate
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Danica Wasney, Pharmacist

All members participated in deliberations and voting on the initial recommendation except:

- Carole McMahon, who was the designated non-voting patient member alternate for this meeting
- Valerie MacDonald who did not vote due to her role as a patient member-in-training
- Anil Abraham Joy who was excluded from deliberations and voting due to a conflict of interest
- Don Husereau who was excluded from voting due to a conflict of interest
- Scott Berry, Kelvin Chan, Matthew Cheung, and Catherine Moltzan who were not present for the meeting

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of nivolumab (Opdivo) for metastatic melanoma through their declarations, two 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

The pCODR Expert Review Committee 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 their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

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

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers 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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