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) plus ipilimumab (Yervoy)

Submitted Funding Request:
Nivolumab in combination with ipilimumab for treatment-naive adult patients with advanced (unresectable or metastatic) melanoma, regardless of BRAF status.

Submitted By: Bristol-Myers Squibb Canada	**Manufactured By:** Bristol-Myers Squibb Canada
NOC Date: October 26, 2016	**Submission Date:** November 30, 2016
Initial Recommendation: October 5, 2017	**Final Recommendation:** November 30, 2017

Drug Costs

Approximate per Patient Drug Costs, per Month (28 days)

Submitted list price of Nivolumab: $1,956.00 per 100 mg/10 mL vial
Submitted list price of Ipilimumab: $23,200.00 per 200 mg/40 mL vial

* Note: Costs are calculated based on an average weight of 70 kg and body surface area of 1.7m².

Nivolumab plus ipilimumab Combination Regimen Costs per Patient:

- Nivolumab: $1,825.23 per 28-day course
- Ipilimumab: $32,480.00 per 28-day course

Nivolumab Maintenance Phase Costs per Patient:

- $8,213.35 per 28-day course

pERC RECOMMENDATION	pERC recommends reimbursement of the combination of nivolumab plus ipilimumab conditional on the feasibility of adoption being addressed (budget impact). Reimbursement should be for patients with unresectable or metastatic melanoma regardless of BRAF status who are treatment-naive, with ECOG performance status 0 - 1 and with stable brain metastases, if present. Treatment should continue until unacceptable toxicity or disease progression. pERC made this Recommendation because it was confident that there is a net clinical benefit with the combination of nivolumab plus ipilimumab in patients with previously untreated unresectable or metastatic melanoma regardless of BRAF status, based on a clinically meaningful improvement in progression-free survival (PFS), overall survival (OS) and no appreciable detrimental effect on quality of life (QoL) compared with ipilimumab monotherapy. pERC was also satisfied that there was a similar direction of effect observed with the combination therapy compared with nivolumab monotherapy for PFS. The Committee also noted the risk of significant toxicities with the use of the combination of nivolumab plus ipilimumab compared with ipilimumab monotherapy and nivolumab monotherapy. The Committee was unable to determine how the combination of nivolumab plus ipilimumab compares with pembrolizumab and with BRAF targeted therapies with regards to outcomes important to decision making such as OS, PFS and QoL. pERC concluded that the combination of nivolumab plus ipilimumab aligns with patient values in that it offers an improvement in PFS and provides patients with another effective treatment option. pERC concluded that based on the submitted economic model, nivolumab plus ipilimumab appears to be cost-effective in patients with unresectable or metastatic melanoma when compared with ipilimumab alone or nivolumab alone; however, pERC cautioned that its conclusion on cost-effectiveness may not translate into clinical practice due to the heterogeneity of the patient population and variance in clinical practice patterns with the use of the combination therapy and with the use of other available therapies. pERC also concluded that due to a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation, the cost-effectiveness of the combination of nivolumab plus ipilimumab compared to pembrolizumab and compared to BRAF targeted therapies is unknown. pERC also highlighted that the potential budget impact of the combination of nivolumab plus ipilimumab was underestimated, and that the actual budget impact would be substantially greater given that the uptake of the combination therapy may be significantly higher because treatment with subsequent ipilimumab after PD-1 immunotherapy (i.e., pembrolizumab and nivolumab) is not available in Canada. pERC had significant concerns about the capacity for jurisdictions to implement the combination therapy due to the high cost of nivolumab and ipilimumab.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Budget Impact** Given that pERC was satisfied that there is a net clinical benefit of the combination of nivolumab plus ipilimumab in patients with previously untreated unresectable or metastatic melanoma, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve affordability. **Wastage and Budget Impact Likely to 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 and ipilimumab, the potential for drug wastage, and the unknown but potentially long duration

of treatment, pERC concluded that a substantial reduction in drug price of both ipilimumab and nivolumab would be required to improve affordability.

Need for Appropriate Monitoring Due to Toxicity Concerns With the Combination of Nivolumab Plus Ipilimumab
Given the risk of significant toxicity with the combination of nivolumab plus ipilimumab, pERC noted that jurisdictions should consider developing guidelines or processes to monitor and manage toxicities in patients who receive this combination.

Collection of Real-World Evidence to Understand the Long-Term Effects of Toxicities Associated with the Combination of Nivolumab Plus Ipilimumab
Given that the long-term side effects of the toxicities associated with the combination of nivolumab plus ipilimumab are not fully understood, pERC noted that jurisdictions should consider collecting real-world evidence on the long-term side effects associated with the combination therapy.

Evidence Generation to Understand Optimal Duration of Therapy
pERC noted that nivolumab is approved and was studied at a dose of 3 mg/kg every two weeks until disease progression or unacceptable toxicity, whichever occurs first. pERC acknowledged that there is currently no evidence to identify an optimal duration of treatment with the nivolumab component of the combination therapy, and agreed that it is necessary to collect data on the optimal duration of therapy. The Committee also noted that patients receiving the combination therapy discontinued treatment earlier than patients receiving nivolumab alone, and that re-initiating treatment with nivolumab alone when treatment with the combination therapy is temporarily interrupted due to toxicity would likely occur in clinical practice, although there is a lack of data to inform this. Therefore, pERC agreed that jurisdictions should consider prospectively collecting data on re-initiating treatment with nivolumab alone following temporary discontinuation of the combination therapy in order to understand the optimal duration of therapy.

Nivolumab dosing of 3 mg/kg up to a Flat Dose of 240 mg
pERC acknowledged that a flat dose (240 mg) of nivolumab has also been approved for other indications. The Committee acknowledged that, although CheckMate-067 assessed nivolumab monotherapy at a dose of 3 mg/kg in the maintenance phase, there is no evidence to suggest that the dosing amount of 3 mg/kg is superior to 240 mg (flat dose). Therefore, pERC felt it would be reasonable that nivolumab be administered at 3 mg/kg up to a total dose of 240 mg (dose capped at 240 mg).

Optimal Sequencing of the Combination of Nivolumab Plus Ipilimumab and Other Therapies Unknown for Treatment Naïve Metastatic Melanoma Patients
pERC concluded that the optimal sequencing of therapies for patients with metastatic melanoma is unknown. pERC noted that the combination therapy may be a desired second line option following first line BRAF targeted therapy; however, the Committee acknowledged that there is no direct evidence investigating head-to-head efficacy and safety nor the appropriate treatment sequence for the combination therapy and BRAF targeted therapies for the treatment of metastatic melanoma patients who are treatment naïve. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments for treatment naïve metastatic melanoma. pERC recognizes that provinces will need to address this issue upon implementation of a reimbursement recommendation for the combination therapy, and noted that

collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.

Time-Limited Need for Patients Currently Receiving Ipilimumab Monotherapy or Nivolumab Monotherapy

At the time of implementing a reimbursement recommendation for the combination of nivolumab plus ipilimumab for patients with unresectable or metastatic melanoma, jurisdictions may consider addressing the short-term, time-limited need to offer patients currently receiving ipilimumab monotherapy or nivolumab monotherapy, without disease progression, treatment with the combination of ipilimumab and nivolumab, based on the clinical discretion of the treating physician. The Committee was unable to comment on switching patients who are currently on pembrolizumab or BRAF targeted therapy without disease progression to the combination therapy.

SUMMARY OF pERC DELIBERATIONS

In 2015, 6,500 Canadians were diagnosed with melanoma and approximately 1,050 patients died of it. Unresectable stage III or stage IV melanoma carries a poor prognosis, with a median survival of approximately six months; only 25% of patients with late-stage disease survive to one year. A wide spectrum of chemotherapeutic and immunological treatment approaches has been explored in metastatic melanoma with limited to no success until recently. Anti-programmed cell death protein 1 (anti-PD-1) checkpoint inhibitors, such as nivolumab and pembrolizumab, are now commonly used in the treatment of unresectable or metastatic melanoma. The immune checkpoint inhibitor ipilimumab has demonstrated improved outcomes when used to treat patients with unresectable or metastatic melanoma, with approximately 20% of patients experiencing prolonged disease control lasting many years. Overall, pERC considered that there is a need for more 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 QoL.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated on the results of two randomized controlled trials (RCTs), CheckMate 067 and CheckMate 069, that compared the combination of nivolumab plus ipilimumab with ipilimumab monotherapy and nivolumab monotherapy, and ipilimumab monotherapy, respectively. The Committee primarily focused the deliberations on the CheckMate 067 trial, a phase III, double-blind RCT that provided evidence on the use of the combination of nivolumab plus ipilimumab for patients with unresectable or metastatic melanoma regardless of BRAF status. pERC noted that at the time the trial was designed, ipilimumab was an appropriate comparator. pERC noted that CheckMate 067 demonstrated a clinically meaningful and statistically significant improvement in PFS in favour of the combination of nivolumab plus ipilimumab compared with ipilimumab monotherapy. Although the median overall survival (OS) was not reached in the combination group, treatment with the combination of nivolumab plus ipilimumab was associated with an increase in OS compared with ipilimumab monotherapy. pERC considered that the CheckMate 067 trial was not designed to formally assess the effect of the combination treatment group compared with the nivolumab treatment group; as such, pERC noted that the analyses between nivolumab plus ipilimumab compared with nivolumab monotherapy were considered descriptive, unplanned, and underpowered. However, the Committee discussed that, despite these limitations, a similar direction of effect with regards to PFS was also observed when the combination of nivolumab plus ipilimumab was compared with nivolumab monotherapy, and that the results were based on a relatively large sample size in each of the treatment groups. However, pERC noted that the magnitude of benefit of the combination therapy compared with nivolumab monotherapy with regards to PFS is uncertain.

The Committee discussed that both trials included patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of less than 2, and noted that PS is a well-established prognostic factor in advanced melanoma. pERC considered that the Clinical Guidance Panel (CGP) recommended that patients with an ECOG of 2 may be eligible for treatment with the combination of nivolumab plus ipilimumab. Furthermore, pERC noted the CGP's opinion that patients with stable brain metastases may be eligible for treatment with the combination of nivolumab plus ipilimumab. However, pERC noted that patients would need to be considered on a case-by-case basis (depending on each patient's prognosis), given that treatment with the combination therapy is associated with significant toxicities.

Upon reconsideration of the Initial Recommendation, pERC noted feedback from PAG expressing concern with the recommendation to use the combination of nivolumab plus ipilimumab in patients with "good performance status" which is usually interpreted to be ECOG 0 to 2. pERC discussed the fact that there are significant infusion-related reactions and significant treatment-related and immune-mediated toxicities associated with the combination therapy. pERC considered that the choice of treatment with the combination therapy will depend on several factors including the aggressiveness of the disease and the overall health status of the patient. pERC therefore concluded that because of the significant toxicities associated with the combination therapy, nivolumab plus ipilimumab should be considered only

for patients with ECOG PS 0-1 as indicated in the CheckMate-067 trial. Upon reconsideration of the Initial Recommendation, pERC noted PAG's feedback requesting guidance on extrapolating eligibility to patients with ocular melanoma and whether the results of the combination therapy could be generalized to include these patients. The Committee noted that the CGP indicated that patients with ocular melanoma were excluded from the CheckMate-067 trial, and therefore, pERC agreed with the CGP that the results of the CheckMate-067 trial cannot be extended to patients with ocular melanoma.

pERC deliberated on the toxicity profile of the combination of nivolumab plus ipilimumab and noted that there were more frequent grade 3 to 4 treatment-related adverse events (TEAEs) and serious adverse events (SAEs) compared with ipilimumab alone and nivolumab alone. The most common adverse events (AEs) reported in patients receiving the combination therapy included diarrhea, fatigue, pruritus, rash, nausea, and pyrexia. pERC noted that more patients on the combination of nivolumab plus ipilimumab had TEAEs that led to the discontinuation of therapy compared with patients receiving nivolumab alone or ipilimumab alone. The Committee also noted that patients on the combination therapy experienced more immune-mediated toxicities, including skin, gastrointestinal, hepatic, and endocrine AEs. Overall, pERC noted that there is a significant risk of toxicities with the use of the combination of nivolumab and ipilimumab. The Committee agreed with the CGP and registered clinicians that treatment should be limited to facilities that have clinicians who are experienced in administering the combination of immunotherapies, and that such centres should have the infrastructure in place to manage the associated infusion-related reactions and significant treatment-related and immune-mediated toxicities. Given that the long-term side effects of the toxicities associated with the combination of nivolumab plus ipilimumab are not fully understood, pERC noted that jurisdictions should consider prospectively collecting real-world evidence on the long-term side effects associated with the combination therapy.

pERC discussed the available patient-reported outcomes (PROs) data from the CheckMate 067 trial. pERC noted that PROs were considered exploratory outcomes. The Committee noted that although there was no clinically meaningful difference in QoL for patients in the nivolumab plus ipilimumab group compared with the monotherapy group, there was no detriment in QoL among patients receiving the combination therapy compared with ipilimumab monotherapy and nivolumab monotherapy. The Committee discussed that, while no difference in QoL was observed between the treatment groups, the increased toxicity associated with the combination of nivolumab plus ipilimumab may have offset the clinical efficacy and any improvement in QoL that may have been observed. Overall, pERC considered that, despite the significant side effects and toxicities associated with treatment with the combination therapy, there was no appreciable detrimental effect in QoL or other PROs.

pERC considered the comparison of the combination therapy with ipilimumab monotherapy and nivolumab monotherapy in the CheckMate-067 trial to be reasonable in the setting of previously untreated patients with metastatic melanoma, but also considered the results of an indirect treatment comparison (ITC) provided by the submitter that compared the combination therapy with other relevant comparators including pembrolizumab monotherapy and BRAF-targeted agents. pERC expressed several concerns with the submitted ITC, and concluded that limited conclusions could be drawn because of the substantial heterogeneity in patient characteristics among the included studies in the ITC. Furthermore, pERC noted that the CGP and Methods team identified differences in treatment effect modifiers across the different treatment comparisons in the network including imbalances in the distribution of BRAF mutation-carrier status, brain metastasis, ECOG status, PD-L1 status, and line of therapy. pERC noted that the CGP and Methods teams concluded that, given these limitations and the uncertainty in the presented data, the comparative efficacy of nivolumab plus ipilimumab and pembrolizumab is uncertain. Additionally, pERC noted that the submitter was unable to compare the relative efficacy of the combination of nivolumab plus ipilimumab and BRAF targeted therapies. Therefore, the effect of nivolumab plus ipilimumab compared with other targeted agents in BRAF mutation-positive carriers is unknown.

Upon reconsideration of the Initial Recommendation, pERC noted feedback from PAG that the combination of nivolumab plus ipilimumab was not compared against pembrolizumab, which PAG considered to be the most relevant comparator in jurisdictions throughout Canada for the first line treatment of patients with metastatic melanoma. Furthermore, it has been recommended for patients regardless of BRAF mutation status and has a more favourable administration schedule than nivolumab. pERC noted that various therapeutic options are available in Canada for the first-line treatment of patients with unresectable or metastatic melanoma including nivolumab monotherapy and ipilimumab monotherapy. pERC acknowledged that pembrolizumab is available in the first line setting regardless of BRAF mutation status, as an option for patients who are treatment naïve, and that a comparison between the combination therapy and pembrolizumab would be of value. However, pERC noted that there were no

trials comparing the combination of nivolumab plus ipilimumab to pembrolizumab in treatment naive patients with metastatic melanoma identified by the pCODR systematic review. pERC noted that the Submitter provided an indirect treatment comparison (ITC) that sought to compare the clinical effectiveness of the combination of nivolumab plus ipilimumab compared to pembrolizumab. However, due to limitations and concerns with the ITC, pERC re-iterated that no conclusions could be drawn regarding the relative efficacy of the combination therapy compared with pembrolizumab.

Overall, pERC concluded that there is a net clinical benefit of the combination of nivolumab plus ipilimumab compared with ipilimumab monotherapy, based on the clinically meaningful results in PFS and OS, no observed detriment in QoL, and the need for more effective treatment options. In making this conclusion, the Committee acknowledged that there was a trend favouring the combination of nivolumab plus ipilimumab over nivolumab monotherapy with respect to PFS outcomes; therefore, it concluded that the combination therapy may be more effective compared with treatment with nivolumab alone. However, the Committee acknowledged that, although the descriptive analysis of OS favoured the combination therapy compared with nivolumab alone, the trial was not designed to compare these groups. The Committee noted that there was uncertainty in the magnitude of benefit of the combination therapy compared with nivolumab with regards to outcomes important to decision-making, such as PFS, OS, and QoL, due to limitations in the available clinical trial data. Upon reconsideration, the Committee reaffirmed that it was unable to determine how the combination of nivolumab plus ipilimumab compares with pembrolizumab and with BRAF targeted therapies with regards to outcomes important to decision making such as OS, PFS and QoL.

pERC acknowledged input from registered clinicians regarding the value of the combination therapy with regards to improvement in response rate and PFS compared with ipilimumab monotherapy or nivolumab monotherapy. The clinicians providing input felt that that the combination of nivolumab plus ipilimumab is more toxic, with a greater proportion of patients experiencing grade 3 or grade 4 AEs and more than 35% of patients discontinuing therapy due to toxicity. Although registered clinicians considered that the combination of nivolumab plus ipilimumab may be superior to the current treatment regimen, they also cautioned that PFS has not been shown to be a reliable marker for the superiority of ipilimumab-based regimens, suggesting that until the pending OS data are presented, true OS benefit is uncertain. pERC noted that, although the median OS for the combination of nivolumab plus ipilimumab was not reached in the CheckMate 067 trial, treatment with the combination of nivolumab plus ipilimumab was associated with an increase in OS compared with ipilimumab monotherapy. Furthermore, registered clinicians noted that the combination is equally efficacious in both BRAF wild-type and BRAF-mutated disease. pERC agreed that based on the results from the CheckMate 067 trial, the combination therapy appears to be effective in all patients with metastatic melanoma, regardless of BRAF status.

pERC deliberated on input from two patient advocacy groups. Patient input indicated that patients value effective treatment options that improve QoL, manage pain and symptoms, provide durable responses, increase PFS, and prolong survival. Patients indicated that the benefits of treatment outweighed the risk of side effects; most patient respondents did not complete the full course of treatment, but still received benefit. pERC agreed that the results from the CheckMate 067 trial did not demonstrate an improvement in PROs, including QoL, but noted that the combination of nivolumab plus ipilimumab showed no detriment in QoL, which pERC appreciated, considering the high rates of toxicities associated with the combination therapy. Overall, pERC concluded that the therapeutic intent of the combination of nivolumab plus ipilimumab to delay progression aligns with patient values. However, the Committee was limited by the OS data from the CheckMate 067 trial and was unable to confidently conclude that the combination of nivolumab plus ipilimumab prolongs survival compared with nivolumab alone.

pERC noted that the Committee deferred making a recommendation during the first deliberations on the submission of the combination of nivolumab plus ipilimumab for the first-line treatment of patients with metastatic melanoma because a clinically relevant comparison with nivolumab monotherapy was not provided by the submitter. pERC noted that the pCODR review team had requested this comparison from the submitter during the review, but it was not provided at the time. Following the deferral of the pERC Recommendation, the submitter provided an updated economic analysis comparing the combination of nivolumab plus ipilimumab with nivolumab monotherapy.

pERC deliberated on the cost-effectiveness of nivolumab plus ipilimumab compared with ipilimumab monotherapy and nivolumab monotherapy. The Committee concluded that, at the submitted price and based on the submitted economic analysis, the combination of nivolumab plus ipilimumab appears cost-effective compared to ipilimumab monotherapy and compared to nivolumab monotherapy. pERC reached

this conclusion noting the uncertainty regarding the incremental cost-effectiveness ratio (ICER) due to the uncertainty in the clinical effectiveness of the combination of nivolumab plus ipilimumab because of the short-term survival data from the CheckMate-067 trial. In addition, there was uncertainty in the magnitude of benefit of the combination therapy compared with nivolumab monotherapy because the trial was not designed to make that comparison. Furthermore, pERC discussed the fact that the cost of the combination therapy was being compared with drugs with high costs (i.e., nivolumab monotherapy and ipilimumab monotherapy). pERC also noted that the manufacturer provided ICERs for the combination of nivolumab plus ipilimumab compared with relevant comparators, including pembrolizumab and other BRAF targeted agents, such as dabrafenib/trametinib and vemurafenib. However, due to significant concerns about the lack of robust indirect comparative effectiveness data for the combination therapy and pembrolizumab, and BRAF targeted therapies obtained from the submitted ITC, pERC noted that the Economic Guidance Panel (EGP) could not provide reliable reanalysis estimates for the comparisons against these relevant comparators.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from PAG that the combination was not compared against pembrolizumab, the standard of care therapy in most Canadian jurisdictions. Furthermore, pERC also considered feedback from PAG that the combination was not compared against BRAF/MEK targeted agents. pERC noted that there is considerable uncertainty in the clinical effect estimates of nivolumab plus ipilimumab compared with pembrolizumab, due to limitations in the submitter's ITC and in the absence of a direct comparison in an RCT. pERC also noted the absence of direct RCT and indirect evidence comparing the combination of nivolumab plus ipilimumab and BRAF targeted therapies. Therefore, the Committee reaffirmed that due to a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation, the cost-effectiveness of the combination of nivolumab plus ipilimumab compared to pembrolizumab and compared to BRAF targeted therapies is unknown.

pERC accepted the EGP's reanalysis estimates for the comparison of the combination therapy and ipilimumab monotherapy and nivolumab monotherapy, noting several limitations in the submitter's base-case analysis. pERC noted that assumptions around time horizon, choice of utility estimates (CheckMate 067 trial data versus Canadian estimates), and patient weight, and the inclusion of subsequent therapies following progression, had a significant impact on the cost-effectiveness estimates. Furthermore, the Committee noted that the median OS was not yet reached in the CheckMate 067 trial, which created a high degree of uncertainty in the OS estimates for the combination of nivolumab plus ipilimumab. The Committee noted that the frequency of grade 3 and 4 AEs may occur in higher frequency in clinical practice than reported in the trial. Additionally, the Committee discussed the fact that more resources, including emergency room visits and hospitalizations, may be required to monitor and treat toxicities while on the combination therapy; therefore, the costs of monitoring and managing such toxicities are likely underestimated in the pharmacoeconomic model and would be substantially higher. Furthermore, due to the high cost of nivolumab and the unknown but potentially long duration of treatment, pERC agreed that a substantial reduction in the drug price of both nivolumab and ipilimumab would be required. The Committee also discussed the fact that patients receiving the combination therapy discontinued nivolumab treatment earlier than patients receiving nivolumab alone, and that re-initiating with nivolumab alone when the combination treatment is temporarily interrupted due to toxicity would likely occur in clinical practice. However, pERC noted that re-initiating treatment with nivolumab alone following discontinuation of the combination therapy due to drug toxicity was not explored in the submitted pharmacoeconomic model. Therefore, pERC noted that the impact of re-initiating treatment with nivolumab alone is unknown, and may likely have a significant impact on the cost-effectiveness of the combination therapy. Overall, pERC accepted the EGP's reanalysis estimates and concluded that, based on the CheckMate 067 trial data and the submitter's pharmacoeconomic model, the combination of nivolumab plus ipilimumab appears to be cost-effective. However, the Committee cautioned that their conclusion on cost-effectiveness may not translate into real-world clinical practice due to the heterogeneity of the patient population and the variance in clinical practice patterns with the use of the combination therapy and with the use of other available therapies.

pERC considered the feasibility of implementing a reimbursement recommendation for the combination of nivolumab plus ipilimumab for first-line metastatic melanoma. pERC acknowledged that registered clinicians indicated that the number of eligible patients in this setting would be small. However, pERC considered that the combination of nivolumab plus ipilimumab as a first-line treatment option will likely have a significant impact on provincial budgets. Furthermore, pERC discussed the fact that as more clinicians become comfortable with treating AEs associated with the combination therapy, more patients may be treated with the combination of nivolumab plus ipilimumab in the first-line setting. Therefore,

the population of patients eligible for the combination therapy may be substantially greater than estimated in the submitter's budget-impact analysis (BIA). Upon reconsideration of the Initial Recommendation, pERC noted PAG's feedback that the actual budget impact would be substantially greater given that the uptake of the combination therapy may be significantly higher because treatment with subsequent ipilimumab after PD-1 immunotherapy is not available in Canada. While there is no evidence to inform sequencing, pERC agreed that the uptake of the combination therapy may be significantly higher than estimated in the submitted BIA. Furthermore, pERC noted that the potential for drug wastage, given the weight-based dosing, together with the high costs of nivolumab and ipilimumab, would have a significant effect on the budget impact and, therefore, on the affordability of the combination therapy. Given the potentially substantial budget impact of the combination of nivolumab plus ipilimumab, the provinces should consider taking steps to limit the budget impact. pERC noted that the submitted BIA was sensitive to market share, treatment duration, and the number of cases of advanced melanoma. The Committee also discussed that re-initiating treatment with nivolumab alone following temporary discontinuation of the combination therapy due to drug toxicity was not explored in the submitted BIA model. Therefore, pERC noted that the impact of re-initiating treatment with nivolumab alone is unknown and will likely impact the budget impact substantially. The Committee agreed that jurisdictions will need to consider the uncertainty in these factors upon implementation, and agreed that the BIA is substantially underestimated.

The Committee noted input from the pCODR Provincial Advisory Group (PAG), which requested information and clarification on sequencing. pERC acknowledged that registered clinicians providing input indicated that the combination of nivolumab plus ipilimumab can be given as first-line immunotherapy or second-line post–BRAF-targeted therapy for patients with the BRAF v600 mutation. Upon reconsideration of the Initial Recommendation, pERC discussed registered clinician feedback indicating that they disagree with the recommendation to limit reimbursement to treatment naïve patients, as the clinicians strongly support the use of nivolumab plus ipilimumab either as a first line immunotherapy or second line post-BRAF targeted therapy. The latter choice would also be consistent with Ontario's reimbursement for single agent immunotherapies. Furthermore, a patient group, Melanoma Network of Canada, provided feedback on pERC's Initial Recommendation that the combination therapy should be considered as first line treatment and as second-line treatment for patients who have failed targeted therapies. pERC noted that the combination therapy may be a favourable second line option following first line BRAF targeted therapy; however, the Committee acknowledged that there is no direct evidence investigating head-to-head efficacy and safety or the appropriate treatment sequence for the combination therapy compared with BRAF targeted therapies for the treatment of metastatic melanoma patients who are treatment naïve. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments for treatment naïve metastatic melanoma patients.

pERC discussed that there may be a time-limited need for adding nivolumab in combination with ipilimumab for patients who are currently receiving ipilimumab monotherapy. Furthermore, pERC noted uncertainty in the use of the combination therapy in the following clinical situations for patients without disease progression: in patients who have recently finished ipilimumab monotherapy; in patients who are currently on nivolumab monotherapy; and in patients who are currently on pembrolizumab. pERC agreed that the optimal sequencing of therapies for patients with metastatic melanoma is unknown due to a lack of evidence. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing. pERC noted that provinces will need to address optimal sequencing upon implementation of reimbursement, and noted that a national collaboration by the provinces to help guide consistency in drug reimbursement will be necessary.

Upon reconsideration of the Initial Recommendation, pERC discussed PAG's feedback requesting guidance on a number of clinical scenarios to assist with implementation. PAG requested guidance on whether it would be clinically reasonable to use pembrolizumab after induction with the combination of nivolumab plus ipilimumab instead of nivolumab, since pembrolizumab is given every 3 weeks, a more favourable administration schedule, and is used regardless of BRAF status. pERC re-iterated that there is no documented evidence to support the use pembrolizumab as maintenance therapy after the induction of the combination of nivolumab plus ipilimumab. pERC agreed that maintenance therapy should be administered as per the CheckMate-067 trial, with nivolumab monotherapy until unacceptable toxicity or disease progression. PAG also requested clarification on re-starting treatment with nivolumab monotherapy in the clinical scenarios of toxicity resolution with no disease progression, or after disease progression during a treatment break. The Committee noted that if discontinuation of the combination therapy was due to side effects from ipilimumab and not nivolumab, the re-initiation of nivolumab monotherapy would be reasonable. However, pERC noted that if there is disease progression on nivolumab

during a treatment break, nivolumab monotherapy should not be re-started. pERC also discussed feedback from PAG requesting guidance on whether re-initiation of the combination therapy could be considered and in which clinical settings. The Committee noted that the combination of nivolumab plus ipilimumab should be administered as per the CheckMate-067 trial. pERC noted that there is no evidence to support the re-induction of the combination therapy following progression on nivolumab monotherapy.

Furthermore, the Committee noted PAG's feedback requesting guidance on whether patients previously treated with ipilimumab could be treated with nivolumab plus ipilimumab upon disease progression. pERC noted that there is no data to support the use of the combination of nivolumab plus ipilimumab in patients previously treated with ipilimumab. PAG also requested guidance on the potential time-limited need for the combination therapy in patients who have not progressed on pembrolizumab monotherapy or alternatively, those patients who are currently receiving BRAF targeted therapy without progression. The Committee was unable to comment on switching patients who are currently on pembrolizumab or BRAF targeted therapy without disease progression to the combination therapy. Finally, pERC noted feedback from PAG requesting clarity on treatment with ipilimumab upon disease progression on nivolumab or pembrolizumab. The Committee noted that there is currently no evidence to support the addition of ipilimumab upon disease progression on nivolumab or pembrolizumab.

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 pCODR clinical and economic review panels
- Input from two patient advocacy groups: Melanoma Network of Canada (MNC) and 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:

- two patient advocacy groups: MNC and SYSF
- one clinician group
- the PAG
- the submitter: Bristol-Myers Squibb Canada

The pERC Initial Recommendation was to recommend reimbursement of the combination of nivolumab plus ipilimumab for metastatic melanoma. Feedback on the pERC Initial Recommendation indicated that the manufacturer, and patient advocacy groups, agreed with the Initial Recommendation, while registered clinicians agreed in part with the Initial Recommendation and PAG disagreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of nivolumab in combination with ipilimumab for treatment-naive adult patients with advanced (unresectable or metastatic) melanoma. The submitter, Bristol-Myers Squibb Canada, has requested reimbursement of nivolumab in combination with ipilimumab for treatment-naive adult patients with advanced (unresectable or metastatic) melanoma, regardless of BRAF status.

Studies included: Two randomized controlled trials

The pCODR systematic review included two randomized controlled trials (RCTs):

- CheckMate 067, a phase III RCT that randomized patients 1:1:1 with previously untreated unresectable stage III or IV melanoma, regardless of BRAF status, to one of the following:
  - 1 mg/kg dose of nivolumab plus a 3 mg/kg dose of ipilimumab every three weeks for four doses followed by a 3 mg/kg dose of nivolumab every two weeks (n = 314)
  - placebo-matched nivolumab plus a 3 mg/kg dose of ipilimumab every three weeks for four doses followed by the placebo-matched nivolumab every two weeks (n = 315)
  - 3 mg/kg nivolumab once every two weeks plus placebo matched ipilimumab every three weeks for four doses, followed by a 3 mg/kg of nivolumab every two weeks (n = 316)
- CheckMate 069, a phase II RCT that randomized patients 2:1 with previously untreated unresectable stage III or IV melanoma, regardless of BRAF status, to one of the following:
  - 1 mg/kg dose of nivolumab plus a 3 mg/kg dose of ipilimumab every three weeks for four doses followed by a 3 mg/kg dose of nivolumab every two weeks (n = 95)
  - 1 mg/kg of nivolumab-placebo followed by 3 mg/kg of ipilimumab every three weeks for four doses and then 3 mg/kg of nivolumab placebo every two weeks (n = 47)

In the two trials, patients received treatment until Response Evaluation Criteria in Solid Tumors (RECIST)-defined disease progression, unacceptable toxicity, or withdrawal of consent. Treatment beyond RECIST-defined disease progression was permitted for patients who had clinical benefits (as assessed by the investigator) and did not have a substantial burden of adverse events (AEs).

pERC noted that CheckMate 067 was only designed to assess the effect of: 1) nivolumab versus ipilimumab; or 2) nivolumab plus ipilimumab versus ipilimumab on the effect of progression-free survival

(PFS) and overall survival (OS). The manufacturer claimed that adding a third statistical comparison would have increased the risk of multiplicity and required a larger sample size. As well, at the time of trial design, ipilimumab was considered the standard of care for all patients with melanoma.

Patient populations: Previously untreated unresectable stage III or IV melanoma, regardless of BRAF status

Baseline characteristics were generally well balanced between the treatment arms in both trials.In CheckMate 067, the median age of patients was 61 years. Approximately 65% of patients were male. The trial included patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 (73% versus 71%) or 1 (26% versus 28%). Approximately 32% of patients were BRAF V600 mutation-positive. Patients could not have received prior therapy with an immune checkpoint inhibitor (e.g., anti-programmed cell death protein 1 [anti-PD-1], anti-cytotoxic-T-lymphocyte-associated antigen 4 [anti-CTLA-4], etc.). Patients with active brain metastases and ocular melanoma were also excluded.

In CheckMate 069, the median age of patients ranged from 64 years to 67 years. Approximately 66% of patients were male. The trial included patients with ECOG PS 0 (83% versus 79%) or 1 (15% versus 21%). Fewer than 25% 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.

Upon reconsideration of the Initial Recommendation, pERC noted feedback from PAG expressing concern with the recommendation to use the combination of nivolumab plus ipilimumab in patients with "good performance status" which is usually interpreted to be ECOG 0 to 2. pERC discussed the fact that that there are significant infusion-related reactions and significant treatment-related and immune-mediated toxicities associated with the combination therapy. pERC considered that the choice of treatment with the combination therapy will depend on several factors including the aggressiveness of the disease and overall health status of the patient. pERC therefore concluded that because of the significant toxicities associated with the combination therapy, nivolumab plus ipilimumab should be considered only for patients with EGOC PS 0-1 as indicated in the CheckMate-067 trial. Upon reconsideration of the Initial Recommendation, pERC noted PAG's feedback requesting guidance on extrapolating eligibility to patients with ocular melanoma and whether the results of the combination therapy could be generalized to include these patients. The Committee noted that the CGP indicated that patients with ocular melanoma were excluded from the CheckMate-067 trial, and therefore, pERC agreed with the CGP that the results of the CheckMate-067 trial cannot be extended to patients with ocular melanoma.

Key efficacy results: Clinically meaningful improvements in progression-free survival for previously untreated patients

pERC noted that the CheckMate 067 trial demonstrated a statistically significant and clinically meaningful improvement in PFS in favour of the combination of nivolumab plus ipilimumab compared with ipilimumab alone. At the database lock on February 17, 2015, median PFS was 6.9 months (95% confidence interval [CI], 4.3 to 9.5) for patients treated with nivolumab; 11.5 months (95% CI, 8.9 to 16.7) for patients treated with nivolumab plus ipilimumab; and 2.9 months (95% CI, 2.8 to 3.4) for patients treated with ipilimumab. Treatment with nivolumab plus ipilimumab was associated with a prolonged PFS compared with ipilimumab in patients with advanced melanoma (hazard ratio [HR] 0.42; 99.5% CI, 0.31 to 0.57; $P < 0.001$). pERC noted that a similar effect was also observed when nivolumab plus ipilimumab was compared with nivolumab for PFS (HR 0.74; 95% CI, 0.60 to 0.92); however, this analysis was descriptive and the results should be interpreted with caution.

pERC noted that subgroup analyses demonstrated a consistent effect of nivolumab plus ipilimumab as compared with ipilimumab on the effect of PFS among BRAF mutation-positive carriers (HR 0.47; 95% CI, 0.32 to 0.68) and wild-type-carriers (HR 0.41; 95% CI, 0.32 to 0.53); but the median PFS for both BRAF mutation-positive and wild-type carriers had not been reached in the nivolumab plus ipilimumab group.

The effect estimates for OS were obtained from the later September 13, 2016 database lock, which represents 28 months of follow-up for all patients. At the September 13, 2016 database lock, 44.9% (N = 142) of patients on nivolumab, 40.8% (N = 128) of patients on combination therapy, and 62.5% (N = 197) of patients on ipilimumab had died. The median time to OS was 20.0 months (95% CI, 17.1 to 24.6) in the ipilimumab group; it had not been reached for the nivolumab or in the nivolumab plus ipilimumab groups. Treatment with the combination of nivolumab plus ipilimumab was associated with longer survival compared with the ipilimumab group (HR 0.55; 98% CI, 0.42 to 0.72; $P < 0.0001$). In

contrast, there was no statistical difference between nivolumab plus ipilimumab and nivolumab on OS (HR: 0.88, 95% CI, 0.69 to 1.12). pERC considered that the Methods team and CGP noted that these results should be interpreted with caution, since the comparisons between nivolumab and the combination of nivolumab plus ipilimumab were considered descriptive only and the median OS time had not been reached for one of the treatment groups. However, pERC noted that the direction of effect favoured the combination therapy.

Overall response rate (ORR) was a key secondary end point in the CheckMate 067 trial. At the February 17, 2015 database lock, patients in the nivolumab plus ipilimumab group were more likely to demonstrate an ORR compared with those in the ipilimumab group (57.6% [95% CI, 52.0 to 63.2] versus 19.0% [95% CI, 14.9 to 23.8]). The ORR in the nivolumab-alone treatment group was 43.7% (95% CI, 38.1 to 49.3).

The primary end point in CheckMate 069 was ORR in BRAF wild-type carriers. ORR was assessed at the January 30, 2015 database lock. BRAF wild-type carriers treated with nivolumab plus ipilimumab experienced a higher ORR compared with those treated with ipilimumab alone (61% [95% CI, 49 to 72] versus 11% [95% CI, 3 to 25]). Comparable observations were reported for all randomized patients (both BRAF wild-type and mutant carriers), where there was a higher ORR in patients in the nivolumab plus ipilimumab group (59%; 95% CI, 48 to 69) as compared with the ipilimumab alone group (11%; 95% CI, 3 to 23). Descriptive analyses demonstrated that BRAF mutation-positive carriers treated with nivolumab plus ipilimumab had a higher ORR (52%; 95% CI, 31 to 73) compared with those treated with ipilimumab alone (10%; 95% CI, 0 to 45).

PFS was a key secondary outcome in the CheckMate 069 trial. The PFS effect estimates were obtained from the February 29, 2016 database lock date, which represents two years of follow-up. At this time point, 43.1% of the BRAF wild-type carriers treated with the nivolumab plus ipilimumab and 75.7% of patients treated with ipilimumab had disease progression or died. Median PFS had not been reached for those treated with nivolumab plus ipilimumab compared with 4.4 months (95% CI, 2.8 to 5.3) in the ipilimumab group. Although the median PFS survival had not been met in the nivolumab plus ipilimumab group, a prolonged PFS compared with ipilimumab among BRAF wild-type carriers was demonstrated (HR 0.35; 95% CI, 0.21 to 0.59; $P < 0.001$). Similar findings were reported for PFS in all randomized patients. The submitter claimed that there was a consistent protective effect of the combination of nivolumab plus ipilimumab as compared with ipilimumab on PFS (HR 0.36, 95% CI, 0.22 to 0.56; $P < 0.0001$); yet the median PFS had not been reached in the nivolumab plus ipilimumab group. The submitter also performed a subgroup analysis of PFS in all randomized patients, which showed that there were no significant differences across subgroups (interaction $P \geq 0.05$ for all).

OS was reported as an exploratory outcome. At the February 29, 2016 database lock, the median OS for BRAF wild-type carriers had not been reached for either treatment group. pERC noted that there were no statistical differences between nivolumab plus ipilimumab and ipilimumab on OS ($P = 0.262$). Similar patterns were reported for all randomized patients. Although this estimate was immature, it is most likely confounded because patients who progressed could start a subsequent anti-cancer therapy or those randomized to ipilimumab could cross over and received nivolumab.

Quality of life: No clinically meaningful difference in health-related quality of life between patients in the nivolumab plus ipilimumab, nivolumab and ipilimumab treatment groups

Patient-reported quality of life (QoL) was evaluated in both trials and measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) and the EuroQoL five-dimension questionnaire (EQ-5D).

In CheckMate 067, the completion rates at baseline for on-treatment patients were 89.9% for the nivolumab group, 92.4% for the nivolumab plus ipilimumab group, and 88.6% for the ipilimumab group. These remained stable throughout the trial. Overall, there was no clinically meaningful difference in QoL for patients in the nivolumab, nivolumab plus ipilimumab and ipilimumab treatment groups using a minimal important difference of ≥ 10 points. Similarly, there were no clinically meaningful differences using the EQ-5D instrument. In CheckMate 069, the completion rates at baseline were 65.3% in the nivolumab plus ipilimumab arm and 78.7% in the ipilimumab arm. There was a reduction in the completion rate at week 13 for patients randomized to the nivolumab plus ipilimumab arm compared with the ipilimumab arm (48.4% versus 75%). The submitter claimed that this change most likely coincides with patients switching from nivolumab plus ipilimumab to the nivolumab maintenance phase. Health-related quality of life worsened at week 7, but improved and remained stable over time after week 13 for both the nivolumab plus ipilimumab and ipilimumab treatment arms.

Safety: Significant toxicity experienced by the majority of patients

pERC noted there were more treatment-related adverse events (TEAEs) in the nivolumab plus ipilimumab group (95.8%) compared with the nivolumab group (86.3%) and the ipilimumab group (86.2%). At the database cut-off of September 13, 2016, more grade 3 to grade 4 TEAEs were reported in the nivolumab plus ipilimumab group (58.5%) than in the ipilimumab (27.7%) or the nivolumab (20.8%) groups. Similar patterns were reported for grade 3 to grade 4 treatment-related serious adverse events (SAEs) (nivolumab plus ipilimumab: 36.7%; ipilimumab: 16.7%; nivolumab: 8.0%). Similarly, a higher proportion of select AEs occurred in the nivolumab plus ipilimumab group compared with the ipilimumab and nivolumab groups, including skin (nivolumab plus ipilimumab: 61.3%; ipilimumab: 55.3%; nivolumab: 45.7%), gastrointestinal AEs (nivolumab plus ipilimumab: 47.9%; ipilimumab: 37.6%; nivolumab: 22.4%), hepatic AEs (nivolumab plus ipilimumab: 32.6%; ipilimumab: 7.4%; nivolumab: 7.7%), and endocrine (nivolumab plus ipilimumab: 33.2%; ipilimumab: 11.6%; nivolumab: 17.3%). These trends were also observed for grade 3 and grade 4 events of special interest.

At the time of the database lock, there was a higher proportion of patients on ipilimumab who had died (62.7%) compared with those on nivolumab plus ipilimumab (40.6%). The primary reason for death in both groups was disease progression (ipilimumab: 58.2%; nivolumab: 39.3%; nivolumab plus ipilimumab: 34.8%). Furthermore, patients were more likely to die within 100 days of their last dose (ipilimumab: 19.0%; nivolumab: 16.6%; nivolumab plus ipilimumab: 14.7%) than within 30 days of their last dose (ipilimumab: 6.4%; nivolumab: 4.5%; nivolumab plus ipilimumab: 6.7%). One death (0.3%) related to drug toxicity occurred in the nivolumab group, while two deaths (0.6%) occurred in the nivolumab plus ipilimumab group and one death (0.3%) occurred in the ipilimumab arm.

Toxicity profiles in CheckMate 069 were similar to those observed in CheckMate 067, as almost all patients experienced an AE. In particular, patients in the combination treatment group were more likely to experience a grade 3 to grade 4 AE (69.0% versus 44%), a grade 3 to grade 4 TEAE (54.0% versus 20.0%), a grade 3 to grade 4 treatment-related SAE (36.0% versus 9.0%), and treatment-related death (3.0% versus 0%) compared with those receiving ipilimumab alone. A higher proportion of select AEs of interest occurred in the nivolumab plus ipilimumab group versus the ipilimumab group, including skin AEs (73.4% versus 63.0%), gastrointestinal AEs (48.9% versus 34.8%), hepatic AEs (31.9% versus 8.7%) and endocrinal AEs (30.9% versus 15.2%). This trend was consistent for grade 3 and grade 4 events of special interest.

At the time of the database lock, 37% of patients in the nivolumab plus ipilimumab arm and 48% in the ipilimumab arm had died. The submitter stated that three deaths in the combination group were treatment-related; no deaths occurred in the ipilimumab group.

Limitations: No direct comparison comparing nivolumab plus ipilimumab with pembrolizumab

The pCODR-conducted literature search identified only two RCTs that assessed the efficacy of nivolumab plus ipilimumab versus ipilimumab in patients with advanced melanoma. Thus, there is a lack of direct evidence comparing nivolumab plus ipilimumab with other PD-L1 inhibitors (i.e., pembrolizumab) or to other targeted therapies (i.e., dabrafenib with trametinib and/or vemurafenib). Given the absence of head-to-head trials, the submitter conducted an indirect treatment comparison (ITC) that compared nivolumab plus ipilimumab with pembrolizumab 2 mg every three weeks in patients with advanced melanoma. The submitter also sought to compare nivolumab plus ipilimumab with other targeted therapies in BRAF mutation-positive carriers, but were unable to do so. As a result, the Methods team conducted a critical appraisal of the submitted ITC that provided evidence for the efficacy of nivolumab plus ipilimumab versus active therapies in treatment-naive adult patients with advanced melanoma.

pERC discussed the results of the submitted ITC. The results of the ITC indicated that treatment with nivolumab plus ipilimumab was associated with a statistically significant protective effect on PFS (HR 0.64; 95% CI, 0.44 to 0.93) compared with 2 mg pembrolizumab every three weeks. However, the results for OS were not statistically significant (HR 0.78; 95% CI, 0.51 to 1.19). Furthermore, the manufacturer was unable to assess the effect of nivolumab plus ipilimumab versus other relevant targeted therapies, such as dabrafenib plus trametinib and vemurafenib, because the proportional hazard assumptions were violated. The overall conclusions of the ITC were limited because of substantial heterogeneity in patient characteristics among the included studies (CheckMate 067, KEYNOTE-002, and KEYNOTE-006). The CGP and Methods team identified systemic differences in treatment effect modifiers across the different treatment comparisons in the network. This included imbalances in the distribution of the following effect modifiers across the studies: BRAF mutation-carrier status, brain metastasis, ECOG status, PD-L1 status, and line of therapy. Given these limitations, pERC noted that the CGP and Methods team

concluded that the comparative efficacy of nivolumab plus ipilimumab and pembrolizumab is uncertain. Additionally, pERC noted that the submitter was unable to compare the relative efficacy of the combination of nivolumab plus ipilimumab and BRAF targeted therapies. Therefore, the effect of nivolumab plus ipilimumab compared with other targeted agents in BRAF mutation-positive carriers is unknown.

Upon reconsideration of the Initial Recommendation, pERC noted feedback from PAG that the combination of nivolumab plus ipilimumab was not compared against pembrolizumab, which PAG considered to be the most relevant comparator in jurisdictions throughout Canada for the first line treatment of patients with metastatic melanoma, as it has been recommended for patients regardless of BRAF mutation status and has a more favourable administration schedule than nivolumab. pERC noted that, various therapeutic options are available in Canada for the first-line treatment of patients with unresectable or metastatic melanoma including nivolumab monotherapy and ipilimumab monotherapy. pERC acknowledged that pembrolizumab is available in the first line setting regardless of BRAF mutation status, as an option for patients who are treatment naïve, and that a comparison between the combination therapy and pembrolizumab would be of value. However, pERC noted that there were no trials comparing the combination of nivolumab plus ipilimumab to pembrolizumab in treatment naive patients with metastatic melanoma identified by the pCODR systematic review. pERC noted that the Submitter provided an ITC that sought to compare the clinical effectiveness of the combination of nivolumab plus ipilimumab compared to pembrolizumab. However, due to limitations and concerns with the ITC, pERC re-iterated that no conclusions could be drawn regarding the relative efficacy of the combination therapy compared with pembrolizumab.

Registered clinician input: The combination of nivolumab plus ipilimumab showed an improvement in response rate and progression-free survival compared with ipilimumab monotherapy or nivolumab monotherapy

pERC considered input from registered clinicians that noted that the combination of nivolumab plus ipilimumab showed an improvement in response rate and PFS compared with ipilimumab monotherapy or nivolumab monotherapy. They noted that there is currently no biomarker or criteria available for patient selection. Registered clinicians noted that some clinical data suggest more durable long-term responses with the combination of ipilimumab and nivolumab compared with single-agent anti-PD1 and targeted therapies. However, the clinicians providing input noted that the combination is more toxic, with a higher proportion of patients experiencing grade 3 or grade 4 AEs and more than 35% of patients discontinuing therapy due to toxicity. Although the registered clinicians feel that the combination of nivolumab plus ipilimumab may be superior to the current treatment regimen, they also cautioned that PFS has not been shown to be a reliable marker for the superiority of ipilimumab-based regimens, suggesting that until the pending OS data are presented, the true OS benefit remains uncertain. In terms of sequencing, clinicians providing input indicated that the combination of nivolumab plus ipilimumab can be given as first-line immunotherapy or second-line post–BRAF-targeted therapy. Furthermore, they indicated that the combination is equally efficacious in both BRAF wild-type and BRAF-mutated disease. pERC noted that although Health Canada indicates that PD-L1 status may impact response rate, the registered clinicians noted that data on PD-L1 testing is not consistent and should not be used for patient selection at this time. Finally, the clinicians providing input indicated that treating facilities administering the combination of immunotherapies should have the infrastructure in place to manage the significant treatment-related toxicities.

Need: More effective treatment options required that improve survival and offer more favourable toxicity profiles

In Canada, 6,800 new cases of primary melanoma were reported in 2015. The incidence of melanoma has been steadily increasing over the past several decades, with increases of 2.3% per year among men between 2001 and 2010 and 2.9% per year among women between 2001 and 2010. Although only 5% of patients present with metastatic disease, the majority of those who die from melanoma will have developed recurrent and/or distant disease. Approximately one-third of patients with early-stage melanoma will develop metastasis, whereas half of patients with nodal disease will experience a recurrence and likely die from the development of metastatic disease. Brain metastases are relatively common in advanced melanoma, and occur in up to 75% of patients with overt metastatic disease. They often prove to be relatively refractory to radiotherapy and systemic treatment, and are associated with a dismal prognosis. pERC noted that patients with metastatic melanoma are often younger than those affected by other types of cancer, and that while this cancer may affect a small patient population, incidence is increasing and it cannot be considered a rare disease.

A wide spectrum of chemotherapeutic and immunological treatments approaches has been explored in metastatic melanoma with limited to no success until recently. Patient outcomes have not changed significantly over the past three decades. 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; patients typically have short survival durations. AEs with ipilimumab are also significant and potentially life-threatening, with approximately 15% of patients experiencing grade 3 or grade 4 immune-mediated side effects that require management and monitoring, including risks for severe and fatal events (in particular, colitis). Overall, pERC considered that there is a need for new and effective therapies for patients with unresectable stage III or stage IV metastatic melanoma, regardless of BRAF status, that provide durable improvements in patient survival, have more favourable toxicity profiles, and improve QoL.

PATIENT-BASED VALUES

Patient values on treatment: Control disease, prolong survival, improve quality of life, relieve symptoms of metastatic melanoma

MNC received input from a total of 102 patients across Canada, the US, and Australia. SYSF received a total of 86 responses from patients and caregivers. For patients providing input, the most important factors to control were disease progression, death, pain associated with disease progression or treatment, and symptoms including fatigue, anxiety, and gastrointestinal issues. Patient input indicated that patients value effective treatment options that improve QoL, manage pain and symptoms, provide durable response, increase PFS, and prolong survival. The input from patients and their families indicated that families experience huge challenges, including time lost from work and significant financial impact, increased burden of caregiving and responsibilities for the family, anxiety and depression, and the physical challenges of assistance and lifting. A number of caregivers indicated that the frequency of travel and associated costs to attend appointments and receive treatment on an ongoing basis were difficult.

Patients indicated that the benefits of treatment outweighed the risk of side effects. Most patient respondents did not complete the full course of treatment, but still received benefit. pERC agreed that the results from the CheckMate 067 trial did not demonstrate an improvement in patient-reported outcomes (PROs), including QoL; but noted that the combination of nivolumab plus ipilimumab showed no detriment in QoL, which pERC appreciated considering the high rates of toxicities associated with the combination therapy.

Respondents who have experience with the combination of nivolumab plus ipilimumab indicated that the combination therapy eliminates the cancer or stops its progression. According to MNC, the new combination therapy has indicated response rates in the 60% level, which is well above current monotherapies. MNC noted that most respondents would accept PFS. Patients are able to resume their lives symptom-free after treatment if treatment is effective. MNC noted that the combination therapy is challenging and the side effects must be managed by experienced oncologists. According to patient input, side effects are manageable or worth tolerating. Of the 20 patients in the MNC survey who had used the combination therapy, less than 60% of respondents indicated fatigue; 50% reported a skin rash; 30% indicated diarrhea; 25% reported liver problems, headaches, and joint aches as common side effects. Only one respondent indicated that the side effects were not worth it. SYSF acknowledged that there were higher adverse events with the combination therapy than with other available treatment options but because of higher success rates patients were willing to undergo side effects for better chances of survival. Overall, pERC concluded that the combination of nivolumab plus ipilimumab aligns with patient values in that it offers an improvement in PFS and provides patients with another effective treatment option. However, the Committee noted that there are considerable toxicities associated with the combination therapy and that the long term side effects are unknown.

ECONOMIC EVALUATION

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

pERC noted that the Committee deferred making a recommendation during the first deliberations on the submission of the combination of nivolumab plus ipilimumab for the first-line treatment of patients with metastatic melanoma because a clinically relevant comparison with nivolumab monotherapy was not provided by the submitter. pERC noted that the pCODR review team had requested this comparison from the submitter during the review, but it was not provided at the time. Following the deferral of the pERC Recommendation, the submitter provided an updated economic analysis comparing the combination of nivolumab plus ipilimumab with nivolumab monotherapy.

The cost-effectiveness analysis and cost-utility analysis submitted to pCODR by the manufacturer compared the combination of nivolumab plus ipilimumab with nivolumab monotherapy, ipilimumab monotherapy, and pembrolizumab as a first-line treatment for patients with unresectable or metastatic melanoma regardless of BRAF status. In secondary analyses, the cost-effectiveness of the combination of nivolumab plus ipilimumab was compared with other therapies indicated in the first-line setting for patients with BRAF V600 mutation-positive advanced melanoma, including dabrafenib/trametinib and vemurafenib.

Basis of the economic model: Uncertainties due to immaturity of OS data, and submitted indirect comparison

The partitioned survival model comprised three health states: progression-free, progressed disease, and death. The submitter's base-case analysis used a 20-year time horizon.

Efficacy data for nivolumab plus ipilimumab were sourced from one head-to head phase III clinical trial (CheckMate 067) to compare nivolumab plus ipilimumab with ipilimumab monotherapy and nivolumab monotherapy in terms of efficacy, treatment duration, and AEs. ITCs and naive comparisons were used to compare nivolumab plus ipilimumab with pembrolizumab and treatments for BRAF V600 mutation-positive, respectively.

The results presented by the manufacturer do not include post-progression treatment costs in the base-case analysis. Rather, the manufacturer presented a scenario analysis based on the distribution of subsequent systematic treatments observed in CheckMate 067 following disease progression. The cost-effectiveness analysis was based on an average body weight of 70 kg.

Utility values were derived from Canadian-based utility data from a sample of 87 healthy respondents from the general population in Toronto and Vancouver (using the standard gamble technique to assign utility values to various health states in melanoma [Hogg et al. 2010]) in the base-case analysis. EQ-5D utility data collected in CheckMate 067 were used in a sensitivity analysis. Furthermore, one Canadian expert opinion was used to derive and validate the health care resource utilization. Cost information was sourced from Ontarian and Canadian literature data and IMS Brogan DeltaPA.

Drug costs: High cost of nivolumab and ipilimumab

The list price of nivolumab is $293.33 per day, or $8,213.35 per 28-day course at 3 mg/kg every two weeks. At the recommended dose of 1 mg/kg every three weeks for the first four doses in combination with ipilimumab, nivolumab costs $1,825.23 (assuming an average weight of 70 kg).

The list price of ipilimumab is $1,160.00 per day or $32,480.00 per 28-day course at 3 mg/kg every three weeks x four doses (assuming an average weight of 70 kg).

Cost-effectiveness estimates: Utilities, overall survival, and treatment beyond progression

pERC deliberated upon the cost-effectiveness of nivolumab plus ipilimumab compared with nivolumab monotherapy and ipilimumab monotherapy for previously untreated metastatic melanoma patients. The submitter's best estimate of the incremental cost-effectiveness ratio (ICER) for the comparison versus nivolumab is $47,119 per quality-adjusted life-year (QALY). The pCODR Economic Guidance Panel (EGP) estimated the ICER to be between $6,601 per QALY and $72,128 per QALY. The submitter's best estimate of the ICER for the comparison versus ipilimumab is $66,750 per QALY. The EGP's best estimate of the ICER is between $86,758 per QALY and $116,541 per QALY. The submitter's best estimate of the ICER for the comparison versus pembrolizumab with 24 months maximum is $100,868 per QALY; pembrolizumab

treat-to-progression was dominant. The submitter's ICER for the comparison with targeted therapies was $56,896 per QALY gained for vemurafenib, and was dominant for dabrafenib plus trametinib.

Although the submitter provided an ITC of nivolumab plus ipilimumab versus pembrolizumab, the EGP did not undertake reanalysis estimates for this comparison given that the CGP and Methods team identified substantial heterogeneity in patient characteristics across all included studies in the submitted ITC. Similarly, the CGP and Methods team concluded that the effect of nivolumab plus ipilimumab compared with other targeted agents in BRAF mutation-positive carriers is unknown based on the submitted ITC; therefore, the EGP did not perform reanalysis estimates for the comparisons against dabrafenib/trametinib and vemurafenib. As a result, due to the poor quality of the available data, due to limitations of the submitted ITC to inform the clinical benefit estimates for the comparisons of the combination of nivolumab plus ipilimumab versus pembrolizumab or versus BRAF-targeted therapies, the EGP did not provide reanalysis estimates for those comparisons.

pERC noted that short-term model projections were compared versus the literature and trial data. pERC noted that the submitted cost-effectiveness analysis was based on an average body weight of 70 kg; however, the mean body weight in CheckMate 067 was 82 kg. As well, the submitted model had the option to use two sets of utility data. In the submitter's base-case analysis, the utility data were derived from a sample of 87 healthy respondents from the general population living in Toronto and Vancouver (mean age of 46 years and 49% male) using the standard gamble technique to assign utility values to various health states in melanoma (Hogg et al. 2010). This set of Canadian data was previously used in the EGP base-case reanalysis of nivolumab monotherapy for advanced melanoma (March 2016). The second set of utility data used by the manufacturer in a sensitivity analysis was based on the EQ-5D utility data collected in CheckMate 067, which was a multinational trial. Transferring utilities from other jurisdictions to Canada may result in bias. The EGP noted that while both sources of utility data are not ideal (e.g., none of these studies or data have been published and a critical appraisal is difficult), the two sets of utility data provide different results, illustrating the uncertainty associated with the utility data.

Additionally, the results presented by the manufacturer do not include post-progression treatment costs in the base-case analysis. Instead, these analyses were presented in a scenario analysis based on the distribution of subsequent systematic treatments observed in CheckMate 067 following disease progression. pERC noted that the factors that had the greatest impact on the ICER were time horizon, patient weight, and the inclusion of subsequent systematic treatment costs following disease progression. The Committee noted that grade 3 and grade 4 AEs may occur in higher frequencies in clinical practice than reported in the trial. Additionally, the Committee discussed the fact that more resources, including emergency room visits and hospitalization, may be required to monitor and treat toxicities while patients are on the combination therapy; therefore, the costs of monitoring and managing toxicities are likely underestimated in the pharmacoeconomic model, and would be substantially higher. Furthermore, due to the high cost of nivolumab and the unknown but potentially long duration of treatment, pERC agreed that a substantial reduction in drug price would be required. The Committee also discussed the fact that patients receiving the combination therapy discontinued treatment earlier than patients receiving nivolumab alone, and that re-initiating treatment with nivolumab alone when treatment with the combination therapy is temporarily interrupted due to toxicity would likely occur in clinical practice. Re-initiating treatment with nivolumab monotherapy following discontinuation of the combination therapy was not explored in the submitted pharmacoeconomic model. Overall, pERC accepted the EGP's reanalysis estimates and concluded that, based on the CheckMate 067 trial data and the manufacturer's pharmacoeconomic model, nivolumab plus ipilimumab appears to be cost-effective compared to ipilimumab monotherapy and nivolumab monotherapy.

Additionally, pERC concluded that the cost-effectiveness of nivolumab plus ipilimumab compared with pembrolizumab in patients with unresectable or metastatic melanoma is unknown. Similarly, the cost-effectiveness of nivolumab plus ipilimumab compared with other targeted agents in BRAF V600 mutation patients is unknown.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from PAG that the combination was not compared against pembrolizumab, the standard of care therapy in most Canadian jurisdictions. Furthermore, pERC also considered feedback from PAG that the combination was not compared against BRAF/MEK targeted agents. pERC noted that there is considerable uncertainty in the clinical effect estimates of nivolumab plus ipilimumab compared with pembrolizumab, due to limitations in the submitter's ITC and in the absence of a direct comparison in an RCT. pERC also noted the absence of direct RCT and indirect evidence comparing the combination of nivolumab plus ipilimumab and BRAF

targeted therapies. Therefore, the Committee reaffirmed that due to a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation, the cost-effectiveness of the combination of nivolumab plus ipilimumab compared to pembrolizumab and compared to BRAF targeted therapies is unknown.

ADOPTION FEASIBILITY

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

pERC discussed the feasibility of implementing a reimbursement recommendation for the combination of nivolumab plus ipilimumab for first-line metastatic melanoma. pERC acknowledged that registered clinicians indicated that the number of eligible patients in this setting would be small. However, pERC considered that the introduction of the combination of nivolumab plus ipilimumab as an additional first-line treatment option will likely have a significant impact on provincial budgets. Therefore, the eligible population of patients for the combination therapy may be greater than estimated in the budget impact analysis. Upon reconsideration of the Initial Recommendation, pERC noted PAG's feedback that the actual budget impact would be substantially greater given that the uptake of the combination therapy may be significantly higher, because subsequent treatment with ipilimumab after PD-1 immunotherapy such as pembrolizumab and nivolumab is not available in Canada. The Committee agreed that the uptake of the combination therapy may be significantly higher than estimated in the submitted BIA. Furthermore, pERC noted that the potential for drug wastage, given the weight-based dosing, together with the high cost of nivolumab and ipilimumab, would have a substantial impact on the budget impact and on the affordability of the combination therapy. pERC considered that the budget impact of the combination of nivolumab plus ipilimumab would be substantial, and that provinces should consider taking steps to limit the budget impact. The Committee also noted that re-initiating treatment with nivolumab alone following discontinuation of the combination therapy was not explored in the submitted BIA model. Therefore, pERC noted that the impact of re-initiating treatment with nivolumab alone is unknown, and will likely impact the budget impact substantially. pERC noted that the submitter's BIA was sensitive to market share, treatment duration, and the number of cases of advanced melanoma. The Committee agreed that jurisdictions will need to consider the uncertainty in these factors upon implementation, and agreed that the BIA is substantially underestimated.

The Committee noted input from the pCODR PAG, which requested information and clarification on the appropriate use of and patient eligibility for the combination therapy. Specifically, PAG is seeking guidance on patient eligibility for the use of the combination of nivolumab plus ipilimumab: previous or current treatment with oral BRAF-targeted therapies; previous treatment with ipilimumab monotherapy; and previous or current treatment with PD-1 inhibitor therapy (either nivolumab or pembrolizumab) in the first-line setting without disease progression. PAG is also seeking guidance on whether, if considering the addition of ipilimumab in combination, there would be any reasonable timeline restriction and, for those receiving pembrolizumab, a requirement to switch to nivolumab. PAG has the same concerns for patients previously treated with ipilimumab monotherapy who are currently being treated with PD-1 inhibitor therapy in the second-line setting. The Committee noted input from the pCODR PAG, which requested information and clarification on sequencing. pERC acknowledged that registered clinicians providing input indicated that the combination of nivolumab plus ipilimumab can be given as first-line immunotherapy or second-line, post–BRAF-targeted therapy for patients with BRAF v600 mutation. Upon reconsideration of the Initial Recommendation pERC discussed registered clinician feedback indicating that they disagree with the recommendation to limit reimbursement to treatment naïve patients, as the clinicians strongly support the use of nivolumab plus ipilimumab either as a first line immunotherapy or second line post-BRAF targeted therapy. The latter choice would also be consistent with Ontario's reimbursement for single agent immunotherapies. Furthermore, a patient group, Melanoma Network of Canada, provided feedback on pERC's Initial Recommendation that the combination therapy should be considered in second line as well as first line, for patients who have failed targeted therapies. pERC noted that the combination therapy may be a desired second line option following first line BRAF targeted therapy; however, the Committee acknowledged that there is no direct evidence investigating head-to-head efficacy and safety or the appropriate treatment sequence for the combination therapy and BRAF targeted therapies for the treatment of metastatic melanoma patients who are treatment naïve. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments for treatment naïve metastatic melanoma.

Furthermore, upon reconsideration of the Initial Recommendation, the Committee noted PAG's feedback requesting guidance on whether patients previously treated with ipilimumab could be treated with nivolumab plus ipilimumab upon disease progression. pERC noted that there is no data to support the use of the combination of nivolumab plus ipilimumab in patients previously treated with ipilimumab. Finally, pERC noted feedback from PAG requesting clarity on treatment with ipilimumab upon disease progression on nivolumab or pembrolizumab. The Committee noted that there is currently no documented evidence to support the addition of ipilimumab upon disease progression on nivolumab or pembrolizumab.

pERC noted that there may be a time-limited need for adding nivolumab in combination with ipilimumab for patients who are currently receiving ipilimumab monotherapy. Furthermore, pERC noted uncertainty regarding the use of the combination therapy in the following clinical situations for patients without disease progression: in patients who recently finished ipilimumab monotherapy; in patients who are currently on nivolumab monotherapy; and in patients who are currently on pembrolizumab. Furthermore, pERC agreed that the optimal sequencing of therapies for patients with metastatic melanoma is unknown due to a lack of evidence. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing. pERC noted that provinces will need to address optimal sequencing upon implementation of reimbursement, and noted that a national collaboration among the provinces to help guide consistency in drug reimbursement will be necessary.

pERC also noted PAG's concern that treatment with nivolumab plus ipilimumab can be given until treatment is no longer tolerated. PAG indicated that there may be requests to replace nivolumab with pembrolizumab in the monotherapy maintenance phase, as the administration schedule for pembrolizumab is every three weeks compared with every two weeks for nivolumab. pERC noted that there is currently no evidence to use pembrolizumab instead of nivolumab in the maintenance phase. Upon reconsideration of the Initial Recommendation, PAG requested guidance on whether it would be clinically reasonable to use pembrolizumab after induction with the combination of nivolumab plus ipilimumab instead of nivolumab, since pembrolizumab is given every 3 weeks, a more favourable administration schedule, and is used regardless of BRAF status. pERC re-iterated that there is no evidence to support the use pembrolizumab as maintenance therapy after the induction of the combination of nivolumab plus ipilimumab. pERC agreed that maintenance therapy should be administered as per the CheckMate-067 trial, with nivolumab monotherapy until unacceptable toxicity or disease progression.

pERC noted PAG's concern for potential dosing errors with the different dose and administration schedule for nivolumab when administered with ipilimumab and when administered as monotherapy. Nivolumab monotherapy is continued as long as clinical benefit is observed. PAG is seeking guidance on discontinuation criteria, as treatment could potentially be continued beyond progression.
PAG is also seeking information on whether combination treatment should restart after treatment is temporarily interrupted due to toxicity, and within what timelines. pERC noted that patients receiving the combination therapy discontinued treatment earlier than patients receiving nivolumab alone. The Committee also noted that re-initiating treatment with nivolumab alone upon early discontinuation of the combination therapy due to treatment toxicity may be done on a case-by-case basis in clinical practice. pERC agreed that jurisdictions should consider prospectively collecting data on re-initiating treatment with nivolumab alone following temporary discontinuation of the combination therapy in order to understand the optimal duration of therapy. Upon reconsideration of the Initial Recommendation, pERC discussed PAG's feedback requesting guidance on clarification of re-starting treatment with nivolumab monotherapy in the clinical scenarios of toxicity resolution with no disease progression, or after disease progression during a treatment break. The Committee noted that if discontinuation of the combination therapy was due to side effects from ipilimumab and not nivolumab, the re-initiation of nivolumab monotherapy would be reasonable. However, pERC noted that if there is disease progression on nivolumab during a treatment break, nivolumab monotherapy should not be re-started. pERC also discussed feedback from PAG requesting guidance on whether re-initiation of the combination therapy could be considered and in what clinical settings. The Committee noted that the combination of nivolumab plus ipilimumab should be administered as per the CheckMate-067 trial. pERC noted that there is no evidence to support the re-induction of the combination therapy following progression on nivolumab monotherapy.

pERC also noted PAG's concern about the long duration of therapy with nivolumab versus other immunotherapies that have shorter treatment cycles. pERC noted that the mechanism of action of immunotherapies suggests 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 collect this data prospectively to manage the budget impact of a reimbursement recommendation. Upon reconsideration of the Initial Recommendation, pERC acknowledged that a flat dose (240 mg) of nivolumab has also been approved for other indications. The Committee acknowledged that, although CheckMate-067 assessed nivolumab monotherapy at a dose of 3 mg/kg in the maintenance phase, there is no evidence to suggest that the dosing amount of 3 mg/kg is superior to 240 mg (flat dose). Therefore, pERC felt it would be reasonable that nivolumab be administered at 3 mg/kg up to a total dose of 240 mg (dose capped at 240 mg). pERC acknowledged that drug wastage is an important concern for PAG. pERC noted that the EGP included wastage in the model and that it is also reflected in the ICER in both settings. Finally, PAG noted that the administration of nivolumab and ipilimumab requires significant chemotherapy chair time: nivolumab is a 60-minute infusion, and is followed by 90 minutes for ipilimumab infusion in the combination phase; the administration of nivolumab is every two weeks in the monotherapy phase.

DRUG AND CONDITION INFORMATION

Drug Information	• Combination phase: Nivolumab 1 mg/kg is administered as an intravenous infusion over 60 minutes every three weeks for the first four doses in combination with ipilimumab 3 mg/kg administered intravenously over 90 minutes, followed by the single-agent phase. • Single-agent phase: Nivolumab 3 mg/kg is administered as an intravenous infusion over 60 minutes every two weeks.
Cancer Treated	• Unresectable stage III or IV metastatic melanoma
Burden of Illness	• In 2015, 6,500 Canadians were diagnosed with melanoma and about 1,050 died from it. • Unresectable stage IV melanoma carries a poor prognosis. The median survival is approximately six months, with about 25% of patients surviving to one year.
Current Standard Treatment	• Ipilimumab • Nivolumab • Pembrolizumab • Dabrafenib • Trametinib • Vemurafenib
Limitations of Current Therapy	• Ipilimumab offers limited efficacy, with a sustained response in approximately 20% of patients • Ipilimumab is associated with immune-related toxicity. • There is rapid progression following BRAF inhibitors.

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:

pERC Membership During Deliberation of the Initial Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)	Don Husereau, Health Economist
Dr. Paul Hoskins, Oncologist (Vice Chair)	Dr. Anil Abraham Joy, Oncologist
Dr. Scott Berry, Oncologist	Karen MacCurdy Thompson, Pharmacist
Dr. Kelvin Chan, Oncologist	Valerie McDonald, Patient Member Alternate
Lauren Flay Charbonneau, Pharmacist	Carole McMahon, Patient Member
Dr. Matthew Cheung, Oncologist	Dr. Catherine Moltzan, Oncologist
Dr. Craig Earle, Oncologist	Jo Nanson, Patient Member
Dr. Allan Grill, Family Physician	Dr. Marianne Taylor, Oncologist

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

- Dr. Allan Grill, Dr. Marianne Taylor, and Dr. Paul Hoskins, who were not present for the meeting
- Dr. Anil Abraham Joy and Don Husereau, who did not vote due to conflicts of interest

- Valerie McDonald, who did not vote due to her role as a patient member alternate.

pERC Membership During Deliberation of the Final Recommendation

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

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

- Dr. Craig Earle and Lauren Flay Charbonneau who were not present for the meeting.
- Dr. Anil Abraham Joy, and Dr. Winson Cheung who did not vote due to a conflict of interest.
- Cameron Lane, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pCODR 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 plus ipilimumab 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 was excluded from voting. For the Final Recommendation, two members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, two members were excluded from voting.

Information sources used

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

Consulting publicly disclosed information

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

Use of this Recommendation

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

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