pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

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: Cobimetinib (Cotellic) and vemurafenib (Zelboraf) **Submitted Funding Request:** For the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation	
Submitted By: Hoffmann-La Roche Limited	**Manufactured By:** Hoffmann-La Roche Limited
NOC Date: February 22, 2016	**Submission Date:** December 11, 2015
Initial Recommendation: May 5, 2016	**Final Recommendation:** June 30, 2016

pERC RECOMMENDATION

pERC recommends reimbursement of cobimetinib conditional on the cost-effectiveness being improved to an acceptable level. Reimbursement should be in combination with vemurafenib, for the treatment of patients with previously untreated BRAF V600 mutation-positive unresectable stage III or stage IV melanoma who have a good performance status. Treatment should continue until unacceptable toxicity or disease progression. If brain metastases are present, patients should be asymptomatic or have stable symptoms. The Committee made this recommendation because it was satisfied that there is a net clinical benefit of cobimetinib plus vemurafenib compared with single-agent vemurafenib, based on improvements in overall survival and progression-free survival, and manageable toxicity compared with single-agent vemurafenib in patients with previously untreated unresectable or metastatic melanoma. In addition, although the currently available data are limited, pERC considered quality of life with cobimetinib plus vemurafenib to be similar to that with single-agent vemurafenib. pERC was satisfied that treatment with cobimetinib plus vemurafenib aligned with patient values, as there is a need for treatment options that offer improvements in overall survival and disease progression in previously untreated BRAF V600 mutation-positive unresectable or metastatic melanoma.

pERC does not recommend reimbursement of cobimetinib plus vemurafenib for the treatment of patients with previously treated BRAF V600 mutation-positive unresectable metastatic melanoma. pERC made this recommendation because it was not satisfied that there is a net clinical benefit of cobimetinib plus vemurafenib in patients with previously treated BRAF V600 mutation-positive unresectable or metastatic melanoma, due to a lack of randomized comparative evidence. The uncertainty regarding the clinical benefit of cobimetinib plus vemurafenib compared with vemurafenib plus

	placebo led pERC to conclude that cobimetinib plus vemurafenib only partially aligns with patient values. The Committee concluded that, at the submitted price, cobimetinib plus vemurafenib compared with single-agent vemurafenib could not be considered cost-effective in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Patients With Disease Progression After Immune Checkpoint Therapy** pERC noted that there is no evidence to support or refute the use of cobimetinib plus vemurafenib in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma with disease progression after treatment with an immune checkpoint inhibitor. Therefore, pERC does not recommend reimbursement for cobimetinib plus vemurafenib in this group of patients. **Patients With Disease Progression on First-Line Vemurafenib** pERC noted that patients with BRAF V600 mutation-positive unresectable or metastatic melanoma with disease progression on first-line vemurafenib were excluded from the pivotal trial for this submission (coBRIM). The Committee also considered evidence from a small phase 1, non-comparative trial (BRIM7) that demonstrated poor response rates with cobimetinib plus vemurafenib in the cohort of patients whose disease had progressed while receiving vemurafenib. Therefore, pERC does not recommend reimbursement for cobimetinib plus vemurafenib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma whose disease has progressed on first-line vemurafenib. **Time-Limited Need for Cobimetinib Plus Vemurafenib in Patients Currently Receiving First-Line Treatment With Single-Agent Vemurafenib** At the time of implementing a reimbursement recommendation for cobimetinib plus vemurafenib, jurisdictions may consider addressing the short-term, time-limited need to offer cobimetinib plus vemurafenib to patients currently receiving a single-agent BRAF inhibitor or MEK inhibitor for the first-line treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma and whose disease has not progressed. **Pricing Arrangements to Improve Cost-Effectiveness** Given that pERC was satisfied that there is a net clinical benefit of cobimetinib plus vemurafenib in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who have not received previous therapy for unresectable or metastatic melanoma, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve cost-effectiveness to an acceptable level. pERC noted that the high price of the combination of cobimetinib plus vemurafenib was the key driver of the incremental cost-effectiveness estimates and that these estimates reflected a comparison of a high-cost combination with a high-cost single agent. Furthermore, pERC considered that the cost of cobimetinib plus vemurafenib should not exceed the cost of other combinations of BRAF and MEK inhibitors.

Potentially Higher Resource Use With Cobimetinib Plus Vemurafenib

pERC noted that the combination of cobimetinib plus vemurafenib requires a higher pill burden (> 10 pills required per day at recommended dose on days 1 to 21) than other combinations of BRAF and MEK inhibitors and has a number of potential drug interactions that require review and management. The complexity of the treatment may be potentially challenging for patients and caregivers to manage and would add workload for pharmacists (e.g., in order to assist with optimizing adherence and minimizing potential for drug interactions, etc.). In addition, pERC noted that cobimetinib plus vemurafenib requires regular ophthalmologist visits and cardiac monitoring for adverse events.

Evidence Generation to Understand Optimal Duration of Therapy

pERC noted that the combination regimen is approved at a dose of cobimetinib at 60 mg once daily and of vemurafenib at 960 mg twice daily, for 21 days, every 28 days, until disease progression or unacceptable toxic effects. pERC acknowledged that there is currently no evidence on the optimal duration of treatment with cobimetinib plus vemurafenib and agreed that it is important to prospectively collect such data.

Optimal Sequencing of BRAF-Targeted Therapies and Immune Checkpoint Therapies is Unknown

pERC concluded that the optimal sequencing of cobimetinib plus vemurafenib and other treatments now available for the treatment of BRAF mutation-positive metastatic melanoma is currently unknown. pERC was therefore unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement for cobimetinib plus vemurafenib and noted that collaboration among provinces to develop a common approach would be of value. pERC noted that the development and implementation of an evidence-based guideline would be of value and that the collection of real-world evidence may also be of value.

SUMMARY OF pERC DELIBERATIONS

pERC noted that the estimated incidence of new cases of melanoma in Canada in 2015 was 6,800 cases and that there are approximately 1,150 deaths annually from melanoma. Approximately 5% of patients with metastatic disease and another one-third of patients with early-stage disease will subsequently develop metastases. Surgery is not an option for most patients with metastatic melanoma, and systemic therapy is the only alternative. pERC noted that the prognosis for patients with unresectable or metastatic melanoma has historically been poor, with median survival of six to nine months and five-year survival of 6%. Approximately half of patients with melanoma have BRAF mutation-positive disease. Despite the availability of BRAF (e.g., vemurafenib, dabrafenib) and MEK inhibitors (e.g., trametinib) as first-line treatment of patients with unresectable or metastatic melanoma, the Committee noted that resistance to BRAF inhibitors ultimately develops, leading to rapid and often unrelenting disease progression. Therefore, pERC recognized the need for therapies that would delay or prevent the development of resistance to BRAF inhibitors.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of one randomized controlled trial (RCT; coBRIM) comparing cobimetinib plus vemurafenib with single-agent vemurafenib in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who have not received previous treatment for unresectable or metastatic melanoma. pERC concluded that there is a net clinical benefit of cobimetinib plus vemurafenib compared with single-agent vemurafenib. In drawing this conclusion, pERC noted that the overall survival and progression-free survival results favoured cobimetinib plus vemurafenib and were clinically meaningful. The Committee noted that, while there were slight increases in the incidence of some adverse events (e.g., central serous retinopathy, diarrhea, photosensitivity, reduction in left ventricular ejection fraction), there were decreases in the incidences of others (e.g., keratoacanthomas, squamous cell carcinomas, arthralgia). pERC concluded that the toxicities associated with treatment with cobimetinib plus vemurafenib were manageable. Additionally, pERC noted that the available, but limited, health-related quality of life (HRQoL) data from the coBRIM trial suggest that patients' HRQoL is at least stable with cobimetinib plus vemurafenib compared with single-agent vemurafenib.

pERC noted that there was a lack of high-quality evidence investigating the use of cobimetinib plus vemurafenib in patients with previously treated BRAF V600 mutation-positive unresectable or metastatic melanoma, as previously treated patients were excluded from the coBRIM trial. The Committee noted that the non-comparative BRIM7 trial of cobimetinib plus vemurafenib included previously treated patients who had never received a BRAF inhibitor and patients who were previously treated with, and had recent disease progression on, vemurafenib. pERC noted low response rates for cobimetinib plus vemurafenib in the cohort of patients with disease progression on vemurafenib and, due to the non-comparative design of the BRIM7 trial, could not conclude that there is a net clinical benefit of cobimetinib plus vemurafenib in patients previously treated with, and who have disease progression on, vemurafenib. Furthermore, the Committee noted that although the BRIM7 trial included patients who were previously treated, but were naive to treatment with a BRAF inhibitor, no data were available on the number of those patients who may have previously received an immune checkpoint inhibitor for the treatment of unresectable or metastatic melanoma. pERC also noted that conducting a higher quality study in this patient population is feasible. Therefore, pERC could not draw any conclusions on the clinical benefit of cobimetinib plus vemurafenib compared with other available therapies in patients previously treated with immune checkpoint inhibitors for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from the pCODR Provincial Advisory Group (PAG) regarding the benefit of cobimetinib plus vemurafenib in patients who:

- received cobimetinib plus vemurafenib in the adjuvant setting:

    - pERC noted that patients treated in the adjuvant setting who subsequently develop metastatic disease would be considered treatment-naive with respect to their metastatic disease.
- have active brain metastases:
    - The Committee noted that patients with active brain metastases were not included in the coBRIM trial and, therefore, could not draw a conclusion on the clinical benefit of cobimetinib plus vemurafenib in this specific group of patients.
- have failed immune checkpoint therapy (e.g., ipilimumab) :
    - pERC noted that patients who have failed immune checkpoint therapy (e.g., ipilimumab) were not included in the coBRIM trial. Given the lack of evidence, pERC could not draw a conclusion on the clinical benefit of cobimetinib plus vemurafenib in this specific group of patients.
- had recently progressed while receiving prior vemurafenib:
    - pERC noted that the best available evidence in this group of patients was from a phase 1 trial (BRIM7). The Committee noted that although the trial had a non-comparative design and included only a small number of patients who failed prior vemurafenib, the response rates for those who received cobimetinib plus vemurafenib were poor. Therefore, pERC could not conclude that there is a net overall clinical benefit of cobimetinib plus vemurafenib in patients who have progressed while receiving prior vemurafenib.

pERC noted that in the absence of a direct RCT comparing cobimetinib plus vemurafenib with single-agent dabrafenib or with dabrafenib plus trametinib, the relative efficacy of cobimetinib plus vemurafenib with respect to these agents is unknown. pERC discussed the results of a network meta-analysis (NMA) that indirectly compared cobimetinib plus vemurafenib with single-agent dabrafenib and with dabrafenib plus trametinib. The Committee noted several limitations in the NMA, including differences in the trials' characteristics and a paucity of information on the presence or absence of effect modifiers in the trials and whether those were controlled for in the analysis. These substantial limitations decreased pERC's confidence in the results of the indirect comparisons such that the Committee was unable to draw any firm conclusion on the relative efficacy and safety of cobimetinib plus vemurafenib compared with single-agent dabrafenib or with dabrafenib plus trametinib.

pERC reviewed patient advocacy group input that indicated that patients value effective treatment options that improve overall survival, duration of response, and quality of life. Patient input also indicated that patients value additional treatment options. pERC considered this input in the context of the coBRIM trial, which demonstrated that cobimetinib plus vemurafenib extends life, improves the duration of response, and has manageable toxicities compared with single-agent vemurafenib in patients with previously untreated BRAF V600 mutation-positive unresectable or metastatic melanoma. The Committee also considered quality of life to be maintained with cobimetinib plus vemurafenib in this group of patients. Therefore, pERC concluded that cobimetinib plus vemurafenib, for the treatment of previously untreated BRAF V600 mutation-positive unresectable or metastatic melanoma, aligns with patients' expressed values. However, the uncertainty in the clinical benefit of cobimetinib plus vemurafenib in patients with previously treated unresectable or metastatic melanoma led pERC to conclude that the combination only partially aligns with patients' expressed values in this group of patients.

pERC deliberated upon the cost-effectiveness of cobimetinib plus vemurafenib. The Submitter provided one model that made comparisons of cobimetinib plus vemurafenib with single-agent vemurafenib, single-agent dabrafenib, and dabrafenib plus trametinib. For the comparisons of cobimetinib plus vemurafenib with single-agent dabrafenib and dabrafenib plus trametinib, pERC considered the estimates of clinical effectiveness to be highly uncertain, as they were derived from an NMA that had several limitations. Therefore, the Committee relied on the comparison of cobimetinib plus vemurafenib with single-agent vemurafenib. pERC noted several limitations in the Submitter's model, as identified by the pCODR Economic Guidance Panel (EGP), which included the model structure, the model population (which differed from the coBRIM trial population), choice of source of health utility data for the post-progression health state in the model, and the cost of second-line treatments. pERC considered that using either the Submitter's or the EGP's estimates of the incremental cost-effectiveness, cobimetinib plus vemurafenib was not cost-effective at the submitted prices compared with single-agent vemurafenib. pERC noted that the high estimates of the incremental cost-effectiveness were due to the high incremental cost of

cobimetinib plus vemurafenib, which was driven largely by the high cost of the combined prices of cobimetinib and vemurafenib. Furthermore, pERC also noted that the estimates of the incremental cost-effectiveness represent an incremental cost of a high-cost treatment compared with another high-cost treatment.

pERC discussed the feasibility of implementing a reimbursement recommendation for cobimetinib plus vemurafenib. The Committee noted that the submitted budget impact analysis considered only patients who presented with new metastatic melanoma from year to year, which would underestimate the budget impact of cobimetinib plus vemurafenib, as patients with earlier-stage disease in past years who would develop metastatic disease in later years were not included in the analysis. pERC also noted that the budget impact analysis was most sensitive to changes in the proportion of patients testing positive for a BRAF V600 mutation, market share assumptions, and the actual dose of the combination therapy used by patients in practice. pERC noted that there may be a time-limited need to offer cobimetinib plus vemurafenib to patients currently receiving a single-agent BRAF inhibitor or MEK inhibitor for the first-line treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma and whose disease has not yet progressed.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from the PAG regarding the sequencing of available therapies for patients with BRAF mutation-positive metastatic melanoma. pERC noted that the optimal sequencing of cobimetinib plus vemurafenib and other treatments now available for the treatment of BRAF mutation-positive metastatic melanoma is currently unknown. The Committee was, therefore, unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement for cobimetinib plus vemurafenib and noted that collaboration among provinces to develop a common approach would be of value. pERC noted that the development and implementation of an evidence-based guideline would be of value and that the collection of real-world evidence may also be of value. pERC also considered feedback from the PAG regarding differences between pERC's recommendation for cobimetinib plus vemurafenib compared with pERC's recommendation for dabrafenib plus trametinib. The Committee noted that for the review of dabrafenib plus trametinib, the key RCTs, as well as the submitted economic model, included only patients who had not received prior systemic therapy. However, the funding request for the review of cobimetinib plus vemurafenib was irrespective of prior treatment status. Therefore, pERC concluded that its deliberations in both reviews were consistent.

The Committee noted that the cost of cobimetinib plus vemurafenib should not exceed the cost of other combinations of BRAF and MEK inhibitors for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.

Lastly, pERC considered that there is the potential for higher resource use with cobimetinib plus vemurafenib than with other combinations of BRAF and MEK inhibitors. The Committee noted that the recommended dose of cobimetinib plus vemurafenib requires a higher quantity of pills than the recommended doses of other combinations of BRAF and MEK inhibitors. This may be potentially challenging for patients and caregivers to manage, and for pharmacists to prepare and monitor adherence, especially in the event of dose modifications. It was also noted that cobimetinib plus vemurafenib requires regular ophthalmologist and cardiac monitoring for adverse events.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from the Submitter that disagreed that there is a potential for higher resource use with cobimetinib plus vemurafenib than with other combinations of BRAF and MEK inhibitors. Upon discussion of the expected resource use with cobimetinib plus vemurafenib, the Committee reiterated its original conclusion that there is a potential for higher resource use with this combination than with other combinations of BRAF and MEK inhibitors.

EVIDENCE IN BRIEF

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

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from 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 pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- PAG
- One patient advocacy group (MNC)
- The Submitter (Hoffmann-La Roche).

The pERC Initial Recommendation was to fund the combination of cobimetinib with vemurafenib, for the treatment of patients with previously untreated BRAF V600 mutation-positive disease conditional on cost-effectiveness being improved to an acceptable level. However, the pERC Initial Recommendation was to not fund the combination of cobimetinib with vemurafenib, for the treatment of patients with previously treated BRAF V600 mutation-positive disease.

Feedback on the pERC Initial Recommendation indicated that the MNC agreed with the pERC Initial Recommendation. However, the PAG and Submitter agreed only in part with the pERC Initial Recommendation.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial Recommendation was not eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC, as there was not unanimous consensus from stakeholders on the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of cobimetinib in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Studies included: One randomized controlled trial

The pCODR systematic review included one double-blind, phase 3, randomized controlled trial (RCT), coBRIM, which compared cobimetinib plus vemurafenib with vemurafenib plus placebo in adult patients with previously untreated unresectable locally advanced or metastatic BRAF V600 mutation-positive melanoma.

The key inclusion criteria required that patients have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, be naive to treatment for unresectable locally advanced or metastatic melanoma, and have documented BRAF V600 mutation-positive disease, measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, and adequate hematologic values and organ function. Treatment was continued until disease progression or unacceptable toxicity.

The pCODR review also provided contextual information on a critical appraisal of a network meta-analysis (NMA) comparing cobimetinib plus vemurafenib with dabrafenib alone and with dabrafenib plus trametinib. pERC noted that differences in some trial characteristics and a paucity of information on other trial and patient characteristics increased the uncertainty in the estimates of effect provided for cobimetinib plus vemurafenib compared with either dabrafenib alone or dabrafenib plus trametinib, thus limiting the interpretation of these results.

In addition, the pERC review provided contextual information of a non-comparative phase 1 trial (BRIM7) investigating cobimetinib plus vemurafenib in two cohorts of patients with unresectable locally advanced or metastatic melanoma. Cohort 1 included patients who had recently progressed on treatment with vemurafenib (n = 66). Cohort 2 included patients who were previously treated, but naive to previous BRAF or MEK inhibitor therapy or patients who had not received previous therapy for advanced melanoma (n = 63).

Patient populations: ECOG Performance Status ≤ 1

Patients in the coBRIM trial were randomized 1:1 to receive vemurafenib at 960 mg twice daily together with either cobimetinib (n = 247) at 60 mg once daily or placebo (n = 248) for 21 days, followed by seven days off. Dose modifications were permitted for pre-specified levels of toxic events.

coBRIM enrolled patients with a median age of 56 years in the cobimetinib plus vemurafenib group and 55 years in the vemurafenib plus placebo group. The two treatment arms were well balanced for a number of patient characteristics, including sex (male, 59% and 56%, cobimetinib plus vemurafenib versus vemurafenib plus placebo, respectively), metastatic status (unresectable stage IIIC, 9% versus 5%; M1a, 16% versus 16%; M1b, 16% versus 17%; M1c, 59% versus 62%), and BRAF mutation genotype (V600E, 69% versus 70%; V600K, 10% versus 13%). Of note, 76% of patients in the cobimetinib plus vemurafenib group had an ECOG performance status of 0, compared with 67% of patients in the vemurafenib plus placebo group, indicating that more patients in the cobimetinib plus vemurafenib group had a good performance status at baseline than the vemurafenib group.

pERC considered feedback from the Submitter and the PAG regarding the benefit of cobimetinib plus vemurafenib in patients who previously received cobimetinib plus vemurafenib in the adjuvant setting. The Committee noted that patients treated in the adjuvant setting and who subsequently develop metastatic disease would be considered treatment-naive with respect to their metastatic disease. pERC also considered feedback from the PAG regarding the use of cobimetinib plus vemurafenib in patients with BRAF mutation-positive metastatic melanoma who have active brain metastases. The Committee noted that this group of patients was excluded from the coBRIM trial and that there is a lack of data upon which to draw any conclusions regarding clinical benefit.

The BRIM7 trial included a cohort of patients who had not received previous treatment with a BRAF or MEK inhibitor, but pERC noted that some of those patients may have received previous treatment for advanced melanoma (e.g., ipilimumab). However, pERC noted that no data were available on the type or number of previous treatments that those patients may have received.

pERC considered feedback from the Submitter and the PAG regarding the use of cobimetinib plus vemurafenib in patients with previously treated BRAF mutation-positive metastatic melanoma. pERC noted that patients who have failed immune checkpoint therapy (e.g., ipilimumab) were not included in the coBRIM trial and that there is a lack of evidence in this specific group of patients. The Committee also noted that in patients who had recently progressed on vemurafenib (for metastatic disease), the best available evidence is a small phase 1 trial (BRIM7), which demonstrated poor response rates.

Key efficacy results: Clinically meaningful improvement in overall survival and progression-free survival

The key efficacy outcomes deliberated on by pERC were overall survival (OS) and progression-free survival (PFS), the secondary and primary outcomes, respectively, in the coBRIM trial. At the final analysis of OS (August 2015), the median OS was statistically significantly longer in the cobimetinib plus vemurafenib group compared with the vemurafenib plus placebo group (22.3 months versus 17.4 months, respectively), with a hazard ratio (HR) of 0.70, 95% confidence interval (CI) of 0.55 to 0.90, $P = 0.005$.

The median PFS, by investigator assessment, was 9.9 months for the cobimetinib plus vemurafenib group (median follow-up 7.4 months) and 6.2 months for the vemurafenib plus placebo group (median follow-up 7.0 months) with a stratified HR of 0.51 (95% CI, 0.39 to 0.68), $P < 0.001$. The PFS results by independent review were similar, with median values of 11.3 months and 6.0 months and an HR of 0.60 (95% CI, 0.45 to 0.79), $P = 0.0003$. At an updated analysis by investigator assessment (January 2015), median PFS was 12.3 months for the cobimetinib plus vemurafenib group (median follow-up 14.9 months) and 7.2 months for the vemurafenib group (median follow-up 13.6 months), with an HR of 0.58 (95% CI, 0.46 to 0.72).

pERC also noted that the BRIM7 trial reported the results for 63 patients who were completely treatment-naive or were previously treated but naive to a BRAF or MEK inhibitor, combined in a single cohort. However, the Committee noted that the number of patients in this cohort who were previously treated with an immune checkpoint inhibitor was not available. pERC also considered the results from the cohort of 66 patients who were previously treated with and recently progressed on vemurafenib. In particular, the Committee noted the poor objective response rate of 15.2%. The median duration of response was 6.7 months and the median PFS was 2.8 months with a one-year OS of 31.9%.

Quality of life: QoL stable over time; limited available data

Patient-reported outcomes were measured in coBRIM using the EORTC QLQ-C30. Completion rates were high (88%) among all cycles for both treatment groups. pERC noted that insomnia was improved in the cobimetinib plus vemurafenib group, but that diarrhea worsened. The Committee also noted that the proportion of responders for social functioning and, to a smaller extent, pain and fatigue scales were in favour of the cobimetinib plus vemurafenib group. However, pERC noted that many details of the patient-reported outcomes were not available, and insufficient information was therefore available to properly assess the patient-reported outcome data from the coBRIM trial. Based on the limited available information, pERC concluded that patient-reported outcomes, as measured by the EORTC QLQ-C30, appeared to be similar over time with cobimetinib plus vemurafenib and with vemurafenib plus placebo.

Safety: Manageable toxicities

pERC discussed the toxicity profile of cobimetinib plus vemurafenib observed in the coBRIM trial. Grade 3 to 4 adverse events occurred in 71.3% of patients in the cobimetinib plus vemurafenib group and in 59.3% of patients in the vemurafenib plus placebo group. In addition, a higher proportion of patients experienced an adverse event leading to discontinuation of cobimetinib or placebo in the cobimetinib plus vemurafenib group compared with the vemurafenib plus placebo group (19.0% versus 9.8%). Similarly, the rate of discontinuation of vemurafenib was higher in the cobimetinib plus vemurafenib group than in the vemurafenib plus placebo group (15.8% versus 9.8%). pERC noted that cobimetinib plus vemurafenib had higher rates of some grade 3 or higher toxicities (e.g., alanine aminotransferase increase, aspartate aminotransferase increase, blood creatinine phosphokinase increase, diarrhea, blood alkaline phosphatase increase, photosensitivity reaction, hyponatremia, and retinal detachment) but had lower rates of other grade 3 or higher toxicities (e.g., keratoacanthomas, squamous cell carcinoma, and arthralgia).

Need: Treatment with improved survival and duration of response, and manageable toxicities

Unresectable locally advanced or metastatic melanoma carries a poor prognosis and, until recently, the median survival of such patients was six to nine months and five-year survival of 6%. Newer treatments such as immune checkpoint inhibitors have demonstrated significant improvements in treatment for patients with advanced or metastatic melanoma; however, only a relatively small proportion of patients experience long-term survival. For the approximately half of patients who harbour a BRAF-mutated melanoma, BRAF inhibitors, and the combination of BRAF plus MEK inhibitors, have also demonstrated significant improvements in outcomes. However, for these targeted therapies, resistance typically develops in nine to 11 months. Given that the majority of patients with unresectable advanced or metastatic melanoma still succumb to the disease, there is a need for more effective therapies that improve survival and duration of response and that have manageable toxicities.

PATIENT-BASED VALUES

Values of patients with metastatic melanoma: Improved disease control and overall survival and more treatment options

Patients expressed the importance of having new effective therapies that have a longer-lasting impact on their disease, extend life expectancy, have reduced toxicity, and provide improvements in quality of life. Patients indicated that current therapies for advanced melanoma are limited and have significant side effects that have a negative impact on the quality of life for both the patient and the caregiver. Patients commonly experience pain, scarring, fatigue, disrupted sleep, fear, depression, and anxiety as a result of their disease. As related to current treatments, patients experience a myriad of symptoms attributed to treatments, including fatigue, irritability, flu-like symptoms (chills, sweats), headaches, weight loss,

diarrhea (including colitis), and nausea and vomiting. In some patients, significant and devastating side effects result in patients deciding not to use the available treatments. Patients also indicated that while some patients achieve a long-lasting response to current therapies, the majority achieve a response of approximately 10 months and eventually have disease progression.

Patient values on treatment: Improved overall survival, slower disease progression, and availability of additional treatment options with new therapy

Patients indicated that they expected cobimetinib plus vemurafenib to offer improvements in tumour burden, to stop or slow disease progression, to have manageable side effects, and to offer an alternative treatment option for patients for whom current therapies are not effective. pERC noted that patients indicated that cobimetinib plus vemurafenib offered more durable responses. Patients also indicated that the combination was an oral therapy that reduced the time and cost required to travel to receive treatment. Furthermore, patients indicated that they experienced side effects such as fatigue, fever, rash, and nausea, but that all were tolerated or manageable and that they felt that the side effects were acceptable.

ECONOMIC EVALUATION

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

The pCODR Economic Guidance Panel (EGP) assessed cost-effectiveness and cost-utility analyses comparing cobimetinib plus vemurafenib with single-agent vemurafenib. The analyses also compared cobimetinib plus vemurafenib with single-agent dabrafenib and with dabrafenib plus trametinib; however, pERC considered the estimates of clinical effectiveness for these latter two comparisons to be highly uncertain as they were derived from an NMA that had several limitations. Therefore, the Committee relied on the comparison of cobimetinib plus vemurafenib with single-agent vemurafenib.

pERC noted that while the coBRIM trial, which enrolled patients with previously untreated BRAF V600 mutation-positive unresectable or metastatic melanoma, was used to inform the submitted model, the model population was patients with either previously untreated or previously treated BRAF V600 mutation-positive unresectable or metastatic melanoma. Furthermore, pERC noted that the submitted model was a partitioned-survival model, which limited the ability of the EGP to evaluate the effect of uncertainty of survival estimates on the incremental cost-effectiveness.

Basis of the economic model: Source of utility data; cost of second-line treatment

Costs included were cost of the drugs, drug administration costs, supportive care costs, and adverse events management costs. pERC noted that the combined price of cobimetinib and vemurafenib had the largest impact on the incremental cost of combination treatment compared with single-agent vemurafenib. pERC also noted that the Submitter did not include the costs of second-line treatment in the model and that the unit costs of adverse events reflected treatment costs of the adverse events in an acute care (hospital) setting.

Key clinical effects considered in the analysis included OS, PFS, and utilities. pERC noted that the Submitter relied on expert opinion to select the grade 3 or 4 adverse events included in the model; however, the probability of these events occurring came from the coBRIM trial. Baseline utility values were obtained from the coBRIM trial using the EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D) and applying UK weights. However, post-progression utilities were taken from a UK study of societal preferences using a standard gamble approach, which may not reflect the preferences of a Canadian melanoma population.

Drug costs: High cost of drug

Vemurafenib* costs $46.54 per 240 mg tablet; at the recommended dose of 960 mg twice daily, the average cost per day in a 28-day course of vemurafenib is $372.34 and the average cost per 28-day course is $10,425.41.

Drug costs for vemurafenib, dabrafenib, and trametinib are based on costing information under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc.

Cobimetinib costs $120 per 20 mg tablet; at the recommended dose of 60 mg daily for 21 days followed by a seven-day break, the average cost per day in a 28-day course of cobimetinib is $270.25 and the average cost per 28-day course is $7,567.00. Therefore, the average cost per day in a 28-day course of cobimetinib plus vemurafenib is $642.59 and the average cost per 28-day course is $17,992.41.

Dabrafenib* costs $63.33 per 75 mg capsule; at the recommended dose of 150 mg twice daily, the average cost per day in a 28-day course of dabrafenib is $253.33 and the average cost per 28-day course is $7,093.33.

Trametinib* costs $290.00 per 2 mg tablet; at the recommended dose of 2 mg once daily, the average cost per day in a 28-day course of trametinib is $290.00 and the average cost per 28-day course is $8,120.00. Therefore, the average cost per day in a 28-day course of dabrafenib plus trametinib is $543.33 and the average cost per 28-day course is $15,213.33.

Cost-effectiveness estimates: Price of cobimetinib plus vemurafenib is largest driver of incremental cost; uncertainty in survival estimates leads to uncertainty in incremental effect

pERC discussed the EGP's best estimate of the incremental cost-effectiveness ratio (ICER) of cobimetinib plus vemurafenib compared with single-agent vemurafenib in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. pERC accepted the EGP's reanalysis estimates and concluded that cobimetinib plus vemurafenib is not cost-effective, even when compared with another high-cost drug.

pERC noted that the costs of second-line treatments were not included in the submitted model and agreed with the EGP's approach of including these. pERC also noted that the submitter used health utilities derived from a study of the general population of the UK for the post-progression state in the model and agreed with the EGP's approach to use utility data from a general Canadian population. pERC noted that using Canadian population-derived utility data had only a small impact on the incremental cost-effectiveness. The Committee also discussed the adverse event treatment costs used by the Submitter in the model and noted that the EGP identified several Canadian studies that provided more reasonable and justifiable cost estimates for the management of some adverse events included in the model. pERC noted that the sources used by the Submitter may have overestimated the cost of treating the adverse events considered in the model; however, the Committee also accepted the EGP's conclusion that the impact of using the alternate sources of adverse event treatment costs had a non-significant impact on the incremental cost-effectiveness due to the rarity of the adverse events. Finally, pERC discussed the impact of the choice of distribution to extrapolate OS and PFS in the model. The Committee noted that there is a large amount of uncertainty regarding the extrapolation of survival probabilities, which leads to a large amount of uncertainty in the incremental effectiveness estimates, which is, in turn, reflected in the large range for the estimates of incremental cost-effectiveness provided by the EGP. pERC noted that the high price of the combination of cobimetinib plus vemurafenib was the key driver of the incremental cost-effectiveness estimates and that these estimates reflected a comparison of the incremental cost of a high-cost combination with a high-cost single agent.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: High drug cost

pERC discussed factors affecting the feasibility of implementing a reimbursement recommendation for cobimetinib plus vemurafenib in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

The Committee noted that the submitted budget impact analysis considered only patients who presented with new metastatic melanoma from year to year, which would underestimate the budget impact of cobimetinib plus vemurafenib, as the analysis did not include patients with earlier-stage disease in past years who would develop metastatic disease in later years. pERC also noted that the budget impact analysis was most sensitive to changes in the proportion of patients testing positive for a BRAF V600 mutation, market share assumptions, and the actual dose of the combination therapy used by patients in practice. pERC discussed feedback from the Submitter that disagreed with the EGP's reanalysis approach for determining the dose of therapy. pERC agreed with the EGP's reanalysis approach and reiterated pERC's original conclusion that the budget impact analysis was sensitive to changes in the actual dose of

the combination therapy used by patients in practice, in addition to changes in the proportion of patients testing positive for a BRAF V600 mutation and market share assumptions.

Input from the PAG indicated concerns regarding the high cost of cobimetinib plus vemurafenib as a barrier to implementation. pERC considered that the price of the two drugs was a major driver of the high ICER and that those estimates reflect the incremental cost of a high-cost combination compared with a high-cost single agent. pERC also noted that the results of the submitted budget impact analysis were sensitive to changes to the prevalent population, the proportion of patients expected to present with BRAF V600 mutation-positive disease, the market share assumptions, and the dose of the combination therapy. Therefore, pERC noted that jurisdictions may want to consider pricing arrangements and/or cost structures that would improve cost-effectiveness to an acceptable level. Furthermore, pERC discussed the issue that there is an absence of high-quality evidence to inform the choice of cobimetinib plus vemurafenib compared with dabrafenib plus trametinib. The Committee concluded that, in the absence of that evidence, the cost of cobimetinib plus vemurafenib should not exceed the cost of dabrafenib plus trametinib.

pERC considered feedback from the Submitter that cobimetinib plus vemurafenib does not have the potential for higher resource usage than other combinations of BRAF and MEK inhibitors; however, the Committee reiterated its original conclusion that there is a potential for higher resource use with cobimetinib plus vemurafenib than with other combinations, due to the high pill burden (> 10 pills required per day at recommended dose on days 1 to 21), the potential for drug interactions, the complexity of the treatment for patients and caregivers, the workload for pharmacists (e.g., in order to assist with optimizing adherence and minimizing potential for drug interactions), and requirements for regular ophthalmologist visits and cardiac monitoring for adverse events.

pERC noted that there may be a time-limited need to offer cobimetinib plus vemurafenib to patients currently receiving a single-agent BRAF inhibitor or MEK inhibitor for the first-line treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.

pERC also discussed input from the PAG that indicated concern regarding the appropriate sequencing of BRAF inhibitors and MEK inhibitors and immune checkpoint inhibitors in this patient population. pERC noted that there is no evidence to support or refute the use of cobimetinib plus vemurafenib in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma that has progressed after treatment with an immune checkpoint inhibitor; therefore, pERC could not make an informed recommendation on this matter. pERC also noted that patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, who progressed on first-line vemurafenib, were excluded from the coBRIM trial. Furthermore, the Committee considered evidence from the phase 1 BRIM7 trial that demonstrated poor response rates with cobimetinib plus vemurafenib in the cohort of patients whose disease progressed while receiving vemurafenib. Therefore, pERC could not make a recommendation for the use of cobimetinib plus vemurafenib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma whose disease has progressed on first-line vemurafenib.

pERC considered feedback from the PAG regarding the sequencing of available therapies for patients with BRAF mutation-positive metastatic melanoma. The Committee noted that the optimal sequencing of cobimetinib plus vemurafenib and other currently available treatments is unknown and that the development and implementation of an evidence-based guideline would be of value. pERC also noted that the collection of real-world evidence to inform optimal sequencing might be of value. pERC also considered feedback from the PAG regarding differences between pERC's Final Recommendation for dabrafenib plus trametinib and the Initial Recommendation for cobimetinib plus vemurafenib. The Committee noted that for the review of dabrafenib plus trametinib, the key RCTs, as well as the submitted economic model, included only patients who had not received prior systemic therapy. However, the funding request for the review of cobimetinib plus vemurafenib was irrespective of prior treatment status.

DRUG AND CONDITION INFORMATION

Drug Information	• Cobimetinib is a MEK inhibitor; Vemurafenib is a BRAF inhibitor. • Cobimetinib is available in 20 mg tablets; Vemurafenib is available in 240 mg tablets. • The recommended dose of cobimetinib is 60 mg orally, twice daily for 21 days, followed by seven days off treatment; and the recommended dose of vemurafenib is 960 mg orally, twice daily for 28 days. Both drugs are given until disease progression or unacceptable toxicity.
Cancer Treated	• BRAF V600 mutation-positive unresectable stage III or stage IV melanoma
Burden of Illness	• 6,800 new cases of primary melanoma were diagnosed in 2015 and approximately 1,150 individuals will die from melanoma each year. • Unresectable stage III or stage IV (metastatic) melanoma carries a poor prognosis. Median survival is approximately six months with about 25% of patients surviving to one year.
Current Standard Treatment	• Single-agent vemurafenib, single-agent dabrafenib, and single-agent trametinib (select jurisdictions) are available for the first-line treatment of unresectable stage III or stage IV melanoma in patients with a BRAF V600 mutation.
Limitations of Current Therapy	• Single-agent BRAF inhibitors and MEK inhibitors are approved and single-agent BRAF inhibitors are commonly used in BRAF mutation-positive unresectable stage III or stage IV melanoma; however, resistance typically develops within six to eight months of treatment initiation, and survival at that point is poor.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

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

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

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

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

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

- Valerie McDonald, who was the designated non-voting patient member alternate for this meeting.
- Kelvin Chan and Paul Hoskins, who were not present for the meeting.

Avoidance of conflicts of interest

All members of pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website, and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of cobimetinib (Cotellic) and vemurafenib (Zelboraf) for metastatic melanoma, through their declarations, five members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

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

Consulting publicly disclosed information

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

Use of this Recommendation

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

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