# pCODR EXPERT REVIEW COMMITTEE (pERC)
## FINAL RECOMMENDATION

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

**pERC Final Recommendation**
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

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| **Drug:**<br>Dabrafenib (Tafinlar) in combination with Trametinib (Mekinist)<br>**Submitted Funding Request:**<br>Dabrafenib and trametinib in combination for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation | |
| **Submitted By:**<br>GlaxoSmithKline Inc. | **Manufactured By:**<br>GlaxoSmithKline Inc. |
| **NOC Date:**<br>March 6, 2015 | **Submission Date:**<br>February 13, 2015 |
| **Initial Recommendation:**<br>July 3, 2015 | **Final Recommendation:**<br>July 21, 2015 |

**pERC RECOMMENDATION**

The pCODR Expert Review Committee (pERC) recommends funding dabrafenib (Tafinlar) plus trametinib (Mekinist), conditional on cost-effectiveness being improved to an acceptable level. Funding should be for patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma in the first-line setting and who have an ECOG performance status of 0 or 1. Treatment is until 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 dabrafenib plus trametinib compared with either single-agent dabrafenib or single-agent vemurafenib based on improvements in overall survival and progression-free survival, stable quality of life, and manageable toxicities. pERC was also satisfied that dabrafenib plus trametinib treatment aligns with patient values. However, pERC noted that dabrafenib plus trametinib could not be considered cost-effective at the submitted prices based on the Economic Guidance Panel's estimates of the range of incremental cost-effectiveness ratios when compared with either single-agent dabrafenib or single-agent vemurafenib.

## POTENTIAL NEXT STEPS FOR STAKEHOLDERS

**Pricing Arrangements to Improve Cost-Effectiveness**
Given that pERC was satisfied that there is a net clinical benefit of dabrafenib plus trametinib 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 price of the combination of dabrafenib plus trametinib was a key driver of the incremental cost-effectiveness estimates. Therefore, pERC concluded that a substantial reduction in the price of the two drugs would likely be required in order to improve the cost-effectiveness.

**Time-Limited Need for Dabrafenib Plus Trametinib in Patients Currently Receiving First-Line Treatment with a Single-Agent BRAF Inhibitor or MEK Inhibitor**
At the time of implementing a funding recommendation for dabrafenib plus trametinib, jurisdictions may consider addressing the short-term, time-limited need to offer dabrafenib plus trametinib to patients currently receiving a single-agent BRAF or MEK inhibitor for the first-line treatment of unresectable or metastatic melanoma and whose disease has not progressed.

**Sequencing of Treatments in Metastatic Melanoma**
pERC was unable to make an informed recommendation on the use of dabrafenib plus trametinib after progression on either a single-agent BRAF inhibitor or single-agent MEK inhibitor as the Committee noted that, as yet, there is no evidence to inform this clinical situation. In addition, pERC noted that there is no evidence to inform the optimal sequencing of the combination of dabrafenib plus trametinib with immune checkpoint inhibitors as yet. Therefore, pERC was unable to make an informed recommendation regarding the optimal sequencing of these agents. pERC also noted that the prospective collection of data regarding the efficacy and safety of dabrafenib plus trametinib administered before or after immune checkpoint inhibitors would help define the optimal sequencing of these agents in this patient population.

# SUMMARY OF pERC DELIBERATIONS

pERC noted that the estimated incidence (new cases) of melanoma in Canada in 2014 was 6,500 cases and that there are approximately 1,100 deaths annually from melanoma. Approximately 5% of patients present 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 6-9 months and 5-year survival of 6%. Approximately half of patients with melanoma have BRAF mutation-positive disease. Despite the availability of BRAF inhibitors such as dabrafenib and vemurafenib in the 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: | |
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| **CLINICAL BENEFIT** | **PATIENT-BASED VALUES** |
| **ECONOMIC EVALUATION** | **ADOPTION FEASIBILITY** |

pERC deliberated upon the results of two randomized controlled trials comparing dabrafenib plus trametinib with single-agent dabrafenib (the Combi-d study) or single-agent vemurafenib (the Combi-v study), and concluded that there is a net clinical benefit for dabrafenib plus trametinib compared with both single-agent dabrafenib and single-agent vemurafenib. In drawing this conclusion, pERC noted that the overall survival and progression-free survival results were statistically significant and clinically meaningful in favour of combination treatment in both studies. Additionally, pERC noted that measures of quality of life were either stable or improved for many subscales of the quality of life instruments used in the Combi-d study and the Combi-v study . pERC also concluded that the toxicities associated with treatment with dabrafenib plus trametinib were manageable and that there was a lower incidence of hyper-proliferative cutaneous adverse events in patients treated with dabrafenib plus trametinib compared with a single-agent BRAF inhibitor.

pERC noted that in the absence of direct randomized controlled trials comparing dabrafenib plus trametinib with single-agent trametinib or with ipilimumab, the relative efficacy and safety of dabrafenib plus trametinib with respect to these agents is uncertain. pERC discussed the results of a network meta-analysis (NMA) that indirectly compared dabrafenib plus trametinib with single-agent trametinib, with ipilimumab, and with dacarbazine. The Committee noted several limitations in the NMA including differences in the trials' characteristics and included patient populations. 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 dabrafenib plus trametinib compared with single-agent trametinib, ipilimumab, or dacarbazine.

pERC reviewed patient advocacy group input that indicated that patients value effective treatment options that improve overall survival and quality of life and reduce toxicity. pERC considered this input in the context of the Combi-d and Combi-v studies, which demonstrated that dabrafenib plus trametinib extends life and has manageable toxicities compared with single-agent dabrafenib and single-agent vemurafenib, and consequently it concluded that dabrafenib plus trametinib aligns with patients' expressed values. pERC also noted the high quality of the submissions received from the two patient advocacy groups that provided input, based on the richness of patient experiences and clarity of patient values gathered.

pERC deliberated upon the cost-effectiveness of dabrafenib plus trametinib. The Submitter provided a model that made comparisons of dabrafenib plus trametinib with single-agent dabrafenib, single-agent vemurafenib, single-agent trametinib, ipilimumab, and dacarbazine. For the three comparisons of dabrafenib plus trametinib with single-agent trametinib, ipilimumab, and dacarbazine, pERC considered the estimates of clinical effectiveness to be highly uncertain as they were derived from an NMA which had several methodological limitations. Therefore, the Committee relied on the two comparisons of dabrafenib plus trametinib with either single-agent dabrafenib or single-agent vemurafenib. pERC considered that using either the manufacturer's or the pCODR Economic Guidance Panel's estimates of the incremental cost-effectiveness, the combination of dabrafenib plus trametinib was not cost-effective at the submitted prices compared with either single-agent dabrafenib or compared with single-agent

vemurafenib. pERC noted that the high estimates of incremental cost-effectiveness were due to the high incremental cost of dabrafenib plus trametinib which was driven largely by the combined prices of dabrafenib and trametinib.

pERC discussed the feasibility of implementing a funding recommendation for dabrafenib plus trametinib. pERC noted that there may be a time-limited need to offer dabrafenib plus trametinib to patients currently receiving a single-agent BRAF inhibitor or MEK inhibitor for the first-line treatment of unresectable or metastatic melanoma and whose disease has not yet progressed. pERC considered that presently, there is no evidence to support or contraindicate the use of a MEK inhibitor after progression on a BRAF inhibitor or vice versa. Therefore, pERC could not make an informed recommendation on the use of dabrafenib plus trametinib either before or after treatment with a single-agent MEK inhibitor or BRAF inhibitor. In addition, pERC noted that there is, as yet, no evidence to inform the appropriate sequencing of dabrafenib plus trametinib with immune checkpoint inhibitors; however, pERC noted that the provinces may want to consider prospectively collecting data to inform the appropriate sequencing of dabrafenib plus trametinib with immune checkpoint inhibitors.

# EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from two patient advocacy groups (Melanoma Network of Canada, Save Your Skin Foundation)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- two patient advocacy group (Melanoma Network of Canada, Save Your Skin Foundation)
- the Submitter (GlaxoSmithKline Inc.)

The pERC initial recommendation was to fund dabrafenib (Tafinlar) plus trametinib (Mekinist), conditional on cost-effectiveness being improved to an acceptable level

Feedback on the pERC Initial Recommendation indicated that the manufacturer, patient advocacy group and pCODR's Provincial Advisory Group agreed with the initial recommendation.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

## OVERALL CLINICAL BENEFIT

### pCODR review scope

The pCODR review evaluated the safety and efficacy of dabrafenib in combination with trametinib compared to commonly used therapies, placebo, or best supportive care in the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation who have not received prior systemic therapy for unresectable, advanced or metastatic melanoma.

### Studies included: Two well-conducted RCTs in untreated patients

The pCODR systematic review included two randomized controlled trials comparing dabrafenib plus trametinib with single-agent dabrafenib (the Combi-d study) or with single-agent vemurafenib (the Combi-v study). pERC noted that both trials were generally well conducted.

pERC noted that there were no trials comparing dabrafenib plus trametinib with single-agent trametinib or with ipilimumab; however, the pCODR Clinical Guidance Report provided contextual information on a network meta-analysis (NMA) comparing dabrafenib plus trametinib with single-agent dabrafenib, trametinib, vemurafenib, ipilimumab, and dacarbazine for metastatic melanoma.

### Patient populations: Previously untreated, BRAF V600 mutation-positive, unresectable or metastatic melanoma

Both Combi-d and Combi-v trials included patients with previously untreated metastatic melanoma (stage IV or unresectable stage IIIC). Patients in both trials were generally fit, with an ECOG performance status of 0 or 1. Patients included in both trials also had a confirmed BRAF V600 mutation.

### Key efficacy results: Consistent improvement in overall survival and progression-free survival

pERC noted that a statistically significant and clinically meaningful difference in overall survival was demonstrated in favour of dabrafenib plus trametinib compared with single-agent BRAF inhibitor therapy, in both trials. In the Combi-d trial, the final analysis of overall survival (secondary outcome),

demonstrated a statistically significant improvement in favour of the dabrafenib plus trametinib arm (median 25.1 months) compared with the single-agent dabrafenib arm (median 18.7 months; hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.55 to 0.92; p=0.0107). In the Combi-v trial, overall survival was the primary outcome of the trial, which was stopped early for efficacy (pre-specified stopping boundary; p<0.0214). The median overall survival for the dabrafenib plus trametinib arm had not been reached compared with a median of 17.2 months in the single-agent vemurafenib arm (HR 0.69, 95% CI 0.53 to 0.89; p=0.005) after a median follow-up duration of 11 months in the combination arm and 10 months in the vemurafenib arm.

pERC noted that progression-free survival was also statistically significantly longer in favour of the dabrafenib plus trametinib arm compared with the BRAF inhibitor therapy alone arm, in both trials. In the Combi-d trial, progression-free survival was the primary outcome and it was statistically significantly longer in the dabrafenib plus trametinib arm (median 11.0 months) compared with the dabrafenib plus placebo arm (median 8.8 months; hazard ratio [HR] 0.67, 95% CI 0.53 to 0.84; p=0.0004) after a median follow-up of 9 months. In the Combi-v trial, median progression-free survival in the dabrafenib plus trametinib group was longer than in the vemurafenib group (11.4 months versus [vs.] 7.3 months; HR 0.56; 95% CI 0.46 to 0.69; p<0.001).

### Quality of life: Stable or improved quality of life with combination therapy

Quality of life in both trials was measured using the EORTC QLQ-C30 generic cancer questionnaire. pERC considered that for most subdomains of the EORTC QLQ-C30, scores were stable or improved for patients who received dabrafenib plus trametinib compared with patients who received a BRAF inhibitor alone. pERC noted that in the Combi-d trial, the global health/quality of life dimension was statistically significantly better at weeks 8, 16, and 24 in favour of dabrafenib plus trametinib. Pain scores were statistically significantly improved and clinically meaningful (6-13 point difference) in favour of dabrafenib plus trametinib compared with dabrafenib alone, at all assessment visits. pERC also noted that the nausea and vomiting symptom domain was worse at weeks 16 and 24 in the dabrafenib plus trametinib group than in the dabrafenib alone group. In the Combi-v trial, the global health/quality of life dimension was statistically significantly better at all assessment visits for patients who received dabrafenib plus trametinib compared with those who received vemurafenib. The role, social, and physical functioning domains as well as the appetite loss, insomnia, and pain symptom domains all demonstrated statistically significant differences in favour of the combination therapy arm compared with the vemurafenib arm. In addition, the Combi-v trial also demonstrated statistically significant differences in FACT-M Melanoma subscale scores in favour of the dabrafenib plus trametinib arm compared with the vemurafenib arm. pERC considered the quality of life results from both studies to be meaningful from a patient perspective.

### Safety: Manageable toxicities; lower incidence of hyper-proliferative cutaneous adverse events with dabrafenib plus trametinib

pERC noted that in the Combi-d trial, grade 3 or 4 adverse events occurred in 73 patients (35%) in the dabrafenib and trametinib group and in 79 patients (37%) in the dabrafenib and placebo group. In the dabrafenib plus trametinib group, the most common grade 3 adverse events were pyrexia (6%), hypertension (4%), and elevated aspartate aminotransferase (3%), whereas hypertension (5%) was the most common in the dabrafenib alone group. pERC noted that the toxicities associated with dabrafenib plus trametinib were manageable. The Committee also noted that cutaneous squamous-cell carcinomas, including keratoacanthomas, occurred in 2% of patients who received dabrafenib plus trametinib and in 4% of patients who received dabrafenib alone.

pERC noted that in the Combi-v trial, grade 3 or 4 adverse events occurred in 52% of patients in the combination group and in 63% of patients in the vemurafenib group. The most common grade 3 adverse events in the dabrafenib plus trametinib arm were hypertension (14%), pyrexia (4%), and elevated alanine aminotransferase (3%), whereas in the vemurafenib arm, hypertension (9%), rash (9%), elevated alanine aminotransferase (4%), arthralgia (4%), and elevated aspartate aminotransferase (4%) were most common. A total of 17 patients in the dabrafenib plus trametinib arm experienced a grade 4 adverse event compared with 24 in the vemurafenib arm. Again, pERC noted that the toxicities associated with dabrafenib plus trametinib were manageable. The Committee also noted that cutaneous squamous cell carcinomas, including keratoacanthomas, occurred in 1% of patients who received dabrafenib plus trametinib whereas they occurred in 17% of patients who received vemurafenib.

### Need: Treatments required to prevent or delay resistance to BRAF inhibitor therapy

pERC noted that single-agent BRAF inhibitors were previously reviewed by the committee and are routinely used and funded across Canada for BRAF mutation-positive metastatic melanoma. However, resistance typically develops within 6 to 8 months of treatment initiation and survival at that point is poor, thus additional treatment options are required. pERC also noted that hyper-proliferative cutaneous adverse events are a significant problem with BRAF inhibitors and noted the lower incidence of hyper-proliferative cutaneous adverse events in patients receiving dabrafenib plus trametinib compared to single agent use.

### Comparators: uncertainty in NMA results

pERC noted several limitations with the NMA that decreased its confidence in the results. The NMA included studies of patients with only BRAF V600E/K metastatic melanoma, as well as data from studies that had included patients with no mutations, but did not report data for the subgroups separately. The Committee noted that a primary assumption in a network meta-analysis is that the included studies need to be sufficiently similar to yield meaningful results, and that differences between trials with respect to study or patient characteristics may bias the indirect comparison. In addition, pERC noted that the inclusion of results from studies that were adjusted for early crossover would further decrease confidence in the assumptions of similarity of the trials required for a valid NMA.

## PATIENT-BASED VALUES

### Values of patients with metastatic melanoma: Need for treatments that extend survival, improve quality of life and reduce toxicities

pERC noted that the patient advocacy group input indicated that patients with unresectable or metastatic melanoma value prolongation of life and a reduction in the symptoms of their disease without a significant increase in side effects of treatment. pERC noted that the most common symptoms that patients wanted to manage better were pain, open skin lesions, loss of mobility, fatigue, fear, and anxiety, all of which impact on their quality of life.

pERC noted that patients reported that the side effects of current therapies also affect their quality of life. Commonly reported side effects from current therapies include extreme flu like symptoms and fatigue, cognitive impairment, nausea, fever, rigours, pain, arthritis, headaches, liver failure, low platelet counts, diarrhea, and severe depression. Respondents reported that many of these side effects last beyond a year, depending on the patient's ability to tolerate the therapy. Most patients do not complete the full year of treatment due to side effects. pERC noted that respondents expect that dabrafenib plus trametinib could either eliminate the disease altogether, slow progression or span the gap until another potentially more effective therapies are developed.

### Patient values on treatment: willing to tolerate side effects

pERC noted that input from patients who had been treated with the dabrafenib plus trametinib combination had experienced a benefit from the treatment, and in some patients, that benefit was continuing. Patients reported that the most common side effects included flu like symptoms and fatigue, fever, arthritis or joint pain, headaches, nausea and diarrhea. However, pERC noted that most respondents indicated that aside from persistent fatigue, the negative side effects of the combination treatment were worth the benefits from treatment.

## ECONOMIC EVALUATION

### Economic model submitted: cost-utility analysis; partition survival model

The pCODR Economic Guidance Panel assessed a cost-utility analysis of dabrafenib plus trametinib as first-line therapy for patients with BRAF V600 mutation-positive unresectable or metastatic melanoma in comparison to the following monotherapies: vemurafenib, dabrafenib, trametinib, ipilimumab, and dacarbazine. The health states considered in the model were alive and progression-free; alive with disease progression, and; dead.

### Basis of the economic model: Clinical and economic inputs

For the model, the cost of medications, one-time costs (diagnostic testing, progression, death), monthly

costs (direct medical cost per month for progression-free and post-progression), direct medical cost for the administration of medication in the presence and absence of AEs, and medical treatment of AE costs were considered. pERC noted that the combined price of dabrafenib and trametinib had the largest impact on the incremental cost of combination treatment compared with single-agent therapy.

In terms of clinical effect inputs into the model, the following were considered: disease progression, adverse event probabilities, the relative dose intensity, progression-free survival, overall survival and health utilities. Health utility data were obtained from the Combi-d and Combi-v studies using the EQ-5D questionnaire.

### Drug costs: Differences in submitted price and available list price

The cost of the combination of dabrafenib plus trametinib and of each agent as monotherapy in the main analysis was based on a confidential price submitted by the manufacturer. At the submitted confidential price, dabrafenib costs $[redacted] per capsule of 75 mg, and trametinib costs $[redacted] per tablet of 2 mg. *(The costs of dabrafenib and trametinib are based on confidential prices submitted by the manufacturer and cannot be disclosed to the public according to the pCODR Disclosure of Information Guidelines.)*
At the current list price, dabrafenib costs $63.33 per 75mg capsule, with a total dose cost per day of $253.33. The cost per 28 days is $7,093.64. Trametinib costs $290.00 per 2mg tablet for a total dose cost per day of $290.00. The cost over 28 days is $8120.00.

For the comparative monotherapies, vemurafenib costs $46.54 per 240mg tablet with a dose of eight tablets for a total cost of $372.32. The cost over 28 days is $10,424.96. Ipilimumab costs $5,800 per vial per 50mg with a dose of five vials for a total dose cost of $29,000. The cost over 28 days is $38,677. Dacarbazine costs $0.35 per mg with a total dose cost of $731.90. The cost over 28 days is $975.86.

### Cost-effectiveness estimates: Price of dabrafenib plus trametinib is largest driver of incremental cost-effectiveness

pERC noted that for each of the five comparisons of dabrafenib plus trametinib to a single-agent therapy, primary and secondary analyses were conducted, where the primary analysis did not consider a class effect for the two BRAF inhibitor treatments (dabrafenib and vemurafenib) and the secondary analysis did consider a class effect. pERC did not consider dacarbazine a clinically relevant comparator; therefore, the results of that comparison were not considered further. pERC noted that not only were the comparisons of dabrafenib plus trametinib with single-agent trametinib and ipilimumab based upon indirect estimates of clinical effect that were derived from an NMA, but that for the comparisons of dabrafenib plus trametinib with single-agent dabrafenib and vemurafenib, the estimates of clinical effect were also derived from the NMA (i.e., a combination of direct and indirect evidence). pERC noted several limitations in this NMA and noted that the estimates of incremental clinical effectiveness for the combination therapy versus single-agent trametinib, ipilimumab and dacarbazine were all uncertain given the identified limitations. In addition, pERC noted that given those same limitations, an analysis using the efficacy data directly from the Combi-d and Combi-v trials may have increased the Committee's confidence in the cost-effectiveness estimates.

pERC noted that the EGP's range of incremental cost-effectiveness ratios included the manufacturer's base case for each of the five comparisons. pERC also considered that given the high estimates of the incremental cost effectiveness, the assumption of a class effect for BRAF inhibitors did not sufficiently change the incremental cost-effectiveness estimates to impact upon the Committee's interpretation of these estimates.

pERC noted that the incremental cost of dabrafenib plus trametinib was largely driven by the high price of the two agents, dabrafenib and trametinib, which, consequently, was the major driver of the incremental cost-effectiveness for all five comparisons.

Notwithstanding the potential limitations of the estimates of the incremental cost-effectiveness, pERC concluded that dabrafenib plus trametinib could not be considered cost-effective in comparison with any of the five comparators and that the price of the two agents is the largest driver of the incremental cost-effectiveness.

## ADOPTION FEASIBILITY

**Considerations for implementation and budget impact:**
pERC discussed factors affecting the feasibility of implementing a funding recommendation for dabrafenib plus trametinib in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who have not received prior therapy for unresectable or metastatic melanoma.

Input from the pCODR Provincial Advisory Group indicated concerns regarding the high cost of dabrafenib plus trametinib as a barrier to implementation. pERC considered that the prices of the two drug was a major driver of the high incremental cost-effectiveness ratio. pERC also noted that the results of the budget impact analysis were sensitive to the prevalent population and the proportion of patients expected to present with BRAF mutation-positive disease.

pERC discussed the use of dabrafenib plus trametinib in the treatment of patients with unresectable or metastatic melanoma, who had not received prior therapy for their disease and who are currently receiving a single-agent BRAF inhibitor or MEK inhibitor. pERC considered that at the time of implementing a funding recommendation for dabrafenib plus trametinib, jurisdictions may consider addressing the short-term, time-limited need to offer dabrafenib plus trametinib to patients receiving first-line single-agent BRAF or MEK inhibitor therapy for unresectable or metastatic melanoma if the disease has not progressed.

pERC also discussed input from the pCODR Provincial Advisory Group that indicated concern regarding the appropriate sequencing of BRAF inhibitors, MEK inhibitors, and immune checkpoint inhibitors. pERC considered input from the pCODR Clinical Guidance Panel that as yet, there is no evidence to support or contraindicate the use of dabrafenib plus trametinib after progression on either a single-agent BRAF inhibitor or a single-agent MEK inhibitor; therefore, pERC could not make an informed recommendation on this matter. pERC also noted input from the pCODR Clinical Guidance Panel that as yet, there is no evidence to inform the optimal sequencing of dabrafenib plus trametinib with immune checkpoint inhibitors. Therefore, pERC was also unable to make an informed recommendation regarding the optimal sequencing of these agents in patients with unresectable or metastatic melanoma who have not received prior therapy. Finally, pERC noted that the provinces may want to consider prospectively collecting data regarding the efficacy and safety of dabrafenib plus trametinib administered before or after immune checkpoint inhibitors to help define the optimal sequencing of these agents in this patient population.

# DRUG AND CONDITION INFORMATION

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| **Drug Information** | • Dabrafenib is a BRAF V600 inhibitor; Trametinib is a MEK inhibitor<br>• Dabrafenib is available in 50 and 75 mg capsules; Trametinib is available in 0.5 mg and 2 mg tablets<br>• The recommended dose of dabrafenib is 150 mg orally, and of trametinib 2mg orally, both once daily, until disease progression |
| **Cancer Treated** | • BRAF V600 mutation-positive metastatic melanoma |
| **Burden of Illness** | • 6,500 new cases of primary melanoma were diagnosed in 2014 and approximately 1,100 individuals die from melanoma each year<br>• Most metastatic patients are not candidates for surgical resection and systemic treatment is the only alternative. The prognosis for these patients remains poor. The median survival has been 6-9 months with a 5-year survival of approximately 6%. |
| **Current Standard Treatment** | • Vemurafenib is currently a standard first line treatment of advanced, unresectable melanoma in patients with a BRAF V600 mutation.<br>• For patients with resistance to BRAF inhibitors, ipilimumab, a monoclonal antibody has been shown to improve survival in the first and second line settings in the treatment of metastatic melanoma |
| **Limitations of Current Therapy** | • Single agent BRAF inhibitors are approved and commonly used in BRAF positive metastatic melanoma; however, resistance typically develops within 6 to 8 months of treatment initiation and survival at that point is poor |

# ABOUT THIS RECOMMENDATION

**The pCODR Expert Review Committee (pERC)**

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

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Matthew Cheung, Oncologist
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Wasney, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Tallal Younis, Oncologist
Dr. Kelvin Chan, Oncologist

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

- Drs. Sunil Desai who was not present for the meeting
- Jo Nanson who was the designated Patient Member Alternate for this meeting

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

### Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of dabrafenib (Tafinlar) in combination with trametinib (Mekinist) 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

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

### Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. The manufacturer, as the primary data owner, did not agree to the disclosure of clinical and economic, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

### Use of this recommendation

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

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