pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

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
This 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: Dabrafenib (Tafinlar) **Submitted Funding Request:** For use as monotherapy for the treatment of patients with unresectable or metastatic melanoma, with a BRAF V600 mutation	
Submitted By: GlaxoSmithKline	**Manufactured By:** GlaxoSmithKline
NOC Date: July 16, 2013	**Submission Date:** March 18, 2013
Initial Recommendation: October 3, 2013	**Final Recommendation:** December 5, 2013

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding dabrafenib (Tafinlar) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for first-line treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma and ECOG performance status 0 or 1. If brain metastases are present, patients should be asymptomatic or stable. The Committee made this recommendation because it was satisfied that there is an overall net clinical benefit of dabrafenib compared with dacarbazine. However, at the submitted price and the Economic Guidance Panel's best estimates of the incremental cost-effectiveness ratio, dabrafenib could not be considered cost-effective compared with dacarbazine. In the absence of a direct comparison of clinical effectiveness with vemurafenib, the uncertainty in the economic analyses was too great for the Committee to determine dabrafenib's net clinical benefit or cost-effectiveness compared with 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 in metastatic melanoma, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of dabrafenib to an acceptable level.

Confirming Cost-Effectiveness of Dabrafenib
Provinces should be aware that the cost-effectiveness estimates of dabrafenib compared with vemurafenib assumed that the price of vemurafenib in all jurisdictions is the same as the list price. Because the economic analysis is very sensitive to drug price, any change in the price of vemurafenib could considerably change the cost-effectiveness of dabrafenib compared with vemurafenib.

Implementation of Dabrafenib and BRAF Mutation Testing
Because use of dabrafenib requires patients to have BRAF V600 mutation positive melanoma, diagnostic testing for BRAF V600 mutations should be made available with funding for dabrafenib.

Time-Limited Need for Dabrafenib in Second-Line Setting
At the time of implementing a funding recommendation for dabrafenib, jurisdictions may consider addressing the short-term, time-limited need for dabrafenib in the second-line setting for those patients with BRAF V600 mutations who were treated with chemotherapy in the first line setting, prior to BRAF inhibitors being available, while recognizing that there is a lack of robust evidence available on the clinical benefit and cost-effectiveness of dabrafenib in the second-line setting.

SUMMARY OF pERC DELIBERATIONS

pERC noted that metastatic melanoma affects a small patient population but the incidence of melanoma is increasing. pERC also recognized that, until recently, there have been very few effective treatment options for metastatic melanoma and there is a need for new and effective therapies in this setting. One randomized controlled trial comparing dabrafenib with dacarbazine in untreated patients (BREAK-3, Hauschild 2012) was included in the pCODR systematic review. pERC noted that at the time the trial was designed, dacarbazine was an appropriate comparator. However, vemurafenib, another BRAF inhibitor, has recently become available and has become the standard of care in patients who are BRAF mutation positive.

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 BREAK-3, which evaluated dabrafenib as a first-line therapy for metastatic melanoma. pERC concluded that there is a net clinical benefit of dabrafenib compared with dacarbazine based on a significant improvement in progression-free survival (PFS). pERC noted that no overall survival benefit was demonstrated for dabrafenib in the BREAK-3 study but observed that the results were likely confounded because cross-over of dacarbazine patients to dabrafenib treatment was permitted upon disease progression. pERC also noted that quality of life was measured in the BREAK-3 study but that the interpretation of the results was challenging.

pERC discussed the toxicity profile of dabrafenib based on the adverse events observed in BREAK-3. pERC considered that toxicities appeared manageable compared with dacarbazine. pERC noted that in the absence of a head-to-head trial, the relative efficacy and safety of dabrafenib compared with vemurafenib was uncertain. pERC discussed the results of an indirect comparison of dabrafenib and vemurafenib conducted by the manufacturer but noted that there are limitations to indirect and cross-trial comparisons and did not consider the evidence to be sufficient to assume that the two therapies have similar efficacy and harms. pERC was, therefore, unable to draw any conclusions from the results of the indirect comparison between dabrafenib and vemurafenib. However, pERC noted that the pCODR Clinical Guidance Panel considered that, in clinical practice, dabrafenib may provide another treatment option for patients who do not tolerate vemurafenib due to toxicities such as severe phototoxicity.

pERC discussed two additional studies that provided supporting information on the use of dabrafenib in patients previously treated with chemotherapy (BREAK-2, Ascierto 2013) and in patients with brain metastases (BREAK-MB, Long 2012). However, pERC considered that these were single-arm studies, which, in this situation, did not provide sufficient evidence to recommend funding dabrafenib in these populations. pERC considered that, in the short-term, there may be a prevalent population of patients who have received prior chemotherapy but who have a need for dabrafenib and provinces should consider addressing this short-term, time-limited need. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the submitter regarding the use of dabrafenib in patients with the V600K mutation. pERC discussed that BREAK-3 only included patients with the BRAF V600E mutation. Therefore the effectiveness of dabrafenib in patients with other mutations such as V600K is uncertain. However, considering the totality of evidence evaluating dabrafenib in patients with different V600 mutation types, i.e. randomized controlled trials and single arm studies, pERC concluded that it would be reasonable to use dabrafenib in patients with different V600 mutations.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the submitter and pCODR's Provincial Advisory Group regarding the use of dabrafenib in patients with brain metastases. pERC noted that the BREAK-MB study evaluated dabrafenib in patients with asymptomatic brain metastasis (with or without prior treatment). However, pERC discussed that patients with stable brain metastases is a broad group and could include both previously treated and untreated patients. pERC also considered that there may be some patients with brain metastases who are asymptomatic but not stable and it would be clinically reasonable to treat these patients with dabrafenib.

pERC reviewed input provided by two patient advocacy groups and determined that dabrafenib aligns with patient values. Patients indicated that they were willing to accept some risks and side effects even if life were extended only for a short period of time. In addition, patients reported that the newer treatment options for metastatic melanoma have produced a substantial positive impact on their quality of life. Patients also indicated that they found the side effects of dabrafenib easier to tolerate than other available treatments. pERC considered this input in the context of the BREAK-3 study, which demonstrated that dabrafenib has a clinical benefit and manageable toxicities compared with dacarbazine and concluded that dabrafenib aligns with patient values.

pERC also deliberated upon the cost-effectiveness of dabrafenib. pERC noted that the economic analysis was strongly influenced by the overall survival estimates and the price of dabrafenib. pERC considered that at both the manufacturer's and the pCODR Economic Guidance Panel's estimates, dabrafenib was not cost-effective at the submitted price compared with dacarbazine. pERC also discussed the cost-effectiveness of dabrafenib compared with vemurafenib. However, pERC considered that there was insufficient evidence to assume that dabrafenib and vemurafenib are clinically equivalent and that there was considerable uncertainty in the incremental cost effectiveness ratios based on the indirect comparison of dabrafenib with vemurafenib. In addition, pERC noted that the economic analysis was based on the list price of vemurafenib but noted that the effective price of vemurafenib is unknown and may vary across jurisdictions. Therefore, pERC considered that there was too much uncertainty to determine the relative cost-effectiveness of dabrafenib compared with vemurafenib.

pERC discussed the feasibility of implementing a funding recommendation for dabrafenib. It was noted that because the clinical effect of BRAF inhibitors is limited to patients with BRAF V600 mutation, diagnostic testing for BRAF mutations is essential and diagnostic testing for BRAF V600 mutations should be made available with funding for dabrafenib. Input from pCODR's Provincial Advisory group indicated that BRAF testing is now available in some jurisdictions so many patients already have access to testing.

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:

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

The pERC initial recommendation was to fund dabrafenib (Tafinlar) conditional on the cost-effectiveness being improved to an acceptable level. Funding was recommended for first-line treatment of patients with BRAF V600E mutation-positive unresectable or metastatic melanoma and ECOG performance status 0 or 1 and if brain metastases are present, they should be stable. Feedback on the pERC Initial Recommendation indicated that the manufacturer, one patient advocacy group and pCODR's Provincial Advisory Group agreed in part with the initial recommendation while the second patient advocacy group agreed with the initial recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the efficacy and safety of dabrafenib on patient outcomes including overall survival, progression free survival, quality of life, and adverse events compared with standard therapies

or best supportive care in the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Studies included: one randomized controlled trial in untreated patients

The pCODR systematic review included one open-label, randomized controlled trial (N=250), the BREAK-3 study (Hauschild 2012), which compared dabrafenib (150 mg orally twice daily) to dacarbazine (1000 mg/m^2 intravenously every three weeks). Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from the pCODR Provincial Advisory Group seeking guidance on the stopping criteria for dabrafenib therapy. It was noted in the BREAK-3 study, that patients continued treatment until radiologic progression of disease, occurrence of unacceptable toxicities, death, or withdrawal of consent. In the absence of additional data to inform optimal duration of dabrafenib therapy, pERC was unable to provide further guidance on stopping criteria.

Patients were allowed to crossover to the dabrafenib group from dacarbazine at disease progression. At the pre-specified analysis date of December 19, 2011, 44% of dacarbazine patients crossed-over to dabrafenib while at the June 25, 2012 data cut-off, a total of 56% of dacarbazine patients had crossed over to the dabrafenib group. pERC discussed this study design and noted that allowing cross-over upon disease progression may have confounded overall survival results from the BREAK-3 study.

The pCODR review also provided contextual information on:

- relevant comparators including a critical appraisal of an indirect comparison of dabrafenib with vemurafenib based on the BREAK-3 (Hauschild 2012) and BRIM-3 (Chapman 2011) studies
- two relevant single-arm studies, BREAK-2 (Ascierto 2013) and BREAK-MB (Long 2012)
- BRAF mutation testing in metastatic melanoma.

Patient populations: untreated, BRAF V600 mutation positive, stable or asymptomatic brain metastases

BREAK-3 included patients with previously untreated metastatic melanoma (stage IV or unresectable stage III). As per the trial inclusion criteria, patients in BREAK-3 had an ECOG status of 0 and 1 (66% and 33%, respectively). Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from the pCODR Provincial Advisory Group on the use of dabrafenib in patients with an ECOG status greater than 1. It was noted that in the absence of data to support the use of dabrafenib in patients with ECOG performance status greater than 1, pERC was unable to make an inference for its use in a broader patient population.

Patients included in BREAK-3 also had a confirmed BRAF V600E mutation. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the submitter regarding the use of dabrafenib in patients with the V600K mutation. pERC noted that BREAK-3 only included patients with the BRAF V600E mutation. Therefore, the effectiveness of dabrafenib in patients with other mutations such as V600K is uncertain. However, considering the totality of evidence evaluating dabrafenib in patients with different V600 mutation types, i.e. randomized controlled trials and single arm studies, pERC considered it would be reasonable to use dabrafenib for patients with different V600 mutations.

pERC considered that because the clinical effect of BRAF inhibitors is limited to patients with a BRAF V600 mutation, diagnostic testing for BRAF V600 mutation status is essential and should be made available with funding for dabrafenib. However, pERC noted that the specificity of testing for specific amino acid mutations such as V600E and V600K is unclear.

pERC noted that the BREAK-3 study only included patients with stable brain metastases (i.e. no evidence of active metastases for more than 3 months after surgery or stereotactic radiosurgery). However, BREAK-MB (Long 2012), provided supporting information on the use of dabrafenib in patients with asymptomatic brain metastasis (with or without prior treatment) who were either BRAF V600E or V600K mutation positive. pERC noted that BREAK-MB was a single-arm study. Therefore, pERC could not draw a robust conclusion on the magnitude of clinical benefit associated with dabrafenib in this population. Therefore, pERC considered that there was insufficient evidence to recommend funding dabrafenib for these patients. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the submitter and pCODR's Provincial Advisory Group regarding the use of dabrafenib in patients with brain metastases. pERC noted that the BREAK-MB study evaluated dabrafenib in patients with asymptomatic brain metastasis (with or without prior treatment). However, pERC discussed that patients with stable brain metastases is a broad group and could include both previously treated and untreated patients. pERC also considered that there may be some patients with brain metastases who are

asymptomatic but not stable. pERC also discussed that some patients may be stable but symptomatic as patients could have residual symptoms from previous metastases but be stable from a central nervous system perspective. These patients would have other metastatic disease requiring therapy. pERC considered that it would be clinically reasonable to treat these patients with dabrafenib.

Key efficacy results: improvement in progression-free survival, overall survival confounded by cross-over

Key outcomes deliberated on by pERC included investigator-assessed progression free survival (PFS), the primary endpoint of the BREAK-3 study, and overall survival. pERC noted that the median investigator-assessed progression-free survival was 5.1 versus 2.7 months in the dabrafenib and dacarbazine groups, respectively (HR=0.30, 95% CI: 0.18 to 0.51) at the December 19, 2011 data cut-off and 6.9 versus 2.7 months (HR=0.37, 95% CI: 0.23 to 0.58) at the June 2012 data cut-off.

pERC noted that a statistically significant overall survival benefit favouring dabrafenib compared with dacarbazine was not observed in any of the analyses. pERC discussed that it would be challenging to demonstrate an overall survival benefit given the design of BREAK-3, which permitted cross-over of dacarbazine patients to dabrafenib upon disease progression. Therefore, pERC considered that the progression-free survival advantage demonstrated in BREAK-3 was sufficient to conclude that there is a clinical benefit of dabrafenib in untreated patients with metastatic melanoma.

Quality of life: interpretation of quality of life outcomes challenging

In the BREAK-3 study, quality of life was measured at week 12 using the EORTC QLQ C-30 and EQ-5D scales. pERC noted that, although statistical significance was not assessed, improvements from baseline in EORTC QLQ C-30 were observed in the dabrafenib group, for emotional functioning, social functioning and all symptoms except fatigue and dyspnea. In the dacarbazine group, role functioning was improved but patients reported worsening of symptoms compared with baseline. For EQ-5D, most patients had incomplete assessments post-baseline. pERC discussed the quality of life outcomes but considered that the interpretation of results was challenging given the lack of statistical assessment and large proportion of missing data.

Safety: toxicities manageable compared with dacarbazine

pERC discussed the toxicity profile of dabrafenib based on the adverse events observed in BREAK-3. The proportion of patients reporting serious non-fatal adverse events and who discontinued treatment due to adverse events was similar between dabrafenib and dacarbazine. However, more patients in the dacarbazine group reported grades three and four adverse events compared to dabrafenib (41% vs. 33%, respectively). Non-fatal serious adverse events occurred in 23% of patients in the dabrafenib group and included cutaneous squamous cell carcinoma (6%), pyrexia (4%), and malignant melanoma (2%). Adverse events commonly seen in dabrafenib patients included hyperkeratosis, headache, pyrexia, arthralgia, skin papilloma, alopecia and palmar-plantar erythrodysaesthesia syndrome. pERC discussed these data and considered that the toxicity of dabrafenib appeared manageable compared with dacarbazine.

Comparator information: uncertainty of efficacy and safety compared with vemurafenib

pERC noted that both pCODR's Provincial Advisory Group and the pCODR Clinical Guidance Panel considered vemurafenib to be the current standard of care for patients with BRAF V600 mutations. The BREAK-3 study compared dabrafenib with dacarbazine. Therefore, pERC also discussed the results and critical appraisal of an indirect comparison of dabrafenib (BREAK-3, Hauschild 2012) with vemurafenib (BRIM-3, Chapman 2011), which had been conducted by the manufacturer. pERC noted that the conclusions drawn from indirect comparisons are not as robust as those from direct, head-to-head trial data and, therefore, the findings should be interpreted with caution. pERC also discussed that an overall survival advantage was observed for vemurafenib compared with dacarbazine in the BRIM-3 study, but an overall survival advantage for dabrafenib was not clearly demonstrated in the BREAK-3 study. Therefore, pERC did not consider that the evidence was sufficient to assume that dabrafenib and vemurafenib have similar efficacy. However, pERC noted that patient advocacy group input indicated that not all patients can tolerate the adverse events associated with the new melanoma treatments. In addition, the pCODR Clinical Guidance Panel indicated that, although the two treatments have not been evaluated in a head-to-head trial, dabrafenib may have a lower incidence of phototoxicity (2% in BREAK-3) and second primary malignancies compared with vemurafenib. Therefore, dabrafenib may provide another treatment option for patients who do not tolerate vemurafenib due to toxicities such as severe phototoxicity.

Previously treated patients: evidence not robust and magnitude of benefit uncertain
pERC also discussed relevant contextual information provided from the BREAK-2 study (Ascierto 2013), which was a single arm study evaluating dabrafenib in previously treated patients with a BRAF V600E or V600K mutation who had not received a prior BRAF inhibitor or MEK inhibitor. pERC discussed the limitations of non-randomized, non-comparative studies and considered that the interpretation of the evidence presented in such studies to be challenging. pERC considered that the evidence for dabrafenib in this setting was not robust in this situation. Given the lack of a direct comparator arm, the magnitude of dabrafenib benefit is uncertain and the manufacturer's submission likely overestimates the magnitude of clinical benefit associated with dabrafenib in previously treated patients. However, pERC concluded that, in the short-term, there may be a prevalent population of patients who have previously received chemotherapy but who might benefit from dabrafenib.

Need: choice of effective treatment options for patients who cannot tolerate vemurafenib
pERC noted that until recently, there have been no effective therapies to treat metastatic melanoma. It was discussed that there is no evidence that dacarbazine improves overall survival and it has associated side effects that patients frequently find difficult to tolerate. pERC noted that although vemurafenib has recently become the standard treatment for patients who are BRAF V600 mutation positive, there is still a need for new effective treatments that would allow patients a choice of therapies. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the patient advocacy group indicating that dacarbazine is not an appropriate comparator because it is not effective in treating metastatic melanoma. However, pERC noted that at the time the BREAK-3 study was designed, dacarbazine was an appropriate comparator as it was widely used in practice.

Patient advocacy group input indicates that patients experience serious and severe side effects with currently available therapies and seek alternative treatment options. Patient advocacy group input also indicated that patients found the side effects of dabrafenib easier to tolerate than other available treatments. Therefore, pERC considered that dabrafenib may provide another treatment option for patients who do not tolerate the side effects of vemurafenib. pERC also noted that patients with metastatic melanoma are often young and while this cancer may affect a small patient population, the incidence is increasing.

PATIENT-BASED VALUES

Values of patients with metastatic melanoma: extending life and improving quality of life
pERC discussed input on dabrafenib provided by two patient advocacy groups. Their input indicated that without treatment, patients with metastatic melanoma face the certainty of disease progression or death. Worsening of symptoms as disease progresses includes increasing shortness of breath, severe pain, fatigue, memory loss, loss of coordination, cognitive impairment from brain metastases or radiation, loss of sight, lymphedema and weight loss. From a patient perspective, the primary concerns include increasing life expectancy and preventing disease progression. pERC considered this input in the context of the BREAK-3 study, which demonstrated that dabrafenib improves progression-free survival compared with dacarbazine and concluded that dabrafenib has a clinical benefit that aligns with patient values. Patients also reported that the newer treatment options for metastatic melanoma have produced a substantial positive impact on their quality of life, although pERC considered that interpretation of quality of life outcomes from BREAK-3 was challenging.

Patient values on treatment: side effects tolerable, choice of treatment options
Patient advocacy group input reported on patients' experiences with side effects of treatments for metastatic melanoma. Depending upon the site of metastases and type of treatment, many patients suffer from adverse events such as headaches, neuropathy, bone fractures, blindness, hair loss, depression, anxiety, memory loss, decreased mobility, colitis, and disfiguring surgeries. Many patients have had extensive surgery to remove lymph nodes and/or tumours, which has caused decreased mobility, loss of functioning or capacity of certain organs, scarring and body image issues. In general, patient advocacy group input indicates that patients experience serious and severe side effects with currently available therapies and seek alternative treatment options. Patients also indicated that they were willing to accept some risks and side effects even if life were extended only for a short period of time. Patients also indicated that they found the side effects of dabrafenib easier to tolerate than other available treatments. pERC considered that based on the BREAK-3 study, the toxicity profile of dabrafenib was tolerable. Therefore, pERC concluded that dabrafenib aligns with patient values. pERC also noted that

dabrafenib is an oral treatment and the number of capsules required each day is less for dabrafenib than for vemurafenib (4 versus 8 capsules), a factor that patients value.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness and cost-utility

The pCODR Economic Guidance Panel assessed a cost-effectiveness and cost utility analysis of dabrafenib compared with dacarbazine in untreated patients with metastatic melanoma who are BRAF V600E mutation positive based on the results of the BREAK-3 study. An economic analysis comparing dabrafenib with vemurafenib, based on an indirect comparison, was also assessed.

Basis of the economic model: clinical and economic inputs

Costs included in the model were medication costs, the cost of BRAF testing and costs of follow-up both pre-progression and post-progression.

Key clinical effects included progression-free survival and overall survival. In the analysis versus dacarbazine these were based on the BREAK-3 study and, in the analysis versus vemurafenib, they were based on the indirect comparison.

Drug costs: uncertainty in pricing

At the list price dabrafenib costs $42.22 and $63.33 per 50mg and 75 mg capsule, respectively. At the recommended daily dose of 150 mg twice daily (4 x 75 mg capsules per day), the cost of dabrafenib is $253 per day and the average cost per 28-day course is $7,093.

At the list price, vemurafenib costs $46.54 per 240 mg tablet. At the recommended dose of 960 mg twice daily (8 tablets per day), the cost of vemurafenib is $372 per day. The average cost per 28-day course is $10,425.

pERC noted that the manufacturer assumed that the price of vemurafenib is the same as the list price in all jurisdictions. However, the effective price of vemurafenib may vary across jurisdictions and be lower than the list price if it is based upon a confidential price that is unknown to pCODR. pERC noted that this created substantial uncertainty in the cost-effectiveness of dabrafenib relative to vemurafenib.

Cost-effectiveness estimates: not cost-effective compared with dacarbazine, uncertainty in cost-effectiveness compared with vemurafenib

pERC deliberated upon the cost-effectiveness of dabrafenib compared with dacarbazine. pERC noted that the economic analysis was strongly influenced by overall survival estimates and the price of dabrafenib. pERC discussed that there was no significant difference in overall survival between treatments in the BREAK-3 study. It was also noted that sensitivity analyses conducted by the manufacturer around overall survival estimates produced a wide range of cost-effectiveness estimates. pERC noted that the manufacturer's estimates of cost-effectiveness compared with dacarbazine were similar to the pCODR Economic Guidance Panel's estimates. However, at the range of incremental cost-effectiveness ratios reported and at the submitted price, pERC concluded that dabrafenib was not cost-effective compared with dacarbazine. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the patient advocacy group indicating that the high cost of dabrafenib should not limit patients' access to this treatment and related comments should be removed. However, pERC noted that assessing cost-effectiveness is an essential component of pERC's deliberative framework.

pERC also discussed the cost-effectiveness of dabrafenib compared with vemurafenib. pERC noted that one of the scenarios submitted by the manufacturer assumed a class effect of dabrafenib and vemurafenib. However, pERC considered that there was insufficient evidence to assume that dabrafenib and vemurafenib are clinically equivalent. pERC also discussed the incremental cost effectiveness ratios based on the indirect comparison of dabrafenib with vemurafenib. pERC noted that there was a very wide range of possible incremental cost-effectiveness ratios and considerable uncertainty as to where in the range the true cost-effectiveness estimate lies given the limitations of relying on indirect comparisons. In addition, pERC noted that the economic analysis was based on the list price of vemurafenib but that the effective price of vemurafenib is unknown and may vary across jurisdictions. Therefore, pERC considered

that there was too much uncertainty to determine the relative cost-effectiveness of dabrafenib compared with vemurafenib.

pERC also noted that the cost-effectiveness of dabrafenib in the second-line setting of previously treated patients is unknown as these patients were not included in the BREAK-3 study, upon which the cost-effectiveness analysis was based.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: BRAF V600 mutation testing and time-limited access for previously treated patients

pERC considered the feasibility of implementing a funding recommendation for dabrafenib. It was noted that because the clinical effect of BRAF inhibitors is limited to patients with a BRAF V600 mutation, diagnostic testing for BRAF mutations is essential and diagnostic testing for BRAF V600 mutations should be made available with funding for dabrafenib. Input from pCODR's Provincial Advisory group indicated that BRAF testing is now available in some jurisdictions so many patients will already have access to appropriate testing. pERC also further discussed that BREAK-3 only included patients with the V600E mutation, and not patients with the V600K mutation and the specificity of diagnostic testing for specific amino acid mutations such as E and K, is unclear.

pERC considered that prior to the availability of dabrafenib, there may have been patients who received other treatments in the first-line setting. Therefore, for a time-limited period it would be clinically reasonable for BRAF V600 mutation positive patients who progressed after first-line therapy (e.g. chemotherapy, treatment in a clinical trial) to have access to dabrafenib in the second-line setting. pERC noted that this need was likely to diminish as BRAF inhibitors become the established first-line treatment option for BRAF V600 mutation positive patients.

DRUG AND CONDITION INFORMATION

Drug Information	• BRAF V600 inhibitor • Available as 50 and 75 mg capsules, oral administration • Recommended dose is 150 mg twice daily
Cancer Treated	• BRAF V600 mutation-positive metastatic melanoma
Burden of Illness	• Estimated 5,500 new cases of primary melanoma in 2011 and approximately 950 patients will die from melanoma annually. • Unresectable Stage III and IV melanoma is an incurable malignancy with approximately 6% of patients surviving 5 years, and 75% percent of patients dying within one year of diagnosis
Current Standard Treatment	• Vemurafenib is currently a standard first line treatment of advanced, unresectable melanoma in patients with a BRAF V600 mutation. • Until recently, dacarbazine was standard first-line treatment although it does not have an overall survival benefit and has serious toxicities
Limitations of Current Therapy	• Newer treatments may not be tolerated by all patients, therefore, there is a need for effective alternative therapies

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. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
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. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

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

- Jo Nanson, Dr. Chaim Bell and Dr. Sunil Desai who were not present for the meeting

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

- Dr. Bill Evans who was not present for the meeting

Avoidance of conflicts of interest

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

Information sources used

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

Consulting publicly disclosed information

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

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.

Disclaimer

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report. This document is composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).