pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Dabrafenib (Tafinlar) for Metastatic Melanoma

December 5, 2013

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

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.

Reports generated by pCODR are 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 report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
1 University Avenue, suite 300
Toronto, ON
M5J 2P1

Telephone: 416-673-8381
Fax: 416-915-9224
Email: info@pcodr.ca
Website: www.pcodr.ca

TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy 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.

Dabrafenib is a reversible and potent ATP-competitive inhibitor which selectively inhibits BRAF V600E kinase.[1] Health Canada recently approved dabrafenib as monotherapy for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.[2] The recommended dose is 150 mg administered orally twice daily.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one study, BREAK-3, which assessed the efficacy and safety of dabrafenib, 150 mg orally twice daily (n=187), compared with dacarbazine, 1000 mg/m^2 intravenously every three weeks (n=63), in an international, multicentre, open-label, randomized controlled trial.[3,4]

BREAK-3 enrolled patients with previously untreated metastatic melanoma (stage IV or unresectable stage III) with a BRAF V600E mutation confirmed by allele-specific polymerase chain reaction assay (Response Genetics Inc.). More than 95% of patients had Stage IV melanoma at screening. The majority of patients also had and ECOG status of 0 (66% and 70%) and 1 (33% and 25%) in the dabrafenib and dacarbazine group, respectively Dacarbazine patients were allowed to cross-over to the dabrafenib group at disease progression. At the pre-specified analysis date of December 19, 2011, 44% of 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.

Efficacy

The primary end-point for the study was progression free survival (PFS) as assessed by the investigator. Key secondary outcomes included overall survival (OS) and PFS assessed by an independent review committee (IRC). The median investigator-assessed progression-free survival was 5.1 and 2.7 months at the December 19 2011 data cut-off in the dabrafenib and dacarbazine groups, respectively (HR: 0.30, 95% CI: 0.18, 0.51) with a 2.4 months difference in PFS (Table 6). At the June 25 2012 data cut-off, the investigator assessed progression-free survival hazard ratio was 0.37 (95% CI: 0.23, 0.58).

The median PFS based on the IRC assessment was 6.7 and 2.9 months in the dabrafenib and dacarbazine arms at the Dec 19, 2011 cut-off, respectively (HR: 0.35, 95% CI: 0.20, 0.61). The overall survival analysis at three data cut-offs showed no statistically significant difference between dabrafenib and dacarbazine (Table 7).The overall survival estimates are however confounded by dacarbazine patients who crossed over to dabrafenib. An analysis that adjusted for confounding effects of cross-over on overall survival showed no statistically significant difference in OS between dabrafenib and dacarbazine.[5]

Health related quality of life was measured using the EORTC QLQ C-30 and EQ-5D. In the dabrafenib group, improvements from baseline in EORTC QLQ C-30 were seen at week 12

for emotional functioning and social functioning, and for all symptoms except fatigue and dyspnea. In the dacarbazine group, role functioning was improved but patients reported worsening of symptoms at week 12.[3,6] For the EQ-5D measure, given that most patients had incomplete assessments post-baseline, interpreting the findings was challenging.

Harms

Up to the December 19, 2011 data cut-off, approximately 11% and 14% of patients had died in the dabrafenib and dacarbazine arms, respectively. Serious non-fatal adverse events occurred in 23% vs. 22% of patients receiving dabrafenib (predominantly due to squamous cell carcinomas and pyrexia) compared to dacarbazine, respectively. Five patients experienced a fatal serious adverse event (not related to disease progression) with dabrafenib, none of which were attributed to the study treatment, while no fatal serious adverse event (not related to disease progression) was reported with dacarbazine. Patients in the dacarbazine group experienced a higher frequency of grades three and four adverse events compared to dabrafenib (41% vs. 33%, respectively). Adverse events commonly seen in dabrafenib patients (occurring ≥20% of patients) included hyperkeratosis, headache, pyrexia, arthralgia, skin papilloma, alopecia and palmar-plantar erythrodysaesthesia (PPE) syndrome. In each treatment arm, 3% patients permanently discontinued treatment due to adverse events.

1.2.2 Additional Evidence

pCODR received input on dabrafenib for metastatic melanoma from two patient advocacy group, (Melanoma Network of Canada and Save Your Skin Foundation). Provincial Advisory group input was obtained from five of the nine provinces participating in pCODR.

In addition, three supplemental questions were identified during development of the review protocol as relevant to the pCODR review of dabrafenib and are discussed as supporting information:

- **Summary of Indirect comparison of Dabrafenib to vemurafenib**

  The indirect comparison was based on data from the BREAK-3 and BRIM-3 studies, which evaluate dabrafenib and vemurafenib, respectively. Conclusions drawn from such indirect comparisons are not as robust as those from direct, head-to-head trial data, and therefore the findings should be interpreted with caution.

- **Summary of two Supportive Phase II trials, BREAK-2 and BREAK-MB**

  BREAK-2 and BREAK-MB were open-label, phase 2, multi-centre, single-arm trials conducted in patients with BRAF V600E or V600K metastatic melanoma. Although the two studies did not meet the pCODR systematic review protocol's inclusion criteria, they were identified as relevant to the review. BREAK-2 included previously treated patients while BREAK-MB included patients with brain metastases with or without prior treatments for brain metastases.

- **Summary of BRAF Mutation Testing in Metastatic Melanoma**

1.2.3 Interpretation and Guidance

Burden of Illness and Need

In Canada, 5500 new cases of primary melanoma are expected in 2011 and approximately 950 patients will die from melanoma.[7]

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. Brain metastases are relatively common in advanced melanoma and occur in up to 75% of patients with overt metastatic disease.[8] They often prove to be relatively refractory to radiotherapy and systemic treatment and are associated with a particularly dismal prognosis.

Select patients with metastatic disease would benefit from surgery or radiotherapy alone. Systemic treatment is most commonly offered. Over the past 30 years, the standard first line systemic therapy has been dacarbazine but complete responses are rare and have never been shown to improve survival in metastatic melanoma.[9-14] A very wide spectrum of chemotherapeutic and immunological treatments approaches have been explored in metastatic melanoma with limited to no success.

Vemurafenib is a BRAF inhibitor that selectively targets the mutated BRAF V600 and is currently a standard first line treatment of advanced, unresectable melanoma in patients harbouring a V600 mutation.

Effectiveness

In BREAK-3 dabrafenib improved progression free survival and yielded high response rates in comparison to dacarbazine. The benefit in PFS was seen in all subgroups including ECOG PS, LDH normal versus elevated, stage of disease, age and sex. An overall survival benefit was not seen as of the data cut-off. Future analysis for overall survival benefit will however be confounded by patients' crossing over to dabrafenib.

In the dabrafenib group, improvements in HRQoL from baseline were seen at week 12 for emotional functioning and social functioning, and for all symptoms except fatigue and dyspnea. Whether or not any of these findings were clinically meaningful is unknown as a minimal clinically important difference has not been determined in melanoma patients. The lack of blinding may also have resulted in bias in Quality of Life assessments by the patients.

Supporting Information

Although not formally compared in an RCT to vemurafenib, the current standard of care in first line setting, dabrafenib has a similar mechanism of action. It has similar high response rates and progression free survival when considering BRIM-3, which evaluates vemurafenib and was included in the manufacturer's indirect comparison. Dabrafenib may have a lower incidence of phototoxicity and a lower rate of secondary skin cancers than vemurafenib. This would however need to be confirmed by a head to head comparison of the two drugs.

The consistent high response rates and median survival in phase I and II trials (eg. BREAK-2) suggest that dabrafenib would not be less efficacious in the 2nd line in patients harbouring V600E mutation who have not received a prior BRAF or MEK inhibitor. Break-MB demonstrated that dabrafenib was also well tolerated in V600E patients with either untreated or pre-treated brain metastases with the expected adverse event profile except that 6% of patients had an intracranial haemorrhage. In patients treated with dabrafenib,

the investigator assessed OIRR (overall intracranial response rate) in the untreated and pre-treated patients was 39% and 31% respectively, while the overall response rates were 38% and 31%.

Safety

Overall dabrafenib was well tolerated with dose reductions needed in 28% of patients receiving dabrafenib and 17% in patients receiving dacarbazine.

1.3 Conclusions

The pCODR Melanoma Guidance Panel concluded that there is a net overall clinical benefit to dabrafenib based on one randomized clinical trial, BREAK-3 which demonstrated an improvement of progression free survival when compared to dacarbazine in previously untreated patients with a V600E mutation positive unresectable or metastatic melanoma. An overall survival benefit was not seen but may have been confounded by the crossover of patients to dabrafenib after progressing on dacarbazine. The panel considered that crossover was justified because it would have been unethical to deny a BRAF inhibitor to patients after progressing on dacarbazine.

In making this conclusion, the Clinical Guidance Panel also considered that:

- Dabrafenib is effective in the second line setting based on the results of the single arm BREAK-2 study.
- Dabrafenib has clinical benefit in patients with treated or untreated brain metastases or asymptomatic brain metastases that harbour the V600E mutation based on the single arm BREAK-MB study. Therefore, it would be reasonable to use dabrafenib in patients with clinically stable brain metastasis. i.e., those who don't require steroids or who are on a stable dose of steroids.
- Although the most robust evidence for dabrafenib is in patients with V600E mutations dabrafenib would still be clinically reasonable treatment option for patients with other V600 mutations.
- There was no evidence to support the use of Dabrafenib in patients who had received a prior BRAF inhibitor or a MEK inhibitor.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding dabrafenib for unresectable or metastatic melanoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding dabrafenib conducted by the Melanoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on dabrafenib and a summary of submitted Provincial Advisory Group Input on dabrafenib are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

The Notice of Compliance for dabrafenib was granted on July 16 2013. It is indicated as monotherapy for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation. The recommended dose is 150 mg administered orally twice daily.

Dabrafenib is a reversible and potent ATP-competitive inhibitor which selectively inhibits BRAF V600E and V600K kinase.[1] Other selective BRAF inhibitors include vemurafenib (Zelboraf, Roche) and LGX818 (in clinical trials, Novartis). BRAF mutations are present in approximately 50% of cutaneous melanomas. More than 75% of these mutations have the genotype V600E and less commonly V600K.[1]

2.1.2 Objectives and Scope of pCODR Review

The objective of this review is to evaluate the effect 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.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

The efficacy and safety of dabrafenib 150 mg orally twice daily (n=187) were compared with dacarbazine 1000 mg/m^2 intravenously every three weeks (n=63) in BREAK-3, an international, multicentre, open-label, randomized controlled trial.[3,4]

The study enrolled patients with previously untreated metastatic melanoma (stage IV or unresectable stage III) with a BRAF V600E mutation confirmed by allele-specific polymerase chain reaction assay (Response Genetics Inc.). Patients were also included if

they had an Eastern Cooperation Oncology Group (ECOG) performance status of 0 or 1, no brain metastases, and adequate renal, hepatic, haematological and cardiac functions. Median age was 53 years in the dabrafenib group and 50 years in the dacarbazine group. Treatment groups were balanced for patient and disease characteristics. More than 95% of the patients had Stage IV melanoma at screening.

The primary outcome of BREAK-3 was progression-free survival (PFS) as assessed by the investigator. Dacarbazine patients were allowed to cross-over to the dabrafenib group at disease progression. Treatment was first initiated on February 16, 2011 and the cut-off date for data analysis was December 19, 2011. A target sample size of 200 patients was calculated to observe 102 PFS events with a statistical power of 99.7% to detect a hazard ratio of 0.33. At the data cut off of December 19, 2011, median overall survival had not been reached on either arm. Two unplanned analyses were performed at data cut offs of June 25, 2012 and December 18, 2012.

Patients treated with dabrafenib had a statistically significant improvement in PFS (hazard ratio=0.30; 95% CI: 0.18 to 0.51) at the December 19, 2011 data cut-off. The difference in median PFS between the two treatment groups was 2.4 months.

Overall survival analyses at three data cut-offs showed no statistically significant difference between dabrafenib and dacarbazine.[3,15] The overall survival estimates were confounded by dacarbazine patients who crossed over to dabrafenib. An analysis that adjusted for confounding effects of cross-over on overall survival using data from June 2012 using two different methods showed no statistically significant difference between dabrafenib and dacarbazine under two different sets of assumptions.[5]

Health related quality of life was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C-30). What constitutes a minimal clinically important difference (MCID) has not been determined in melanoma patients. In the dabrafenib group, improvements from baseline were seen at week 12 for emotional functioning and social functioning, and for all symptoms except fatigue and dyspnea. In the dacarbazine group, role functioning was improved but patients reported worsening of symptoms at week 12.[3,6]

Up to the first data cut-off, approximately 11% of patients in the dabrafenib group had died, compared with 14% of those treated with dacarbazine. Serious non-fatal adverse events occurred in 23% of patients receiving dabrafenib (predominantly due to squamous cell carcinomas and pyrexia) versus 22% of dacarbazine patients. Adverse events commonly seen in dabrafenib patients (occurring ≥20% of patients) included hyperkeratosis, headache, pyrexia, arthralgia, skin papilloma, alopecia and palmar-plantar erythrodysaesthesia (PPE) syndrome. Patients in the dacarbazine group experienced a higher frequency of grades three and four adverse events (41% vs. 33%). When a dose modification was required due to an adverse event caused by dabrafenib, it was mostly due to pyrexia or PPE syndrome. In each treatment arm, 3% patients permanently discontinued treatment due to adverse events.

Study limitations include:

- The data analyses subsequent to December 19, 2011 were not based on a pre-specified statistical plan and these results can only be considered as exploratory.
- Patients and investigators were not blinded to study treatment (open-label design). This type of study design may limit the interpretation of the results reported for patient relevant outcomes including adverse events and health related quality of life.

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

Critical Appraisal of an Indirect Comparison of Dabrafenib and Vemurafenib

The manufacturer submitted an indirect comparison of dabrafenib and vemurafenib as part of its evaluation of the cost-effectiveness of dabrafenib for the treatment of BRAF V600E mutation positive patients with unresectable or metastatic melanoma. Indirect statistical assessments using the Bucher method were used to compare dabrafenib to vemurafenib. No statistically significant differences were found between the two treatments for progression free survival and overall survival with and without adjustments for duration of follow-up. Conclusions drawn from such indirect comparisons are not as robust as those from direct, head-to-head trial data, and therefore the findings should be interpreted with caution.

Summary of two Phase II trials relevant to the review, BREAK-2 and BREAK-MB

Two phase 2 trials, BREAK-2[16] and BREAK-MB,[17] which did not meet the protocol's inclusion criteria, were identified as relevant to the review. *See section 7.2 for more information.*

BREAK-2 and BREAK-MB were open-label, phase 2, multi-centre, single-arm trials conducted in patients with BRAF V600E or V600K metastatic melanoma. The patient populations were different from that of BREAK-3. BREAK-3 was conducted in patients with a BRAF V600E mutation and untreated for metastatic disease. BREAK-2 included pre-treated patients. Whereas BREAK-3 and BREAK-2 excluded patients with brain metastases, BREAK-MB included patients with brain metastases with or without prior treatments for brain metastases. BREAK-2 and BREAK-MB studies included patients with both BRAF V600E and V600K mutations. Because of the differences in patient populations, a comparison of results is inappropriate but nonetheless the trials provided information on the benefits and harms of dabrafenib when administered under different patient circumstances. It is safe to say that the sub-group sample sizes were too small in BREAK-2 and BREAK-MB to draw conclusions on the effectiveness of dabrafenib in patients with BRAF V600K mutations. Furthermore, the lack of comparator groups in BREAK-2 and BREAK-MB make the interpretation of the results challenging. Furthermore, in some instances there is large discrepancy between the investigators' assessment and the independent review committee's assessment.

Summary of Results – Dabrafenib				
		BRAF V600E		
	BREAK-3 N=187	**BREAK-2 N=76**	**BREAK-MB**	
Key outcomes			Cohort A N=74	Cohort B N=65
Median duration of follow-up	5 months	6 months	5 months	5 months
Overall response, investigator assessed	53%	59%	38%	31%
Median duration of overall response	5.6 months	5.2 months	5.1 months	4.6 months
PFS, investigator assessed	5.1 months	6.3 months	3.7 months	3.8 months
Overall survival	not reached	9.5 months	7.6 months	7.2 months

Cohort A= had not received previous local treatments for brain metastases
Cohort B= had disease progression in the brain after surgery, whole brain radiotherapy or stereotactic radiosurgery

Summary of BRAF Mutation Testing in Metastatic Melanoma

The cobas® 4800 BRAF V600 Mutation Test, developed by Roche Diagnostics Canada, has received regulatory approval and is currently an approved test available for use in Canada to detect BRAF V600E genetic mutations. Use of BRAF inhibitors (dabrafenib and vemurafenib) or a MEK inhibitor (trametinib), requires confirmation of BRAF V600 mutation by a validated test. Canadian testing centres may utilize their own validated BRAF tests. As a result, there is variability in mutation reporting, with some centres reporting specific mutations (V600E and/or V600K) and other not specifying the specific mutation.

The cobas® test is a fully automated in vitro diagnostic device intended for the qualitative detection of the BRAF V600E mutation in DNA extracted from formalin-fixed, paraffin-embedded human melanoma tissue; one 5-micron specimen is sufficient to conduct the analysis. The cobas® test is able to detect V600E mutations with a higher sensitivity than the reference method of Sanger sequencing, but it is not as specific.[18-20] The test showed cross-reactivity with non-V600E mutants, predominantly V600E2 (≥65%), V600K (≥35%), and V600D (≥10%).

See section 7.3 for more information.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient perspective, extending life expectancy to allow more time with family is an important aspect when consideration is given to treatment. There are currently very few effective treatments available in Canada for unresectable or metastatic melanoma and patients welcome new effective therapies. Although dabrafenib is associated with some side effects, patients indicated that they are willing to tolerate side effects that are easily managed. Patients are seeking a therapy that is easy to use and will help to improve their quality of life and enable them to continue to work, provide financially for their families and contribute to their community.

PAG Input

Input on the dabrafenib review was obtained from five of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, issues surrounding the sequential use of BRAF inhibitors in patients that are intolerant to vemurafenib may present as a barrier to implementation as it would incur additional costs.

PAG also indicated that there is a potential for dabrafenib to be used in the adjuvant treatment settings. As such, PAG would appreciate any evidence on dabrafenib in the adjuvant treatment of melanoma. Clarity was also sought on whether dabrafenib should be used in the first or second-line treatment of advanced melanoma.

With regards to the need for molecular testing of patients, PAG recognized that BRAF testing is available in some jurisdictions. It was however noted that there may be issues around the accessibility of testing for patients in many other jurisdictions.

Other

On-going trials are comparing dabrafenib combined with trametinib to dabrafenib monotherapy, or to vemurafenib monotherapy.

See section 6.4 for more information.

2.2 Interpretation and Guidance

Burden of Illness and Therapeutic Options for Advanced Melanoma
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. Prior to the advent of CTLA-4 blocking antibodies and selective type I BRAF inhibitors there was no evidence that either single agent chemotherapy or multi-agent chemotherapy improved either quality of life or overall survival. Ipilimumab, a CTLA-4 blocking antibody was the first agent to show an improvement in overall survival in unresectable melanoma patients who had received prior therapy. It was approved by Health Canada as a second line agent in February 2012, and previously by the FDA in any line. Vemurafenib, a selective Type I BRAF showed an improvement in overall survival and progression free survival when compared to DTIC in patients with advanced, untreated melanoma. It was subsequently approved in BRAF mutation positive unresectable melanoma patients in Canada. Despite the recent advances in the treatment of metastatic melanoma the majority of patients with unresectable melanoma will ultimately succumb to their disease, and therefore researchers need to continue to further research into melanoma and improve outcomes.

Dabrafenib is a small molecule Type I inhibitor of the activating mutation of the BRAF protein. BRAF mutations exist in about 45% of all patients with melanoma with the V600E mutation accounting for 75 – 80% of all the mutations (Substitution of Valine by glutamic acid). BRAF mutations are more common in younger patients and in areas of the skin intermittently exposed to the sun.

BREAK -3 Clinical Trial
Only one randomized clinical study of dabrafenib compared to a suitable control was identified in the pCODR systematic review. In the Phase III study reported by Hauschild et al (BREAK-3), 250 patients with a V600E mutation were randomized in a 3:1 manner to receive either dabrafenib 150 mg orally twice daily versus dacarbazine 1000 mg/m^2 IV every three weeks. The study was open label and patients who were randomized to receive Dacarbazine if the IRC confirmed they had progressive disease. The primary endpoint was investigator assessed progression free survival.

Patient demographics were well balanced for age, sex, race and disease status. 187 patients were randomized to Dabrafenib, and 63 patients to dacarbazine. Response, outcome measures and toxicity data were presented as of the data cut off of December 19, 2011.

Effectiveness and Safety of Dabrafenib: First-Line Setting
Of the 187 patients randomized to dabrafenib 57% (107) were still on treatment. Of the 80 patients who discontinued treatment 66 did so for progressive disease, 5 discontinued due to adverse events, 4 by investigator discretion and 5 withdrew consent. Of the dacarbazine patients 22% (14) were still on treatment and 44% (28) had crossed over to dacarbazine.

The estimated progression free survival for the dabrafenib group was 5.1 months and 2.7 months for the dacarbazine group. The HR for progression was 0.30 (95% CI 0.18 – 0.51; p <0.0001). PFS as assessed by IRC was 6.7 months for dabrafenib and 2.9 months for dacarbazine (HR 0.35; 95% CI 0.20 – 0.61). The benefit in PFS was seen in all subgroups including ECOG PS, LDH normal versus elevated, stage of disease, age and sex. An overall survival benefit was not seen at the data cut-off HR 0.61; 95% CI 0.25 – 1.48. Overall survival benefit analysis in the future will be confounded by patients' crossing over to dabrafenib. Overall response rates as confirmed by the IRC for dabrafenib was 50% with a 3% CR rate with a median time to response of 6.3 weeks. The estimated duration of response as assessed by the IRC was 5.6 months. Of the patients in the dacarbazine group the overall response rate as assessed by the IRC was 6% and a 2% CR.

Dabrafenib improved progression free survival and yielded high response rates in comparison to dacarbazine. Overall survival benefit was not seen as of the latest data cut-off (December 18, 2012) but may become apparent with further follow-up. The pre-planned cross-over in the study may diminish the overall survival benefit. It was not possible to design the study with a primary endpoint of overall survival as equipoise did not exist and with the availability of another BRAF inhibitor vemurafenib, patients who were randomized to dacarbazine would have access to vemurafenib.

Health related quality of life was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C-30). The lack of blinding may have resulted in bias in Quality of Life assessments by the patients. Likewise the cross over design of this study may diminish a future potential survival benefit, although a previous phase II study of dabrafenib showed a similar survival curve to vemurafenib. In the dabrafenib group, improvements from baseline were seen at week 12 for emotional functioning and social functioning, and for all symptoms except fatigue and dyspnea.

Dabrafenib was well tolerated with an expected toxicity profile and a low rate of dose reductions and discontinuations. There was a low rate of photosensitivity in the phase III study (3%), and a secondary skin cancer rate of 8%, although this incidence may increase with further follow up. Adverse events included cutaneous ((hyperkeratosis, papillomas, palmer-plantar erythrodysaesthesia), pyrexia, fatigue, headache and arthralgia. 12 patients developed keratoacanthoma or squamous cell carcinoma of the skin. Four patients had basal cell carcinomas, 1 had mycosis fungoides, and 2 new primary melanomas were seen. Overall dabrafenib was well tolerated with dose reductions needed in 28% of patients receiving dabrafenib and 17% in patients receiving dacarbazine.

Recently another selective BRAF inhibitor vemurafenib was approved by Health Canada for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma. The manufacturer provided an indirect comparison of dabrafenib with vemurafenib based on the BREAK-3 and BRIM-3 trials. The BRIM 3 study showed that vemurafenib improved both progression free and overall survival compared to dacarbazine. Although not formally compared to vemurafenib in an RCT, dabrafenib has a similar mechanism of action, has similar high response rates and progression free survival. Dabrafenib may have a lower incidence of phototoxicity (2%) and a lower rate of secondary skin cancers compared with vemurafenib. This would however need to be confirmed by a head to head comparison of the two drugs.

Effectiveness of Dabrafenib: Second line Setting

The BREAK-3 was the only randomized trial that accrued 1st line patients except for 1 patient who had received prior IL-2. This was the only randomized trial against a suitable control. The BREAK-2 trial was an open label phase II study that accrued pre-treated patients with a V600E or V600K mutation to dabrafenib 150 mg twice daily. The overall response rate in 92 patients accrued to the study was 60% with a CR rate of 7% in the V600E cohort but in the V600K cohort the response rate was 13% with no complete responses. The median PFS was 27 weeks in the V600E group and 20 weeks in the V600K group. Adverse events were common but dose reductions occurred in only 14% of patients and only 1% discontinued study medication due to toxicity. 9% of patients developed squamous cell carcinomas and 4% basal cell carcinomas.

A phase I trial showed a response rate of 78% in the 27 patients with a V600E mutation and a 39% response rate in the 7 patients who harboured a V600K mutation.[21]

The lack of a randomized second line trial is complicated by the fact that there was no standard second line treatment available at the time this trial was completed. Carboplatin and taxol has been used in some centers as a second line treatment albeit without and randomized evidence that it improves overall survival, and only about 10 - 12% of patients obtain a meaningful response.

The consistent high response rates and impressive median survival in the phase I and II trial does not suggest that dabrafenib would be less efficacious in the 2nd line in patients harbouring V600E mutation who have not received a prior BRAF or MEK inhibitor.

V600 Mutation Status

The Phase III randomized trial only included patients with a V600E mutation, and the small numbers of V600K mutation patients in the Phase I and II studies and the corresponding low response rates fails to prove whether dabrafenib is effective in the V600K mutation patients. While recognizing that the most robust evidence for dabrafenib is in patients with V600E mutations, dabrafenib would still be a clinically reasonable treatment option for patients with other V600 mutations.

Patients with Brain Metastases: BREAK-MB

A phase II study in patients with either pre-treated brain metastases that were progressing, or untreated brain metastases was performed due to impressive results seen in 10 patients who had brain metastases and V600 mutations in the phase I trial. Patients could not have previously received a MAPK inhibitor. In the V600E patients the investigator assessed OIRR in the untreated and pre-treated patients was of 39% and 31% respectively, while the overall response rates were 38% and 31%. The median overall progression free survival in both cohorts of the V600E mutation patients was 16 weeks. Dabrafenib was well tolerated with the expected adverse event profile except that 6% of patients had an intracranial haemorrhage. Dabrafenib can therefore reasonably be used in patients with clinically stable brain metastasis. i.e., those who don't require steroids or who are on a stable dose of steroids. In the untreated and previously treated V600K patients (n = 33) OIRR were 7 and 22% respectively. The true effectiveness of dabrafenib in the V600K mutation patients was limited due to the small sample size.

2.3 Conclusions

The pCODR Melanoma Guidance Panel concluded that there is a net overall clinical benefit to dabrafenib based on one randomized clinical trial, BREAK-3 which demonstrated an improvement of progression free survival when compared to dacarbazine in previously untreated patients with a V600E mutation positive unresectable or metastatic melanoma. An overall survival benefit was not seen but may have been confounded by the crossover of patients to dabrafenib after progressing on dacarbazine. The panel considered that crossover was justified because it would have been unethical to deny a BRAF inhibitor to patients after progressing on dacarbazine.

In making this conclusion, the Clinical Guidance Panel also considered that:

- Dabrafenib is effective in the second line setting based on the results of the single arm BREAK-2 study.
- Dabrafenib has clinical benefit in patients with treated or untreated brain metastases or asymptomatic brain metastases that harbour the V600E mutation based on the single arm BREAK-MB study. Therefore, it would be reasonable to use dabrafenib in patients with clinically stable brain metastasis. i.e., those who don't require steroids or who are on a stable dose of steroids.
- Although the most robust evidence for dabrafenib is in patients with V600E mutations dabrafenib would still be clinically reasonable treatment option for patients with other V600 mutations.
- There was no evidence to support the use of Dabrafenib in patients who had received a prior BRAF inhibitor or a MEK inhibitor.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Melanoma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Melanoma is a malignancy of melanocytes which are distributed throughout the body including skin, eyes, and gastrointestinal tract. Although primary melanomas can occur in a variety of anatomical sites, the skin is the most common, comprising 95% of cases. In Canada, 5500 new cases of primary melanoma are expected in 2011 and approximately 950 patients will die from melanoma.[7] The incidence of melanoma has been steadily increasing over the past 50 years. At present, the lifetime probability of developing a melanoma for women is 1 in 85 and for men is 1 in 67.[22]

Staging of melanoma is based on the current AJCC 7th Edition Classification.[23] The tumour characteristics principally involve the Breslow height, mitotic rate and the presence of ulceration in the primary. The detection of microscopic and macroscopic lymph node involvement, serum lactate dehydrogenase and the sites of metastatic disease are integral components to the staging classification. All of these factors have been shown to be important prognostic variables which influence patient outcomes and which help to guide management decisions.

3.2 Accepted Clinical Practice

In early stage melanoma, cures are commonly achieved with surgery alone. The primary tumour is excised with appropriate margins. Depending upon the Breslow height, mitotic rate, presence of ulceration and location of the primary, the sentinel node biopsy is performed to assess nodal status. If the sentinel node is positive then a completion node dissection of the surrounding nodal basin is often performed in order to reduce the risk of a regional recurrence.[24] Although only 5% of patients actually present with metastatic disease, the majority of patients who die from melanoma will have developed recurrent and/or distant disease. Approximately one-third of patients with early stage melanoma will develop metastasis whereas half of patients with nodal disease will recur and likely die from the development of metastatic disease.[25] Brain metastases are relatively common in advanced melanoma and occur in up to 75% of patients with overt metastatic disease.[8] They often prove to be relatively refractory to radiotherapy and systemic treatment and are associated with a particularly dismal prognosis.

Select patients with metastatic disease would benefit from surgery or radiotherapy alone. Systemic treatment is most commonly offered. Unfortunately, the prognosis has remained poor. The median survival is six to nine months and the five-year survival is approximately 6%.[26] In spite of multiple phase II and III trials with systemic therapy, the objective response to systemic agents remains low and has generally been less than 15%. Until recently, the median survival rates with both single and multiple drug combinations have not changed and have remained within the range of six to twelve months.

Over the past 30 years, the standard first line systemic therapy has been dacarbazine.[24,27] Although this intravenous alkylating agent is generally well tolerated, complete responses are rare.[14] In comparative studies, it has never been shown to improve survival in metastatic melanoma.[9-13] Temozolomide, an oral imidazazole tetrazene derivative of DTIC which is activated to the active metabolite of dacarbazine (MTIC), has also been commonly

used. However, in a phase III trial which compared temozolomide directly with dacarbazine, equivalent progression free and overall survival were observed, although the temozolomide tended to be better tolerated.[28-30] In the 1990's the FDA approved the use of high dose interleukin-2 based on phase II data showing an overall response rate of 16% but also a durable response rate of 5%, extending beyond five years.[31,32] Unfortunately, high dose interleukin-2 is accompanied with significant toxicity and requires intense cardiac monitoring and hemodynamic support. Interleukin-2 has been used in a few selective centres but is largely unavailable throughout Canada.

A very wide spectrum of chemotherapeutic and immunological treatments approaches have been explored in metastatic melanoma with limited to no success. Patient outcomes have not changed significantly over the past three decades until recently.[14] Nevertheless, what has become apparent is that melanoma represents a heterogeneous group of diseases which appear to have varying genetic abnormalities which drive cellular proliferation and metastases.[33-35] The MAP kinase signalling pathway appears to be a key regulatory mechanism for cell growth, and differentiation in melanoma.[36] Mutations in the BRAF protein in this pathway can alter the activity of BRAF and result in uncontrolled cellular proliferation and increased potential for metastatic spread.[37] Approximately 50% of human melanomas appear to have an activated mutation in BRAF and has consequently become a potential key target for inhibition and potential therapeutic site.[38]

Vemurafenib is a BRAF inhibitor that selectively targets the mutated Braf V600 and was approved in August 2011 by the FDA as a treatment of late stage or unresectable melanoma in patients harbouring a V600E mutation, and subsequently by health Canada in February 2012.[39-41] Just fewer than 50% of all melanoma patients will harbour a V600 mutation, with the majority being V600E. In the randomized Phase III study (BRIM3) there was a relative reduction of 63% in the risk of death and a 74% relative reduction in the risk of tumor progression. The overall response rate was 48%.[42] This is now a standard first line treatment of advanced, unresectable melanoma in patients harbouring a V600 mutation.

Likewise the immune checkpoint inhibitor of CTLA-4, ipilimumab was approved by Health Canada in February 2012 in a second line indication in pre-treated patients with advanced melanoma.[43,44]

3.3 Evidence-Based Considerations for a Funding Population

Dabrafenib is a BRAF inhibitor that selectively targets the mutated BRAF V600 and has been under clinical trials since 2009.[4,21,45] In 2012, a multicentre non-blinded phase III study of dabrafenib in comparison to dacarbazine in the first line treatment of 250 patients with unresectable or metastatic melanoma with a BRAF V600E mutation was reported. The key inclusion criterion was the presence of V600 mutation. The use of dabrafenib is dependent upon the accuracy and availability of BRAF mutation testing of each prospective patient's primary or metastatic tumour (See Section 7.1).

Patients treated with dabrafenib had a statistically significant improvement in PFS (hazard ratio=0.30; 95% CI: 0.18 to 0.51) at the December 19, 2011 data cut-off. The difference in median PFS between the two treatment groups was 2.4 months.

Overall survival analyses at three data cut-offs showed no statistically significant difference between dabrafenib and dacarbazine.[3,15] The overall survival estimates were confounded by dacarbazine patients who crossed over to dabrafenib. An analysis that adjusted for confounding effects of cross-over on overall survival using data from June 2012 using two different methods showed no statistically significant difference between dabrafenib and dacarbazine under two different sets of assumptions.[5]

Health related quality of life was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C-30). What constitutes a minimal clinically important difference (MCID) has not been determined in melanoma patients. In the dabrafenib group, improvements from baseline were seen at week 12 for emotional functioning and social functioning, and for all symptoms except fatigue and dyspnea. In the dacarbazine group, role functioning was improved but patients reported worsening of symptoms at week 12.[3,6]

Up to the first data cut-off, approximately 11% of patients in the dabrafenib group had died, compared with 14% of those treated with dacarbazine. Serious non-fatal adverse events occurred in 23% of patients receiving dabrafenib (predominantly due to squamous cell carcinomas and pyrexia) versus 22% of dacarbazine patients. Adverse events commonly seen in dabrafenib patients (occurring ≥20% of patients) included hyperkeratosis, headache, pyrexia, arthralgia, skin papilloma, alopecia and palmar-plantar erythrodysaesthesia (PPE) syndrome. Patients in the dacarbazine group experienced a higher frequency of grades three and four adverse events (41% vs. 33%). When a dose modification was required due to an adverse event caused by dabrafenib, it was mostly due to pyrexia or PPE syndrome. In each treatment arm, 3% patients permanently discontinued treatment due to adverse events.

The efficacy of dabrafenib in patients with brain metastases was assessed in a separate Phase II study.[17] The single-arm study, assessed the use of dabrafenib in patients who had received no prior local therapy for brain metastases (Cohort A), and those that had received at least one local therapy for brain metastases (Cohort B). The primary endpoint was the proportion of patients with the V600E BRAF-mutant melanoma with investigator assessed overall intracranial response rate (OIRR). Secondary endpoints were the proportion of patients with the V600K BRAF-mutant melanoma with an OIRR, progression free survival (PFS), and overall survival in patients with the V600E and V600k mutations. For the primary endpoint in the V600E group OIRR (overall intracranial response rate) was 39.2% (C.I. 28.0 – 51.2) and 30.8% (C.I. 19.9 – 43.4) for cohort A and B respectively. The median duration of response was 20.1 weeks for cohort A and 28.1 weeks for cohort B in the V600E BRAF mutant population and 12.4 weeks cohort A and 16.6 weeks in cohort B in the V600K BRAF mutant population. In the V600E BRAF mutation group overall survival was 33.1 weeks and 31.4 weeks for Cohort A and B respectively, and in the V600K group it was 16.3 and 21.9 weeks for Cohort A and B respectively.

As patients with ECOG performance of two or less were specifically excluded from the above Phase II trial and BREAK-3, the impact of dabrafenib on patients with a particularly grave prognosis is unknown.

Dabrafenib use can therefore be used in patients with the following eligibility criteria:

1. metastatic and/or unresectable melanoma;
2. BRAF V600 mutation present in primary or secondary tumour;
3. ECOG performance status < 2;
4. If present, stable or progressing brain metastases;
5. Adequate haematological, renal and liver functions.

3.4 Other Patient Populations in Whom the Drug May Be Used

Dabrafenib may be potentially used in patients with high risk melanoma as an adjuvant treatment. Adjuvant clinical trials are being developed to address whether the combination of dabrafenib and a MEK inhibitor will reduce the risk of developing recurrence; however, it is expected to be several years before these trials will have been reported. It may also be used in patients who do not tolerate vemurafenib as the toxicity profile is different.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy groups provided input on dabrafenib for the treatment of unresectable or metastatic melanoma and their input is summarized below:

- Melanoma Network of Canada
- Save Your Skin Foundation

Melanoma Network of Canada conducted an anonymous online survey to gather information about patient and caregiver experiences with melanoma. The survey was promoted through cancer centres in Canada that treat melanoma and on the Melanoma Network of Canada website. Part I of the online survey (24 respondents) requested information about patients' experience with advanced melanoma (stage III and IV) as well as their (prospective) thoughts about any future drug therapy. Part II (3 respondents) specifically requested retrospective information from patients who have had direct experience with dabrafenib. Part III (4 respondents) requested feedback from caregivers who had experiences with caring for someone who has taken dabrafenib. The survey questions consisted of a mix of multiple choice, ranking and free-form commentary.

The Save Your Skin Foundation conducted one-on-one interviews with 75 patients and 25 caregivers to gather information about the patient and caregiver experience related to the medical condition and the drug under review. Five (5) patients had direct experience with dabrafenib.

From a patient perspective, extending life expectancy to allow more time with family is an important aspect when consideration is given to treatment. There are currently very few effective treatments available in Canada for unresectable or metastatic melanoma and patients welcome new effective therapies. Although dabrafenib is associated with some side effects, patients indicated that they are willing to tolerate side effects that are easily managed. Patients are seeking a therapy that is easy to use and will help to improve their quality of life and enable them to continue to work, provide financially for their families and contribute to their community.

Please see below for a summary of specific input received from the patient advocacy groups. Cited responses are not corrected for spelling or grammar.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Unresectable of Metastatic Melanoma

Patients with advanced melanoma may experience of number of debilitating symptoms as a result of their cancer, which can have a negative impact on their quality of life. Some of these symptoms include shortness of breath, severe pain, fatigue, loss of coordination, loss of sight, lymphedema and weight loss. In addition, patients with metastatic disease may experience further symptoms dependent upon the site of the metastases, including headaches, numbness in the extremities, bone fractures, hair loss, depression, anxiety, memory loss, decreased mobility and constipation. 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.

Among the people who self-identified as having metastatic melanoma on the Melanoma Network of Canada survey, the following sentiments were expressed by patients that reinforce that ongoing symptoms have a large impact on quality of life:

"The limitations I have are my energy level has not returned to what it was and I have developed lymphedema in my leg, which requires regular lymphatic drainage therapy.

"Less outdoor activity due to sunlight exposure, less energy, listlessness, tired, lump in groin, compression stocking needed daily and they are expensive (financial hardship), less walking daily."

"I have metastatic Melanoma, lung tumor and adrenal tumor. I am feeling quite well, able to do all regular activity. Limitations are due to time taken up going to and from testing and treatment. A lot of financial expense due to holistic treatment I have pursed, and expenses of traveling for appointments."

"I had tumours growing that made it impossible for me to have a life. I was in a lot of pain and was confined to my couch or bed. Each day without a medication that shrunk the tumours was painful and without hope."

Patients report experiencing various psychological effects with their diagnosis, including fear, anxiety and depression. Moreover, it is not uncommon for patients to experience moderate to severe emotional distress when dealing with melanoma. The following are some responses from the Melanoma Network of Canada survey that reflect this:

"Fear and uncertainty for my life going forward is often debilitating and removes motivation."

"I was diagnosed with melanoma in October 2012. Initially all I could think about was the fact that I have cancer and that I now have to consider whether or not I will be still living in 5 years. It was all consuming."

"The psychological impact is probably the greatest issue in that I have a wife and two young children. Knowing the severity and prognosis of Stage 4 metastatic melanoma continues to affect our lives and causes a lot of stress."

Many patients with unresectable or metastatic melanoma are unable to continue employment, either due to anxiety and depression surrounding the diagnosis or loss of mobility due to muscle and tissue removal during surgery. This can lead to considerable emotional and financial hardships for patients and their families.

From a patient perspective, treatment alternatives that prevent the progression of the disease or securing funding for new treatments that can stop the progression of the cancer are important considerations.

4.1.2 Patients' Experiences with Current Therapy for Unresectable of Metastatic Melanoma

For many decades there have been very limited and ineffective treatment options for advanced stage melanoma patients. More recently, patients have found great hope in the development of new-targeted therapies that have successfully shrunk tumours and stopped the progression of their cancer – sometimes indefinitely or for extended periods of time.

Current therapies for advanced melanoma include interferon, dacarbazine, temozolomide, stereotactic radiation (for brainstem tumors), interleukin-2, ipilimumab and vemurafenib. Many current therapies have poor survival rates and there are still not enough treatment

options available for patients not qualifying for or not having positive results from vemurafenib or ipilimumab.

Of the patients who participated in the Melanoma Network of Canada survey, interferon was extensively reported on by 8 patients as having severe and debilitating side- effects including extreme nausea/flu-like symptoms, fatigue, decreased mood, decreased mobility, fever, chills, trembling, sore eyes, compromised liver function, foggy brain, hair loss, taste and weight loss. Two (2) patients reported that the side effects were so extreme that they had to discontinue their treatments and one reported that they refused treatment all together.

Other treatments that patients indicated being on or had been on in the past included dacarbazine (4), radiation (3), vemurafenib (4), ipilimumab (2) interleukin (1), and naturopathic options (1). Some of the side effects on these treatments included photosensitivity, digestive issues, foot and joint pain, nausea, less energy, low hemoglobin and iron levels, and multiple rashes.

Of the 24 patients that responded to the Melanoma Network of Canada survey, 19% indicated that they did experience hardships in accessing drug treatments. Some patients indicated there was not enough information from their oncologists on trials available to them. Others indicated feeling fortunate because they were able to access clinical trials and therefore did not have to incur costs for these treatments. One (1) patient noted that only part of their treatment was covered and they still had to pay 10% of their treatment costs per month. Those patients who have chosen alternative methods of treatment have taken on all of the costs.

While most patients surveyed have direct experience with the serious and severe side effects of therapies currently available, the survey results indicate that 70% of the respondents are still willing to accept side effects and the serious risks associated with a future new drug if they know those side effects can be effectively managed. Additionally 68% of respondents indicated that they would be willing to tolerate the potential side effects if they knew the results would extend their lives and 60% said they would tolerate those side effects even if the benefits of the treatment were only short-term.

Patients were asked the following in the survey. "*If you were to consider taking a new drug to treat melanoma, how would you rate the importance of quality of life while on the drug in your decision to take it or not take it*?" When surveyed on a ranking of very important, important, somewhat important, and not important, 71% ranked their quality of life as either important or very important.

Patients interviewed by the Save Your Skin Foundation reported that adverse side effects of currently available treatment, such as extreme fatigue, diarrhea, skin issues, nausea, rash, and low sodium levels were difficult to tolerate. One (1) patient reported severe headaches and mania, "*While on Interferon I became manic and this took a toll on my marriage*". Many side effects were so severe that patients are not able to perform daily functions. Half of the patients responded "yes" they would "try anything" to win their fight with melanoma. The other half responded, "yes" depending on the severity of the side of effects of treatment.

Patients had to travel to receive IL-2. Patients receiving Interferon were given the treatment locally. Patients who travelled to receive treatment incurred flight, hotel, meal, and car rental costs. Other financial implications involved unemployment as patients could not work while being administered the drugs.

There is concern that the psychological aspect of living with melanoma is being ignored. One (1) patient interviewed by the Save Your Skin Foundations said "*I feel that current therapy ignores the effects of melanoma surgeries and the psychological toll that this diagnosis takes on a person*."

4.1.3 Impact of Unresectable or Metastatic Melanoma and Current Therapy on Caregivers

Patient advocacy group input indicates that the impact of this cancer on caregivers can be quite significant. Caregivers are required to take on a number of additional roles, including helping patients in managing adverse effects of treatment, making up for lost income, assuming additional unpaid household duties, and providing emotional support.

Caregivers are often required to cancel any long-term plans that they may have in place and career, community and social involvement can be adversely affected by the physical requirements, time commitments and emotional stress of caring for the patient. Often it is difficult for caregivers to determine if the symptoms experienced by patients are related to the cancer or are a result of treatment. Caregivers would like additional information about the potential side effects of treatment.

The following are some comments from caregivers who participated in the Melanoma Network of Canada survey:

> *"The stress and anxiety felt for caring for someone with this disease is all consuming. Fortunately, I had the flexibility to take time off work and manage the needs of my boyfriend, however, I have no idea how people could take this on without that luxury. Getting to the hospital for treatment, managing the side effects at home, and always looking for signs of adverse reactions really takes over your life. Not to mention the stress of not knowing what the end results is going to be."*
>
> *"It is a challenge to maintain regular meals as the patients tends to eat smaller meals as a result of loss of appetite. Time off from work is also a major issue. The patient also looses a lot of their energy and their attention, which makes daily tasks difficult to manage."*
>
> *"Cost and access to medications. The added stress of knowing the low proportion of long-term survivors."*

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Dabrafenib

Input from patients highlighted the fact that there are currently very few effective treatments available in Canada for metastatic melanoma and effective treatment options with manageable side effects would be welcomed by patients with this disease as well as by their families.

The Melanoma Network of Canada indicated that other therapies like DTIC (dacarbazine) and interferon often have very severe and lasting side effects – including liver failure, nausea, debilitating depression, headaches, loss of memory, rheumatoid arthritis, diarrhea, hair loss, fatigue, confusion, rigors and other flu like symptoms.

Drugs therapies are evolving rapidly and hold more and more promise that melanoma will be defeated or at least managed as more of a chronic condition to allow patients to live their lives and contribute to the community. Patients with unresectable or metastatic melanoma are seeking drug therapies that can extend their life expectancy and allow them more time to spend with their family. Treatments which result in a positive impact on quality of life, such as milder side effects or more manageable treatment protocols, would be considered an additional benefit of any therapy for advanced melanoma. Patients seek treatment options that will enable them to continue to work and continue to provide financially for their families.

Patients with direct experience with dabrafenib had positive effects from the treatment and experienced manageable side effects which included fevers, chills, body and muscular aches, night sweats, dizziness, nausea, vomiting, gastrointestinal problems and fatigue. Overall, patients deem the benefits of dabrafenib to outweigh the potential risks of treatment and are willing to tolerate short-term side effects.

All respondents (4) to the Melanoma Network of Canada survey with direct experience with dabrafenib were effectively able to manage the side effects of treatment. More than half of patients indicated the side effects were much milder than other treatments they had experienced. Two (2) of the three (3) patients noted that their melanoma was stabilized with no progression and the third patient indicated there was no evidence of disease. Patients did not report sustaining any ongoing side effects from dabrafenib. These patients hope they will continue to have a durable response –even if not sustained indefinitely.

The following are some comments from patients with direct experience with dabrafenib who participated in the Melanoma Network of Canada survey:

> *"Early on in my treatment (BRAF/MEK inhibitors from GSK), I had 2 instances of fevers/chills. I has been 19 months with no side effects. All of the tumors in my lungs have disappeared except for one, which has shrunk 79%."*

> *"After a few months I asked for some relief from the side effects and was given steroids which have completely taken away all of the side effects - I feel great, I had no light sensitivity at all but did have another form of skin cancer appear, I just had it removed which took care of the problem, it has not returned nor was it life-threatening."*

Within one week of starting treatment with dabrafenib one (1) patient interviewed by the Save Your Skin Foundation was able to able to breath on his own without the use of oxygen.

Patients indicate the side effects of dabrafenib were very well tolerated more so than other therapies. This is providing patients with an excellent quality of life and significant hope for the future. Patients surveyed by the Melanoma Network of Canada were asked what their quality of life has been like since taking dabrafenib. Patients indicated:

"Very normal. Very active life (skiing, baseball, normal workload)"

"*My quality of life is excellent, after being put on steroids for some side effects, I have not experienced any side effects, and I can do what I want whenever I want, as long as I take 2 pills a day, absolutely amazing!"*

4.3 Additional Information

One of the patient advocacy groups indicated that locating patient members in the community can be a challenge. In addition, they indicated that it would be helpful if physicians who treat advanced cancer had more knowledge and understanding of the pCODR process. It was also suggested that a set of standardized patient questions which could be passed by a Research Ethics Board on a one-time basis on behalf of all patient groups could help to avoid delays in submitting patient advocacy input.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for dabrafenib (Tafinlar) for metastatic melanoma. The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on the dabrafenib review was obtained from five of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, issues surrounding the sequential use of BRAF inhibitors in patients that are intolerant to vemurafenib may present as a barrier to implementation as it would incur additional costs.

PAG also indicated that there is a potential for dabrafenib to be used in the adjuvant treatment settings. As such, PAG would appreciate understanding if there is any evidence on dabrafenib in the adjuvant treatment of melanoma. Clarity was also sought on whether dabrafenib should be used in the first or second-line treatment of advanced melanoma.

With regards to the need for molecular testing of patients, PAG recognized that BRAF testing is available in some jurisdictions. It was however noted that there may be issues around the accessibility of testing for patients in many other jurisdictions.

Please see below for more detailed PAG input on individual parameters.

5.1 Factors Related to Comparators

PAG noted that in most jurisdictions the current standard of care in the 1st and 2nd line treatment of patients with unresectable or metastatic BRAF V600 positive melanoma is vemurafenib while ipilimumab is standard in the 2nd line treatment of patients with unresectable or advanced melanoma. However, PAG noted that the clinical data for dabrafenib, BREAK-3, does not have a head-to-head comparison to vemurafenib or ipilimumab and instead compares dabrafenib to dacarbazine. PAG did note that the submitter intends to use vemurafenib as the comparator in the economic analysis which is a relevant comparator for those provinces that fund this oral agent.

5.2 Factors Related to Patient Population

As advanced melanoma affects a relatively small patient population, and even less of these patients are likely to have the BRAF mutation, PAG recognized that there may only be a small number of patients eligible to receive dabrafenib. As a BRAF inhibitor, dabrafenib may be an alternative treatment option to patients that are intolerant to vemurafenib. Both of these factors were noted to be enablers to implementation.

However sequential use of BRAF inhibitors may present as a barrier to implementation as it would incur additional costs. PAG also indicated that there is no evidence to support the use of dabrafenib in patients that have developed resistance to vemurafenib. PAG identified that there is a potential for dabrafenib to be used in the adjuvant treatment settings. Although the pivotal study assessed the use of dabrafenib in patients who have had previous treatment with IL-2, surgery and radiotherapy, PAG noted that the requested Health Canada indication does not specify

the line of therapy or prior treatment history of patients in which dabrafenib should be used. As such PAG noted the potential for indication creep.

5.3 Factors Related to Accessibility

PAG noted that dabrafenib is an oral therapy administered in an outpatient setting which facilitates the ease of distribution and administration. Additionally, an oral therapy was noted to be beneficial for patients living in rural areas. However, in some jurisdictions, patients would first require an application to their pharmacare program to acquire oral medications and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of- pocket expenditure.

PAG recognized that BRAF testing is now available in jurisdictions that fund vemurafenib and so availability of testing will not be a concern. However, in jurisdictions that have not implemented vemurafenib, patients may not have accessibility to BRAF testing.

5.4 Factors Related to Dosing

As dabrafenib is available as an oral agent in 50mg and 75mg capsules, patients will be required to take two tablets twice daily to get the standard dosage of 300mg daily. PAG noted this dosing schedule to be less of a pill burden that what is available with another BRAF inhibitor (eight tablets a day) which may have a positive impact on patient compliance. Dabrafenib does not require concomitant medications and is relatively a straightforward treatment protocol, further assisting patient compliance.

PAG noted that the availability of the low dose capsule (50mg) will likely make the management of dose adjustments easier.

5.5 Factors Related to Implementation Costs

PAG recognized that BRAF molecular testing is required to identify appropriate patients for dabrafenib therapy. BRAF testing is now available in some jurisdictions so that patients will already have access to testing. In addition other patient requirements around drug interaction monitoring and toxicity assessment protocol required for anti-BRAF therapy are already established in those jurisdictions.

PAG noted that the packaging of dabrafenib in the Canadian setting is currently unknown. As a result there may be additional implementation steps that impact healthcare system resources, such as the potential need for biologic safety cabinets if the product is not available in unit-dose packaging.

5.6 Other Factors

Packaging of the drug may present as either a barrier or enabler. PAG indicated that unit-dose packaging would be preferred to minimize occupational exposure while capsules supplied in a bulk bottle would require additional costs through the need of a biological safety cabinet.

PAG also requested clarity regarding which line of therapy dabrafenib should be used, especially in relation to currently available lines of therapy. In addition, it was noted that the trial included patients with ECOG status of 0 or 1 and PAG requested that treatment of patients with ECOG 2 or more be addressed.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of dabrafenib on patient outcomes compared to standard therapies or best supportive care in the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma (see Table 1 in Section 6.2.1 for outcomes of interest and comparators).

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- Critical appraisal of indirect treatment comparison of dabrafenib and vemurafenib
- Summary of two Supportive Phase II trials, BREAK-2 and BREAK-MB
- Summary of BRAF Mutation Testing in Metastatic Melanoma

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs	Patients with BRAF V600 mutation-positive unresectable or metastatic melanoma	Dabrafenib monotherapy at recommended dose of 150 mg orally twice daily	• Dacarbazine • Temozolomide • Interleukin-2 • Carboplatin / paclitaxel • Ipilimumab • Vemurafenib • Best supportive care	• Overall survival • Progression-free survival • Response rate (CR, PR) • Duration of response • Dose modification • **HRQoL** • **SAEs** • **AEs** -Secondary cancers -Dermatological AEs -pyrexia • WDAEs

AE=adverse events; CR=complete response; HRQoL=health related quality of life; OS=overall survival; PFS=progression-free survival; PR=partial response; RCT=randomized controlled trial; SAE=serious adverse event; WDAE=withdrawal due to adverse events

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (2013, Issue 6 of 12) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were dabrafenib and Tafinlar.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but not limited by publication year. The search is considered up to date as of August 29, 2013.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer – Canadian Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided

guidance and developed conclusions on the net overall clinical benefit of the drug.

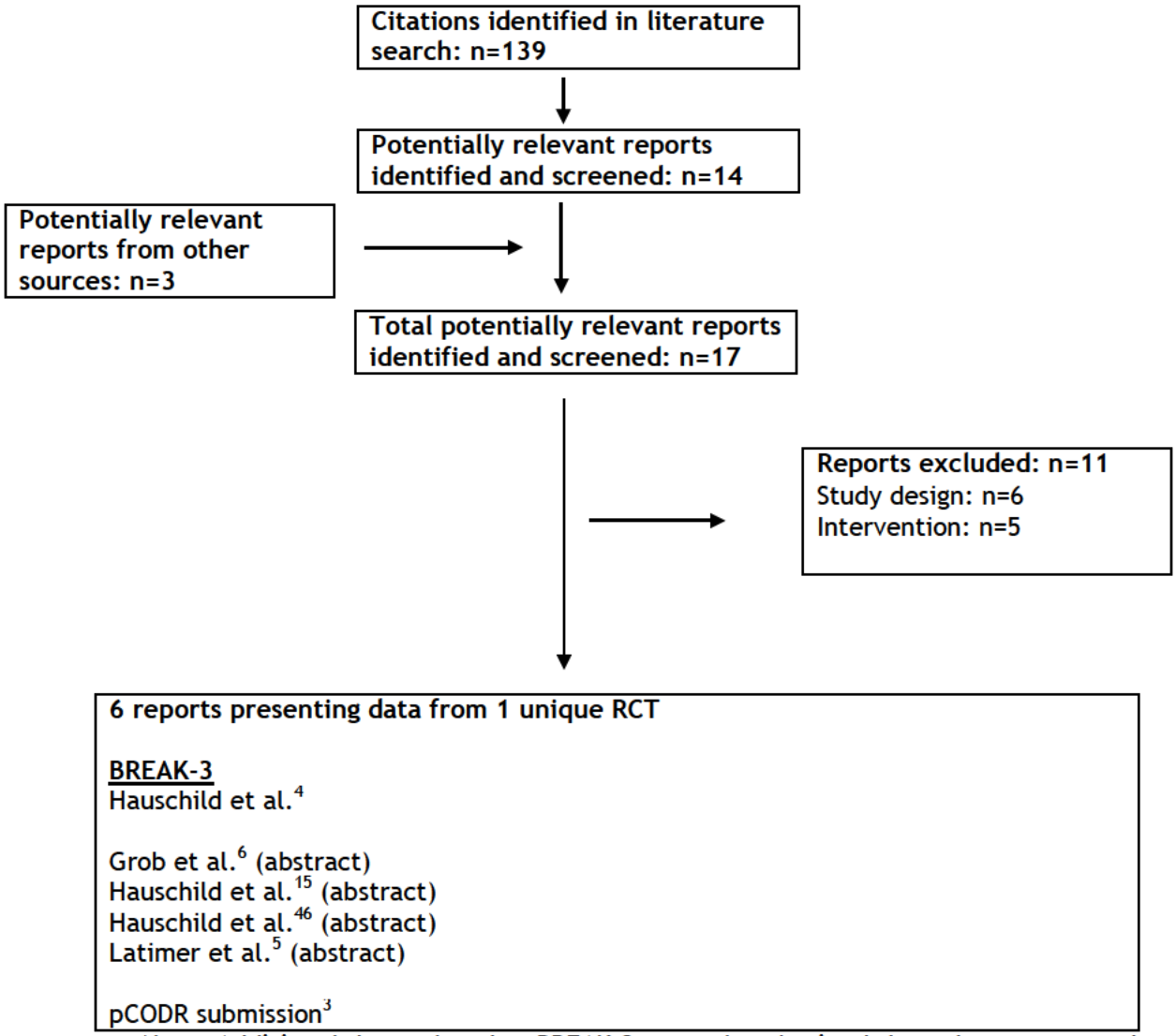
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 139 potentially relevant reports identified, one study was included in the pCODR systematic review[3-6,15,46] and 11 studies were excluded. Studies were excluded due to the study design[17,21,45,47-49] or intervention.[50-54]

QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to BREAK-3 were also obtained through requests to the Submitter by pCODR[55]

6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 2: Summary of Trial Characteristics of BREAK-3 Study[3,4]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Phase 3 RCT, open-label, active control 70 sites in 12 countries Randomized 3:1 ratio stratified by AJCC stage (III+IVM1a+IV M1b vs. IVM1c) N=250 randomized N=246 received treatment Funded by Glaxo Smith Kline	• Histologically confirmed measurable metastatic melanoma stage IV or unresectable stage III melanoma with a BRAF V600E mutation • Age ≥18 years • ECOG PS ≤1 • Adequate organ functions • Treatment-naïve for metastatic disease (interleukin 2, surgery, radiotherapy allowed) <u>Exclusion criteria:</u> • CNS metastases • History of HIV infection • Glucose-6-dehydrogenase deficiency • Previous malignancy within five years • History of a cardiac condition • Cardiac metastases	**dabrafenib** 150 mg orally twice daily vs. **dacarbazine** 1000 mg/m^2 intravenously every 3 weeks. Dose reductions or interruptions were pre-specified in case of ≥ grade 2 AEs.	<u>Primary</u>: PFS assessed by investigator <u>Secondary</u>: PFS assessed by IRC OS ORR according to RECIST Duration of response HRQoL Safety Tolerability

AEs=adverse events; **AJCC**=American Joint Committee on Cancer; **ECOG PS**=Eastern Cooperative Oncology Group performance status; **HRQoL**=quality of life; **IRC**=independent radiology committee; **ORR**=overall response rate; **OS**=overall survival; **PFS**=progression free survival; **RECIST**= Response Evaluation Criteria in Solid Tumours; **RCT**= randomized controlled trial

a) Trials

One multicentre phase 3 randomized controlled trial (study BREAK-3) was included in this review.[3,4] The trial was conducted in 70 centres in 12 countries and was manufacturer-sponsored (Table 2).

The trial included patients with histologically confirmed measurable metastatic melanoma (stage IV or unresectable stage III) with a BRAF V600E mutation confirmed by allele-specific polymerase chain reaction assay (Response Genetics Inc.). Patients had not received prior antitumour therapy for metastatic disease. Previous treatment with interleukin 2, surgery, or radiotherapy was allowed unless received within four weeks of trial initiation. Additional eligibility criteria included age 18 years or older, an ECOG performance status of 0 or 1, and adequate renal, hepatic, haematological and cardiac functions. Patients were also excluded if they had CNS metastases unless they were

without evidence of active CNS metastases for more than three months after surgery or stereostatic radiosurgery. Further exclusion criteria included: history of HIV infection, glucose-6-dehydrogenase deficiency, previous malignancy within five years, history of a cardiac condition within the previous 24 weeks (for example acute coronary syndrome or cardiac arrhythmia), and cardiac metastases. The use of other anti-cancer therapy was prohibited while on study treatment.

Treatment was first initiated on February 16, 2011 and the cut-off date for data analysis was December 19, 2011. No interim efficacy analysis was planned. A target sample size of 200 patients was calculated to observe 102 PFS events with a statistical power of 99.7% to detect a hazard ratio (HR) of 0.33 (median PFS of 2 months for the dacarbazine group and 6 months in the dabrafenib group). A one-sided test with a significance level of 0.02 was used for progression free survival. Secondary end points were tested at the two-sided 0.05 level of significance if the primary end point was statistically significant.

At the data cut off of December 19, 2011, median overall survival had not been reached on either arm. A second unplanned analysis for PFS, overall survival and tumour response was performed at a data cut off of June 25, 2012 and a third unplanned analysis of overall survival was done at a data cut off of December 18, 2012.[15]

Trial procedures for randomization and allocation concealment were considered adequate. Allocation to treatment was done randomly using a centralized, computerised, voice activated response system controlling assignment of patients to treatment groups.

Pre-defined subgroup analyses were conducted for age, gender, baseline lactodehydrogenase levels, ECOG performance status, presence of visceral disease, and number of disease sites.

b) Populations

Patients received open-label dabrafenib (n=187) or open-label dacarbazine (n=63). Median age was 53 years (range 22 to 93) in the dabrafenib group and 50 years (range 21 to 82) in the dacarbazine group. Treatment groups were balanced for patient and disease characteristics. Patients less than 65 years old represented 79% of the population. The study population comprised mostly of men (60%) and patients were white (100%). A total of 66% and 33 % of patients had an ECOG performance status of 0 and ≥1 respectively in the dabrafenib group. This compared to 70% and 25% of patients with ECOG performance status of 0 and ≥1 respectively in the dacarbazine group. ECOG performance status was unknown in 5% of patients in the dacarbazine group. More than 95% of the patients had Stage IV melanoma at screening. Elevated lactodehydrogenase levels were reported in 36% and 30% of patients at baseline in the dabrafenib group and in the dacarbazine group respectively. Most patients had received previous treatment (mostly immunotherapy or radiotherapy), with 4% of patients having received adjuvant biologic therapy or adjuvant chemotherapy previously.

c) Interventions

Patients were randomized 3:1 to receive oral dabrafenib 150 mg twice daily or intravenous dacarbazine 1000 mg/m^2 every three weeks. Patients were stratified according to the American Joint Committee on Cancer Stage (unresectable III+IVM1a+IVM1b vs. IVM1c).

All randomized patients were included in the efficacy analyses. The safety analyses included randomized patients who received at least one dose of the study medication.

The median duration of treatment among the dabrafenib group was 4.9 months compared to 2.8 months in the dacarbazine group. The mean dabrafenib daily dose was 285 mg (standard deviation 34) with a median of 300 mg (minimum 118, maximum 300). The mean dacarbazine daily dose was 312 mg (standard deviation 34) with a median of 332 mg (minimum 204, maximum 350).

Disease assessments were conducted at six and 12 weeks post-baseline and every nine weeks thereafter. Patients were treated until radiologic progression of disease, occurrence of unacceptable toxicities, death, or withdrawal of consent. Patients randomized to dacarbazine were permitted to cross-over to the dabrafenib group when radiologic progression was confirmed by independent review. Cross-over was not permitted when patients chose to discontinue dacarbazine for reasons other than disease progression (adverse event or withdrawal of consent for example). Patients who discontinued treatment were followed for survival and additional cancer therapies every 12 weeks until death. Patients without disease progression who chose to discontinue treatment were followed until disease progression, start of new cancer therapy, or death. Adverse events were collected until 28 days after treatment discontinuation.

Dose interruptions and reductions were pre-specified in case of an adverse event. In the dabrafenib group, dose interruptions occurred for adverse events of grade 2 or higher. For grade 2 AEs, treatment was restarted at the current dose when the adverse event resolved or decreased to grade 1. For grade 3 AEs, treatment was restarted at a lower dose (first reduction 100 mg twice daily, second reduction 75 mg twice daily and third reduction 50 mg twice daily[2]), unless the adverse event was deemed to be unrelated to the drug. When a grade 4 adverse event occurred, the drug was discontinued. Treatment at a lower dose could be restarted if the investigator thought the event was not drug-related and unlikely to recur. If the adverse event was pyrexia, the following applied: For fever of grade ≥3, or of any grade with rigors, dehydration, hypotension, dizziness or weakness, dabrafenib treatment was interrupted until the fever dropped <38º C and symptoms resolved. Treatment was restarted at a lower dose. For fever of grade ≤2, treatment was interrupted until fever resolved to <38º C and then restarted at the original dose.

In the dacarbazine group, dose interruptions occurred in case of adverse events of grade ≥3 until the adverse event returned to grade ≤1. Treatment was restarted with a 20% dose reduction. Treatment was stopped if the adverse event did not resolve to grade ≤2 within four weeks or if a hematological grade 4 AE recurred after the dose reduction.

A dose reduction was seen in 52/187 (28%) of dabrafenib patients and of these, 38% were due to an adverse event and 54% were due to missed dose (reported as non-compliance). A dose interruption was seen in 58/187 (31%) of dabrafenib patients and of these, 81% were due to an adverse event. Five patients (3%) discontinued treatment due to an adverse event. A dose reduction was required in 10/63 (17%) of dacarbazine patients and two patients (3%) discontinued treatment due to an adverse event.

Up to December 2012, 36% (67/187) of dabrafenib patients received subsequent cancer treatment following disease progression (Table 3).[55] Of these, 20% (38/187) choose to continue dabrafenib despite progression with dabrafenib (Table 4).[55]

Table 3: Follow-up Systemic Therapy in Patients who Discontinued Study Treatment - December 18, 2012 data cut-off[55]		
# follow-up systemic therapies, n (%)	**Dabrafenib (n=187)**	**Dacarbazine (n=63)**
0	84 (45)	14 (22)
1	67 (36)	29 (46)
2	25 (13)	14 (22)
≥3	11 (6)	6 (10)

Table 4: Type of Systemic Therapy, First Occurrence - December 18, 2012 data cut-off[55]		
Drug, n (%)	**Dabrafenib (n=187)**	**Dacarbazine (n=63)**
Dabrafenib	38 (20)	37 (59)
Ipilimumab	25 (13)	2 (3)
Dacarbazine	16 (9)	2 (3)
Vemurafenib	9 (5)	6 (10)
Fotemustine	4 (2)	1 (2)
Lenvatinib mesilate	4 (2)	0
Carboplatin/ placitaxel	3 (2)	0
Interleukin-2	2 (1)	0
Temozolomide	1 (1)	1 (2)
Mitogen-activated protein/ extracellular signal-regulated kinase	1 (1)	0
Mk-3475	1 (1)	0

A total of 172/187 (92%) of dabrafenib patients and 58/59 (98%) dacarbazine patients received concomitant medications. The most common concomitant medications administered were antipyretics/analgesics (paracetamol, ibuprofen, acetylsalicylic acid) and proton pump inhibitors (omeprazole, pantoprazole) in the dabrafenib arm and antiemetics (ondansetron, metoclopramide, aprepitant), steroids (dexamethasone), and paracetamol in the dacarbazine arm.[55]

Patient Disposition

A total of 250 patients were randomized and included in the intention to treat analysis (Table 5).

The safety population (patients receiving at least one dose of the medication) included 187 patients treated with dabrafenib and 59 patients treated with dacarbazine.

At data cut-off of December 19, 2011, 17/63 (27%) of patients were receiving dacarbazine. A total of 44% of patients in the dacarbazine group chose to cross-over to dabrafenib.

At the June 25, 2012 data cut-off, a total of 35/63 (56%) of dacarbazine patients had crossed over to the dabrafenib group.

Table 5: Number of Patients[3]		
	Dabrafenib	**Dacarbazine**
Randomized	187	63
Received treatment	187	59*
Intention to treat analysis	187	63
Safety analysis	187	59
Still receiving treatment on December 19, 2011 (%)	107 (57)	17 (27)

Table 5: Number of Patients[3]		
	Dabrafenib	**Dacarbazine**
Reason for Treatment Discontinuation (%)	80 (43)	46 (73)
• Disease progression	66 (35)	43 (68)
• Adverse event	5 (3)	0
• Investigator discretion	4 (2)	2 (3)
• Decision by patient	5 (3)	1 (2)
Subject status (%)		
• Died	21 (11)	9 (14)
• Ongoing	160 (86)	49 (78)
o On study treatment	106 (57)	14 (22)
o In follow-up	54 (29)	14 (22)
o On cross-over study treatment	NA	21 (33)
• Withdrawn from study	6 (3)	5 (8)
NA=not applicable		

*One patient randomized to dacarbazine but received dabrafenib; one randomized in error; two withdrew after being randomized.

d) Limitations/Sources of Bias

The study used a 3:1 randomization design wherein more patients received the new treatment. The sponsor indicated that this design was chosen to obtain better information on efficacy and safety given a large hypothesized improvement of 200%. The advantages of using this design are: i) patients may be more willing to enter the trial if they know there is a higher chance of getting the new treatment; ii) by having more patients in the new treatment arm, more information is gained on harms.[56] The disadvantage is that it decreases the power of the study compared to a study using a 1:1 randomization of identical design and size[56] - but this was not an issue in BREAK-3 as the primary endpoint was statistically significant.

A second data analysis of PFS, overall survival and response rate was conducted and was not based on a pre-specified statistical plan. The results can only be considered as exploratory. The same can be said for the third analysis of overall survival.

Patients and investigators were not blinded to study treatment (open-label design). This type of study design may limit the interpretation of the results reported for patient outcomes (for example symptom improvements and quality of life).

Health related quality of life was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C-30). The manufacturer referred to one publication[57] which suggested an MCID of 5 to 10 points for breast cancer or small cell lung cancer patients.[55] A more recent study by Hong and colleagues reported that the MCID for QLQ-C30 score change differs across domains, and differs for perceived improvement and deterioration. It was further suggested that a 6 point decrease or a 3 point increase on QLQ-C30 domains may be clinically relevant. This study was conducted in patients who suffered from various types of cancer.[58] There were no MCID specific to melanoma cancer.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Table 6: Summary of Key Outcomes from the BREAK study – December 19, 2011 data cut-off[3,4]			
EFFICACY (ITT)			
Outcome	**Study group**	**Median Months (95% CI)**	**HR (95% CI)**
Overall Survival	dabrafenib	ND	0.61 (0.25, 1.48)
	dacarbazine	ND	
PFS investigator	dabrafenib	5.1 (4.9, 6.9)	0.30 (0.18, 0.51)*
	dacarbazine	2.7 (1.5, 3.2)	
Outcome	**Study group**	**n/N**	**% (95% CI)**
Deaths	dabrafenib	21/187	11
	dacarbazine	9/63	14
ORR investigator	dabrafenib	99/187	53 (46, 60)
	dacarbazine	12/63	19 (10, 31)
HARM			
Outcome	**Study group**	**n/N**	**%**
Fatal AE	dabrafenib	5/187	3
	dacarbazine	0	0
SAE	dabrafenib	43/187	23
	dacarbazine	13/59	22
AE	dabrafenib	185/187	99
	dacarbazine	54/59	92
WDAE	dabrafenib	5/187	3
	dacarbazine	2/59**	3
AE=adverse events; **CI**=confidence interval; **HR**=hazard ratio; **ITT**=intention to treat; **ND**=not reached; **ORR**=overall response rate; **PFS**=progression free survival; **SAE**=serious adverse events **WDAE**=withdrawal due to adverse events			

*P value<0.0001 (using a stratified log rank test)
**primary reason for treatment discontinuation was reported as disease progression

Efficacy Outcomes

Overall Survival

Overall survival was a secondary end point defined as the time interval between dates of randomization and death due to any cause. For patients who did not die, overall survival was censored at the date of the last contact.

The overall survival analysis at three data cut-offs showed no statistically significant difference between dabrafenib and dacarbazine (Table 7).The overall survival estimates are confounded by dacarbazine patients who crossed over to dabrafenib.

An analysis that adjusted for confounding effects of cross-over on overall survival using data from June 2012 was presented at ASCO 2013.[5] Two methods were used: the rank preserving structural failure time model (RPSFT) and the iterative parameter estimation (IPE). Results showed no statistically significant difference between dabrafenib and dacarbazine (data not shown) under two different sets of assumptions (treatment effect is maintained until death regardless of treatment duration or treatment effect disappeared upon discontinuation).[5]

Table 7: Overall Survival – ITT[3-5,15]		
	Dabrafenib (n=187)	**Dacarbazine (n=63)**
Data cut-off December 19, 2011		
n (%) patients crossing over	NA	28 (44)
Follow-up, median months (range)	5.0 (0, 9.9)	4.8 (0, 9.3)
Deaths, n (%)	21 (11)	9 (14)
Overall Survival (95% CI)		
• median, months	ND	ND
• OS rate at 6 months*	87% (79, 92)	79% (60, 90)
• HR†	0.61 (0.25, 1.48)	
Data cut-off June 25, 2012		
n (%) patients crossing over	NA	35(56)
Follow-up, median months (range)	10.5 (0, 16.5)	9.9 (0, 15.5)
Deaths, n (%)	55 (29)	21 (33)
Overall Survival (95% CI)		
• median, months	ND	ND
• OS rate at 9 months*	78% (71, 83)	74% (60, 83)
• HR†	0.75 (0.44, 1.29)	
Data cut-off December 18, 2012		
n (%) patients crossing over	NA	36 (57)
Follow-up, median months	15.2	12.7
Deaths, n (%)	78 (42)	28 (44)
Overall survival (95% CI)		
• median, months	18.2 (16.6, ND)	15.6 (12.7, ND)
• HR	0.76 (0.48, 1.21)	
CI=confidence interval; **HR**=hazard ratio; **ITT**=intention to treat; **NA**=not applicable; **ND**=not reached; **OS**=overall survival		

*****Kaplan-Meier estimates

† Pike estimator

Progression Free Survival

Progression-free survival based on investigator assessment was the primary end point (Table 8). Progression-free survival based on a blinded independent radiology committee (IRC) assessment was a secondary end point. Progression-free survival was defined as the time between the date of randomization and the earlier of date of disease progression or death due to any cause. Patients who had not progressed or died were censored at the date of the last assessment.

At the December 19 2011 data cut-off, the investigator-assessed progression-free survival hazard ratio was 0.30 (95% CI: 0.18, 0.51). The difference in median PFS between the two treatment groups was 2.4 months (Table 6). The IRC assessed progression-free survival hazard ratio was 0.35 (95% CI: 0.20, 0.61). The median PFS based on the IRC assessment was 6.7 months with dabrafenib and 2.9 months with dacarbazine.

At the June 25 2012 data cut-off, the investigator assessed progression-free survival hazard ratio was 0.37 (95% CI: 0.23, 0.58).

Table 8: Progression Free Survival Investigator Assessed – ITT[3,4,15]		
	Dabrafenib (n=187)	**Dacarbazine (n=63)**
Data cut-off December 19, 2011		
Patients with events, n (%)	77 (41)	41 (65)
PFS (95% CI)		
• median, months*	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)
• HR**	0.30 (0.18, 0.51), p<0.0001	
Data cut-off June 25, 2012		
Patients with events, n (%)	117 (63)	50 (79)
PFS (95% CI)		
• median, months*	6.9 (5.2, 9.0)	2.7 (1.5, 3.2)
• HR**	0.37 (0.23, 0.58), p<0.0001†	
CI=confidence interval; **HR**=hazard ratio; **ITT**=intention to treat; **PFS**=progression free survival		

*Kaplan Meyer estimates and Brookmeyer Crowley method
** Pike estimator
† P value using log rank test stratified on disease staging

Subgroup analyses for progression-free survival:

The treatment effect of dabrafenib across pre-specified subgroups was estimated using a Cox proportional hazards model and these effects were consistent with the primary analysis for progression-free survival. However, the hazard ratio estimate was not statistically significant for patients aged ≥65 years.

Tumour Response

Overall response rate was as secondary end point defined as the percentage of patients who achieved a complete or partial response as per the RECIST criteria, by investigator assessment. Patients with unknown or missing response were treated as non-responders. Duration of response included patients who showed a complete or partial response (Table 9).

At the data cut-off of December 19, 2011, 99/187 (53%) of patients in the dabrafenib group had a complete (6/187, 3%) or partial response (93/187, 50%). This compared to 12/63 (12%) of patients in the dacarbazine group (all were partial responses). The median duration of response was 5.6 months (95% CI: 5.6, not reached) in the dabrafenib group and had not been reached in the dacarbazine group.

At the data cut-off of June 25, 2012, 110/187 (59%) of patients in the dabrafenib group had a complete (17/187, 9%) or partial response (93/187, 50%). This compared to 15/63 (24%) of patients in the dacarbazine group [complete response 4/63 (6%) and partial response 11/63 (17%)]. The median duration of response was 8.0 months (95% CI: 6.6, 11.5) in the dabrafenib group and 7.6 months (95% CI: 5.0, 9.7) in the dacarbazine group.

Table 9: Tumour Response Investigator Assessed- ITT[3,4]		
	Dabrafenib (n=187)	**Dacarbazine (n=63)**
Data cut-off December 19, 2011		
Response rate, n (%) [95% CI]	99 (53) [46, 60]	12 (19) [10, 31]

Table 9: Tumour Response Investigator Assessed- ITT[3,4]		
	Dabrafenib (n=187)	**Dacarbazine (n=63)**
Data cut-off December 19, 2011		
• Complete response • Partial response	6 (3) 93 (50)	0 12 (19)
Difference in response rate*, % (95% CI)	34 (20, 48)	
Median duration of response†, months (95% CI)	5.6 (4.8, ND)	ND (5.0, ND)
Data cut-off June 25, 2012		
Response rate, n (%) [95% CI] • Complete response • Partial response	110 (59) 17 (9) 93 (50)	15 (24) 4 (6) 11 (17)
Difference in response rate*, % (95% CI)	35 (21, 49)	
Median duration of response†, months (95% CI)	8.0 (6.6, 11.5)	7.6 (5.0, 9.7)
CI=confidence interval; **ITT**=intention to treat; **ND**=not reached		

*Chi-square test
†Kaplan-Meier estimates

Health Related Quality of Life

Health related quality of life was evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the European Quality of Life Scale (EQ-5D). Both instruments were administered at screening, week 6, week 12, week 15, at disease progression and 30 days after progression.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30:

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. It's comprised of 5 functional scales (physical, role, cognitive, emotional, social), 9 symptom scales or single items (fatigue, pain, nausea and vomiting etc.), and a summary scale (global health status and quality of life). Scoring is from 0 to 100, and an increase in score is associated with an improvement in functioning or worsening of symptoms.

In the dabrafenib group, improvements from baseline were seen at week 12 for emotional functioning (increase by 9 points) and social functioning (increase by 3 points), and for all symptoms (decrease by 1 to 4 points) except fatigue (increase by 2 points) and dyspnea (no change). Appetite loss was the most improved at week 12 with a 9 point decrease. In the dacarbazine group, role functioning was improved at week 12 by 3 points. Patients reported worsening of symptoms at week 12 except for constipation (no change). Overall global health status was increased by 2 points with dabrafenib and by one point with dacarbazine at week 12. Whether or not if any of these findings were clinically meaningful is unknown. Furthermore, it is unknown if these effects were sustained after week 12.[3,6]

European Quality of Life Scale:

The EQ-5D includes an index-based summary score (based on societal preference weights) and a visual analogue scale (VAS). The index-based summary score is comprised of five dimensions (mobility, self-care, usual activities, pain/ discomfort, and anxiety/depression) from which a utility index score is computed (scores less than 0 represent health states that are valued by society as being worse than dead, while scores

of 0 and 1.00 are assigned to the health states 'dead' and 'perfect health', respectively). VAS measures how good or bad a patient feels on a scale of 0 (worst imaginable health state) to 100 (best imaginable health state).

At baseline, EQ-5D scores were unavailable for 2% and 8% of dabrafenib and dacarbazine groups, respectively. A total of 49% and 21% of patients completed all assessments in the dabrafenib and the dacarbazine groups, respectively. At baseline, median EQ-5D utility values were similar between treatment groups but at week 6, 12 and 15, median values were higher in the dacarbazine group. At baseline and at weeks 6 and 12, some patients had negative values (worse than dead) whereas other patients had a score of 1.0 in the dabrafenib group. Negative values were seen in the dacarbazine group at baseline and week 6.

At baseline, mean VAS score was [redacted] (±standard deviation [redacted]) for dabrafenib (n=[redacted]) which increased to [redacted] (±standard deviation [redacted]) at week [redacted] (n=[redacted]). (*Non-disclosable clinical information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.*). For dacarbazine, mean VAS score at baseline was 62 (±standard deviation 31; n=58) with an increase to 71 (±standard deviation 27; n=19) at week 12.[55]

Given that most patients had incomplete assessments post-baseline, it is challenging to interpret these findings.

Outcomes of dacarbazine patients who crossed over to dabrafenib

A total of 28 dacarbazine patients crossed over at time of data cut-off (December 19, 2011) following independently confirmed progression. The median time on dabrafenib after cross over was 2.8 months. Median PFS (investigator assessed) in the cross-over phase was 4.1 months (compared to 1.6 months in the same patients prior to cross over). Of the 28 patients who crossed over, 13 patients (46%) had a partial response. No complete response was seen.

Harms Outcomes

Serious Adverse Events

It is reported that five patients experienced a fatal serious adverse event (not related to disease progression) with dabrafenib; none of which were attributed to the study treatment: One patient chose elective euthanasia. One patient had Grade 4 sepsis and subsequent severe respiratory failure following an aspiration event. Three patients had a brain haemorrhage. No fatal serious adverse event (not related to disease progression) was reported with dacarbazine.

Non-fatal serious adverse events occurred in 43/187 (23%) of patients in the dabrafenib group and included squamous cell carcinoma of the skin or cutaneous squamous cell carcinoma (6%, 10 events), pyrexia (4%, 7 events), and malignant melanoma (2%, 3 events). In the dacarbazine group, non-fatal serious adverse events were reported in 13/59 (22%) and included neutropenia, abdominal pain and sepsis.

Table 10: Nonfatal Serious Adverse Events (≥2% of patients) in BREAK-3[3]		
	Dabrafenib (n=187)	**Dacarbazine (n=59)**
Total, n (%)	**43 (23)**	**13 (22)**
Squamous cell carcinoma	7 (4)	0
Pyrexia	7 (4)	0
Squamous cell carcinoma of skin	3 (2)	0
Anemia	1 (<1)	1 (2)
Vomiting	2 (1)	1 (2)
Nausea	1 (<1)	1 (2)
Malignant melanoma	3 (2)	0
Pulmonary embolism	1 (<1)	1 (2)
Abdominal pain	0	2 (3)
Neutropenia	0	1 (2)
Sepsis	0	1 (2)

Adverse Events

Adverse events were reported in 185/187 (99%) of dabrafenib patients and in 54/59 (92%) of dacarbazine patients (Table 11). Of these, 53% of the dabrafenib related AEs were Grade ≥2 compared to 44% for dacarbazine. The most common AEs (AEs of any grade) were hyperkeratosis (37%), headache (32%), pyrexia (28%), arthralgia (27%), skin papilloma (24%), alopecia (22%), palmar-plantar erythrodysaesthesia (20%), fatigue (19%), and nausea (19%) in the dabrafenib group. In the dacarbazine group, common AEs included nausea (51%), vomiting (25%), fatigue (24%), neutropenia (17%), asthenia (15%), constipation (14%), abdominal pain (14%), and anemia (12%).

When a dose reduction or a dose interruption was required due to an adverse event, it was mostly due to pyrexia or palmar-plantar erythrodysaesthesia (PPE syndrome) for dabrafenib, and neutropenia for dacarbazine.

Table 11: Most Common Adverse Events (≥10% of Patients) in BREAK-3[3]				
	Dabrafenib (n=187)		**Dacarbazine (n=59)**	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Total, n (%)	**185 (99)**	**62 (33)**	**54 (92)**	**24 (41)**
Hyperkeratosis	69 (37)	2 (1)	0	0
Headache	59 (32)	0	5 (8)	0
Pyrexia	52 (28)	6 (3)	6 (10)	0
Arthralgia	51 (27)	2 (1)	1 (2)	0
Skin papilloma	45 (24)	0	1 (2)	0
Alopecia	41 (22)	0	1 (2)	0
PPE syndrome	37 (20)	4 (2)	1 (2)	0
Fatigue	36 (19)	2(1)	14 (24)	0
Nausea	35 (19)	1 (<1)	30 (51)	0
Asthenia	33 (18)	1 (<1)	9 (15)	1 (2)
Rash	31 (17)	0	0	0
Vomiting	23 (12)	2 (1)	15 (25)	0
Cough	23 (12)	0	3 (5)	0
Back pain	22 (12)	5 (3)	4 (7)	0

Table 11: Most Common Adverse Events (≥10% of Patients) in BREAK-3[3]				
	Dabrafenib (n=187)		**Dacarbazine (n=59)**	
Constipation	21 (11)	3 (2)	8 (14)	0
Diarrhea	20 (11)	1 (<1)	7 (12)	0
Myalgia	20 (11)	0	0	0
Nasopharyngitis	19 (10)	0	2 (3)	0
Pain in extremity	16 (9)	1 (<1)	7 (12)	0
Abdominal pain	7 (4)	1 (<1)	8(14)	1 (2)
Anemia	7 (4)	1 (<1)	7 (12)	2 (4)
Neutropenia	2 (1)	1 (<1)	10 (17)	8 (14)
Leukopenia	1 (<1)	0	6 (10)	2 (3)
PPE=palmar-plantar erythrodysaesthesia				

Withdrawals Due to Adverse Events

Five patients in the dabrafenib group (3%) and two patients in the dacarbazine group (3%) permanently discontinued treatment due to adverse events. The two dacarbazine patients were considered withdrawn from the trial primarily because of disease progression (and hence in Table 5 they are not counted as withdrawn due to adverse events).

6.4 Ongoing Trials

No ongoing RCTs were identified evaluating dabrafenib monotherapy. Three phase 3 RCTs sponsored by Glaxo Smith Kline are on-going (Table 12).

Table 12: On-going Dabrafenib Combination Therapy Phase 3 RCTs[59-61]		
Study Characteristics	**Interventions/ Comparators**	**Outcomes**
Patients with unresectable or metastatic BRAF V600E/K mutation positive cutaneous melanoma		
NCT 01584648[59] Start May 2012 End May 2015 Double-blind N=340	dabrafenib 150 mg po BID + trametinib 2 mg po OD vs. dabrafenib 150 mg po BID + placebo OD	Primary outcome: PFS Secondary outcomes: OS, ORR, Duration of response
NCT 01597908[60] Start Jun 2012 End June 2015 Open-label N=694	dabrafenib 150 mg po BID + trametinib 2 mg po OD vs. vemurafenib 960 mg po BID	Primary outcome: OS Secondary outcomes: PFS, ORR, Duration of response
Patients receiving adjuvant treatment of high risk BRAF V600 mutation positive melanoma after surgical resection		
NCT 01682083[61] Start Jan 2013 End July 2015 Double-blind N=842	dabrafenib 150 mg po BID + trametinib 2 mg po OD vs. 2 placebos	Primary outcome: RFS Secondary outcomes: OS, DMFS, FFR, Harm
BID=twice daily; **DMFS**=distant metastasis free survival; **FFR**=freedom from relapse; **ORR**=overall objective response; **OD**=once daily; **OS**=overall survival; **PFS**=progression free survival; **po**=orally; **RCT**=randomized controlled trial; **RFS**=relapse free survival		

7 SUPPLEMENTAL QUESTIONS

The following supplemental topic was identified during development of the review protocol as relevant to the pCODR review of dabrafenib for unresectable or metastatic melanoma. Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

- Critical Appraisal of an Indirect Comparison of Dabrafenib and Vemurafenib
- Summary of two Phase II trials relevant to the review, BREAK-2 and BREAK-MB
- Summary of BRAF Mutation Testing in Metastatic Melanoma

7.1 Critical Appraisal of an Indirect Comparison of Dabrafenib and Vemurafenib

7.1.1 Objective

The manufacturer submitted an indirect comparison of dabrafenib and vemurafenib as part of its evaluation of the cost-effectiveness of dabrafenib for the treatment of BRAF V600E mutation positive patients with unresectable or metastatic melanoma. This section of this report provides a summary and critical appraisal of the methods and findings of the indirect comparison.

7.1.2 Findings

A. Characteristics of the Included Trials

The results of two studies were used: BREAK-3[4] and BRIM-3.[42] BREAK-3 compared dabrafenib with dacarbazine and BRIM-3 compared vemurafenib with dacarbazine. Study characteristics are listed in Table 1.

Both BRIM-3 and BREAK-3 enrolled patients with previously untreated metastatic melanoma with the BRAF V600E mutation. Baseline characteristics were similar in both trials with the exception of a higher proportion of patients in the BRIM-3 study with elevated lactate dehydrogenase.

Patients in the BRIM-3 study were stratified according to the American Joint Committee on Cancer (AJCC) stage, ECOG performance status, geographic region and serum lactate dehydrogenase level (normal or elevated). Patients in the BREAK-3 study were stratified only by AJCC stage. BREAK-3 patients were randomized 3:1 and the sample size was 250 patients, while the BRIM-3 study enrolled 650 patients who were randomized 1:1. In BREAK-3, the primary end point was progression free survival, whereas progression free survival and overall survival were co-primary end points in BRIM-3. Finally, in BREAK-3, the trial design used a one sided test with an alpha of 0.02 for progression free survival, whereas BRIM-3 used a two sided test with an alpha level 0.005 for progression free survival.

Dose reductions were permitted in the BRIM-3 trial and BREAK-3 for intolerable side effects. In both trials tumor assessments were performed at baseline, at weeks 6 and 12, and every 9 weeks thereafter, using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Both trials were open-label. In BREAK-3, a masked independent review committee reviewed all scans and confirmed progression but this was not the case for BRIM-3.

In BREAK-3, dacarbazine patients were allowed to cross over to dabrafenib at any time point when progression was confirmed. Cross over was only permitted in BRIM-3 following a pre-planned interim analysis by an independent data and safety monitoring board.

Median follow-up times are provided in Table 2. Data cut offs of February 2012 (vemurafenib) and June 2012 (dabrafenib) were used for the indirect comparison.

Table 1: Summary of Trials

Trial, Publication	Study Design	Patient Population	Intervention and Comparator	Outcomes
BRIM-3 Chapman et al 2011[42]	Phase 3, randomized, open label, multinational, multicentre 1:1 randomization Stratified by AJCC stage (IIIC, M1a, M1b, or M1c), ECOG, geographic region, and serum LDH level (normal or elevated)	N=675 • Patients with unresectable, previously untreated, BRAF V600E mutation-positive, stage IIIC or stage IV melanoma • Life expectancy >3 months • ECOG ≤1	Vemurafenib 960 mg orally twice daily Dacarbazine 1000 mg/ m^2 IV every 3 weeks Crossovers allowed after the interim analysis	Co-Primary • Overall survival • Progression-free survival Secondary • Best overall response rate • Duration of overall response • Time to overall response • AEs
BREAK-3 Hauschild et al 2012[4]	Phase 3, randomized, open label, multinational, multicentre 3:1 randomization Stratified by AJCC stage (III+IVM1a+IVM1b vs. IVM1c)	N=250 • Patients with measureable metastatic melanoma stage IV or unresectable stage III melanoma, previously untreated, BRAF V600E mutation-positive • ECOG ≤1	Dabrafenib 150 mg orally twice daily Dacarbazine 1000 mg/ m^2 IV every 3 weeks Crossovers allowed upon disease progression	Primary • Progression-free survival assessed by investigator Secondary: • Progression-free survival assessed by independent review committee • Overall survival • Overall response rate • Duration of response • HRQoL • AEs
AEs=adverse events; **AJCC=**American Joint Committee on Cancer; **ECOG=**Eastern Cooperative Oncology Group; **HRQoL**=health related quality of life; **IV**=intravenously; **LDH**=serum lactate dehydrogenase				

Table 2: Duration of Follow-Up

BREAK-3[4,15]				**BRIM-3**[42,62]			
Start of trial: Feb 2011				Start of trial: Jan 2010			
Date of data cut-off	% dacarbazine patients cross-over	Median follow-up for **dabrafenib**	Median follow-up for dacarbazine	Date of data cut-off	% dacarbazine patients cross-over	Median follow-up for **vemurafenib** (months)	Median follow-up for dacarbazine

BREAK-3[4,15]				BRIM-3[42,62]			
Start of trial: Feb 2011				Start of trial: Jan 2010			
off	(n/N)	(months)	(months)		(n/N)		(months)
Dec 2011	44 (28/63)	5.0	4.8	Dec 2010	0	3.8	2.3
Jun 2012	56 (35/63)	10.5	9.9	Mar 2011	15	6.2	4.5
Dec 2012	57 (36/63)	15.2	12.7	Feb 2012	34	12.5	9.5

B. Results

In a pharmacoeconomic evaluation provided with the manufacturer submission, various treatment effects assumptions were examined.

Class Effect:
Although not an indirect comparison, one analysis assumed a class effect of BRAF inhibitors (no difference in measure of effectiveness between dabrafenib and vemurafenib) under different scenarios: 1)treatment effects of vemurafenib were equal to that of dabrafenib; 2)treatment effects of dabrafenib were equal to that of vemurafenib; 3)treatment effects of dabrafenib and vemurafenib were obtained in a meta-analysis of BREAK-3 and BRIM-3.

Under scenario 3, pooled hazard ratios for progression free survival and overall survival were calculated using a random effects model. Meta-analysing these results gave a pooled hazard ratio for progression free survival of 0.38 (95% CI: 0.32, 0.45), a statistically significant result in favour of BRAF inhibitors compared to dacarbazine (Table 3).

Overall survival with vemurafenib was statistically significantly better than dacarbazine in BRIM-3. Dabrafenib did not have a statistically significant result for overall survival compared to dacarbazine in BREAK-3. The pooled hazard ratio for overall survival was calculated using the Rank Preserving Structural Failure Time (RPSFT) hazard ratios (adjusted for censoring) and was calculated to be 0.63 (95% CI: 0.47, 0.85).

Table 3: Hazard Ratios for BREAK-3 and BRIM-3

Hazard Ratios (95% CI)	BREAK-3[5] June 2012	BRIM-3[63] February 2012	Pooled Results
Progression free survival	0.37 (0.23, 0.58)	0.38 (0.32, 0.46)	0.38 (0.32, 0.45)
Overall survival RPFST	0.57 (0.22, 1.5)	0.64 (0.53, 0.78)	0.63 (0.47, 0.85)
RPFST= Rank Preserving Structural Failure Time			

No Class Effect:
An alternate assumption was that there was no class effect. The relative efficacy of dabrafenib compared to vemurafenib was estimated using Bucher, an indirect treatment comparison method.

An indirect comparison can provide information in the situation where trials have not been designed to directly compare specific treatments. The Bucher method uses aggregate data. The effect measure comparing two treatments within a randomized controlled trial is used rather than the individual results for each treatment group, which partially maintains the strength of randomization. The indirect comparison is based on the paired comparison of the direct estimates of the drugs against a common comparator (in this case dacarbazine) and as such, this method assumes independence between pairwise comparisons. One assumption of this model is that the patient and trial characteristics are similar between trials. Another assumption is that the

magnitude of the treatment effect is consistent between the different studies being compared. The assumptions were met, with the exception of duration of follow-up.

The estimated progression free survival and overall survival based on the results of the indirect comparison are presented in Table 4. There were no statistically significant differences in hazard ratios for progression free survival and overall survival comparing dabrafenib and vemurafenib. The disparity between studies (BRIM-3 and BREAK-3) in terms of duration of follow-up would affect our confidence in the results of the analysis. However, for overall survival, adjustments were made to account for different lengths of follow-up (see results for restricted follow-up).

Table 4: Indirect Treatment Comparison Results

Dabrafenib vs. Vemurafenib[3,64]		
	Hazard Ratio	**95% CI**
Progression free survival	0.97	(0.6-1.57)
Overall survival† unrestricted follow-up*	0.89	(0.33-2.37)
Overall survival† restricted follow up**	[redacted]	([redacted]-[redacted])
CI=confidence interval		

† Rank Preserving Structural Failure Time adjusted hazard ratio was used in calculation
*not adjusted for the different duration of follow-up
**adjusted for duration of follow up
(*Non-disclosable clinical information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.*)

C. Limitations

The indirect comparison analysis was appraised using the ISPOR criteria (Table 5). No information was given on: the eligibility criteria for included RCTs; the search strategy; the review and data extraction methods; the information sources and study selection; and the validity of individual studies. Furthermore, it was not reported whether a random or fixed effects model was used for Bucher. Summaries of patient and trial characteristics were not provided.

Whereas overall survival was statistically significant with vemurafenib vs. dacarbazine in BRIM-3, this was not the case for dabrafenib vs. dacarbazine in BREAK-3. This could perhaps have been due to the fact that the number of patients who had crossed over was higher in BREAK-3 or due to the larger sample size in BRIM-3. Adjusted hazard ratios (using Rank Preserving Structural Failure Time methods) were used in the indirect comparison. The different lengths of follow-up were also accounted for.

7.1.3 Summary

Analyses were performed under various treatment effect assumptions. When a class effect was assumed (no difference in measure of effectiveness between dabrafenib and vemurafenib), BRAF inhibitors (dabrafenib and vemurafenib) were statistically significantly better than dacarbazine for progression free survival and overall survival when pooling the results of BRIM-3 and BREAK-3. These findings were limited by the fact that only two trials were included in the meta-analysis and that the results of BRIM-3 may have influenced the overall survival treatment effect.

Under a no class effect assumption (differential effectiveness of dabrafenib and vemurafenib), indirect statistical assessments using the Bucher method were used to compare dabrafenib to vemurafenib. No statistically significant differences were found between the two treatments for

progression free survival and overall survival with and without adjustments for duration of follow-up. Conclusions drawn from such indirect comparisons are not as robust as those from direct, head-to-head trial data, and therefore the findings should be interpreted with caution.

Table 5: Appraisal of the indirect comparison analyses using ISPOR criteria

ISPOR Checklist Item		Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting an indirect comparison analysis and the study objectives were stated.
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility criteria for RCTs were not clearly stated. • A detailed search strategy was not presented. • Review and data extraction were not discussed. • Information sources and study selection were not discussed. • Similarity of trials was assessed. Differences between trials that may modify treatment effect measures were discussed; trials were deemed similar but one important difference existed (duration of follow up). • Validity of individual studies was not discussed.
3.	Are the outcome measures described?	• Outcomes assessed in the indirect comparison analysis (overall survival and progression-free survival) were stated but not defined for comparison purposes.
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• Relative effectiveness was estimated by the Bucher method. • For overall survival, hazard ratios were calculated by adjusting for duration of follow-up (unrestricted and restricted).
5.	Are sensitivity analyses presented?	• N/A
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• Summaries of patient and trial characteristics were not presented. • Individual study results were presented.
7.	Does the study describe an assessment of model fit? Are competing models being compared?	• N/A
8.	Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for PFS and OS) including point estimates and 95% confidence intervals.
N/A=not applicable; **RCTs**=randomized controlled trial; **RPSFT**=Rank Preserving Structural Failure Time		

7.2 Summary of two Phase II trials relevant to the review, BREAK-2 and BREAK-MB

Two phase 2 trials, which did not meet the protocol's inclusion criteria, were identified as relevant to the review.

BREAK-2 was an open-label, phase 2, multi-centre, single-arm trial conducted in patients with BRAF V600E or V600K, cutaneous metastatic melanoma (stage IV).[3,16,45] Inclusion criteria included laboratory confirmation of BRAF status, an ECOG performance status of 0 or 1, and no brain metastases. Dabrafenib 150 mg orally twice daily was administered until disease progression, death or unacceptable adverse events. The primary endpoint was the proportion of patients with an overall response rate (confirmed complete or partial response) as assessed by the investigators.[3,16,45]

A total of 92 patients were enrolled between August 9, 2010 and February 10, 2011: 53% (49/92) were males, 83% (76/92) were BRAF positive for V600E, 63% (58/92) had M1c-stage disease; and 84% (77/92) had received treatment for metastatic disease. Patients had a median age of 55 years (range 22-83 years).[16,45] The primary efficacy analysis was conducted in patients with a V600E mutation. At data cut-off (July 7, 2011), median duration on treatment was 4.8 months and median duration of follow-up was 6 months.[3] The PFS hazard ratio (investigator assessed) was 0.30 (95% confidence interval: 0.18, 0.51) in BRAF V600E patients (hazard ratio estimated using a Pike estimator; adjusted for disease stage at screening).[3]

BREAK-2 Results[3,16]		
Outcomes	**Results, BRAF V600E patients, n=76**	**Results, BRAF V600K patients, n=16**
Overall response % (95% CI)		
Investigator assessed	59* (48.2, 70.3)	13** (0, 28.7)
Independent review committee	41 (29.7, 51.8)	25 (3.8, 46.2)
Duration of response median months (95% CI)		
Investigator assessed	5.2 (3.9, ND), n=45	5.3 (3.7, 6.8), n=2
Independent review committee	6.2 (5.1, ND), n=31	5.0 (3.4, ND), n=4
PFS median months (95% CI)		
Investigator	6.3 (4.6, 7.7)	4.5 (2.6, 6.2)
Independent review committee	6.1 (4.6, ND)	4.5 (2.6, 6.2)
Overall survival median months (95% CI)		
At 6 months follow-up	9.5 (9.5, ND)	7.9 (5.5, ND)
At 12 months follow-up	13.1 (10.4, ND)	12.9 (6.9, 17.1)
CI=confidence interval; **NP**=not provided; **ND**=not reached; **PFS**=progression free survival		

*complete response=7%; partial response=53%
**all partial responses

A total of 93% of patients experienced an adverse event, most commonly (≥20%) arthralgia, hyperkeratosis, pyrexia, fatigue, headache, and nausea.[3] Twenty-five patients (27%) experienced a Grade 3 adverse event (cutaneous squamous cell carcinoma, lymphopenia, basal cell carcinoma, anemia and hypophosphatemia) and eight patients (9%) experienced a Grade 4 adverse event. Serious adverse events were reported in 25 patients (27%) including basal cell carcinoma, squamous cell carcinoma, anemia, pyrexia, non-cardiac chest pain and vomiting. One patient discontinued treatment when experiencing pancytopenia. Dose reduction or interruption was required in 13 patients (14%) and 27 patients (29%) respectively, due to adverse events.[3]

BREAK-MB was an open-label, phase 2, multi-centre, single-arm trial conducted in patients with histologically confirmed BRAF mutant melanoma [Val600Glu (V600E) or Val600Lys (V600K)] and asymptomatic brain metastases.[17] Other inclusion criteria included having at least one measurable brain metastasis between 5 mm and 40 mm in diameter, an ECOG performance status of 0 or 1 and

adequate organ function. Patients were split into two cohorts: cohort A (n=89) had not received previous local treatments for brain metastases and cohort B (n=83) had disease progression in the brain after surgery, whole brain radiotherapy or stereotactic radiosurgery. Patients could have received up to two previous treatments for extracranial metastatic melanoma, but no BRAF or MEK inhibitors. Patients in cohort B could have had any number of previous local treatments. Dabrafenib 150 mg orally twice daily was administered until disease progression, death or unacceptable adverse events. Patients with radiologically confirmed disease progression, who continued to have clinical benefits, as determined by the investigators, could continue treatment. The primary endpoint was the proportion of patients with V600E BRAF mutant melanoma with overall intracranial response as assessed by the investigators.[17]

A total of 172 patients were enrolled between February 2, 2011 and August 5, 2011.[17] Patients had a median age of 52.5 years (range 19-87 years). In cohort A: 73% (65/89) were males, 83% (74/89) were BRAF positive for V600E, 55% (49/89) had a baseline LDH level greater than the upper limit of normal, and 54% (48/89) had two or more brain metastases. In cohort B, 66% (55/83) were males, 78% (65/83) were BRAF positive for V600E, 53% (44/83) had a baseline LDH level greater than the upper limit of normal, and 64% (53/83) had two or more brain metastases.[17] At data cut-off (November 28, 2011), median duration of follow-up was 5 months with more than 50% of the patients still alive.[3] Disease progression was experienced by 86/139 (62%) of patients with a BRAF V600E mutation and in 16/33 (48%) of patients with a BRAF V600K mutation. New brain lesions were seen in 24% and 15% of patients respectively.[17] Patient with higher levels of LDH had lower overall intracranial response and overall response, and shorter median PFS and overall survival.[17]

BREAK-MB Results[3,17]				
	BRAF V600E patients		**BRAF V600K patients**	
Outcomes	Cohort A (n=74)	Cohort B (n=65)	Cohort A (n=15)	Cohort B (n=18)
Overall intracranial response % (95% CI)				
Investigator assessed	39 (28.0, 51.2)	31 (19.9, 43.4)	7 (0.2, 31.9)	22 (6.4, 47.6)
IRC	20 (11.8, 31.2)	18 (9.9, 30.0)	0 (0, 21.8)	11 (1.4, 34.7)
Overall intracranial response duration median months (95% CI)				
Investigator assessed	4.6 (2.8, ND) N=29	6.5 (4.6, 6.5) N=20	2.9 N=1	3.8 (ND, ND) N=4
IRC	4.7 (4.5, 6.5) N=15	4.6 (4.2, 4.6) N=12	NA	ND N=2
Overall response % (95% CI)				
Investigator assessed	38 (26.8, 49.9)	31 (19.9, 43.4)	0 (0, 21.8)	28 (9.7, 53.5)
IRC	28 (18.5, 40.1)	23 (13.5, 35.2)	0 (0, 21.8)	11 (1.4, 34.7)
Overall response duration median months (95% CI)				
Investigator assessed	5.1 (3.7, ND) N=28	4.6 (4.6, 6.5) N=20	NA	3.1 (2.8, ND) N=5
IRC	4.6 (4.3, ND) N=21	4.6 (2.78, ND) N=15	NA	ND N=2
PFS median months (95% CI)				
Investigator	3.7 (3.6, 5.0)	3.8 (3.6, 5.5)	1.9 (0.7, 3.7)	3.6 (1.8, 5.2)
IRC	3.6 (2.6, 5.2)	3.7 (3.5, 3.8)	1.8 (0.7, 1.9)	3.5 (1.9, 5.6)
Overall survival median months (95% CI)				
	7.6 (5.9, ND)	7.2 (5.9, ND)	3.7 (1.6, 5.2)	5.0 (3.5, ND)
CI=confidence interval; **IRC**=Independent review committee; **NA**=not applicable; **ND**=not reached; **PFS**=progression free survival				

A total of 92% of patients experienced an adverse event, most commonly (≥20%) hyperkeratosis, pyrexia, fatigue, headache, nausea, and vomiting.[3] The most common Grade 3 adverse events reported by >2% of patients were headache, squamous cell carcinoma, lymphopenia, and hypokalemia. Serious adverse events were reported in 30% of patients and included intracranial hemorrhage, squamous cell

carcinoma, and pyrexia. Four patients discontinued treatment when experiencing intolerable adverse events.[3] Dose reduction or interruption due to adverse events was required in 33 patients (37%) in cohort A and 46 patients (55%) in cohort B.[17]

The patient populations were different in the BREAK-3, BREAK-2 and BREAK-MB studies. BREAK-3 was conducted in patients with a BRAF V600E mutation and untreated for metastatic disease. BREAK-2 included pre-treated patients. Whereas BREAK-3 and BREAK-2 excluded patients with brain metastases, BREAK-MB included patients with brain metastases with or without prior treatments for brain metastases. BREAK-2 and BREAK-MB studies included patients with both BRAF V600E and V600K mutations. Because of the differences in patient populations, a comparison of results is inappropriate but nonetheless the trials provided information on the benefits and harms of dabrafenib when administered under different patient circumstances. It is safe to say that the sub-group sample sizes were too small in BREAK-2 and BREAK-MB to draw conclusions on the effectiveness of dabrafenib in patients with BRAF V600K mutations. Furthermore, the lack of comparator groups in BREAK-2 and BREAK-MB make the interpretation of the results challenging. Furthermore, in some instances there is large discrepancy between the investigator assessment and the independent review committee.

Summary of Results				
	BREAK-3	**BREAK-2**	**BREAK-MB, BRAF V600E**	
Key outcomes			Cohort A	Cohort B
Median duration of follow-up	5 months	6 months	5 months	5 months
Overall response, investigator assessed	53%	59%	38%	31%
Median duration of overall response	5.6 months	5.2 months	5.1 months	4.6 months
PFS, investigator assessed	5.1 months	6.3 months	3.7 months	3.8 months
Overall survival	not reached	9.5 months	7.6 months	7.2 months

7.3 Summary of BRAF Mutation Testing in Metastatic Melanoma

7.3.1 Objective

This section summarizes BRAF mutation testing and its role in identifying metastatic melanoma patients who may be treated with dabrafenib.

The provincial advisory group (PAG) is interested in the implementation and additional costs of BRAF mutation testing, including different test methods available, cost differences, differences with respect to the level of evidence to support them, intellectual property differences and issues associated with tissue sampling (See Section 5 of the report).

7.3.2 Findings

Dabrafenib is indicated for use specifically in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. Several different DNA-based methodologies can be used to detect these mutations, including Sanger sequencing, allele-specific polymerase chain reaction (PCR), amplification refractory mutation system (ARMS), or ligase detection reaction in order to identify patients who are candidates for therapy with a BRAF inhibitor.[65]

Health Canada and the U.S. FDA both approved Roche's cobas® 4800 BRAF V600 Mutation Test in 2011.[66,67]

Description of the cobas® 4800 BRAF V600 Mutation Test[68]

The cobas® 4800 BRAF V600 Mutation Test is an in vitro diagnostic device intended for the qualitative detection of the BRAF V600E mutation in DNA extracted from formalin-fixed,

paraffin-embedded human melanoma tissue. It is a validated, real-time polymerase chain reaction (PCR) test.

There are two kits included with the cobas@ 4800 BRAF V600 Mutation Test:

1. The cobas@ 4800 DNA Sample Preparation kit: It provides reagents for manual specimen preparation to obtain genomic DNA from formalin-fixed, paraffin-embedded tissue (FFPET).
2. The BRAF V600 Mutation Test kit: It provides reagents for automated real-time PCR amplification and detection of the BRAF target DNA.

The tissue sections for FFPET specimens are routinely removed as part of the diagnosis of melanoma by pathologists. There is no additional biopsy or invasive testing required. The test can be performed on DNA extracted from a single 5-micron FFPET specimen and full results reported in approximately eight hours.

The cobas® 4800 system is controlled by the cobas® 4800 system SR2 (v. 2.0) software (provides the core software engines and user interfaces) and accompanied by the cobas z 480 analyzer (tracks each specimen during processing and analysis). This system is capable of performing multiple assays at one time. A dedicated Control Unit computer runs the cobas® 4800 system SR2 software and provides an interface to the cobas z 480 and Laboratory Information System.

Performance of the cobas® 4800 BRAF V600 Mutation Test

The cobas® 4800 BRAF V600 Mutation Test was clinically validated with 433 clinical samples from patients screened for the BRIM-2 and BRIM-3 studies (based on analysis submitted to the U.S. FDA).[18-20] The reference method was retroactive 2x bi-directional Sanger, a quantitative pyrosequencing method. This analysis indicated that the cobas® 4800 BRAF V600 Mutation Test has a very low failure rate (<1%) compared with 9.2% with Sanger Sequencing (gold standard) performed on the clinical samples. Discordant results were resolved using 454 Sequencing. Compared with Sanger Sequencing, the following analytical qualities of the test were generated: sensitivity 95.80%; specificity 82.43%; false-positive rate 17.57%; false-negative rate 4.20%; positive predictive value 84.44%; and negative predictive value 95.17%.[18] Fifty discordant specimens were subjected to 454 sequencing; 17 initially recorded as cobas® test V600E-positive and Sanger non-V600E/wild type were confirmed V600E mutants by 454 sequencing. Sanger Sequencing plus 454 Sequencing confirmed that the cobas® test cross-reacts with BRAF V600K mutations (the second most frequent BRAF V600 mutation) at ≥35% tissue mutation content. Pre-clinical studies indicated that the cobas® test also detects a proportion of BRAF V600E2 (≥65%) and BRAF V600D (≥10%) mutations.[19,20] Therefore, it was anticipated that some cases (approximately 10%) identified by the cobas test as being mutation positive would in fact harbor BRAF V600E2, BRAF V600D or BRAF V600K mutations.[18]

Of note, the above comparison test indicated that bi-directional sequencing has a limit of detection of approximately 20% of mutant alleles in FFPET specimens DNA. Therefore, it may not adequately confirm mutation status at lower percentages of mutant alleles.[68]

Implementation of the cobas® 4800 BRAF V600 Mutation Test

A decision analytic protocol requested by the medical services advisory committee (MSAC) in Australia reported some issues relevant to implementation of BRAF mutation testing:[65]

- the in-house BRAF V600 mutation tests should be performed in laboratories accredited for genetic testing in humans. Since laboratories accredited are unlikely located in rural or remote areas, tissue biopsies or specimens would need to be sent to accredited laboratories in metropolitan areas or large regional laboratories;
- the tissue sample for analysis would be selected by an anatomical pathologist and macro-dissected or micro-dissected as required;

- competence to perform the test would need to be monitored through quality assurance programme (QAP) and a pilot QAP for BRAF V600 would be needed;
- repeat testing or re-biopsying may be required if there is insufficient tumour material to provide a definitive result;

There is future potential for BRAF V600 mutation testing to be used in high risk primary melanoma, testing occurring at an earlier stage, and testing on biopsies from primary cutaneous tumour or on specimens (e.g. fine needle aspiration) from metastatic tumour.

7.3.3 Summary

The cobas® 4800 BRAF V600 Mutation Test, developed by Hoffman LaRoche, has received regulatory approval in Canada. The cobas® test is a fully automated in vitro diagnostic device intended for the qualitative detection of the BRAF V600E mutation in DNA extracted from formalin-fixed, paraffin-embedded human melanoma tissue; one 5-micron specimen is sufficient to conduct the analysis. It is a validated, real-time polymerase chain reaction test. The cobas® test is able to detect V600E mutations with a higher sensitivity than the reference method of Sanger sequencing, but it is not as specific.[18-20] The test showed cross-reactivity with non-V600E mutants, predominantly V600E2 (≥65%), V600K (≥35%), and V600D (≥10%).

8 ABOUT THIS DOCUMENT

This Final Clinical Guidance Report was prepared by the pCODR Melanoma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on dabrafenib for unresectable or metastatic melanoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report 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 some clinical information, therefore, this information was redacted from this publicly available Guidance Report.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report.

The Melanoma Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **Embase** 1974 to present**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search date: July 26, 2013

#	Searches	Results
1	(dabrafenib* or Tafinlar* or GSK2118436* or GSK 2118436*).ti,ab,ot,sh,hw,rn,nm.	535
2	(1195765-45-7 or 1195768-06-9 or QGP4HA4G1B).rn,nm.	286
3	or/1-2	535
4	3 use pmez	84
5	*dabrafenib/	87
6	(dabrafenib* or Tafinlar* or GSK2118436* or GSK 2118436*).ti,ab.	239
7	or/5-6	249
8	7 use oemezd	176
9	4 or 8	260
10	exp animals/	36539012
11	exp animal experimentation/ or exp animal experiment/	1713294
12	exp models animal/	1132721
13	nonhuman/	4098525
14	exp vertebrate/ or exp vertebrates/	35585206
15	or/10-14	37731082
16	exp humans/	28228832
17	exp human experimentation/ or exp human experiment/	327014

18	or/16-17	28230919
19	15 not 18	9501758
20	9 not 19	254
21	limit 20 to english language	246
22	remove duplicates from 21	186

2. Literature search via PubMed

Search date: July 26, 2013

Search	Add to builder	Query	Items found	Time
#1	Add	Search **(dabrafenib OR tafinlar OR GSK2118436* OR GSK 2118436*) AND publisher [sb]**	9	14:25:57

3. Cochrane Central Register of Controlled Trials (Central)

Issue 6 of 12, June 2013

There are 2 results from 704315 records for your search on 'dabrafenib* or tafinlar* or GSK2118436* or GSK 2118436* in title abstract keywords in Trials'

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search terms: Tafinlar or dabrafenib or GSK2118436 or "GSK 2118436"

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search terms: Tafinlar or dabrafenib

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

Search terms: Tafinlar or dabrafenib or GSK2118436 or "GSK 2118436"/ last 5 years

REFERENCES

1. Menzies AM, Long GV, Murali R. Dabrafenib and its potential for the treatment of metastatic melanoma. Drug Des Devel Ther [Internet]. 2012 [cited 2013 Apr 30];6:391-405. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3523565/pdf/dddt-6-391.pdf

2. Tafinlar™ dabrafenib (as dabrafenib mesylate): capsules, 50 mg and 75 mg [product monograph]. Mississauga (ON): GlaxoSmithKline Inc.; 2013 Feb 28.

3. pan-Canadian Oncology Drug Review manufacturer submission: Tafinlar™ (dabrafenib); Company: GlaxoSmithKline. Mississauga (ON): GlaxoSmithKline; 2013 Mar 18.

4. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012 Jul 28;380(9839):358-65.

5. Latimer N, Abrams KR, Amonkar M, Stapelkamp C, Swann RS. Adjusting for treatment crossover in the BREAK-3 metastatic melanoma trial for dabrafenib: preliminary analysis [abstract]. J Clin Oncol. 2013;31(Suppl):9044. (Presented at 2013 Annual Meeting of the American Society of Clinical Oncology, ASCO. Chicago, IL; 2013 May 31-June 4).

6. Grob J, Algarra SM, Amonkar MM, Demidov LV, Goodman VL, Grotzinger K, et al. Dabrafenib vs dacarbazine (DTIC) in patients with BRAF V600+ advanced and metastatic melanoma in BREAK-3: quality of life (QOL) analysis [abstract]. Pigment Cell Melanoma Res. 2013;26(1):152. (Presented at Society for Melanoma Research 2012 Congress. Hollywood, CA; 2012 Nov 8-11).

7. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian cancer statistics 2011 [Internet]. Toronto: Canadian Cancer Society; 2011. [cited 2013 Jun 26]. Available from: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2011-EN.pdf

8. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med. 2010 Aug 26;363(9):809-19.

9. Agarwala SS. Current systemic therapy for metastatic melanoma. Expert Rev Anticancer Ther. 2009 May;9(5):587-95.

10. Falkson CI, Ibrahim J, Kirkwood JM, Coates AS, Atkins MB, Blum RH. Phase III trial of dacarbazine versus dacarbazine with interferon alpha-2b versus dacarbazine with tamoxifen versus dacarbazine with interferon alpha-2b and tamoxifen in patients with metastatic malignant melanoma: an Eastern Cooperative Oncology Group study. J Clin Oncol. 1998 May;16(5):1743-51.

11. Flaherty KT, Lee SJ, Schuchter LM, Flaherty LE. Final results of E2603: a double-blind, randomized phase III trial comparing carboplatin©/paclitaxel (P) with or without sorafenib (S) in metastatic melanoma [abstract]. J Clin Oncol. 2010;28(15S):8511.

12. Huncharek M, Caubet JF, McGarry R. Single-agent DTIC versus combination chemotherapy with or without immunotherapy in metastatic melanoma: a meta-analysis of 3273 patients from 20 randomized trials. Melanoma Res. 2001 Feb;11(1):75-81.

13. Ives NJ, Stowe RL, Lorigan P, Wheatley K. Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2,621 patients. J Clin Oncol. 2007 Dec 1;25(34):5426-34.

14. Eggermont AM, Kirkwood JM. Re-evaluation the role of dacarbazine in metastatic melanoma – what have we learned in 30 years. Eur J Cancer. 2004;40:1825-36.

15. Hauschild A, Grob JJ, Demindov LV, Jouary T, Gutzmer R, Millward M. An update on BREAK-3, a phase III, randomized trial: dabrafenib (DAB) versus dacarbazine (DTIC) in patients with BRAF V600E-positive mutation metastatic melanoma (MM) [abstract]. J Clin Oncol. 2013;31(Suppl):9013. (Presented at 2013 Annual Meeting of the American Society of Clinical Oncology, ASCO. Chicago, IL; 2013 May 31-June 4).

16. Ascierto PA, Minor D, Ribas A, Lebbe C, O'Hagan A, Arya N, et al. Phase II trial (BREAK-2) of the BRAF inhibitor dabrafenib (GSK2118436) in patients with metastatic melanoma. J Clin Oncol. 2013 Aug 5. Epub ahead of print.

17. Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012 Nov;13(11):1087-95.

18. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s) [Internet]. In: Zelboraf (vemurafenib) tablet. Company: Hoffmann-La Roche Inc. Application no.: 202429. Approval date: 08/17/2011. Rockville (MD): The Center; 2011 [cited 2013 Sep 5]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202429s000TOC.cfm.

19. Anderson S, Bloom K, Vallera DU, Rueschoff J, Meldrum C, Schilling R, et al. Molecular testing for BRAF V600 mutations in clinical trials of the BRAF inhibitor vemurafenib (RG7204/PLX4032) in metastatic melanoma: clinical validation studies of the analytic performance of a companion diagnostic assay. Poster presented at: 36th European Society for Medical Oncology (ESMO) Congress / European Multidisciplinary Cancer Congress; 2011 Sep 23-27; Stockholm, Sweden.

20. Halait H, DeMartin K, Shah S, Soviero S, Langland R, Cheng S, et al. The analytical performance of a real-time PCR-based assay for the BRAF V600E mutation used as the companion diagnostic test for the novel BRAF inhibitor vemurafenib (RG7204/PLX4032) in metastatic melanoma. Poster presented at: American Association for Cancer Research (AACR) 102nd Annual Meeting; 2011 April 2-6; Orlando (FL).

21. Falchook GS, Long GV, Kurzrock R, Kim KB, Arkenau TH, Brown MP, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. Lancet. 2012 May 19;379(9829):1893-901.

22. Rigel DS, Russak J, Friedman R. The evolution of melanoma diagnosis: 25 years beyond the ABCDs. CA Cancer J Clin. 2010 Sep;60(5):301-16.

23. American Joint Committee on Cancer. Melanoma of the skin staging [Internet]. 7th ed. Chicago: The Committee; 2009. [cited 2013 Jun 26]. Available from: http://www.cancerstaging.org/staging/posters/melanoma8.5x11.pdf

24. National Comprehensive Cancer Network. Melanoma [Internet]. Version 2. Fort Washington (PA): NCCN; 2012. [cited 2013 Jun 26]. (NCCN Clinical Practice Guidelines in Oncology). Available from: http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf Registration required.

25. SEER cancer statistics review, 1975-2006 [Internet]. Bethesda (MD): National Cancer Institute; 2010. [cited 2013 Mar 26]. Available from: http://seer.cancer.gov/csr/1975_2006/

26. Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol. 2008 Feb 1;26(4):527-34.

27. BCCA protocol summary for palliative therapy for metastatic malignant melanoma using high dose dacarbazine (DTIC) [Internet]. Vancouver: BC Cancer Agency; 2011. [cited 2013 Jun 25]. Available from: http://www.bccancer.bc.ca/NR/rdonlyres/D8C83698-5BBF-4A8E-9059-82B513089CB2/51450/SMDTIC_Protocol_1Jun2011.pdf

28. Agarwala SS, Kirkwood JM, Gore M, Dreno B, Thatcher N, Czarnetski B, et al. Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. J Clin Oncol. 2004 Jun 1;22(11):2101-7.

29. Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol. 2000 Jan;18(1):158-66.

30. Quirt I, Verma S, Petrella T, Bak K, Charette M. Temozolomide for the treatment of metastatic melanoma: a systematic review. Oncologist. 2007 Sep;12(9):1114-23.

31. Atkins MB, Lotze MT, Dutcher JP. High dose recombinant Interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol. 1999;17(7):2105-16.

32. Atkins MB, Kunkel L, Sznol M, Rosenberg SA. High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update. Cancer J Sci Am. 2000 Feb;6 Suppl 1:S11-S14.

33. Whiteman DC, Pavan WJ, Bastian BC. The melanomas: a synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin. Pigment Cell Melanoma Res. 2011 Oct;24(5):879-97.

34. Puzanov I, Flaherty KT. Targeted molecular therapy in melanoma. Semin Cutan Med Surg. 2010 Sep;29(3):196-201.

35. Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med. 2005 Nov 17;353(20):2135-47.

36. Tsao H, Goel V, Wu H, Yang G, Haluska FG. Genetic interaction between NRAS and BRAF mutations and PTEN/MMAC1 inactivation in melanoma. J Invest Dermatol [Internet]. 2004 Feb [cited 2013 Jun 25];122(2):337-41. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2586668

37. Flaherty KT, McArthur G. BRAF, a target in melanoma: implications for solid tumor drug development. Cancer. 2010 Nov 1;116(21):4902-13.

38. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature. 2002 Jun 27;417(6892):949-54.

39. Yang H, Higgins B, Kolinsky K, Packman K, Go Z, Iyer R, et al. RG7204 (PLX4032), a selective BRAFV600E inhibitor, displays potent antitumor activity in preclinical melanoma models. Cancer Res. 2010 Jul 1;70(13):5518-27.

40. Sondergaard JN, Nazarian R, Wang Q, Guo D, Hsueh T, Mok S, et al. Differential sensitivity of melanoma cell lines with $BRAF^{V600E}$ mutation to the specific Raf inhibitor PLX4032. J Transl Med [Internet]. 2010 [cited 2013 Jun 25];8:39. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2876068

41. Ribas A, Kim KB, Schuchter LM, Gonzalez R, Pavlick AC, Weber JS, et al. BRIM-2: an open-label, multicenter phase II study of vemurafenib in previously treated patients with BRAF V600E mutation-positive metastatic melanoma [abstract]. J Clin Oncol. 2011;29 Suppl:8509.

42. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011 Jun 30;364(26):2507-16.

43. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010 Aug 19;363(8):711-23. Erratum in: N Engl J Med. 2010 Sep 23;363(13):1290.

44. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Erratum: Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010 Sep 23;363:1290.

45. Trefzer U, Minor D, Ribas A, Lebbe C, Siegfried A, Arya N, et al. BREAK-2: A phase IIA trial of the selective BRAF kinase inhibitor GSK2118436 in patients with BRAF mutation-positive (V600E/K) metastatic melanoma [abstract]. Pigment Cell Melanoma Res. 2011;24(5):1020.

46. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Phase III, randomized, open-label, multicenter trial (BREAK-3) comparing the BRAF kinase inhibitor dabrafenib (GSK2118436) with dacarbazine (DTIC) in patients with BRAFV600E-mutated melanoma [abstract]. J Clin Oncol. 2012;30(18 Suppl 1):LBA8500. (Presented at 2012 Annual Meeting of the American Society of Clinical Oncology, ASCO. Chicago, IL; 2012 June 1-5).

47. Azer M, Menzies A, Haydu L, Kefford R, Long G. Patterns of progression in patients with V600 BRAF-mutated melanoma metastatic to the brain treated with dabrafenib (GSK2118436) [abstract]. Asia Pac J Clin Oncol. 2012;8:48.

48. Kirkwood JM, Long GV, Trefzer U, Davies MA, Ascierto PA, Chapman PB, et al. BREAK-MB: a phase II study assessing overall intracranial response rate (OIRR) to dabrafenib (GSK2118436) in patients (pts) with BRAF V600E/k mutation-positive melanoma with brain metastases (mets) [abstract]. J Clin Oncol. 2012;30(15 Suppl 1):8501.

49. Azer MWF, Menzies AM, Haydu L, Kefford R, Long GV. Patterns of progression in patients (pts) with V600 BRAF-mutated melanoma metastatic to the brain treated with dabrafenib (GSK2118436) [abstract]. J Clin Oncol. 2012;30(15 Suppl 1):8558.

50. Infante JR, Falchook GS, Lawrence DP, Weber JS, Kefford RF, Bendell JC, et al. Phase I/II study to assess safety, pharmacokinetics, and efficacy of the oral MEK 1/2 inhibitor GSK1120212 (GSK212) dosed in combination with the oral BRAF inhibitor GSK2118436 (GSK436) [abstract]. J Clin Oncol. 2011;29(18 Suppl):CRA8503.

51. Lee C, Menzies A, Haydu L, Kefford R, Clements A, Long G. Correlates of fever in patients receiving combined dabrafenib (GSK2118436) and trametinib (GSK1120212) for V600 BRAF-mutant metastatic melanoma [abstract]. Asia Pac J Clin Oncol. 2012;8:36-7.

52. Incani UC, Del Curatolo A, Di Sanza C, Falcone I, Cognetti F, Ciuffreda L, et al. Synergistic activity of vertical combinations of agents targeting multiple steps along the RAF/MEK/ERK cascade as a therapeutic strategy in human tumors [abstract]. J Clin Oncol. 2012;30(15 Suppl 1):e13572.

53. Weber J, Daud A, Infante J, Sosman J, Flaherty K, Kefford R, et al. Clinical status of RAF/MEK inhibitors [abstract]. Eur J Cancer. 2012;48:10.

54. Lee CI, Menzies AM, Haydu L, Clements A, Kefford R, Long GV. Correlates of fever in patients (pts) receiving combined dabrafenib (GSK2118436) plus trametinib (GSK1120212) for V600 BRAF-mutant metastatic melanoma (MM) [abstract]. J Clin Oncol. 2012;30(15 Suppl 1):e19011.

55. GlaxoSmithKline response to pCODR checkpoint meeting questions on dabrafenib (Tafinlar) for metastatic melanoma [additional manufacturer's information]. Mississauga (ON): GlaxoSmithKline; 2013 Jun 21.

56. Dumville JC, Hahn S, Miles JN, Torgerson DJ. The use of unequal randomisation ratios in clinical trials: a review. Contemp Clin Trials. 2006 Feb;27(1):1-12.

57. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998 Jan;16(1):139-44.

58. Hong F, Bosco JL, Bush N, Berry DL. Patient self-appraisal of change and minimal clinically important difference on the European organization for the research and treatment of cancer quality of life questionnaire core 30 before and during cancer therapy. BMC Cancer [Internet]. 2013 [cited 2013 May 23];13(1):165. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3637270/pdf/1471-2407-13-165.pdf

59. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01584648: A study comparing tramaetinib and dabrafenib combination therapy to dabrafenib monotherapy in subjects wtih BRAF-mutant melanoma; 2013 Jun 12 [cited 2013 Jun 24]. Available from: http://clinicaltrials.gov/ct2/show/NCT01584648

60. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01597908: Dabrafenib plus trametinib vs vemurafenib alone in unresectable or metastatic BRAF V600E/K cutaneous melanoma (COMBI-v); 2013 Jun 20 [cited 2013 Jun 24]. Available from: http://clinicaltrials.gov/ct2/show/NCT01597908

61. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01682083: A study of the BRAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib in the adjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection (COMBI-AD); 2013 Feb 7 [cited 2013 Jun 24]. Available from: http://clinicaltrials.gov/ct2/show/NCT01682083

62. McArthur G, Hauschild A, Robert C, Haanen JB, Ascierto P, Lee RJ, et al. Vemurafenib improves overall survival compared to dacarbazine in advanced BRAFV600E-mutated melanoma: updated survival results from a phase III randomised, open-label, multicentre trial [abstract]. Eur J Cancer. 2011 Sep;47(Suppl 2):14. (Presented at 2011 European Multidisciplinary Cancer Congress; Stockholm, Sweden; 2011 Sep 23-27).

63. National Institute for Health and Clinical Excellence. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma [Internet]. London: NICE; 2012. [cited 2013 Jun 3]. (NICE technology appraisal guidance 269). Available from: http://www.nice.org.uk/nicemedia/live/14005/61877/61877.pdf

64. Srivastava K, Pathak P, Amonkar M, Stapelkamp C, Swann RS, Casey M. Systematic review and indirect treatment comparison (ITC) of dabrafenib (Dab) and trametinib (Tram) versus first-line (1L) treatments for metastatic melanoma (MM) [abstract]. J Clin Oncol. 2013;31(Suppl):e20012. (Presented at 2013 Annual Meeting of the American Society of Clinical Oncology, ASCO. Chicago, IL; 2013 May 31-June 4).

65. Medical Services Advisory Committee. MSAC application 1172. Consultation decision analytic protocol (DAP) to guide the assessment of BRAF V600 testing in unresectable stage IIC or metastatic stage IV cutaneous melanoma [Internet]. Canberra (AU): MSAC, Australian Government Department of Health and Aging; 2011 Sep. [cited 2013 Sep 5]. Available from: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/284249A4E03C3431CA2578E10017643B/$File/Consultation%20DAP_1172_BRAF%207-10-11.pdf

66. Roche Canada. Health Canada approves the cobas® 4800 BRAF V600 Mutation Test, the first Roche companion diagnostic developed with a drug [Internet]. Mississauga (ON): Hoffmann-La Roche Ltd.; 2011 Nov 29. [cited 2013 Sep 5]. Available from: http://www.rochecanada.com/portal/ca/media_releases?siteUuid=re7234008&paf_gear_id=45200037&pageId=re7540115&synergyaction=show&paf_dm=full&nodeId=1415-cac9b65f19fe11e1975e61e9b0e2e4f6

67. U.S. Food and Drug Administration. cobas® 4800 BRAF V600 Mutation Test - P110020 [Internet]. Silver Spring (MD): FDA; 2012. [cited 2013 Sep 5]. Available from: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm268836.htm

68. U.S. Food and Drug Administration. cobas® 4800 BRAF V600 Mutation Test - P110020. Summary of safety and effectiveness data (SSED) [Internet]. Silver Spring (MD): FDA; 2011 Aug 17. [cited 2013 Sep 5]. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110020b.pdf