PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Vemurafenib (Zelboraf) for Advanced Melanoma

October 1, 2012

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1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the effect of vemurafenib on patient outcomes including overall survival, progression free survival, quality of life, and adverse events compared with standard treatment, placebo, or best supportive care in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One open-label randomized controlled trial (BRIM-3) met the inclusion criteria for the pCODR systematic review.[1-4] BRIM-3 randomized 675 adult patients with unresectable, previously untreated, BRAF V600E mutation-positive, stage IIIC or IV melanoma. Patients were randomized in a 1:1 ratio to one of two groups, either vemurafenib 960 mg twice daily orally (n=337) or dacarbazine 1000 mg/m^2 intravenously infused every three weeks (n=338).

The co-primary outcomes of BRIM-3 were overall survival and progression-free survival. At the planned interim analysis, conducted at approximately six-months, patients treated with vemurafenib had a statistically significant improvement in overall survival and in progression-free survival compared with dacarbazine. Based on these results, the trial was terminated early and dacarbazine patients were permitted to cross-over to vemurafenib.

Overall survival was defined as the time interval from randomization until death due to any cause. After the third and most recent overall survival analysis (Oct 2011 data cut-off), the median survival (with censoring) was estimated at 13.2 months for the vemurafenib group compared with 9.6 months for the dacarbazine group (HR=0.62; 95% CI: 0.49 to 0.77; p<0.001).[4] Progression-free survival was defined as the time from randomization to documented disease progression or death based on investigator assessment according to RECIST criteria. At the time of the pre-planned interim analysis (Dec 2010 data cut-off), progression-free survival was 5.3 months for the vemurafenib group versus 1.6 months for the dacarbazine group (HR: 0.26; 95% CI: 0.20 to 0.33; p<0.001). Quality of life was assessed using the Functional Assessment of Cancer Therapy-Melanoma v.4 (FACT-M) questionnaire. Analyses of FACT-M and its subscales suggested that there was no difference in quality of life measured over time on study treatment in patients treated with vemurafenib compared with patients treated with dacarbazine. Interpretation of data was limited because fewer patients completed FACT-M assessment at later cycles as per protocol.

Nonfatal serious adverse events occurred in 42.9% of patients receiving vemurafenib and in 17.8% receiving dacarbazine. A total of 7.1% (24/336) of patients treated with vemurafenib and 4.2% (12/293) of patients treated with dacarbazine discontinued treatment due to adverse events.

1.2.2 Additional Evidence

pCODR received input on vemurafenib from one patient advocacy group, Melanoma Network of Canada. Provincial Advisory Group input was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

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

- Summary of BRAF mutation testing in metastatic melanoma
- Summary of BRIM-2: a single-arm, non-randomized study evaluating the efficacy and safety of vemurafenib in patients with BRAF V600E mutation-positive metastatic melanoma who had received prior treatment for their disease. The primary endpoint of BRIM-2 was best overall response rate, with a target of 30%, and of the 132 patients who received treatment with vemurafenib, 53% achieved the primary outcome of best overall response rate after a median follow-up of 12.9 months. In addition, median progression-free survival was seven months and median overall survival was 16 months. In general, the efficacy and safety effects of vemurafenib observed in BRIM-2 are similar to those observed in the randomized, controlled phase III trial, BRIM-3.[1] However, given the non-comparative, unblinded design and limited robustness of the data, caution should be used when drawing conclusions from these results.

1.2.3 Interpretation and Guidance

Unresectable stage III and IV melanoma is an incurable malignancy with approximately six percent of all patients surviving at five years. 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. Metastatic melanoma is the eighth most common cancer in Canada, accounting for approximately 950 deaths in Canada per year. There is limited evidence that conventional treatments such as dacarbazine improve either quality of life or overall survival, therefore, effective new treatments are needed in both the first and second line setting.

There were several potential limitations identified with the BRIM-3 study in untreated patients including a lack of blinding and a short follow-up time for overall survival, which could mean that differences in median overall survival between groups was not as robust. In addition, following the planned interim analyses, patients in the dacarbazine group were permitted to crossover to receive vemurafenib, which could have resulted in inflated overall survival hazard ratios at subsequent analyses. Despite these limitations, BRIM-3 represents the first randomized trial in first-line treatment of metastatic melanoma to show improved overall survival and the magnitude of observed benefit was such that these limitations do not decrease confidence in the trial results. The use of vemurafenib is also dependent upon the accuracy and availability of BRAF mutation testing of each prospective patient's primary or metastatic tumour.

BRIM-2 was a single-arm non-randomized study of vemurafenib in previously treated patients with metastatic melanoma. Despite the limitations of relying on non-randomized evidence, BRIM-2 was completed at a time when there were no accepted second-line treatment options. The median survival of approximately 16 months seen in BRIM-2 was far greater than expected, as was the percentage of patients alive at one year (58%), both of which help to demonstrate the efficacy of vemurafenib in the second-line setting. The response rate of 53% was much higher than response typically

observed with second-line treatments for metastatic melanoma (e.g.10-12% for taxol or carboplatin/taxol). In addition, an expanded access program used to treat first and second line patients has provided further experience in the second-line setting and there is no evidence to suggest that vemurafenib is less efficacious than other therapies that are currently used in this setting.

In general, adverse events reported for vemurafenib appeared to be well-tolerated and manageable. Patients in the vemurafenib group experienced a greater incidence of grade three and four adverse events, including arthralgia, rash, elevated liver enzymes, photosensitivity reaction, and squamous cell carcinoma of skin. Approximately one-quarter of patients in the vemurafenib group experienced cutaneous squamous cell carcinomas (including both squamous cell carcinomas of skin and keratoacanthoma) and new primary malignant melanomas compared to less than one percent of dacarbazine patients.

1.3 Conclusions

The pCODR Melanoma Clinical Guidance Panel concluded that there **is a net overall clinical benefit** to vemurafenib based on one randomized controlled trial, BRIM-3, which demonstrated an improvement in overall survival with vemurafenib when compared to dacarbazine in previously untreated patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. In addition, the Panel considered that vemurafenib is effective in the second line setting based on better than anticipated survival observed in the BRIM-2 study, and response rates similar to those seen in BRIM-3.

The Clinical Guidance Panel also considered that from a clinical perspective:

- Vemurafenib has an acceptable tolerability profile with predictable and manageable toxicities.
- Metastatic melanoma is the eighth most common cancer in Canada, accounting for approximately 950 deaths in Canada per year. There is limited evidence that conventional treatments such as dacarbazine improve either quality of life or overall survival, therefore, new treatments are much needed. This trial represents the first randomized trial in first-line treatment of metastatic melanoma to show improved overall survival and the magnitude of observed benefit is considerable.
- Vemurafenib in the second line setting also led to better than expected survival in a group of patients with a poor prognosis.

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 vemurafenib. 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 vemurafenib conducted by the pCODR Melanoma Clinical Guidance Panel 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 Clinical Guidance Panel, a summary of submitted Patient Advocacy Group Input on vemurafenib and a summary of submitted Provincial Advisory Group Input on vemurafenib are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

The manufacturer of vemurafenib has a Health Canada approved indication for the treatment patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. The recommended dose is 960 mg administered orally twice daily.

Vemurafenib is a BRAF inhibitor that selectively targets the mutated BRAF V600E isoform. BRAF is part of the RAS/mitogen activated protein (MAP) kinase signalling pathway, which helps regulate the proliferation, differentiation, and apoptosis of cells. BRAF V600E, is present in approximately 50% of malignant melanomas.[1] A companion diagnostic test, the cobas 4800 BRAF V600 Mutation Test, has been developed by the manufacturer of vemurafenib (Hoffmann-La Roche) to test whether a patient's melanoma is BRAF V600E-positive.

2.1.2 Objectives and Scope of pCODR Review

The objective of this review is to evaluate the effect of vemurafenib on patient outcomes including overall survival, progression free survival, quality of life, and adverse events compared with standard treatment, placebo, or best supportive care in 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 vemurafenib 960 mg orally twice daily (n=337) were compared with dacarbazine 1000 mg/m^2 intravenously every three weeks

(n=338) in one international, multicentre, open-label, randomized controlled trial, BRIM-3.[1-4]

The study enrolled patients with unresectable, previously untreated, BRAF V600E mutation-positive (identified using the cobas 4800 BRAF V600 Mutation Test), stage IIIC or IV melanoma. Patients were also included if they had a life expectancy of greater than three months, an Eastern Cooperation Oncology Group (ECOG) performance status of zero or one, no brain metastases, and adequate hematologic, hepatic, and renal functions. Median age was 56 years in the vemurafenib group and 52 years in the dacarbazine group. Patients were equally distributed between groups regarding ECOG performance status (zero=68%, one=32% in both groups). Approximately two-thirds of patients in the vemurafenib and dacarbazine groups had M1c stage metastases (66% and 65%, respectively).

The co-primary outcomes of BRIM-3 were overall survival and progression-free survival. The final analysis for overall survival was planned after 196 deaths, with an interim analysis after 50% of the projected deaths had occurred. In total, three survival analyses were conducted: first, a pre-planned interim analysis conducted at the cut-off date of December 30, 2010; second, an unplanned interim analyses with a data cut-off date of March 31, 2011; and a third (and most recent) unplanned interim analysis with a data cut-off date of October 3, 2011. The final analysis for progression-free survival, as well as the secondary outcomes related to tumour response, quality of life, and adverse events,was conducted at the time of the interim analysis for overall survival.[1-4]

Patients treated with vemurafenib had a statistically significant improvement in overall survival compared with dacarbazine at the six month interim analysis (hazard ratio=0.37; 95% CI: 0.26 to 0.55), as well as in progression-free survival (hazard ratio=0.26; 95% CI: 0.20 to 0.33). Based on these results, the Independent Data and Safety Monitoring Board recommended a protocol amendment to close accrual and allow cross-over, so that patients treated with dacarbazine could crossover to receive vemurafenib. One potential limitation of ending a study early is that it reduces the ability to assess long term safety with the study drug, as well as limiting the ability to determine the durability of response.[1-3]

Because the median overall survival had not been reached at the time of the planned (first) interim analysis, two subsequent unplanned (exploratory) analyses of overall survival were conducted at three and 10 months after the first interim analysis. Median overall survival was not achieved until the third analysis, at which point a total of 81 dacarbazine patients had crossed over to receive vemurafenib. The median survivals were estimated at 13.2 and 9.6 months for the vemurafenib and dacarbazine groups, respectively (hazard ratio=0.62; 95% CI: 0.49 to 0.77).[4]

Quality of life was assessed using the Functional Assessment of Cancer Therapy-Melanoma v.4 (FACT-M) questionnaire. Analyses of FACT-M and its subscales suggested that there was no difference in quality of life measured over time on study treatment in patients treated with vemurafenib compared with patients treated with dacarbazine. Interpretation of data was limited because fewer patients completed FACT-M assessment at later cycles as per protocol.

Data regarding adverse events were extracted from the U.S. FDA medical review of vemurafenib.[5] Up to the first interim analysis, approximately 20% of patients in the vemurafenib group had died, compared with almost 34% of those treated with dacarbazine. All of the deaths among the vemurafenib group were attributed to underlying medical conditions and interventions, or to advanced melanoma progression.[5] Serious non-fatal adverse events occurred in 43% of patients receiving vemurafenib (predominantly due to squamous cell carcinomas of skin) versus 18% of dacarbazine patients. Non-serious adverse events commonly seen in this trial (occurring ≥20% of patients) included arthralgia, alopecia, fatigue, rash, elevated liver enzymes, nausea, photosensitivity reaction, diarrhea, hyperkeratosis, headache, pruritus, and skin papilloma; all occurred more frequently with vemurafenib compared with dacarbazine. Patients in the vemurafenib group also experienced a greater incidence of grades three and four adverse events, including arthralgia, rash, elevated liver enzymes, photosensitivity reaction, and squamous cell carcinoma of skin. Adverse events leading to treatment discontinuation included arthralgia, dysphagia, and pneumonia.[5]

An important limitation of the BRIM-3 trial was the lack of blinding and the absence of an independent radiological committee to assess progression free survival, which may have resulted in observer bias and contributed to a high dropout rate for the dacarbazine group. Additionally, the short follow-up period for overall survival (approximately seven months) likely limits the robustness of differences in median overall survival between groups. Furthermore, the confounding effect of the crossover of dacarbazine-treated patients to receive vemurafenib influences the determination of the absolute outcome impact of vemurafenib.

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

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 the only approved test available for use in Canada to detect BRAF V600E genetic mutations, and thereby identifying patients eligible to receive vemurafenib for advanced melanoma. 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 that was applied in BRIM-2 and BRIM-3.[6,7] 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.[5,8,9] The test showed cross-reactivity with non-V600E mutants, predominantly V600E2 (≥65%), V600K (≥35%), and V600D (≥10%).

See section 7.1 for more information.

Summary of BRIM-2: a Single-Arm, Non-Randomized Study Evaluating Vemurafenib in Previously Treated Patients

This supplemental issue summarized data from BRIM-2,[6,10] a single-arm, non-randomized phase II trial examining the efficacy and safety of vemurafenib among patients with BRAF V600E mutation-positive metastatic melanoma who had received prior treatment for their disease. The primary endpoint of the study was best overall response rate, with a target of 30%, as determined by a blinded independent radiologic committee. Over half of patients had an ECOG performance status of one, 61% had M1c disease, and 49% had elevated lactate dehydrogenase levels. Fifty-one percent of patients had one prior systemic therapy and 27% received two prior systemic therapies. Of the 132 patients who received treatment, 53% achieved the primary outcome of best overall response rate after a median follow-up of 12.9 months. Median progression-free survival was seven months and median overall survival was 16 months. However, the absence of a control group is an important limitation of the BRIM-2 results. It is uncertain whether equipoise would exist in the second-line setting between vemurafenib and other available systemic therapeutics to conduct a randomized controlled trial. Nonetheless, randomized controlled trials have been conducted in similar circumstances, such as one evaluating ipilimumab for the second-line treatment of metastatic melanoma. Furthermore, other options to include a comparison group, such as an historical control group, could have been used by the investigators to potentially address concerns of equipoise. Given the non-comparative, unblinded design and limited robustness of the data, caution should be used when drawing conclusions from these results. Almost all patients experienced an adverse event, 64% of which were rated as grade three or more. The most frequent (>30%) adverse events related to the study drug were arthralgia, rash, photosensitivity reaction, alopecia, pruritis, skin papilloma and squamous cell carcinoma of the skin. Squamous cell carcinoma of the skin was the most common grade 3 or higher adverse event (26%). In general, the efficacy and safety effects of vemurafenib observed in BRIM-2 are similar to those observed in the randomized, controlled phase III trial, BRIM-3.[1]

See section 7.2 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 advanced melanoma and many of the available therapies have severe side effects associated with them. Patients indicated that they are willing to tolerate certain side effects of a new treatment, particularly if those side effects can be effectively managed and the treatment they are receiving could extend their life expectancy. Patients are also looking for a therapy that will help to improve their quality of life.

Provincial Advisory Group (PAG) Input

Input on the vemurafenib review was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, issues surrounding the implementation and additional costs of BRAF mutational testing would be of great importance. PAG also identified that ipilimumab would likely enter the Canadian market at a similar time as vemurafenib and therefore, any comparative data between the two agents would be beneficial to help PAG determine which patient populations would be best suited for each treatment and potential funding criteria for each agent. PAG would also appreciate any evidence on vemurafenib in the adjuvant treatment of melanoma and whether vemurafenib should be used in the first or second-line treatment of advanced melanoma.

Other

One of the more frequent and serious adverse events observed with vemurafenib in BRIM-3 was squamous cell carcinoma of the skin.[1] There is molecular evidence that BRAF inhibitors, such as vemurafenib, induce hyperactivation of the MAP kinase pathway in BRAF wild-type cells. This upregulation of the MAP-kinase system may help activate mutations in RAS, which has been linked with the development of squamous cell carcinoma of the skin. Thus, treating one form of skin cancer may put patients at risk for another form of skin cancer. A manufacturer-sponsored molecular analysis of squamous cell carcinoma of the skin lesions taken from patients who participated in the vemurafenib phase I to phase III trials was recently published.[11] Among the tumour samples, 60% harbored RAS mutations and increased proliferation of mutant cell lines, via the MAP-kinase signaling pathway, occurred when exposed to vemurafenib.

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 six percent of all patients surviving at five years. 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. It is a challenging cancer for both patients and oncologists as no effective treatment options exist.

Treatment options have included dacarbazine, temozolomide, and carboplatin plus paclitaxel. The objective response rates to systemic agents are low and have generally been less than 15%. There is no evidence that standard chemotherapy regimens used either as single agents or as combinations improve either quality of life or overall survival. As such the standard treatment at most academic centers has been to enroll patients into clinical trials of new agents. Thus, effective new treatments are needed for patients with metastatic melanoma.

Vemurafenib is a small molecule inhibitor of the activating mutation of the BRAF protein. BRAF mutations exist in about 50% of all patients with metastatic melanoma, particularly in younger patients and in those areas of the skin intermittently exposed to the sun.

BRIM-3 Clinical Trial

Only one randomized study of vemurafenib compared to a suitable control was identified in this pCODR systematic review. In the Phase III study by Chapman et al (BRIM-3), 675 patients with BRAF V600 mutation positive, untreated melanoma were enrolled from 104 centers in 12 countries. Patients were randomized to either dacarbazine (1000 mg/m^2) or to vemurafenib (960 mg twice daily). The study was not blinded and 14% of patients randomized to dacarbazine never received treatment but were included in the intention-to-treat analysis. The co-primary endpoints of the study were to assess overall survival and progression free survival. Secondary outcomes included best overall response rates, duration of response, time to overall response and adverse events.

Patients were well balanced for age, sex and other demographics. The final survival analysis was planned after 196 deaths had occurred, with an interim analysis planned after 50% of the deaths had occurred. The Data and Safety Monitoring Board recommended a protocol amendment to close accrual after the planned interim analysis and patients randomized to dacarbazine be allowed to cross over to vemurafenib after progression on dacarbazine.

Effectiveness of Vemurafenib: First-Line Setting

The Data and Safety Monitoring Board recommended a protocol amendment to close accrual of the study after 118 patients had died because the *a priori* criteria for statistical significance had been met showing a difference in overall survival and progression free survival in favour of vemurafenib. As of the third analysis in October 2011, the median overall survival estimate was 13.2 months for vemurafenib versus 9.6 months for dacarbazine. This analysis includes several patients who had crossed over to vemurafenib from dacarbazine. The evidence shows that vemurafenib improves both overall survival and progression free survival with a tolerable safety profile.

Quality of life was assessed using the Functional Assessment of Cancer Therapy-Melanoma v.4 (FACT-M) questionnaire. Analyses of FACT-M and its subscales suggested that there was no difference in quality of life measured over time on study treatment in patients treated with vemurafenib compared with patients treated with dacarbazine. Interpretation of data was limited because fewer patients completed FACT-M assessment at later cycles as per protocol. The best overall response rate of 48% for the vemurafenib arm was considered very high relative to response rates observed in previous phase III trials in metastatic melanoma.

The lack of blinding and the absence of an independent radiological committee to assess progression free survival may have resulted in observer bias. Lack of blinding likely also led to a high dropout rate on the dacarbazine arm, as dacarbazine is felt to be an ineffective treatment. Thus, one of the reasons the response rate to dacarbazine was only 5.5%. Despite the limitations, the progression free survival of 1.6 months with dacarbazine is in keeping with other randomized studies where dacarbazine was the control arm. Likewise an additional 11 patients randomized to dacarbazine did not receive treatment due to progressive disease leading to a decline in performance status or discovery of brain metastases. Only two patients in the vemurafenib arm were withdrawn for similar reasons. The lower withdrawal in the vemurafenib arm may be due to investigator bias as phase I trials had shown that such patients could still respond to vemurafenib.

Because of the emergent improvement in survival, the Data and Safety Monitoring Board recommended a protocol amendment to close accrual early and allow patient patients to cross over from the dacarbazine to the vemurafenib arm. However, subsequent analyses conducted three months and ten months after the planned interim analysis affirmed the consistency of the survival benefit conferred by the vemurafenib. The short follow up for overall survival (approximately seven months) was also a potential concern, limiting the robustness of differences in median overall survival between groups. Furthermore, the confounding effect of the crossover will influence the determination of the absolute outcome impact of vemurafenib. However, such studies are difficult to perform when it is known among clinicians and patients that there is a promising drug that has demonstrated marked improvements and it is evaluated against an ineffective, although standard, therapy such as dacarbazine. Equipoise did not exist for this trial as mentioned in an editorial in the New England Journal of Medicine.[12] Nevertheless, the magnitude of the benefit observed in the trial is unique in the treatment of metastatic melanoma and will likely help define a new standard of care in select patients.

Effectiveness of Vemurafenib: Second-Line Setting

BRIM-3 only included first line untreated melanoma patients but a prior phase II study (see summary of BRIM-2, section 7.2) and phase I study in previously treated melanoma patients also showed high response rates.[13]

In the phase I study previously reported in the New England Journal of Medicine, once the recommended phase II dose of vemurafenib was reached, an expanded cohort of 32 V600E patients were treated with vemurafenib 960 mg/m^2.[13] The response rate was 81%. This lead to a multicenter phase II trial done in the USA and Australia at 13 centers (BRIM-2). In the original design, 90 patients were to be enrolled and treated to demonstrate a response rate of 30% or greater. There were 132 patients enrolled and treated at a dose of 960 mg/m^2. Many of these patients were already in screening when the target accrual was met, leading to a larger than planned sample size. The overall response rate in BRIM-2 based on independent review committee assessment was 53% with a complete response rate of 6%. The median overall survival was 15.9 months, and the median progression free survival was 6.8 months. Primary progression was observed in only 14% of patients. Toxicities were similar to that seen in BRIM-3 and the rate of squamous cell carcinomas was 26% with the majority being keratoancanthoma like malignancies. Patients had good performance status (ECOG 0 or 1), 61% had M1c disease, and 49% of patients had an elevated LDH, the latter two are prognostic factors typically associated with a poor survival.

Despite the limitations of relying on non-randomized evidence, at the time of BRIM-2 there was no accepted second line treatment in metastatic melanoma, and no randomized evidence existed that any currently available treatments improved survival. Although taxol or carboplatin/taxol have been used as second line treatment options, the response rates are low (approximately 10-12%), and there is no improvement in overall survival. From a clinical perspective, to have conducted a trial in the second line setting using a taxol regimen would have been difficult, and possibly unethical, as clinical equipoise may not have existed. In addition, the BRAF V600E mutation is associated with a worse prognosis in melanoma patients and treatment options are required for this population. In BRIM-2 the median survival of 15.9 months

was far greater than expected, as was the percentage of patients alive at one year (58%). The results from the phase I expanded cohort of 32 patients and from BRIM-2 attest to the efficacy of vemurafenib in the second line setting. In addition, an expanded access program used to treat first and second line patients has provided additional experience in the second line setting. None of the evidence available from these studies suggests that vemurafenib is less efficacious in the second-line setting than any other available treatments.

Safety of Vemurafenib

Adverse events were reported and demonstrated that the drug was well tolerated. Approximately, one quarter of patients receiving vemurafenib developed 25% of patients developed a secondary skin malignancy or new primary malignant melanoma compared with less than one percent of dacarbazine patients. However, this did not result in discontinuation of treatment by any patients. Other literature has reported that combinations of BRAF inhibitors and a MEK inhibitor appear to significantly lower the incidence of secondary skin cancers without an increase in toxicity, or a loss of efficacy.

BRAF Mutation Testing and Clinical Practice

Because the clinical effect of vemurafenib is limited to those patients with the V600 BRAF mutation, diagnostic testing prior to initiating treatment is essential. Currently, routine testing for BRAF mutations or other potential therapeutic targets in melanoma are not being performed. The use of vemurafenib is dependent upon the accuracy and availability of BRAF mutation testing of each prospective patient's primary or metastatic tumour (See Section 7.1). The Roche cobas® 4800 BRAF V600 Mutation Test has been approved by Health Canada and the US FDA. However alternate methodologies, such as the Sanger sequencing process for determining mutation status can be utilized. All methods require meticulous quality controls and should only be performed in laboratories with the appropriate infrastructure and trained personnel. The laboratories must also be able to communicate the findings in a timely manner to the clinicians. Patients with BRAF positive metastatic melanoma often follow an aggressive clinical course and therefore, the ability to provide life extending treatment, should not be significantly hampered by excessive delays in testing. Nineteen patients with a V600K mutation were identified (rather than the V600E mutation) and an exploratory analysis was performed that suggested improvements in overall survival and progression free survival were observed.

2.3 Conclusions

The pCODR Melanoma Clinical Guidance Panel concluded that there **is a net overall clinical benefit** to vemurafenib based on one randomized controlled trial, BRIM-3, which demonstrated an improvement in overall survival with vemurafenib when compared to dacarbazine in previously untreated patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. In addition, the Panel considered that vemurafenib is effective in the second line setting based on better than anticipated survival observed in the BRIM-2 study, and response rates similar to those seen in BRIM-3.

The Clinical Guidance Panel also considered that from a clinical perspective:

- Vemurafenib has an acceptable tolerability profile with predictable and manageable toxicities.
- Metastatic melanoma is the eighth most common cancer in Canada, accounting for approximately 950 deaths in Canada per year. There is limited evidence that conventional treatments such as dacarbazine improve either quality of life or overall survival, therefore, new treatments are much needed. This trial represents the first randomized trial in first-line treatment of metastatic melanoma to show improved overall survival and the magnitude of observed benefit is considerable.
- Vemurafenib in the second line setting also led to better than expected survival in a group of patients with a poor prognosis.

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 the 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.[14] 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.[15]

Staging of melanoma is based on the current American Joint Committee on Cancer 7th Edition Classification.[16] The tumour characteristics principally involve the Breslow height, mitotic rate and the presence of ulceration in the primary tumour. 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 tumour, 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.[17] 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.[18] Brain metastases are relatively common in advanced melanoma and occur in 15% to 20% of patients with overt metastatic disease.[13] They often prove to be relatively refractory to radiotherapy and systemic treatment and are associated with a particularly dismal prognosis.

Few 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 rate is approximately six percent.[19] 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.[17,20] Although this intravenous alkylating agent is generally well tolerated, complete responses are rare.[21] In comparative studies, it has never been shown to improve survival in metastatic melanoma.[22-26] Temozolomide, an oral nitrosurea which is activated to the active metabolite of dacarbazine, has also been commonly used. However, in phase III trials which compare temozolomide directly with dacarbazine, similar progression free survival and overall survival were observed, although temozolomide tended to be better tolerated.[27-29] 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.[30,30] 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.[21] Nevertheless, what has become apparent is that melanoma represents a heterogeneous group of diseases which appear to have varying genetic abnormalities that drive cellular proliferation and metastases.[31-33] The MAP kinase signalling pathway appears to be a key regulatory mechanism for cell growth, and differentiation in melanoma.[34] 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.[35] 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.[36]

3.3 Evidence-Based Considerations for a Funding Population

Vemurafenib is a BRAF inhibitor that selectively targets the mutated BRAF V600 and has been under clinical development for the past three years.[37-39] In 2011, a multicentre non-blinded phase III study of vemurafenib in comparison to dacarbazine in the first line treatment of 675 patients with unresectable or metastatic melanoma was reported.[1] (The details of this trial are provided in Section 6.3.) The key inclusion criterion was the presence of V600 mutation. Although other isoforms were included, 97% of patients had the V600E isoform. The use of vemurafenib is dependent upon the accuracy and availability of BRAF mutation testing of each prospective patient's primary or metastatic tumour (See Section 7.1).

The efficacy of vemurafenib in patients with brain metastases is uncertain. In the BRIM-3 trial, patients who had previously treated brain metastases and in whom the central nervous system disease was stable for more than three months were included. In the reports of the interim multivariate analyses, brain metastases has not appeared to affect disease-free or overall survival. Furthermore, patients with ECOG performance of two or more were specifically excluded and therefore it is unknown the impact that vemurafenib would have on patients with a particularly grave prognosis.

Therefore, the following eligibility criteria could be applied for vemurafenib:

1. Metastatic and/or unresectable melanoma;
2. BRAF V600 mutation present in primary or secondary tumour;
3. ECOG performance status of zero or one;
4. If present, stable brain metastases;
5. Adequate haematological, renal and liver function.

3.4 Other Patient Populations in Whom the Drug May Be Used

Vemurafenib may be potentially used in patients with high risk melanoma. Adjuvant clinical trials are being developed to address whether vemurafenib will reduce the risk of developing recurrence; however, it is expected to be several years before these trials will have been reported.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy group provided input on vemurafenib for advanced melanoma and their input is summarized below: Melanoma Network of Canada.

The Melanoma Network of Canada conducted an anonymous online survey to gather information about the patient and caregiver experience related to the medical condition and drug under review. The survey consisted of multiple choice questions, ranking questions and free-form commentary. Response to the survey was solicited via cancer centers in Canada and on the Melanoma Network of Canada website. There were a total of 21 respondents to Part I of the survey regarding patients experience with advanced melanoma, two respondents to Part II of the survey regarding information from caregivers and four respondents to Part III of the survey regarding feedback from patients with direct experience with vemurafenib.

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 advanced melanoma and many of the available therapies have severe side effects associated with them. Patients indicated that they are willing to tolerate certain side effects of a new treatment, particularly if those side effects can be effectively managed and the treatment they are receiving could extend their life expectancy. Patients are also looking for a therapy that will help to improve their quality of life.

Please see below for a summary of specific input received from the patient advocacy group(s).

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Advanced Melanoma

Patients with advanced melanoma may experience of number of debilitating symptoms as a result of their cancer, which typically worsen as their disease progresses and 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 depending upon the site of the metastases and type of treatment they receive, including headaches, numbness in the extremities, bone fractures, hair loss, depression, anxiety, memory loss, decreased mobility and constipation.

As there are relatively few effective treatment options for advanced stage melanoma, patients are conscious of the fact that their disease will ultimately progress. Patients may also experience severe side effects from the medical treatments that they receive. Patients who have no further treatment options for their melanoma indicated that they experience feelings of fear, anxiety and hopelessness.

Input from the patient advocacy group indicated that a patient's physical appearance can be severely affected by advanced melanoma. Surgeries performed on patients to remove tumours can lead to scarring which can further impact the physical appearance of the patient and cause body image issues. Furthermore, surgeries to remove tumours or lymph nodes can lead to decreased mobility and a loss of functioning or capacity of certain organs.

4.1.2 Patients' Experiences with Current Therapy for Advanced Melanoma

Current therapies that patients have had experience with for advanced melanoma include interferon, dacarbazine, interleukin-2, ipilimumab and docetaxel. Patient input highlighted that most of the medications currently available for the treatment of melanoma are fairly limited and relatively ineffective.

With the currently available treatment options, patients often experience numerous side effects, many of which were felt by patients to be severe and debilitating. Patients indicated that side effects related to treatment can lead to a decreased quality of life. For example, patients receiving treatment with interferon reported experiencing fatigue, nausea, flu-like symptoms, decreased mood, fever, chills, compromised liver function, decreased mobility, sore eyes, trembling, foggy brain, hair loss, loss in the sense of taste and weight loss. As a result of side effects, some patients have had to discontinue treatment prematurely. Other patients have refused a treatment on the basis of its severe side effect profile.

Input from the patient advocacy group also highlighted that many patients have difficulty accessing the currently available treatment agents. Some patients have been required to travel considerable distances to receive treatment which required time off from work and additional costs related to travel. A number of patients also reported having difficulty with funding of their treatment, especially treatments that were not received in the hospital setting.

Patients indicated that there is a high tolerance for side effects from new treatments, particularly if those side effects can be effectively managed and the treatment they are receiving could extend their life expectancy. A survey of patients indicated that quality of life is considered an important aspect when deciding to take a new treatment for advanced melanoma.

4.1.3 Impact of Advanced Melanoma and Current Therapy on Caregivers

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

The career, community and social involvement of the caregiver can be adversely affected by the physical requirements, time commitments and emotional stress of caring for the patient with advanced melanoma. Some families have had to hire a caregiver for the patient at considerable expense if they cannot free themselves from work obligations.

Being a caregiver can be a challenging role and some caregivers report being overstressed.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to Date with Vemurafenib

Input from patients without direct experience with vemurafenib highlighted the fact that there are currently very few effective treatments available in Canada for advanced melanoma and of the treatments that do exist, patients have experienced side effects. Patients are looking forward to seeing new treatment options for advanced melanoma.

Patients with advanced melanoma are seeking drug therapies which would help to 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 for patients and their families or a treatment which would allow them to return to a reasonable quality of life following treatment would be considered an additional benefit of any therapy for advanced melanoma. Overall, patients deem that the benefits of a new therapy which offers the above benefits outweigh the potential risks that may be encountered.

There were four patients in the patient survey who reported having direct experience with vemurafenib, three of which were still completing their treatments and one patient had completed treatment. Patients with direct experience with vemurafenib indicated that they had positive effects from the treatment. The patient advocacy group that made the submission indicated that it was still too early to understand the full benefits. One patient reported that their cancer had been eliminated, two patients reported that their cancer had been stabilized and another patient indicated that although their cancer continued to progress, the progression has slowed. Patients also reported that the reduction in tumour number and/or size with vemurafenib treatment helped to relieve the discomfort and severe symptoms caused by the tumours, thereby improving their quality of life.

All four patients indicated that they experienced side effects with vemurafenib therapy. Three patients experienced mild side effects which included fatigue, joint pain, chills, night sweats, hair loss, body rash, mild swelling of the feet, warts and photosensitivity. One patient experienced severe side effects that were effectively managed with corticosteroid treatment. A survey of patients indicated that the side effects from vemurafenib were found to be much milder overall compared to other treatments for advanced melanoma such as dacarbazine or interferon.

Input from the patient advocacy group also highlighted that vemurafenib is an oral therapy, which makes treatment easier for patients to receive treatment in their home environment, and is especially beneficial for those unable to travel to treatment centers to receive intravenous chemotherapy. In addition, some patients reported that they were able to return to work and provide financially for their families while receiving vemurafenib treatment.

Patients indicated that vemurafenib has provided them with hope for the future and enabled them to have additional time with their families

4.3 Additional Information

No additional comments within the scope of the patient advocacy group input requested were provided.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group (PAG) as factors that could affect the feasibility of implementing a funding recommendation for vemurafenib for the treatment of advanced 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).

Input on the vemurafenib review was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, issues surrounding the implementation and additional costs of BRAF mutational testing would be of great importance. PAG also identified that ipilimumab would likely enter the Canadian market at a similar time as vemurafenib and therefore, any comparative data between the two agents would be beneficial to help PAG determine which patient populations would be best suited for each treatment and potential funding criteria for each agent. PAG would also appreciate any evidence on vemurafenib in the adjuvant treatment of melanoma and whether vemurafenib should be used in the first or second-line treatment of advanced melanoma.

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

5.1 Factors Related to Comparators

PAG noted that there are few options available for the treatment of advanced melanoma and there continues to be a need for more effective treatments in this clinical setting. Dacarbazine was recognized as the current standard of care for advanced melanoma in many jurisdictions; however, it is administered intravenously and an oral agent, such as vemurafenib, would likely be a more appealing option, making it an enabler for vemurafenib therapy. On the other hand, it was noted that the price of vemurafenib would likely be considerably higher than that of dacarbazine, which may pose as a barrier to vemurafenib treatment.

Due to the inadequate treatment options available for advanced melanoma, some patients may receive treatment through participation in clinical trials held out-of-province. Having the option of vemurafenib may allow these patients to remain home during their treatment period, which would be an enabler for vemurafenib therapy.

PAG noted that another agent for the treatment of advanced melanoma, ipilimumab, is currently being reviewed by Health Canada. As ipilimumab and vemurafenib may enter the Canadian market at similar times, it would be helpful to know which patient populations and specific funding criteria each agent should have.

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 accessing vemurafenib; however, as the price of vemurafenib is expected to be substantial, there may still be a large budget impact on each jurisdiction.

PAG identified that there is a potential for vemurafenib to be used in other treatment settings, such as the second-line treatment of advanced melanoma, and information on whether there is any evidence to support this clinical setting would be appreciated.

PAG recognized that the pivotal trial for vemurafenib did not report on subsequent therapies used in the second-line treatment setting after progression on vemurafenib but noted that any information on agents used after vemurafenib therapy would be helpful in allowing jurisdictions to determine potential second-line treatment options.

5.3 Factors Related to Accessibility

PAG recognized that BRAF testing is required to identify potential candidates for vemurafenib therapy. In addition, PAG noted that there may be different tests available for BRAF mutational testing and as a result, there may be differences associated with each of these tests, such as cost differences, differences with respect to the level of evidence to support them, intellectual property differences and issues associated with tissue sampling. Although PAG recognized that a full review of BRAF testing is not within the pCODR mandate, as these issues could impact implementation of and accessibility to vemurafenib testing, PAG felt that information on each of the different available tests would be helpful when implementing a recommendation for vemurafenib. As the BRAF test is relatively new, it was noted that some jurisdictions may not have access to BRAF testing, which would pose as a barrier to vemurafenib therapy. Furthermore, given that some jurisdictions will have very small numbers of patients with advanced melanoma, BRAF testing may not be feasible in each jurisdiction. In addition, it was noted that BRAF testing would add to the costs of vemurafenib therapy, which would pose as an additional barrier to this therapy.

PAG noted that vemurafenib is an oral therapy administered in an outpatient setting which may help to relieve the strain on specialized chemotherapy treatment centers. Additionally, an oral therapy was noted to be beneficial for patients living in rural areas. However, in some jurisdictions, oral medications are not covered through public funding, and patients without private insurance would have to pay for the therapy out-of-pocket.

5.4 Factors Related to Dosing

As vemurafenib is available as a 240 mg tablet, patients will be required to take four tablets twice daily to get the standard dosage of 960 mg twice daily. PAG noted that the pill burden of eight tablets a day may have a negative effect on patient compliance, which may pose as a barrier to vemurafenib therapy. On the other hand, since no other concomitant medications are required with vemurafenib and it is a relatively straightforward treatment protocol, there may not be a problem with patient compliance. Furthermore, as vemurafenib is available in 240 mg tablets, dosage adjustments would likely be easily managed.

5.5 Factors Related to Implementation Costs

PAG recognized that BRAF molecular testing is required to identify appropriate patients for vemurafenib therapy. As this is a new testing method not yet available in each jurisdiction, additional costs would be associated with BRAF testing implementation and the actual testing procedure.

As vemurafenib is an oral therapy, PAG identified that utilization of chemotherapy clinics would be reduced, which would be an enabler for vemurafenib therapy.

PAG noted that there may be additional strains placed on many healthcare resources, such as the need for drug interaction monitoring, the potential need for biologic safety cabinets if product is not available in unit-dose packages, and the requirement of medical expertise to excise squamous cell carcinoma of the skin (occurs in 18% of patients on vemurafenib therapy).

5.6 Other Factors

PAG questioned whether it would be more appropriate to use vemurafenib in the first or second-line treatment setting and what level of evidence was available to support its use in each setting.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of vemurafenib, either alone or in combination, on patient outcomes compared to standard therapies, placebo, 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.

- Summary of BRAF Mutation Testing in Metastatic Melanoma
- Summary of BRIM-2: a Single-Arm, Non-Randomized Study Evaluating Vemurafenib in Previously Treated Patients

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 <u>Subgroups:</u> • Previously treated • Different BRAF V600 mutation types	Vemurafenib alone or in combination with other standard therapies at recommended dose 960mg twice daily	Dacarbazine Temozolomide Interleukin-2 Carboplatin / paclitaxel Ipilimumab Best supportive care Placebo	• Overall survival • Progression-free survival • Time to response • Response rate (CR, PR) • **QOL** • **SAEs** • **AEs** • WDAEs
AE=adverse events; CR=complete response; PR=partial response; QOL=quality of life; RCT=randomized controlled trial; SAE=serious adverse events; WDAE=withdrawals 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 (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2011, Issue 4 of 4) 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 concept was Zelboraf (vemurafenib).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language.

The search was completed on December 9, 2011 and was updated during the review. The search is considered up to date as of March 6, 2012.

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 Ontario Institute for Cancer Research. Ontario 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:

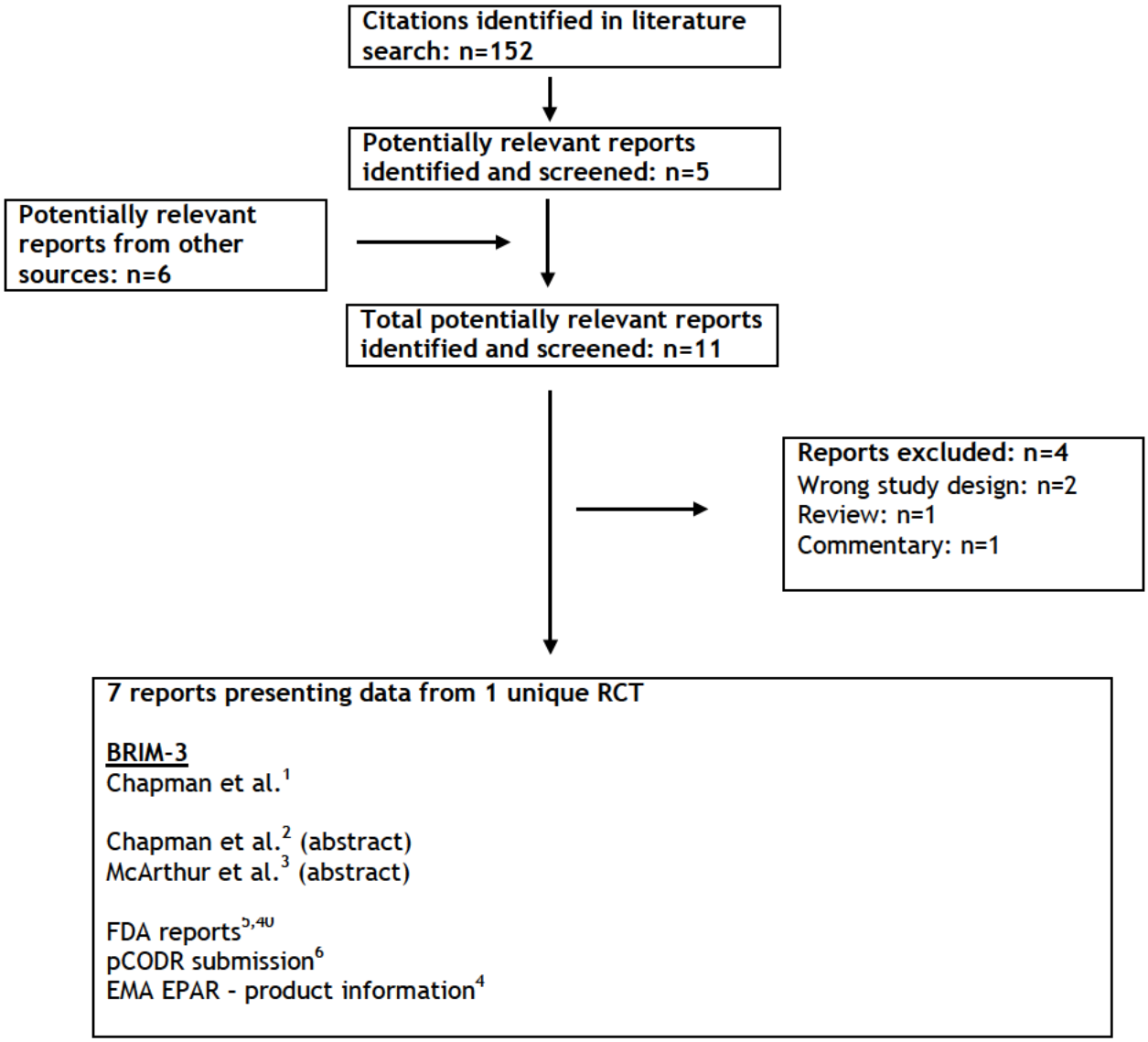
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions 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 11 potentially relevant reports identified, 7 reports related to one study were included in the pCODR systematic review[1-6,40] and 4 reports were excluded. Studies were excluded because they were the wrong study design (non-randomized, single-arm),[39,41] a review article,[42] or a commentary.[43]

Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 2: Summary of Trial Characteristics of the Included Study

Trial Design	Inclusion Criteria	Intervention and Comparator	Outcomes
BRIM-3[1-3] 104 centres in 12 countries* January 2010 to January 2011* OL, AC, Phase III RCT Randomized 1:1 ratio stratified by AJCC stage (IIIC, M1a, M1b, or M1c), ECOG-PS, geographic region, and serum LDH level (normal or elevated) n = 675 randomized n = 672 ITT analysis Funded by Hoffmann-La Roche	• Patients with unresectable, previously untreated, BRAF V600E mutation-positive, stage IIIC or stage IV melanoma • Age ≥18 years • Life expectancy >3 months • ECOG-PS ≤1 • Sufficient hematologic, hepatic, renal function • No history of cancer within past 5 years (except BCC or SCC of the skin or carcinoma of the cervix) • No metastases to the CNS (unless successfully treated ≥3 months prior with no progression, no requirement for corticosteroids) • No concomitant treatment with any other anticancer therapy	• **Vemurafenib** 960 mg orally twice daily vs. **dacarbazine** 1000 mg per m^2 intravenously every 3 weeks • Treatment interruptions and/or dose adjustments were permitted for both groups for ≥grade 2 AEs • Treatment was discontinued on disease progression unless continued treatment in the best interest of patient • Anti-emetics and GCSF were permitted at the investigator's discretion	<u>Co-Primary</u> • Overall survival • Progression-free survival <u>Secondary</u> • Best overall response rate • Duration of overall response • Time to overall response • AEs

AC = active treatment control; **AE** = adverse event; AJCC = American Joint Committee on Cancer; **BCC** = basal cell carcinoma; **CNS** = central nervous system; **ECOG-PS** = Eastern Cooperation Oncology Group performance status; **GCSF** = granulocyte colony-stimulating factor; **ITT** = intention-to-treat; LDH = lactate dehydrogenase; **OL** = open-label; **RCT** = randomized controlled trial; **SCC** = squamous cell carcinoma

*Trial accrual stopped due to protocol amendment recommended by the Data and Safety Monitoring Board based on pre-planned interim analysis

a) Trials

One randomized, open-label, active treatment controlled trial (BRIM-3) met the inclusion criteria for this review (Table 2).[1-3]

BRIM-3 enrolled adult patients with unresectable, previously untreated, BRAF V600E mutation-positive, stage IIIC or IV melanoma. BRAF V600 mutations were

identified using real-time polymerase chain reaction assay (Cobas 4800 BRAF V600 Mutation Test; see Section 7, Supplemental Questions). In approximately one-third of patients, BRAF sequencing was performed retrospectively using standard Sanger and 454 sequencing techniques in order to assess the sensitivity and specificity of the initial mutation screening assay.

The co-primary outcomes of BRIM-3 were overall survival and progression-free survival. The final analysis for overall survival was planned after 196 deaths, with an interim analysis after 50% of the projected deaths had occurred (Pocock boundary, $P \leq 0.028$ at the interim analysis and $P \leq 0.0247$ at the final analysis by the log-rank test). The final analysis for progression-free survival was conducted at the time of the interim analysis for overall survival. Both of the analyses were to allow for stopping for lack of efficacy (futility) and for outstanding efficacy. Secondary outcomes included best overall response rate, duration of response, and time to response, as well as adverse events observed in each treatment group.

An estimated 680 patients were to be enrolled in the study based on 80% power to detect a hazard ratio of 0.65 for overall survival (improvement in median survival from 8 months for dacarbazine to 12.3 months with vemurafenib; alpha level 0.045) and a power of 90% to detect a hazard ratio of 0.55 for progression-free survival (improvement in median survival from 2.5 months for dacarbazine to 4.5 months with vemurafenib; alpha level 0.005). A two-sided unstratified log-rank test was used to compare survival rates between the treatment groups.

Trial procedures for randomization and allocation concealment appeared to be appropriately conducted.

b) Populations

A total of 337 and 338 patients were randomized to receive vemurafenib or dacarbazine, respectively. Median age was 56 years (range 21 to 86 years) in the vemurafenib group and 52 years (range 17 to 86 years) in the dacarbazine group. Patients were predominantly male (59% and 54% in the vemurafenib and dacarbazine groups, respectively) and Caucasian. Randomization was balanced by geographic region with most patients (approximately 60%) located in Western Europe. Patients were equally distributed between groups regarding ECOG performance status, with 68% having a performance status of zero and with 32% having a performance status of one in both groups. There was also little difference between groups regarding the extent of metastatic melanoma. Approximately two-thirds of patients in the vemurafenib and dacarbazine groups had M1c stage metastases (66% and 65%, respectively), followed by M1b stage (18% and 19%, respectively), M1a stage (10% and 12%, respectively), and unresectable stage IIIC disease (6% and 4%). Most patients in both groups (58% respectively) also had lactate dehydrogenase levels above the upper limit of the normal range.

Twenty-one patients were included with non-BRAF V600E mutations as identified on Sanger and 454 sequencing, 11 of which were treated with vemurafenib and 10 with dacarbazine. The most common non-BRAF V600E mutation identified was V600K (vemurafenib = 10; dacarbazine = 9). One

tumour sample was identified with V600E2 mutation (vemurafenib-treated) and one with sample was designated as an "other" mutation (dacarbazine-treated).

There was no substantial imbalance between treatment groups with respect to demographic or disease characteristics.

c) Interventions

Patients received vemurafenib 960 mg twice daily orally or dacarbazine 1000 mg per m^2 intravenously infused every three weeks. Both treatment groups received antiemetics and granulocyte colony-stimulating factor as needed. Treatment interruption or a dose reduction for both vemurafenib and dacarbazine were pre-specified for intolerable grade two toxic effects or worse. Vemurafenib treatment was discontinued until resolution of the effect to at least grade one and restarted at 720 mg twice daily (480 mg twice daily for grade 4 events). The dose was further reduced to 480 mg twice daily if the toxic effects recurred. Treatment with vemurafenib was discontinued permanently if the toxic effect did not improve to grade one or lower or recurred at the 480 mg twice daily dose. Dacarbazine treatment was interrupted for grade three or four toxic effects and could be restarted on recovery within one week to grade one (at full dose) or grade two (at 75% dose) or at 75% dose for grade four neutropenia or febrile neutropenia. A second dose reduction was permitted as needed.

There was no fixed duration of treatment, as patients were allowed to continue treatment until they experienced tumour progression, unacceptable toxicity, or death or study discontinuation for other reasons.

The median duration of treatment among the vemurafenib group was 4.2 months compared with 0.8 months among the dacarbazine group. Three times as many patients in the vemurafenib group required a dose modification (47.3% versus 15.2%). One hundred and twelve (33.3%) vemurafenib-treated patients and 44 (15.2%) dacarbazine-treated patients required dose reduction; most patients in both groups required only one dose reduction.

d) Patient Disposition

Patient disposition is presented in Table 3 below:

Table 3: Number of Patients

	Vemurafenib	Dacarbazine
Screened	2107	
Randomized	337	338
Treated • Refused treatment/Withdrew consent • Never received treatment (other reasons)	336* 0 2	289 37 11
Intention-to-treat analysis	337	338
Safety analysis	336*	293
Discontinued treatment • Disease progression or death • Adverse event • Refused treatment/Withdrew consent • Other	113 95 12 6 0	206 181 10 12 3

*One patient was randomized to dacarbazine but was mistakenly given vemurafenib. This patient was analyzed as dacarbazine-treated in the efficacy analysis, but as vemurafenib-treated in the safety analysis.

e) Limitations/Sources of Bias

- Clinical trials in which progression-free survival is a primary endpoint should be double-blinded. However, in instances where blinding of patients and/or investigators is not possible, a blinded review of tumour assessments is recommended.[44] In BRIM-3, lack of blinding of investigators and the absence of an independent radiologic committee to assess progression-free survival may have resulted in observer bias for this outcome, even though an independent data and safety monitoring board provided oversight and evaluated interim results on efficacy data.
- The short follow-up time for overall survival (with most patients contributing <7 months) means there was a small number of patients at risk when the Kaplan-Meier curves reached the median, making estimates of median overall survival and differences in medians between treatment groups not robust.
- Patients in the dacarbazine group were permitted to crossover to receive vemurafenib following the December 30, 2010 planned interim analysis. Thus, because of the potential confounding associated with crossover, the updated overall survival data with longer follow-up may not truly reflect the effect of vemurafenib compared with dacarbazine (i.e., the estimate of the overall survival hazard ratio may be inflated). Additionally, the second and third overall survival analyses were post hoc and, therefore, can only be considered as exploratory.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Following the intention-to-treat principle, patients were analyzed according to the treatment they were assigned to at randomization. The safety population consists of all patients who received at least one dose of study drug and who had at least one valid post-baseline safety assessment.

Patients were examined every three weeks from baseline and tumour assessments were conducted at baseline, at weeks six and 12, and every nine weeks thereafter.

Three data analyses were conducted for the BRIM-3 population. The first analysis was conducted with a cut-off date of December 30, 2010. At the time of this planned interim analysis, a total of 118 patients had died. The Independent Data and Safety Monitoring Board recommended a protocol amendment to close accrual because the a priori criteria for statistical significance had been met showing a difference in overall survival and progression-free survival in favour of vemurafenib. From this point on, patients treated with dacarbazine could crossover to receive vemurafenib. The data from this analysis were the basis for the BRIM-3 publication.[1] There were no further planned analyses for progression-free survival and best overall response rate after the December 30, 2010 analysis.

The second analysis for BRIM-3 had a data cut-off date of March 31, 2011. This analysis was only performed for overall survival data because the median overall survival for vemurafenib had not yet been reached as the December 30, 2010 analysis. However, the median overall survival for vemurafenib had still not been reached at the second cut-off date. Therefore, a third overall survival analysis for BRIM-3 was conducted, with a cut-off date of October 3, 2011. Both of these unplanned analyses were conducted, in part, following regulatory guidance in order to provide a longer duration for follow-up to gain more robust overall survival data than what was available from the first cut-off date.

Key outcomes of BRIM-3 at the time of planned interim analysis (December 30, 2010 cut-off) are summarized in Table 4.

Table 4: Summary of Key Outcomes* from the BRIM-3 Trial[1-3]

Efficacy			
	Vemurafenib (n = 337)	**Dacarbazine (n = 338)**	**Statistical Analysis**
Primary outcomes			
Overall survival†, median (95% CI)	NE	NE	**Hazard Ratio‡:** 0.37 (0.26 to 0.55) **P-value (log-rank test):** <0.001
Progression-free survival†, median (95% CI) months	5.3 (4.8 to 6.3)	1.6 (1.5 to 1.7)	**Hazard Ratio‡:** 0.26 (0.20 to 0.33) **P-value (log-rank test):** <0.001

Table 4: Summary of Key Outcomes* from the BRIM-3 Trial[1-3]			
Efficacy			
Secondary outcomes			
Time to response, median (range) months	1.45 (1.0 to 5.5)	2.72 (1.6 to 5.8)	NE
Best overall response rate (CR+PR), % (95% CI)	48.4 (41.6 to 55.2)	5.5 (2.8 to 9.3)	**P-value (Chi-square test):** <0.001
Harms[§]			
Deaths¶, n/N (%)	63/336 (18.8)	99/293 (33.8)	NE
Nonfatal serious adverse events, n/N (%)	144/336 (42.9)	51/287 (17.8)	NE
Adverse events, n/N (%)	331/336 (98.5)	261/287 (90.9)	NE
Withdrawals due to adverse event, n/N (%)	24/336 (7.1)	12/293 (4.2)	NE

CI=confidence interval; NE=not estimated; NR=not reported

* Data from analysis conducted at the December 30, 2010 cut-off point, planned interim analysis
† Kaplan-Meier estimate at 6 months of follow-up
‡ Cox proportional hazards model
§ Harms data were extracted from the U.S. FDA medical review analysis based on the safety population, where n = 336 for vemurafenib and n = 293 for dacarbazine
¶ In the vemurafenib group, 53/63 deaths were due to disease progression; in the dacarbazine group, 94/99 deaths were due to disease progression

Efficacy Outcomes

Overall survival

Overall survival was a co-primary outcome defined as the time interval from randomization until death due to any cause. Data from the three overall survival analyses are presented in Table 5. Forty-three (12.8%) and 75 (22.2%) vemurafenib and dacarbazine patients, respectively, had died by the time of the planned interim analysis of December 2010. The median survival times were not estimated, however, because there were insufficient numbers of patients in both groups to reliably estimate median survival (most patients had less than 7 months of follow-up at that point). Nonetheless, a survival benefit was observed in the vemurafenib group at six months, with a hazard ratio of 0.37 (95% CI: 0.26 to 0.55).

In the updated analysis with cut-off date of March 31, 2011, the hazard ratio continued to show a statistically significant survival benefit for vemurafenib.[5,40] A third and more recent overall survival analysis was conducted with a cut-off date of October 3, 2011, for which the median survivals were estimated as 13.2 and 9.6 months for the vemurafenib and dacarbazine groups, respectively.[4] In both analyses, the hazard ratio was similar between the groups with and without censoring at crossover.

Table 5: Overall Survival from BRIM-3 at Three Analysis Time Points, ITT Population		
	Vemurafenib (n = 337)	**Dacarbazine (n = 338)**
Cut-off Date: December 30, 2010		
Number of events	43	75
Overall survival*, median (95% CI)	NE	NE
Hazard ratio† (95% CI) P-value (log-rank test, two-sided)	0.37 (0.26 to 0.55) <0.001	
Median duration of follow-up, months	3.8	2.3
Cut-off Date: March 31, 2011‡		
Analysis with censoring at crossover		
Number of events	78	121
Overall survival*, median (95% CI)	NE (9.59 to NE)	7.89 (7.20 to 9.63)
Hazard ratio† (95% CI) P-value (log-rank test, two-sided)	0.44 (0.33 to 0.59) <0.001	
Median duration of follow-up, months	6.2	4.5
Analysis without censoring at crossover		
Number of events	78	122
Overall survival*, median (95% CI)	NE (9.59 to NE)	8.80 (1.33 to 10.28)
Hazard ratio† (95% CI) P-value (log-rank test, two-sided)	0.47 (035 to 0.62) NR	
Median duration of follow-up, months	6.2	4.5
Cut-off Date: October 3, 2011§		
Analysis with censoring at crossover		
Number of events	159	152
Overall survival*, median (95% CI)	13.2 (12.0 to 15.0)	9.6 (7.9 to 11.8)
Hazard ratio† (95% CI) P-value (log-rank test, two-sided)	0.62 (0.49 to 0.77) <0.001	
Median duration of follow-up, months	10.5	8.4
Analysis without censoring at crossover		
Number of events	159	175
Overall survival*, median (95% CI)	13.2 (12.0 to 15.0)	9.6 (9.1 to 12.2)
Hazard ratio† (95% CI) P-value (log-rank test, two-sided)	0.67 (0.54 to 0.84) =0.0003	
Median duration of follow-up, months	10.5	8.4

CI=confidence interval; ITT=intention-to-treat; NE=not estimated; NR=not reported

*Kaplan-Meier estimate †Cox proportional hazards model

‡ This analysis included 50 patients who crossed over from dacarbazine to vemurafenib since December 30, 2010

§ This analysis included a total of 81 patients who crossed over from dacarbazine to vemurafenib since December 30, 2010

Subgroup analyses for overall survival:

The treatment effect of vemurafenib across pre-specified subgroups was estimated using Cox proportional hazards models and these effects were consistent with the primary analysis for overall survival (as of December 30, 2010). However, hazard ratio estimates were not statistically significant for the following subgroups: four out of five disease stage subgroups (except M1c); Australia/New Zealand region; and those aged ≤40 and ≥75 years.

Progression-free survival

Progression-free survival was the other co-primary end-point in BRIM-3. It was defined as the time from randomization to documented disease progression or death based on investigator assessment according to RECIST criteria. Progression-free survival was estimated only at the December 30, 2010 interim analysis. Progression-free survival could be evaluated in a total of 549 patients (81%), with a median value of 5.3 and 1.6 months for the vemurafenib and dacarbazine groups, respectively (Table 4). The hazard ratio for progression-free survival was in favour of vemurafenib at 0.26 (95% CI: 0.20 to 0.33; Table 4).

Subgroup analyses for progression-free survival:

The treatment effect of vemurafenib across pre-specified subgroups was estimated using Cox proportional hazards models and these effects were consistent with the primary analysis for progression-free survival. However, the hazard ratio estimates were not statistically significant for patients aged ≥75 years.

Tumour response

Time to response:

Time to response was a secondary outcome in BRIM-3 and was defined as the interval (days) between the date of randomization and the first date when the qualifying response criteria were met. Time to response was calculated among those patients who had a response (vemurafenib n = 106; dacarbazine n = 12; see Response rate below).

Median time to response was 1.45 months for the vemurafenib-treated group and 2.7 months among patients treated with dacarbazine (Table 4).

Response rate:

Best overall response rate was defined as the total number of patients whose best overall response is complete response or partial response, divided by the total number of patients in the group for which the best overall response rate is estimated. The analysis population for best overall response rate consisted of all intention-to-treat patients randomized at least 14 weeks prior to the clinical cutoff date of December 30, 2010. A total of 439 patients (65%) could be evaluated for tumour response.

A total of 48% (106 of 219 patients; 95% CI: 42 to 55) of patients in the vemurafenib group had a response to treatment. In comparison, 5.5% (12 of 220

patients; 95% CI: 3 to 9) of patients treated with dacarbazine were reported as responders to treatment (P<0.001 for between group difference).

Quality of life (Patient relevant outcome)

The effect of vemurafenib on quality of life was a pre-specified secondary outcome in the BRIM-3 protocol and was assessed using the Functional Assessment of Cancer Therapy-Melanoma [FACT-M] version 4 questionnaire. Patients were asked to complete the FACT-M questionnaire at baseline, on Day 1 (pre-dose) of Cycles 2, 3, 4, 6, 9 and 12, and within 28 days after documented disease progression.

Quality of life was assessed using the Functional Assessment of Cancer Therapy-Melanoma v.4 (FACT-M) questionnaire. Analyses of FACT-M and its subscales suggested that there was no difference in quality of life measured over time on study treatment in patients treated with vemurafenib compared with patients treated with dacarbazine. Interpretation of data was limited because fewer patients completed FACT-M assessment at later cycles as per protocol.

Systematic review subgroups

Two subpopulations of interested were a priori identified in the systematic review protocol:

(*1) Patients who had previously received treatment for unresectable or metastatic melanoma*

BRIM-3 excluded patients with prior treatment therefore no subgroup analyses were available. However, a phase II, single treatment group study of vemurafenib among patients previously treated for unresectable or metastatic melanoma, BRIM-2,[10] is summarized in the Supplemental Questions section of the systematic review (section 7.2). This study was excluded from the systematic review because of its lack of a comparator treatment group.

(2) Patients with different BRAF V600 mutation types.

A small proportion of patients in BRIM-3 were identified as carrying BRAF mutations other than V600E (n=21). An exploratory analysis presented in the U.S. FDA statistical review of vemurafenib[40] compared overall survival and progression-free survival between V600E and non-V600E mutations. The hazard ratios were similar in both groups indicating no differences in effect of treatment. However, the analyses were conducted among very few patients, and they did not preserve the randomized allocation of patients and, likely, did not preserve the balance in baseline demographic and disease characteristics of the patients.

Harms Outcomes

Data regarding adverse events were sparsely reported in the BRIM-3 publication.[1] Consequently, data for this section of the systematic review were extracted primarily from the U.S. FDA medical review of vemurafenib.[5]

Serious adverse events (Patient relevant outcome)

According to the FDA medical review, 99 deaths occurred in the dacarbazine group (99/293; 33.8%) and 63 in the vemurafenib group (63/336; 18.8%). All deaths were attributable to underlying medical conditions and interventions, and to disease progression (53/63, 84% for vemurafenib; 94/99, 95% for dacarbazine), except for two patients treated with dacarbazine whose deaths may have been related to treatment.[5]

Nonfatal serious adverse events occurred in 42.9% of patients receiving vemurafenib and in 17.8% receiving dacarbazine (Table 6). Notably, over one-quarter of patients in the vemurafenib group experienced cutaneous squamous cell carcinomas (including both squamous cell carcinomas of skin and keratoacanthoma) and new primary malignant melanomas; however, all lesions were resolved with local therapies, except in two cases of cutaneous squamous cell carcinomas for whom the outcome was not reported before the December 30, 2010 data cut-off.[5]

Table 6: Nonfatal Serious Adverse Events (≥1% of patients) in BRIM-3 Safety Population[5]

	Vemurafenib (n = 336)	**Dacarbazine (n = 287)**
Total, n (%)	**144 (42.9)**	**51 (17.8)**
Squamous cell carcinomas of skin	58 (17.3)	1 (<1)
Keratoacanthoma	29 (8.6)	0
Malignant melanoma	7 (2.1)	0
Pyrexia	4 (1.2)	4 (1.4)
Thrombosis	0	3 (1)

In addition, three cardiac disorders occurred more frequently in the vemurafenib group than in the dacarbazine group, respectively: atrial fibrillation (9 versus 2 patients), myocardial infarction (3 versus 0 patients), and pericarditis (3 versus 0 patients).[5] There were at least two Grade 3 to 4 events for each disorder among the vemurafenib group. Furthermore, QT prolongation was observed in 10.7% of patients in the vemurafenib group and in none in the dacarbazine group. However, no large changes in QTc interval (>20 ms) were reported. There were no reported cases of torsade de pointes in any vemurafenib-treated patients.[5]

Adverse events (Patient relevant outcome)

Adverse events of any grade occurring in ≥10% of patients were extracted from the FDA medical review and are summarized in Table 7.[5] Grades 3-4 adverse

events occurred more frequently in the vemurafenib group (58.6%) compared with the dacarbazine group (33.4%), including a greater incidence of arthralgia, rash, elevated liver enzymes, photosensitivity reaction, and squamous cell carcinoma of skin. Neutropenia of any grade occurred much more often among patients treated with dacarbazine.

Adverse events leading to dose modification in the vemurafenib group (in ≥3 patients) were most frequently rash (10.7%), elevated liver enzymes (11.1%), and arthralgia (6.5%). Neutropenia and thrombocytopenia were the most frequent adverse events associated with dose reduction in the dacarbazine group (10% and 2.1%, respectively).

Table 7: Most Common Adverse Events (≥10% of Patients) in BRIM-3 Safety Population[5]

	Vemurafenib (n = 336)		**Dacarbazine (n = 287)**	
	Grade 1-4	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**
Total, n (%)	**331 (98.5)**	**197 (58.6)**	**261 (90.9)**	**96 (33.4)**
Arthralgia	180 (53.6)	15 (4.5)	9 (3.1)	2 (<1)
Alopecia	150 (44.6)	2 (<1)	6 (2.1)	0
Fatigue	127 (37.8)	7 (2.1)	96 (33.4)	6 (2.1)
Rash	124 (36.9)	28 (8.3)	7 (2.4)	0
Elevated liver enzymes	117 (34.8)	33 (9.8)	12 (4.2)	2 (<1)
Nausea	116 (34.5)	7 (2.1)	124 (43.2)	5 (1.7)
Photosensitivity reaction	110 (32.7)	9 (2.7)	10 (3.5)	0
Diarrhea	95 (28.3)	3 (<1)	37 (12.9)	1 (<1)
Hyperkeratosis	82 (24.4)	4 (1.2)	2 (<1)	0
Headache	78 (23.2)	3 (<1)	30 (10.4)	0
Pruritus	77 (22.9)	5 (1.5)	4 (1.4)	0
Skin papilloma	72 (21.4)	1 (<1)	0	0
Pyrexia	64 (19)	2 (<1)	25 (8.7)	3 (1)
Dry skin	63 (18.8)	0	3 (1)	0
Vomiting	60 (17.9)	4 (1.2)	76 (26.4)	3 (1)
Pain in extremity	60 (17.9)	2 (<1)	17 (5.9)	5 (1.7)
Decreased appetite	60 (17.9)	0	24 (8.3)	1 (<1)
Squamous cell carcinoma of skin	58 (17.3)	55 (16.4)	1 (<1)	1 (<1)
Peripheral edema	56 (16.7)	3 (<1)	13 (4.5)	0
Erythema	48 (14.3)	0	7 (2.4)	0
Dysgeusia	48 (14.3)	0	9 (3.1)	0
Myalgia	42 (12.5)	1 (<1)	4 (1.4)	0
Constipation	40 (11.9)	1 (<1)	68 (23.6)	0
Asthenia	36 (10.7)	2 (<1)	25 (8.7)	2 (<1)
Neutropenia	2 (<1)	1 (<1)	34 (11.8)	26 (9.1)

Withdrawals due to adverse events

According to the FDA medical review, a total of 7.1% (24/336) and 4.2% (12/293) of patients treated with vemurafenib or dacarbazine, respectively,

discontinued treatment due to adverse events. The most frequent adverse events associated with discontinuation in the vemurafenib group were arthralgia, dysphagia, and pneumonia (2 cases for each of these); no particular adverse events occurred at a higher frequency in the dacarbazine group (all events ≤1 case).[5]

6.4 Ongoing Trials

No ongoing randomized controlled trials were identified evaluating vemurafenib.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of vemurafenib (Zelboraf) for BRAF V600 mutation-positive unresectable or metastatic melanoma:

- Summary of BRAF mutation testing in metastatic melanoma
- Summary of BRIM-2: single-arm, non-randomized study evaluating vemurafenib in previously treated patients

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Summary of BRAF Mutation Testing in Metastatic Melanoma

7.1.1 Objective

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

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).

7.1.2 Findings

Vemurafenib is indicated for use specifically in patients with late-stage melanoma whose tumours have the BRAF V600E type mutation.[45] 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 vemurafenib.[46]

Health Canada and the U.S. FDA both approved Roche's cobas® 4800 BRAF V600 Mutation Test in 2011.[6,47] This test was applied in the BRIM 2 and BRIM 3 clinical trials examining the efficacy and safety of vemurafenib for advanced melanoma.[6]

Description of the cobas® 4800 BRAF V600 Mutation Test[48]

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 BRIM-2 and BRIM-3 (data not yet published; based on analysis submitted to the U.S. FDA).[5,8,9] 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%.[5] 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.[8,9] 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.[5]

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.[48]

Implementation of the cobas® 4800 BRAF V600 Mutation Test

Since BRAF mutation testing for vemurafenib treatment is quite new, there is limited information on its implementation. A decision analytic protocol requested by the medical services advisory committee (MSAC) in Australia reported:[46]

- 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.

7.1.3 Summary

The cobas® 4800 BRAF V600 Mutation Test, developed by Hoffman LaRoche, has received regulatory approval and is currently the only approved test available for use in Canada, to detect BRAF V600E genetic mutations, and thereby identifying patients eligible to receive vemurafenib for advanced melanoma. 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 that was applied in BRIM-2 and BRIM-3.[6,7] 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.[5,8,9] The test showed cross-reactivity with non-V600E mutants, predominantly V600E2 (≥65%), V600K (≥35%), and V600D (≥10%).

7.2 Summary of BRIM-2: a Single-Arm, Non-Randomized Study Evaluating Vemurafenib in Previously Treated Patients

7.2.1 Objective

To summarize data from the single-arm phase II trial, BRIM-2[6,10] in order to provide additional evidence on the efficacy and safety of vemurafenib in the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma, who have received prior treatment.

7.2.2 Findings

BRIM-2 is a phase II, single-arm trial that preceded the phase III trial included in this systematic review, BRIM-3; BRIM-2 was not eligible for inclusion into the systematic review because it was not a randomized, comparative study. BRIM-2 was conducted among patients who were BRAF V600E mutation-positive (identified by cobas® 4800 BRAF Mutation Test) and who had previously received treatment with another therapeutic agent(s) for their disease. The primary endpoint of the study was best overall response rate (complete plus partial response), with a target of 30% and a lower boundary of the 95% confidence interval of at least 20%, as determined by a blinded independent radiologic committee. BRIM-2 was conducted at 13 centres in two countries (U.S. and Australia).

A total of 132 patients were treated with vemurafenib 960 mg twice daily in BRIM-2. Most patients were male (61.4%) and the median age was 51.5 years (range: 17 to 82). Over half (54%) had an ECOG performance status of one, 61% had M1c disease, and 49% had elevated lactate dehydrogenase levels. Fifty-one percent of patients had one prior systemic therapy and 27% received two prior systemic therapies. The most commonly received prior therapies were interleukin-2 (39%), dacarbazine (23%), and temozolomide (20%).[6] Few patients (5%) received prior ipilimumab or tremelimumab therapy. At the efficacy data cut-off date (July 1, 2011), the median follow-up was 12.9 months (range: 0.6 to 20.1). At the safety data cut-off (January 31, 2011), the median follow-up was 10.4 months (range: 0.6 to 14.7).

The primary endpoint of the study was met with a 53% best overall response rate (95% CI: 44% to 62%), of which 6% had a complete response (Table 8). Median progression-free survival was 6.8 months (95% CI: 5.6 to 8.1); median overall survival was 15.9 months (95% CI: 11.6 to 18.3). During the follow-up, 24% of patients received ipilimumab following disease progression with vemurafenib. A post hoc analysis showed even after removing these patients median overall survival remained 15.9 months (95% CI: 8.0 to not reached).

Table 8: Summary of Key Efficacy and Safety Results from BRIM-2[6,10]	
	IRC Assessment (n = 132)
Efficacy	
BORR* confirmed, n (%) [95% CI] CR PR	70 (53) [44 to 62] 8 (6) 62 (47)
Time to response†, median [range] months	1.4 [1.2 to 5.5]
Duration of response, median [95% CI] months	6.7 [5.6 to 8.6]
Progression-free survival‡, median [95% CI] months	6.8 [5.6 to 8.1]
Overall survival, median [95% CI] months	15.9 [11.6 to 18.3]
Deaths§, n (%)	70 (53)
Harms	
Any adverse event, n (%) Grade ≥3	130 (98) 84 (64)
Withdrawals due to adverse events, n (%)	4 (3)

BORR=best overall response rate; CR=complete response; IRC=independent review committee; NE=not estimated; PR=partial response

* RECIST v1.1 criteria

† Data not presented in publication. Source: pCODR submission material (data cut-off date of September, 2010)[6]

‡ Kaplan-Meier estimate

§ 39 deaths due to disease progression

Adverse events occurred in almost all BRIM-2 patients; 64% of these were rated grade 3 or higher. Grade 3 adverse events were predominantly squamous cell carcinoma of the skin (26%), rash (7%), elevated liver enzymes (6%) which largely resolved with dose modification, arthralgia (6%), and photosensitivity (3%). Approximately 45% of patients required dose reduction and 64% required a dose interruption during treatment, most commonly for rash, arthralgia, elevated liver enzymes, and photosensitivity. Four patients withdrew due to adverse events; one patient due to rapid disease progression and acute renal failure possibly related to treatment.

In BRIM-2, vemurafenib appeared to induce a clinical response in more than half of patients with previously treated BRAF V600E-positive metastatic melanoma. However, several limitations of the study need to be considered. For instance, BRIM-2 was a non-randomized, single-arm study in which all patients received vemurafenib. Although there was no accepted standard of care for second-line treatment of advanced or metastatic melanoma when BRIM-2 was conducted, the absence of a comparison group has important implications for the robustness of the study results. While conducting a randomized trial in this setting may have been challenging, a randomized controlled trial evaluating ipilimumab in the second-line setting was recently conducted, suggesting that this may have been feasible.[49] Moreover, use of an appropriately matched historical control group as a comparator would be a reasonable alternative to randomizing patients to comparator treatment in BRIM-2 and more methodologically robust than a single-arm study. This option not only would have added a degree of efficiency, but it would also have allowed the BRIM-2 investigators to potentially compare vemurafenib with control groups of mixed treatments, including other systemic therapeutics, treatment of "physician's choice", or best supportive care.

The primary efficacy endpoint, best overall response rate, was assessed by an independent review committee blinded to the results of other tumour assessments. Bias in the evaluation is still possible given the somewhat subjective nature of tumour assessment. It seems plausible that the unblinded investigators' knowledge of response status could influence

perceptions of subsequent outcomes such as adverse events. Additionally, the lack of a randomized comparison group makes the overall survival and progression-free survival outcomes almost uninterpretable. Since all patients received vemurafenib, it is also difficult to measure adverse events that may be attributable to the drug versus other factors. Thus, given the non-comparative design and limited robustness of the data, caution should be used when drawing conclusions about the favourable results presented from BRIM-2.

7.2.3 Summary

This supplemental issue summarized data from BRIM-2,[6,10] a single-arm, non-randomized phase II trial examining the efficacy and safety of vemurafenib among patients with BRAF V600E mutation-positive metastatic melanoma who had received prior treatment for their disease. The primary endpoint of the study was best overall response rate, with a target of 30%, as determined by a blinded independent radiologic committee. Over half of patients had an ECOG performance status of one, 61% had M1c disease, and 49% had elevated lactate dehydrogenase levels. Fifty-one percent of patients had one prior systemic therapy and 27% received two prior systemic therapies. Of the total 132 patients who received treatment, 53% achieved the primary outcome of best overall response rate after a median follow-up of 12.9 months. Median progression-free survival was seven months and median overall survival was 16 months. However, the absence of a control group is an important limitation of the BRIM-2 results. It is uncertain whether equipoise would exist in the second-line setting between vemurafenib and other available systemic therapeutics to conduct a randomized controlled trial. Nonetheless, randomized controlled trials have been conducted in similar circumstances, such as one conducted for second-line treatment of metastatic melanoma with ipilimumab.[49] Furthermore, other options to include a comparison group, such as an historical control group, could have been used by the investigators to potentially address concerns of equipoise. Given the non-comparative, unblinded design and limited robustness of the data, caution should be used when drawing conclusions from these results. Almost all patients experienced an adverse event, 64% of which were rated as grade three or more. The most frequent (>30%) adverse events related to the study drug were arthralgia, rash, photosensitivity reaction, alopecia, pruritis, skin papilloma and squamous cell carcinoma of the skin. Squamous cell carcinoma of the skin was the most common grade 3 or higher adverse event (26%). In general, the efficacy and safety effects of vemurafenib observed in BRIM-2 are similar to those observed in the randomized, controlled phase III trial, BRIM-3.[1]

8 ABOUT THIS DOCUMENT

This 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 vemurafenib (Zelboraf) for advanced 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, which was provided to pERC for their deliberations, and this information has been redacted for a time limited basis in this Guidance Report.

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

The pCODR Melanoma Clinical Guidance Panel is comprised of three clinical 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

Embase 1980-present (emez); Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily and Ovid MEDLINE (R) (pmez)

#	Searches	Results
1	*vemurafenib/	32
2	(zelboraf* or vemurafenib* or PLX4032 or PLX 4032 or RG7204 or RG 7204 or RO 5185426 or RO5185426 or R05185426 or R0 5185426 or RO51 85426 or R051 85426).ti,ab.	192
3	or/1-2	203
4	3 use emez	129
5	(zelboraf* or vemurafenib* or PLX4032 or PLX 4032 or RG7204 or RG 7204 or RO 5185426 or RO5185426 or R05185426 or R0 5185426 or RO51 85426 or R051 85426).ti,ab,ot,sh,hw,rn,nm.	543
6	(918504-65-1 or 1029872-54-5).rn,nm.	140
7	or/5-6	543
8	7 use pmez	98
9	4 or 8	227
10	exp animals/	17648816
11	exp animal experimentation/	1482265
12	exp models animal/	985546
13	exp animal experiment/	1482265

14	nonhuman/	3745156
15	exp vertebrate/	31524045
16	or/10-15	33375751
17	exp humans/	24999234
18	exp human experiment/	295264
19	or/17-18	25000618
20	16 not 19	8376063
21	9 not 20	224

2. Literature search via PubMed

Search	Most Recent Queries	Result
#1	Search **(zelboraf OR vemurafenib OR PLX-4032 OR PLX4032 OR RG7204 OR RG-7204 OR RO5185426 OR "RO 5185426" [tiab] OR R05185426 OR "R0 5185426" [tiab] OR "RO51 85426" OR "R051 85426") AND publisher [sb]**	7

3. Cochrane Central Register of Controlled Trials (Central)

Search for trials. Issue 4 of 4, Oct 2011.

ID	Search	Hits
#1	(zelboraf* or vemurafenib* or PLX4032 or PLX 4032 or RG7204 or RG 7204 or RO 5185426 or RO5185426 or R05185426 or R0 5185426 or RO51 85426 or R051 85426)	1

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: Zelboraf OR vemurafenib OR PLX4032 OR PLX 4032 OR RG7204 OR RG 7204 OR RO5185426 OR RO 5185426

Select international agencies including:

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

European Medicines Agency (EMA):
http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp

Search terms: Search terms: Zelboraf OR vemurafenib

Conference abstracts:

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

Search terms: Zelboraf OR vemurafenib OR PLX4032 OR PLX 4032 OR RG7204 OR RG 7204 OR RO5185426 OR RO 5185426 / last 5 years

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