pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Trametinib (Mekinist) for Metastatic Melanoma

October 22, 2013

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INQUIRIES

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

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

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

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of trametinib on patient outcomes compared with standard treatment, placebo, or best supportive care in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Trametinib is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and activity. Trametinib has a Health Canada indication for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation. The recommended dose is 2 mg administered orally once daily.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review assessed the efficacy and safety of trametinib, 2 mg orally once daily (n=214), compared with DTIC, 1000mg/m^2 every 3 weeks (n = 62), or paclitaxel, 175 mg/m^2 every 3 weeks (n = 37), in one international, multicentre, open-label, randomized controlled trial, METRIC.[1-3]

87% of all patients had V600E mutations, and 13% had V600K mutations. Patients could have received one previous chemotherapy regimen for advanced or metastatic melanoma, with the exclusion of BRAF and MEK inhibitors and ipilimumab. 33% of the trametinib group had previous chemotherapy compared to 35% in the chemotherapy group. Patients with stable brain metastases were allowed to enroll. 4% of the trametinib group had a history of brain metastasis compared to 2% in the chemotherapy group. METRIC included patients with ECOG status of 0 (64%) and 1 (36%). Patients were generally well balanced in demographics between the two arms.

Patients in the chemotherapy group were allowed to cross over to receive trametinib after disease progression had been confirmed by an independent review. Treatment for all patients continued until disease progression, death, or withdrawal.

Efficacy

The primary end-point for the METRIC study was progression-free survival (PFS) in the primary efficacy population (patients with the V600E BRAF mutation who did not have brain metastases at baseline). Secondary outcomes included PFS and overall survival (OS) in the ITT population and in subgroups of the primary efficacy population (with and without prior chemotherapy; by BRAF mutation status (V600E and V600K)).

For the primary outcome, median progression-free survival (PFS) in the primary efficacy population was 4.8 and 1.4 months in the trametinib and chemotherapy group, respectively (HR 0.44, 95% CI: 0.31 to 0.64 p<0.0001). Similar results were observed for PFS in the ITT population and in the subgroups except in patients with V600K mutation.

For the secondary outcome of OS, the hazard ratio (HR) for OS was 0.54 (95% CI, 0.32 to 0.92; p=0.01), at the first data cut-off of October 2011 (median follow-up of 4.9 and 4.8 months in the trametinib and chemotherapy arms, respectively) and 0.78 (95% CI, 0.57 to 1.06; p=0.0912) at the second data cut-off of May 20, 2013(median follow up of 14.7 and

8.7 months in the trametinib and chemotherapy arms, respectively). However, OS may however have been confounded by crossover as, 47% of patients randomized to chemotherapy had crossed over to receive trametinib at the time of the first data cut-off.

Health-related quality of life (HRQOL) assessments were performed using EORTC QLQ-C30 and EQ-5D questionnaires. In general, trametinib treatment was associated with smaller functional impairment, smaller declines in health status, and less symptoms exacerbation over the course of treatment as compared to chemotherapy. For patients who experienced disease progression, trametinib was associated with improvement in scores for pain, insomnia, appetite loss and constipation, while chemotherapy was associated with no change or minimal to modest worsening of symptoms. Statistical significance was not assessed.

Harms

Serious adverse events (SAEs) occurred at a similar rate in the trametinib (18%) and chemotherapy (20%) arms, with cellulitis (2%) being the most common in the trametinib arm, and pyrexia (4%) in the chemotherapy arm (treated with DTIC). One death occurred in the trametinib arm due to renal failure that may be related to trametinib.[4] AEs led to dose interruption in 35% and to dose reductions in 27% of patients overall. A higher proportion of patients in the trametinib group experienced AEs that led to dose interruption or dose reduction than in the chemotherapy group.

In the trametinib group, the most common AEs were rash, diarrhea, peripheral edema, fatigue, hypertension and dermatitis acneiform. A decreased ejection fraction occurred in 14 patients (7%) and serious grade 3 cardiac events occurred in 2 patients (0.01%). Ocular events occurred in 19 patients (9%).

1.2.2 Additional Evidence

pCODR received input on trametinib for metastatic melanoma from one patient advocacy group, (Melanoma Network of Canada). Provincial Advisory group input was obtained from nine of the nine provinces participating in pCODR.

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

- **Summary of Indirect comparison to vemurafenib**

  An adjusted indirect treatment comparison was performed between trametinib and vemurafenib based on the METRIC (October 2011 data cut-off) and BRIM-3 studies. Conclusions drawn from such indirect comparisons are not as robust as those from direct, head-to-head trial data.

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

1.2.3 Interpretation and Guidance

Burden of Illness and Need

In Canada, 5500 new cases of primary melanoma are expected in 2011 and approximately 950 patients will die from melanoma.[5]

Unresectable Stage III and IV melanoma is an incurable malignancy with approximately 6% of patients surviving 5 years, and 75% percent of patients dying within one year of diagnosis. Brain metastases are relatively common in advanced melanoma and occur in up to 75% of patients with overt metastatic disease. They often prove to be relatively refractory to radiotherapy and systemic treatment and are associated with a particularly dismal prognosis.

Select patients with metastatic disease would benefit from surgery or radiotherapy alone. Systemic treatment is most commonly offered. Over the past 30 years, the standard first line systemic therapy has been dacarbazine but complete responses are rare and have never been shown to improve survival in metastatic melanoma.[6-11] A very wide spectrum of chemotherapeutic and immunological treatments approaches have been explored in metastatic melanoma with limited to no success.

Vemurafenib and dabrafenib are BRAF inhibitors that selectively target the mutated BRAF V600. Although vemurafenib is currently the standard first line treatment in this patient population, dabrafenib is currently under review for treatment of patients with unresectable stage III or Stage IV melanoma that harbours the BRAF V600E or V600K mutation. Patient advocacy group input indicates that patients experience serious and severe side effects with currently available therapies and seek an alternative treatment option.

Effectiveness

Trametinib demonstrated a statistically significant improvement in its primary endpoint of PFS. The median PFS in the intention-to treat population was 4.8 months and 1.5 months for trametinib and dacarbazine arms, respectively. There was a slightly greater PFS when assessed by the independent review committee; however the results were similar in the primary efficacy population. Overall survival was significantly longer in the trametinib arm but may have been confounded by crossover of patients from the placebo group to trametinib.

In general, at weeks 6 and 12 trametinib treatment was associated with smaller functional impairment, smaller declines in health status, and less symptoms exacerbation over the course of treatment as compared to chemotherapy.

Although there are no randomized clinical trials comparing trametinib to a BRAF inhibitor, an indirect comparison of trametinib and vemurafenib demonstrated that there was a greater likelihood of better PFS and OS rates with vemurafenib therapy than with trametinib while the use of longer follow up data from the BRIM-3 trial demonstrated a greater likelihood of better OS rates with trametinib therapy than with vemurafenib. Conclusions drawn from such indirect comparisons are however not as robust as those from direct head-to-head trial data and therefore must be taken in context. In addition, the indirect comparison used trametinib data from the October 2011 data cut-off and did not incorporate data from the May 2013 cut-off, which demonstrated a potential waning of the trametinib effect over time. Without a head-to-head trial, the relative effectiveness of these two drugs is uncertain, the mechanisms of action differ and results from the BRIM-3 and METRIC studies suggest there could be differences.

Trametinib could therefore be considered in patients who are unable to tolerate a BRAF inhibitor. Therefore the eligibility criteria for trametinib could include patients with metastatic and /or unresectable melanoma whose tumours harbours the V600E or V600K mutation and have not received prior BRAF inhibitor therapy. Patients should have an

ECOG performance of 0 or 1, if present, have stable brain metastases and have an adequate renal, hematologic and liver function.

As patients who received prior BRAF Inhibitor therapy were excluded from this trial, there is no evidence to support the use of trametinib after progression on a BRAF Inhibitor, despite evidence that several pathways of resistance are upstream from MEK and lead to increased activation and phosphorylation of MEK. Similarly, only 9 patients with a history of brain metastases were on the trametinib arm and 2 in the chemotherapy arm. Therefore the true efficacy of trametinib in patients with brain metastases is not assessable.

Safety

Trametinib was well tolerated with an acceptable safety profile. Trametinib can safely be administered to patients with metastatic melanoma.

1.3 Conclusions

The pCODR Melanoma Clinical Guidance Panel concluded that there is a net overall clinical benefit to trametinib compared with chemotherapy based on one randomized controlled trial, METRIC, which demonstrated an improvement in progression free survival with trametinib when compared to dacarbazine or paclitaxel in patients who are BRAF treatment naive and have BRAF V600 (E and K) mutation positive unresectable melanoma.

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

- Trametinib has an acceptable tolerability profile with predictable and manageable toxicities.
- There are no randomized clinical trials comparing trametinib to the BRAF inhibitor, vemurafenib, and the results of an indirect comparison to vemurafenib were not as robust as those from direct, head-to-head trial data, and therefore must be taken in context.
- For those patients in whom a BRAF inhibitor is not tolerated or contraindicated, trametinib would be an effective alternative to BRAF inhibitor monotherapy.
- There is no evidence to support the use of a MEK Inhibitor after progression on a BRAF Inhibitor or in patients with brain metastasis
- Currently trials are ongoing comparing the combination of a MEK inhibitor plus a BRAF inhibitor versus a BRAF inhibitor, which could result in a broader role for MEK inhibitors, like trametinib, in clinical practice.

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 trametinib (Mekinist) for metastatic melanoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding trametinib 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 trametinib and a summary of submitted Provincial Advisory Group Input on trametinib are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Trametinib is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and activity. Trametinib has been developed specifically to address known oncogenic mutations in the upstream mitogen-activated protein kinase (MAPK) pathway proteins BRAF and RAS, which signal through MEK1 and MEK2.

The FDA approved trametinib on May 29, 2013 for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. Trametinib was submitted to Health Canada and a Notice of Compliance was received in July 2013 with an indication -"for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation". The recommended dose is 2 mg administered orally once daily.

2.1.2 Objectives and Scope of pCODR Review

The objective of this review is to evaluate the effect of trametinib 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 trametinib 2 mg orally once daily (n=214) were compared with DTIC 1000mg/m2 every 3 weeks (n = 62) or paclitaxel 175 mg/m2 every 3 weeks (n = 37) in one international, multicentre, open-label, randomized controlled trial, METRIC.[1-3]

The study enrolled 322 patients who had histologically confirmed unresectable stage IIIC or IV cutaneous melanoma with a V600E or V600K BRAF mutation. 87% of all patients had

V600E mutations, and 13% had V600K mutations. Patients could have received one previous chemotherapy regimen for advanced or metastatic melanoma, with the exclusion of BRAF and MEK inhibitors and ipilimumab. Patients with stable brain metastases were allowed to enroll. Median age was 55 years in the trametinib group and 54 in the chemotherapy group. METRIC included patients with ECOG status of 0 (64%) and 1 (36%). There was no substantial imbalance between treatment groups with respect to demographic or disease characteristics. 4% of the trametinib group had a history of brain metastasis compared to 2% in the chemotherapy group. 33% of the trametinib group had previous chemotherapy compared to 35% in the chemotherapy group. In the chemotherapy group, 62 patients received DTIC, and 37 patients received paclitaxel. Patients in the chemotherapy group were allowed to cross over to receive trametinib after disease progression had been confirmed by an independent review. Treatment for all patients continued until disease progression, death, or withdrawal.

The primary efficacy endpoint was progression-free survival (PFS) defined as the time from randomization until the earliest date of disease progression documented by the investigator or death due to any cause. The primary efficacy analysis was restricted to patients who had V600E BRAF mutation and who did not have brain metastases at baseline. The secondary endpoints were PFS, overall survival (OS), overall response rate (ORR), duration of response, adverse event rate and quality of life. Secondary outcomes were restricted to the Intent to Treat (ITT) population.

At the time of the first data cut-off (October 2011), the hazard ratio (HR) for overall survival rate (OS) in the ITT population was 0.54 (95% CI, 0.32 to 0.92; p=0.01), representing a 46% reduction in the risk of death for patients treated with trametinib compared to those treated with chemotherapy. At the second data cut-off (May 2013), the hazard ratio (HR) for OS was 0.78 (95% CI, 0.57 to 1.06; p=0.0912).

Median progression-free survival (PFS) in the ITT population was 4.8 months in the trametinib group and 1.5 months in the chemotherapy group. HR was 0.45 [95% CI: 0.33, 0.63]; p<0.0001, representing a 55% reduction in the risk of tumor progression in trametinib arm compared to chemotherapy. Similar results were observed in the primary efficacy population. Subgroup analyses in the primary efficacy population revealed statistically significant 53% reduction in risk of tumour progression in patients with V600E mutation (PFS HR 0.47 (95% CI: 0.33, 0.67)), while risk reduction in a small number of patients with V600K mutation (n = 40) was not statistically significant (PFS HR 0.50 (95% CI: 0.18, 1.35). Also, for the subset of patients with no prior treatment, the tumour progression HR was 0.44 (95% CI, 0.28 to 0.69); for patients with prior treatment, the HR was 0.52 (95% CI, 0.29 to 0.93).

Health-related quality of life (HRQOL) assessments were performed at baseline and throughout active therapy using EPRTC QLQ-C30 and EQ-5D questionnaires. In general, at weeks 6 and 12, trametinib treatment was associated with smaller functional impairment, smaller declines in health status, and less symptoms exacerbation over the course of treatment as compared to chemotherapy. Statistical analysis was not assessed.

There was a statistically significant improvement in overall response rate (ORR) 22% of the patients (n = 47) in the trametinib arm as compared to 8% (n = 9) in the chemotherapy arm (p=0.01).

The median duration of response for the 47 patients in the trametinib group was 5.5 months and was not reached for the 9 patients in the chemotherapy group.

The majority of adverse events (AEs) in the trametinib group was mild to moderate in severity and occurred in a greater proportion of patients in the trametinib group than in the chemotherapy group, except fatigue. A higher proportion of patients in the trametinib group experienced AEs that led to dose interruption or dose reduction than in the chemotherapy group even though the proportion of patients reporting permanent discontinuation of study drug due to AEs was similar between the treatment arms (9%). In the trametinib group, the most common AEs were rash, diarrhea, peripheral edema, fatigue, hypertension and dermatitis acneiform. AEs led to dose interruption in 35% and to dose reductions in 27% of patients.

In the chemotherapy group, the most common AEs were fatigue, nausea, constipation, vomiting, and alopecia. AEs led to dose interruption in 22% and to dose reduction in 10% of patients.

Severe adverse events (SAEs) occurred at a similar rate in the trametinib (18%) and chemotherapy (20%) arms, with cellulitis (2%) being the most common in the trametinib arm, and pyrexia (4%) in the chemotherapy arm (treated with DTIC). One death occurred in the trametinib arm due to renal failure that may be related to trametinib.[4]

Limitations of the METRIC trial included the lack of blinding which may have resulted in observer bias for the progression-free survival outcome. The short follow-up period for overall survival likely limits the robustness of differences in median overall survival between groups. The small number of patients with V600K mutation may contribute to the lack of statistical significance in subgroup analyses. The confounding effect of the crossover of dacarbazine-treated patients to receive trametinib also influences the determination of the absolute outcome impact of trametinib.

2.1.4 Comparison with Other Literature

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

2.1.5 Summary of Supplemental Questions

Critical appraisal of an Indirect Comparison of Trametinib with Vemurafenib for Metastatic Melanoma

An adjusted indirect treatment comparison was performed between trametinib and vemurafenib that employed the Bucher method to assess efficacy. This analysis found that there was a greater likelihood of better PFS and OS rates with vemurafenib therapy than with trametinib therapy in patients with BRAF V600E mutation positive unresectable or metastatic melanoma. However, there was a greater likelihood of better OS rates with trametinib therapy than with vemurafenib therapy when longer follow-up data from the BRIM-3 trial was used. Conclusions drawn from such indirect comparisons are not as robust as those from direct, head-to-head trial data. In addition, the indirect comparison used trametinib data from the October 2011 data cut-off and did not incorporate data from the more recent May 2013 cut off, which demonstrated a potential waning of the trametinib effect over time.

Summary of BRAF Mutation Testing in Metastatic Melanoma

The cobas® 4800 BRAF V600 Mutation Test, developed by Roche Diagnostics Canada, has received regulatory approval The cobas® test is a fully automated in vitro diagnostic device intended for the qualitative detection of the BRAF V600E mutation in DNA extracted from formalin-fixed, paraffin-embedded human melanoma tissue; one 5-micron specimen is sufficient to conduct the analysis. The cobas® test is able to detect V600E mutations

with a higher sensitivity than the reference method of Sanger sequencing, but it is not as specific.[12-14] The test showed cross-reactivity with non-V600E mutants, predominantly V600E2 (≥65%), V600K (≥35%), and V600D (≥10%).

Canadian testing centres may utilize their own (non-commercial) validated BRAF tests. As a result, there is variability in mutation reporting, with some centres reporting specific mutations (V600E and/or V600K) and other not specifying the specific mutation.

See section 7.1 and 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, there is a critical need to provide more treatment options and alternatives to treat metastatic melanoma. While there are therapies approved for metastatic melanoma patients that have shown a positive impact on overall survival rates; however, it is reported that these drugs do not work effectively for all advanced stage patients. In addition, there have been reports of severe side effects with the existing therapies. When asked about potential side effects, respondents noted that they were willing to accept side effects and the serious risks associated with a future new drug if they knew those side effects can be effectively managed. With respect to trametinib, it was noted that the side effects were reported to be well tolerated more so than other current therapies. The respondents on trametinib also noted that their melanoma has been stabilized with no progression. Because metastatic melanoma has few treatment options, 71% of the respondents ranked the importance of quality of life while on treatment as either important or very important.

PAG Input

Input on trametinib (Mekinist) for metastatic melanoma was obtained from the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, trametinib has enablers that include being an oral therapy that can be easily delivered in the community setting and BRAF testing being in place in many jurisdictions. However, potential barriers include PAG's concerns with sequential therapy of trametinib, vemurafenib and other treatments and the lack of direct comparison trials of trametinib with other targeted therapies in the treatment of BRAF mutated metastatic melanoma.

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 had not changed and had remained within the

range of six to twelve months. It is a challenging cancer for both patients and oncologists, as until recently no effective treatment options existed.

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 the quality of life or overall survival. More recently vemurafenib, a selective BRAF inhibitor of melanoma with the activating mutation V600, was shown to improve overall survival and progression free survival when compared to single agent dacarbazine and was subsequently approved. 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. For those patients who are BRAF mutation negative the standard treatment at most academic centers has been to enroll patients into clinical trials of new agents. Ipilimumab, a CTLA-4 inhibitor, was also recently approved by Health Canada in a second line indication of unresectable melanoma. Ipilimumab improved overall survival when compared to a comparator gp100 vaccine. Still only about 20% of unresectable melanoma patients have long term survival and for those patients who do not have a V600 activating mutation and do not respond to ipilimumab the prognosis is poor. Thus, effective new treatments are needed for patients with metastatic melanoma.

Effectiveness and Safety of Trametinib

Trametinib is a small molecule inhibitor of MEK1 and MEK2. The METRIC study met its primary endpoint of an improvement in progression free survival. The median PFS in the intention-to treat population was 4.8 months and 1.5 months for trametinib and chemotherapy respectively (H.R. for progression 0.45; 95% C.I. 0.33 – 0.63; p<0.001), as assessed by site investigators. There was a slightly greater PFS when assessed by the independent review committee, and the results were similar in the primary efficacy population. A total of 195 patients (61%) had disease progression or had died at the time of the preliminary analysis. The 6 month overall survival in the intention-to-treat population was 81% for trametinib and 67% in the chemotherapy group (findings were identical in the primary efficacy population).The hazard ratio for death in the trametinib was 0.54 (95% C.I., 0.32 – 0.92 p=0.01), despite 51 of 108 patients in the chemotherapy group crossing over to receive trametinib. Based on a subsequent data cut in May 2013, after a median follow up of follow-up of 14.7 (trametinib) and 8.7 (chemotherapy) months, the median OS was 15.6 and 11.3 months for the trametinib and chemotherapy arms, respectively (HR = 0.78; 95% CI, 0.57 to 1.06; p=0.0912). Patients in the chemotherapy group were allowed to cross over to receive trametinib after disease progression had been confirmed by an independent review. The confounding effect of the crossover of dacarbazine-treated patients to receive trametinib also influences the determination of the absolute outcome impact of trametinib. The response rate for trametinib was 22% and 8% for the chemotherapy group as assessed by RECIST criteria in the intention-to-treat population, and the median duration of response was 5.5 months for trametinib (95% C.I., 4.1 -5.9) and had not been reached for the chemotherapy arm (9 patients).

Health-related quality of life (HRQOL) assessments were performed at baseline and throughout active therapy using EORTC QLQ-C30 and EQ-5D questionnaires. In general, at weeks 6 and 12 trametinib treatment was associated with smaller functional impairment, smaller declines in health status, and less symptoms exacerbation over the course of treatment as compared to chemotherapy. Trametinib was well tolerated with an acceptable safety profile. Adverse events occurred in at least 15% of the 310 patients evaluable for toxicity. The most common adverse events were rash, diarrhea, peripheral

edema, fatigue and dermatitis acneiform. A decreased ejection fraction occurred in 7 % of patients leading to permanent discontinuation of the drug. Ocular events occurred in 9% of patients (mostly Grade 1 or 2) in the trametinib group with blurred vision (4%) the most common; reversible chorioretinopathy (grade 3) occurred in 1 patient (<1%).

At the time that the study was undertaken BRAF inhibitors were not approved for clinical use; however, they were widely available through clinical trials. Although there are no randomized clinical trials comparing trametinib to a BRAF inhibitor, the pCODR review assessed an indirect comparison of trametinib and vemurafenib submitted by the manufacturer. The IDC demonstrated that there was a greater likelihood of better PFS and OS rates with vemurafenib therapy than with trametinib therapy in patients with BRAF V600E mutation positive unresectable or metastatic melanoma when data with shorter but similar follow-up time on trametinib and vemurafenib was used. However, there was a greater likelihood of better OS rates with trametinib therapy than with vemurafenib therapy when longer follow-up data from the BRIM-3 trial was used. Conclusions drawn from such indirect comparisons are not as robust as those from direct, head-to-head trial data, and therefore must be taken in context. Without a head-to-head trial, the relative effectiveness of these two drugs is uncertain, the mechanisms of action differ and results from the BRIM-3 and METRIC studies suggest there could be differences.

Trametinib could therefore be considered in patients who are unable to tolerate a BRAF inhibitor. Therefore the eligibility criteria for trametinib use should include patients with metastatic and /or unresectable melanoma whose tumours harbours the V600E or V600K mutation and have not received prior BRAF inhibitor therapy. Patients should have an ECOG performance of 0 or 1, if present, have stable brain metastases and have an adequate renal, hematologic and liver function.

As patients who received prior BRAF Inhibitor therapy were excluded from the this trial, there is no evidence to support the use of trametinib after progression on a BRAF Inhibitor, despite evidence that several pathways of resistance are upstream from MEK and lead to increased activation and phosphorylation of MEK. Similarly, only 9 patients with a history of brain metastases were on the trametinib arm and 2 in the chemotherapy arm. Therefore the true efficacy of trametinib in patients with brain metastases is not assessable.

Need

With the approval of vemurafenib and dabrafenib for the treatment of unresectable, BRAF V600 mutation positive tumors it is likely that the majority of patients will receive such therapy. For those patients in whom a BRAF inhibitor is not tolerated or contraindicated, trametinib would be an effective alternative to BRAF inhibitor therapy. There is no evidence to support the use of trametinib in patients who have demonstrated resistance to BRAF inhibitor therapy. Currently trials are ongoing comparing the combinations of a MEK inhibitor plus a BRAF inhibitor versus a BRAF inhibitor.

2.3 Conclusions

The pCODR Melanoma Clinical Guidance Panel concluded that there is a net overall clinical benefit to trametinib compared with chemotherapy, based on one randomized controlled trial, METRIC, which demonstrated an improvement in progression free survival with trametinib when compared

to dacarbazine or paclitaxel in patients who are BRAF treatment naive and have BRAF V600 (E and K) mutation positive unresectable melanoma.

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

- Trametinib has an acceptable tolerability profile with predictable and manageable toxicities.
- There are no randomized clinical trials comparing trametinib to the BRAF inhibitor, vemurafenib, and the results of an indirect comparison to vemurafenib were not as robust as those from direct, head-to-head trial data, and therefore must be taken in context.
- For those patients in whom a BRAF inhibitor is not tolerated or contraindicated, trametinib would be an effective alternative to BRAF inhibitor monotherapy.
- There is no evidence to support the use of a MEK Inhibitor after progression on a BRAF Inhibitor or in patients with brain metastasis
- Currently trials are ongoing comparing the combination of a MEK inhibitor plus a BRAF inhibitor versus a BRAF inhibitor, which could result in a broader role for MEK inhibitors, like trametinib, in clinical practice.

3 BACKGROUND CLINICAL INFORMATION

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

3.1 Description of the Condition

Melanoma is a malignancy of melanocytes which are distributed throughout the body including skin, eyes, and gastrointestinal tract. Although primary melanomas can occur in a variety of anatomical sites, the skin is the most common, comprising 95% of cases. In Canada, 5500 new cases of primary melanoma are expected in 2011 and approximately 950 patients will die from melanoma.[5] 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 AJCC 7th Edition Classification.[16] The tumour characteristics principally involve the Breslow height, mitotic rate and the presence or absence of ulceration in the primary. The detection of microscopic and macroscopic lymph node involvement, serum lactate dehydrogenase and the sites of metastatic disease are integral components to the staging classification. All of these factors have been shown to be important prognostic variables which influence patient outcomes and which help to guide management decisions.

3.2 Accepted Clinical Practice

In early stage melanoma, cures are commonly achieved with surgery alone. The primary tumour is excised with appropriate margins. Depending upon the Breslow height, mitotic rate, presence of ulceration and location of the primary, a sentinel node biopsy may be 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 up to 75% of patients with overt metastatic disease.[19] They often prove to be relatively refractory to radiotherapy and systemic treatment and are associated with a particularly dismal prognosis.

Highly selected patients with Stage IV disease may benefit from surgical resection of the metastases and 5 year survival in these patients ranges from 15 to 25%. For those patients who were not candidates for surgical resection systemic treatment with chemotherapy was most commonly offered. Unfortunately, the prognosis for these patients has remained poor. The median survival is six to nine months and the five-year survival is approximately 6%.[20] In spite of multiple phase II and III trials with systemic therapy, the objective response to systemic chemotherapy 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.[17,21] Although this intravenous alkylating agent is generally well tolerated, complete responses are rare.[11] In comparative studies, it has never been shown to improve survival in

metastatic melanoma.[6-10] Temozolomide, an oral imidazazole tetrazene derivative of DTIC which is activated to the active metabolite of dacarbazine (MTIC), has also been commonly used. However, in a phase III trials which compared temozolomide directly with dacarbazine, equivalent progression free and overall survival were observed, although the temozolomide tended to be better tolerated.[22-24] 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 complete response rate of 5%, extending beyond five years.[25,26] 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 until recent limited to no success. Patient outcomes have not changed significantly over the past three decades.[11] Nevertheless, what has become apparent is that melanoma represents a heterogeneous group of diseases which appear to have varying genetic abnormalities which drive cellular proliferation and metastases.[27-29] The MAP kinase signalling pathway appears to be a key regulatory mechanism for cell growth, and differentiation in melanoma.[30] 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.[31] 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.[32]

Vemurafenib is a BRAF inhibitor that selectively targets the mutated BRAF V600 and was approved in August 2011 by the FDA as a treatment of late stage or unresectable melanoma in patients harbouring a V600E mutation, and subsequently approved by Health Canada in February 2012.[33-35] Just fewer than 50% of all melanoma patients will harbour a V600 mutation, with the majority being V600E. In the randomized Phase III study (BRIM3) there was a relative reduction of 63% in the risk of death and a 74% relative reduction in the risk of tumor progression. The overall response rate was 48%.[36] This is now a standard first line treatment of advanced, unresectable melanoma in patients harbouring a V600 mutation.

Likewise the immune checkpoint inhibitor of CTLA-4, ipilimumab was approved by Health Canada in February 2012 in a second line indication in pre-treated patients with advanced melanoma.[37]

Dabrafenib is a BRAF inhibitor that selectively targets the mutated BRAF V600 and has been under clinical trials since 2009.[38-40] In 2012, a multicentre non-blinded phase III study of dabrafenib in comparison to dacarbazine in the first line treatment of 250 patients with unresectable or metastatic melanoma with a BRAF V600E mutation was reported. Patients were randomized 3 to 1 to receive either dabrafenib (187) or DTIC (63) respectively. Those patients who received DTIC could cross-over to receive dabrafenib at disease progression. The primary endpoint was Progression Free Survival as determined by the Investigator. The key inclusion criterion was the presence of V600 mutation. The use of dabrafenib is dependent upon the accuracy and availability of BRAF mutation testing of each prospective patient's primary or metastatic tumour (See Section 7.1). Dabrafenib was approved by Health Canada in July 2012 for unresectable stage III or Stage IV melanoma that harbours the BRAF V600E or V600K mutation.

3.3 Evidence-Based Considerations for a Funding Population

Trametinib is an orally available selective inhibitor of MEK1 and MEK2. In pre-clinical trials trametinib inhibited melanoma growth in tumours that harboured a V600E or V600K mutation when they were transplanted into mice. In phase I and Phase II trials trametinib led to regressions and stabilization of tumours in patients with metastatic melanoma with V600E or V600K mutation. The pivotal Phase III trial was an open label, randomized trial of trametinib (2 mg orally daily) versus Dacarbazine (1000 mg/kg q 3weeks) or paclitaxel (175 mg/m^2 q 3weekly) with a 2:1 randomization.[1] Patients in the chemotherapy arm who had progression could cross over and receive trametinib. The primary endpoint was Progression Free Survival (PFS), and secondary endpoints of overall survival, overall response rate, duration of response, and safety. Progression Free Survival was chosen as the primary endpoint as although vemurafenib and ipilimumab were not commercially available when this study was undertaken it was felt that access to these treatments could confound a survival benefit. The primary efficacy analysis was restricted to the patients who had the V600E mutation and no evidence of brain metastases, although since no significant differences were observed between the primary efficacy population and the intention-to-treat population, the data from the intention-to-treat population were presented. From December 2010 to July 2011 322 patients with unresectable Stage IIIC or IV melanoma with either a BRAF V600E or V600K mutation were enrolled from 103 centres worldwide. Patients could have received one prior chemotherapy regimen but could not have received a prior BRAF inhibitor or MEK inhibitor.

Patients were well balanced in demographics between the two arms with only slightly more patients with M1C disease in the trametinib arm. Of the 322 patients 273 (85%) were in the primary efficacy population.

Trametinib was well tolerated as assessed in the 310 patients who had received at least 1 dose of study drug. Adverse events were reported in at least 15% of patients in either group and the most common adverse events in the trametinib arm were rash, diarrhea, peripheral edema, fatigue, and dermatitis acneiform. Only 8% of patients with a rash had a Grade 3 or 4 rating. Decreased ejection fraction was seen in 14 patients (7%) in the trametinib group and 2 patients in the trametinib group had Grade 3 cardiac-related event. Ocular events occurred in 9% of the trametinib group with blurred vision in 4%, reversible chorioretinopathy in 1, and no cases of retinal vein occlusion. Trametinib can safely be administered to patients with metastatic melanoma.

Patients who received prior BRAF Inhibitor therapy were excluded from the this trial and therefore there is no evidence to support the use of a MEK Inhibitor after progression on a BRAF Inhibitor, despite evidence that several pathways of resistance are upstream from MEK and lead to increased activation and phosphorylation of MEK.

Only 9 patients with a history of brain metastases were on the trametinib arm and 2 in the chemotherapy arm. Therefore the true efficacy of trametinib in patients with brain metastases is not assessable.

Therefore the following eligibility criteria could be applied for Trametinib:

1. Metastatic and /or unresectable melanoma patients whose tumours harbours the V600E or V600K mutation and have not received prior BRAF inhibitor therapy.
2. ECOG performance of 0 or 1.
3. If present, stable brain metastases.
4. Adequate renal, hematologic and liver function

3.4 Other Patient Populations in Whom the Drug May Be Used

Trametinib may be potentially used in patients with high risk melanoma in an adjuvant setting. It could also be used after progression on BRAF inhibitor therapy either as a single agent, or in combination with a BRAF inhibitor albeit the evidence does not support this use.

Trametinib could also be used in combination with a BRAF inhibitor as initial therapy in patients whose tumours have a BRAF mutation. Phase II trials consistently show higher response rates and longer progression free survival. The results of Phase III trials comparing single agent BRAF inhibitors versus a MEK inhibitor and a BRAF Inhibitor are pending.

Trametinib could be considered in patients who are unable to tolerate a BRAF inhibitor.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

A patient advocacy group, Melanoma Network of Canada, provided input on trametinib (Mekinist) for use as a monotherapy for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600, and their input is summarized below.

The Melanoma Network of Canada conducted an anonymous online survey to gather information about the patient and caregiver experience with advanced melanoma and the therapies, in particular with trametinib. The survey was promoted through cancer centres in Canada that treat melanoma and on the Melanoma Network Canada website. 24 respondents responded to questions about their experience with advanced melanoma and their consideration about any future drug therapy; one respondent responded to questions regarding their direct experience with trametinib; and one respondent provided input from a caregiver experience.

From a patient perspective, there is a critical need to provide more treatment options and alternatives to treat metastatic melanoma. While there are therapies approved for metastatic melanoma patients that have shown a positive impact on overall survival rates; however, it is reported that these drugs do not work effectively for all advanced stage patients. In addition, there have been reports of severe side effects with the existing therapies. When asked about potential side effects, respondents noted that they were willing to accept side effects and the serious risks associated with a future new drug if they knew those side effects can be effectively managed. With respect to trametinib, it was noted that the side effects were reported to be well tolerated more so than other current therapies. The respondent on trametinib also noted that their melanoma has been stabilized with no progression. Because metastatic melanoma has few treatment options, 71% of the respondents ranked the importance of quality of life while on treatment as either important or very important.

Please see below for a summary of specific input received from the patient advocacy groups.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Metastatic Melanoma

Generally, patients with metastatic melanoma face the certainty of disease progression including worsening of symptoms such as increasing shortness of breath, severe pain, fatigue, memory loss, loss of coordination, cognitive impairment from brain metastases or radiation, loss of sight, lymphedema, weight loss and death without treatment.

Depending upon the site of metastases and type of treatment, many patients suffer from additional effects of treatment and of the current treatment therapies including headaches, neuropathy, bone fractures, blindness, hair loss, depression, anxiety, memory loss, decreased mobility, colitis, and disfiguring surgeries. Many patients have had extensive surgery to remove lymph nodes and/or tumours, which has caused decreased mobility, loss of functioning or capacity of certain organs, scarring and body image issues. Some of the comments from the respondents include:

- The limitations I have are my energy level has not returned to what it was and I have developed lymphedema in my leg, which requires regular lymphatic drainage therapy.
- The psychological impact is probably the greatest issue in that I have a wife and two young children. Knowing the severity and prognosis of Stage 4 metastatic melanoma continues to affect our lives and causes a lot of stress.

- Less outdoor activity due to sunlight exposure, less energy, listlessness, tired, lump in groin, compression stocking needed daily and they are expensive (financial hardship), less walking daily.
- I had tumours growing that made it impossible for me to have a life. I was in a lot of pain and was confined to my couch or bed. Each day without a medication that shrunk the tumours was painful and without hope.
- Fear and uncertainty for my life going forward is often debilitating and removes motivation.

From a patient perspective, while there are therapies approved for metastatic patients and have a positive impact on overall survival rates; however, these drugs simply do not work effectively for all advanced stage patients.

4.1.1 Patients' Experiences with Current Therapy for Metastatic Melanoma

Melanoma Network of Canada reported that the commonly product used as a first line therapy in stage III patients is Interferon. Respondents reported having severe and debilitating side effects including extreme nausea/flu-like symptoms, fatigue, decreased mood, decreased mobility, fever, chills, trembling, sore eyes, compromised liver function, foggy brain, hair loss, taste and weight loss. Some respondents reported that the side effects were so extreme that they had to discontinue their treatments and one reported that they refused treatment all together.

Other treatments that respondents reported that they are currently taking or had previously took in the past included: dacarbazine, radiation, vemurafenib, ipilimumab, interlukin, and naturopathic options. Some of the side effects of these treatments included photosensitivity, digestive issues, foot and joint pain, nausea, less energy, low hemoglobin and iron levels, and multiple rashes, loss of hair, cognitive impairment, depression, compromised liver function.

Respondents reported that they experienced serious and severe side effects with the therapies currently available. Despite the above, the survey results indicated that 70% of the respondents were willing to accept side effects and the serious risks associated with a future new drug if they knew those side effects can be effectively managed. Additionally, 68% of the respondents indicated that they would be willing to tolerate the potential side effects if they knew the results would extend their lives, and 60% indicated they would tolerate those side effects even if the benefits of the treatment were only short-term. 71% of the respondents ranked the importance of quality of life while on treatment as either important or very important on a 4-point scale.

Of the 24 patients that responded to the survey, 19% indicated that they experienced hardships in accessing drug treatments. Some respondents indicated that there was not enough information from their oncologists on trials available to them. Others indicated feeling fortunate because they were able to access clinical trials and therefore did not have to incur costs for these treatments. A respondent noted that only part of their treatment was covered and they still had to pay 10% of their treatment costs per month. Those respondents who have chosen alternative methods of treatment were required to cover 100% of the costs.

4.1.2 Impact of Metastatic Melanoma and Current Therapy on Caregivers

The Melanoma Network of Canada reported that the impact of advanced stage melanoma on caregivers is significant. It was noted that caregivers provide a key role by providing supportive care to the patient in managing adverse side effects, providing emotional support and financial support, and assuming additional unpaid work duties in the home. Moreover, a caregiver's paid work and community and social involvement are adversely affected by the physical requirements, time commitments, and emotional stress of caring for a patient.

The following are some comments from the respondents who participated in this part of the survey:

- My husband has been on the trial for the drug and it has saved his life and our family's life. We can't live without him - his kids need him and I do too. If he is doing well, we all are.

- We need two parents in this country to raise our family. We need to find a cure for this disastrous disease. It has just crushed us. We will survive, but I live in fear that my husband won't. Then what will we do. Please let us have a future.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Trametinib

The Melanoma Network of Canada reported that the expectations of new therapies, including trametinib, would be for a measureable and improved impact on overall survival rates and a positive impact on quality of life for patients and their families. Respondents indicated their expectation was to return to a reasonable quality of life following treatment. Respondents also indicated that they wanted to be around, even if for a shortened period of life, to be with their families.

The Melanoma Network of Canada stated that current therapies for melanoma, including chemotherapy, DTIC and radiation were ineffective for the metastatic patient, with less than a 10% response rate in most cases and very little impact on overall survival rates. Additionally, there are also reports of severe side effects with the existing therapies and that options are needed for melanoma patients. Other newer drug therapies have reported more success, but these results are limited to a small percentage of the metastatic patient population. As a result, there is a critical need to provide more treatment options and alternatives to improve on response rates.

The respondent who is currently using trametinib indicated that the side effects experienced on this drug were dry itchy skin, fatigue and headaches. They were effectively able to manage their side effects on this treatment, and indicated that the side effects from trametinib were much milder than other treatments they have experienced. The respondent did not report sustaining any ongoing side effects from trametinib. The respondent expects that they will continue to have a durable response even, if not sustained indefinitely. The respondent on trametinib also noted that their melanoma has been stabilized with no progression.

The Melanoma Network of Canada stated that there may be a possibility of using trametinib in combination with other therapies to improve overall response rates for survival. The patient advocacy group also indicated that trametinib has lower side effects than other current therapies, and has shown positive responses as a new type of therapy targeting the MEK pathway. As an example, a respondent reported thinking of returning to work while on the therapy. From a patient perspective, the risks associated with this drug are manageable and respondents have indicated that they are willing to accept that risk.

4.3 Additional Information

The Melanoma Network of Canada submits that physicians who are treating advanced cancer may not necessarily understand or have an awareness of the role of the patient advocacy groups in the new pCODR process and the requirements for patient groups when preparing a submission.

With this case in particular, the patient advocacy group was aware that there were 15 participants in a clinical trial across the country; however, the patient advocacy group was only able to locate one patient within the timeframe provided by this process. As such, this makes it difficult to provide a quality response from patients or patient organizations when there is little to no access to connect with those who have been on a clinical trial. If the process is to work more effectively, it is proposed that changes be made to improve the process for patient feedback. The Melanoma Network of Canada believes that the physicians need to feel less conflicted when connecting patient advocacy groups with their patients and assisting organizations to reach out to their patients.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

Input on trametinib (Mekinist) for metastatic melanoma was obtained from the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, trametinib has enablers that include being an oral therapy that can be easily delivered in the community setting and BRAF testing being in place in many jurisdictions. However, potential barriers include PAG's concerns with sequential therapy of trametinib, vemurafenib and other treatments and the lack of direct comparison trials of trametinib with other targeted therapies in the treatment of BRAF mutated metastatic melanoma.

Please see below for more details.

5.1 Factors Related to Comparators

PAG noted that the current standard in many jurisdictions is vemurafenib and direct comparative clinical data would be ideal to compare two oral drugs as monotherapy for BRAF V600 mutation positive metastatic melanoma. In jurisdictions that fund vemurafenib, it would be a potential barrier to implement if there are no head-to-head trials of trametinib with oral targeted therapies for metastatic melanoma.

5.2 Factors Related to Patient Population

PAG noted that metastatic melanoma is a relatively small patient population. PAG expressed concerns for indication creep into the adjuvant setting and for use after failure with vemurafenib therapy, both settings where the clinical benefits are unknown. PAG noted that there is no data demonstrating clinical activity in patients who have progressed on other BRAF inhibitors. PAG would like clarity on line of therapy and sequential therapy of the oral targeted therapies for metastatic melanoma.

5.3 Factors Related to Accessibility

PAG noted that trametinib is another oral drug for metastatic melanoma that can be delivered to patients more easily than intravenous therapy in both rural and urban settings. As such, PAG identified the oral route of administration as an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause

financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

5.4 Factors Related to Dosing

PAG indicated that the one tablet once daily dosing is an enabler and is a very convenient dosing schedule for patients, especially when compared to other oral targeted therapies, some of which require up to 4 tablets twice daily.

PAG noted that the dose of trametinib in the METRIC trial was 2mg once daily. However, there are three strengths of trametinib (0.5mg, 1mg, and 2mg) and PAG would like clarity on the potential for dose escalations or reductions, which may lead to wastage.

5.5 Factors Related to Implementation Costs

PAG noted that the BRAF V600 mutation testing is already in place in many jurisdictions and this is enabler to implementation.

An implementation barrier identified is the use of trametinib and other oral BRAF or MEK inhibitors in sequential therapy.

PAG also noted that additional resources may be required to monitor drug interactions, manage dose reductions, and treat adverse events associated with trametinib.

5.6 Other Factors

None identified.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of trametinib 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).

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

- Critical appraisal of manufacturer-submitted indirect comparison (trametinib vs vemurafenib)
- Summary of BRAF Mutation Testing in Metastatic Melanoma

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the Table 1 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> • Different BRAF V600 mutation types (V600E or V600K) • Patients with or without brain metastases	Trametinib 2 mg orally once daily	Chemotherapy (Dacarbazine, Paclitaxel, Temozolomide, Carboplatin) Immunotherapy (Interleukin-2) Vemurafenib Dabrafenib Best supportive care Placebo	• Overall survival • Progression-free survival • **QOL** Time to response Response rate (CR, PR) Duration of response • **AEs, SAEs** • 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 (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (2013, Issue 5) 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 trametinib (Mekinist).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but was not limited by publication year. The search is considered up to date as of September 5, 2013.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and 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.

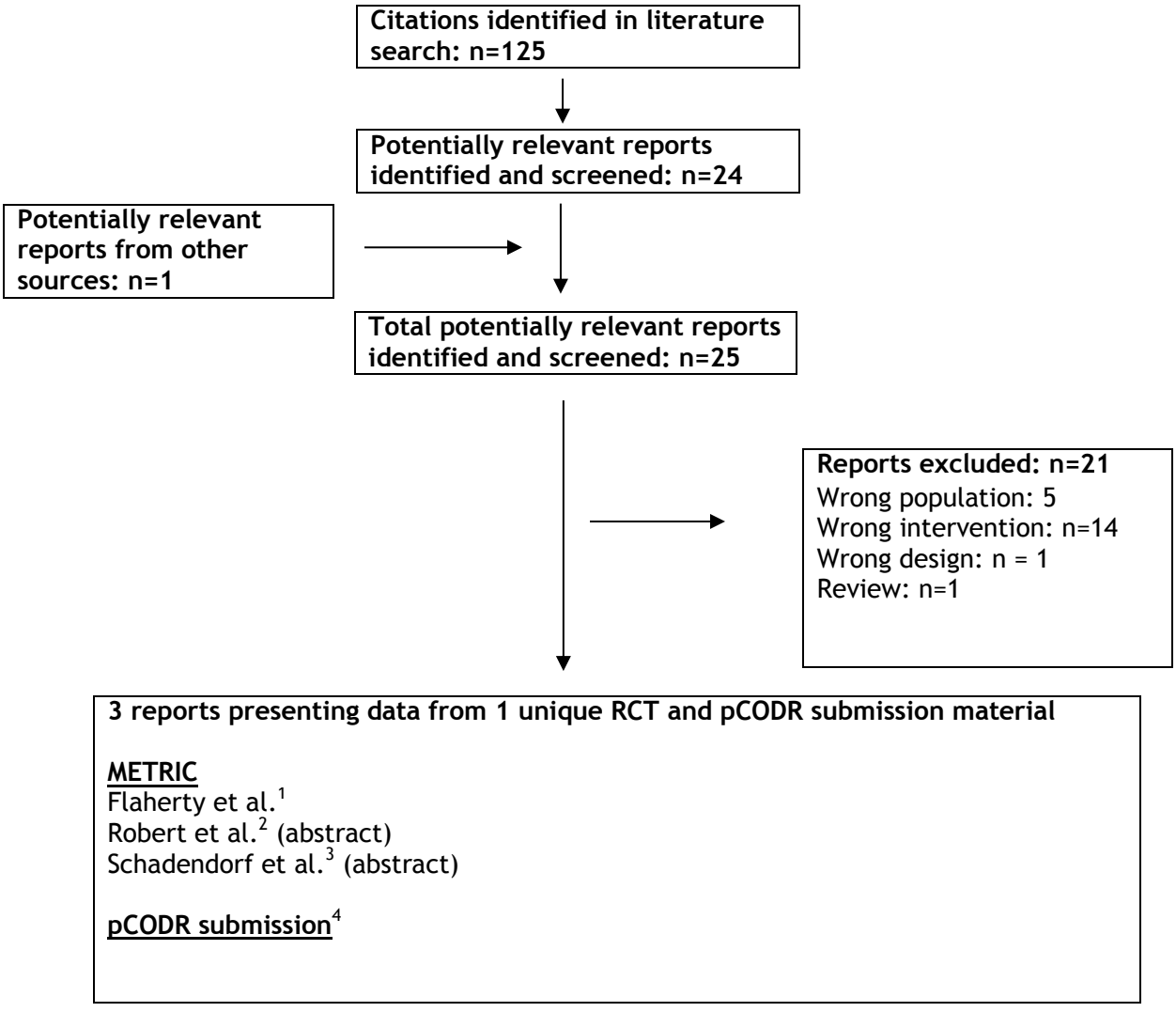
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 25 potentially relevant reports identified, 4 reports related to one study were included in the pCODR systematic review,[1-4] and 21 reports were excluded. Studies were excluded because they were the wrong intervention (combination therapy),[41-54], wrong population,[55-59] wrong design,[60] or a review article.[61]

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Summary of trial characteristics of the included study is in Table 2 below.

Table 2: Summary of Trial Characteristics of the Included Study

Trial Design	Inclusion Criteria	Intervention and Comparator	Outcomes
Flaherty (METRIC)1 103 centres in 19 countries December 2010 to July 2011 OL, AC, Phase III RCT Patients stratified for serum LDH level (normal or elevated) and chemotherapy (yes vs no) Randomized = 322 patients ITT: 322 patients Trametinib arm: 214 patients Chemotherapy arm: 108 patients (of which 51 patients for cross-over) Supported by GlaxoSmothKline	• Patients with unresectable or metastatic stage IIIC or IV melanoma, BRAF V600E or V600K mutation-positive, previously untreated, or treated with 1 prior chemotherapy regimen, with the exclusion of BRAF and MEK inhibitors and ipilimumab. • Age ≥18 years • Life expectancy >3 months • ECOG-PS ≤1 • Sufficient hematologic, hepatic, renal function • Patients with stable brain metastases allowed to enroll	Eligible patients were randomized 2:1 to receive trametinib 2 mg once daily or one of the following two chemotherapies at the discretion of the investigator (provided the patient had not received that type of chemotherapy before randomization): DTIC 1000mg/m^2 every 3 weeks (n = 62) or paclitaxel 175 mg/m^2 every 3 weeks (n = 37). • Patients in the chemotherapy group were allowed to cross over to receive trametinib after disease progression had been confirmed by an independent review. • Treatment for all patients continued until disease progression, death, or withdrawal.	<u>Primary</u> PFS (progression-free survival) in patients with BRAF V600E mutation, and no prior brain metastases (primary efficacy population) <u>Secondary</u> • PFS in ITT and subpopulations • OS (overall survival) in Primary and ITT • QOL • ORR (overall response rate) in Primary and subpopulations • Duration of overall response • AE

AC = active treatment control; **AE** = adverse event; **ECOG-PS** = Eastern Cooperation Oncology Group performance status; **ITT** = intention-to-treat; **LDH** = lactate dehydrogenase; **OL** = open-label; **QOL**: quality of life; **RCT** = randomized controlled trial

a) Trials

One randomized, open-label, active treatment controlled trial (METRIC) met the inclusion criteria for this review (Table 2). This was a two-arm, open-label, randomized Phase III pivotal study comparing oral trametinib with intravenous DTIC or paclitaxel (Figure 2). Patients with histologically confirmed advanced (unresectable Stage IIIC) or metastatic (Stage IV) melanoma were screened for eligibility. Screening included testing for the BRAF V600E/K mutation performed by a central laboratory. Patients were required to be treatment naïve for metastatic disease or have been on one previous chemotherapy regimen for advanced or metastatic melanoma in order to participate.

The main purpose of METRIC was to evaluate whether trametinib was superior to chemotherapy in patients with advanced (unresectable Stage IIIC) or metastatic (Stage IV) BRAF V600E positive melanoma without a history of prior brain metastases. The safety and tolerability of trametinib as a first-line and second-line (after chemotherapy) compared with chemotherapy in patients with BRAF-V600E/K mutation positive advanced or metastatic melanoma was also evaluated.

The primary efficacy endpoint was PFS defined as the time from randomization until the earliest date of disease progression documented by the investigator per RECIST v1.1 or death due to any cause. The primary efficacy analysis was restricted to the patients with the V600E BRAF mutation who did not have brain metastases at baseline (Primary Efficacy Population). The Primary Efficacy Population was based on data from the Phase II study (MEK113583) of trametinib, which showed that the median PFS was longer in the group of patients with the V600E BRAF mutation who did not have brain metastases at enrolment than in the overall study population (5.3 months vs. 4.0 months.

The secondary endpoints were:
Progression-free survival in the ITT population, in the Primary Efficacy Population with and without prior chemotherapy; by BRAF mutation status (V600E and V600K). Overall survival in the Primary Efficacy and ITT Populations, and in the Primary Efficacy Population with and without prior chemotherapy; by BRAF mutation status (V600E and V600K).
Quality of life
Overall response rate in the Primary Efficacy and ITT Populations, and in the Primary Efficacy Population with and without prior chemotherapy; by BRAF mutation status (V600E and V600K).
Duration of response in the Primary Efficacy and ITT Populations, and in the Primary Efficacy Population with and without prior chemotherapy; by BRAF mutation status (V600E and V600K).
Crossover population: PFS, ORR, and duration of response.

The study was designed with a power of at least 99% at a one-sided alpha level of 0.025 to detect a relative improvement of 133% in PFS. The Kaplan-Meier method was used to estimate rates of PFS and OS, and a stratified log-ranked test was used for all comparisons except for subgroup analyses, which were not stratified. The reported results are based on interim analyses with data from February 2012.

b) Populations

A total of 322 patients were centrally randomized 2:1 at 86 centers in 19 countries Treatment groups were well balanced for age, sex, race and disease status.

Patients who had histologically confirmed, unresectable stage IIIC or IV cutaneous melanoma with a V600E or V600K BRAF mutation were eligible for the study (87% of all

patients had V600E mutations, and 13% had V600K mutations). Mutational status was determined with the use of an allele-specific, investigational polymerase-chain-reaction (PCR) assay performed at Response Genetics. Additional eligibility criteria were an age of at least 18 years, measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (fully active) or 1 (ambulatory but restricted in physically strenuous activity),15 and adequate organ function. Patients could have received one previous chemotherapy regimen for advanced or metastatic melanoma, with the exclusion of BRAF and MEK inhibitors and ipilimumab. Patients with stable brain metastases were allowed to enroll. Patients with a history of clinically significant cardiovascular or interstitial lung disease and those with evidence or a risk of retinal-vein occlusion or central serous retinopathy were excluded. The Intent to Treat (ITT) population (N=322) included all randomized patients with advanced or metastatic BRAF V600E and V600K mutation positive melanoma with or without a prior history of brain metastases. A subset of the ITT population, the Primary Efficacy Population (N=273), included patients with advanced or metastatic BRAF V600E mutation positive melanoma without a prior history of brain metastases.
There was no substantial imbalance between treatment groups with respect to demographic or disease characteristics. 4% of the trametinib group had a history of brain metastasis compared to 2% in the chemotherapy group. 33% of the trametinib group had previous chemotherapy compared to 35% in the chemotherapy group. In the chemotherapy group, 62 patients received DTIC, and 37 patients received paclitaxel. All patients provided written informed consent at screening.

c) Interventions

Eligible patients were randomized 2:1 to receive trametinib 2 mg once daily or one of the following two chemotherapies at the discretion of the investigator (provided the patient had not received that type of chemotherapy before randomization): DTIC 1000mg/m2 every 3 weeks (n = 62) or paclitaxel 175 mg/m2 every 3 weeks (n = 37).

Patients in the chemotherapy group were allowed to cross over to receive trametinib after disease progression had been confirmed by an independent review. Treatment for all patients continued until disease progression, death, or withdrawal.

Data cut-off was 11 months after initiation of treatment. A total of 169 (79%) patients in the trametinib group and 65 (60%) in the chemotherapy group were still ongoing in the study (either continuing to receive randomized study treatment, being observed in follow-up, or receiving treatment in the crossover group). However, 51 (47%) patients randomized to chemotherapy had crossed over to receive trametinib.

d) Patient Disposition

Patient disposition is presented in Table 3 below:

Table 3: Number of Patients

	Trametinib	**DTIC or paclitaxel**
Screened	1059	
Randomized	214	108
Received drugs	211 (99%)*	99 (92%) (62 for DTIC; 37 for paclitaxel)
Did not receive drug	3 (1%)	9 (8%)

Table 3: Number of Patients		
(withdrew consent, brain metastasis, too ill or death)		
Intention-to-treat analysis	214	108 (51 patients crossed over to receive trametinib following disease progression)
Efficacy analysis	178 (83%)	95 (88%)
Safety analysis	211 (99%)	99 (92%)
Discontinued treatment • Lost to follow-up • Investigator discretion • Withdrew consent	10 (5%) 2 2 6	14 (13%) 1 3 10

The % were calculated by the Methods Team

e) Limitations/Sources of Bias

- In METRIC, lack of blinding of investigators may have resulted in observer bias for the progression-free survival outcome, even though a blinded, independent central review of tumor assessment was performed.
- The short follow-up time for overall survival may lead to not robust estimates of median overall survival and differences in medians between treatment groups.
- Permission of patients in the chemotherapy group to crossover to receive trametinib after disease progression had been confirmed by an independent review is a potential confounding factor affecting overall survival data.
- The small number of patients in the V600K subgroup may contribute to the statistical insignificance of the findings.
- The generalizability of the findings is restricted to a small subset of patients. More sub analyses comparing patients with and without prior brain metastases are needed.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

EFFICACY OUTCOMES

In patients with BRAF mutation positive melanoma, in general, compared to chemotherapy, trametinib significantly improved the chance of progression-free survival (the benefit was statistically significant in the V600E population, but not in the V600K population). Trametinib significantly reduced the risk of overall death and improved the overall response rate compared to chemotherapy.

Key efficacy outcomes of METRIC based on data analyses from February 2012 are summarized in Table 4.

Table 4: Summary of key investigator-assessed efficacy outcomes from the METRIC trial based on 11-month data cut-off (October 2011)[1,2]		
Endpoint	**Trametinib**	**Chemotherapy**[a]
PRIMARY EFFICACY POPULATION (patients with the V600E BRAF mutation who did not have brain metastases at baseline)		
Progression-free Survival	**(N = 178)**	**(N = 95)**

Table 4: Summary of key investigator-assessed efficacy outcomes from the METRIC trial based on 11-month data cut-off (October 2011)[1,2]		
Endpoint	**Trametinib**	**Chemotherapy[a]**
Median PFS (months) (95% CI)	4.8 (3.5, 4.9)	1.4 (1.4, 2.7)
Hazard Ratio (95% CI) *P* value	0.44 (0.31, 0.64) <0.0001	
Overall Survival[b] Hazard Ratio (95% CI) *P* value	0.53 (0.30, 0.94) <0.0181	
ITT POPULATION		
Progression-free Survival	**(N = 214)**	**(N = 108)**
Median PFS (months) (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
Hazard Ratio (95% CI) *P* value	0.45 (0.33, 0.63) <0.0001	
Overall Survival[b]		
Died, n (%)	35 (16)	29 (27)
Hazard Ratio (95% CI) *P* value	0.54 (0.32, 0.92) 0.0136	
Survival at 6 months (%) (95% CI)	81 (73, 86)	67 (55, 77)
Overall Response ORR (CR+PR), (%) (95% CI) CR PR	 22 (17, 28) 4 (2) 43 (20)	 8 (4, 15) 0 9 (8)
Duration of Response Median, months (95% CI)	**(N = 47)** 5.5 (4.1, 5.9)	**(N = 9)** Data not reached ?

ITT = Intent to treat; PFS = Progression-free survival; CI = Confidence interval; CR = Complete response; PR = Partial response; [a] Chemotherapy included patients on dacarbazine (DTIC) 1000 mg/m$_2$ every 3 weeks or paclitaxel 175 mg/m$_2$ every 3 weeks.
[b] OS results are confounded by the 51 (47%) patients that crossed over to receive trametinib.

Overall survival (OS)

OS was defined as the time from randomization until death from any cause. At the time of the first data cut-off (11 months after treatment initiation), in the primary population, the HR for OS in the trametinib arm was 0.53 (95% CI, 0.30, 0.94; p=0.0181), representing a 47% reduction in the risk of death for patients treated with trametinib compared to those

treated with chemotherapy. In the ITT population, at cut-off time, 16% (35/214) of patients in the trametinib group died, while 27% (29/108) died in the chemotherapy group. The HR for OS in the trametinib group was 0.54 (95% CI, 0.32 to 0.92; p=0.01), representing a 46% reduction in the risk of death for patients treated with trametinib compared to those treated with chemotherapy. An updated overall survival analysis was performed on data cutoff of May 20, 2013. As of this date, 73% of the ITT patients had died or were lost to follow-up and 65% of patients on chemotherapy crossed over to trametinib. With a median follow-up of 14.7 months for the trametinib arm and 8.7 months for the chemotherapy arm, the median OS was 15.6 months in the trametinib arm compared to 11.3 months in the chemotherapy arm (HR = 0.78; 95% CI, 0.57 to 1.06; p=0.0912). This represents a 22% reduction in the risk of death for patients treated with trametinib compared to chemotherapy.

Subgroup analyses based on mutation status showed that, for the ITT population, patients with V600E mutation had a statistically significant reduction of 48% in risk of death ((HR 0.52 (95% CI, 0.3 to 0.93)), while risk reduction in patients with V600K mutation was not statistically significant ((HR 0.70 (95% CI, 0.16 to 3.04)). For the subset of patients with V600E mutation, no prior brain metastases and no prior treatment, the HR was 0.55 (95% CI, 0.26 to 1.13); for patients with V600E mutation, no prior brain metastases and with prior treatment, the HR was 0.53 (95% CI, 0.21 to 1.31).

Progression-free survival (PFS)

In the primary efficacy population (patients who did not have brain metastases at baseline), trametinib reduced the risk of tumor progression or death by 56% (PFS HR 0.44 (95% CI: 0.31, 0.64; p<0.0001)) compared to chemotherapy in patients with BRAF V600 mutation positive advanced or metastatic melanoma (median PFS was 4.8 months in the trametinib arm and 1.4 months in the chemotherapy arm). In the ITT population the median PFS by investigator assessment was 4.8 months in the trametinib arm and 1.5 months in the chemotherapy arm (HR = 0.45 [95% CI: 0.33,0.63]; p<0.0001), representing a 55% reduction in the risk of tumor progression in trametinib arm compared to chemotherapy. There was no subgroup analysis between patients with and without brain metastases, but the findings above showed similar reduction in risk of tumour progression or death between patients who did not have brain metastases (primary efficacy population) and all patients combined (ITT population).

Subgroup analyses based on mutation status showed that, for the ITT population, patients with V600E mutation had a statistically significant reduction of 53% in risk of death ((HR 0.47 (95% CI, 0.33 to 0.67)), while risk reduction in patients with V600K mutation was not statistically significant ((HR 0.50 (95% CI, 0.18 to 1.35)). For the subset of patients with V600E mutation, no prior brain metastases and no prior treatment, the HR was 0.44 (95% CI, 0.28 to 0.69); for patients with V600E mutation, no prior brain metastases and with prior treatment, the HR was 0.52 (95% CI, 0.29 to 0.93).

Quality of life[3]

Health-related quality of life (HRQOL) assessments were performed at baseline and throughout active therapy at weeks 6, 12, 21, and 30, and at every 12 weeks (± 7 days) until determination of progressive disease, and then at progression of disease (PD) visit and 6 weeks following disease. Patients in both treatment groups had similar HRQOL assessment levels at baseline according to EPRTC QLQ-C30 and EQ-5D questionnaires. In general, trametinib treatment was associated with smaller functional impairment, smaller

declines in health status, and less symptoms exacerbation over the course of treatment as compared to chemotherapy.

At weeks 6 and 12, global health status scores decreased by 4-5 points from baseline for the patients with chemotherapy while increased by 2-3 points for the trametinib-treated patients. Substantive reductions in QOL functionality and worsening of symptoms such as fatigue were observed in the chemotherapy group at weeks 6 and 12, and small reductions or light improvements were seen in the trametinib group at week 12. Statistical significance was not assessed.

For patients who experienced disease progression, trametinib was associated with improvement in scores for pain, insomnia, appetite loss and constipation, while chemotherapy was associated with no change or minimal to modest worsening of symptoms.

Overall response rate (ORR)

For the ITT population, trametinib showed a statistically significant improvement in ORR (ORR was 22% (or 47 patients) in the trametinib arm (95% CI: 17, 28) vs. 8% (or 9 patients) in the chemotherapy arm (95% CI: 4, 15); p=0.01)).

Duration of response

The median duration of response for the 47 patients in the trametinib group was 5.5 months (95% CI: 4.1, 5.9) and was not reached for the 9 patients in the chemotherapy group.

There was no data on subgroup analyses based on status of mutation, or on brain metastases.

SAFETY OUTCOMES

Adverse events (AEs) were assessed in a population of 310 patients who received at least one dose of the study drug (211 in the trametinib group and 99 in the chemotherapy group). In general, the majority of AEs in the trametinib group was mild to moderate in severity, was skin-related and in the chemotherapy group was cytotoxicity-related. AEs occurred in a greater proportion of patients in the trametinib group than in the chemotherapy group, except fatigue. A higher proportion of patients in the trametinib group experienced AEs that led to dose interruption or dose reduction than in the chemotherapy group even though the proportion of patients reporting permanent discontinuation of study drug due to AEs was similar between the treatment arms (9% patients in the trametinib arm, 9% patients in the chemotherapy arm).[4] A list of most common AEs (occurring in ≥15% of patients) was listed in Table 5.

In the trametinib group, the most common AEs were rash, diarrhea, peripheral edema, fatigue, hypertension and dermatitis acneiform. A decreased ejection fraction occurred in 14 patients (7%) and serious grade 3 cardiac events occurred in 2 patients (0.01%). Ocular events occurred in 19 patients (9%). AEs led to dose interruption in 35% and to dose reductions in 27% of patients.

In the chemotherapy group, the most common AEs were fatigue, nausea, constipation, vomiting, and alopecia. AEs led to dose interruption in 22% and to dose reduction in 10% of patients.

Serious adverse events (SAEs) occurred at a similar rate in the trametinib (18%) and chemotherapy (20%) arms, with cellulitis (2%) being the most common in the trametinib arm, and pyrexia (4%) in the chemotherapy arm (treated with DTIC). At the time of data cut-off, 16% of patients died in the trametinib arm, and 13% died in the chemotherapy arm, with the majority attributed to disease progression. One death occurred in the trametinib arm due to renal failure that may be related to trametinib.[4]

Table 5: Summary of key safety outcomes from the METRIC trial[1]

Adverse events	**Trametinib** (N = 211) Number (%)	**Chemotherapy** (N = 99) Number (%)
Rash	121 (57)	10 (10)
Grade 2	40 (19)	3(3)
Grade 3 or 4	16 (8)	0
Diarrhea	91 (43)	16 (16)
Grade 2	13 (6)	3 (3)
Grade 3 or 4	0	2 (2)
Fatigue	54 (26)	27 (27)
Grade 2	11 (5)	7 (7)
Grade 3	8 (4)	3 (3)
Peripheral edema	54 (26)	3 (3)
Grade 2	8 (4)	0
Grade 3	2 (1)	0
Acneiform dermatitis	40 (19)	1 (1)
Grade 2	20 (9)	0
Grade 3	2 (1)	0
Nausea	38 (18)	37 (37)
Grade 2	5 (2)	10 (10)
Grade 3	2 (1)	1 (1)
Alopecia	36 (17)	19 (19)
Grade 2	3 (1)	8 (8)
Grade 3	1 (<1)	0
Hypertension	32 (15)	7 (7)
Grade 2	6 (3)	3 (3)
Grade 3	26 (12)	3 (3)
Constipation	30 (14)	23 (23)

Table 5: Summary of key safety outcomes from the METRIC trial[1]		
Adverse events	**Trametinib** (N = 211) Number (%)	**Chemotherapy** (N = 99) Number (%)
Grade 2 Grade 3	3 (1) 0	5 (5) 1 (1)
Vomiting Grade 2 Grade 3	27 (13)3 (1) 2 (1)	19 (19) 4 (4) 2 (2)

6.4 Ongoing Trials

No ongoing trials evaluating trametinib monotherapy were identified. However, the pCODR Clinical Guidance Panel indicated that trametinib may be used in combination with a BRAF inhibitor and the following ongoing trial was identified:

A two-arm, double-blinded, randomized, Phase III study compared dabrafenib (GSK2118436) and trametinib (GSK1120212) combination therapy to dabrafenib + placebo (dabrafenib monotherapy). Subjects with histologically confirmed cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV, and BRAF V600E/K mutation positive will be screened for eligibility. Subjects who have had prior systemic anti-cancer treatment in the advanced or metastatic setting will not be eligible although prior systemic treatment in the adjuvant setting will be allowed. Approximately 340 subjects will be randomized 1:1 (combination therapy: dabrafenib monotherapy). Subjects will be stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus less than or equal to the ULN) and BRAF mutation (V600E versus V600K). The primary endpoint is investigator-assessed, progression-free survival (up to 13 months) for subjects receiving the combination therapy compared with those receiving dabrafenib monotherapy. Secondary outcome measures are overall survival (up to 3 years), overall response rate (up to 13 months), and duration of response (up to 13 months); crossover will not be permitted.

7 SUPPLEMENTAL QUESTIONS

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

- Critical Appraisal of an Indirect Comparison of Trametinib with Vemurafenib for Metastatic Melanoma
- Summary of BRAF mutation testing in metastatic melanoma

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

7.1 Critical Appraisal of an Indirect Comparison of Trametinib with Vemurafenib for Metastatic Melanoma

7.1.1 Objective

The manufacturer conducted an adjusted indirect treatment comparison (ITC) of trametinib versus other first-line therapies for metastatic melanoma to evaluate the efficacy and safety of these interventions. The cost-effectiveness of trametinib was compared with chemotherapy and vemurafenib for the treatment of BRAF V600E mutation positive patients with unresectable or metastatic melanoma. ITC data was used for the comparison between trametinib and vemurafenib as there have been no trials designed to directly compare these treatments. This section of this report provides a summary and critical appraisal of the methods and findings of this ITC, with particular focus on the comparison between trametinib and vemurafenib.

7.1.2 Findings

A network diagram of studies used for the ITC is shown in Figure 1. Randomized controlled trials (RCTs) of therapies in patients with advanced/metastatic melanoma who were previously untreated with ipilimumab, DTIC, vemurafenib, fotemustine, and temozolomide were included.

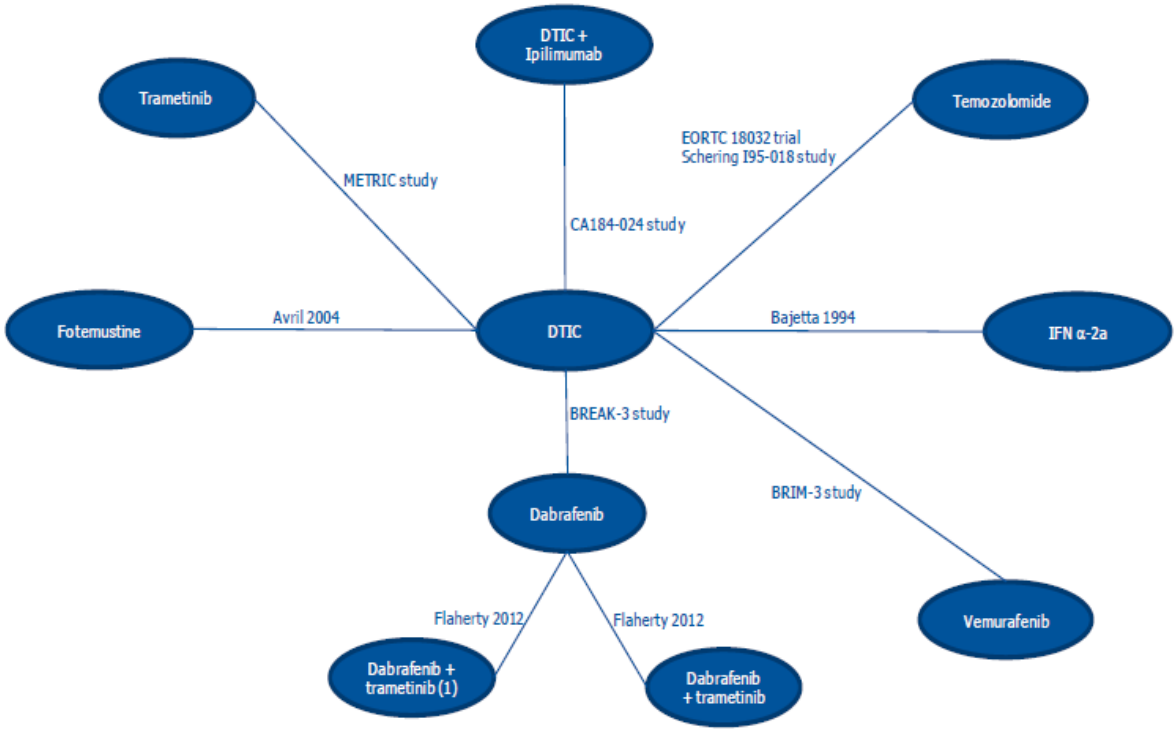


Figure 1. Network diagram of studies used in the ITC.

Adjusted ITCs for PFS and OS for vemurafenib versus trametinib were performed using data from the BRIM-3 and METRIC trials through the common comparator, DTIC (Table 1).[1,36] In both METRIC and BRIM-3 trials, patients with unresectable, stage IIIC or stage IV BRAF V600 mutation positive melanoma were enrolled. The BRIM-3 trial included only previously untreated patients, while the METRIC trial included patients who had received up to one prior chemotherapy regimen. The chemotherapy group in the METRIC trial was administered either DTIC or paclitaxel, while in the BRIM-3 trial, the chemotherapy group was administered DTIC only. The median follow-up time for the METRIC trial was 4.9 months, while that of the BRIM-3 trial was 11.1 months.

Table 1. Summary of studies used for indirect comparison of trametinib and vemurafenib.

Trial, Publication	Study design	Patient population	Intervention and Comparator	Outcomes
METRIC Flaherty et al. (2012)[1]	Multinational, multicenter, open-label RCT Median follow-up: 4.9 months (Oct 2011)	322 patients with unresectable stage IIIC or stage IV BRAF V600E/K mutation positive melanoma who have received no prior chemotherapy or up to one prior regimen of chemotherapy - 176 patients with no brain metastasis and no previous treatment	Trametinib 2 mg once-daily, orally (n=214) Chemotherapy (n=108) - DTIC 1000 mg/m^2, IV infusion every 3 weeks - Paclitaxel 175 mg/m^2, IV infusion every 3 weeks *crossovers were	Primary: PFS in primary efficacy population (V600E BRAF mutations with no brain metastases) Secondary: PFS, OS, ORR, safety

Trial, Publication	Study design	Patient population	Intervention and Comparator	Outcomes
			permitted upon disease progression	
BRIM-3 Chapman et al. (2011)[36]	Multinational, multicenter, open-label RCT Median follow-up: 3.1 months (Dec 2010) or 11.1 months (Feb 2012)	675 patients with unresectable, previously untreated stage IIIC or stage IV V600E mutation positive melanoma	Vemurafenib 960 mg twice-daily, orally (n=337) DTIC 1000 mg/m^2, IV infusion every 3 weeks (n=338) *crossovers permitted only after review of interim analysis	Co-primary: OS, PFS Secondary: response rate, duration of response, time to response, safety
IV = intravenous; ORR = OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial				

The Bucher method was used to perform ITCs, which is an adjusted indirect comparison approach using aggregate data. The effect measure comparing two treatments within an RCT is used rather than the individual results for each treatment group in order to partially maintain the strength of randomization. One assumption of this model is that the relative efficacy of a treatment is similar in all trials included in the indirect comparison.

The reported hazard ratios (HRs) for trametinib versus chemotherapy from the first-line subgroup of the primary efficacy population of METRIC (patients with V600E mutations and no brain metastasis at baseline) and for vemurafenib versus DTIC from BRIM-3 (Feb 2012 data cut-off, unrestricted analysis; Dec 2010 data cut-off, restricted analysis) were used in the ITC analysis for PFS. The HR for OS of vemurafenib versus DTIC based on the Feb 2012 BRIM-3 trial data was adjusted using the rank preserving structural failure time model (RPSFTM) to control for crossover from DTIC to vemurafenib upon disease progression (unrestricted analysis). The HR for OS of vemurafenib versus DTIC was also calculated for a median follow-up of 4.9 months using RPSFTM adjusted curves from the Feb 2012 data cut-off (restricted analysis) to match the follow-up duration of the METRIC trial. In addition, the HR for OS of vemurafenib versus DTIC in the restricted analysis was calculated using pseudo individual patient data.

A summary of results of the ITC between trametinib and vemurafenib for progression-free survival (PFS) and overall survival (OS) in patients with V600E mutation positive unresectable or metastatic melanoma is presented in Table 2. According to these results, HRs for PFS and OS in patients with V600E mutation positive unresectable or metastatic melanoma favoured vemurafenib in the restricted analyses. The HR for OS favoured trametinib when the February 2012 adjusted BRIM-3 trial data was used (unrestricted analysis)

Table 2. Summary of trial data and ITC results for PFS and OS for vemurafenib versus trametinib

PFS		
Treatment	**Hazard Ratio**	**95% CI**
Trametinib vs. Chemotherapy (METRIC-3 October 2011 data)	0.44	0.28-0.69
Vemurafenib vs. DTIC (BRIM-3 Feb 2012 data; unrestricted)	0.38	0.32-0.46
Vemurafenib vs. DTIC (BRIM-3 Dec 2010 data; restricted)	0.26	0.20-0.33
Vemurafenib (unrestricted) vs. Trametinib	**0.86**	**0.53-1.40**
Vemurafenib (restricted) vs. Trametinib	**0.59**	**0.35-0.99**

OS		
Treatment	**Hazard Ratio**	**95% CI**
Trametinib vs. Chemotherapy (METRIC-3 October 2011 data)	0.54	0.27-1.07
Vemurafenib vs. DTIC (BRIM-3 Feb 2012 data, RPSFTM; unrestricted)	0.64	0.47-0.88
Vemurafenib vs. DTIC (BRIM-3 Dec 2012 data, RPSFTM curves at 4.9 month follow-up, IPD; restricted)	0.46	0.36-0.60
Vemurafenib (unrestricted) vs. Trametinib	**1.19**	**0.56-2.53**
Vemurafenib (restricted) vs. Trametinib	**0.86**	**0.59-1.24**
DTIC = dacarbazine; IPD = individual patient data; RPSFTM = rank preserving structural failure time model		

Limitations

In the METRIC trial, patients receiving chemotherapy were permitted to crossover to receive trametinib upon confirmed disease progression. This may have confounded OS data and resulted in a more conservative estimate of the benefit of trametinib on OS.

In the METRIC trial, patients in the chemotherapy group received either DTIC or paclitaxel, while in the BRIM-3 trial, patients in the chemotherapy group received only DTIC. The assumption had to be made that patients receiving paclitaxel in METRIC were similar to patients receiving DTIC in both trials.

The number of patients in the METRIC trial that were treatment-naïve were relatively small (n=176), which resulted in larger confidence intervals. In addition, the duration of follow-up for the METRIC trial (mean 4.9 months) was shorter than that in the BRIM-3 trial (mean 11.1 months). In the BRIM-3 trial, crossovers were recommended after a review of the interim analysis by an independent data monitoring committee (January 14, 2011). Over time, crossovers from DTIC to vemurafenib in the control group may diminish the effect of vemurafenib on OS. For this reason, the manufacturers conducted separate analyses using two different follow-up times from the BRIM-3 trial. The two analyses produced different HRs for PFS and OS.

There are limitations in the use of the RPSFTM adjusted curves and individual patient data to extrapolate data from the BRIM-3 trial to match the follow-up duration of the METRIC to calculate HRs for OS in the restricted analysis. There was no data from BRIM-3 at the same follow-up duration as METRIC, so results from this analysis must be interpreted with caution.

The quality of the manufacturer-submitted indirect analyses was assessed according to the recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[62] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 3.

Table 3. Appraisal of the indirect comparison analyses using ISPOR criteria[62]

ISPOR Checklist Item	Details and Comments
1. Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting an indirect comparison analysis and the study objectives were clearly stated.
2. Does the methods section include the following? • Eligibility criteria • Information sources	• The eligibility criteria for studies were clearly stated: first-line treatment for patients with advanced or metastatic melanoma who were previously untreated with ipilimumab, DTIC, vemurafenib, fotemustine, and temozolomide.

ISPOR Checklist Item	Details and Comments
• Search strategy • Study selection process • Data extraction • Validity of individual studies	• No details were reported on information sources, search strategies, study selection processes, data extraction, and validity of individual studies.
3. Are the outcome measures described?	• Outcomes assessed in the indirect comparison analysis (overall survival, OS; progression-free survival, PFS) were clearly stated. • Justification of the outcome measures analyzed in the indirect comparison was not provided.
4. Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• The Bucher method was used for the indirect comparisons between trametinib and vemurafenib. • Survival data were analyzed by using the hazard ratio and its standard error. • Description and justification of using the Bucher method was not provided.
5. Are sensitivity analyses presented?	• No sensitivity analyses were reported.
6. Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• A summary of patient characteristics of studies used for the indirect comparison was provided. Detailed information included the proportion of previously untreated patients without brain metastases in the METRIC trial. • Forest plots were provided. • Two separate analyses were performed using different follow-up data in the BRIM-3 trial to account for varying lengths in follow-up times.
7. Does the study describe an assessment of model fit? Are competing models being compared?	• Neither assessment of model fit nor comparison of competing models was reported.
8. Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for PFS and OS including point estimates and 95% confidence intervals as a measure of uncertainty.
9. Sensitivity/scenario analyses	• No sensitivity analysis was reported.

7.1.3 Summary

An adjusted indirect treatment comparison was performed between trametinib and vemurafenib that employed the Bucher method to assess efficacy. This analysis found that there was a greater likelihood of better PFS and OS rates with vemurafenib therapy than with trametinib therapy in patients with BRAF V600E mutation positive unresectable or metastatic melanoma. However, there was a greater likelihood of better OS rates with trametinib therapy than with vemurafenib therapy when longer follow-up data from the BRIM-3 trial was used. Conclusions drawn from such indirect comparisons are not as robust as those from direct, head-to-head trial data. In addition, the indirect comparison used trametinib data from the October 2011 data cut-off and did not incorporate data from the May 2013 cut off, which demonstrated a potential waning of the trametinib effect over time.

7.2 Summary of BRAF Mutation Testing in Metastatic Melanoma

7.2.1 Objective

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

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).

7.2.2 Findings

Trametinib is indicated for use in patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Several different DNA-based methodologies can be used to detect these mutations, including Sanger sequencing, allele-specific polymerase chain reaction (PCR), amplification refractory mutation system (ARMS), or ligase detection reaction in order to identify patients who are candidates for therapy with a BRAF inhibitor.[63]

Health Canada and the U.S. FDA both approved Roche's cobas® 4800 BRAF V600 Mutation Test in 2011.[64,65]

Description of the cobas® 4800 BRAF V600 Mutation Test[66]

The cobas® 4800 BRAF V600 Mutation Test is an in vitro diagnostic device intended for the qualitative detection of the BRAF V600E mutation in DNA extracted from formalin-fixed, paraffin-embedded human melanoma tissue. It is a validated, real-time polymerase chain reaction (PCR) test.

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

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

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

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

Performance of the cobas® 4800 BRAF V600 Mutation Test

The cobas® 4800 BRAF V600 Mutation Test was clinically validated with 433 clinical samples from patients screened for the BRIM-2 and BRIM-3 studies (based on analysis submitted to the U.S. FDA).[12-14] 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%.[14] 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.[12,13] 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.[14]

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.[66]

Implementation of the cobas® 4800 BRAF V600 Mutation Test

A decision analytic protocol requested by the medical services advisory committee (MSAC) in Australia reported some issues relevant to implementation of BRAF mutation testing:[63]

- 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.

7.2.3 Summary

The cobas® 4800 BRAF V600 Mutation Test, developed by Hoffman LaRoche, has received regulatory approval in Canada. The cobas® test is a fully automated in vitro diagnostic device intended for the qualitative detection of the BRAF V600E mutation in DNA extracted from formalin-fixed, paraffin-embedded human melanoma tissue; one 5-micron specimen is sufficient to conduct the analysis. It is a validated, real-time polymerase chain reaction test. The cobas® test is able to detect V600E mutations with a higher sensitivity than the reference method of Sanger sequencing, but it is not as specific.[12-14] The test showed cross-reactivity with non-V600E mutants, predominantly V600E2 (≥65%), V600K (≥35%), and V600D (≥10%).

Canadian testing centres may utilize their own validated, non-commercial BRAF tests. As a result, there is variability in mutation reporting, with some centres reporting specific mutations (V600E and/or V600K) and other not specifying the specific mutation.

8 ABOUT THIS DOCUMENT

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

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical 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. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

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

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **Embase** 1974 to 2013 August 28**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

#	Searches	Results
1	(mekinist* or trametinib* or GSK 1120212* or GSK1120212* or JTP 74057 or JTP74057 or 33E86K87QN).ti,ab,rn,nm,sh,hw,ot.	469
2	871700-17-3.rn,nm.	258
3	1 or 2	469
4	3 use pmez	59
5	*trametinib/	85
6	(mekinist* or trametinib* or GSK 1120212* or GSK1120212* or JTP 74057 or JTP74057 or 33E86K87QN).ti,ab.	206
7	5 or 6	216
8	7 use oemezd	162
9	4 or 8	221
10	remove duplicates from 9	175

2. Literature search via PubMed

#1	Add	Search **mekinist*[tiab] OR trametinib*[tiab] OR GSK 1120212*[tiab] OR GSK1120212*[tiab] OR JTP 74057[tiab] OR JTP74057[tiab] OR 33E86K87QN[tiab] OR 871700-17-3[rn] AND publisher[sb]**	5	11:10:02

3. Cochrane Central Register of Controlled Trials (Central)

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There are 2 results from 705372 records for your search on 'mekinist* or trametinib* or GSK 1120212* or GSK1120212* or JTP 74057 or JTP74057 or 33E86K87QN in title abstract keywords in Trials'

4. **Grey Literature search via:**

Clinical trial registries:

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

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

Search terms: mekinist OR trametinib OR GSK 1120212 OR GSK1120212

Select international agencies including:

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

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

Search terms: mekinist or trametinib

Conference abstracts:

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

Search terms: mekinist or trametinib or GSK 1120212 / last 5 years

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