



pan-Canadian Oncology Drug Review Final Clinical Guidance Report

Dabrafenib (Tafinlar) in Combination with Trametinib (Mekinist)

July 21, 2015

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FUNDING

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

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1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the effectiveness and safety of dabrafenib (Tafinlar) in combination with trametinib (Mekinist) for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation who have not received prior systemic therapy for unresectable advanced or metastatic melanoma.

Dabrafenib is a targeted oral BRAF inhibitor that has shown effectiveness in patients with BRAF V600 mutant metastatic melanoma.¹⁻⁴ Trametinib is a targeted oral inhibitor of the mitogen-activated protein kinase (MAPK) pathway. The recommended doses are dabrafenib, 150 mg orally twice daily, and trametinib, 2 mg orally once daily. Treatment was given until disease progression, withdrawal from study or death.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Two randomized controlled trials investigating the use of combination therapy with dabrafenib plus trametinib in patients with unresectable or metastatic melanoma were identified and included in the pCODR systematic review (Combi-d trial and Combi-v trial).

The Combi-d trial^{5,6} was a phase 3, double-blind trial that randomized (1:1) a total of 423 patients to receive either dabrafenib (150 mg twice daily) plus trametinib (2 mg once daily) or to receive dabrafenib (150 mg twice daily) plus placebo.

The Combi-v trial⁷ was a phase 3, open-label trial that randomized (1:1) 704 patients to receive either dabrafenib (150 mg twice daily) plus trametinib (2 mg once daily) or to receive vemurafenib (960 mg twice daily).

Efficacy

Overall survival was statistically significantly longer in favour of dabrafenib plus trametinib compared with BRAF inhibitor therapy alone, in both trials. In the Combi-d trial, the final analysis of overall survival (secondary outcome; conducted in January 2015), demonstrated a statistically significant improvement in favour of the combination arm (median 25.1 months) compared with the dabrafenib alone arm (median 18.7 months; HR 0.71, 95% CI 0.55 to 0.92; p=0.0107).⁶ In the Combi-v trial, overall survival was the primary outcome of the trial, which was stopped early for efficacy after an interim analysis of overall survival conducted in July 2014 crossed the prespecified stopping boundary (p<0.0214). The median overall survival for the dabrafenib plus trametinib arm was not yet reached compared with a median of 17.2 months in the vemurafenib arm (HR 0.69, 95% CI 0.53 to 0.89; p=0.005) after median follow-up duration of 11 months in the combination arm and 10 months in the vemurafenib arm.⁷

Progression-free survival was also statistically significantly longer in favour of dabrafenib plus trametinib arm compared with the BRAF inhibitor therapy alone, in both trials. In the Combi-d trial, progression-free survival was the primary outcome and it was statistically significantly longer in the dabrafenib plus trametinib arm (median 9.3 months) compared with the dabrafenib plus placebo arm (median 8.8 months; hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.57 to 0.99; p=0.03) after a median follow-up of 9 months.⁵ At a data cut of January 2015, median progression-free survival was 11.0 months in the combination arm and 8.8 months in the dabrafenib alone arm (HR 0.67, 95% CI 0.53 to

0.84; $p=0.0004$).⁶ In the Combi-v trial, median progression-free survival was longer in the dabrafenib plus trametinib group (11.4 months) compared with the vemurafenib group (7.3 months; HR 0.56, 95% CI 0.46 to 0.69; $p<0.001$).⁷

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

Harms

In the Combi-d trial, permanent discontinuation and dose reductions occurred in 9% of the dabrafenib plus trametinib group and in 5% of the dabrafenib alone group. Dose reduction and dose interruption occurred in 25% and 49% of the combination group compared with 13% and 33% of the dabrafenib alone group. In the dabrafenib plus trametinib group, the most common grade 3 adverse events were pyrexia (6%), hypertension (4%), and elevated aspartate aminotransferase (3%), whereas hypertension (5%) was the most common in the dabrafenib alone group. Seven patients in each arm experienced grade 4 adverse events. Cutaneous squamous-cell carcinoma, including keratoacanthoma, occurred in 2% of patients who received dabrafenib plus trametinib and in 4% of patients who received dabrafenib alone.⁵

In the Combi-v trial, the rate of treatment discontinuation was 13% in the dabrafenib plus trametinib group and 12% in the vemurafenib group. Dose reduction and dose interruption occurred in 33% and 55% of the combination group and in 39% and 56% of the vemurafenib group. Grade 3 or 4 adverse events occurred in 52% of patients in the combination group and in 63% of patients in the vemurafenib group. The most common grade 3 adverse events in the dabrafenib plus trametinib arm were hypertension (14%), pyrexia (4%), and elevated alanine aminotransferase (3%), whereas in the vemurafenib arm hypertension (9%), rash (9%), elevated alanine aminotransferase (4%), arthralgia (4%), and elevated aspartate aminotransferase (4%) were most common. A total of 17 patients in the dabrafenib plus trametinib arm experienced a grade 4 adverse event compared with 24 in the vemurafenib arm. Cutaneous squamous cell carcinoma, including keratoacanthoma, occurred in 1% of patients who received dabrafenib plus trametinib and in 17% of patients who received vemurafenib.⁷

1.2.2 Additional Evidence

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

In addition, one supplemental question was identified during development of the review protocol as relevant to the pCODR review of dabrafenib and trametinib and is discussed as supporting information:

- **Critical appraisal of a network meta-analysis comparing dabrafenib plus trametinib with single-agent dabrafenib, trametinib, vemurafenib, ipilimumab, and dacarbazine for unresectable or metastatic melanoma.**

There is uncertainty with this NMA since the the differences in the trials characteristics may have affected the treatment effects observed in each trial thus violating the similarity assumption and confounding these comparisons. In addition the submitter felt that there was a well-established correlation between progression free survival and overall survival in metastatic melanoma, and used this in the analysis. Investigator-assessed progression-free survival and overall survival were the primary outcomes for the NMA and they have the potential to be biased in favour of whichever treatment the investigator feels is superior. The definition of progression-free survival and overall survival in each of the included studies was not provided and therefore may not have been the same and thus increasing the uncertainty around the estimates of the indirect comparisons Although the submitter used a Rank Preserving Structural Failure Time Model (RPSFTM), the crossover in the BRIM-3 study could have confounded the results for overall survival and also for cost effectiveness of the drug. The results of the NMA should be interpreted with caution.

1.2.3 Interpretation and Guidance

Burden of Illness and Need

In Canada, it was estimated that in 2014 that there would be 6,500 new cases of primary melanoma and that approximately 1,050 individuals would die from melanoma.⁸ The majority of these patients will present with early stage disease and be cured; however, those who present with advanced disease or who relapse have a poor prognosis. Melanoma remains the leading cause of cancer death in women aged 25 to 35 years, and causes a disproportionate number of years of life lost.

Immune checkpoint inhibitors have resulted in improvements in the prognosis of metastatic melanoma, but only a minority of patients respond, with a small proportion experiencing long term survival, and in non-responders, survival is poor. Single-agent BRAF inhibitors and single-agent MEK inhibitors have resulted in improved outcomes compared to standard chemotherapy for the 40-50% of patients with BRAF mutations; however, resistance to these agents typically develops within 6 to 8 months. Most patients with metastatic melanoma succumb to the disease, therefore more effective treatments are needed.

Hyperproliferative cutaneous side effects are a significant problem with BRAF inhibitors and are thought to be due to paradoxical activation of the MAPK pathway, which results in increased rates of cutaneous squamous cell carcinoma and cutaneous hyperkeratosis.

Effectiveness

The Combi-d trial demonstrated statistically significant and clinically meaningful improvements in overall survival and progression-free survival in favour of the dabrafenib plus trametinib arm compared with the dabrafenib alone arm. Global quality of life was improved on the combination arm at weeks 8, 16, and 24. Pain was also improved on the combination arm; however, nausea and vomiting scores were higher in the combination arm compared with the dabrafenib alone arm.⁵

The Combi-v trial demonstrated statistically significant and clinically meaningful improvements in overall survival and progression-free survival in favour of the dabrafenib plus trametinib arm compared with the vemurafenib alone arm. Global quality of life was significantly improved for the combination arm at weeks 8 to 48 and at progressive disease, and were largest in the global health domain, the role, social, and physical functioning domains, and in the appetite loss and insomnia symptoms domains.⁷

Safety

The rate of Grade 3 adverse events was similar in both arms of the Combi-d trial and in both arms of the Combi-v trial. The most common adverse events in the dabrafenib plus trametinib arms in both studies were pyrexia, fatigue, nausea, headache, chills, diarrhea, and arthralgia. In both studies, there was a lower rate of squamous cell carcinoma and keratoacanthomas in the dabrafenib plus trametinib arm than in the single-agent BRAF inhibitor arm (Combi-d, 2% vs. 4%, respectively; Combi-v, 1% versus [vs.] 17%).^{5,7}

1.3 Conclusions

The Clinical Guidance Panel concluded that there is an overall net clinical benefit to dabrafenib plus trametinib in the treatment of BRAF V600 mutated, unresectable or metastatic (i.e., Stage III-IV) melanoma. This conclusion was based on several factors:

- Two well-conducted randomized controlled trials that demonstrated a clear benefit in overall survival and progression free survival in favour of combination therapy with dabrafenib plus trametinib versus treatment with a single agent BRAF inhibitor.
- Side effect profile of combination therapy is acceptable, predictable, and manageable
- Side effect profile of combination therapy shows significant improvement in the rate of the hyperproliferative cutaneous side effects of single agent BRAF inhibitors, notably the rate of treatment related squamous cell carcinoma.

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

- There is no evidence to support the use of MEK inhibitors after progression on a BRAF inhibitor.
- There is no evidence to support the use of a BRAF inhibitor after progression on a MEK inhibitor.
- There is no evidence to support the use of dual MEK and BRAF inhibitors after progression on single agent MEK or BRAF inhibitors.
- The CGP is unaware of any evidence to guide the optimal sequencing of immune checkpoint drugs (CTLA-4 and PD1 inhibitors) and BRAF/MEK inhibitors.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding dabrafenib and trametinib 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.cadth.ca/pcodr.

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

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

2.1 Context for the Clinical Guidance

2.1.1 Introduction

In Canada 6,500 new cases of primary melanoma were diagnosed in 2014 and approximately 1,100 individuals die from melanoma each year.⁸ In early stage melanoma, cures are commonly achieved with surgery alone. Although only 5% of patients present with metastatic disease, the majority of patients who ultimately die from melanoma will have developed recurrent and/or distant disease. About 1/3 of patients with early stage melanoma will develop metastasis; however, 1/2 of the patients with nodal disease will recur and likely die from metastatic disease.⁹ Unfortunately, most metastatic patients are not candidates for surgical resection and systemic treatment is the only alternative. The prognosis for these patients remains poor. The median survival has been 6-9 months with 5 year survival of approximately 6%.¹⁰

Over the past 30 years, standard first-line systemic treatment has been dacarbazine.^{11,12} Although this alkylating agent is generally well tolerated, response rates are low and complete responses are rare.¹³ Temozolomide, an oral imidazole tetrazone derivative of dacarbazine has also been commonly used. In phase III trials comparing temozolomide directly to dacarbazine, similar progression free and overall survival rates were observed.¹⁴⁻¹⁶ In the early 1990s the FDA approved the use of high dose Interleukin-2 based on phase II data showing a response rate of 16% and a durable complete response of 5%.^{17,18} Unfortunately, high dose Interleukin-2 is associated with severe toxicity and requires intense cardiac monitoring and hemodynamic support. Interleukin-2 is largely unavailable in Canada.

A variety of genetic abnormalities exists within primary melanomas and their respective metastases and influence both cellular proliferation and ultimately response to therapy.^{19,20} The MAP kinase signaling pathway appears to be a key regulatory mechanism for cell growth and differentiation in melanoma.²¹ Mutations in the BRAF protein within this pathway can result in uncontrolled cellular

proliferation and increased potential for metastatic spread.²² Approximately 50% of human melanomas appear to have an activated mutation in BRAF which has become a key target for inhibition and potential therapeutic site.²³ Vemurafenib is a BRAF inhibitor that selectively targets the V600E mutation approved by Health Canada in February 2012.²⁴⁻²⁶ In a randomized phase III study, vemurafenib use led to a relative reduction of 63% in risk of death and 74% reduction in the risk of tumor progression. The overall response rate was 48%.²⁷ Vemurafenib has become the first-line treatment of advanced unresectable melanoma in patients harboring the V600 BRAF mutation. Dabrafenib is a similar targeted oral BRAF inhibitor which has a slightly different toxicity profile and which is similarly efficacious in the therapy of patients with BRAF mutant metastatic melanoma.¹⁻⁴ Unfortunately, for those patients who are BRAF positive, resistance to the BRAF inhibitors ultimately develops and they experience rapid and often unrelenting disease progression.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness and safety of dabrafenib (Tafinlar) in combination with Trametinib (Mekinist), for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

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.

Two randomized controlled trials met the inclusion criteria for this systematic review, Combi-d^{5,6} and Combi-v⁷. Characteristics of the trials' designs can be found in Table XX. Combi -d was a phase 3, double blind and randomized trial. A total of 423 patients (dabrafenib 150 mg twice daily and trametinib 2 mg once daily, n=211; dabrafenib 150 mg twice daily plus placebo, n=212) were randomized. Treatment was given until disease progression, withdrawal from study or death.²⁸ Combi-v was a phase 3, open label randomized trial. A total of 704 patients (dabrafenib 150 mg twice daily and trametinib 2 mg once daily, n=352; vemurafenib 960 mg twice daily, n=352) were randomized.⁷ Treatment was given until disease progression, withdrawal from study or death.

Progression Free survival

The primary outcome in the Combi-d trial was investigator-assessed, progression-free survival. It was significantly longer in the dabrafenib plus trametinib group than in the dabrafenib plus placebo group (9.3 months vs. 8.8 months; HR 0.75 (95% CI, 0.57-0.99; p=0.03).⁵ At the time of the final analysis in January 2015 the estimated median progression free survival was longer in the dabrafenib plus trametinib arm 11.0 (95%CI;8.0-13.9) months compared to 8.8 (95% CI;5.9-9.3) months in the dabrafenib monotherapy arm, HR 0.67; 95%CI 0.53-0.84; p=0.0004).⁶

In the Combi-v trial, the median progression-free survival in the dabrafenib plus trametinib group, was longer than in the vemurafenib group (11.4 months vs. 7.3 months; HR 0.56; 95% CI, 0.46 - 0.69; P<0.001).⁷

Overall survival

In the Combi-d trial overall survival was a secondary outcome and based on an interim analysis. The overall survival rate at six months was 93% in the dabrafenib plus trametinib group and 85% in the dabrafenib plus placebo group.⁵ At the time of this analysis a median overall survival was not reached by either group.⁵ In the figure for overall survival reported in Long et al, the Kaplan-Meier curves separate at 2 months with the combination group on top, with the curves crossing at 14 months and remaining parallel and close together beyond 14 months.⁵ From a January 2015 analysis the median overall survival was 25.1 month in the combination arm compared to 18.7 months in the dabrafenib plus placebo arm. The combination arm demonstrated a statistically significant reduction 29% in the risk of death (HR 0.71, 95% CI 0.55-0.92; p=0.0107).⁶

Overall survival was the primary outcome in the Combi-v trial and it was based on an interim analysis after 222 events had occurred. The trial was stopped for efficacy on July 14, 2014 since the prespecified stopping boundary (P<0.0214) was crossed. The median overall survival for the dabrafenib plus trametinib group was not yet reached and the median overall survival was 17.2 months for patients in the vemurafenib group. The survival curves separate around 3.5 months and then stay separate.⁷ In the dabrafenib plus trametinib arm the rate of overall survival at 12 months was 72% (95% CI, 67 to 77) and it was 65% (95% CI, 59 to 70) in the vemurafenib group.⁷

Response Rate

The investigator-assessed overall response rate in the Combi-d trial was 67% (95% CI, 60 to 73) in the dabrafenib plus trametinib group versus 51% (95% CI, 45 to 58) in the dabrafenib plus placebo group (P=0.002). The median duration of response was extremely censored since the majority of investigator-assessed responses (60%) were still ongoing. In the dabrafenib plus trametinib group, the median duration of response was 9.2 months and 10.2 months in the dabrafenib plus placebo group.⁵ The results for disease response can be seen in Table 1.

Table 1: Disease response⁵

	BRAF V600E and BRAF V600K		BRAF V600E		BRAF V600K	
	Dabrafenib + trametinib N=210 (%)	Dabrafenib + placebo N=210 (%)	Dabrafenib + trametinib N=179 (%)	Dabrafenib + placebo N=180 (%)	Dabrafenib + trametinib N=31 (%)	Dabrafenib + placebo N=30 (%)
Complete response	22 (10)	18 (9)	19 (11)	16 (9)	3 (10)	2 (7)
Partial response	118 (56)	90 (43)	102 (57)	80 (44)	16 (52)	10 (33)
Stable response	54 (26)	69 (33)	46 (26)	62 (34)	8 (26)	7 (23)
Progressive disease	13 (6)	19 (9)	10 (6)	11 (6)	3 (10)	8 (27)
Could not be evaluated	3 (1)	14 (7)	2 (1)	11 (6)	1(3)	3 (10)

In the Combi-v trial, the objective response rate was 64% (95% CI, 59 to 69) in the dabrafenib plus trametinib group versus 51% (95% CI, 46 to 57) in the vemurafenib group (P<0.001).⁷ The median duration of response in the dabrafenib plus trametinib arm was 13.8 months (95% CI, 11.0 to not reached) and in the vemurafenib arm it was 7.5 months (95% CI, 7.3 to 9.3).⁷ The results for disease response can be seen in Table 2.

Table 2: investigator-assessed response in the Combi-v trial⁷

Response	Dabrafenib plus trametinib N=351 (%)	Vemurafenib N=350 (%)
Complete response	47 (13)	27 (8)
Partial response	179 (51)	153 (44)
Stable response	92 (26)	106 (30)
Progressive disease	22 (6)	38 (11)
Could not be evaluated	11 (3)	26 (7)
Data are missing from 1 patient in the dabrafenib plus trametinib group and for 2 patients in the vemurafenib group because these patients did not have measurable disease at baseline		

Quality of Life

Quality of Life was assessed in the Combi-d trial by the EORTC QLQ-C30 generic cancer questionnaire. Both arms in the Combi-d trial were comparable at baseline, however, the global health QOL portion of the questionnaire was significantly better at weeks 8, 16 and 24 for the combination arm. In functional dimensions (physical, social, role emotional and cognitive functioning) most of the scores favoured the combination arm. For symptom impact, the pain scores were significantly improved and clinically meaningful (6-13 point difference) for the combination arm on follow-up assessments. However, other symptoms such as nausea, vomiting, diarrhea, dyspnea and constipation all favoured the dabrafenib plus placebo, with nausea and vomiting being significant.²⁹

In the Combi-V trial health-related quality of life (HRQOL) was assessed by the EORTC-QLQ-C30, the EQ-5D and the Melanoma subscale of the FACT-M.³⁰

In the EORTC-QLQ-C30, quality of life as measured by the global health status score was significantly better for patients who received the combination therapy compared to vemurafenib at Weeks 8, 16, 24, 32, 40, 48, and at progressive disease. The domains of the EORTC-QLQ-C30 that showed the best improvements relative to baseline scores and largest clinically meaningful differences compared to vemurafenib are as follows: global health (5.2 to 7.9 points), role functioning (7.4 to 14.7 points), social functioning (8.5 to 11.8 points), physical functioning (5.6 to 9.2), appetite loss (7.4 to 14.3), insomnia (6.2 to 13.8), pain (8.1 to 13.2). The mean EQ-5D utility values at baseline were higher for the combination therapy arm (0.751 vs. 0.715 for vemurafenib monotherapy), although, EQ-5D utility values were lower for subjects in the vemurafenib monotherapy arm at all assessments. The difference in mean change in EQ-5D utility score was significantly different at all assessments.³⁰

The FACT-M Melanoma subscale scores were higher than baseline for the dabrafenib plus trametinib group combination therapy and they were lower than baseline for vemurafenib at all assessments. The differences between treatment arms were statistically significant and clinically meaningful in favour of the combination arm.³¹

Harms Outcomes

In the Combi-d trial, grade 3 or 4 adverse events occurred in 73 patients (35%) in the dabrafenib plus trametinib group and in 79 patients (37%) in the dabrafenib plus placebo group. In the dabrafenib plus trametinib arms, pyrexia, hypertension and elevated aspartate aminotransferase were the most common grade 3 adverse events, which occurred in at least 10% of patients who received at least one dose of the study drug.⁵ In the dabrafenib plus placebo arms, hypertension was the most common grade 3 adverse events, which occurred in at least 10% of patients who received at least one dose of the study drug and cutaneous squamous-cell carcinoma including keratoacanthoma was the most common adverse event in this group that occurred in <10% of patients.⁵ In the dabrafenib plus trametinib arm seven patients had a grade 4 event in the following categories, anemia, decreased lymphocyte count, hypoglycaemia, pulmonary embolism, brain edema, hepatic hematoma, metastases to the central nervous system and pancytopenia. In the dabrafenib plus placebo arm seven patients had grade 4 events in the following categories: dyspnea, thrombocytopenia, hypokalemia, cutaneous squamous-cell carcinoma, brain edema, hypercalcemia, febrile neutropenia and hypovolemic shock.⁵

In the Combi-v trial, grade 3 or 4 adverse events occurred in 52% of the patients in the dabrafenib plus trametinib group and in 63% in the vemurafenib group.⁷ In the dabrafenib plus trametinib arm, pyrexia, hypertension and elevated alanine aminotransferase were the most common grade 3 adverse events, which occurred in $\geq 10\%$ of patients.⁷ In the vemurafenib arm, hypertension, arthralgia, rash and elevated alanine aminotransferase were the most common grade 3 adverse events, which occurred $\geq 10\%$ of patients. The most common adverse event that occurred in <10% of patients in the combination group was decreased ejection fraction. In the vemurafenib group it was cutaneous squamous-cell carcinoma including keratoacanthoma.⁷ In the dabrafenib plus trametinib arm, 16 patients had a grade 4 events in the following categories; blood creatine phosphokinase increased (3 subjects), hyperglycemia (2 subjects); hyponatremia, headache, asthenia, aspartate amino transferase increased, hepatic enzyme increased, electrocardiogram QT prolonged, cellulitis, renal failure, duodenal ulcer, lipase increased, haemorrhage, sepsis, acute myeloid leukaemia, duodenal perforation, Escherichia sepsis, hypertransaminasaemia, tumor rupture (1 subject each).³⁰ In the vemurafenib group 23 patients had grade 4 events in the following categories: increased gamma-glutamyl transferase (3 subjects), alanine aminotransferase increased (2 subjects), hepatic enzyme increased (2 subjects), hypocalcaemia (2 subjects); hypertension, constipation, neutropenia, dyspnea, hyperglycemia, blood creatine phosphokinase increased, electrocardiogram QT prolonged, blood bilirubin increased, squamous cell carcinoma, urticaria, cerebral haemorrhage, febrile neutropenia, general physical health deterioration, cholelithiasis, keratoacanthoma, squamous cell carcinoma of skin, ileus, large intestine perforation, metastases to meninges, uterine haemorrhage (1 subject each).³⁰

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 a network meta-analysis comparing dabrafenib plus trametinib with other interventions for the treatment of metastatic melanoma

See section 7.1 for more information.

The network meta-analysis provided by the manufacturer investigated combination dabrafenib plus trametinib compared to other pharmacological interventions for patients with BRAF V600K/E metastatic melanoma, using a fixed effects mode. The submitter used these results to estimate the clinical effect between treatments that were not directly compared in RCTs. The results of this NMA were used to inform the submitters' economic evaluation.

There is uncertainty with this NMA since the differences in the trials characteristics may have affected the treatment effects observed in each trial thus violating the similarity assumption and confounding these comparisons. In addition the submitter felt that there was a well-established correlation between progression free survival and overall survival in metastatic melanoma, and used this in the analysis. Investigator-assessed progression-free survival and overall survival were the primary outcomes for the NMA and they have the potential to be biased in favour of whichever treatment the investigator feels is superior. The definition of progression-free survival and overall survival in each of the included studies was not provided and therefore may not have been the same and thus increasing the uncertainty around the estimates of the indirect comparisons. Although the submitter used a Rank Preserving Structural Failure Time Model (RPSFTM), the crossover in the BRIM-3 study could have confounded the results for overall survival and also for cost effectiveness of the drug. The results of the NMA should be interpreted with caution.

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 are a number of symptoms associated with metastatic melanoma, which include loss of energy, fear, anxiety and depression. Respondents experienced moderate to severe emotional distress, and some respondents suffered fatigue, mood swings, loss of vitality and low energy levels. These symptoms greatly impact a patient's quality of life. Respondents reported that while current treatments may help to slow the spread of disease, but these treatments were not effective in preventing the metastasis. It was reported that the side effects from current therapies include extreme flu like symptoms and fatigue, cognitive impairment, nausea, fever, rigours, pain, arthritis, headaches, liver failure, low platelet counts, diarrhea, and severe depression. Respondents reported that many of these side effects last beyond a year, depending on the patient's ability to tolerate the therapy; and most patients do not complete the full year treatment due to side effects. Respondents expect that the dabrafenib

plus trametinib combination therapy could either eliminate the disease altogether, slow progression or span the gap until another potentially more effective therapy is developed - not only for the length of survival but also in terms of the quality of life. According to MNC, 21/63 of respondents had been treated with the combination therapy of dabrafenib plus trametinib. MNC indicated that most respondents had received a benefit - and for some, it seems to be enduring. According to SYSF, respondents that had experienced with the combination treatment noted positive effects in that some observed a complete response and the complete disappearance of all signs of cancer. Other respondents had other tumours appear and will need new treatment options. Both SYSF and MNC reported that the most common side effects included flu like symptoms and fatigue, fever, arthritis or joint pain, headaches, nausea and diarrhea. However, most respondents indicated that aside from persistent fatigue, the side effects were worth the results of treatment.

PAG Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of dabrafenib/trametinib combination therapy for melanoma:

Clinical factors:

- Availability of data regarding the sequencing of BRAF inhibitors: vemurafenib, dabrafenib monotherapy, trametinib monotherapy
- Relative benefits and risks of combination therapy versus monotherapy
- The benefits of adding the second drug when patients have already started with one

Economic factors:

- High cost of combination drugs
- Cost-effectiveness of combination therapy compared to monotherapy

2.2 Interpretation and Guidance

Burden of Illness

It is estimated that 6,500 Canadians will be diagnosed with melanoma in 2014, and approximately 1,100 patients will die of melanoma in 2014. The majority of patients will present with early stage disease and be cured by surgery but those who present with advanced disease or who subsequently relapse, the prognosis remains poor. Although the number of patients developing melanoma is small compared to breast cancer or lung cancer, melanoma remains the number one cause of cancer death in women age 25 to 35, and causes a disproportionate number of years of life lost. Unresectable stage III or stage IV melanoma carries a poor prognosis, and up until very recently the median survival was 6.2 months and only 25.5% of patients survived to one year. There is no evidence that standard cytotoxic chemotherapy improves overall survival or quality of life in metastatic melanoma and objective response rate is low, in the 7-10% range. Immune checkpoint inhibitors (cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1) inhibitors) have also resulted in improvements in the prognosis of metastatic melanoma, but only a minority of patients respond and survival is poor in non-responders; overall only a small proportion will experience long term survival. Single

agent BRAF and single agent MEK inhibitors have resulted in improved outcomes as compared to standard chemotherapy for the 40-50% of patients with BRAF mutations, however resistance to these agents typically develops within 6 to 8 months. Most patients with metastatic melanoma succumb to the disease, more effective treatments are needed.

Effectiveness

In BRAF V600 mutation-positive unresectable or metastatic melanoma patients, two large, randomized, double-blind trials have reported on the efficacy of dual BRAF + MEK inhibition, using dabrafenib in combination with trametinib, versus single agent BRAF inhibition.

The Combi-V trial by Robert

This phase 3, open label trial compared dabrafenib 150mg BID + trametinib 2mg OD vs. vemurafenib 960mg BID in 704 patients. This trial was an open-label phase 3 trial with overall survival (OS) as the primary end point. Patient groups were well balanced except for sex (59% men in combination group vs. 51% men in vemurafenib group). A pre-planned interim analysis for OS was conducted when 222 events had occurred. OS at 12 months was 72% in the combination group vs. 65% in the vemurafenib group, HR for death 0.69, $p=0.005$ which crossed the prespecified interim stopping boundary. Median PFS was 11.4 months in the combination group vs 7.3 months in the vemurafenib group $p<0.001$. Objective response rate was 64% in the combination group vs. 51% in the vemurafenib group $p<0.001$. Cross-over was not allowed until after the trial was stopped for efficacy after reaching the prespecified stopping boundary. The most common therapy given after disease progression was ipilimumab in both groups (12% of combination group vs. 22% of vemurafenib group).⁷

The Combi-D trial by Long

This phase 3 trial compared dabrafenib 150mg BID + trametinib 2mg OD vs dabrafenib 150mg BID + placebo. The primary end point was PFS in this trial of 423 patients. OS, response rate, and safety were secondary endpoints. Baseline characteristics were similar between the two groups. The data was analyzed when the prespecified number of events had occurred (disease progression or death). Median progression free survival was 9.3 months in the dabrafenib plus trametinib combination group vs 8.8 months in the dabrafenib group (HR 0.75, $p=0.03$). Overall response rate was 67% in the combination group vs 51% in the dabrafenib group $p=0.002$. The 6 month interim OS was 93% (combination) vs 85% (dabrafenib) but this did not cross the specified efficacy-stopping boundary. The submitter provided updated results from a January 2015 analysis showing a median OS of 25.1 months (combination) vs 18.7 months (dabrafenib) HR 0.71, $p=0.0107$. Ipilimumab was the most common treatment given after progression in both arms (9% combination group vs 15% dabrafenib group).^{5,6}

Network Meta-Analysis (NMA)

Dabrafenib plus trametinib has not been directly compared to single agent dacarbazine, single agent trametinib, or to the combination ipilimumab + dacarbazine. A NMA is a tool used to make indirect comparisons (cross trial comparisons). In general, cross-trial comparisons should be avoided as patient and trial design characteristics are often insufficiently similar to draw reliable results. The NMA provided by the submitter provides no assurance of similarity between the included trials and should not be used to assess the relative efficacy or cost-effectiveness of combination dabrafenib plus trametinib as compared to single agent dacarbazine, single agent trametinib, or to the combination ipilimumab + dacarbazine.

Safety

The Combi-V trial by Robert

Safety analysis included the 699 patients that had at least 1 dose of a study medication. Grade 3 or 4 adverse events occurred in 52% (combination) vs 63% (vemurafenib) of patients. Rates of treatment discontinuation were similar 13% (combination) vs 12% (vemurafenib), the most common reason was pyrexia 3% and decreased ejection fraction 3% (combination) vs arthralgia 2% (vemurafenib). Dose reductions and dose interruptions occurred in 33% and 55% of the combination group vs 39% and 56% of the vemurafenib group. Pyrexia was more common in the combination group than in the vemurafenib group (53% vs 21%). The most common adverse events in the combination group were pyrexia (53%), nausea (35%), diarrhea (32%), chills (31%), fatigue (29%), headache (29%), and vomiting (29%). The most common adverse events in the vemurafenib group were arthralgia (51%), rash (43%), alopecia (39%), diarrhea (38%), nausea (36%), fatigue (33%). The combination group had a lower rate of skin toxic effects vs the vemurafenib group: rash (22% vs 43%), photosensitivity reaction (4% vs 22%), hand-foot syndrome (4% vs 25%), skin papillomas (2% vs 23%), squamous-cell carcinomas and keratoacanthomas (1% vs 17%). No fatal side effects were attributed study medications. Health related quality of life (HR-QOL) was assessed using the EORTC-QLQ-30, EQ-5D, and the Melanoma subscale of the FACT-M. Global health status score was significantly better for the combination arm at weeks 8 - 48 and at progressive disease. The largest clinically meaningful differences favoring the combination group were in global health, role functioning, social functioning, physical functioning, appetite loss, and insomnia.³¹

The Combi-D trial by Long

Grade 3 or 4 adverse events occurred in 35% of the combination dabrafenib plus trametinib group vs 37% of the dabrafenib group. Permanent discontinuation and dose reductions occurred in 9% of the combination group vs 5% of the dabrafenib group. Dose reduction and dose interruption occurred in 25% and 49% of the combination group vs 13% and 33% of the dabrafenib group. Pyrexia was the most common reason for dose interruption (32%) and dose reduction (13%) in the combination group. Pyrexia was the most common reason for dose interruption (13%) and dose reduction (3%) in the dabrafenib group. Pyrexia was the most common reason (2%) for permanent discontinuation of the combination; decreased ejection fraction was the most common reason (1%) in the dabrafenib group. Overall the most common side effects in both groups were pyrexia, fatigue, nausea, headache, chills, diarrhea, arthralgia, rash, and hypertension. Incidence of cutaneous squamous-cell carcinoma was lower in the combination group (2% vs 9%) than in the dabrafenib group. Cutaneous pherkeratoses was also lower in the combination group (3% vs 32%). The combination group had higher rates of pyrexia, hypertension, peripheral edema, and diarrhea. Pyrexia occurred in 51% of the combination group vs 28% of the dabrafenib group. No deaths were attributed to study medication in either group. Quality of life was assessed using the EORTC QLQ-30 and global health scores were improved in the combination arm at 8/16/24 weeks, pain was significantly better on the combination arm, however nausea and vomiting were increased.^{5,6}

Need

Single agent BRAF inhibitors are approved and commonly used in BRAF V600 mutation-positive unresectable or metastatic melanoma, however, resistance typically develops within 6 to 8 months of treatment initiation and survival at that point is poor. Hyperproliferative cutaneous side effects are a significant problem with BRAF inhibitors and are thought due to paradoxical activation of the MAPK pathway. This results in increased rates of cutaneous squamous-cell carcinomas and cutaneous hyperkeratosis with single agent BRAF inhibitors. Dual inhibition with BRAF and MEK inhibitors was undertaken to address these needs. Of note, there is no evidence to support the use of dual MEK and

BRAF inhibitors after progression on single agent MEK or BRAF inhibitors. Furthermore, the optimal sequencing of BRAF targeted inhibitors and immune checkpoint inhibitors is not yet defined.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is an overall net clinical benefit to dabrafenib plus trametinib in the treatment of BRAF V600 mutated, unresectable or metastatic (i.e., Stage III-IV) melanoma. This conclusion was based on several factors:

- Two well-conducted randomized controlled trial that demonstrated a clear benefit in overall survival and progression free survival in favour of combination therapy with dabrafenib plus trametinib versus treatment with a single agent BRAF inhibitor.
- Side effect profile of combination therapy is acceptable, predictable, and manageable
- Side effect profile of combination therapy shows significant improvement in the rate of the hyperproliferative cutaneous side effects of single agent BRAF inhibitors, notably the rate of treatment related squamous cell carcinoma.

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

- There is no evidence to support the use of MEK inhibitors after progression on a BRAF inhibitor.
- There is no evidence to support the use of a BRAF inhibitor after progression on a MEK inhibitor.
- There is no evidence to support the use of dual MEK and BRAF inhibitors after progression on single agent MEK or BRAF inhibitors.
- The CGP is unaware of any evidence to guide the optimal sequencing of immune checkpoint drugs (CTLA-4 and PD1 inhibitors) and BRAF/MEK inhibitors.

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. Although primary melanoma can occur in a variety of sites, skin is the most common, comprising 95% of cases. In Canada 6,500 new cases of primary melanoma were diagnosed in 2014 and approximately 1,100 individuals die from melanoma each year.⁸ The incidence of melanoma has been steadily increasing over the past 60 years. Currently the lifetime probability of developing melanoma for women is 1 in 85 and for men is 1 in 67.³² Staging of melanoma is based on the current American Joint Committee on Cancer (AJCC) 7th edition classification.³³ The tumour characteristics principally involve the Breslow height, presence or absence of ulceration, and mitotic rate. The detection of microscopic and macroscopic lymph node involvement, lactate dehydrogenase (LDH) and sites of metastatic disease are also incorporated in the staging classification. All of these prognostic factors have important impact upon patient outcomes and also serve to guide management decisions.

3.2 Accepted Clinical Practice

In early stage melanoma, cures are commonly achieved with surgery alone. The primary site is excised with appropriate surgical margins. Depending upon the T stage and location of the primary, a sentinel node biopsy (SNB) may be performed to assess regional nodal status. If the sentinel node contains metastatic disease, then a completion lymph node dissection of the regional basin is often performed. This additional procedure has been shown to reduce the risk of regional occurrence.¹¹

Although only 5% of patients present with metastatic disease, the majority of patients who ultimately die from melanoma will have developed recurrent and/or distant disease. About 1/3 of patients with early stage melanoma will develop metastasis; however, 1/2 of the patients with nodal disease will recur and likely die from metastatic disease.⁹ Brain metastases are common and occur in up to 75% of patients with overt metastatic disease. In highly selected patients with metastatic disease, clinical benefit may occur from surgical resection of known sites of disease and may result in long term survival. Unfortunately, most metastatic patients are not candidates for surgical resection and systemic treatment is the only alternative. The prognosis for these patients remains poor. The median survival has been 6-9 months with 5 year survival of approximately 6%.¹⁰ With the more recent introduction of new and effective treatments, a significant improvement in survival is being realized.

Over the past 30 years, standard first-line systemic treatment has been dacarbazine.^{11,12} Although this alkylating agent is generally well tolerated, response rates are low and complete responses are rare.¹³ In comparative studies the use of dacarbazine has not been shown to improve survival in metastatic melanoma.³⁴⁻³⁷ Temozolomide, an oral imidazole tetraene derivative of dacarbazine, is activated to the active metabolite of dacarbazine, and has also been commonly used. In phase III trials comparing temozolomide directly to dacarbazine, similar progression free and overall survival rates were observed.¹⁴⁻¹⁶ In the early 1990s the FDA approved the use of high dose Interleukin-2 based on phase II data showing a response rate of 16% and a durable complete response of 5%.^{17,18} Unfortunately,

high dose Interleukin-2 is associated with severe toxicity and requires intense cardiac monitoring and hemodynamic support. Interleukin-2 is largely unavailable in Canada.

A wide spectrum of chemotherapeutic and immunological treatments has been explored in patients with metastatic melanoma. Until recently limited to no success has been achieved. It has become increasingly apparent that melanoma represents a heterogeneous group of diseases. A variety of genetic abnormalities exists within primary melanomas and their respective metastases and influence both cellular proliferation and ultimately response to therapy.^{19,20,38} The MAP kinase signaling pathway appears to be a key regulatory mechanism for cell growth and differentiation in melanoma.²¹ Mutations in the BRAF protein within this pathway can result in uncontrolled cellular proliferation and increased potential for metastatic spread.²² Approximately 50% of human melanomas appear to have an activated mutation in BRAF which has become a key target for inhibition and potential therapeutic site.²³

Vemurafenib is a BRAF inhibitor that selectively targets the V600E mutation approved by Health Canada in February 2012.²⁴⁻²⁶ In a randomized phase III study, vemurafenib use led to a relative reduction of 63% in risk of death and 74% reduction in the risk of tumor progression. The overall response rate was 48%.²⁷ Vemurafenib has become the first-line treatment of advanced unresectable melanoma in patients harboring the V600 BRAF mutation. Dabrafenib is a similar targeted oral BRAF inhibitor which has a slightly different toxicity profile and which is similarly efficacious in the therapy of patients with BRAF mutant metastatic melanoma.¹⁻⁴ Unfortunately, for those patients who are BRAF positive, resistance to the BRAF inhibitors ultimately develops and they experience rapid and often unrelenting disease progression. In the remaining 50% of the patients who do not have BRAF mutation, the BRAF inhibitors are uniformly ineffective and additional therapies are needed. More recently Ipilimumab, a monoclonal antibody that binds to and blocks the cytotoxic T-lymphocyte associated antigen 4 (CTLA4) located on cytotoxic T-lymphocytes has been shown to improve survival in first and second line settings in the treatment of metastatic melanoma.^{39,40}

3.3 Evidence-Based Considerations for a Funding Population

Resistance to BRAF inhibition (with vemurafenib or dabrafenib) is thought to occur via reactivation of the MAPK pathway. Combined BRAF and MEK inhibition has been shown to delay the development of BRAF inhibition and to reduce the incidence of serious side effects of BRAF inhibition such as the development of cutaneous squamous cell carcinomas. Recent multi-centre phase 3 trials of combined BRAF + MEK inhibition vs BRAF inhibition alone have been reported by Long and Robert in the first line treatment of BRAF 600E/K mutated unresectable or metastatic melanoma. In the trial by Long, 423 BRAF mutated patients were randomized to dabrafenib 150mg BID + trametinib 2mg OD vs dabrafenib + placebo. The primary endpoint was PFS and at the preplanned interim analysis the combination of BRAF and MEK inhibition demonstrated a statistically significant improvement in median PFS (9.3 months vs 8.8 months, HR 0.75, p=0.03). The 6 month OS was also improved in the combination arm (93% vs 85%, HR for death was 0.63 p = 0.02), however the specified stopping boundary was not reached at this interim analysis. Overall rates of adverse events were similar, however cutaneous squamous cell carcinoma rates were lower in the combination arm (2% vs 9%), however rates of pyrexia were higher (51% vs 28%).^{5,6}

In the trial by Robert, 704 BRAF V600 mutated patients were randomized to Dabrafenib 150mg BID + trametinib 2mg daily vs vemurafenib 960mg BID. The primary end point was OS and at the preplanned interim analysis, conducted after 222 events had occurred, OS at

12 months favoured the combination arm (72% vs 65%, HR death 0.69, p=0.005). Median PFS was also improved (11.4mos vs 7.3mos, HR 0.56, p<0.001). Response rate and duration of response were also significantly longer in the combination arm and rates of cutaneous squamous cell carcinoma and keratoacanthoma were lower (1 vs 18%). Response rate, PFS and OS outcomes were similar in the combination arm for the 10% of patients that had the BRAF V600K mutation as compared to the 90% of patients with the BRAF V600E mutation. Similar to the study by Long, pyrexia was the most common side effects (53%) in the combination arm.⁷

3.4 Other Patient Populations in Whom the Drug May Be Used

Immunomodulator drugs such as ipilimumab and nivolumab are commonly used in the first and second line setting for metastatic malignant melanoma. These drugs have been shown to improve OS compared to standard chemotherapy as first line therapy and are effective in both BRAF positive and negative patients and are associated with a 10-15% chance for long term disease control. A significant portion of patients may receive immunomodulator therapies in first and sometimes second line treatment of melanoma, however the majority will progress and the BRAF mutated patients would then be candidates for BRAF and MEK inhibition therapy.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following two patient advocacy groups, Melanoma Network of Canada (MNC) and Save Your Skin Foundation (SYSF), provided input on dabrafenib (Tafinlar) and trametinib (Mekinist) in combination for the treatment of patients with unresectable or metastatic melanoma with a BRAF 600 mutation, and their input is summarized below.

MNC conducted a confidential on-line survey of patients from across Canada and the United States. Patients were recruited through a generic letter and email and an on-line website posting requesting input from patients that had been treated with the dabrafenib and trametinib combination for metastatic melanoma or patients who may see a need for this therapy in the future. MNC received a total of 63 patient respondents, of which 21 respondents had been treated with the dabrafenib and trametinib combination. The survey had a combination of multiple choice and open ended questions, as well as rating and options for comment. MNC has provided selected commentary of respondents that are reflective of various perspectives.

SYSF conducted one-on-one interviews with 50 patients with late stage melanoma patients, of which 20 have gone through the treatment under review, and 15 caregivers.

From a patient perspective, there are a number of symptoms associated with metastatic melanoma, which include loss of energy, fear, anxiety and depression. Respondents experienced moderate to severe emotional distress, and some respondents suffered fatigue, mood swings, loss of vitality and low energy levels. These symptoms greatly impact a patient's quality of life. Respondents reported that while current treatments may help to slow the spread of disease, but these treatments were not effective in preventing the metastasis. It was reported that the side effects from current therapies include extreme flu like symptoms and fatigue, cognitive impairment, nausea, fever, rigours, pain, arthritis, headaches, liver failure, low platelet counts, diarrhea, and severe depression. Respondents reported that many of these side effects last beyond a year, depending on the patient's ability to tolerate the therapy; and most patients do not complete the full year treatment due to side effects. Respondents expect that the dabrafenib

and trametinib combination therapy could either eliminate the disease altogether, slow progression or span the gap until another potentially more effective therapy is developed - not only for the length of survival but also in terms of the quality of life. According to MNC, 21/63 of respondents had been treated with the combination therapy of dabrafenib and trametinib. MNC indicated that most respondents had received a benefit - and for some, it seems to be enduring. According to SYSF, respondents that had experienced with the combination treatment noted positive effects in that some observed a complete response and the complete disappearance of all signs of cancer. Other respondents had other tumours appear and will need new treatment options. Both SYSF and MNC reported that the most common side effects included flu like symptoms and fatigue, fever, arthritis or joint pain, headaches, nausea and diarrhea. However, most respondents indicated that aside from persistent fatigue, the side effects were worth the results of treatment.

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

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Metastatic Melanoma

MNC asked respondents to identify symptoms and issues associated with melanoma. Below is a list of the key findings from the survey on symptoms and issues that respondents reported.

Cancer and the different stages of cancer affect people in different ways. What symptoms and issues have you experienced having melanoma? Please select as many responses as appropriate.		
Answer Options	Response Percent	Response Count
Pain	66%	42
Scarring or disfigurement	76%	48
Mobility issues (unable to walk or impaired movement)	30%	19
Gastrointestinal issues	37%	23
Fluid around lungs	8%	5
Headaches	57%	36
Disrupted sleep	73%	46
Appetite loss or weight gain	49%	31
Bleeding problems	11%	7
Fear or anxiety	81%	51
Fatigue	68%	43
Depression	33%	21
Post-traumatic stress	10%	6
Nausea or vomiting	21%	13
Shortness of breath	17%	11
Infections	8%	5
Damage to organs, such a lungs, liver, brain	35%	22
None		0

SYSF also noted that ongoing symptoms from patients include loss of energy, fear, anxiety and depression. All of the patients experienced moderate to severe emotional distress. Some patients suffered fatigue, mood swings, loss of vitality and low energy levels.

According to SYSF, the aspects of melanoma that are most important to control are pain from tumour growth and the pain from those tumours on the patients' body, especially in the areas of movement (e.g., legs, arms etc.).

SYSF also noted some other key impact on patients with this disease, include the inability to mentally and physically return to work, the inability to return to "normal" daily life, and anxiety and depression due to their prognosis. Some patients have also suffered from loss of mobility due to muscle and tissue removal of surgery or treatment. The scars from surgery to remove tumours greatly impact the physical appearance of the patient. Other issues identified include problems with surgery if the tumour is in a difficult location on the body.

Below are some of the key comments gathered from respondents through the MNC surveys:

- The cancer spread everywhere - on my skin, in my pancreas, my bones, liver and lungs. Only place spared so far has been my brain. I can't breathe without oxygen now. I can't walk, work or even make it up the stairs to my room. I need care 24/7. It is really hell.
- Melanoma has now hit my spine and is snapping it in two. I am facing paralysis. I am frightened for my wife and kids. Who is going to look after them? I will miss so much it kills me to think about it.
- I was lucky at first. The primary melanoma was removed surgically and it took 6 months to heal. Two years later I had 26 others in the same area. My life was restricted every other week to being at home because of pain and swelling.
- Uncertainty of future and longevity of life, not sure how hard I should work because of uncertain future. All doctor said to me was 5 year survival of 40 %, no prevention ideas; no ideas to self-monitor; no follow up scans; no treatment other than surgery; no regular follow up. What type of cancer is this that leaves us hanging out there in the wind?
- Socially I felt I didn't want to be out and about among people which simply is not me; having been involved in local theatre groups and working with families daily. Many days I simply didn't feel up to doing much of anything with nausea, fatigue and anxiety. My general outlook and way of thinking overall has changed.
- Less activity, problems walking, less social, anxious, angry, resentful, unable to work.
- I had to step back from being the primary care provider to my two young kids for a period of time, I had to quit my job, I couldn't do some of the day to day things that were "normal" for a 30 year old woman.
- Had anxiety and depression before but it increased to the point of needing medication after the diagnosis. I love the outdoors and loved the sun now I am fearful and have restricted my life to avoid the outdoors. This in itself has increased my depression.
- I had tumours everywhere. I refused to see my friends and family. I was a freak - fluid was leaking everywhere and I was in constant pain. It felt like an alien had taken over. I would wake in the morning and there were new growths.

4.1.2 Patients' Experiences with Current Therapy for Metastatic Melanoma

SYSF reported that current drugs used to treat melanoma include interferon, surgery, radiation, dacarbazine (DTIC), temozolomide, stereotactic radiation (used on brainstem tumours), vemurafenib and ipilimumab, trametinib and dabrafenib.

According to MNC, below were the treatments that respondents reported receiving for the treatment of melanoma.

What types of therapies or interventions have been used to try to eliminate or control your melanoma before you were put on the combination therapy? Select as many as you have experienced in your treatment.		
Answer Options	Response Percent	Response Count
Surgery	96.0%	20
Biological therapies (interferon)	26.0%	6
Radiation	19.0%	4
BRAF Inhibitor (Zelboraf)	7.0%	2
Immunotherapy (Yervoy - ipilimumab)	10.0%	2
A combination of the above	7.0%	2
None of the above	0.1%	1

MNC reported that of the patients pre-treated with vemurafenib, 78% of respondents indicated less side effects with the dabrafenib and trametinib combination.

According to SYSF, there were few positive results recorded with any of the respondents interviewed that had experienced with interferon, DTIC and temozolomide. While these respondents felt these treatments probably slowed the spread of disease, but they were not effective in preventing the metastasis. Respondents stated that they experienced fatigue and pain from the cancer while using these therapies. The adverse side effects that were most difficult to tolerate for respondents were extreme fatigue, diarrhea, skin issues, nausea, rash, low sodium levels and colitis. According to SYSF, many side effects have been so severe that patients were not able to perform daily functions.

Similarly MNC noted that from prior surveys, the side effects from interferon have included extreme flu like symptoms and fatigue, cognitive impairment, nausea, fever, rigours, pain, arthritis, headaches, liver failure, low platelet counts, diarrhea, and severe depression. Many of these side effects last beyond a year, depending on the patient's ability to tolerate the therapy. Most patients do not complete the full year treatment due to side effects. In addition, standard therapies have poor results in preventing spread of the disease.

SYSF noted that while newer therapies are becoming more readily available, they do not work for all patients and is not easily accessible. As such, patients feel frustrated as time is very important when dealing with melanoma and access to treatment.

SYSF stated that 90% of the respondents responded "yes" that they would "try anything" to win their fight with this cancer. The other 10% of respondents responded, "yes" depending on the severity of the side of effects.

In addition, SYSF indicated that other challenges that patients face include financial implications (i.e., patients could not work while being administered the drugs and have to travel to specific centres for treatment).

While current therapies have a better survival rate, getting the right patient to the right treatment in the right centers are issues of concern for patients. SYSF found that there is a large unmet need for these patients due to lack of treatment, in particular when doctors are unable to control spread of the disease through surgery.

4.1.3 Impact of Metastatic Melanoma and Current Therapy on Caregivers

SYSF conducted interviews with 15 caregivers who had a close family member who was diagnosed with melanoma. Respondents reported on the emotional distress due to an uncertain prognosis and unknown treatment plan, cancellation of any long-term plans, and time away from work to assist the patient all impacted the routine of the caregiver.

Respondents indicated that there is a lack of information about the side-effects, which result in confusion and distress. As such, respondents found it difficult to know if the symptoms were treatment related or cancer related. The main challenge for some respondents was finding treatments that might work for their loved ones.

Respondents also reported that the cost to the family to travel to centers for treatment is very difficult. Moreover, time away from family while getting treatment was also an issue for some.

MNC did not include caregivers in this survey as MNC have surveyed caregivers in past submissions. According to previous surveys, it was found that there were negative impacts such as the loss of income either from the patient's inability to work or from the caregiver having to take time off work or having to leave employment to care for the patient. There are also significant impacts on the family unit - mental health, anxiety, stress, physical demands of caring for an ill family member.

Moreover, additional costs and time for attending appointments, managing home care, taking on additional home and family management responsibilities also greatly impact caregivers. Some of these challenges include having to communicate the situation to children and managing their anxiety as well as other family members and friends. MNC reported that trying to be a caregiver both physically and emotionally while dealing with their own stress and challenges could lead to a breakdown in the marriage.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Dabrafenib & Trametinib Combination

According to SYSF, the respondents interviewed are hoping that this treatment will help with long-term survival. The negative effect is that it takes a long time to know if the treatment will work for them.

MNC indicated that the respondents' expectations for the therapy include that it could either eliminate the disease altogether, slow progression or span the gap until another potentially more effective therapy is developed is important - not only for the length of

life but as well, for the quality of life. Moreover, respondents believe that this combination therapy could have less side-effects.

The unmet need for patients includes a therapy that controls or eliminates disease with few or fewer side effects than other therapies. Some of the comments included:

- Fewer side effects would allow for much better quality of life. I would like this to be available if my disease progresses.
- It would be of tremendous benefit if it would control and possibly eliminate the disease. I would try anything that could possibly help me and extend my life.
- I would think it would give the patient hope of survival or longer survival rate, instead of sitting and waiting and not doing anything to try to cure it.
- It plays a big role in the need for better and more targeted therapies. What is clear is that what works for one doesn't always work for the other. In addition to the obvious physical benefits of the slowing or elimination of the cancer having access to this therapy plays a big role in the emotional and mental being of a patient in knowing there is something being done beyond a "wait and see"!

MNC reported that, of those surveyed, 21/63 of respondents (33%) had been treated with the combination therapy of dabrafenib and trametinib. It was noted that 21% of respondents had been treated with another BRAF inhibitor prior to the combination therapy. Another 16% of respondents had received an immunotherapy (e.g., ipilimumab). MNC observed that while some respondents had stopped responding to vemurafenib, these respondents had seen a response with the combination therapy of dabrafenib and trametinib.

MNC indicated that most respondents had received a benefit - and for some, it seems to be enduring, which is the ultimate end goal. As well, most respondents indicated that this combination therapy was better tolerated than vemurafenib. One respondent stated *"I wasn't able to tolerate Zelboraf. I am doing amazing on this combo. This is my life - I am alive. I am working and a stage 4 patient on potent drugs. It is a bloody miracle. Need I say more? That is the gap. I would likely not be here without it."*

Most respondents experienced side effects, but the vast majority indicated those side effects were well tolerated. Two respondents indicated that they had to be taken off the therapy - one due to progression of disease and the other due to a persistent and ongoing rash. One respondent reported that she has been on the combination for almost two years, and had to be put on steroids. Due to the side effects of the steroids, she was removed from those and then slowly removed from the combination therapy. She has been off all drug treatments for 8 months, and despite of persistent joint pain, remains completely cancer free and has returned to a relatively normal life.

According to the survey conducted by MNC, the most common side effects included flu like symptoms and fatigue, fever, arthritis or joint pain, headaches, nausea and diarrhea. However, most indicated that aside from persistent fatigue, the side effects were worth the results of treatment. Below is the list of responses surveyed.

Cancer and the different stages of cancer affect people in different ways. What symptoms and issues have you experienced having melanoma? Please select as many responses as appropriate.		
Answer Options	Response Percent	Response Count
Fever or flu like symptoms	81%	17

Gastrointestinal issues	29%	6
Edema	10%	2
Headaches	52%	11
Disrupted sleep	33%	7
Appetite loss or weight gain	43%	9
Fatigue	76%	16
Nausea or vomiting	67%	14
Shortness of breath	10%	2
None	4%	1

SYSF reported that respondents noted symptoms of fatigue and mild flu like symptoms such as fever and chills, but noted that these symptoms were manageable. None of respondents interviewed showed any severe side effects to treatment. But when asked, they were willing to go to extreme lengths to work through any side effects as they still felt treatment options are not readily available for patients with melanoma.

Respondents who were interviewed by SYSF reported the benefits outweighing the risks of treatment. According to SYSF, respondents that had experienced with the combination treatment noted positive effects in that some observed a complete response and the complete disappearance of all signs of cancer. Other respondents had other tumours appear and will need new treatment options.

To help provide context on patient experiences with the combination therapy, MNC highlighted the key comments that were reported by the respondents to help illustrate the impact of the combination treatment of dabrafenib and trametinib:

- My husband has been on it since February with stable disease as of July's scans. Prior to that he was treated with stereotactic brain radiation surgery x 8 brain tumors on two occasions, Vemurafenib alone, and Vemurafenib + XL888(pre-clinical trial drug) and dabrafenib alone. Now, his energy level and skin color have returned to his pre stage 4 level on the dabrafenib and Mekinist combo.
- I've been on the GSK combo since last August (started one year ago on this day). I believe that the reported progression free survival median is 10.5 months. In my case, the GSK combo dramatically reduced my tumor burden (let's say ballpark 70%) initially. I've been stable since my February scans.
- I've had significant reduction on the Vemurafenib however was too weak a therapy for the brain mets and 5 new mets developed after radiation in spite of the Vemurafenib, which is what prompted the change to dabrafenib and Mekinist. So far no new brain mets since October. Seven of the 8 brain mets no longer detectable on MRI.
- I started the combo in Dec 2013 and had dramatic reduction in size of many of the subQ masses and stabilization of the rest. Over time I had continued reduction in size, but they only lasted 5 months for me before things started growing again. Not all at once, but the tumors that were the last to shrink were the first to grow. My local oncologist rushed to get me into a PD-1 EAP and things moved incredibly quickly. I feel extremely lucky to have gotten the care that I have received. The PD-1, so far, appears to be working as again subQ masses are shrinking (though they seem to swell for a bit first). Last May/early June I had 7 brain mets with possible leptomeningeal disease so had to do whole brain radiation last summer. I then had to do stereotactic radiosurgery for 4 more in January and again for 6 or so in May. The last 2 were while I

was on the combo. I have to say I'm a bit nervous about the scans in as I've been having some headaches lately. I think it's just been from overheating and/or dehydration, but it still makes me nervous.

- Diagnosed stage IV with high tumor burden last February. On the Combo, blood improved rapidly, scans in May showing considerable shrinkage. I know it may only be for a short time, but it may get me to the next treatment.
- I did the Ipi/Yervoy last year and the oncologist deemed it a failure. He started me on Braf/MEK in May. I had a scans in July and out of the 15 internal metastases I had, 11 are "resolved", 1 shrunk more than 1 cm and the other 4 in my brain are still in question as I'm getting a Brain MRI next week. They were too small to show up on the PET scan. My Doctor seems to think that the Yervoy is actually helping the Braf/MEK as I had some spots disappear very early on with the Braf/MEK. Either way, the Braf/MEK is definitely working and I'm glad to hear that the expected extension of wellness is 25 months, not just 10.
- She was diagnosed with Stage IV with heavy tumor load in June 2014 (first CT); started on the combo on the 14th. Her second CT (August) showed >30% reduction in tumor burden. September she had her first PET/CT scan and the PET part was fully negative / complete response, HURRAY :). So she's been on the combo for 8 months now, and we hope she can get more mileage out of it.
- I progressed after 6 months of side-effect hell on Zelboraf. Started Tafinlar this past August and it was like a miracle drug. Large tumor in my ear is nearly gone, brain mets after gamma knife still shrinking. Added MEK in December, and while nothing so dramatic happened, my only side-effect has been peeling feet and one day of fever.
- I've been on MEK combo for about eight months. Have had several bouts of fevers/chills (none recently). One time I went to the ER and was given fluids--they mostly check for what is causing the fever, to make sure that it's not caused by an infection. I try to stay well-hydrated, and when I'm feeling light-headed or fatigued often drinking a sports drink, like Gatorade, will relieve it somewhat. Often the RN is more up-to-date than the oncologist about side-effects--especially in places where there have not yet been many MEK patients. If the difficulty climbing the stairs was the result of fatigue, that sounds unusual--if it's because of the severe foot soreness that comes seemingly randomly, it's totally normal and will likely pass.
- My side effects didn't kick in till around the 6 week mark. Up till then I only experienced mild sensations of warm/hot hands & feet & mild aching legs - nothing that required painkillers. At 6 weeks I had fever, mouth ulcers, dehydration, & painful legs. Ended up having Dabrafenib and Mek dose reduced and a course of prednisone. Have been fine ever since & pretty much live life as I used to. Even rocked along at a Bruce Springsteen concert on the weekend! I am NED (i.e., no evidence of disease) now - started my treatment last August.
- Been on the combo since mid-December and have yet to have any side effects (I think). I've had an increase in acne most likely due to extra dry skin that isn't exfoliating well, but that could also just be winter. I have to really scrub my face every day to keep it at bay. Otherwise, no side effects at all.

- I have been on the "combo" since Sept 30, 2014 and started experiencing the chills and liver level increases a month later. My doctor pulled me off the drugs until Nov 12 when my levels were more normal. He then put me back on dabrafenib only for a couple weeks and then added only 1/2 dose of mekinist. I got the chills again and took another break. I'm now trying 1/2 dose of each drug in the hopes that I can tolerate them at lower doses. I have several lung nodules, all of which have decreased in size and metabolic activity (PET done last week) so I am determined to find a way to stay on this. It really seems to be working for me.
- The combo is much less harsh in that regard than the Zelboraf was, at least for me. I have some increased fatigue, which I also had with the Zelboraf, and increased digestive sensitivity, particularly to any foods that are spicy.

4.3 Additional Information

MNC indicated that while there are a couple of therapies that have been approved for the treatment of metastatic melanoma in the last few years, it is currently at the infancy stage in determining which drug or combination therapy works the best or can continue to be offered when another has failed. According to MNC, while the number of respondents who had been on the combination therapy were relatively small, the combination BRAF inhibitor therapies have the ability to act to stop or control the disease that a monotherapy alone cannot.

Similarly, SYSF report that many melanoma patients indicated their concerns that there are still not enough treatment options available in a timely fashion. Some had to find this treatment on their own and most had to travel outside of their province to get the treatment. This added emotional and financial stress to an already very stressful diagnosis. There is also concern that their needs are not being met and that their issues are not being heard. SYSF also believes that there should be unified melanoma protocols across the country.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of dabrafenib/trametinib combination therapy for melanoma:

Clinical factors:

- Availability of data regarding the sequencing of BRAF inhibitors: vemurafenib, dabrafenib monotherapy, trametinib monotherapy
- Relative benefits and risks of combination therapy versus monotherapy
- The benefits of adding the second drug when patients have already started with one

Economic factors:

- High cost of combination drugs
- Cost-effectiveness of combination therapy compared to monotherapy

Please see below for more details.

5.1 Factors Related to Comparators

Vemurafenib is the standard of care in all of the provinces, except one, in the treatment of BRAF mutation positive metastatic melanoma. PAG noted that some provinces already fund dabrafenib and trametinib as monotherapy. The comparators in the trials provided with this submission include dabrafenib monotherapy and vemurafenib, so are relevant for the Canadian context.

5.2 Factors Related to Patient Population

PAG is seeking information on whether adding dabrafenib or trametinib would be beneficial for patients who have already started one as monotherapy and either have not yet progressed or have progressed on monotherapy.

Recognizing that the data may be not be available or be limited, PAG is seeking information on the benefits of using dabrafenib/trametinib combination therapy, either before or after treatment with

1. Ipilimumab
2. Vemurafenib
3. dabrafenib monotherapy
4. trametinib monotherapy

5.3 Factors Related to Dosing

Taking two different drugs may not appeal to patients if taking one drug provides similar clinical outcomes. PAG has concerns with patient compliance due to pill burden and dose confusion. The dose of dabrafenib is two capsules twice daily and the dose of trametinib is one tablet once daily. There are some concerns that patients may confuse the number of tablets versus the number of capsules and the frequency of the tablets versus the frequency of the capsules. These are barriers to implementation.

In addition, although the standard dose is a flat dose for both drugs, there are two strengths for each drug to allow for dose adjustments and there may be the potential for dosing errors if patients have multiple strengths.

5.4 Factors Related to Implementation Costs

In most provinces, dabrafenib and trametinib are funded as monotherapy and there is familiarity with their use. These are enablers to implementation.

PAG is seeking information on the clinical benefits and cost-effectiveness of combination therapy over monotherapy.

5.5 Factors Related to Health System

PAG noted that both dabrafenib and trametinib are oral drugs that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is 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.

With two different drugs, two dispensing fees, two co-payments and varying deductibles would be applied in provinces where oral drugs are funded through its pharmacare program.

PAG also noted that the BRAF testing is already available in the provinces but in some provinces, the assay is conducted out-of-province and there may be delays in receiving the results to begin treatment promptly.

5.6 Factors Related to Manufacturer

The high cost of combination therapy compared to monotherapy is a barrier to implementation.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness and safety of dabrafenib (Tafinlar) in combination with Trametinib (Mekinist), for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

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

- Critical appraisal of a network meta-analysis comparing dabrafenib plus trametinib with single-agent dabrafenib, trametinib, vemurafenib, ipilimumab, and dacarbazine for unresectable or metastatic melanoma.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Phase III Randomized control trials	- Unresectable or metastatic melanoma - Validated test for BRAF V600 mutation	dabrafenib (Tafinlar) 150mg (2-75mg capsules) twice daily for a daily dose of 300mg plus Trametinib (Mekinist) 2mg tablet once daily	dabrafenib placebo vemurafenib ipilimumab dacarbazine temozolomide fotemustine carboplatin paclitaxel interleukin-2	-Response rate - Overall survival -Progression free survival - Adverse events - Quality of life

Notes:

* 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- 2015) with in-process records & daily updates via Ovid; EMBASE (1980-2015) via Ovid; The Cochrane Central Register of Controlled Trials (February 2015) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were [dabrafenib (Tafinlar) and trametinib (Mekinist)] and {metastatic or unresectable melanoma}.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was limited to the English language.

The search is considered up to date as of June 8, 2015.

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 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:

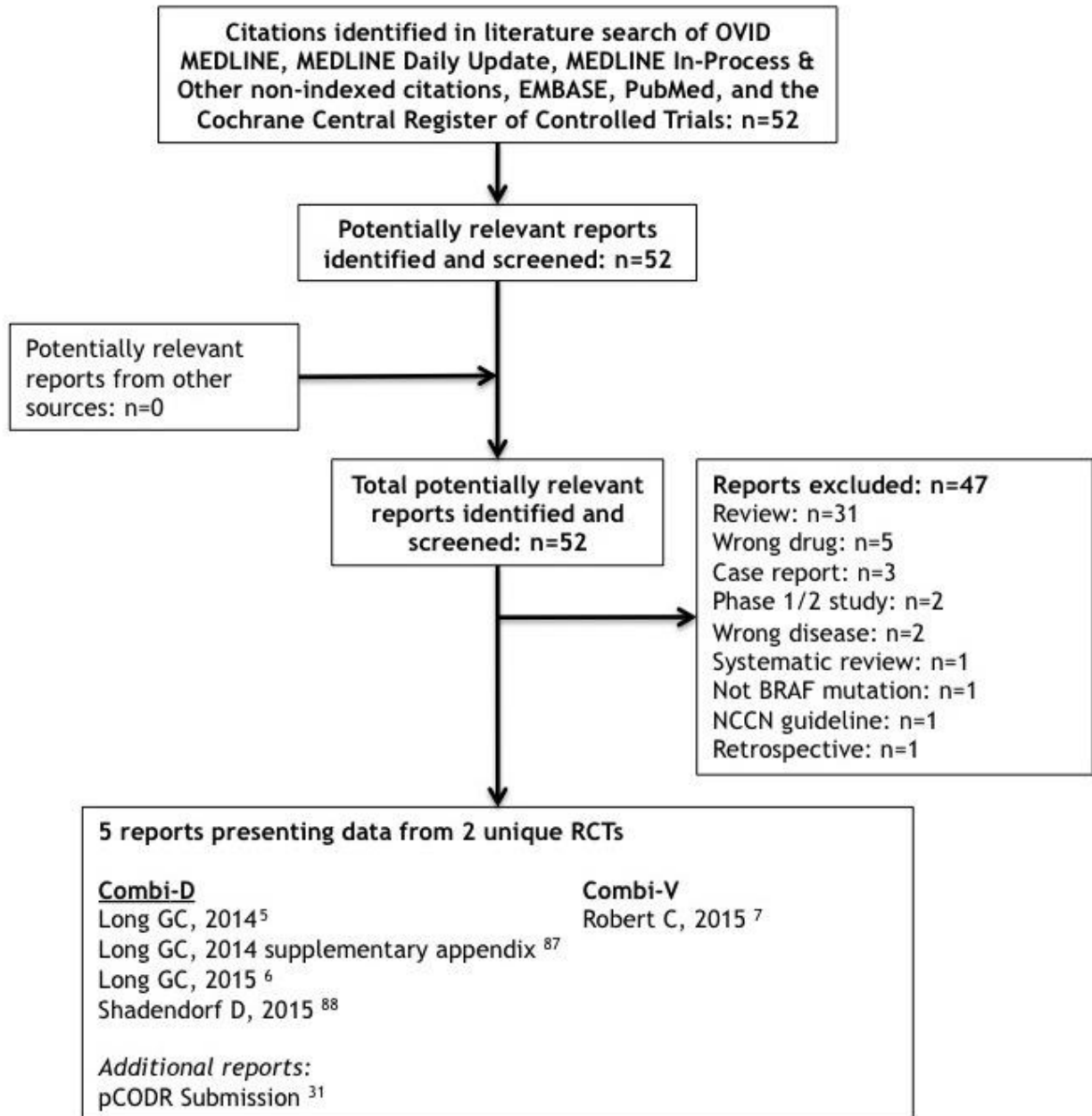
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions 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 [52] potentially relevant reports identified, [4] reports were included in the pCODR systematic review [Long, 2015 #356; Long, 2014 #308; Robert, 2015 #307; Schadendorf, 2015 #348] and [31] studies were excluded. Studies were excluded because they were [reviews, ^{29,41-70}], [wrong drug, ⁷¹⁻⁷⁵], [wrong disease, ^{76,77}], [systematic review, abstract ⁷⁸], [Not BRAF mutation, ⁷⁹], [case report, ⁸⁰⁻⁸²], [NCCN guideline, ⁸³], [phase 1/2 study, ^{84,85}].

Figure1: QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to studies [Combi-d and Combi-v] were also obtained through requests to the Submitter by pCODR

6.3.2 Summary of Included Studies

Two randomized controlled trials met the inclusion criteria for this systematic review, Combi-d^{5,6} and Combi-v.⁷

6.3.2.1 Detailed Trial Characteristics

Table 4. Summary of Trial characteristics of the included Study			
Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Combined BRAF and MEK inhibition versus BRAF inhibition alone in Melanoma - Combi-d ^{5,28}			
<p>NCT01584648 Combi-d</p> <p>Phase 3, randomized, double blind</p> <p>N=423</p> <p>dabrafenib and trametinib N=211</p> <p>dabrafenib and placebo N= 212</p> <p>113 centres in 14 countries including: Argentina, Australia, Canada, France, Germany, Greece, Italy, Netherlands, Russian federation, Spain, Sweden, Ukraine, United Kingdom and the United States of America</p> <p>Patients enrolled from: May 2012 to January 2013</p> <p>Funded by: GlaxoSmithKline. Studied products were later acquired by Novartis</p>	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Histologically confirmed cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV (metastatic), and determined to be BRAF V600E/K mutation-positive using the bioMerieux (bMx) investigational use only (IUO) THxID BRAF Assay (IDE: G120011). Subjects with ocular or mucosal melanoma are not eligible. • A radiologically measurable tumour • ECOG PS of 0 or 1 • Able to swallow and retain oral medication • Use acceptable methods of contraception during the study • Adequate organ system function and blood counts • Age ≥18 years <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Prior treatment with a BRAF or a MEK inhibitor • Prior systemic anti-cancer treatment for Stage IIIC (unresectable) or Stage IV (metastatic) melanoma. Prior systemic treatment in the adjuvant setting is allowed. (Note: Ipilimumab treatment must end at least 8 weeks prior to randomization.) • Major surgery or certain types of cancer therapy with 21 days of starting treatment • Use of prohibited medication listed in the protocol 	<p>dabrafenib 150 mg twice daily and trametinib 2 mg once daily</p> <p>vs.</p> <p>dabrafenib 150 mg twice daily and placebo</p>	<p>Primary outcome</p> <ul style="list-style-type: none"> • Progression-Free Survival <p>Secondary Outcomes</p> <ul style="list-style-type: none"> • Overall Survival • Overall response rate • Duration of response for patients with a confirmed response • Adverse events • Pharmacokinetics

Table 4. Summary of Trial characteristics of the included Study			
Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
	<ul style="list-style-type: none"> • Left ventricular ejection fraction less than the lower limit of normal • Uncontrolled blood pressure • Retinal vein occlusion or central serous retinopathy • Active brain metastases • The subject is pregnant or nursing 		
Improved overall survival in melanoma with Combined dabrafenib and trametinib - Combi-v ^{7,86}			
<p>NCT01597908 Combi-v</p> <p>Phase 3, randomized, open label</p> <p>N=704</p> <p>dabrafenib and trametinib N=352 vemurafenib N= 352</p> <p>193 centres in 28 countries including: Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech republic, Denmark Finland, France, Germany, Hungary, Ireland, Israel, Italy, South Korea, Netherlands, New Zealand, Norway, Poland, Russian federation, Spain, Sweden, Switzerland, Taiwan, Ukraine, United Kingdom and the United States of America</p> <p>Study start date: June 2012 Study Completion date: September 2018</p> <p>Funded by: GlaxoSmithKline. Studied products were later acquired by Novartis</p>	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • >= 18 years of age • Stage IIIC or Stage IV BRAF V600E/K cutaneous melanoma • Measurable disease according to RECIST 1.1 • Women of childbearing potential with negative serum pregnancy test • ECOG PS of 0 or 1 • Adequate baseline organ function <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Any prior use of a BRAF or MEK inhibitor • Prior systemic anti-cancer treatment for Stage IIIC (unresectable) or Stage IV (metastatic) melanoma; prior systemic treatment in the adjuvant setting is allowed • History of another malignancy (except subjects who have been disease free for 3 years or with a history of completely resected non-melanoma skin cancer) • Known active HIV, HBV, HCV infection • Active brain metastases • History or evidence of cardiovascular risk • History or current evidence/risk of retinal vein occlusion or central serous retinopathy 	<p>dabrafenib 150 mg twice daily and trametinib 2 mg once daily</p> <p>vs.</p> <p>vemurafenib 960 mg twice daily</p>	<p>Primary Outcome:</p> <ul style="list-style-type: none"> • Overall Survival <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • Progression-free survival • Overall response • Duration of response
ECOG PS= Eastern Oncology Group Performance Status;			

a) *Trials*

Characteristics of the trials' designs can be found in Table 4. Combi-d included patients with BRAF V600 mutation-positive metastatic melanoma that was not previously treated in the metastatic stage and unresectable melanoma that is stage IIIC and has also not been previously treated in this stage.⁵ This was a phase 3, double blind and randomized trial. Patients received either dabrafenib 150 mg twice daily and trametinib 2 mg once daily or dabrafenib 150 mg twice daily and a placebo. The patients and their caregivers, investigators, and the outcome assessors were blinded to the treatment given.²⁸

Combi-v included patients with stage IIIC (unresectable) and IV (metastatic) melanoma that was not previously treated in the metastatic setting. This was a phase 3 open label randomized trial. Patients received either dabrafenib 150 mg twice daily and trametinib 2 mg once daily or vemurafenib 960 mg twice daily.⁷

Both trials were multicentre studies: the Combi-d study was conducted at 113 sites in Europe, Australia, and North America²⁸), while the Combi-v study was conducted at 193 sites in Asia, Europe, Australia, and North and South America.⁸⁶ Both studies were funded by Glaxo Smith Kline. Studied products were later acquired by Novartis.^{5,7} The method of randomization was the same for the two trials. Both trials were stratified by baseline lactate dehydrogenase level and BRAF genotype.^{5,7} Patients were then centrally randomized by a computer-generated number in a 1:1 ratio.³⁰

The primary outcome in the Combi-d trial was investigator-assessed, progression-free survival. It was defined as the time from randomization until radiologic disease progression or death from any cause. In addition, a central review committee that was unaware of the study assignment reviewed the radiologic findings on which a sensitivity analysis of progression free survival was based.⁵ The secondary outcomes were overall survival, response rate, response duration, adverse events and pharmacokinetics.⁵ The Combi-d trial was not terminated early and the results in the Long et al. report are based on an August 2013 analysis when the prescribed number (n=193) of disease progressions or death had occurred.⁵ The trial was originally powered at 90% to detect a 41% reduction in the risk of disease progression or death (HR 0.59) in the dabrafenib plus trametinib group with a one-sided type 1 error rate of 0.025. The study was over-enrolled by 24% and therefore the power increased to 95%.⁵ An interim analysis was planned for the time of the progression free analysis. "The stopping boundary for the interim analysis of overall survival was a two-sided alpha level of less than 0.00028."⁵ The final overall survival analysis will be done when 70% of the patients have died or have been lost to follow-up.⁵

The primary outcome in the Combi-v trial was overall survival. This was defined as the time from randomization until death from any cause.⁷ The secondary outcomes were progression free survival, overall response rate, duration of response and safety.⁷ The investigators estimated that 288 events would be needed to detect a hazard ratio of 0.675.⁷ The Combi-v trial was stopped early for efficacy and thus the interim summary for overall survival is deemed to be the final analysis of overall survival.⁷ The planned interim analysis for overall survival was to be conducted when 202 events had been observed. Due to the slowness of data entry, the actual number of events was 222 at the time of the interim analysis. As a result, per protocol efficacy boundaries were adjusted. The adjusted stopping boundary was $P < 0.0214$ for the efficacy analysis and $P > 0.2210$ for the futility analysis.⁷

b) Populations

A total of 423 patients (dabrafenib plus trametinib, n=211; dabrafenib plus placebo, n=212) were randomized in the Combi-d trial⁵ and 704 patients (dabrafenib plus trametinib, n=352; vemurafenib, n=352) were randomized in the Combi-v trial.⁷ The baseline characteristics of both trials can be found in table 5.

Table 5: Baseline patient characteristic.

Characteristic	Combi-d ⁵			Combi-v ⁷		
	Dabrafenib + trametinib N=211	Dabrafenib + placebo N=212	All Combi-d patients N=423	Dabrafenib + trametinib N=352	Vemurafenib N=352	All Combi-v patients N=704
Median age (range) - year	55.0 (22-89)	56.5 (22-86)	56.0 (22-89)	55(18-91)	54 (18-88)	55 (18-91)
Male sex - n (%)	111 (53)	114 (54)	225 (53)	208 (59)	180 (51)	388 (55)
Previous immunotherapy n (%)	56 (27)	61 (29)	117 (28)	61 (17)	93(26)	154 (22)
ECOG PS - n (%)						
0	155 (74)	150 (71)	305 (72)	248 (71)	248 (70)	496 (71)
1	55 (26)	61 (29)	116 (28)	102 (29)	104 (30)	206 (29)
BRAF mutation - n (%)	*	*	*	¶	¶	¶
V600E	179 (85)	181 (85)	360 (85)	312 (90)	317 (90)	629 (89)
V600K	32 (15)	30 (14)§	62 (15)	34 (10)	34 (10)	68 (10)
Tumour stage - n (%)						
IVM1c	142 (67)	138 (65)	280 (66)	221 (63)	208 (59)	429 (61)
IIIC, IVM1a or IVM1b	69 (33)	73 (34)	142 (34)	130 (37)	143 (41)	273 (39)
Metastasis stage - n (%)						
M0	5(2)	10 (5)	15 (4)	14 (4)	26 (7)	40 (6)
M1a	19 (9)	31 (15)	50 (12)	55 (16)	50(14)	105 (15)
M1b	45 (21)	32 (15)	77 (18)	61 (17)	67 (19)	128 (18)
M1c	142 (67)	138 (65)	280 (66)	221 (63)	208 (59)	429 (61)
Lactate dehydrogenase level -n (%)						
> ULN	77 (37)	71 (34)	148 (35)	118 (34)	114 (32)	232 (33)
≤ ULN	133 (63)	140 (66)	273 (65)	233 (66)	238 (68)	471 (67)
Visceral disease						
Yes	165 (78)	145 (68)	310 (73)	278 (79)	271 (77)	549 (78)
No	46 (22)	66 (31)	112 (26)	73 (21)	81 (23)	154 (22)
Number of disease sites n (%)§						

Characteristic	Combi-d ⁵			Combi-v ⁷		
	Dabrafenib + trametinib N=211	Dabrafenib + placebo N=212	All Combi-d patients N=423	Dabrafenib + trametinib N=352	Vemurafenib N=352	All Combi-v patients N=704
≤ 2	109 (52)	119 (56)	228 (54)	177 (50)	201 (57)	378 (54)
≥ 3	101 (48)	92 (44)	193 (46)	174 (50)	151 (43)	325 (46)

* A patient with both BRAF V600E and V600K mutation was included in the V600K group
¶ Six patients in the Combination and one in the vemurafenib group had both BRAF V600E and V600K mutations and were excluded from either subgroup
§ This category refers to the number of unique target and nontarget sites that were identified by the investigator on the basis of Response Evaluation Criteria in Solid Tumours (RECIST) and not by the number of metastases

c) Interventions

In the Combi-d, trial patients were randomized to receive dabrafenib plus trametinib versus dabrafenib plus placebo⁵ and in Combi-v, patients were randomized to receive dabrafenib plus trametinib versus vemurafenib. Details of the dose and administration of treatment and control arms for both trials can be found in Table xx. For the Combi-d trial the mean daily dose of trametinib was 1.9mg (0.20 SD) and 275.0mg (SD 40.54) for dabrafenib. The median time on treatment was 8.0 months for the combination arm 7.0 months for the dabrafenib only arm. In the Combi-v trial the mean daily dose of trametinib was 1.8mg (0.27 SD) and 261.0mg (SD 52.58) for dabrafenib. The mean daily dose of vemurafenib was 1615.9mg (358.76 SD). The median time on treatment was 10.0 months for the combination arm 6.0 months for the vemurafenib arm.³⁰

In both trials, if a single or consecutive dose was missed it was classified as an interruption. If a dose was missed for more than two consecutive days it was classified as a dose reduction.^{5,7} Patients in the Combi-d trial who had grade 2 adverse events were recommended to have dose interruptions or modifications. Patients were required to have dose modification or interruptions for grade 3 and 4 adverse events.⁵ Patients who permanently stopped the drug were reported in 19 out of 209 patients (9%) in the dabrafenib plus trametinib arm and in 11 of the 211 patients (5%) in the dabrafenib plus placebo arm. Dose reductions were needed in 52 (25%) of patients in the combination arm and in 28 (13%) of patients in the dabrafenib plus placebo arm. The interruptions of treatment due to adverse effects were required on 103 patients (49%) in the combination arm and in 70 patients (33%) in the dabrafenib only arm.⁵

Treatment was permanently discontinued in the Combi-v trial in 13% of patients in the dabrafenib plus trametinib arm and in 12% of the patients in the vemurafenib arm.⁷ Some of the reasons for discontinuation in the dabrafenib plus trametinib were pyrexia and decreased ejection fraction (3% for each event) and arthralgia (2%) in the vemurafenib group. Dose reductions occurred in 33% of patients in the dabrafenib plus trametinib arm and in 39% of patients in the vemurafenib arm. Dose interruptions took place in 55% and 56% of patients respectively. In the dabrafenib plus trametinib arm the most common reason for a dose interruption or reduction was pyrexia (30%) and (14%) respectively. In the vemurafenib arm the most common reason for a dose interruption or reduction was rash (14%) and (11%).⁷

d) Patient Disposition

In the Combi-d trial, 211 patients were randomized to the dabrafenib plus trametinib arm and included in the intention to treat analysis (ITT). One patient did not receive treatment because of a randomization error and another because of non-compliance. Therefore 209 patients received the medications and were included in the safety analysis. Of these 102 (48%) died or progressed; 111 (53%) continued treatment, 41 (19%) continued beyond progression, 43 (20%) are in follow-up; 11 withdrew consent, 2 withdrew at the investigators discretion and 4 were lost to follow up. In the dabrafenib plus placebo arm, 212 patients were randomized and were included in the ITT analysis. One patient was randomized, but did not receive the study drug. Therefore, 211 patients were included in the safety analysis. Of these, 109 (51%) died, 90 (42%) continued treatment; 34 (16%) continued beyond progression; 57 (27%) are in follow up; 5 withdrew consent; 2 withdrew at the investigators discretion and 3 were lost to follow up.⁵ In the dabrafenib plus trametinib arm six patients were censored in the first 2 months after randomization: 1 due to clinical progression, 1 commenced a new anti-cancer therapy, 1 randomization error, 1 withdrew consent for tolerability and travel; 1 withdrew to try a new treatment and 1 was withdrawn by the investigator for noncompliance. In the dabrafenib plus placebo group 18 patients were censored during the first two months after randomization; 13 due to clinical progression or a new anti-cancer therapy; 1 randomization error; 1 withdrew consent for travel, 1 was withdrawn by the investigator for noncompliance; 1 withdrew after an adverse event and 1 was lost to follow up.⁸⁷ There were less patients in the dabrafenib plus trametinib group than in the dabrafenib plus placebo group who received a second type of anticancer treatment n=43 (20%) vs. n= 65 (31%). However, there were a greater number of patients in the dabrafenib plus trametinib group n=41 (19%) than in the dabrafenib plus placebo group n=34 (16%) who continued treatment beyond progression. This was still at the time of the August 2013 data cut-off n=19 (46%) vs. n=7 (21%).^{5,30} Beyond progression was defined as the time difference between the date of progression and the date of the last dose was at least 15 days %).³⁰

In the Combi-v trial 352 patients were randomized to the dabrafenib plus trametinib arm and included in the ITT analysis. Two patients did not receive the drug as they were randomized in error. Three hundred and fifty patients received the drug and were included in the safety analysis. Of these 4 were lost to follow up; 2 withdrew due to investigator decision and 10 patients withdrew consent.⁷ One hundred and seventy four (49%) patients continued treatment, of these 80 (23%) continued beyond progression. Sixty two (5%) patients are in follow-up and 100 (28%) patients died.³¹

Three hundred and fifty two patients were randomized to vemurafenib and included in the ITT analysis. Three patients did not receive the drug because they withdrew consent. Therefore, 349 patients received the drug and were included in the safety analysis. Of these 9 were lost to follow up; 1 withdrew due to investigator decision and 18 patients withdrew consent.⁷ Eighty nine (25%) patients continued treatment, of these 81 (23%) continued beyond progression. One hundred and thirteen (32%) patients are in follow-up and 122 (35%) patients died³¹ There were more patients in the vemurafenib group that received subsequent anticancer treatment after the discontinuation of study treatment 43% compared to 20% in the dabrafenib plus trametinib group.⁷ Treatment beyond progression was continued for at least 15 days after disease progression in 80 (23%) patients in the dabrafenib plus trametinib group and 81 (23%) patients in the vemurafenib

group. The protocol approved for continuing treating beyond progression for patients who appear to benefit from the treatment in spite of RECIST progression.⁷ The two groups had a similar median duration of treatment after progression and it was less than three months for most of the patients. Nine percent of patients in the dabrafenib plus trametinib group received treatment beyond progression for longer than six months, compared to one percent of patients in the vemurafenib group.⁷

e) Limitations/Sources of Bias

Both trials were generally well conducted, however, the study personnel, treating physicians, and patients were not blinded to treatment assignment in the Combi-d trial. This could have affected the results, especially for patient-reported outcomes, in favour of whichever arm the assessor felt was likely to provide benefit. More importantly, tumour response and progression-free survival (the primary outcome) were unbiased outcomes, as a blinded and independent committee conducted tumour assessments.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Progression Free survival

The primary endpoint in the Combi-d trial was progression free survival. It was significantly longer in the dabrafenib plus trametinib group than in the dabrafenib plus placebo group (9.3 months vs. 8.8 months; HR 0.75 (95% CI, 0.57-0.99; p=0.03).⁵ At the time of the final analysis in January 2015 the estimated median progression free survival was longer in the dabrafenib plus trametinib arm 11.0 (95% CI; 8.0-13.9) months compared to 8.8 (95% CI; 5.9-9.3) months in the dabrafenib monotherapy arm. HR 0.67; 95% CI 0.53-0.84; p=0.0004).⁶

In addition the dabrafenib plus trametinib combination showed a benefit in progression free survival in the following subgroups: V600 mutation type, stage, number of site, visceral disease present, sex, age (<65 years), baseline LDH level, greater than three disease sites and ECOG status. The only groups that did not show a benefit were age ≥65 and less than 2 disease sites.⁵ In patients with an elevated lactate dehydrogenase levels at baseline, the median progression free survival rate was 7.1 months in the dabrafenib plus trametinib group, compared to 3.8 months for the dabrafenib plus placebo group, (HR 0.64; 95%CI, 0.42-0.95).⁵

Pre-planned sensitivity analyses for progression free survival were performed in the Combi-d trial. In these analyses the hazard ratio for progression and median progression-free survival for the dabrafenib plus trametinib group “remained the same when clinical progression was considered or decreased by 0.1 month when the initiation of a new anticancer therapy was considered”.⁵ However, “the median progression-free survival in the dabrafenib plus placebo group decreased by 1.2 months when clinical progression was considered and by 1.6 months when the initiation of a new anticancer therapy was considered”.⁵ These results can be seen in table 5.

Table 5: Sensitivity analysis for progression free survival⁸⁷

	Clinical progression		New Anticancer Therapy		Independent review committee	
	Dabrafenib + trametinib N=211	Dabrafenib + placebo N=212	Dabrafenib + trametinib N=211	Dabrafenib + placebo N=212	Dabrafenib + trametinib N=211	Dabrafenib + placebo N=212
Events - N	103	113	108	124	93	94
Median - months	9.3	7.6	9.2	7.2	10.2	9.5
HR for progression (95% CI)	0.73 (0.56-0.96)		0.71 (0.55 - 0.92)		0.78 (0.59 - 1.04)	

In the Combi-v trial, progression free survival was a secondary outcome. In the dabrafenib plus trametinib group, the median progression-free survival was lengthier than in the vemurafenib group (11.4 months vs. 7.3 months; HR 0.56; 95% CI, 0.46 - 0.69; P<0.001) Subgroup analyses were conducted for V600 mutation type, sex, age (<65 years vs. ≥65 years), baseline LDH level, tumour stage, number of disease sites and ECOG status. The hazard ratio in all the above subgroup favoured combination therapy in all subgroups.⁷ An update of progression free survival for this group is not available.

Overall survival

In the Combi-d trial overall survival was a secondary outcome and the results that follow are based on an interim analysis. At the time of this interim analysis 40 patients (19%) in the dabrafenib plus trametinib group and 55 patients (26%) in the dabrafenib plus placebo group had died (hazard ratio for death, 0.63; 95% CI, 0.42 to 0.94; P=0.02). The overall survival rate at six months was 93% in the dabrafenib plus trametinib group and 85% in the dabrafenib plus placebo group.⁵ It should be noted that “the between-group difference did not cross the pre-specified stopping boundary (two-sided P=0.00028).”⁵ From a January 2015 analysis the median overall survival was 25.1 month in the combination arm compared to 18.7 months in the dabrafenib plus placebo arm. The combination arm demonstrated a statistically significant reduction 29% in the risk of death (HR 0.71;95%CI0.55-0.92;p=0.0107).⁶ In patients with an elevated lactate dehydrogenase level the median survival for the dabrafenib plus trametinib group was 13.7 months versus 8.9 months for dabrafenib plus placebo group (hazard ratio for death, 0.48; 95% CI, 0.29 to 0.80). In these patients 24 out of 77 (31%) deaths occurred in the dabrafenib plus trametinib group and 36 out of 71 (51%) deaths occurred in the dabrafenib plus placebo group. There is a difference between deaths that occurred in patients with an elevated lactate dehydrogenase level and those with a normal level. In the normal lactate dehydrogenase level group, there were 16 of 133 patients (12%) deaths in the dabrafenib plus trametinib group and 19 of 140 patients (14%) in the dabrafenib plus placebo group.⁵ In the figure for overall survival, the curve separates at 2 months with the combination group on top and then the lines cross at 14 months and are very close together and are parallel. The same phenomena happens in the patients with an elevated lactate dehydrogenase level at baseline, but the curves are wider apart from 3 months to 13 months when they cross and remain parallel.⁵

Overall survival was the primary outcome in the Combi-v trial and it was based on an interim analysis after 222 events had occurred. There were 100 (28%) deaths in the dabrafenib plus trametinib group and 122 (35%) deaths in the vemurafenib group (HR for death in the dabrafenib plus trametinib group, 0.69; 95% CI, 0.53 to 0.89; P=0.005).⁷ The trial was stopped for efficacy on July 14, 2014 since the prespecified stopping boundary (P<0.0214) was crossed. Patients were then allowed to cross over the dabrafenib plus trametinib group as a protocol amendment was issued. However, no patient crossed over before the data freeze date of June 27, 2014.⁷ The median overall survival for the dabrafenib plus trametinib group was not yet reached and the median overall survival was 17.2 months for patients in the vemurafenib group. The survival curves separate around 3.5 months and then stay separate.⁷ In the dabrafenib plus trametinib arm the rate of overall survival at 12 months was 72% (95% CI, 67 to 77) and it was 65% (95% CI, 59 to 70) in the vemurafenib group. Subgroup analyses were conducted for V600 mutation type, sex, age (<65 years vs. ≥65 years), baseline LDH level, and ECOG status. These were not powered to demonstrate a significant between-group difference, but they all favoured the dabrafenib plus trametinib group except for the analysis of patients with an ECOG score of 1; the HR for this was 1.03.⁷ An update of overall survival for this group is not available.

Response Rate

The investigator-assessed overall response rate in the Combi-d trial was 67% (95% CI, 60 to 73) in the dabrafenib plus trametinib group versus 51% (95% CI, 45 to 58) in the dabrafenib plus placebo group (P=0.002).⁵ A complete response was seen in 22 (10%) patients in the dabrafenib plus trametinib group and in 18 (9%) in the dabrafenib plus placebo group. A partial response was seen in 118 (56%) of the dabrafenib plus trametinib group and in 90 (43%) in the dabrafenib plus placebo group.⁵ The full results can be seen in table 6. The median duration of response was extremely censored since the majority of investigator-assessed responses (60%) were still ongoing. In the dabrafenib plus trametinib group, the median duration of response was 9.2 months and 10.2 months in the dabrafenib plus placebo group.⁵

Table 6: Disease response⁵

	BRAF V600E and BRAF V600K		BRAF V600E		BRAF V600K	
	Dabrafenib + trametinib N=210 (%)	Dabrafenib + placebo N=210 (%)	Dabrafenib + trametinib N=179 (%)	Dabrafenib + placebo N=180 (%)	Dabrafenib + trametinib N=31 (%)	Dabrafenib + placebo N=30 (%)
Complete response	22 (10)	18 (9)	19 (11)	16 (9)	3 (10)	2 (7)
Partial response	118 (56)	90 (43)	102 (57)	80 (44)	16 (52)	10 (33)
Stable response	54 (26)	69 (33)	46 (26)	62 (34)	8 (26)	7 (23)
Progressive disease	13 (6)	19 (9)	10 (6)	11 (6)	3 (10)	8 (27)
Could not be evaluated	3 (1)	14 (7)	2 (1)	11 (6)	1(3)	3 (10)

In the Combi-v trial, the objective response rate was 64% (95% CI, 59 to 69) in the dabrafenib plus trametinib group versus 51% (95% CI, 46 to 57) in the vemurafenib

group (P<0.001).⁷ A complete response was seen in 47 patients (13%) in the dabrafenib plus trametinib group, and in 27 patients (8%) in the vemurafenib group.⁷ The results can be seen in table 7. The median duration of response in the dabrafenib plus trametinib arm was 13.8 months (95% CI, 11.0 to not reached) and in the vemurafenib arm it was 7.5 months (95% CI, 7.3 to 9.3).⁷ Subgroup analyses were conducted in the BRAF subgroups. In the BRAF V600E subgroup the response was comparable to that in the overall population in both study groups. It was 64% for the dabrafenib plus trametinib group and 52% in the vemurafenib group. In the BRAF V600K subgroup, the response rates were 65% for the combination group and 44% for the vemurafenib group.⁷

Table 7: investigator-assessed response in the Combi-v trial ⁷

Response	Dabrafenib plus trametinib N=351 (%)	Vemurafenib N=350 (%)
Complete response	47 (13)	27 (8)
Partial response	179 (51)	153 (44)
Stable response	92 (26)	106 (30)
Progressive disease	22 (6)	38 (11)
Could not be evaluated	11 (3)	26 (7)
Data are missing from 1 patient in the dabrafenib plus trametinib group and for 2 patients in the vemurafenib group because these patients did not have measureable disease at baseline		

Quality of Life

Quality of Life was assessed in the Combi-d trial by the EORTC QLQ-C30 generic cancer questionnaire that assesses global health quality of life, functional status and symptom impact.⁸⁸ The completion rates for the questionnaire were >90% at baseline and at weeks, 8, 16, 24 and 32 and 71% at progression. Both arms in the Combi-d trial were comparable at baseline.⁸⁸ However, the global health QOL portion of the questionnaire was significantly better at weeks 8, 16 and 24 for the combination arm. In the other areas of the questionnaire such as functional dimensions (physical, social, role emotional and cognitive functioning) most of the scores leaned towards the combination arm. For symptom impact, the pain scores were significantly improved and clinically meaningful (6-13 point difference) for the combination arm on follow-up assessments. However, other symptoms such as nausea, vomiting, diarrhea, dyspnea and constipation all leaned towards dabrafenib plus placebo, with nausea and vomiting being significant.⁸⁸

Table 8: Quality of Life changes ⁸⁸

Dimension	Week 8	Week 16	Week 24	Week 32	Progression
Global health/QOL	+ *	+ *	+ *	+	+
Functioning					
Cognitive	+	-	-	-	-

Dimension	Week 8	Week 16	Week 24	Week 32	Progression
Emotional	+	+	+	+	+
Physical	+	+ *	+	+	+
Role	+	+	+ *	+*	+
Social	+	+	+	+ *	+
Symptoms					
Appetite loss	-	-	+	-	+
Constipation	-	-	-	-	+
Diarrhea	-	-	-	-	-
Dyspnea	-	-	-	-	-
Fatigue	-	+	+	+	+
Insomnia	+	+	+	+	+
Nausea and vomiting	-	- *	- *	-	-
Pain	+ *	+ *	+ *	+ *	+ *
+ favours dabrafenib plus trametinib * p< 0.05 - favours dabrafenib plus placebo					

In the Combi-V trial health-related quality of life (HRQOL) was assessed by the EORTC-QLQ-C30, the EQ-5D and the Melanoma subscale of the FACT-M. Completion rates for both treatment arms were higher than 95% at baseline, above 80% at all assessments until week 56, and 70% or higher at the disease progression.³⁰

In the EORTC-QLQ-C30, quality of life as measured by the global health status score was significantly better for patients who received the combination therapy compared to vemurafenib at Weeks 8, 16, 24, 32, 40, 48, and at progressive disease. The domains of the EORTC-QLQ-C30 that showed the best improvements relative to baseline scores and largest clinically meaningful differences compared to vemurafenib are as follows: global health (5.2 to 7.9 points), role functioning (7.4 to 14.7 points), social functioning (8.5 to 11.8 points), physical functioning (5.6 to 9.2), appetite loss (7.4 to 14.3), insomnia (6.2 to 13.8), pain (8.1 to 13.2). This can be seen in Table 9.³⁰

Table 9. Mixed-model repeated measures analysis of change from baseline in domains of the EORTC-QLQ-C30 in COMBI-V: differences between dabrafenib plus trametinib combination vs. vemurafenib, 17 April 2014 data cut-off³⁰

Domain	Change from Baseline to:							
	Week 8	Week 16	Week 24	Week 32	Week 40	Week 48	PD	Week 5 Post PD
Global Health Status/QoL	7.92‡	7.62‡	6.86‡	7.47‡	5.16†	7.56‡	7.57‡	6.46
Functional Domains								
Physical Functioning	6.49‡	6.27‡	5.61‡	7.08‡	7.90‡	8.74‡	9.15‡	8.92*
Role Functioning	10.00‡	7.44‡	8.96‡	12.61‡	9.93‡	14.68‡	13.60‡	11.31‡
Emotional Functioning	4.15†	5.36‡	4.95†	6.19‡	4.66*	6.23†	6.32‡	6.01
Cognitive Functioning	3.53†	2.82*	2.28	3.27*	2.24	3.22	5.44†	11.71†
Social Functioning	9.91‡	9.20‡	8.48‡	11.81‡	11.12‡	9.73‡	10.09‡	16.55‡
Symptom Domains								
Fatigue	-0.99‡	-6.18‡	-4.25‡	-8.05‡	-8.05‡	-9.29‡	-8.27‡	-7.05‡
Nausea & Vomiting	-5.33‡	-2.38	-1.62	-4.17†	-2.01	-0.02	-4.12*	1.89
Pain	-13.20‡	-8.05‡	-8.82‡	-12.69‡	-12.46‡	-11.41‡	-10.57‡	-10.74‡
Dyspnoea	-2.94	0.65	-1.76	0.59	-1.21	-2.68	-3.29	-0.89
Insomnia	-11.19‡	-6.62†	-7.25‡	-11.19‡	-11.99‡	-13.78‡	-10.53‡	-9.46
Appetite Loss	-14.26‡	-10.38‡	-10.75‡	-8.92‡	-7.43†	-7.44†	-11.90‡	-3.75
Constipation	3.46	4.15*	3.07	4.32*	3.67*	3.84	0.54	-2.17
Diarrhea	-8.82‡	-13.87‡	-16.08‡	-16.19‡	-13.74‡	-16.76‡	-11.24‡	-0.07‡
Financial Difficulties	-3.12	-1.06	-0.55	-3.53	-6.18†	-3.65	-2.99	-16.37‡

*p<.05; †p<.01; ‡p<.001

The mean EQ-5D utility values at baseline were higher for the combination therapy arm (0.751 vs. 0.715 for vemurafenib monotherapy), although, EQ-5D utility values were lower for subjects in the vemurafenib monotherapy arm at all assessments. The difference in mean change in EQ-5D utility score was significantly different at all assessments.³⁰

The FACT-M Melanoma subscale scores were higher than baseline for the dabrafenib plus trametinib group combination therapy and they were lower than baseline for vemurafenib at all assessments. The differences between treatment arms were statistically significant and clinically meaningful in favour of the combination arm.³¹

Harms Outcomes

In the Combi-d trial, grade 3 or 4 adverse events occurred in 73 patients (35%) in the dabrafenib plus trametinib group and in 79 patients (37%) in the dabrafenib plus placebo group. In the dabrafenib plus trametinib arms, pyrexia, hypertension and elevated aspartate aminotransferase were the most common grade 3 adverse events, which occurred in at least 10% of patients who received at least one dose of the study drug.⁵ In the dabrafenib plus placebo arms, hypertension was the most common grade

3 adverse events, which occurred in at least 10% of patients who received at least one dose of the study drug and cutaneous squamous-cell carcinoma including keratoacanthoma was the most common adverse event in this group that occurred in <10% of patients.⁵ The full list can be seen in table 10. The table only lists grade 3 events since there were only 14 patients that had grade 4 events. In the dabrafenib plus trametinib arm seven patients had a grade 4 event in the following categories, anemia, decreased lymphocyte count, hypoglycaemia, pulmonary embolism, brain edema, hepatic hematoma, metastasis to the central nervous system and pancytopenia. One patient experienced two events, brain edema and metastasis to the central nervous system.³⁰ In the dabrafenib plus placebo arm six patients had grade 4 events in the following categories: dyspnea, thrombocytopenia, hypokalemia, cutaneous squamous-cell carcinoma, brain edema, hypercalcemia, febrile neutropenia and hypovolemic shock.⁵ One patient experienced two events, febrile neutropenia and hypovolemic shock.³⁰ The pharmacokinetic analysis indicated a probable link between “pyrexia and exposure to the hydroxy-dabrafenib metabolite and, to a lesser extent, to dabrafenib in the two study groups.”⁵ Likewise, trametinib exposure was related to pyrexia in the combination group.⁵

In the Combi-v trial, grade 3 or 4 adverse events occurred in 52% of the patients in the dabrafenib plus trametinib group and in 63% in the vemurafenib group.⁷ In the dabrafenib plus trametinib arms, pyrexia, hypertension and elevated alanine aminotransferase were the most common grade 3 adverse events, which occurred in $\geq 10\%$ of patients.⁷ In the vemurafenib arm, hypertension, arthralgia, rash and elevated alanine aminotransferase were the most common grade 3 adverse events, which occurred $\geq 10\%$ of patients. The most common adverse event that occurred in <10% of patients in the combination group was decreased ejection fraction. In the vemurafenib group it was cutaneous squamous-cell carcinoma including keratoacanthoma.⁷ The full list can be seen in table 10. The table only lists grade 3 events since only 16³⁰ patients had grade 4 events. In the dabrafenib plus trametinib arm the following grade 4 events occurred: blood creatine phosphokinase increased (3 subjects), hyperglycemia (2 subjects); hyponatremia, headache, asthenia, aspartate amino transferase increased, hepatic enzyme increased, electrocardiogram QT prolonged, cellulitis, renal failure, duodenal ulcer, lipase increased, haemorrhage, sepsis, acute myeloid leukaemia, duodenal perforation, Escherichia sepsis, hypertransaminasaemia, tumor rupture (1 subject each).³⁰ In the vemurafenib group 23³⁰ patients had grade 4 events in the following categories: increased gamma-glutamyl transferase (3 subjects), alanine aminotransferase increased (2 subjects), hepatic enzyme increased (2 subjects), hypocalcaemia (2 subjects); hypertension, constipation, neutropenia, dyspnea, hyperglycemia, blood creatine phosphokinase increased, electrocardiogram QT prolonged, blood bilirubin increased, squamous cell carcinoma, urticaria, cerebral haemorrhage, febrile neutropenia, general physical health deterioration, cholelithiasis, keratoacanthoma, squamous cell carcinoma of skin, ileus, large intestine perforation, metastases to meninges, uterine haemorrhage (1 subject each)³⁰

Table 10: Adverse events

Event	Combi-d ⁵		Combi-v ⁷	
	Dabrafenib + trametinib N=209 (%)	Dabrafenib + placebo N=211 (%)	Dabrafenib + trametinib N=350 (%)	Vemurafenib N=349
	Grade 3	Grade 3	Grade 3	Grade 3 (%)
	Adverse events that occurred in at least 10% of patients who received at least one dose of a study drug		Clinically significant adverse events occurring in ≥ 10% of patients	
Any adverse event	66 (32)	72 (34)	167 (48)	198 (57)
Pyrexia	12 (6)	4 (2)	15 (4)	2(<1)
Fatigue	4 (2)	2 (1)	4 (1)	6 (2)
Headache	1 (<1)	3(1)	3 (<1)	2 (<1)
Nausea	0	3 (1)	1 (<1)	2 (<1)
Chills	0	0	3 (1)	0
Arthralgia	1 (<1)	0	3 (1)	15 (4)
Diarrhea	2(1)	2 (1)	4 (1)	1 (<1)
Rash	0	2 (1)	4 (1)	30 (9)
Hypertension	8(4)	10 (5)	48 (14)	32 (9)
Vomiting	2(1)	1 (<1)	4 (1)	3(<1)
Peripheral edema	1(<1)	1 (<1)	1 (<1)	1 (<1)
Pain in limb	3 (1)	1 (<1)	4 (1)	1 (<1)
Decreased appetite	1 (<1)	2 (1)	2 (<1)	0
Elevated alanine aminotransferase	4(2)	1 (<1)	9 (3)	13 (4)
Elevated aspartate aminotransferase	6 (3)	1 (<1)	4 (1)	9 (3)
Asthenia	1 (<1)	1 (<1)	4 (1)	4 (1)
Adverse events occurring in <10% of patients				
Cutaneous squamous-cell carcinoma including keratoacanthoma	4(2)	8 (4)	5 (1)	60 (17)
Decreased ejection fraction	1 (<1)	1 (<1)	13 (4)	0
Dermatitis acneform	0	0	0	4 (1)

Deaths

As of April 10, 2014 in the Combi-d trial, there were 40 deaths in the dabrafenib plus trametinib arm and 55 deaths in the dabrafenib plus placebo arm.²⁸ There were four deaths related to adverse events that took place in the dabrafenib plus trametinib group. There were three deaths from cerebral hemorrhage (two

happened during study treatment and one took place 5 days after treatment ended) and one another death from pneumonia. This took place 22 days after the end of treatment. The study investigator believed the deaths to be unrelated to study treatment. There were no deaths related to adverse events in the dabrafenib plus placebo group.⁵

As of April 17, 2014 in the Combi-v trial, there were 99 deaths in the dabrafenib plus trametinib arm and 122 deaths in the vemurafenib arm.³⁰ In the Combi-v trial, there were six deaths related to adverse events, however the investigator believed them to be unrelated to the study drugs. In the dabrafenib plus trametinib arm, two patients died from cerebral hemorrhage and one from a brain-stem hemorrhage, and in the vemurafenib group one patient from acute coronary syndrome, another from cerebral ischemia, and the third from pleural infection.⁷

6.4 Ongoing Trials

Six ongoing trials were found through searching in clinicaltrials.gov.

Table 11: Ongoing clinical trials

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Phase 1 Study of the BRAF Inhibitor Dabrafenib +/- MEK Inhibitor Trametinib in Combination With Ipilimumab for V600E/K Mutation Positive Metastatic or Unresectable Melanoma ⁸⁹ https://www.clinicaltrials.gov/ct2/show/NCT01767454?term=dabrafenib+trametinib&rank=2			
<p>NCT01767454</p> <p>Phase 1, randomized, open label</p> <p>Estimated enrolment N=72</p> <p>Location: United States of America</p> <p>Start date: February 2013</p> <p>Completion date: December 2014</p> <p>Funded by: GlaxoSmithKline</p>	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • >= 18 years of age • Stage IIIC (unresectable) or Stage IV (metastatic), and determined to be BRAF V600E or V600K mutation-positive. Subjects with ocular or mucosal melanoma are not eligible • Measurable tumor • Not more than 1 previous treatment with chemotherapy, interferon, or IL-2 for metastatic melanoma • All prior anti-cancer treatment-related toxicities must be <= Grade 1 • ECOG PS of 0 or 1 • Adequate baseline organ function tests • Negative pregnancy test • Agree to use effective contraception • Able to swallow and retain oral study treatment <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Prior treatment with a BRAF inhibitor • Any major surgery • Radiotherapy, or systemic treatment with delayed toxicity 21 days prior to randomization • HIV, HBV, or Hepatitis C Virus • A history of glucose-6-phosphate dehydrogenase (G6PD) deficiency 	<p>Dabrafenib 100 mg or 150 mg BID plus ipilimumab 3 mg/kg intravenously over 90 minutes Q3W for a total of 4 doses</p> <p>vs.</p> <p>Dabrafenib 100 mg or 150 mg BID orally plus Trametinib 1 mg or 2 mg orally, once daily plus Ipilimumab 3 mg/kg intravenously over 90 minutes Q3W for a total of 4 doses</p>	<p>Primary outcome</p> <ul style="list-style-type: none"> • Number of subjects with Adverse • Changes in laboratory values, vital signs, and physical examinations as a measure of safety <p>Secondary Outcome</p> <ul style="list-style-type: none"> • Overall response rate

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
	<ul style="list-style-type: none"> • Most brain metastasis are excluded • History or evidence of cardiovascular risk • A history or current evidence/risk of retinal vein occlusion (RVO) or Central serous retinopathy (CSR) • Autoimmune diseases • Active pneumonitis or interstitial lung disease • History of another malignancy • Serious and/or unstable pre-existing medical, psychiatric disorder or other conditions • Any prohibited medication 		
<p>COMBI-AD: A Phase III Randomized Double Blind Study of Dabrafenib (GSK2118436) in COMBINATION With Trametinib (GSK1120212) Versus Two Placebos in the ADJUVANT Treatment of High-risk BRAF V600 Mutation-positive Melanoma After Surgical Resection⁹⁰ https://www.clinicaltrials.gov/ct2/show/study/NCT01682083?term=dabrafenib+trametinib&rank=3&show_locs=Y#locn</p>			
<p>NCT01682083 Combi-AD</p> <p>Phase 3, randomized, double blind</p> <p>Estimated enrolment N=852</p> <p>Location: Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech republic, Denmark, France, Germany, Greece, Israel, Italy, Japan, Netherlands, New Zealand, Norway, Poland, Russian federation, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States of America</p> <p>Start date: January 2013 Completion date: July 2015</p> <p>Funded by: GlaxoSmithKline</p>	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Completely resected histologically confirmed high-risk [Stage IIIA (LN metastasis more than 1 mm), IIIB or IIIC cutaneous melanoma determined to be V600E/K mutation positive .Patients presenting with initial resectable lymph node recurrence after a diagnosis of Stage I or II melanoma are eligible. • Surgically rendered free of disease no more than 12 weeks before randomization. • Recovered from definitive surgery • ECOG PS of 0-1. • Adequate hematologic, hepatic, renal and cardiac function. <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Known mucosal or ocular melanoma or the presence of unresectable in-transit metastases. • Evidence of distant metastatic disease. • Prior systemic anti-cancer treatment and radiotherapy for melanoma • History of another malignancy or concurrent malignancy including prior malignant melanoma. • History or current evidence of cardiovascular risk. • History or current evidence of retinal vein occlusion (RVO) or central serous retinopathy (CSR) 	<p>dabrafenib (150 milligram (mg) twice daily [BID]) and trametinib (2 mg once daily [QD])</p> <p>Vs. Placebos</p>	<p>Primary Outcome</p> <ul style="list-style-type: none"> • Relapse-free survival (RFS) <p>Secondary Outcomes</p> <ul style="list-style-type: none"> • Overall survival • Distant metastasis-free survival (DMFS) • Freedom from relapse (FFR) • Safety of dabrafenib and trametinib
<p>Phase II Biomarker Study Evaluating The Upfront Combination Of BRAF Inhibitor Dabrafenib With MEK Inhibitor Trametinib Versus The Combination After Eight Weeks Of Monotherapy With Dabrafenib Or Trametinib In Patients With Metastatic And Unresectable Stage III Or IV Melanoma Harbouring An Activating BRAF Mutation⁹¹ https://www.clinicaltrials.gov/ct2/show/NCT02314143?term=dabrafenib+trametinib&rank=10</p>			

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
<p>NCT02314143</p> <p>Phase 2, randomized, open label</p> <p>Estimated enrolment N=54</p> <p>Location: France,</p> <p>Start date: November 2013</p> <p>Completion date: May 2015</p> <p>Funded by: GlaxoSmithKline</p>	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • signed written informed consent • age >=18 years • Participants with histologically confirmed cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV (metastatic) • BRAF V600E/K mutation-positive • Accessible tumours for biopsies • Measurable disease according to RECIST 1.1 on not biopsied lesions. • All prior anti-cancer treatment-related toxicities must be <= Grade 1 • Able to swallow and retain orally administered medication. • Women of childbearing potential must have a negative pregnancy test use effective contraception, throughout the study • ECOG PS of 0 or 1. • Adequate baseline organ function <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Prior treatment with a BRAF or MEK inhibitor • Any major surgery, extensive radiotherapy, systemic treatment with delayed toxicity • Taken an investigational drug within 28 days or 5 half-lives prior to randomisation • Current use of a prohibited medication. • Refusal of tumour and skin biopsies. • History of another malignancy. • Any serious and/or unstable pre-existing medical conditions. • Known HIV, HBV or HCV). • A history of glucose-6-phosphate dehydrogenase (G6PD) deficiency. • Most brain metastases are excluded • A history or evidence of cardiovascular risk • A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) • Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO). • Pregnant or lactating females • Interstitial lung disease or pneumonitis 	<p>Arm A Dabrafenib 150 milligrams (mg) twice a day (BID) continuously during 8 weeks followed by trametinib 2 mg once daily with dabrafenib 150 mg BID</p> <p>Arm B Trametinib 2 mg/day continuously during 8 weeks followed by trametinib 2 mg once daily with dabrafenib 150 mg BID</p> <p>Arm C Trametinib 2 mg/day plus dabrafenib 150 mg BID</p>	<p>Primary Outcome</p> <ul style="list-style-type: none"> • Percentage Change of ERK phosphorylation score from Baseline. • Secondary Outcome • Evaluation of the overall response rate • Characterisation of the safety profile of dabrafenib and trametinib in monotherapy with vital signs and physical examinations • Adverse events and safety • Pharmacodynamics and toxicity
<p>A Randomized Phase II Trial of Intermittent Versus Continuous Dosing of Dabrafenib (NSC-763760) and Trametinib (NSC-763093) in BRAF V600E/K Mutant Melanoma⁹² https://www.clinicaltrials.gov/ct2/show/NCT02196181?term=dabrafenib+trametinib&rank=13</p>			
<p>NCT02196181</p> <p>Phase 2, randomized, open label</p>	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Patients must have confirmed stage IV or unresectable stage III BRAF V600E or BRAF V600K mutant melanoma 	<p>Arm I (continuous dosing) Patients receive dabrafenib PO BID</p>	<p>Primary Outcome</p> <ul style="list-style-type: none"> • progression-free survival

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
<p>Estimated enrolment N=280</p> <p>Location: Multicentred in the United States of America</p> <p>Start date: November 2013 Completion date: May 2015</p> <p>Funded by: National Cancer Institute (NCI)</p>	<ul style="list-style-type: none"> • Contrast-enhanced computed tomography (CT) scans of the neck, chest, abdomen and pelvis are required • Patients must not have received a prior BRAF or mitogen-activated protein kinase kinase (MEK) inhibitor • Patients must not have brain metastases • Not received any anti-cancer drug within 28 days prior to registration, and must not have received any nitrosoureas or mitomycin C within 42 days prior to registration • Not received any major surgery, radiotherapy, or immunotherapy within 28 days prior to registration • Not have any unresolved toxicity greater than grade 1 from previous anti-cancer therapy except alopecia • Adequate baseline organ function • Must have lactate dehydrogenase (LDH) obtained within 28 days prior to registration in order to obtain baseline stratification information • Must have a left ventricular ejection fraction (LVEF) \geq institutional lower limit of normal (ILLN) by echocardiogram (ECHO) or multi gated acquisition scan (MUGA) within 28 days prior to registration • Must have corrected QT interval (QTc) \leq 480 msec by electrocardiogram (ECG) (corrected using the Bazett's formula) within 28 days prior to registration • Known history or current evidence of retinal vein occlusion (RVO) or central serous retinopathy (CSR) are not eligible: • Must be able to take oral medications • Patients receiving anticoagulation treatment are allowed to participate with international normalized ratio (INR) established within the therapeutic range • Not have a history of pneumonitis or interstitial lung disease • Patients must not have any grade II/III/IV cardiac disease as defined by the New York Heart Association criteria • Patients with known hepatitis B or hepatitis C are not eligible, regardless of concomitant antiretroviral therapy or current viral load • Patients with known HIV may be eligible providing they meet certain criteria • Prestudy history and physical must be obtained with 28 days prior to registration • Patients must have dermatology exam • Patients must have Zubrod performance status of 0 or 1 	<p>and trametinib PO QD on days 1-56. Courses repeat every 56 days in the absence of disease progression or unacceptable toxicity.</p> <p>Experimental: Arm II (intermittent dosing) Patients receive dabrafenib PO BID and trametinib PO QD on days 1-7 and 29-56. Courses repeat every 56 days in the absence of disease progression or unacceptable toxicity.</p>	<p>Secondary Outcomes</p> <ul style="list-style-type: none"> • Overall survival • Response rates • Rates of fever

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
	<ul style="list-style-type: none"> No other prior malignancy is allowed Patients must not be pregnant or nursing; women/men of reproductive potential must use an effective contraceptive method <p>Exclusion criteria was not listed</p>		
<p>A Sequential Safety and Biomarker Study of BRAF-MEK Inhibition on the Immune Response in the Context of CTLA-4 Blockade for BRAF Mutant Melanoma⁹³ https://www.clinicaltrials.gov/ct2/show/NCT01940809?term=dabrafenib+trametinib&rank=18</p>			
<p>NCT01940809</p> <p>Phase 1, randomized, open label</p> <p>Estimated enrolment N=40</p> <p>Location: The United States of America</p> <p>Start date: August 2013 Completion date: June 2016</p> <p>Funded by: National Cancer Institute (NCI)</p>	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> Must have confirmed unresectable or metastatic malignant melanoma Must have measurable disease. Must have completed any prior treatment at least 3 weeks prior to treatment on this protocol. (ECOG PS =< 2 Karnofsky >= 60% Adequate baseline organ function tests Left ventricular ejection fraction >= (LLN) by echocardiogram (ECHO) Must not have malabsorption or swallowing difficulties Must have BRAFV600E or BRAFV600K mutations. Therapeutic level dosing of warfarin can be used with close monitoring of PT/INR Women of child-bearing potential must agree to use adequate contraception All prior treatment-related toxicities must be grade =< 1 (except alopecia) at the time of randomization <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> Use of other investigational drugs within 28 days Study participants with a history of prior treatment with BRAF or MEK inhibitors Autoimmune disease: Known immune impairment who may be unable to respond to anti-cytotoxic T-lymphocyte antigen 4 (CTLA 4) antibody Study participants with brain metastases Hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO) Current use of a prohibited medication; Human immunodeficiency virus (HIV)- A history of HBV or HCV Patients with history of rat sarcoma (RAS) mutation-positive tumors are not eligible History or evidence of cardiovascular risks Any condition which in the investigator's opinion makes the subject unsuitable for study participation 	<p>Arm A dabrafenib PO BID and trametinib PO QD for 25 days. Patients then receive ipilimumab IV over 90 minutes. Treatment with ipilimumab repeats every 3 weeks for 4 courses</p> <p>Arm B trametinib PO QD for 25 days. Patients then receive ipilimumab IV over 90 minutes. Treatment with ipilimumab repeats every 3 weeks for 4 courses</p> <p>Arm C dabrafenib PO BID for 25 days. Patients then receive ipilimumab IV over 90 minutes. Treatment with ipilimumab repeats every 3 weeks for 4 courses</p> <p>Arm D ipilimumab IV over 90 minutes Treatment repeats every 3 weeks for 4 courses</p>	<p>Primary Outcome:</p> <p>I. To evaluate the safety and tolerability of ipilimumab following lead-in of v-raf murine sarcoma viral oncogene homolog B1 (BRAF) and mitogen-activated protein kinase kinase (MEK) inhibitors, either alone or in Combination, in patients with BRAFV600 mutant melanoma.</p> <p>SECONDARY OBJECTIVES:</p> <p>I. To determine the response rate to ipilimumab after BRAF and MEK inhibitors, either alone or in Combination, compared to no prior kinase inhibitor treatment.</p> <p>II. To determine the safety and tolerability of dabrafenib and trametinib Combination in the setting of prior ipilimumab alone or ipilimumab proceeded by BRAF and MEK inhibitors, either alone or in Combination.</p> <p>III. To determine the response rate to dabrafenib and trametinib in the setting of prior ipilimumab alone or ipilimumab proceeded by BRAF and MEK inhibitors, either alone or in Combination.</p> <p>IV. To obtain peripheral blood and tumor tissue for biomarker analysis.</p>

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
	<ul style="list-style-type: none"> • History of retinal vein occlusion (RVO) • History of interstitial lung disease or pneumonitis 		<p>V. To describe the immune impact of kinase inhibitor therapy on the immune response associated with ipilimumab treatment.</p> <p>VI. To observe and record anti-tumor activity.</p>

A Randomized Phase III Trial of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab at Progression vs. Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib at Progression in Patients With Advanced BRAFV600 Mutant Melanoma ⁹⁴ <https://www.clinicaltrials.gov/ct2/show/NCT02224781?term=dabrafenib+trametinib&rank=22>

<p>NCT02224781</p> <p>Phase 3, randomized, open label, cross over</p> <p>Estimated enrolment N=300</p> <p>Location: The United States of America</p> <p>Start date: November 2014 Completion date: April 2016</p> <p>Funded by: National Cancer Institute (NCI)</p>	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • ECOG PS 0 or 1 • Women must not be pregnant or breast-feeding • Strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse • Patients must have measurable disease • Patients must have histological or cytological confirmation of melanoma that is metastatic or unresectable and clearly progressive • Patients must have BRAFV600E or BRAFV600K mutations, • Patients may have had prior systemic therapy in the adjuvant setting; but no treatment for advanced or prior treatment with a BRAF or MEK inhibitor or a cytotoxic T-lymphocyte-associated protein 4 (CTLA4) or programmed cell death 1 (PD1) pathway blocker; patients may not have had any prior ipilimumab or BRAF inhibitors in the adjuvant setting • Patients must have discontinued chemotherapy, radiation, surgery, immunotherapy or other investigational agents used in the adjuvant setting \geq 4 weeks prior to entering the study and 	<p>Arm A (immunotherapy) IMMUNOTHERAPY INDUCTION (COURSES 1-2): nivolumab IV over 60 minutes and ipilimumab IV over 90 minutes on days 1 and 22. Treatment repeats every 6 weeks for 2 courses IMMUNOTHERAPY MAINTENANCE (COURSES 3-14): nivolumab IV over 60 minutes on days 1, 15, and 29. Treatment repeats every 6 weeks for up to 12 courses Upon disease progression, patients cross over to Arm C.</p> <p>Arm C dabrafenib PO BID and trametinib PO daily on days 1-42. Courses repeat every 6 weeks</p>	<p>Primary Outcome</p> <ul style="list-style-type: none"> • Overall survival <p>Secondary Outcome Measures:</p> <ul style="list-style-type: none"> • PFS • Response rate • Safety <p>Other Outcome Measures:</p> <ul style="list-style-type: none"> • Genetic characteristics • irAE status • HRQL, • Symptom burden
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Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
	<p>recovered from adverse events due to those agents</p> <ul style="list-style-type: none"> • Patients must not receive any other investigational agents while on study or within four weeks prior to registration • Ineligible if they have any currently active central nervous system (CNS) metastases • No other current malignancies • Adequate baseline organ function tests • Not have a serious intercurrent illness • Patients must not have a history of or evidence of cardiovascular risks • Patients with known HIV may be eligible if they meet certain criteria • No known or anticipated interaction between agents being used in the study • No active hepatitis B virus (HBV) or hepatitis C Virus (HCV) infection • No history of clinically significant autoimmune disease • Patients must not take St. John's wort or hyperforin or grapefruit juice • Patients must not have history of retinal vein occlusion (RVO) • Patients must not have evidence of interstitial lung disease or pneumonitis • Patients must not have malabsorption, or swallowing difficulty, • Patients must not have any serious or unstable pre-existing medical conditions • STEP 2 (CROSSOVER ARM FOR PATIENTS WITH PROGRESSIVE DISEASE) • The patient must have met all eligibility criteria above at the time of crossover • Patients must have melanoma that is metastatic and progressive • Patients must be within 6 weeks of documented progressive disease (PD) on first arms of current study; all sites of disease must be evaluated within 4 weeks prior to randomization; patients must have measurable disease • Must be recovered from AEs of prior therapy • Must have discontinued radiation therapy or surgery \geq 2 weeks prior to registering to Step 2 of the study and recovered from any adverse events associated with treatment • Must not receive any other investigational agents while on study or within two weeks prior to registration • No currently active CNS metastases • No other current malignancies, 	<p>Arm B dabrafenib PO BID and trametinib PO daily on days 1-42. Courses repeat every 6 weeks Upon disease progression, patients cross over to Arm D.</p> <p>Arm D IMMUNOTHERAPY INDUCTION (COURSES 1-2): nivolumab IV over 60 minutes and ipilimumab IV over 90 minutes on days 1 and 22. Treatment repeats every 6 weeks for 2 courses IMMUNOTHERAPY MAINTENANCE (COURSES 3-14): Patients receive nivolumab IV over 60 minutes on days 1, 15, and 29. Treatment repeats every 6 weeks for up to 12 courses</p>	

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of to evaluate the effectiveness and safety of dabrafenib (Tafinlar) in combination with Trametinib (Mekinist), for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation:

- Critical appraisal of a network meta-analysis comparing dabrafenib plus trametinib with single-agent dabrafenib, trametinib, vemurafenib, ipilimumab, and dacarbazine for unresectable or metastatic melanoma.³¹

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

7.1 Critical Appraisal of a Network Meta-Analysis Comparing Dabrafenib Plus Trametinib with Single-Agent Dabrafenib, Trametinib, Vemurafenib, Ipilimumab and Dacarbazine for Unresectable or Metastatic Melanoma.

7.1.1 Objective

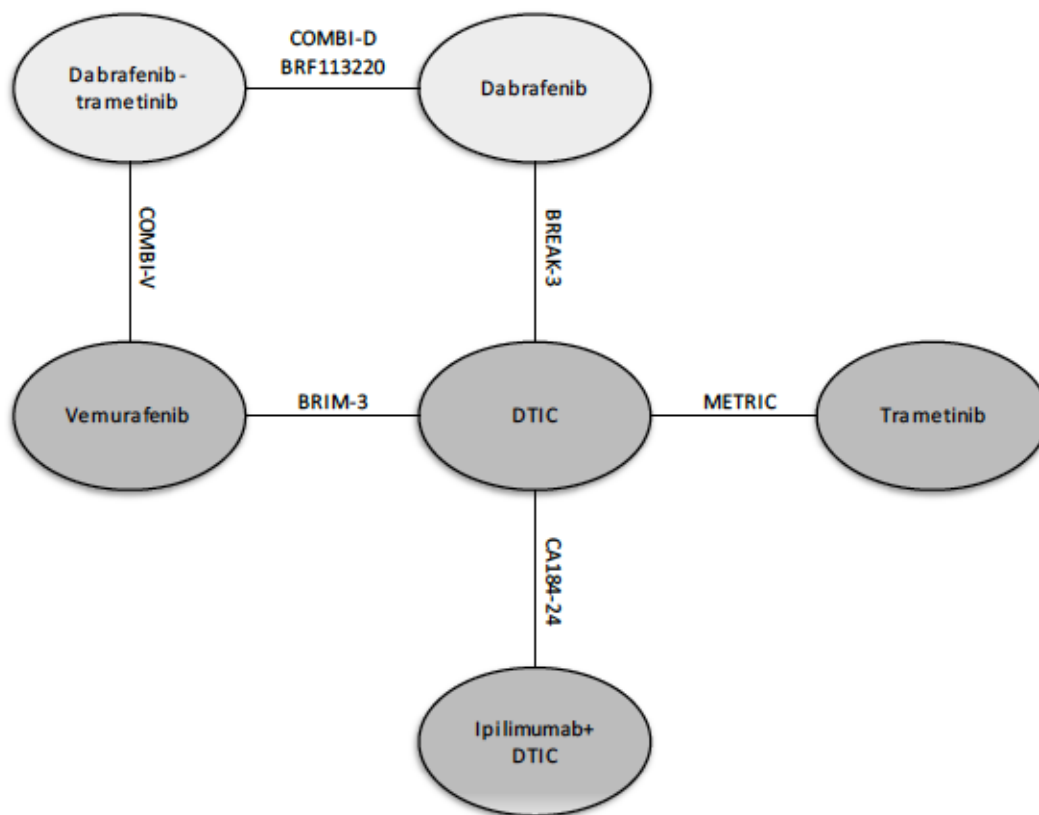
To summarize and critically appraise the methods and findings of the manufacturer-submitted network meta-analysis comparing dabrafenib plus trametinib with single-agent dabrafenib, trametinib, vemurafenib, ipilimumab and dacarbazine for unresectable or metastatic melanoma.

7.1.2 Findings

The manufacturer submitted a network meta-analysis with the objective of estimating the efficacy of dabrafenib plus trametinib indirectly compared to vemurafenib, ipilimumab and dacarbazine. Included in the network were pharmacological interventions for metastatic melanoma. The network diagrams included in the network meta-analysis provided by the manufacturer can be found in Figure 2 and 3.

This network meta-analysis (NMA) used multivariable Bayesian methods to estimate hazard ratios (HRs) for progression free survival and overall survival. The Submitter felt that there is a well-established correlation between treatment effects on PFS and OS in trials of advanced cancer including metastatic melanoma. Therefore, this NMA solved for the HRs for PFS and OS simultaneously. Given the small number of trials a fixed effects model was employed.

Figure 2: Network meta-analysis of Hazard ratios for progression free survival and overall survival assuming no class-effect for BRAF inhibitors.³¹



The main objective of the manufacturer-submitted network meta-analysis (NMA) was to estimate the comparative efficacy of dabrafenib plus trametinib relative to dabrafenib, trametinib, vemurafenib, ipilimumab and dacarbazine for the treatment of patients with metastatic melanoma with BRAF V600E/K mutations. The authors identified seven randomized controlled trials. Five were conducted in patients with BRAF V600E/K mutations (Combi-d, Combi-v, BRF113220, BRIM-3 and METRIC) one was conducted in patients with BRAF V600E mutation only (BREAK-3) and was done in patients not selected for any mutations (CA184-24) In addition, the Combi-d and BRF113220 trial were included in the NMA as the only two randomized controlled trials that have investigated dabrafenib plus trametinib in combination for BRAF V600K/E metastatic melanoma. The submitter commissioned a systematic review that searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to 28 November 2014. The following conferences were searched for abstracts; the American Society of Clinical Oncology, the European Society for Medical Oncology/European Cancer Organization, and the International Congress of the Society for Melanoma Research.³¹ Inclusion was limited to English randomized studies of adult patients with BRAF V600 mutation positive metastatic malignant melanoma. Patients could be receiving their first or second line of therapy for the metastatic stage. The following interventions were identified for inclusion: dabrafenib plus trametinib, dabrafenib, trametinib, vemurafenib + cobimetinib, vemurafenib, and ipilimumab Studies were excluded if they included children and adults and did not provide

subgroup analysis for the adult populations, included patients with melanoma but did not provide subgroup data for patients with metastatic melanoma, studies which recruited patients with all lines of therapy but did not provide subgroup data for patients on first line or second line of treatment, studies that investigated multiple interventions and did not provide subgroup data for biologics interventions of interest and studies that included patients with MMM but did not provide subgroup data for patients with BRAF mutation-positive subtype. The systematic review commissioned for the submitter provided a summary of the trial, study quality and patient characteristics. A brief table is included below. Study quality was appraised using Critical appraisal of included studies was conducted using a comprehensive assessment criteria based on the recommendations in the NICE guidelines (NICE STA 2013).

Table 12: Clinical trials included in the NMA provided by the manufacturer.

Study	Intervention	Comparator	Type	BRAF V600K	BRAF V600E
Combi-d	Dabrafenib and trametinib	Dabrafenib	Phase 3, randomized, double blind trial, Crossover allowed after disease progression. N=423	Yes	Yes
Combi-v	Dabrafenib and trametinib	Vemurafenib	Phase 3, randomized, open label, Crossover prohibited until trial was stopped for efficacy. N=704	Yes	Yes
BRF113220	Dabrafenib and trametinib	Dabrafenib	Phase 1/2, open label, randomized. Crossover allowed after progression. N=247	Yes	Yes
BREAK-3	Dabrafenib	DTIC	Previously untreated, Phase 3, randomized, open label. Crossover allowed after progression. N=250	No	Yes
BRIM-3	Vemurafenib	DTIC	Previously untreated, Phase 3, randomized, open label, Crossover allowed. N=675	Yes	Yes
METRIC	Trametinib	DTIC	Phase 3, randomized, open label, Crossover allowed after disease progression. N=322	Yes	Yes

Study	Intervention	Comparator	Type	BRAF V600K	BRAF V600E
CA184-24	Ipilimumab and DTIC	DTIC	Previously untreated, Phase 3, randomized, double blind trial, crossover not stated N=502	No	No

Note: DTIC=dacarbazine.

The individual progression-free survival and overall survival HR's and 95% confidence intervals (95% CI) can be found in Table 13.

Table 13: Hazard ratios used as inputs for the NMA for primary analysis assuming no class effect for PFS and OS for BRAF inhibitors.³¹

Study	Research	Control	RPSFTM	HR	95% CI	Data Cut-Off	
Progression free survival							
COMBI-V	Dabrafenib-Trametinib	Vemurafenib	n/a	0.56	0.46	0.69	4/17/2014
COMBI-D	Dabrafenib-Trametinib	Dabrafenib	n/a	0.75	0.57	0.99	8/26/2013
BRF113220	Dabrafenib-Trametinib	Dabrafenib	n/a	0.41	0.27	0.64	1/15/2014
BREAK-3	Dabrafenib	DTIC	n/a	0.37	0.23	0.57	6/25/2012
BRIM-3	Vemurafenib	DTIC	n/a	0.38	0.32	0.46	2/12/2012
METRIC	Trametinib	DTIC	n/a	0.44	0.28	0.69	26/11/2011
CA184-24	Ipilimumab + DTIC	DTIC	n/a	0.76	0.63	0.93	n/r
Overall survival							
COMBI-V	Dabrafenib-Trametinib	Vemurafenib	No	0.69	0.53	0.89	4/17/2014
COMBI-D	Dabrafenib-Trametinib	Dabrafenib	No	0.63	0.42	0.94	8/26/2013
BRF113220	Dabrafenib-Trametinib	Dabrafenib	Yes	0.47	0.13	1.66	29/3/2013
BREAK-3	Dabrafenib	DTIC	Yes	0.55	0.21	1.43	12/18/2012
BRIM-3	Vemurafenib	DTIC	Yes	0.64	0.47	0.88	2/12/2012
METRIC (First-line subgroup of primary efficacy population)	Trametinib	DTIC	Yes	0.44	0.20	1.00	16/5/2013
CA184-024	Ipilimumab + DTIC	DTIC	No	0.72	0.59	0.87	n/r
DTIC=dacarbazine; HR= Hazard ratio; n/a = not applicable; n/r = not reported; RPSFTM = Rank Preserving Structural Failure Time Models							

The hazard ratios for progression free survival and overall survival that were in the network meta-analysis are reported in Table 13. The hazard ratios from the METRIC study are based on analyses of the first-line subgroup of the primary efficacy population. The data was taken from the most recent data available for each study. The hazard ratio's for overall survival for the BRIM-3, BREAK-3, METRIC, and BRF113220 trials used rank preserving structural failure time models (RPSFTM) adjusted treatment-group analyses. Model parameters were estimated using the WinBUGS software package (version 1.43), which implements a Markov Chain Monte Carlo (MCMC) sampling method

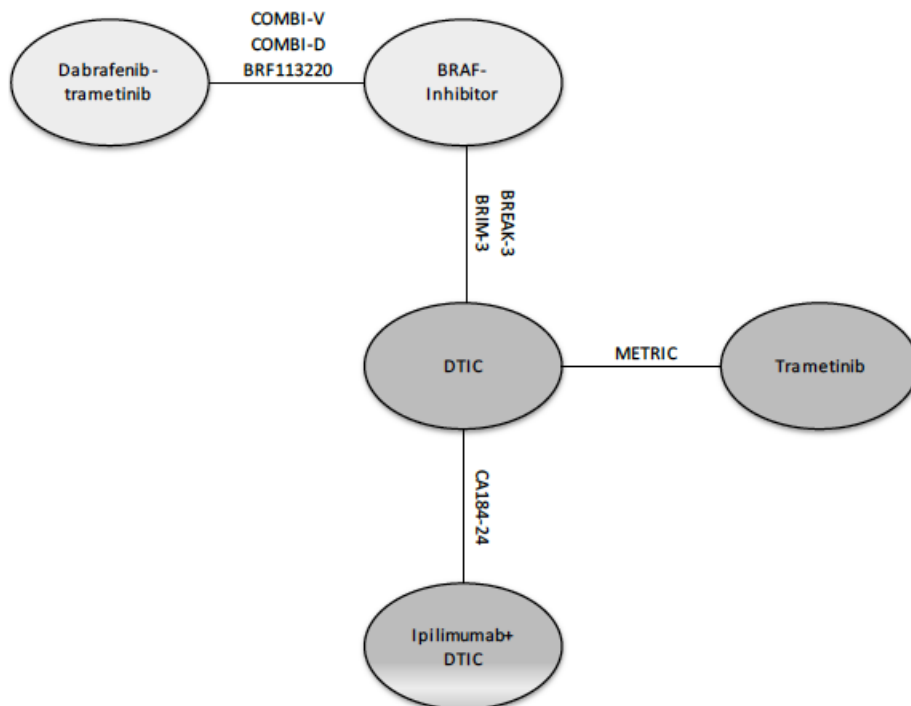
The hazard ratios for progression free survival and overall survival for ipilimumab were based on results of the CA184-024 trial of ipilimumab 10 mg/kg plus dacarbazine vs. dacarbazine alone in treatment-naïve patients. In a previous pCODR review of ipilimumab for first line treatment of metastatic melanoma, pERC and the Clinical Guidance Panel agreed that the 10 mg/kg of ipilimumab used in the study, rather than the approved Canadian dosage of 3 mg/kg for a maximum of four doses would likely be similar.⁹⁵ The pERC also agreed with the Clinical Guidance Panel that there is no evidence that the addition of dacarbazine to ipilimumab provides any

additional effectiveness relative to ipilimumab alone.⁹⁵ The CA184-024 trial is the only RCT in which ipilimumab, alone or in combination with dacarbazine, has been compared with dacarbazine, and is the only trial that is connected (through dacarbazine) to the evidence network for the other therapies included in the NMA.

Secondary analysis

The authors also conducted a secondary analysis where they assumed a class effect for BRAF-inhibitors on PFS and OS. The hazard ratios for the secondary analysis were estimated based on a multivariable Bayesian NMA of the hazard ratios for progression free survival and overall survival from the COMBI-V, COMBI-D, BRF113220, BREAK-3, BRIM-3, METRIC, and CA184-024 trials. The evidence network that was the basis of the network meta-analysis is shown in Figure XX. As a result of the class-effect assumption, the network structure is simplified.

Figure 3. Evidence network for network meta-analysis of hazard ratios for progression free survival and overall survival used in secondary analysis assuming a class-effect for BRAF inhibitors on progression free survival and overall survival³¹



NOTE: The CA184-024 trial compared ipilimumab 10 mg/kg +DTIC vs. DTIC. The model uses the information from this trial to estimate the effectiveness of ipilimumab 3 mg/kg vs. DTIC.

The hazard ratios for progression free survival and overall survival used as inputs in the NMA for the secondary analysis were the same as those used in the primary analysis (Table XX1). The hazard ratios for trametinib, ipilimumab, and dacarbazine vs. the dabrafenib plus trametinib combination that were used in the model were estimated by a multivariable Bayesian NMA using WinBUGS, with the log hazard ratios for progression free survival and overall survival estimated jointly from a multivariate normal distribution.

Limitations

The quality of the manufacturer-submitted NMA was assessed according to the recommendations of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.⁹⁶ Details and commentary with respect to the manufacturer-submitted NMA for each of the items identified by the ISPOR Task Force are provided in Table 14.

There are some limitations with the provided network meta-analysis. The network included studies of patients with only BRAF V600E/K metastatic melanoma as well as data from studies that had included patients with no mutations, but did not report data for the subgroups separately. A primary assumption in meta-analysis is that included studies need to be sufficiently similar to yield meaningful results. In a network meta-analysis, if the trials differ with respect to certain study or patient characteristics, and those characteristics are modifiers of the treatment effect, then the estimate of the indirect comparison may be biased.

Table 14. ISPOR checklist to evaluate a reported network meta-analysis and the scoring for the submitter’s indirect treatment comparison report.⁹⁶		
ISPOR Checklist Item		Details and Comment
1.	Are the rationale for the study and the study objectives stated clearly?	The rationale was not clearly stated, but the objectives were.
2.	Does the methods section include the following: Description of eligibility criteria? Information sources? Study selection process? Data extraction (validity/quality assessment of individual studies)?	Yes, the information sources, search strategy, and study selection criteria were provided by the manufacturer under separate communication. Information was provided on the data extraction process, and on the validity/quality of the individual studies.
3.	Are the outcome measures described?	Yes. Overall survival and progression-free survival.
4.	Is there a description of methods for analysis/synthesis of evidence? Do the methods described include the following: Description of analyses methods/models? Handling of potential bias/inconsistency? Analysis framework?	Bayesian methods were used and described for the meta-analysis. Authors reported results using a fixed effects model. Yes a description of methods used to assess heterogeneity, homogeneity or consistency.
5.	Are sensitivity analyses presented?	Yes. Covariance matrices for the HRs for PFS and OS, used in probabilistic sensitivity analyses are
6.	Do the results include a summary of the studies included in the network meta-analysis? Individual study data? Network of studies?	Yes, a description of the studies with baseline patient characteristics, as well as study design was provided as part of this NMA.
7.	Does the study describe an assessment of model fit? Are competing models being compared?	The authors state that since there was only one comparison for which there was more than one trial to estimate the random effects a fixed effect model was used.
8.	Are the results of the evidence synthesis presented clearly?	Yes. A table summarizing the hazard ratios for individual trials and the indirect comparison are provided. The results of the analyses are presented in tables and in figures.
9.	Does the discussion include the following? Internal validity of analysis? External validity? Implications of results for target audience?	A bit. A very brief description of the findings is included. Internal and external validity of the results are not discussed and the implications of the results for the target audience are very brief as the report focuses more on costs and not clinical implications.

The submitter felt that there was a well-established correlation between progression free survival and overall survival in metastatic melanoma, and used this in the analysis. Therefore the results for the dabrafenib plus trametinib combination compared to other treatments was more favourable than it was when completed assuming independence of treatment effects on progression free survival and overall survival. The submitter also used investigator-assessed progression-free survival and overall survival as the primary outcomes for the NMA. Investigator assessments have the potential to be biased in favour of whichever treatment the investigator feels is superior. This could have led to biased estimates of progression-free survival and overall survival in each of the included studies. By combining the results in a network meta-analysis, the estimate of the indirect comparisons may also be biased. In addition, the definition of progression-free survival and overall survival in each of the included studies may not have been the same. If progression-free survival and overall survival were defined differently across the included trials, the uncertainty around the estimates of the indirect comparisons would increase. This would affect progression-free survival and overall survival estimates. The data from overall survival was incomplete from the Combi-v trial and therefore there is uncertainty regarding the results from this analysis concerning this trial. The differences in the trials' duration of follow-up and other trial characteristics may have also affected the treatment effects observed in each trial thus violating the similarity assumption and confounding these comparisons.

One study allowed for crossover between treatments and cross over was not stated in another. The other studies prohibited crossover until disease progression. The crossover in the BRIM-3 study could have confounded the results for overall survival and also for cost effectiveness of the drug, this was partly solved by using Rank Preserving Structural Failure Time Models (RPSFTM).

7.1.3 Summary

The network meta-analysis provided by the manufacturer investigated combination dabrafenib plus trametinib compared to other pharmacological interventions for patients with BRAF V600K/E metastatic melanoma, using a fixed effects mode. The submitter used these results to estimate the clinical effect between treatments that were not directly compared in RCTs. The results of this NMA were used to inform the submitters' economic evaluation.

There is uncertainty with this NMA since the the differences in the trials characteristics may have affected the treatment effects observed in each trial thus violating the similarity assumption and confounding these comparisons. In addition the submitter felt that there was a well-established correlation between progression free survival and overall survival in metastatic melanoma, and used this in the analysis. Investigator-assessed progression-free survival and overall survival were the primary outcomes for the NMA and they have the potential to be biased in favour of whichever treatment the investigator feels is superior. The definition of progression-free survival and overall survival in each of the included studies was not provided and therefore may not have been the same and thus increasing the uncertainty around the estimates of the indirect comparisons Although the submitter used a Rank Preserving Structural Failure Time Model (RPSFTM), the crossover in the BRIM-3 study could have confounded the results for overall survival and also for cost effectiveness of the drug. The results of the NMA should be interpreted with caution.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Melanoma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on dabrafenib and trametinib 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.cadth.ca/pcodr).

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.

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.cadth.ca/pcodr). 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

1. Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily Update, Ovid EMBASE and Ovid CDSR.

1. Dabrafenib.mp.
2. Tafinlar.mp.
3. Trametinib.mp
4. Mekinist.mp.
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. BRAF.mp.
9. unresectable.mp.
10. melanoma.mp
11. metastatic.mp.
12. unresected.mp.
13. 9 or 12
14. 13 and 10
15. 10 and 11
16. 14 or 15
17. 7 and 16
18. 8 and 17
19. randomized controlled trial.mp.
20. 18 and 19
21. remove duplicates from 20

2. Literature Search via PubMed

1. (Tafinlar AND Mekinist) OR (Dabrafenib AND Trametinib)
2. (melanoma AND BRAF))
3. publisher[sb]
4. 1 and 2
5. 3 and 4

3. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov

www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials

www.ontariocancertrials.ca

Search terms: Tafinlar or Mekinist or Dabrafenib or Trametinib

Select International Agencies:

Food and Drug Administration (FDA):

www.fda.gov

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

Search terms: Tafinlar or Mekinist or Dabrafenib or Trametinib

4. Conference Abstracts:

American Society of Clinical Oncology (ASCO)
via the *Journal of Clinical Oncology* search portal: <http://jco.ascopubs.org/search>

Search terms: Tafinlar or Mekinist or Dabrafenib or Trametinib

REFERENCES

1. Falchook GS, Long GV, Kurzrock R, Kim KB, Arkenau HT, Brown MP. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. *Lancet*. 2012;379(9829):1893-901.
2. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012;380(9839):358-65.
3. Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncology*. 2012;13(11):1087-95.
4. Trefzer U, Minor D, Ribas A, Lebbe C, Siegfried A, Arya N. BREAK-2: a phase IIa trial of the selective BRAF kinase inhibitor GSK2118436 in patients with BRAF mutation-positive (V600E/K) metastatic melanoma Pigment Cell and Melanoma Research. 2011;24(5):1020.
5. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *New England Journal of Medicine*. 2014;371(20):1877-88.
6. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet*. 2015.
7. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *New England Journal of Medicine*. 2015;372(1):30-9.
8. Canadian Cancer Society's Steering Committee. Canadian cancer statistics 2014 [Internet]. Toronto: Canadian Cancer Society; 2014. [cited 2014 Oct 3]. Available from: <http://www.cancer.ca/~media/cancer.ca/cw/cancer-information/cancer-101/canadian-cancer-statistics/canadian-cancer-statistics-2014-en.pdf>.
9. SEER cancer statistics review, 1975-2006 [Internet]. Bethesda (MD): National Cancer Institute; 2010. [cited 2014 Oct 4]. Available from: <http://seer.cancer.gov/csr/1975-2006/>.
10. Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. *Journal of Clinical Oncology*. 2008;26(4):527-34.
11. National Comprehensive Cancer Network. Melanoma [Internet]. Version 2. Fort Washington (PA): NCCN; 2012. [cited 2014 Oct 3]. (NCCN Clinical Practice Guidelines in Oncology). Available from: http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf Registration required.
12. BCCA protocol summary for palliative therapy for metastatic malignant melanoma using high dose dacarbazine (DTIC) [Internet]. Vancouver: BC Cancer Agency; 2011 Jun. [cited 2014 Oct 3].

Available from: <http://www.bccancer.bc.ca/NR/rdonlyres/D8C83698-5BBF-4A8E-9059-82B513089CB2/51450/SMDTIC Protocol 1Jun2011.pdf>.

13. Eggermont AM, Kirkwood JM. Re-evaluating the role of dacarbazine in metastatic melanoma: what have we learned in 30 years? . *European Journal of Cancer*. 2004;40(12):1825-36.
14. Agarwala SS, Kirkwood JM, Gore M, Dreno B, Thatcher N, B. C. Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. *Journal of Clinical Oncology*. 2004;22(11):2101-7.
15. Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *Journal of Clinical Oncology*. 2000;18(1):158-66.
16. Quirt I, Verma S, Petrella T, Bak K, Charette M. Temozolomide for the treatment of metastatic melanoma: a systematic review. *Oncologist*. 2007;12(9):1114-23.
17. Atkins MB, Kunkel L, Sznol M, Rosenberg SA. High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update. *The Cancer Journal from Scientific American*. 2000;6(Suppl 1):S11-54.
18. Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *Journal of Clinical Oncology*. 1999;17(7):2105-16.
19. Whiteman DC, Pavan WJ, Bastian BC. The melanomas: a synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin. *Pigment Cell and Melanoma Research*. 2011;24(5):879-97.
20. Puzanov I, Flaherty KT. Targeted molecular therapy in melanoma. *Seminars in Cutaneous Medicine and Surgery*. 2010;39(3):196-201.
21. Tsao H, Goel V, Wu H, Yang G, F.G. H. Genetic interaction between NRAS and BRAF mutations and PTEN/MMAC1 inactivation in melanoma. *Journal of Investigative Dermatology*. 2004;122(2):337-41.
22. Flaherty KT, McArthur G. BRAF, a target in melanoma: implications for solid tumor drug development. *Cancer*. 2010;116(21):4902-13.
23. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S. Mutations of the BRAF gene in human cancer. *Nature*. 2002;417(6892):949-54.
24. Yang H, Higgins B, Kolinsky K, Packman K, Go Z, Iyer R. RG7204 (PLX4032), a selective BRAFV600E inhibitor, displays potent antitumor activity in preclinical melanoma models. *Cancer Research*. 2010;70(13):5518-27.
25. Ribas A, Kim KB, Schuchter LM, Gonzalez R, Pavlick AC, Weber JS. BRIM-2: An open-label, multicenter phase II study of vemurafenib in previously treated patients with BRAF V600E mutation-positive metastatic melanoma *Journal of Clinical Oncology*. 2011;29(15 Suppl):8509.
26. Sondergaard JN, Nazarian R, Wang Q, Guo D, Hsueh T, Mok S. Differential sensitivity of melanoma cell lines with BRAFV600E mutation to the specific Raf inhibitor PLX4032. *Journal of Translational Medicine*. 2010;8:39.

27. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto PA, Larkin J. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *New England Journal of Medicine*. 2011;364(26):2507-16.
28. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01584648, A Phase III, Randomized, Double-blinded Study Comparing the Combination of the BRAF Inhibitor, Dabrafenib and the MEK Inhibitor, Trametinib to Dabrafenib and Placebo as First-line Therapy in Subjects With Unresectable (Stage IIIC) or Metastatic (Stage IV) BRAF V600E/K Mutation-positive Cutaneous Melanoma; 2012 April 23[Last updated 2014 November 6; cited 2015 April 14]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01584648?term=nct01584648&rank=1>.
29. Schadendorf D, Hauschild A. Melanoma in 2013: Melanoma - The run of success continues. *Nature Reviews Clinical Oncology*. 2014;11(2):75-6.
30. Novartis. Response to checkpoint meeting questions [internal report]. Mississauga (ON): Novartis.
31. pan-Canadian Oncology Drug Review Manufacturer Submission: Tafinlar (dabrafenib) in combination with Mekinist (trametinib) for malignant melanoma; Company: Novartis. Mississauga (ON): Novartis: 2015 February 13.
32. Rigel DS, Russak J, Friedmann R. The evolution of melanoma diagnosis: 25 years beyond the ABCDs. *CA Cancer Journal for Clinicians*. 2010;60(5):301-16.
33. American Joint Committee on Cancer. Melanoma of the skin staging. 7th ed. Chicago: The Committee; 2009.
34. Agarwala SS. Current systemic therapy for metastatic melanoma. *Expert Review of Anticancer Therapy*. 2009;9(5):587-95.
35. Falkson CI, Ibrahim J, Kirkwood JM, Coates AS, Atkins MB, Blum RH. Phase III trial of dacarbazine versus dacarbazine with interferon alpha-2b versus dacarbazine with tamoxifen versus dacarbazine with interferon alpha-2b and tamoxifen in patients with metastatic malignant

melanoma: an Eastern Cooperative Oncology Group study. *Journal of Clinical Oncology*. 1998;16(5):1743-51.

36. Flaherty KT, Lee SJ, Schuchter LM, Flaherty LE, Wright PD, Leming PD. Final results of E2603: a double-blind, randomized phase III trial comparing carboplatin (C)/paclitaxel (P) with or without sorafenib (S) in metastatic melanoma *Journal of Clinical Oncology*. 2010;28(15 Suppl):8511.
37. Huncharek M, Caubet JF, McGarry R. Single-agent DTIC versus combination chemotherapy with or without immunotherapy in metastatic melanoma: a meta-analysis of 3273 patients from 20 randomized trials. *Melanoma Research*. 2001;11(1):75-81.
38. Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H. Distinct sets of genetic alterations in melanoma. *New England Journal of Medicine*. 2005;353(20):2135-47.
39. Hodi Jr FS, O'day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB. Improved survival with ipilimumab in patients with metastatic melanoma. *New England Journal of Medicine*. 2010;363(8):711-23.
40. Robert C, Thomas L, Bondarenko I, O'day S, Garbe C. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *New England Journal of Medicine*. 2011;364(26):2517-26.
41. Glitza IC, Davies MA. Genotyping of cutaneous melanoma. *Chin Clin Oncol*. 2014;3(3):27.
42. Liu Y, Sheikh MS. Melanoma: Molecular Pathogenesis and Therapeutic Management. *Mol Cell Pharmacol*. 2014;6(3):228.
43. Queirolo P, Picasso V, Spagnolo F. Combined BRAF and MEK inhibition for the treatment of BRAF-mutated metastatic melanoma. *Cancer Treat Rev*. 2015.
44. Vella LJ, Andrews MC, Pasam A, Woods K, Behren A, Cebon JS. The kinase inhibitors dabrafenib and trametinib affect isolated immune cell populations. *Oncoimmunology*. 2014;3(7):e946367.
45. Chi M, Puzanov I. Targeted drug development in melanoma and nonsmall cell lung cancer: BRAF, MEK, and ALK inhibitors. *Memo - Magazine of European Medical Oncology*. 2012;5(4):302-8.
46. Filitis DC, Mahalingam M. Cutaneous adverse events to type i BRAF inhibitors: An analysis of effects associated with each inhibitor and therapeutic time interval to onset. *American Journal of Clinical Dermatology*. 2013;14(6):461-71.
47. Gibney GT, Zager JS. Clinical development of dabrafenib in BRAF mutant melanoma and other malignancies. *Expert Opinion on Drug Metabolism and Toxicology*. 2013;9(7):893-9.
48. Jang S, Atkins MB. Which drug, And when, For patients with BRAF-mutant melanoma? *The Lancet Oncology*. 2013;14(2):e60-e9.
49. Jarkowski A, Khushalani N. BRAF and beyond: Tailoring strategies for the individual melanoma patient. *Journal of Carcinogenesis*. 2014;13(1).
50. Karimkhani C, Gonzalez R, Dellavalle RP. A review of novel therapies for melanoma. *American Journal of Clinical Dermatology*. 2014;15(4):323-37.
51. Ku CS. Trametinib plus dabrafenib: Targeting RAS-MAPK pathway for BRAF V600-mutant melanoma. *Gastric and Breast Cancer*. 2012;11(4):208-10.
52. London S. Trametinib, dabrafenib strike at BRAF-mutant disease. *Oncology Report*. 2012(JULY):18.

53. Madureira P, De Mello RA. BRAF and MEK gene rearrangements in melanoma: Implications for targeted therapy. *Molecular Diagnosis and Therapy*. 2014;18(3):285-91.
54. Mandala M, Massi D, De Giorgi V. Cutaneous toxicities of BRAF inhibitors: Clinical and pathological challenges and call to action. *Critical Reviews in Oncology/Hematology*. 2013;88(2):318-37.
55. Menzies AM, Long GV. Systemic treatment for BRAF-mutant melanoma: Where do we go next? *The Lancet Oncology*. 2014;15(9):e371-e81.
56. Noor R, Trinh VA, Kim KB, Hwu WJ. BRAF-targeted therapy for metastatic melanoma: Rationale, clinical activity and safety. *Clinical Investigation*. 2011;1(8):1127-39.
57. Rutkowski P, Blank C. Dabrafenib for the treatment of BRAF V600-positive melanoma: A safety evaluation. *Expert Opinion on Drug Safety*. 2014;13(9):1249-58.
58. Sabbatino F, Wang Y, Wang X, Ferrone S, Ferrone CR. Emerging BRAF inhibitors for melanoma. *Expert Opinion on Emerging Drugs*. 2013;18(4):431-43.
59. Salama AKS. Evolving pharmacotherapies for the treatment of metastatic melanoma. *Clinical Medicine Insights: Oncology*. 2013;7:137-49.
60. Sharma A, Shah SR, Illum H, Dowell J. Vemurafenib: Targeted inhibition of mutated BRAF for treatment of advanced melanoma and its potential in other malignancies. *Drugs*. 2012;72(17):2207-22.
61. Sugihara Y, Vegvari A, Welinder C, Jonsson G, Ingvar C, Lundgren L, et al. A new look at drugs targeting malignant melanoma-An application for mass spectrometry imaging. *Proteomics*. 2014;14(17-18):1963-70.
62. Sullivan RJ, Flaherty K. MAP kinase signaling and inhibition in melanoma. *Oncogene*. 2013;32(19):2373-9.
63. Tsai KY, Nowroozi S, Kim KB. Drug safety evaluation of vemurafenib in the treatment of melanoma. *Expert Opinion on Drug Safety*. 2013;12(5):767-75.
64. Marzuka A, Huang L, Theodosakis N, Bosenberg M. Melanoma Treatments: Advances and Mechanisms. *J Cell Physiol*. 2015.
65. Massey PR, Prasad V, Figg WD, Fojo T. Multiplying Therapies and Reducing Toxicity in Metastatic Melanoma. *Cancer Biol Ther*. 2015:0.
66. Aris M, Barrio MM. Combining immunotherapy with oncogene-targeted therapy: A new road for melanoma treatment. *Frontiers in Immunology*. 2015;6(FEB).
67. Greco M, Mestroni M, de la Vega M, Valsecchi ME, Recondo G, Canton ED. Recent clinical advances in the treatment of cutaneous melanoma. *Clinical Cancer Drugs*. 2015;2(1):16-28.
68. Martin-Liberal J, Larkin J. Vemurafenib for the treatment of BRAF mutant metastatic melanoma. *Future Oncology*. 2015;11(4):579-89.
69. Ranchon F, Boespflug A, Rioufol C, Schwiertz V, Thomas L, Dalle S. New treatments for cutaneous metastatic melanoma: MAPK pathway-targeted and immune based therapies. *Anti-Cancer Agents in Medicinal Chemistry*. 2015;15(4):461-7.
70. Thota R, Johnson DB, Sosman JA. Trametinib in the treatment of melanoma. *Expert Opinion on Biological Therapy*. 2015;15(5):735-47.

71. Rissmann R, Hessel MH, Cohen AF. Vemurafenib/dabrafenib and trametinib. *Br J Clin Pharmacol*. 2015.
72. Burgeiro A, Mollinedo F, Oliveira PJ. Ipilimumab and Vemurafenib: Two different routes for targeting Melanoma. *Current Cancer Drug Targets*. 2013;13(8):879-94.
73. Keating GM, Lyseng-Williamson KA. Vemurafenib: A guide to its use in unresectable or metastatic melanoma. *American Journal of Clinical Dermatology*. 2013;14(1):65-9.
74. Mocellin S, Lens MB, Pasquali S, Pilati P, Chiarion Sileni V. Interferon alpha for the adjuvant treatment of cutaneous melanoma. *Cochrane Database of Systematic Reviews*. 2013(6).
75. Rughani MG, Gupta A, Middleton MR. New treatment approaches in melanoma: Current research and clinical prospects. *Therapeutic Advances in Medical Oncology*. 2013;5(1):73-80.
76. Gibney GT, Weber JS. Expanding targeted therapy to NRAS-mutated melanoma. *The Lancet Oncology*. 2013;14(3):186-8.
77. Thiel A, Ristimaki A. Toward a molecular classification of colorectal cancer: The role of BRAF. *Frontiers in Oncology*. 2013;3 NOV(Article 281).
78. Srivastava K, Pathak P, Amonkar M, Stapelkamp C, Swann RS, Casey M, et al. Systematic review and indirect treatment comparison (ITC) of dabrafenib (Dab) and trametinib (Tram) versus first-line (1L) treatments for metastatic melanoma (MM). *Journal of Clinical Oncology*. 2013;1).
79. Tomei S, Wang E, Delogu LG, Marincola FM, Bedognetti D. Non-BRAF-targeted therapy, immunotherapy, and combination therapy for melanoma. *Expert Opinion on Biological Therapy*. 2014;14(5):663-86.
80. Lindsay JN, Barras M. Facing the challenges of new melanoma-targeted therapies: Treatment of severe fevers associated with dabrafenib/trametinib combination therapy. *J Oncol Pharm Pract*. 2014.
81. Laks S, Brueske KA, Hsueh EC. Neoadjuvant treatment of melanoma: Case reports and review. *Experimental Hematology and Oncology*. 2013;2(1).
82. Galliker NA, Murer C, Kamarashev J, Dummer R, Goldinger SM. Clinical observation of panniculitis in two patients with BRAF-mutated metastatic melanoma treated with a combination of a BRAF inhibitor and a MEK inhibitor. *Eur J Dermatol*. 2015.
83. Bhatia S, Thompson JA. Systemic therapy for metastatic melanoma in 2012: Dawn of a new era. *JNCCN Journal of the National Comprehensive Cancer Network*. 2012;10(3):403-12.
84. Minor DR, Puzanov I, Callahan MK, Hug BA, Hoos A. Severe gastrointestinal toxicity with administration of trametinib in combination with dabrafenib and ipilimumab. *Pigment Cell Melanoma Res*. 2015.
85. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *New England Journal of Medicine*. 2012;367(18):1694-703.
86. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01597908, A Phase III, Randomised, Open-label Study Comparing the Combination of the BRAF Inhibitor, Dabrafenib and the MEK Inhibitor, Trametinib to the BRAF Inhibitor Vemurafenib in Subjects With Unresectable (Stage IIIc) or Metastatic (Stage IV) BRAF V600E/K

Mutation Positive Cutaneous Melanoma; 2012 May 10[Last updated 2014 Dec 4; cited 2015 April 14]. Available from:
<https://www.clinicaltrials.gov/ct2/show/NCT01597908?term=NCT01597908&rank=1>.

87. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. Supplementary appendix. *New England Journal of Medicine*. 2014;371(20):18-77-88.
88. Schadendorf D, Amonkar MM, Stroyakovskiy D, Levchenko E, Gogas H, De Braud F, et al. Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma. *European Journal of Cancer*. 2015;51(7):833-40.
89. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01767454, Phase 1 Study of the BRAF Inhibitor Dabrafenib +/- MEK Inhibitor Trametinib in Combination With Ipilimumab for V600E/K Mutation Positive Metastatic or Unresectable Melanoma; 2013 Jan 10[Last updated 2015 April 20 6; cited 2015 April 14]. Available from: <https://clinicaltrials.gov/show/NCT01767454>.
90. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01682083, COMBI-AD: A Phase III Randomized Double Blind Study of Dabrafenib (GSK2118436) in COMBination With Trametinib (GSK1120212) Versus Two Placebos in the ADjuvant Treatment of High-risk BRAF V600 Mutation-positive Melanoma After Surgical Resection; 2012 Sept 6[Last updated 2015 May 28; cited 2015 April 14]. Available from: <https://clinicaltrials.gov/show/NCT01682083>.
91. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT02314143, Phase II Biomarker Study Evaluating The Upfront Combination Of BRAF Inhibitor Dabrafenib With MEK Inhibitor Trametinib Versus The Combination After Eight Weeks Of Monotherapy With Dabrafenib Or Trametinib In Patients With Metastatic And Unresectable Stage III Or IV Melanoma Harboring An Activating BRAF Mutation; 2013 Sept 25[Last updated 2015 March 26; cited 2015 April 14]. Available from: <https://clinicaltrials.gov/show/NCT02314143>.
92. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT02196181, A Randomized Phase II Trial of Intermittent Versus Continuous Dosing of Dabrafenib (NSC-763760) and Trametinib (NSC-763093) in BRAF V600E/K Mutant Melanoma; 2014 July 18[Last updated 2015 June 5; cited 2015 April 14]. Available from: <https://clinicaltrials.gov/show/NCT02196181>.
93. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT019408091, A Sequential Safety and Biomarker Study of BRAF-MEK Inhibition on the Immune Response in the Context of CTLA-4 Blockade for BRAF Mutant Melanoma; 2013 Sep 9[Last updated 2015 May 28; cited 2015 April 14]. Available from: <https://clinicaltrials.gov/show/NCT01940809>.
94. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT02224781, A Randomized Phase III Trial of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab at Progression vs. Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib at Progression in Patients With Advanced BRAFV600 Mutant Melanoma; 2014 Aug

22[Last updated 2015 April 9; cited 2015 April 14]. Available from:
<https://clinicaltrials.gov/show/NCT02224781>.

95. (pERC) perc. pCODR expert review committee (pERC). Final Recommendation - Ipilimumab (Yervoy). Dec 22, 2014 [June 8, 2015]; Available from:
<https://www.cadth.ca/sites/default/files/pcodr/pcodr-yervoy1st-fn-rec.pdf>.
96. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: Report of the ISPOR task force on indirect treatment comparisons good research practices: Part 1. *Value in Health*. 2011;14(4):417-28.