pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Cobimetinib (Cotellic) for Metastatic Melanoma

June 30, 2016

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the efficacy and safety of cobimetinib in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation, irrespective of prior treatment status.

Cobimetinib is a MEK inhibitor and vemurafenib is a selective inhibitor of BRAF with a V600 mutation. Cobimetinib, in combination with vemurafenib, recently received approval from Health Canada for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One randomized controlled trial (RCT), coBRIM, was identified for inclusion in this systematic review.[1] coBRIM was a double-blind, placebo-controlled trial that randomized 495 patients with previously untreated unresectable locally advanced or metastatic BRAF V600 mutation-positive melanoma to receive cobimetinib in combination with vemurafenib (cobimetinib plus vemurafenib) or to vemurafenib in combination with placebo (vemurafenib plus placebo). Treatment was continued until disease progression or unacceptable toxicity. Dose modifications were allowed in order to manage adverse events. The trial enrolled patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Baseline patient characteristics were well balanced between treatment groups, with the exception of approximately 10% more patients in the cobimetinib plus vemurafenib group with ECOG performance of 0 compared with the vemurafenib plus placebo group.

Efficacy

The primary outcome was investigator assessed progression-free survival (PFS), which demonstrated a statistically significant difference in favour of the cobimetinib plus vemurafenib group (median 9.9 months) compared with the vemurafenib plus placebo group (median 6.2 months); hazard ratio (HR)=0.51, 95% confidence interval (CI) 0.39 to 0.68, p<0.001. PFS results by independent review were similarly statistically significant and showed a larger difference in median PFS in favour of cobimetinib plus vemurafenib (11.3 months versus 6.0 months), but the relative estimate of effect was slightly less with a HR of 0.60 (95% CI 0.45 to 0.79).

Overall survival was a secondary endpoint. An interim analysis of overall survival demonstrated a statistically significant improvement in OS, with a hazard ratio of 0.63 (95% CI, 0.47 to 0.85; p=0.0019).[2] The final OS analysis conducted in August 2015 demonstrated a statistically significant difference favouring the vemurafenib plus cobimetinib arm with a median of 22.3 months (95% CI, 20.3 to NE) versus the single agent vemurafenib arm with a median of 17.4 months (95% CI, 15.0 to 19.8). The hazard ratio for this final OS analysis was 0.70 (95% CI, 0.55 to 0.90; p=0.005).[3,4] The rate of objective response, another secondary outcome, demonstrated a statistically significant difference in favour of cobimetinib plus vemurafenib compared with vemurafenib plus placebo (67.6% versus 44.8%; p<0.0001).

Health-related quality of life, another secondary outcome, was measured in coBRIM using the European Organization for the Research and Treatment of Cancer (EORTC) quality of

life questionnaire (QLQ)-C30. Completion rates were consistently high (≥88%) among all cycles for both treatment groups. A change in score from baseline of 10 or more points was considered the minimally clinical important difference. Patients in the cobimetinib plus vemurafenib group reported better scores at all or most post-baseline assessments when compared with vemurafenib plus placebo.

Harms

In a safety analysis conducted in September 2014, a higher proportion of patients who received cobimetinib plus vemurafenib had at least one Grade 3 or higher adverse event compared with those who received vemurafenib plus placebo (71.3% versus 59.3%, respectively). A total of six Grade 5 adverse events (2.0%) occurred in the cobimetinib plus vemurafenib group while three Grade 5 adverse events (1.2%) occurred in the vemurafenib plus placebo group. A higher proportion of patients experienced an adverse event leading to discontinuation of cobimetinib or placebo in the vemurafenib plus cobimetinib group than in the vemurafenib plus placebo group (19.0% versus 9.8%). Similarly, discontinuation of vemurafenib due to an adverse event occurred more frequently in the vemurafenib plus cobimetinib group than in the vemurafenib plus placebo group (15.8% versus 9.8%). Discontinuation of both agents occurred in 15.0% of patients in the cobimetinib plus vemurafenib group and in 8.1% of patients in the vemurafenib plus placebo group.

1.2.2 Additional Evidence

pCODR received input on cobimetinib in combination with vemurafenib for the treatment of metastatic melanoma from two patient advocacy groups (Melanoma Network of Canada [MNC] and Save Your Skin Foundation [SYSF]). Provincial Advisory Group (PAG) input was obtained from nine of the nine provinces participating in pCODR.

One supplemental issue was identified during the development of the review protocol as relevant to the pCODR review of cobimetinib in combination with vemurafenib for the treatment of metastatic melanoma and is discussed as supporting information: Critical appraisal of a manufacturer-submitter indirect treatment comparison (ITC) of the relative efficacy and safety of cobimetinib plus vemurafenib versus dabrafenib plus 2 mg trametinib and dabrafenib plus 1 mg trametinib.

Other

One additional study, a phase II, open-label, multicentre, dose-escalation, non-comparative study, BRIM7, was also considered as contextual evidence.[5] The trial enrolled patients with advanced or metastatic melanoma that was previously treated, but naïve to BRAF or MEK inhibitor therapy, or that was previously untreated.

1.2.3 Interpretation and Guidance

Burden of Illness and Need

Although the number of patients afflicted with melanoma is small compared to breast or colon cancers, it remains the leading cause of cancer death in women age 23-35, causing a disproportionate number of years of life lost. Unresectable locally advanced or metastatic melanoma carries a poor prognosis. Until very recently, the median survival of such patients was 6.2 months, with only 25% of patients surviving to one year. Newer treatments, such as immune checkpoint inhibitors, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1) inhibitors, have demonstrated significant improvements in treatment for patients with advanced or metastatic melanoma. However, only a relatively small proportion of patients experience long-term survival. For the 40% to 50% of patients who harbour a BRAF-mutated melanoma, BRAF

inhibitors, and the combination of BRAF plus MEK inhibitors, have also demonstrated significant improvements in outcomes. However, for these targeted therapies, resistance typically develops in 9 to 11 months. Given that the majority of patients with unresectable advanced or metastatic melanoma still succumb to the disease, there is a clear need for more effective treatments.

Effectiveness

For patients with previously untreated metastatic melanoma, the results of the coBRIM study demonstrated statistically significant and clinically meaningful improvements in PFS in favour of cobimetinib plus vemurafenib by investigator assessment (median 9.9 months versus 6.2 months; HR 0.51; p<0.001), with similar results by independent assessment. Overall response rates, by RECIST criteria, were also in favour of cobimetinib plus vemurafenib (68% versus 45%; p<0.0001).

The final OS analysis (dated August 2015) similarly demonstrated a statistically significant difference favouring the vemurafenib plus cobimetinib arm with a median of 22.3 months (95% CI, 20.3 to NE) versus the single agent vemurafenib arm with a median of 17.4 months (95% CI, 15.0 to 19.8). The hazard ratio for this final OS analysis was 0.70 (95% CI, 0.55 to 0.90; p=0.005).[3,4]

Health-related quality of life (HRQoL) was measured for each treatment arm using the EORTC QLQ-C30 questionnaire; insufficient information is available at present to draw any conclusions.

While the coBRIM study assessed BRAF-mutated patients who had no prior treatment for metastatic disease, the phase Ib BRIM7 study enrolled two populations of BRAF-mutated patients; those who had recently progressed on single-agent vemurafenib and those who had never received a prior BRAF or MEK inhibitor, but may have received prior treatments. The median PFS was 2.8 months in those patients who recently progressed on vemurafenib and 13.7 months in those who had never received a BRAF or MEK inhibitor.

Network Meta-Analysis (NMA)

Cobimetinib plus vemurafenib has not been directly compared to dabrafenib plus trametinib; therefore the Submitter provided a NMA to estimate the effect of cobimetinib plus vemurafenib compared with dabrafenib plus trametinib. The NMA demonstrated a considerable level of uncertainty for several reasons. These include potential differences in trial characteristics, such as method of randomization, treatment allocation concealment, blinding of outcome assessor, and dropout. There was a paucity of information on the presence/absence of effect modifiers in the trials and whether those were controlled for in the analysis. Therefore, there is uncertainty in the reported estimates (HR's) for OS and PFS and the true values may actually be higher or lower than the bounds of the 95% credible intervals. Hence, the reported results should be interpreted with caution.

Safety

Grade 3 or 4 adverse events occurred in 59% of the vemurafenib plus placebo group and in 65% of the cobimetinib plus vemurafenib group. In an updated safety analysis (September 2014), the rate of Grade 3 or 4 adverse events was also 59% for the vemurafenib plus placebo group but it was 71% in the cobimetinib plus vemurafenib group.

Adverse events leading to withdrawal from treatment were higher in the vemurafenib plus cobimetinib arm (15.0%) than in the vemurafenib plus placebo arm (8.1%).

Compared to vemurafenib plus placebo, the combination of cobimetinib plus vemurafenib was associated with a higher frequency of central serous retinopathy (all grades) (25.5%

versus 2.8%), grade ≥3 diarrhoea (6.5% versus 0.8%), grade ≥ 3 photosensitivity (3.6% versus 0%), and grade ≥2 reduction in LVEF (8.5% versus 3.7%).

There was a decreased frequency of grade ≥3 keratoacanthomas (1.2% versus 8.1%), grade ≥ 3 squamous cell carcinomas (2.8% versus 12.6%), and grade ≥3 arthralgia (2.4% versus 4.9%) in patients who received cobimetinib plus vemurafenib.[6] The side effect profile of cobimetinib plus vemurafenib is acceptable and manageable. While there was an increase in some side effects with the combination, others, such as cutaneous malignancies, were decreased.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is an overall net clinical benefit to vemurafenib plus cobimetinib in the treatment of previously untreated BRAF V600 mutated unresectable stage III or stage IV (metastatic) melanoma. This conclusion was based on several factors:

- The coBrim study was a well-conducted, randomized double-blind placebo controlled trial which demonstrated a clear benefit in progression free and overall survival in favour of the combination therapy with vemurafenib plus cobimetinib compared with treatment with single agent vemurafenib in patients with previously untreated unresectable stage III or stage IV melanoma.
- The side effect profile of the combination is acceptable and manageable. While there was an increase in some side effects with the combination, others, such as cutaneous malignancies, were decreased.

The Clinical Guidance Panel also concluded that there may be an overall net clinical benefit to the combination of vemurafenib plus cobimetinib for previously treated patients with advanced melanoma. This conclusion was based on several factors:

- The magnitude of benefit of the combination of vemurafenib and cobimetinib in the BRIM7 study (a phase 1b, open-label, multi-center dose escalation trial) was similar to that observed in the coBRIM trial.
- The expert opinion of the CGP.

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

- Clinical trial results suggest that there is no significant benefit for the use of the combination of vemurafenib plus cobimetinib following progression on single agent vemurafenib.
- Patients who are responding to single agent vemurafenib should be allowed to receive cobimetinib in addition to vemurafenib
- There is no evidence to support the use of single agent MEK inhibitors following progression on a BRAF inhibitor.
- There is no evidence to support the use single agent BRAF inhibitors following progression on a MEK inhibitor.
- There have been no direct comparisons of the combination of vemurafenib plus cobimetinib with dabrafenib plus trametinib.
- At this time, there is no evidence to guide the optimal sequencing of BRAF plus MEK inhibitors with immune checkpoint drugs (CTLA-4 and PD1 inhibitors) or the combination of these 2 classes of drugs.

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 cobimetinib in combination with vemurafenib for metastatic melanoma with BRAF V600 mutation. 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 CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding cobimetinib in combination with vemurafenib for treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation 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 cobimetinib in combination with vemurafenib for metastatic melanoma with BRAF V600 mutation and a summary of submitted Provincial Advisory Group Input on cobimetinib in combination with vemurafenib for metastatic melanoma with BRAF V600 mutation are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Metastatic Melanoma is one of the most aggressive forms of skin cancer. In Canada, the incidence of melanoma has increased significantly in both genders over the last 25 years. It is estimated that in the year 2015, approximately 6800 Canadians will be diagnosed with Melanoma.[7]

Treating unresectable or metastatic melanoma remains a challenge as the response rate to systemic therapy is low. Current available treatments for unresectable or metastatic melanoma in Canada vary from province to province and generally include chemotherapy, immunotherapy, or targeted therapy (BRAF or MEK inhibitors). Treatments options remain limited for patients who progress after immunotherapies and targeted therapies.

Cobimetinib is a new MEK inhibitor, and vemurafenib is a selective inhibitor of BRAF with a V600 mutation.

The combination therapy cobimetinib vemurafenib is currently a new treatment under review for patients with unresectable or metastatic melanoma with BRAF V600 mutation.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the safety and efficacy of cobimetinib (Cotellic) in combination with vemurafenib (Zelboraf) for treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation, irrespective of prior treatment status.

2.1.3 Highlights of Evidence in the Systematic Review

coBRIM was a phase III, randomized, double-blind, placebo-controlled study which randomly assigned 495 patients with previously untreated unresectable locally advanced or metastatic BRAF V600 mutation-positive melanoma to receive vemurafenib in combination with cobimetinib or vemurafenib plus placebo (control group). Eligible inclusion criteria for patients enrolled in this study was BRAF mutation detected by the *Cobas* 4800 BRAF mutation test. Patients with previously treated brain metastases were eligible if they had at least a 3 week history of stable disease.

Patients were randomly assigned in a 1:1 ratio to receive vemurafenib orally, at a dose of 960 mg twice daily, together with either placebo or cobimetinib, at a dose of 60 mg. once daily for 21 days, followed by 7 days off. Study treatment continued until patients withdrew consent, unacceptable adverse events, or disease progression occurred. Dose modifications were allowed for both vemurafenib and cobimetinib in order to manage adverse events that were ≥ grade 2.

The primary endpoint of the study was progression-free survival by investigator assessment, according to RECIST v 1.1 criteria. Secondary endpoints included overall survival, objective response according to RECIST v 1.1 criteria, duration of response, PFS as assessed by an independent review facility, and safety.

The study was designed to provide >95% power to detect an improvement in median PFS from 6 months in the vemurafenib plus placebo arm to 11 months in the cobimetinib plus vemurafenib arm, corresponding to a hazard ratio of 0.55.

Table 3. Baseline Patient Characteristics in the included studies of cobimetinib vemurafenib in patients with BRAF V600 mutation positive unresectable or metastatic melanoma[1]

	coBRIM	
Patient Characteristics	Vemurafenib & placebo (n=248)	Vemurafenib & cobimetinib (n=247)
Median Age (years)	55 (range 25-85)	56 (range 23-88)
Male	140 (56%)	146 (59%)
White ethnic origin	235 (95%)	227 (92%)
ECOG performance status score		
0	164/244 (67%)	184/243 (76%)
1	80/244 (33%)	58/243 (24%)
2	0/244	1/243 (<1%)
Metastatic status - no. (%)		
Unresectable stage IIIc	13 (5%)	21 (9%)
M1a	40 (16%)	40 (16%)
M1b	42 (17%)	40 (16%)
M1c	153 (62%)	146 (59%)

Elevated LDH	104/242 (43%)	112/242 (46%)
BRAF mutation genotype - no. (%)		
V600E	174 (70%)	170 (69%)
V600K	32 (13%)	24 (10%)
Could not be evaluated	42 (17%)	53 (21%)

ECOG PS= Eastern Cooperative Oncology Group Performance Status Notes: *Data only available for 63 patients of 66
Race was determined by the investigator

Table 4. Key efficacy outcomes of cobimetinib vemurafenib in patients with BRAF V600 mutation positive unresectable or metastatic melanoma in the coBRIM trial[1,3,4,6,8]

Treatment group	Vemurafenib plus cobimetinib N = 247	Vemurafenib plus placebo N= 248
PFS by investigator (median) [Data cut-off May 9 2014] 95% CI	9.9 months (median follow-up 7.4 months) 9.0, NE	6.2 months (median follow-up 7.0 months) 5.6, 7.4
PFS by independent review committee (median) 95% CI	11.3 months 8.5, NE	6.0 months 5.6, 7.5
Updated PFS by investigator (median) [Data cut-off Jan 16 2015] 95% CI	12.3 months (median follow-up 14.9 months) 9.5, 13.4	7.2 months (median follow-up 13.6 months) 5.6, 7.5
Interim OS (median) [data cut-off Jan 2015] 95% CI	NE 20.7, NE	17.02 months 15.0, NE
Final OS (median) [Data cut-off Aug 28 2015] 95% CI	22.3 months 20.3, NE	17.4 months 15.0, 19.8
DOR by investigator review (median) [Data cut-off May 9 2014] 95% CI	NE 9.3, NE	7.3 months 5.8, NE
Effect Estimates		
PFS by investigator review Stratified Hazard Ratio	0.51 (95% CI: 0.39, 0.68) p-value <0.001	
PFS by independent review Stratified Hazard Ratio	0.60 (95% CI: 0.45, 0.79) p-value 0.0003	
Updated PFS by investigator review [Data cut-off Jan 16 2015]	0.58 (95% CI: 0.46, 0.72)	

Stratified Hazard Ratio	
Secondary endpoint: **Overall Survival** **Stratified Hazard Ratio**	Interim analysis:0.63 (95% CI, 0.47 to 0.85; p=0.0019) Final analysis: 0.70 (95% CI, 0.55 to 0.90; p=0.005).
Secondary endpoint: **Overall Response Rate (ORR)**	Difference in ORR between cobimetinib + vemurafenib vs. placebo + vemurafenib : 22.9% (95% CI: 14.1, 31.58) p-value <0.0001
Notes: PFS= progression-free survival; OS= overall survival; ORR= overall response rate; DOR= duration of response; CI= confidence interval; NE= not estimable.	

Treatment groups were well balanced for patient and disease characteristics. However, there were a slightly higher percentage of patients with an ECOG PS of 0 in the vemurafenib and cobimetinib arm (76%) compared to the vemurafenib and placebo arm (67%). The study population was comprised of a greater percentage of males in both arms, vemurafenib and placebo (56%) and vemurafenib and cobimetinib (59%).

The combination of vemurafenib plus cobimetinib significantly prolonged progression-free survival according to investigator assessment in the intention-to-treat population. The PFS was a median of 9.9 months in the combination group compared to 6.2 months in patients treated with vemurafenib plus placebo. The HR for death or progression of disease was 0.51 (95% CI, 0.39 to 0.68) with a p value of less than 0.0001.[6]

An updated data cut-off of January 16 2015 also demonstrated a significantly prolonged progression-free survival according to investigator assessment of 12.3 months (95% CI, 9.5 to 13.4) in the combination group compared to 7.2 months (95% CI, 5.6 to 7.5) in the vemurafenib plus placebo group. The HR for death or progression of disease was 0.58 (95% CI, 0.46 to 0.72).[6]

An interim analysis of overall survival (January 2015) demonstrated a statistically significant improvement in OS, with a hazard ratio of 0.63 (95% CI, 0.47 to 0.85; p=0.0019) (Ref- FDA statistical report).[2]

The final OS analysis, presented at the 2015 Society for Melanoma Research Congress similarly demonstrated a statistically significant difference favouring the vemurafenib plus cobimetinib arm with a median of 22.3 months (95% CI, 20.3 to NE) versus the single agent vemurafenib arm with a median of 17.4 months (95% CI, 15.0 to 19.8). The hazard ratio for this final OS analysis was 0.70 (95% CI, 0.55 to 0.90; p=0.005).[3,4]

Table 7. Summary of Adverse Events for cobimetinib vemurafenib in patients with BRAF V600 mutation positive unresectable or metastatic melanoma[6]

	coBRIM			
	Placebo plus vemurafenib		***Cobimetinib plus vemurafenib***	
	SCS n=239	***Safety Update n=246***	***SCS n=254***	***Safety Update N=247***

Total number (%) of patients with ≥1 AE	***233 (97.5)***	***240 (97.6)***	***250 (98.4)***	***244 (98.8)***
Total number of patients with ≥1:				
Grade ≥3 AEs	142(59.4)	146 (59.3)	***165 (65.0)***	***176 (71.3)***
Grade 5 AEs	***3 (1.3)***	***3 (1.2)***	***6 (2.4)***	***5 (2.0)***
SAEs	***60 (25.1)***	***64 (26.0)***	***75 (29.5)***	***85 (34.4)***
AEs leading to discontinuation of cobimetinib/placebo	***33 (13.8)***	***24 (9.8)***	***42 (16.5)***	***47 (19.0)***
AEs leading to discontinuation of vemurafenib	***32 (13.4)***	***24 (9.8)***	***35 (13.8)***	***39 (15.8)***
AEs leading to discontinuation of cobimetinib and vemurafenib	***28 (11.7)***	***20 (8.1)***	***32 (12.6)***	***37 (15.0)***
Notes: SCS= Summary of clinical safety (data cut-off May 2014) Safety update data cut-off September 19 2014				

In the coBRIM study, the combination of cobimetinib plus vemurafenib was associated with a higher frequency of adverse events compared to single-agent therapy. The most common grade ≥3 AEs which occurred at a higher frequency, as observed with a ≥2% difference, in patients treated with vemurafenib plus cobimetinib compared to patients treated with vemurafenib plus placebo were, respectively, ALT increase (11.4% versus 6.3%), AST increased (8.3% versus 2.1%), blood creatine phosphokinase increased (10.2% versus 0%), diarrhoea (6.3% versus 0%), blood alkaline phosphatase increased (4.3% versus 1.7%), photosensitivity reaction (2.4% versus 0%), hyponatremia (2.4% versus 0.4%), and retinal detachment (2.4% versus 0%).[6]

Health-related quality of life (HRQoL) was measured in the coBRIM trial for each treatment arm using the EORTC QLQ-C30 questionnaire. Completion rates were consistently high (≥88%) among all cycles for both treatment arms. Changes were considered to be clinically meaningful if there was a ≥10 point increase or decrease from baseline.

In terms of global health status, as well as most functioning and symptom scales, the difference in proportion of responders was small. This indicated a similarity in health-related quality of life between the two treatment arms. However, there were larger differences observed for insomnia and social functioning and to a smaller extent, pain and fatigue which all favoured the vemurafenib plus cobimetinib arm.[6]

Time to deterioration analyses and time to improvement analyses were conducted in the coBRIM study, and additional details regarding Quality of life are planned for publication and are non-disclosable at the present moment.

2.1.4 Comparison with Other Literature[5]

One phase 1 trial, BRIM-7, which did not meet the protocol's inclusion criteria, was identified as relevant to the review.

BRIM7 was a phase 1b, open-label, multi-center dose escalation study evaluating the safety, tolerability and pharmacokinetics of vemurafenib in combination with cobimetinib in the BRAFV600 mutation positive patient population. The BRIM7 trial enrolled patients who were previously treated (but naïve to BRAF or MEK inhibitor therapy) or patients previously untreated for metastatic melanoma or those who have progressed after treatment with vemurafenib. Eligible inclusion criteria for patients enrolled in this study was BRAF mutation detected by the *Cobas* 4800 BRAF mutation test in melanoma tumour tissue.

Patients with previously treated brain metastases were eligible if they had at least a 3-week history of stable disease. The BRIM7 trial initially enrolled only patients who had previously received and progressed on vemurafenib. The study protocol was amended on July 13th 2011, to also include patients who were BRAF inhibitor naïve. Patients in the study were assessed separately according to their previous treatment history. There were 2 populations of patients that were assessed: patients whose melanoma had progressed on vemurafenib immediately preceding enrolment in this trial, and individuals who either had never received a BRAF inhibitor, had not received previous treatment for advanced melanoma, or who were previously treated but BRAF or MEK inhibitor naïve.

Of the 63 patients enrolled in the BRAF inhibitor naïve population, 19 (30.2%) had received prior systemic therapy. Additional details regarding systemic therapy received by these patients prior to enrollment have not been reported.

Study treatment continued until patients withdrew consent, experienced unacceptable adverse events, or disease progression. Dose modifications were allowed to the dose of vemurafenib and cobimetinib in order to manage adverse events of grade 3 or higher.

The primary endpoint of the study was to establish the safety, tolerability, and pharmacokinetics of the vemurafenib plus cobimetinib combination. Secondary endpoints included measuring the objective response rate, PFS, duration of response, and overall survival.

In patients that had not been previously treated with vemurafenib (BRAF inhibitor naïve patients, the confirmed objective response rate was 87%, including a complete response in 10% of patients. The median DOR was 12.5 months. The median PFS for BRAF inhibitor naïve patients was 13.7 months, with a median follow-up time of 12.7 months. This is considered to be clinically significant.

In the subgroup of patients who received 60 mg of cobimetinib once daily for 21 days (n=39), the efficacy results were similar to the overall BRAF inhibitor naïve population, with an objective response rate of 85%. The median duration of response in this group was 11.3 months and the median PFS was 12.7 months.

In patients that progressed after treatment on vemurafenib, the ORR at all doses was low at 15% (95% CI: 7.5, 25.5). The median DOR was 6.7 months in those patients who had responses. The median PFS in patients who had progressed on vemurafenib was 2.8 months (95% CI: 2.63, 3.45). In the subgroup of patients who received 60 mg. of cobimetinib once daily for 21 days (n=27), the ORR was 26%, and the median DOR was not estimable. The median PFS was 2.8 months.

Table 5. Key efficacy outcomes of cobimetinib vemurafenib in patients with BRAF V600 mutation positive unresectable or metastatic melanoma in the BRIM7 trial[5,6]			
	Never Received a BRAF inhibitor		Recently progressed on vemurafenib
	All doses n= 63	960 mg vemurafenib + 60 mg cobimetinib N=39	All doses N=66
Objective Response Rate, n (%) 95% CI	55 (87.3) (76.7, 94.4%)	33 (84.6) (69.9%, 93.1%)	10 (15.2) (7.5%, 25.5%)
Best overall response			
Complete response, n (%)	6 (9.5%)	4 (10.3%)	0
Partial response, n (%)	49 (77.8%)	29 (74.4%)	10 (15.2%)
Stable disease, n (%)	6 (9.5%)	4 (10.3%)	28 (42.4%)
Progressive disease, n (%)	2 (3.2%)	2 (5.1%)	24 (36.4%)
Duration of response			
Patients with OR, n	55	33	10
Median DOR (95% CI)	12.5 months	11.3 months	6.7 months
Median PFS (95% CI)	13.7 months	12.7 months	2.8 months
Overall Survival			
Patients with event, n (%)	12 (19.0%)	7 (17.9%)	45 (68.2%)
Estimate of 1 year survival rate 95% CI	82.8% (72.9, 92.6%)	82.4% (69.4, 95.4%)	31.9% (19.4, 44.6%)
Notes: **DOR**= duration of response, **PFS**= progression-free survival, **CI**= confidence interval			

A Phase II open-label ongoing study of cobimetinib in combination with vemurafenib in active melanoma brain metastases (CoBRIM-B) was also identified as part of the literature search for this review. The primary outcome measure of this study is the overall response rate (ORR) and primary efficacy endpoint is the overall intracranial response rate (OIRR). The study start date was February 2015 and the estimated primary completion date is May 2018.

2.1.5 Summary of Supplemental Questions

The following supplemental issues were identified as relevant to the pCODR review of cobimetinib in combination with vemurafenib in patients with BRAF V600 mutation positive unresectable or metastatic melanoma:

Critical appraisal of a manufacturer-submitter indirect treatment comparison (ITC) of relative efficacy and safety of cobimetinib plus vemurafenib (VM. Cobi) versus dabrafenib plus trametinib (DB.TM2mg) and dabrafenib plus trametinib (DB.TM1mg)

The manufacturer submitted an indirect treatment comparison (ITC) of the relative efficacy and safety of vemurafenib plus cobimetinib (VM. Cobi) versus dabrafenib plus trametinib (DB.TM2mg) and dabrafenib plus trametinib (DB.TM21mg). Indirect statistical assessments using the Bucher method were used to compare vemurafenib plus cobimetinib to dabrafenib plus trametinib.

The validity of the manufacturer's ITC hinges on three important assumptions: (1) homogeneity; (2) transitivity/similarity; and, (3) consistency. There is a considerable level of uncertainty associated with this NMA attributable to the differences in the trials characteristics which may have affected the treatment effects observed in each trial, thus violating the similarity assumption and confounding these comparisons. Complete details including the study protocol for each of the included studies was not provided, therefore it is difficult to ascertain whether all systematic differences and levels of heterogeneity across the different trials were identified and accounted for prior to comparing individual study results.

The Methods team also felt that there was an insufficient level of detail provided as part of the systematic review. In particular, there was a lack of search terms listed. This makes it unclear whether placebo or standard of care trials were considered in this network of evidence but not found according to the search strategy mentioned.

The Methods team would like to state that although it may appear from the results of OS that cobimetinib in combination with vemurafenib is the most effective treatment followed by DB.TM2mg,TM2mg, and VM, there is a level of uncertainty in the reported results. This is largely due to the inherent limitations associated with treatment ranking. The use of treatment ranking in a small network of evidence leads to an imprecise estimate of the true treatment effect, due to the small number of trials available. Another limitation with the reported results is also due to the handling of assumptions of heterogeneity. A fixed effects model was chosen due to the limited number of studies as it provided an improved model fit compared to the random effects model, and consequently this led to difficulty in making meaningful inferences.

In addition, the estimates (hazard ratios) of OS and PFS provided by this NMA are the best we have, given the available evidence. However, there is a paucity of information on the presence/absence of effect modifiers in the trials and whether those were controlled for in the analysis. Therefore, there is uncertainty in the reported estimates (HR's) for OS and PFS and the true values may actually be higher or lower than the bounds of the 95% credible intervals. Hence, the reported results should be interpreted with caution.

Please refer to section 7 for further details.

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's perspective, it is expected that cobimetinib in combination with vemurafenib will stop the disease or slow disease progression, not only in terms of increasing the length of life, but also in managing the quality of life. Current treatment for melanoma reported by SYSF and MNC included: interferon, surgery, radiation, dacarbazine, temozolomide, stereotactic radiation (for brainstem tumours), vemurafenib, ipilimumab, dabrafenib in combination with trametinib, and pembrolizumab. Reported side effects from current treatment for melanoma include: fever, hair loss, extreme fatigue, diarrhea, skin issues, nausea, rash, joint pain, and colitis vomiting, low blood counts, stomach upset, and sun sensitivity. Respondents indicated that side effects with current treatment could be difficult to tolerate, but were manageable; and respondents would undergo treatment for as long as needed, despite side effects. While respondents agree that current treatments, such as interferon, dacarbazine and temozolomide may slow the spread of disease, respondents believe they are not effective in preventing metastases. Respondents who have experience with cobimetinib reported the following key side effects: skin rash, fatigue or weakness, fever or flu like symptoms. Other side effects included, shortness of breath, cough or chest pain (pneumonitis), photosensitivity, other skin cancers like squamous cell carcinoma, diarrhea or colitis, muscle or joint pain, headaches, stomach pain and nausea. Respondents reported that the side effects, such as diarrhea, nausea, fever, and vomiting were manageable. Those who were able to manage the side effects reported their quality of life as "normal". Respondents also noted that cobimetinib is an oral therapy which could be taken at home, and therefore, could potentially reduce the amount of time patients have to travel back and forth to hospitals.

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 cobimetinib plus vemurafenib combination therapy for melanoma:

Clinical factors:

- Availability of data regarding the sequencing of BRAF inhibitors +/- MEK inhibitors and immunotherapies
- Relative clinical benefits and risks of cobimetinib + vemurafenib combination therapy compared to vemurafenib monotherapy and compared to dabrafenib + trametinib combination therapy
- The benefits of adding cobimetinib when patients have already started vemurafenib and not yet progressed

Economic factors:

- High cost of combination drugs
- Cost-effectiveness of cobimetinib + vemurafenib combination therapy compared to vemurafenib monotherapy and compared to dabrafenib + trametinib combination therapy and compared to ipilimumab and other immunotherapies

2.2 Interpretation and Guidance

Burden of Illness and Need

In Canada an estimated 6800 new cases of primary melanoma were diagnosed in 2015 and approximately 1150 individuals died from melanoma.[7] The incidence of melanoma has been steadily increasing over the past 60 years. While the majority of patients present with early stage disease that is cured by surgical resection, those who present with subsequent relapse or advanced disease have a very poor prognosis. Until very recently, the median survival of patients with unresectable stage III or stage IV melanoma was 6.2 months, with only 25% of patients surviving to one year. Though the number of patients afflicted with melanoma is small compared to breast or colon cancers, it remains the number one cause of cancer death in women age 25-35, causing a disproportionate number of years of life lost.

Decades of trials with standard cytotoxic chemotherapies have not demonstrated any impact on improving survival or quality life for patients with metastatic melanoma, with very low response rates ranging from 7-10%. More recently, the immune checkpoint inhibitors, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1) inhibitors have demonstrated significant improvements in treatment for patients with malignant melanoma. However, only a relatively small proportion of patients experience long term survival. For the 40-50% of patients who harbor BRAF mutated melanoma, BRAF inhibitors, and the combination of BRAF plus MEK inhibitors, have also demonstrated significant improvements in outcomes. However, for these targeted therapies, resistance typically develops in 9 to 11 months. Given that the majority of patients with metastatic melanoma still succumb to the disease, there is a clear need for more effective treatments.

Effectiveness

The coBRIM trial was a phase III, double-blind placebo controlled study of 495 treatment-naïve patients randomized to vemurafenib in combination with cobimetinib vs vemurafenib plus placebo (control group). Vemurafenib was given at a dose of 960 mg orally BID continuously, and cobimetinib/placebo at 60 mg orally OD for 21 days on, 7 days off. The primary outcome of the study was progression free survival by investigator assessment, with secondary endpoints of overall survival, objective response by RECIST criteria, duration of response, PFS as assessed by an independent review facility and safety. Baseline characteristics were similar between the 2 groups. Median progression free survival was 9.9 months in the combination group compared to 6.2 months in the control group (HR 0.51, p<0.001). PFS by independent review was similar. Interim analysis of 9 month survival rates were 81% vs 73%; HR for death 0.65 (p=0.046). Overall response rates were 68% vs 45% (p<0.0001) favouring the combination treatment arm. The submitter provided an interim analysis from January 2015, showing a median PFS of 12.3 vs 7.2 months (HR 0.58).

An interim analysis of overall survival demonstrated a statistically significant improvement in OS, with a hazard ratio of 0.63 (95% CI, 0.47 to 0.85; p=0.0019).[2]

The final OS analysis similarly demonstrated a statistically significant difference favouring the vemurafenib plus cobimetinib arm with a median of 22.3 months (95% CI, 20.3 to NE) versus the single agent vemurafenib arm with a median of 17.4 months (95% CI, 15.0 to 19.8). The hazard ratio for this final OS analysis was 0.70 (95% CI, 0.55 to 0.90; p=0.005).[3,4]

Health-related quality of life (HRQoL) was measured for each treatment group in coBRIM using the EORTC QLQ-C30 questionnaire; insufficient information is available at present to draw any conclusions.

While the coBRIM study assessed BRAF mutant patients who had no prior treatment for metastatic disease, the phase 1b BRIM 7 study enrolled 2 populations of BRAF mutant patients; those who had recently progressed on single agent vemurafenib and those who had never received a prior BRAF or MEK inhibitor, but may have received prior treatments. The median PFS was 2.8 months in those patients who recently progressed on vemurafenib and 13.7 months in those who had never received a BRAF or MEK inhibitor.

Network Meta-Analysis (NMA)

Vemurafenib plus cobimetinib has not been directly compared to dabrafenib plus trametinib. 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 demonstrated a considerable level of uncertainty for several reasons. These include potential differences in trial characteristics, such as method of randomization, treatment allocation concealment, blinding of outcome assessor, and dropout. There was a paucity of information on the presence/absence of effect modifiers in the trials and whether those were controlled for in the analysis. Therefore, there is uncertainty in the reported estimates (HR's) for OS and PFS and the true values may actually be higher or lower than the bounds of the 95% credible intervals. Hence, the reported results should be interpreted with caution.

Safety

Grade 3 or 4 adverse events occurred in 59% of the vemurafenib/placebo group and 65% of the vemurafenib/cobimetinib group; in the safety update from September, 2014 these were 59% and 71%, respectively.

Adverse events leading to withdrawal from treatment were higher in the vemurafenib plus cobimetinib arm (15.0%) than in the vemurafenib plus placebo arm (8.1%).

Compared to single agent vemurafenib, the combination of vemurafenib plus cobimetinib was also associated with a higher frequency of central serous retinopathy (all grades) (25.5% versus 2.8%), grade ≥3 diarrhoea (6.5% versus 0.8%), grade ≥ 3 photosensitivity (3.6% versus 0%), and grade ≥2 reduction in LVEF (8.5% versus 3.7%).

However, the frequency of grade ≥3 keratoacanthomas (1.2% versus 8.1%), grade ≥ 3 squamous cell carcinomas (2.8% versus 12.6%), and grade ≥3 arthralgia (2.4% versus 4.9%) were lower in the vemurafenib plus cobimetinib treatment arm than single agent vemurafenib.

The discontinuation rates for adverse events were higher in the vemurafenib plus cobimetinib arm (15.0%) than in the vemurafenib plus placebo arm (8.1%).

Table 4.Assessment of generalizability of evidence for cobimetinib vemurafenib in patients with BRAF V600 mutation positive unresectable or metastatic melanoma.				
Domain	**Factor**	**Evidence (trials, and PAG Input)**	**Generalizability Question**	**CGP Assessment of Generalizability**
Population	ECOG PS	BRIM7 and coBRIM enrolled patients who had an ECOG PS of 0 or 1.	Do trial results apply to patients with an ECOG PS greater or equal to 2? If so, why?	Based on tolerability and rapid onset of action, clinical experience supports use in patients with a worse performance status than those enrolled on the clinical trial, based on physician judgement
	Stage of disease	In both the BRIM7 and coBRIM trials, patients were either unresectable stage IIIc or stage IV metastatic disease	Do trial results apply to patients who are in other disease stages?	No, results apply to these stages only. Results of trials in adjuvant setting (stage II, resected stage III) still pending.
	Previous treatment for advanced disease	In the coBRIM trial, all participants had treatment-naïve advanced (Stage IIIC or IV) melanoma.	Do the results of this trial apply to patients who have received previous treatment for advanced melanoma?	Based on the results from BRIM 7 and the expert opinion of the CGP, these results may apply to those who have received prior treatment for advanced melanoma.
	Brain Metastases	In the coBRIM trial, patients with previously treated brain metastases were included if they had a 3-week history of stable disease.	Do the results of this trial apply to patients who have active (untreated brain metastases?	Based on the opinion of the CGP, the results of the co-BRIM trial may apply to patients with active (untreated) brain metastases.
Intervention	Administration of intervention	In the coBRIM trial, participants received placebo plus vemurafenib 960 mg orally twice a day on days 1-28 of each 28 day cycle. Participants received cobimetinib 60 mg orally once daily on days 1-21 of each 28 day cycle along with vemurafenib (960 mg).	Are the results of the trial generalizable to a different dose schedule?	No, would administer as used in trial.

Table 4.Assessment of generalizability of evidence for cobimetinib vemurafenib in patients with BRAF V600 mutation positive unresectable or metastatic melanoma.				
Domain	**Factor**	**Evidence (trials, and PAG Input)**	**Generalizability Question**	**CGP Assessment of Generalizability**
Comparator	Choice of comparator	Both BRIM7 and coBRIM trials used vemurafenib plus placebo as the choice of comparator against the active intervention of cobimetinib vemurafenib	Is the comparator used in the trial appropriate in order to interpret comparative efficacy? Could there have been other comparators used which would be more reflective of Canadian practise and standard of care?	Yes. Not at the time of this trial; treatment algorithms are rapidly changing in this particular disease.
Outcomes	Progression-free survival (PFS)	The primary outcome in the coBRIM trial was PFS. Secondary outcomes were objective response, OS, QoL & AEs.	Were the primary and secondary outcomes appropriate for the trial design?	Yes.
Notes: **CGP** = clinical guidance panel; **ECOG PS** = Eastern Cooperative Oncology Group performance status; **ORR**= objective response rate; **OS**= overall survival; **QoL**= quality of life; **AEs** = adverse events.				

2.3 Conclusions

The Clinical Guidance Panel concluded that there is an overall net clinical benefit to vemurafenib plus cobimetinib in the treatment of previously untreated BRAF V600 mutated unresectable stage III or stage IV (metastatic) melanoma. This conclusion was based on several factors:

- The coBrim study was a well-conducted, randomized double-blind placebo controlled trial which demonstrated a clear benefit in progression free and overall survival in favour of the combination therapy with vemurafenib plus cobimetinib compared with treatment with single agent vemurafenib in patients with previously untreated unresectable stage III or stage IV melanoma.
- The side effect profile of the combination is acceptable and manageable. While there was an increase in some side effects with the combination, others, such as cutaneous malignancies, were decreased.

The Clinical Guidance Panel also concluded that there may be an overall net clinical benefit to the combination of vemurafenib plus cobimetinib for previously treated patients with advanced melanoma. This conclusion was based on several factors:

- The magnitude of benefit of the combination of vemurafenib and cobimetinib in the BRIM7 study (a phase 1b, open-label, multi-center dose escalation trial) was similar to that observed in the coBRIM trial.
- The expert opinion of the CGP.

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

- Clinical trial results suggest that there is no significant benefit for the use of the combination of vemurafenib plus cobimetinib following progression on single agent vemurafenib.
- Patients who are responding to single agent vemurafenib should be allowed to receive cobimetinib in addition to vemurafenib
- There is no evidence to support the use of single agent MEK inhibitors following progression on a BRAF inhibitor.
- There is no evidence to support the use single agent BRAF inhibitors following progression on a MEK inhibitor.
- There have been no direct comparisons of the combination of vemurafenib plus cobimetinib with dabrafenib plus trametinib.
- At this time, there is no evidence to guide the optimal sequencing of BRAF plus MEK inhibitors with immune checkpoint drugs (CTLA-4 and PD1 inhibitors) or the combination of these 2 classes of drugs.

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 an estimated 6800 new cases of primary melanoma were diagnosed in 2015 and approximately 1150 individuals died from melanoma.[9] 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 74 and for men is 1 in 57.[9] Staging of melanoma is based on the current American Joint Committee on Cancer (AJCC) 7th edition classification.[10] The tumour characteristics principally involve the Breslow depth, 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.[12] 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%.[13] 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.[11,14] Although this alkylating agent is generally well tolerated, response rates are low (7-15%) and complete responses are rare.[15] In comparative studies the use of dacarbazine has not been shown to improve survival in metastatic melanoma.[16-20] Temozolomide, an oral imidazole tetrazene 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.[21-23]

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%.[24,25] 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.[26-28]

The MAP kinase signaling pathway appears to be a key regulatory mechanism for cell growth and differentiation in melanoma.[29] Mutations in the BRAF protein within this pathway can result in uncontrolled cellular proliferation and increased potential for metastatic spread.[30] 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.[31] Vemurafenib and Dabrafenib are BRAF inhibitors that target the V600 mutation and are approved by Health Canada based on studies showing improvements in risk of death and risk of tumor progression.[32-39] 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, Robert and Larkin in the first line treatment of BRAF 600E/K mutated unresectable or metastatic melanoma. Compared to single agent BRAF inhibitors, dual inhibition of the MAP kinase pathway by combination BRAF and MEK inhibitors have shown improvements in RR, PFS, and OS.[1,40,41] The combination of Dabrafenib plus Trametinib has received pCODR Expert Review Committee (pERC) recommendation for funding, conditional on the cost-effectiveness being improved to an acceptable level, for patients with previously untreated, unresectable or metastatic melanoma and ECOG status 0-1.[42] Unfortunately, for the vast majority of patients who are BRAF positive, resistance to the BRAF and MEK inhibitors ultimately develops and patients experience rapid and often unrelenting disease progression. In the 50% of the patients who do not have BRAF mutation, the BRAF inhibitors are uniformly ineffective. It is anticipated that this therapy will be a treatment option for BRAF mutation positive patients who are treatment naïve or whom have progressed on immune checkpoint inhibitors.

Another class of therapy, the immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab) has shown improved outcomes, independent of BRAF status, in metastatic melanoma. Ipilimumab is 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.[43,44] Response rates to ipilimumab are low (11-15%), and median OS is modest at 10-11 mos. Of major importance however, is that even though the median OS is modest, a proportion of patients treated with immune checkpoint inhibitors will experience prolonged disease control lasting many years, and the hope is that they are cured of metastatic melanoma. With ipilimumab 15-20% of patients experience prolonged disease

control and may not require further treatment.[44] In 2012, ipilimumab was initially approved by Health Canada for the treatment of unresectable or metastatic melanoma in patients who have failed or do not tolerate other systemic therapy for advanced disease.[9] In September 2014, it was further approved as first line therapy of unresectable or metastatic melanoma.[45] The Health Canada-recommended dose for ipilimumab, in both previously treated and untreated patients, is 3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of four doses.[46] The pCODR Expert Review Committee (pERC) recommended funding ipilimumab, conditional on the cost-effectiveness being improved to an acceptable level, in good performance status patients in first or second line setting for patients with unresectable Stage III or Stage IV melanoma.[46,47] Adverse events are significant and potentially life threatening with ipilimumab therapy; approximately 15% of patients experience grade 3 or 4 immune mediated side effects that require management and monitoring, including risks for severe and fatal events (i.e., colitis). As above, only a minority of patients respond to ipilimumab used in the first or second line setting; treatment options for ipilimumab refractory patients are very limited and patients typically have short survival.

Nivolumab and pembrolizumab are antibodies to programmed death 1 (PD-1) immune-checkpoint inhibitors. In previously untreated patients, nivolumab was superior to dacarbazine with higher ORR (40.0% vs 13.9%), mPFS (5.1 months vs 2.2 months HR 0.43, p<0.001), and OS at 1 year (72.9% vs 42.1% HR 0.42, p<0.001).[48] Grade 3 or 4 adverse events occurred in 11.7% of the nivolumab treated patients and 17.6% of the dacarbazine treated patients. In the KEYNOTE-006 trial of Pembrolizumab compared to Ipilimumab in 1st or 2nd line therapy for advanced melanoma,[49] there were improvements in RR (34% vs 12%), 6 months PFS (47% vs 26% HR 0.58 p<0.001), estimated 12 months OS (74% vs 58% HR 0.63 p=0.0005) and lower grade 3 to 5 treatment related adverse events (13.3% vs 19.9%, all in favour of pembrolizumab. In this trial, prior BRAF inhibitor treatment was not required for BRAF mutation positive patients, if they had a normal LDH, and absence of both significant symptoms of disease and rapidly progressive disease. Recently, the pCODR Expert Review Committee (pERC) recommended funding pembrolizumab, conditional on the cost-effectiveness being improved to an acceptable level, in good performance status patients with unresectable Stage III or Stage IV melanoma, who are either naïve to ipilimumab, or in patients who have failed ipilimumab, and if BRAF mutation positive, have failed a BRAF inhibitor.[50] Recently, a large, randomizing phase 3 study assessed the efficacy of nivolumab (N) alone, or nivolumab in combination with ipilimumab (N+I) versus ipilimumab (I) alone.[51] The study randomized 945 previously untreated patients in a 1:1:1 fashion. The median progression free survival was 11.5 months in the nivolumab plus ipilimumab arm, versus 2.9 months in the ipilimumab arm and 6.5 months for nivolumab. The trial was designed to compare the N=I and N alone arms versus I alone, and these were both statistically significant. Nivolumab plus ipilimumab versus nivolumab alone was not evaluated. There was also a significant increase in treatment-related grade 3 or 4 adverse events, occurring in 55% of nivolumab plus ipilimumab patients, 16.3% of nivolumab patients and 27.3% of patients treated with ipilimumab.

3.3 Evidence-Based Considerations for a Funding Population

In the trial by Larkin et al, 495 BRAF mutation-positive patients with unresectable or metastatic melanoma were randomized to receive vemurafenib 960 mg twice daily plus cobimetinib 60 mg once daily for 21 days versus vemurafenib plus placebo.[1] The primary outcome of the study, investigator-assessed progression free survival, demonstrated a median PFS of 9.9 vs 6.2 months favouring the vemurafenib plus cobimetinib arm (HR for

death or disease progression 0.51 (95 % CI 0.39-0.68; P<0.001). Nine month survival rates were 81% in the combination group and 73% in the control group. While the rates of secondary cutaneous malignancies was decreased in the combination arm, there was also a nonsignificant increase in grade 3 or higher adverse events in that arm.
Additionally, the optimal sequencing of BRAF/MEK drugs and immune checkpoint inhibitors is unknown and will hopefully be clarified in future clinical trials.

3.4 Other Patient Populations in Whom the Drug May Be Used

Immunomodulator drugs such as ipilimumab, nivolumab and pembrolizumab 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 an approximately 20% chance of long term survival with ipilimumab; long term survival data with the PD-1 inhibitors is pending . While a significant portion of patients may receive immune checkpoint inhibitors in first and/or second line treatment of melanoma, there are some patients for whom combination BRAF and MEK inhibitor therapy will be the appropriate first choice. In other BRAF mutation positive patients, this combination will be an appropriate choice for those who have progressed on immunomodulatory 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 cobimetinib (Cotellic) in combination with vemurafenib (Zelboraf) for the treatment of metastatic melanoma and their input is summarized below.

MNC conducted a confidential on-line survey of patients from across Canada. The survey had a combination of multiple choice, rating and open ended questions. Patients were recruited through email, requesting input from patients that had been treated with cobimetinib in combination with vemurafenib for metastatic melanoma or patients who may see a need for this combination therapy in the future. MNC received input from a total of 42 respondents (26 patients and 16 caregivers). MNC suggested that clinical trial sites in Canada were limited and that they were aware of nine (9) patients that participated in a clinical trial. Since the study was blinded, respondents that participated in both the clinical trial and MNC survey indicated they did not know if they had received both cobimetinib and vemurafenib as part of the trial. Based on this information, MNC reported that two (2) respondents may have been treated with cobimetinib in combination with vemurafenib.

SYSF conducted one-on-one interviews, focus groups, and surveys with a total of 150 respondents (130 patients and 20 caregivers), of which 23 were treated with the treatment under review. All respondents were from Canada, most were female (72%, 108 out of 150) and the majority were between the age of 40-60 or older (97%, 145 out of 150).

From a patient's perspective, it is expected that cobimetinib in combination with vemurafenib will stop the disease or slow disease progression, not only in terms of increasing the length of life, but also in managing the quality of life. Current treatment for melanoma reported by SYSF and MNC included: interferon, surgery, radiation, dacarbazine, temozolomide, stereotactic radiation (for brainstem tumours), vemurafenib, ipilimumab, dabrafenib in combination with trametinib, and pembrolizumab. Reported side effects from current treatment for melanoma include: fever, hair loss, extreme fatigue, diarrhea, skin issues, nausea, rash, joint pain, and colitis vomiting, low blood counts, stomach upset, and sun sensitivity. Respondents indicated that side effects with current treatment could be difficult to tolerate, but were manageable; and respondents would undergo treatment for as long as needed, despite side effects. While respondents agree that current treatments, such as interferon, dacarbazine and temozolomide may slow the spread of disease, respondents believe they are not effective in preventing metastases. Respondents who have experience with cobimetinib reported the following key side effects: skin rash, fatigue or weakness, fever or flu like symptoms. Other side effects included, shortness of breath, cough or chest pain (pneumonitis), photosensitivity, other skin cancers like squamous cell carcinoma, diarrhea or colitis, muscle or joint pain, headaches, stomach pain and nausea. Respondents reported that the side effects, such as diarrhea, nausea, fever, and vomiting were manageable. Those who were able to manage the side effects reported their quality of life as "normal". Respondents also noted that cobimetinib is an oral therapy which could be taken at home, and therefore, could potentially reduce the amount of time patients have to travel back and forth to hospitals.

Please see below for a summary of specific input received from the patient advocacy groups. Cited responses are reproduced from the patient input summaries with no modifications made for spelling, punctuation or grammar. The statistical data that were reported have also been reproduced as is according to the submission, without modification.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Metastatic Melanoma

MNC asked respondents to identify specific issues experienced with melanoma. MNC indicated that patients want to control pain, fatigue and stress associated with melanoma. Below is a list of the key findings on specific issues that respondents experienced with melanoma.

Cancer and the different stages of cancer affect people in different ways. What issues have you experienced with your cancer diagnosis? Please select as many responses as appropriate.		
Answer Options	**Response Percent**	**Response Count**
Fear or anxiety	78.3%	18
Scarring or disfigurement	65.2%	15
Depression	60.9%	14
Disrupted sleep	52.2%	12
Fatigue	52.2%	12
Negative Impact to family or social life	47.8%	11
Pain	43.5%	10
Headaches	34.8%	8
Appetite loss or weight gain	34.8%	8
Financial loss or job loss	34.8%	8
Gastrointestinal issues	17.4%	4
Peripheral neuropathy (nerve pain or damage)	17.4%	4
Cognitive Impairment	17.4%	4
Mobility issues (unable to walk or impaired movement)	13.0%	3
Post-traumatic stress	13.0%	3
Nausea or vomiting	13.0%	3
Lymphedema	8.7%	2
Breathing problems	8.7%	2
Edema or fluid retention	4.3%	1
Damage to organs, such a lungs, liver, brain	4.3%	1
None	13.0%	3
Other (please explain)		5
answered question		23
skipped question		3

SYSF also found the following limitations described by respondents: inability to mentally and physically return to work; inability to return to "normal" daily life; and anxiety and depression due to their prognosis, and as a result, are unable to continue to work. SYSF also indicated that respondents have suffered from loss of mobility due to muscle and tissue removal of surgery or treatment.

Below are key comments from respondents reported by MNC (in both current and previous surveys) to help illustrate some of the issues impacting patients with melanoma - both from a physical and from a mental health perspective:

- *"The diagnosis has affected every part of my life. I am not the same person. I no longer feel so positive about the future and I constantly worry about recurrence."*
- *"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.."*

- *"I have fear for my family. My kids are young and I am the major earner in the family. I am only 31. Can it be worse - yes, if I die, it will be worse for them."*
- *"It has nearly cost me my life, my time with my family, I have missed work and I have constant appointments with the doctors to go to. I am scarred and exhausted. Never knowing how much longer I had to live and where the cancer would move to."*
- *"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."*
- *"I have been one of the fortunate ones, my issues have been very slight. The biggest issue has been my financial issues due to loss of job."*
- *"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."*
- *"Even 11 yrs after diagnosis I live with the fear of recurrence. It has been a worry to my spouse, parents, siblings & friends. I hid my cancer diagnosis at the time worried employers would not hire me. It impacted career decisions as I was afraid of being without health and drug insurance. It has affected my social, travel & physical activities ie I modify or decline my participation to avoid being in the sun. I dress differently to hide my scarring & for sun protection."*

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, temozolomide, stereotactic radiation (used on brainstem tumours), vemurafenib, ipilimumab, dabrafenib and trametinib and pembrolizumab. SYSF noted that 20% of patients interviewed have used pembrolizumab. MNC noted (from previous surveys) therapies for patients with metastatic disease included: dacarbazine, ipilimumab; mono – or combination targeted therapies of dabrafenib and trametinib for BRAF positive patients, as well as, vemurafenib for BRAF positive patients.

SYSF stated that 10% of patient respondents had positive recorded results with interferon, dacarbazine, and temozolomide. SYSF indicated that patient respondents experienced fatigue and pain from melanoma while undergoing treatment with therapies such as interferon, dacarbazine, and temozolomide. SYSF highlighted that patient respondents felt treatments such as interferon, dacarbazine, and temozolomide possibly slowed the spread of disease, but were not effective in preventing metastases. SYSF also noted that 40% of patient respondents had positive recorded results with vemurafenib, ipilimumab, trametinib and dabrafenib. SYSF noted that half of respondents had either no response or temporary response with these prescribed treatments.

Notwithstanding, SYSF reported that all patient respondents agreed that symptoms were manageable with these medications and would undergo treatment again, if necessary. SYSF stated that 75 % of patient respondents had adverse side effects (i.e., fever, hair loss, extreme fatigue, diarrhea, skin issues, nausea, rash, joint pain, and colitis) that were most difficult to tolerate. All patient respondents agreed that side effects could be difficult to tolerate, but were manageable, if watched closely. Ultimately, all patient respondents agreed that they would undergo treatment for as long as needed, despite side effects.

MNC also reported similar findings in regards to current therapies. According to MNC, dacarbazine has a 7% response rate and poor results in preventing spread of the disease. MNC noted that from previous surveys, side effects from dacarbazine included: nausea, vomiting, low blood counts, and extreme fatigue.

MNC also stated that ipilimumab has a 20-30% response rate and reported the following side effects from ipilimumab: fatigue, rash, nausea (for some), and colitis (however, was most often controlled with steroids).

MNC highlighted that the most common side effects reported in patients treated with dabrafenib and trametinib were rash, stomach upset and fatigue. MNC stated that reported response rates for the combination therapy were 50-70%, and most often response rates were for a limited length of time (e.g., under a year).

MNC stated that durable response rates are approximately 10 months for the majority of patients treated with vemurafenib, but they were aware of patients with a long lasting and durable response. For instance, patients interviewed have had a durable response lasting years. Side effects from vemurafenib reported by MNC included: sun sensitivity, stomach upset, fatigue, skin rashes and in some, other forms of skin cancer.

Below is a comment from a caregiver reported by SYSF to help illustrate the patient's experience with current therapy: "*My spouse is thrilled with the effect the drug has had on the cancer and with the minimal side effects. Mentally this drug has given him the most positive impact since diagnosis.*"

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

According to MNC, other than time and cost of travel to hospitals providing their particular therapy, over 90% of patient respondents indicated no issue in accessing current treatment for metastatic disease.

SYSF noted that 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. According to SYSF, all patient respondents agreed that the lack of treatment options for melanoma patients in a timely fashion was an unmet need. An unmet need was also noted by MNC. According to MNC, patients are seeking treatment that will have a lasting impact on their survival or provide a good quality of life for an extended period. MNC expressed that while there are therapies that work for some, no one therapy is a solution for all. MNC indicated that patients require options that may work with their individual diagnosis, which may include a combination of therapies or sequential use of therapies.

SYSF raised concerns that patients' needs are not being met and that patients' issues are not being heard. According to SYSF, many patients were not offered newer treatment options from their oncologist and were disappointed that there were no unified melanoma protocols across Canada.

4.1.3 Impact of Metastatic Melanoma and Current Therapy on Caregivers

MNC received input from a total of 16 caregivers. According to MNC, current therapy for treatment has varying impact on caregivers as well as patients. MNC expressed that there are significant impacts on the family unit and highlighted the financial, mental health, anxiety, stress, and physical demands of caring for an ill family member. MNC noted the

impact of melanoma on caregivers which include the loss of income either from the patient's (i.e., inability to work) or from the caregiver (i.e., taking on additional responsibilities of care for the patient or having to take time off work or having to leave employment to care for the patient). MNC also noted the following impacts: additional costs and time for attending appointments; managing home care; taking on additional home and family management responsibilities (i.e., dealing with issues of communicating the situation to children, other family members and friends and managing their anxiety; trying to be a caregiver both physically and emotionally, while dealing with their own stress and challenges). MNC noted that in some cases, the impact of the disease has created a breakdown in the marriage.

SYSF interviewed a total of 20 caregivers who had a close family member who was diagnosed with melanoma. SYSF indicated that 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. One challenge for caregivers noted by SYSF was that caregivers found it difficult to distinguish if symptoms were treatment or cancer related. The lack of information about side effects was noted by the caregivers, and resulted in confusion and distress for caregivers. Other challenges for caregivers were finding treatments that might work for their loved one and the cost to travel to centers for treatment.

Below are comments from respondents provided by MNC to help illustrate the caregiver impact:

- *"The impact of a cancer diagnosis is a challenge to any family not knowing the outcome, but also the impact of the traveling to and from appointments is a challenge, a lot of rearranging has to been done in your daily routine for appointments. Even with treatments and most drugs need being paid for there is a lot of added expense travelling to and from appointment, gas, meals, loss of work time."*
- *"He had to take enormous time out of his busy work schedule. We had to cancel so many plans because of the disease and all the appointments. He also had to provide supportive care on top of his full time job. That was difficult."*

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Cobimetinib (Cotellic) in Combination with Vemurafenib (Zelboraf)

MNC expressed the importance for patients to have a therapy that can 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 life, but as well, for the quality of life. MNC also noted that cobimetinib in combination with vemurafenib is an oral therapy which can be taken at home, and therefore, may reduce the amount of time patients have to travel back and forth to hospitals.

MNC stated that a therapy that controls or eliminates disease is an unmet need for patients. According to MNC, patients expect the combination therapy to stop the disease or slow disease progression to a point that they could get on another more effective treatment, if the combination therapy stops working. MNC stated that the combination therapy offers another therapeutic option and acknowledged that the combination therapy may work well for some, may transition others or may not work at all.

Below are comments provided by MNC, which summarizes some of the key expectations reported by the respondents:

- *"If I needed a treatment that targets the BRAF mutation and could reduce the tumour burden quickly, then I think this would be a good option. I think patients and physicians need to determine what will work best and be best tolerated by their patient. It doesn't always work the same on everyone and I still think there is no chance of cure for the majority, but this could help us live longer."*

- *"I have read that the combination has better results than the Zelboraf alone. Of course I would want to try the one that has better results. Anyone would - we want a cure or at least the chance to live longer."*

- *"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"!"*

According to SYSF, a total of 23 respondents were treated with cobimetinib in combination vemurafenib and provided input on expectations for and experiences with cobimetinib in combination vemurafenib. SYSF indicated that all respondents felt that although melanoma is well-known type of cancer, health care professionals were not up-to-date on melanoma treatment options. More than half of patients interviewed heard about treatment options from an advocacy group. According to SYSF, most patients interviewed were disappointed that they had to find this treatment themselves and that they had to travel outside their provinces to obtain the treatment. Respondents also felt that if they had received this treatment sooner, the end result might have been better for them. All patient respondents agreed that having choice when dealing with any type of cancer is important and that course of treatment should also be the decision of the oncologist and their patient.

SYSF indicated that more than half of respondents travelled outside their cancer center to receive treatment. All respondents agreed that more clinical trials need to be available to them and that the benefits of this treatment outweigh the risks of the drug. Most respondents treated with cobimetinib in combination vemurafenib found that side effects (i.e., diarrhea – approximately 30%; nausea, fever and vomiting – approximately 20%) were manageable and that their oncologist was able to help them with the side effects.

According to MNC, overall survival, objective response rate and complete response rate were higher with cobimetinib in combination with vemurafenib compared to vemurafenib alone. Of those surveyed by MNC, a total of 2 out of 26 respondents may have been treated with the combination therapy. Because the study was blinded, respondents that participated in the clinical trial and in the survey indicated they did not know if they had received both of the drugs as part of the trial. According to MNC, the two patients experienced side effects, but indicated the side effects were well tolerated. Both respondents reported the following side effects: skin rash, fatigue or weakness, fever or flu like symptoms. Other side effects were noted (n=1): shortness of breath, cough or chest pain (pneumonitis); photosensitivity; other skin cancers like squamous cell carcinoma; diarrhea or colitis; muscle or joint pain; headaches; stomach pain; and nausea. Aside from persistent fatigue, the two respondents reported that the side effects were worth the results of the treatment. One respondent indicated that the respondent has

been on the combination for almost two years and has been disease free on all of the scans for the last 20 months.

Below are individual comments from respondents who have experienced with the drug under review, provided by MNC:

- *"I started the trial in Dec 2014 and saw a reduction in size of many of the surface tumours within two weeks and stabilization of the others within two months. Since then, there has been no growth of any tumours and I feel pretty good. Anxious but good."*

- *"Apart from the initial rash, which created some misery and itchiness, I am lucky to have this trial. I suspect I received the combo. It literally melted away my lesions. I feel lucky that it is still working and have had few side effects other than being tired."*

SYSF reported that 80% of respondents interviewed were still undergoing treatment, and 20% of respondents have had re-occurrence of disease and are undergoing another treatment.

4.3 Additional Information

According to MNC, combination targeted BRAF inhibitor therapies have a significant place in the treatment of patients and the reduction of the burden of disease. MNC expressed that combination targeted BRAF inhibitor therapies have the ability to act to stop or control the disease quickly that an immunotherapy often cannot.

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.pcodr.ca). 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 cobimetinib plus vemurafenib combination therapy for melanoma:

Clinical factors:

- Availability of data regarding the sequencing of BRAF inhibitors +/- MEK inhibitors and immunotherapies
- Relative clinical benefits and risks of cobimetinib + vemurafenib combination therapy compared to vemurafenib monotherapy and compared to dabrafenib + trametinib combination therapy
- The benefits of adding cobimetinib when patients have already started vemurafenib and not yet progressed

Economic factors:

- High cost of combination drugs
- Cost-effectiveness of cobimetinib + vemurafenib combination therapy compared to vemurafenib monotherapy and compared to dabrafenib + trametinib combination therapy and compared to ipilimumab and other immunotherapies

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 comparison with vemurafenib monotherapy is appropriate and comparison with ipilimumab would be appropriate for patients with low burden disease.

At the time of this PAG input, dabrafenib + trametinib is not yet funded in any of the participating provinces. However, PAG feels dabrafenib + trametinib would be an appropriate comparator and is seeking information on whether there is direct comparison data for vemurafenib + cobimetinib compared to dabrafenib + trametinib.

5.2 Factors Related to Patient Population

Recognizing that the data may be not be available or be limited, PAG is seeking information on the benefits of using cobimetinib + vemurafenib combination therapy, either before or after treatment with ipilimumab and upcoming PD-1 immunotherapies (pembrolizumab and nivolumab are under review at the time of this PAG input).

PAG noted that the side effects of BRAF inhibitor + MEK inhibitor is better than monotherapy with BRAF inhibitors. PAG recognizes that cobimetinib + vemurafenib would

be an alternate to dabrafenib + trametinib, providing patients with a choice in treatments. These are enablers to implementation.

PAG is seeking information on whether adding cobimetinib would be beneficial for patients who have already started vemurafenib and either have not yet progressed or have progressed.

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 vemurafenib is four tablets twice daily continuously and the dose of cobimetinib is three tablets once daily for 21 days out of 28-day cycle. 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.

5.4 Factors Related to Implementation Costs

PAG is seeking information on the clinical benefits, safety and cost-effectiveness of cobimetinib + vemurafenib combination therapy compared to vemurafenib monotherapy and compared to dabrafenib + trametinib combination therapy.

5.5 Factors Related to Health System

PAG noted that both cobimetinib and vemurafenib 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 cobimetinib + vemurafenib combination therapy compared to vemurafenib monotherapy is a barrier to implementation.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the safety and efficacy of cobimetinib (Cotellic) in combination with vemurafenib (Zelboraf) for treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation, irrespective of prior treatment status.

Note: A Network meta-analysis has been provided by the submitter and will be discussed in the supplemental section.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*†	Outcomes
Published and unpublished RCTs or non RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of cobimetinib plus vemurafenib should be included.	Adult patients with unresectable or metastatic melanoma with BRAF V600 mutation, irrespective of prior treatment status	Cobimetinib in combination with vemurafenib	All appropriate multi-agent chemotherapy regimens including but not limited to: ➢ vemurafenib ➢ dabrafenib ➢ trametinib (MEK inhibitor) ➢ ipilimumab ➢ nivolumab ➢ pembrolizumab	• OS • PFS • ORR • HRQoL • AEs • SAEs • WDAE
[Abbreviations] OS= overall survival; PFS= progression-free survival; ORR= overall response rate; HRQoL= health-related quality of life; RCT=randomized controlled trial; SAE=serious adverse events; AE=adverse events; WDAE=withdrawals due to adverse events				

** All treatments in combination with supportive care.*

† 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 to present) with in-process records & daily updates via Ovid; Embase (1974 to 2015 December 16) via Ovid; The Cochrane Central Register of Controlled Trials (November 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 Cotellic, cobimetinib, Zelboraf, vemurafenib and melanoma.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year. The search is considered up to date as of April 7, 2016.

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

6.2.3 Study Selection

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

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, and the Clinical Guidance Panel.

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental issues.

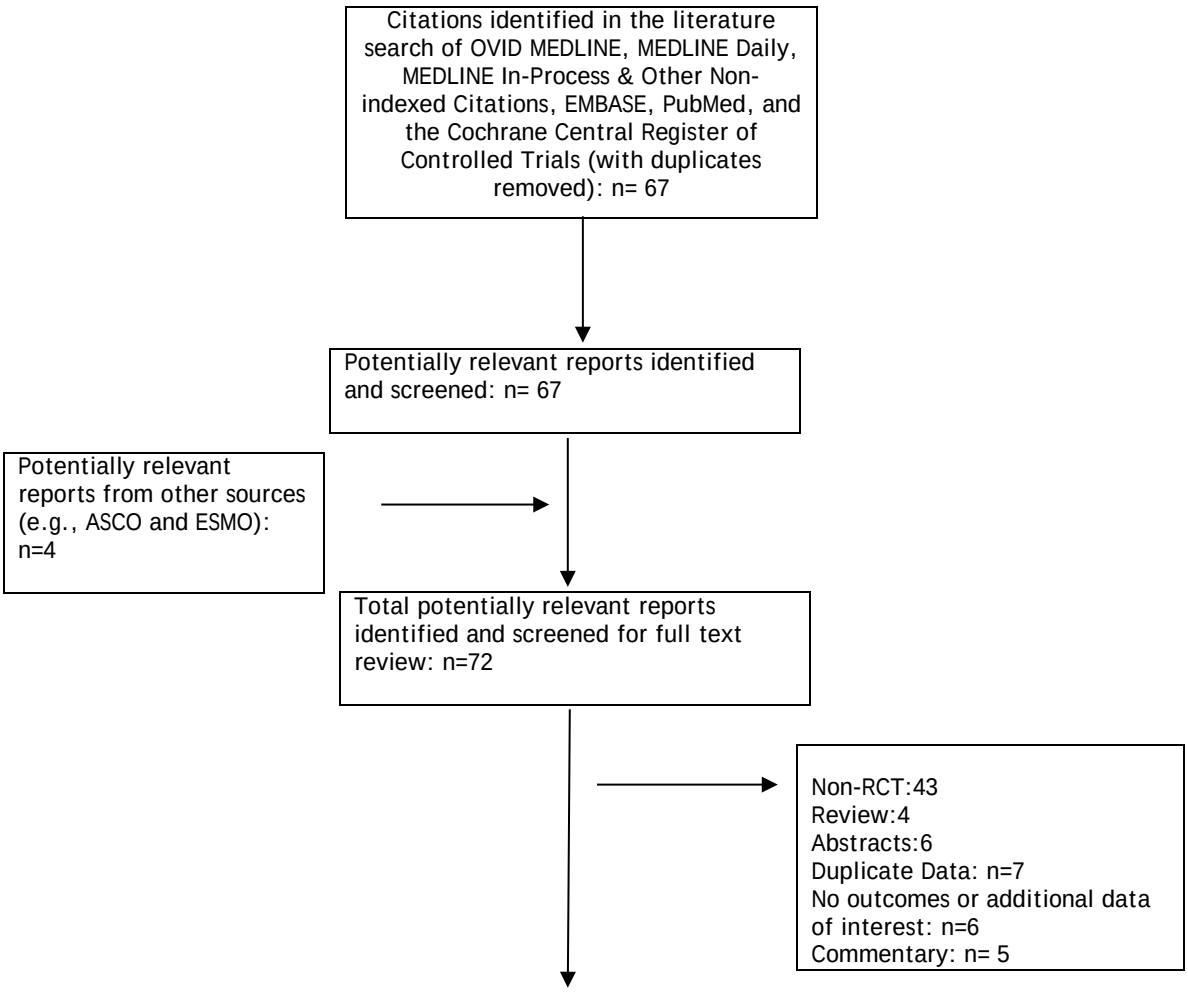
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information, the interpretation of the systematic review and wrote guidance and conclusions for the report.
- The pCODR team wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

One clinical trial NCT01495988[52] was identified that met the eligibility criteria of the protocol, but was not included as part of this review due to the unavailability of study results.
This was a randomized, open-label phase II trial of vemurafenib/cobimetinib with or without bevacizumab in patients with stage IV BRAFV600 mutant melanoma. There were 10 patients enrolled who were randomized to either 1) standard of care (SOC) – BRAF inhibitor vemurafenib in combination with cobimetinib; or 2) SOC plus bevacizumab. Patients in this study may have been previously untreated for advanced disease or treated with up to 2 prior therapies, excluding BRAF and MEK inhibitors. The start date of this study was August 2013 with a primary completion date of January 2016 and an estimated completion date of June 2016. According to the clinicaltrials.gov site, this study was terminated due to slow accrual, toxicity, and a change in priorities.

QUOROM Flow Diagram for Inclusion and Exclusion of studies



3 reports presenting data from 1 clinical trial Study Larkin et al 2014 (coBRIM)[1] *Reports identified and included from other sources:* EPAR[6] FDA statistical report[2]

6.3.2 Summary of Included Studies

One clinical trial was identified that met the eligibility criteria of this systematic review and was selected for inclusion (Please see Table 2). CoBRIM is a phase 3 randomized, double-blind placebo controlled trial that was designed to assess whether cobimetinib plus vemurafenib treatment would substantiate a greater anti-tumour response compared to vemurafenib single agent BRAF inhibition.

Further information was also available from EPAR and FDA reports, information that comes from the trial noted above but that is not found in the primary publication.

6.3.2.1 Detailed Trial Characteristics

Table 2. Summary of Trial characteristics of the included studies of cobimetinib vemurafenib in patients with BRAF V600 mutation positive unresectable or metastatic melanoma[53]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
NCT01689519 Other Study ID numbers: GO28141, 2012-003008-11 coBRIM Phase 3, randomized, double-blind, placebo-controlled study Enrollment: 495 Estimated completion date: December 2017	• Patients with histologically confirmed metastatic melanoma (unresectable Stage IIIc and Stage IV) • Patients must be naïve to treatment for locally advanced unresectable or metastatic disease (i.e., no prior systemic anti-cancer therapy for advanced disease; stage IIIc and IV). Prior adjuvant immunotherapy (including ipilimumab) is allowed • Documentation of BRAF V600 mutation-positive status in melanoma tumor tissue (archival or newly obtained tumor samples) using the	• Drug: Placebo ➢ Placebo was supplied as tablets. • Drug: Vemurafenib ➢ Vemurafenib was supplied as tablets. • Drug: Cobimetinib ➢ Cobimetinib was supplied as tablets.	Primary: • PFS Secondary: • OS • Objective Response • DOR • Safety (AEs) • Pharmacokinetics (min. observed plasma concentration, apparent clearance following oral dosing • QoL

Table 2. Summary of Trial characteristics of the included studies of cobimetinib vemurafenib in patients with BRAF V600 mutation positive unresectable or metastatic melanoma[53]			
Study Sponsor: Hoffman-La Roche	*cobas* 4800 BRAF V600 mutation test. • Measurable disease per RECIST 1.1 • ECOG status of 0 or 1 • Adequate hematologic and end organ function • Life expectancy ≥ 12 weeks • Previously treated brain metastases with a 3-week history of stable disease	Active Comparator: Placebo plus vemurafenib	
Notes: ECOG = Eastern Cooperative Oncology Group; PS = performance status; QOL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumours; AEs = adverse events; PFS= progression-free survival; ORR= objective response rate; OS=overall survival; FDG-PET= fluorodeoxyglucose positron-emission tomography; QLQ-30= European Organization for Research and Cancer Quality of Life Questionnaire; EQ-5D= EuroQol 5 dimension			

a) Trials

coBRIM[1]

coBRIM was a phase III, randomized, double-blind, placebo-controlled study which randomly assigned 495 patients with previously untreated unresectable locally advanced or metastatic BRAF V600 mutation-positive melanoma to receive vemurafenib in combination with cobimetinib or vemurafenib plus placebo (control group). Eligible inclusion criteria for patients enrolled in this study was BRAF mutation detected by the *Cobas* 4800 BRAF mutation test. Patients with previously treated brain metastases were eligible if they had at least a 3 week history of stable disease.

Patients were randomly assigned in a 1:1 ratio to receive vemurafenib orally, at a dose of 960 mg twice daily, together with either placebo or cobimetinib, at a dose of 60 mg. once daily for 21 days, followed by 7 days off. Study treatment continued until patients withdrew consent, unacceptable adverse events, or disease progression occurred. Dose modifications were allowed for both vemurafenib and cobimetinib in order to manage adverse events that were ≥ grade 2.

The primary endpoint of the study was progression-free survival by investigator assessment, according to RECIST v 1.1 criteria. Secondary endpoints included overall survival, objective response according to RECIST v 1.1 criteria, duration of response, PFS as assessed by an independent review facility, and safety.

b) Populations[6]

495 patients were enrolled in the coBRIM trial from January 2013 through January 2014 at 135 sites in the United States, Canada, Australia, New Zealand, Europe, Russia, Turkey and Israel. The primary outcome of the trial was investigator assessed PFS, which was defined as the time from randomization to the first occurrence of disease progression, or death

from any cause. Secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DOR), time to objective response (TTR), and independent-review facility (IRF) assessed PFS.

The study was designed to provide >95% power to detect an improvement in median PFS from 6 months in the vemurafenib plus placebo arm to 11 months in the vemurafenib plus cobimetinib arm, corresponding to a hazard ratio of 0.55.

Treatment groups were well balanced for patient and disease characteristics. However, there were a slightly higher percentage of patients with an ECOG PS of 0 in the vemurafenib and cobimetinib arm (76%) compared to the vemurafenib and placebo arm (67%). The study population was comprised of a greater percentage of males in both treatment arms, vemurafenib and placebo (56%) and vemurafenib and cobimetinib (59%).

Table 3. Baseline Patient Characteristics in the included studies of cobimetinib vemurafenib in patients with BRAF V600 mutation positive unresectable or metastatic melanoma[1]

	coBRIM	
Patient Characteristics	Vemurafenib plus placebo (n=248)	Vemurafenib plus cobimetinib (n=247)
Median Age (years)	55 (range 25-85)	56 (range 23-88)
Male	140 (56%)	146 (59%)
White ethnic origin	235 (95%)	227 (92%)
ECOG performance status score		
0	164/244 (67%)	184/243 (76%)
1	80/244 (33%)	58/243 (24%)
2	0/244	1/243 (<1%)
Metastatic status - no. (%)		
Unresectable stage IIIc	13 (5%)	21 (9%)
M1a	40 (16%)	40 (16%)
M1b	42 (17%)	40 (16%)
M1c	153 (62%)	146 (59%)
Elevated LDH	104/242 (43%)	112/242 (46%)
BRAF mutation genotype - no. (%)		
V600E	174 (70%)	170 (69%)
V600K	32 (13%)	24 (10%)
Could not be evaluated	42 (17%)	53 (21%)

Notes: ECOG PS= Eastern Cooperative Oncology Group Performance Status; LDH= lactate dehydrogenase

c) *Interventions*[6]

Randomization of patients to one of the two treatment arms occurred through the use of an interactive voice response system (IVRS). Randomization was stratified according to metastatic classification and geographic region. In order to obtain a 1:1 allocation between the two treatment groups, a stratified permuted block randomization scheme was used.

Patients were randomly assigned in a 1:1 ratio to receive vemurafenib orally, at a dose of 960 mg twice daily, together with either placebo, or cobimetinib, at a dose of 60 mg once daily for 21 days, followed by 7 days off.

In order to manage adverse events, dose modifications were permitted for pre-specified levels of toxic events (i.e. grade ≥2).

d) *Patient disposition*

A total of 495 patients were randomized and included in the intention to treat analysis.

Details of the patient disposition in the coBRIM study can be found in table 4 below.

Table 4. Patient disposition and Reasons for discontinuation in the coBRIM trial[6]

	Vemurafenib plus placebo (n=248)	Vemurafenib plus cobimetinib (n=247)	All patients (n=495)
Patients discontinued from study	67 (27.0%)	48 (19.4%)	115 (23.2%)
Reasons for discontinuation			
Death	51 (20.6%)	34 (13.8%)	85 (17.2%)
Lost to follow-up	3 (1.2%)	1 (0.4%)	4 (0.8%)
Withdrawal by subject	13 (5.2%)	10 (4.0%)	23 (4.6%)
Physician decision	0	3 (1.2%)	3 (0.6%)

e) *Limitations/Sources of Bias*

- Randomization and allocation concealment (assessment of selection bias)

  The study utilized the interactive voice response system (IVRS) system. Randomization was stratified by metastatic classification and geographic region. A stratified permuted block randomization scheme was used to achieve a 1:1 allocation between the two treatment groups. In addition, baseline characteristics were well balanced. Therefore, the risk of selection bias in the coBRIM trial was low.

- The original protocol was issued on August 3 2012, and there were 3 amendments made to it, including the following: revised guidelines for emergency unblinding to allow investigators the ability to unblind without the Sponsor`s approval. This protocol amendment would limit the interpretation of the results reported for patient outcomes, in particular those relating to symptom improvements and quality of life.

- There was several protocol deviations noted throughout the study. Of particular interest, are the following which can question the rigour and validity of the efficacy and adverse event results
    - A total of 26 patients, 12 (4.9%) in the cobimetinib plus vemurafenib arm and 14 (5.6%) in the vemurafenib plus placebo arm had at least one violation of the inclusion and exclusion criteria set in the study protocol
    - Lack of patient compliance with the dosing regimen (i.e. off treatment longer than 28 days and more than 7 days off between treatment cycles).

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

a) Efficacy Outcomes

Table 5. Key efficacy outcomes of cobimetinib vemurafenib in patients with BRAF V600 mutation positive unresectable or metastatic melanoma in the coBRIM trial[1,3,4,6,8]

Treatment group	Vemurafenib plus cobimetinib N = 247	Vemurafenib plus placebo N= 248
PFS by investigator (median) [Data cut-off May 9 2014] 95% CI	9.9 months (median follow-up 7.4 months) 9.0, NE	6.2 months (median follow-up 7.0 months) 5.6, 7.4
PFS by independent review committee (median) 95% CI	11.3 months 8.5, NE	6.0 months 5.6, 7.5
Updated PFS by investigator (median) [Data cut-off Jan 16 2015] 95% CI	12.3 months (median follow-up 14.9 months) 9.5, 13.4	7.2 months (median follow-up 13.6 months) 5.6, 7.5
Interim OS (median) [data cut-off Jan 2015] 95% CI	NE 20.7, NE	17.02 months 15.0, NE
Final OS (median) [Data cut-off Aug 28 2015] 95% CI	22.3 months 20.3, NE	17.4 months 15.0, 19.8
ORR by investigator review N (pts) (%) 95% CI [Data cut-off January 16 2015]	 172 (70.0) 63.5, 75.3	 124 (50.0) 43.6, 56.4
DOR by investigator review (median) [Data cut-off May 9 2014]	NE	7.3 months

Table 5. Key efficacy outcomes of cobimetinib vemurafenib in patients with BRAF V600 mutation positive unresectable or metastatic melanoma in the coBRIM trial[1,3,4,6,8]		
95% CI	9.3, NE	5.8, NE
Effect Estimates		
PFS by investigator review Stratified Hazard Ratio	0.51 (95% CI: 0.39, 0.68) p-value <0.001	
PFS by independent review Stratified Hazard Ratio	0.60 (95% CI: 0.45, 0.79) p-value 0.0003	
Updated PFS by investigator review [Data cut-off Jan 16 2015] Stratified Hazard Ratio	0.58 (95% CI: 0.46, 0.72)	
Secondary endpoint: Overall Survival Stratified Hazard Ratio	Interim analysis:0.63 (95% CI, 0.47 to 0.85; p=0.0019) Final analysis: 0.70 (95% CI, 0.55 to 0.90; p=0.005).	
Secondary endpoint: Overall Response Rate (ORR)	Difference in ORR between cobimetinib + vemurafenib vs. placebo + vemurafenib : 22.9% (95% CI: 14.1, 31.58) p-value <0.0001	
Notes: PFS= progression-free survival; OS= overall survival; ORR= overall response rate; DOR= duration of response; CI= confidence interval; NE= not estimable.		

In the coBRIM study, there were 3 analysis populations: intent to treat (ITT), safety-evaluable, and patient-reported outcome (PRO). The ITT population included all randomized patients, regardless of whether or not study treatment was received. The safety-evaluable population included all patients who received at least one dose of study treatment. The PRO population included all patients who had a baseline assessment and at least one post-baseline assessment.

The ITT population included a total of 495 patients, the safety-evaluable population included 493 patients and the PRO population included 420 patients. The slight variance in patient numbers included in the ITT and safety evaluable populations is due to two patients (one in each study arm) who did not receive the study treatment.

All the efficacy analyses were carried out in the intention to treat population.

Investigator-assessed progression-free survival was a primary end point in the coBRIM study.

The combination of vemurafenib plus cobimetinib significantly prolonged progression-free survival according to investigator assessment in the intention-to-treat population. The PFS was a median of 9.9 months in the combination group compared to 6.2 months in patients treated with vemurafenib plus placebo. The HR for death or progression of disease was 0.51 (95% CI, 0.39 to 0.68) with a p value of less than 0.0001.[6]

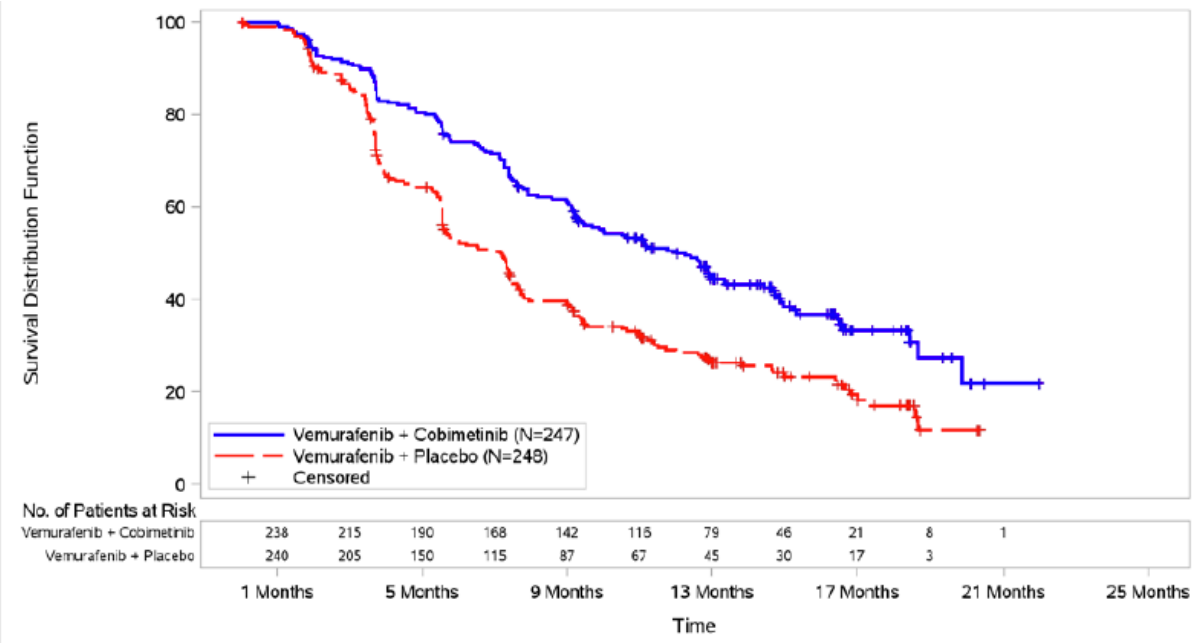
An updated data cut-off of January 16 2015 also demonstrated a significantly prolonged progression-free survival according to investigator assessment of 12.3 months (95% CI, 9.5 to 13.4) in the combination group compared to 7.2 months (95% CI, 5.6 to 7.5) in the vemurafenib plus placebo group. The HR for death or progression of disease was 0.58 (95% CI, 0.46 to 0.72).[6]

An interim analysis of overall survival in the intention to treat (ITT) population, dated January 2015, demonstrated a statistically significant difference in the median OS for the vemurafenib plus cobimetinib group (median OS not estimable) compared with the vemurafenib plus placebo group (median OS 17 months); HR 0.63, 95% CI 0.47 to 0.85, p=0.0019. See Figure 2 for the Kaplan-Meier overall survival curve.

The final analysis of OS was originally planned to occur after a total of 385 deaths which would provide approximately 80% power to detect an improvement in median OS from 15 months in the single agent vemurafenib arm to 20 months in the vemurafenib plus cobimetinib arm (HR for death of 0.75). However, this plan was amended and the final OS analysis was performed after the occurrence of 250 events, which would provide approximately 80% power to detect an improvement in median OS from 15 months in the single agent vemurafenib arm to 21.4 in the vemurafenib plus cobimetinib arm (HR for death of 0.70 with an overall two-sided alpha of 0.05).[6]

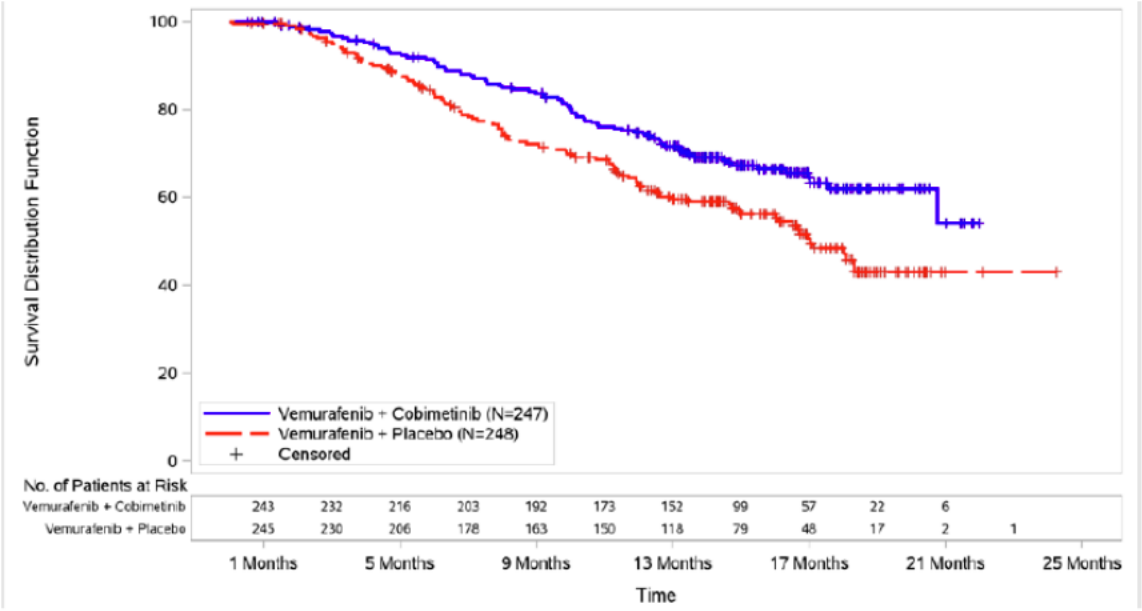
The final data cut-off of August 28, 2015 for overall survival, that was presented at the 2015 Society for Melanoma Research Congress, demonstrated a statistically significant difference favouring the vemurafenib plus cobimetinib arm with a median of 22.3 months (95% CI, 20.3 to NE) versus the single agent vemurafenib arm with a median of 17.4 months (95% CI, 15.0 to 19.8). The hazard ratio for this final OS analysis was 0.70 (95% CI, 0.55 to 0.90; p=0.005).[3,4]

Figure 1. Kaplan-Meier Plot of updated Progression-Free Survival (PFS) in the coBRIM trial (ITT population, data cut-off January 2015[6]



Source: European Medicines Agency, 2014[6]

Figure 2. Kaplan-Meier plot of updated Overall Survival in the coBRIM trial (ITT population, data cut-off January 2015)[6]



Source: European Medicines Agency, 2014[6]

b) Harms Outcomes

Table 6. Summary of Adverse Events for cobimetinib vemurafenib in patients with BRAF V600 mutation positive unresectable or metastatic melanoma[6]

	coBRIM			
	Placebo plus vemurafenib		Vemurafenib plus cobimetinib	
	SCS n=239	Safety Update n=246	SCS n=254	Safety Update n=247
Total number (%) of patients with ≥1 AE	233 (97.5)	240 (97.6)	250 (98.4)	244 (98.8)
Total number of patients with ≥1:				
Grade ≥3 AEs	142(59.4)	146 (59.3)	165 (65.0)	176 (71.3)
Grade 5 AEs	3 (1.3)	3 (1.2)	6 (2.4)	5 (2.0)
SAEs	60 (25.1)	64 (26.0)	75 (29.5)	85 (34.4)
AEs leading to discontinuation of cobimetinib/placebo	33 (13.8)	24 (9.8)	42 (16.5)	47 (19.0)
AEs leading to discontinuation of vemurafenib	32 (13.4)	24 (9.8)	35 (13.8)	39 (15.8)

Table 6. Summary of Adverse Events for cobimetinib vemurafenib in patients with BRAF V600 mutation positive unresectable or metastatic melanoma[6]				
AEs leading to discontinuation of cobimetinib and vemurafenib	28 (11.7)	20 (8.1)	32 (12.6)	37 (15.0)

Notes: SCS= Summary of clinical safety (data cut-off May 2014); AEs= adverse events; SAEs= serious adverse events

Safety update data cut-off September 19 2014

Table 7. Summary of Adverse Events of Special Interest in cobimetinib vemurafenib for patients with BRAF V600 mutation positive unresectable or metastatic melanoma[6]

Adverse Events of Special Interest	*coBRIM*			
	Vemurafenib plus placebo		Vemurafenib plus cobimetinib	
Patient experiencing event, n (%)	*SCS n=239*	*Safety Update n=246*	*SCS n=254*	*Safety Update N=247*
Ocular Events				
RVO, all grades	0	1 (0.4)	0	1 (0.4)
Serous retinopathy, all grades	5 (2.1)	7 (2.8)	61 (24.0)	63 (25.5)
Grade ≥2 visual disturbances (not including RVO or serous retinopathy events)	16 (6.7)	20 (8.1)	19 (7.5)	25 (10.1)
Grade ≥3 photosensitivity	0	0	8 (3.1)	9 (3.6)
Grade ≥2 reduction in LVEF	7 (2.9)	9 (3.7)	17 (6.7)	21 (8.5)
Grade ≥3 elevation in liver laboratory test	36 (15.1)	36 (14.6)	52 (20.5)	53 (21.5)
Cutaneous primary malignancy	47 (19.7)	53 (21.5)	21 (8.3)	26 (10.5)
Secondary non-cutaneous primary malignancies	10 (4.2)	8 (3.3)	2 (0.8)	5 (2.0)
Grade ≥3 Rash	38 (15.9)	40 (16.3)	41 (16.1)	40 (16.2)

Notes: SCS= summary of clinical safety ; RVO= retinal vein occlusion; LVEF= left ventricular ejection fraction

Safety Update data cut-off: September 19 2014

In the coBRIM study, the combination of cobimetinib plus vemurafenib was associated with a higher frequency of adverse events compared to single-agent therapy.

The most common grade ≥3 AEs which occurred at a higher frequency (in at least 2% of patients in either arm), in patients treated with vemurafenib plus cobimetinib compared to patients treated with vemurafenib plus placebo were, respectively, alanine aminotransferase increase (11.4% versus 6.3%), aspartate aminotransferase increased (8.3% versus 2.1%), blood creatine phosphokinase increased (11.3% versus 0%), diarrhoea (6.3% versus 0%), blood alkaline phosphatase increased (4.3% versus 1.7%), photosensitivity reaction (2.4% versus 0%), hyponatremia (2.4% versus 0.4%), and retinal detachment (2.4% versus 0%).[6]

Compared to single agent vemurafenib, the combination of vemurafenib plus cobimetinib was also associated with a higher frequency of central serous retinopathy (all grades) (25.5% versus 2.8%), grade ≥3 diarrhoea (6.5% versus 0.8%), grade ≥ 3 photosensitivity (3.6% versus 0%), and grade ≥2 reduction in LVEF (8.5% versus 3.7%).

Conversely, there was a decreased frequency in the vemurafenib plus cobimetinib compared to the single agent vemurafenib treatment group of grade ≥3 keratoacanthomas (1.2% versus 8.1%), grade ≥ 3 squamous cell carcinomas (2.8% versus 12.6%), and grade ≥3 arthralgia (2.4% versus 4.9%).[6]

The discontinuation rates for adverse events were higher in the vemurafenib plus cobimetinib arm (15.0%) than in the vemurafenib plus placebo arm (8.1%). The discontinuation rates for both arms were 12.6% and 11.7%, respectively.

Treatment discontinuation due to adverse events and adverse events leading to dose interruptions/modifications had a highest occurrence in the first 1-3 cycles and were reported to be lower thereafter.[6]

Similarly, the frequency of dose modification or interruption of cobimetinib, vemurafenib, or both drugs, was higher in the vemurafenib plus cobimetinib arm (54.7%, 58.3%, and 44.5%, respectively) than in the vemurafenib plus placebo arm (37.0%, 49.2%, and 35.4%).

Overall, there were six deaths that were attributed to adverse events in the cobimetinib vemurafenib combination group and three deaths in the control group.

Updated Safety data with a data cut-off of 30 September 2015 was requested from the submitter and due to the intent of publication at a future date is non-disclosable at the present moment. However, the overall safety profile in the updated analysis is consistent with that presented in the primary update and no new safety signals were observed with the longer follow-up date.

Patient Reported Outcomes[6]

Health-related quality of life (HRQoL) was measured in the coBRIM trial for each treatment arm using the EORTC QLQ-C30 questionnaire. The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. It is comprised of 5 functional domains, which include the physical, role, cognitive, emotional and social. There are also 9 symptom scales which include appetite loss, constipation, nausea, and vomiting, dyspnea, pain and fatigue, as well as a summary scale (global health status and quality of life).

Scoring in the EORTC QLQ-C30 is from 0-100, and an increase in score is associated with an improvement in functioning or worsening of symptoms.

Completion rates were consistently high (≥88%) among all cycles for both treatment arms. Changes were considered to be clinically meaningful if there was a ≥10 point increase or decrease from baseline.

Patients in the vemurafenib plus cobimetinib arm experienced either clinically meaningful improvement or marginal improvement in insomnia in time points in 4 treatment cycles. Patients in this combination treatment arm also experienced clinically meaningful worsening of diarrhoea from baseline at day 15 in the first two treatment cycles.

In terms of global health status, as well as most functioning and symptom scales, the difference in proportion of responders was small. This indicated a similarity in health-related quality of life between the two treatment arms. However, there were larger differences observed for insomnia and social functioning and to a smaller extent, pain and fatigue which all favoured the vemurafenib plus cobimetinib arm.

Time to deterioration analyses and time to improvement analyses were conducted in the coBRIM study, and additional details regarding Quality of life are planned for publication and are non-disclosable at the present moment.

6.4 Ongoing Trials

No trials have been identified that meet the eligibility criteria for this review

7 SUPPLEMENTAL QUESTIONS

The following supplemental issues were identified as relevant to the pCODR review of cobimetinib in combination with vemurafenib in patients with BRAF V600 mutation positive unresectable or metastatic melanoma

- Critical appraisal of a manufacturer-submitter indirect treatment comparison (ITC) of relative efficacy and safety of cobimetinib plus vemurafenib (VM. Cobi) versus dabrafenib plus trametinib (DB.TM2mg) and dabrafenib plus trametinib (DB.TM21mg).[54]

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

7.1 Critical Appraisal of Indirect Treatment Comparison of cobimetinib plus vemurafenib versus dabrafenib plus trametinib

7.1.1 Objective

The objective of this section is to summarize and critically appraise the methods and findings of the manufacturer-submitted ITC of relative efficacy and safety of cobimetinib plus vemurafenib versus dabrafenib plus trametinib among adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

The following are reasons for which this critical appraisal was necessary:

- Dabrafenib trametinib combination therapy was identified as a relevant comparison in the protocol,
- No available direct comparison of cobimetinib plus vemurafenib to dabrafenib plus trametinib,
- And the manufacturer-submitted an economic evaluation which included dabrafenib trametinib as a comparator.

It should also be noted that along with the indirect comparison of cobimetinib vemurafenib versus dabrafenib trametinib in the BRAF positive mutation status population of patients, the manufacturer also included an ITC of cobimetinib vemurafenib versus dabrafenib trametinib, dacarbazine plus fotemustine, and dacarbazine plus interferon, as well as various dose regimens of ipilimumab in the patient population regardless of BRAF status.

7.1.2 Findings

The manufacturer submitted an ITC with the primary objective of assessing the relative efficacy (measured by PFS, OS, and ORR, where available) of cobimetinib plus vemurafenib versus other comparative regimens for the treatment of metastatic or unresectable melanoma. These results were based on networks of evidence identified in a systematic review assessing cobimetinib in combination with vemurafenib in both the first line (treatment-naïve) and second-line setting. There were 5 scenarios presented that were considered clinically appropriate to assess the

available evidence for first-line treatment of metastatic or unresectable malignant melanoma. A publication by Wolchok et al, 2010 was the only one identified as reporting outcomes based on patients receiving second-line treatment. This publication was excluded from the analyses and not included in the networks of evidence. Scenario 3 was the only one that presented an evidence base restricted to studies reporting patients with a BRAF mutation positive status and was outcome specific to either OS or PFS. This produced a small connected network and was deemed suitable for a network meta-analysis. Scenarios 4 and 5 were also deemed suitable for a network meta-analysis; however they included a more inclusive patient population regardless of the BRAF mutation status. Scenario 4 presented outcome specific evidence when grouping all doses of DTIC, IFN and TMZ, regardless of a BRAF mutation status of patients. Scenario 5 similarly also presented outcome specific evidence when grouping all doses of DTIC, IFN, TMZ, and the various doses and regimens of IPI, regardless of BRAF mutation status of patients.[54]

For the purposes of this review, and according to the requested funding indication, scenario 3 will be main network evidence of interest.

Systematic Literature Review

A systematic review of the clinical RCT evidence for cobimetinib in combination with vemurafenib for patients with metastatic melanoma was commissioned by the submitter. Details describing the systematic review were comprehensive and included a PRISMA flow diagram identifying the number of records identified, screened, assessed for eligibility and included. However, the full list of search terms and list of conference proceedings searched were not listed. The following databases were searched on April 7th 2015 using a detailed search strategy: MEDLINE (R) In-Process and other non-indexed citations and Ovid Medline (R) 1946-present (via OVID), Embase 1980 to present (via OVID), the Cochrane Library (with no study design filter), via the OVID platform, incorporating: the Cochrane Central Register of Controlled Trials (CENTRAL), the HTA database, Cochrane Database of Systematic Reviews (Cochrane Reviews), Database of Abstracts of Reviews of Effects (DARE), and NHS Economic Evaluation Database (NHS EED).

The following were identified as treatments of interest in the feasibility assessment conducted:

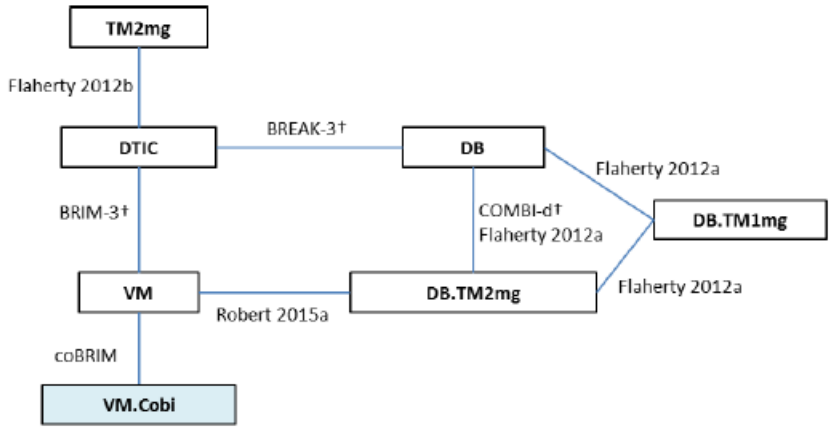
- Cobimetinib vemurafenib
- Targeted single-agent drugs (cobimetinib, dabrafenib, trametinib, and vemurafenib)
- Immunotherapy (interferon, ipilimumab, nivolumab, pembrolizumab)
- Chemotherapy (cisplatin (DDP), dacarbazine, fotemustine (FM), TMZ, placebo)

Inclusion was limited to trials that reported OS, PFS, or TTP. Studies were excluded from the meta-analysis if they did not report outcomes of interest. Based on the feasibility assessment, the submitter conducted a network meta-analysis (NMA) for OS and PFS. Although feasibility was assessed for the outcome of TTP, the author stated that there were no data reported for this outcome in the CoBRIM study. Therefore, analyses were not completed for TTP as no comparisons could be made with the treatment of interest cobimetinib plus vemurafenib (VM. Cobi).

Indirect Treatment Comparison[4,54]

The network diagram included in the indirect treatment comparison provided by the manufacturer can be found in Figures 3 and 4 below.

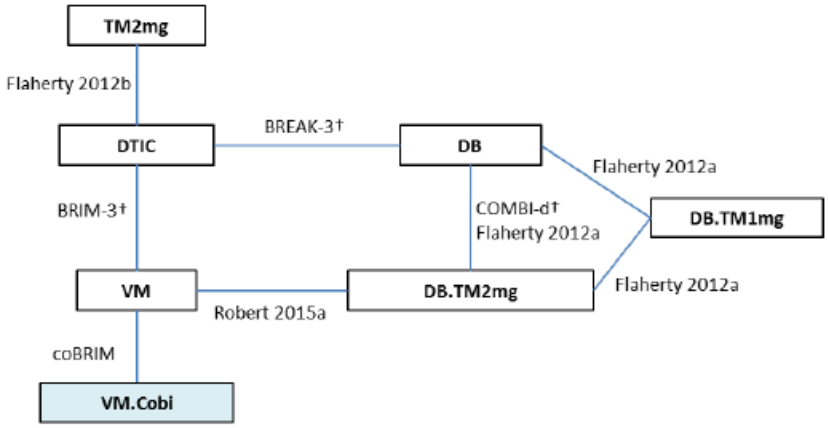
Figure 3. Network of Evidence for overall survival (OS) in studies with reported the BRAF mutation status of patients (the blue box represents the treatment of interest).[4,54]



Abbreviations: BD, twice daily; DB, dabrafenib; DB.TM1mg, dabrafenib plus trametinib 1mg; DB.TM2mg, dabrafenib plus trametinib 2mg DTIC, dacarbazine; OS, overall survival VM, vemurafenib, VM.Cobi, vemurafenib plus cobimetinib
† Trial names with more than one publication contributing data for the same trial

Source: Network meta-analysis, 2015[54]

Figure 4. Network of Evidence for progression-free survival (PFS) in studies which reported the BRAF mutation status of patients (the blue box represents the treatment of interest).[4,54]



Abbreviations: BD, twice daily; DB, dabrafenib; DB.TM1mg, dabrafenib plus trametinib 1mg; DB.TM2mg, dabrafenib plus trametinib 2mg DTIC, dacarbazine; OS, overall survival VM, vemurafenib, VM.Cobi, vemurafenib plus cobimetinib
† Trial names with more than one publication contributing data for the same trial

Source: Network meta-analysis, 2015[54]

Scenario 3 above presented the evidence base restricted to studies reporting patients with a BRAF positive mutation status and their outcome was either OS or PFS. This scenario following clinical validation, made the assumption that the treatment node of DTIC or paclitaxel in the trial reported by Flaherty et al, 2012b is considered to interact in the same way to DTIC as reported in other trials.

The authors used the Bucher method for single loops of evidence in order to test for consistency in the NMA. The method was used as outlined in the NICE technical support document (TSD4). In the first stage, the evidence for

the comparison between two trials was synthesized and a weighted invariance was used. In the second stage, the direct evidence was contrasted with the indirect evidence.

Base-Case Analyses for Scenario 3: studies reporting patients with a BRAF positive mutation status[54]

The authors stated a total of 15 publications, including 10 unique trials, that either mentioned patient BRAF status in the inclusion criteria (2 trials) or reported the proportion of patients with a BRAF mutation status (8 trials). Of the studies reporting BRAF mutation status, 12 publications detailing seven unique trials, reported OS. In cases where there was more than one publication which presented data for the same trial, the data from the longest follow-up was used. The network of evidence for OS in studies which reported the BRAF mutation status of patients is presented in Figure 3 above.

Accelerated failure time model (AFT)[54]

The AFT is an alternative to the Cox PH model. The COX PH model measures the effect on the hazard ratio, whereas the AFT measures the effect on the survival time ratio scale. The AFT model assumes that the covariates of the analysis affect the survival by a constant factor and that the time to event outcomes follows a generalized gamma distribution.

A treatment effect of less than one indicates prolonged survival for patients on vemurafenib plus cobimetinib. Credible intervals (Crls) that do not cross one (the axis) demonstrate statistical significance.

Summary of scenario 3: studies reporting OS in patients with a BRAF positive mutation status[54]

The four most effective treatments to treat melanoma based on this scenario were in order VM Cobi, DB. TM2mg, TM2mg, and VM. The uncertainty about TM2mg is very high, as can be seen from the credible intervals and statistically insignificant value in Figure 3.

Summary of scenario 3: studies reporting PFS in patients with a BRAF positive mutation status[54]

The four most effective treatments in this scenario were in order VM Cobi, DB. TM2mg, DB.TM1mg, and VM.

Table 8. Baseline Patient Characteristics of the Included Studies in the ITC Analysis for Scenario 3[54]

Study	Treatment arms	Number randomized	Male n (%)	Age, median, years (range)	BRAF mutation status		ECOG PS, n (%)			Duration of treatment, median (range)
					BRAF V600E n (%)	BRAF V600K n (%)	0	1	≥2	
Larkin et al 2014 coBRIM	Vemurafenib	248	56	55	174 (70)	32 (13)	164/244 (67)	80/244	0 (0)	NR
	cobiVM	247	59	56	170 (69)	24 (10)	184/243 (76)	58/243	1/243 (<1%)	NR
Flaherty et al 2012a	Dabrafenib (DB)	54	29 (54.0%)	50	45 (83)	9 (17)	34 (63.0)	20 (37.0)	NR	NR
	DB.TM1mg	54	30 (56.0%)	49	45 (83)	9 (17)	38 (70.0)	16 (30.0)	NR	NR
	DB.TM2mg	54	34 (63.0%)	58	47 (87)	7 (13)	35 (65.0)	19 (35.0)	NR	NR
Flaherty et al 2012b	TM	214	120 (56.0)	55	NR	NR	136 (64.0)	78 (36.0)	NR	NR
	Chemo-therapy (DTIC or Paclitaxel)	108	53 (49.0)	54	NR	NR	69 (64.0)	39 (36.0)	NR	NR
Robert et al 2015a	DB.TM2mg	352	59	55	312 (90)	34 (10)	248/350 (71)	102/350 (29)	NR	Median exposure duration: 10 months
	Vemurafenib (VM)	352	51	54	317 (90)	34 (10)	248/352 (70)	104/352 (30)	NR	Median exposure duration: 6 months

Notes: cobiVM= cobimetinib plus vemurafenib; DB.TM= dabrafenib plus trametinib; DTIC= dacarbazine

Sensitivity Analysis[54]

There were two types of sensitivity analysis performed that explored the impact of removing studies with a high risk of bias (assessed using the Cochrane Risk of Bias tool) or including studies that reported the ECOG performance status of patients. It is important to note that in scenario 3, when studies with a high risk of bias were removed, there was a lack of studies which led to the network no longer being feasible for both OS and PFS, as there were no comparisons with the treatment of interest.

Limitations

The quality of the manufacturer-submitted ITC was assessed in accordance with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparison.[55] Details and commentary with respect to the manufacturer-submitted ITC for each items identified by the ISOR Task Force are provided in Table 9.

Table 9. ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis[4,54,55]

ISPOR Questions	Details and Comments
1. Is the population relevant?	Yes. First-line treatment of metastatic or unresectable melanoma
2. Are there any critical interventions missing?	No.
3. Are any relevant outcomes missing?	Yes. Time to Response (TTP), Duration of response and HRQoL were not considered.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Yes
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Somewhat. Details describing the full systematic literature review were limited. A summary of the systematic review process including the search strategy and selection criteria was provided. However, a full list of conference proceedings and search terms was not provided. Therefore, it is unclear whether placebo or standard of care interventions were considered in the network but not found in the above mentioned strategy.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes. Anchored indirect treatment comparison.
7. Is it apparent that poor quality studies were included thereby leading to bias?	Yes, somewhat. When studies with a high risk of bias were removed from scenario 3, this scenario was no longer feasible. Also, study characteristics of each RCT such as method of randomization, treatment allocation concealment, blinding of outcome assessor, and dropout were not reported.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	It is possible that bias was induced by selective reporting of outcomes. Complete study details including the protocol of studies included in the network of evidence were not provided. Thus, it is difficult to rule out the role of bias in selective reporting of outcomes.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	Yes, there are systematic differences. For example, duration of treatment was not reported in most of the studies included in the ITC analysis.

Table 9. ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis[4,54,55]	
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Information provided by the author regarding individual study details (i.e. prior treatments that patients received) was not comprehensive enough to conclude whether all the effect modifiers were identified prior to comparing individual study results.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Yes. The Bucher Method was used.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	Not applicable as there was no direct comparison available.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	The cobimetinib vemurafenib node is not part of a closed loop in the network. Thus, there was no direct evidence included in the network that compared cobimetinib plus vemurafenib with any treatment other than single-agent vemurafenib.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	Yes, a fixed effects analysis was recommended over the random effects due to the fact that most comparisons in the evidence networks were informed by a single study. The number of studies was too few in order to perform a random effects analysis.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	Yes.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Yes, assumptions about heterogeneity were discussed. Both base case and sensitivity analyses were provided. Sensitivity analyses were analyzed using the HR and AFT model and the fixed effects model. A random effects model was not used towards the handling of heterogeneity.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	No, subgroup analyses and meta-regression was not performed.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes. Please refer to Figures 1 and 2.
19. Are the individual study results reported?	Yes, hazard ratios from the individual studies are reported.
20. Are results of direct comparisons reported separately from results of the	Not applicable as there were no direct comparisons.

Table 9. ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis[4,54,55]	
indirect comparisons or network meta-analysis?	
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Not applicable as there were no pairwise contrasts.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes, treatment ranking was provided along with the credible intervals.
23. Is the impact of important patient characteristics on treatment effects reported?	Yes, however the list of important patient characteristics was not comprehensive enough to conclude the full impact on treatment effects.
24. Are the conclusions fair and balanced?	The Methods team would like to state that although it may appear from the results of OS that cobimetinib in combination with vemurafenib is the most effective treatment followed by DB.TM2mg, TM2mg, and VM, there is a level of uncertainty in the reported results due to the limitations associated with treatment ranking. The treatment rankings are subject to uncertainty given the small number of trials in the network. When only a small number of trials are available, the addition of a single trial to the network may have a profound impact on the treatment rankings. Therefore the treatment rankings should be interpreted with great caution. In addition, Although the network meta-analysis included important effect modifiers such as ECOG performance status, it is uncertain whether this effect modifier was controlled for in the analysis.
25. Were there any potential conflicts of interest?	Not reported.
26. If yes, were steps taken to address these?	Not reported/not applicable.

7.1.3 Summary

The validity of the manufacturer's ITC hinges on three important assumptions: (1) homogeneity; (2) transitivity/similarity; and, (3) consistency. There is a considerable level of uncertainty associated with this NMA attributable to the differences in the trials characteristics which may have affected the treatment effects observed in each trial, thus violating the similarity

assumption and confounding these comparisons. Complete details including the study protocol for each of the included studies was not provided, therefore it is difficult to ascertain whether all systematic differences and levels of heterogeneity across the different trials were identified and accounted for prior to comparing individual study results.

The Methods team also felt that there was an insufficient level of detail provided as part of the systematic review. In particular, there was a lack of search terms listed. This makes it unclear whether placebo or standard of care trials were considered in this network of evidence but not found according to the search strategy mentioned.

The Methods team would like to state that although it may appear from the results of OS that cobimetinib in combination with vemurafenib is the most effective treatment followed by DB.TM2mg,TM2mg, and VM, there is a level of uncertainty in the reported results. This is largely due to the inherent limitations associated with treatment ranking. The use of treatment ranking in a small network of evidence leads to an imprecise estimate of the true treatment effect, due to the small number of trials available. Another limitation with the reported results is also due to the handling of assumptions of heterogeneity. A fixed effects model was chosen due to the limited number of studies as it provided an improved model fit compared to the random effects model, and consequently this led to difficulty in making meaningful inferences.

In addition, the estimates (hazard ratios) of OS and PFS provided by this NMA are the best we have, given the available evidence. However, there is a paucity of information on the presence/absence of effect modifiers in the trials and whether those were controlled for in the analysis. Therefore, there is uncertainty in the reported estimates (HR's) for OS and PFS and the true values may actually be higher or lower than the bounds of the 95% credible intervals. Hence, the reported results 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 cobimetinib in combination with vemurafenib 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 CADTH 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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Melanoma Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH 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

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** November 2015**, Embase** 1974 to 2015 December 16**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	(Cotellic* or cobimetinib* or GDC-0973 or GDC0973 or RG 7420 or RG7420 or XL 518 or XL518 or ER29L26N1X or 934660 93 2).ti,ot,ab,sh,rn,hw,nm,kf.	332
2	(Zelboraf* or vemurafenib* or HSDB 8143 or HSD8143 or PLX 4032 or PLX4023 or RG 7204 or RG7024 or RO 51 85426 or RO 5185426 or 207SMY3FQT or 91850 65 1).ti,ot,ab,sh,rn,hw,nm,kf.	5170
3	exp Melanoma/ or (melanoma* or melanocarcinoma* or melanomalignoma* or naevocarcinoma* or nevocarcinoma* or pigmentary cancer* or skin cancer*).ti,ab.	278039
4	1 and (2 or 3)	236
5	4 use pmez	32
6	4 use cctr	2
7	5 or 6	35
8	Cotellic/ or (Cotellic* or cobimetinib* or GDC-0973 or GDC0973 or RG 7420 or RG7420 or XL 518 or XL518).ti,ab.	138
9	Vemurafenib/ or (Zelboraf* or vemurafenib* or HSDB 8143 or HSD8143 or PLX 4032 or PLX4023 or RG 7204 or RG7024 or RO 51 85426 or RO 5185426).ti,ab.	4879
10	exp Melanoma/ or (melanoma* or melanocarcinoma* or melanomalignoma* or naevocarcinoma* or nevocarcinoma* or pigmentary cancer*).ti,ab.	278039

11	8 and (9 or 10)	91
12	11 use oemezd	61
13	7 or 12	96
14	remove duplicates from 13	72
15	limit 14 to english language	69

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#9	Search **#8** Filters: **English**	2
#8	Search **#7 AND #6**	2
#7	Search **#3 AND (#4 OR #5)**	33
#6	Search **publisher[sb]**	499616
#5	Search **Melanoma[mh] OR melanoma*[tiab] OR melanocarcinoma*[tiab] OR melanomalignoma*[tiab] OR naevocarcinoma*[tiab] OR nevocarcinoma*[tiab] OR pigmentary cancer*[tiab] OR skin cancer*[tiab]**	115111
#4	Search **PLX4032 [Supplementary Concept] OR 91850 65 1[rn] OR Zelboraf*[tiab] OR vemurafenib*[tiab] OR HSDB 8143[tiab] OR HSD8143[tiab] OR PLX 4032[tiab] OR PLX4023[tiab] OR RG 7204[tiab] OR RG7024[tiab] OR RO 51 85426[tiab] OR RO 5185426[tiab]**	1177

3. Cochrane Central Register of Controlled Trials (Central)

Searched via Ovid

4. Grey Literature search via:

Clinical trial registries:

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

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

Search terms: Cotellic, cobimetinib + melanoma

Select international agencies including:

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

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

Search terms: Cotellic, cobimetinib

Conference abstracts:

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

Search terms: Cotellic, cobimetinib / last 5 years

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