# pan-Canadian Oncology Drug Review
# Final Economic Guidance Report

## Cobimetinib (Cotellic) for Metastatic Melanoma

**June 30, 2016**

# DISCLAIMER

**Not a Substitute for Professional Advice**

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

**Liability**

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

# FUNDING

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

## INQUIRIES

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

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: requests@cadth.ca
Website: www.cadth.ca/pcodr

# TABLE OF CONTENTS

# 1 ECONOMIC GUIDANCE IN BRIEF

## 1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Roche Canada compared cobimetinib in combination with vemurafenib versus vemurafenib alone in BRAF600-mutation positive patients with unresectable locally advanced (stage IIIC) or metastatic melanoma (stage IV). Both medications are taken orally. The effectiveness and cost parameter estimates for the pharmacoeconomic model were mainly taken from the coBRIM trial, which compared cobimetinib in combination with vemurafenib versus vemurafenib alone in stage IIIC and IV, previously untreated BRAF600-mutation positive melanoma patients. Since the cost-effectiveness of these treatments is uncertain in previously treated patients, the Economic Guidance Panel (EGP) can only make recommendations for the previously untreated melanoma patients.

| Table 1. Submitted Economic Model | |
|---|---|
| Funding Request/Patient Population Modelled | ***Funding request:*** patients with unresectable locally advanced (stage IIIC) or metastatic melanoma (stage IV), irrespective of history of prior treatment.<br><br>***Patient Population Modelled***: patients with unresectable locally advanced (stage IIIC) or metastatic melanoma (stage IV), **previously untreated.** |
| Type of Analysis | *CEA and CUA* |
| Type of Model | *Partitioned-survival* |
| Comparator | cobimetinib in combination with vemurafenib against vemurafenib monotherapy |
| Year of costs | *2015* |
| Time Horizon | *9-11 years* |
| Perspective | *Government* |
| Cost of vemurafenib (Zelboraf®)* | • $0.19/mg or $46.54 per 240mg tablets (oral)<br>• Per day: 960mg (4*240mg) twice daily (1920mg/day); $372.34<br>• Per 28-day course: 1920 mg daily (twice 4*240mg tablets) for 28 consecutive days (56 tabs in total); $10,425.41 |
| Cost of vemurafenib* plus cobimetinib (Cotellic™)<br><br>*Price source for cobimetinib: Submitter* | Cobimetinib (Cotellic™)<br>• $6.01/mg or $120 per 20mg tablet (oral)<br>• Per 28-day course: 60 mg daily (three*20mg tablets) for 21 consecutive days followed by a 7-day break); $7,567<br>• Per day: 20mg three times (60mg/day); $270.25<br>Vemurafenib (Zelboraf®)<br>• $0.19/mg or $46.54 per 240mg tables (oral)<br>• Per day: 960mg (4*240mg tablets) twice daily (1920mg/day); $372.34<br>• Per 28-day course: 1920 mg daily (twice 4*240mg tablets) for 28 consecutive days (56 tabs in total); $10,425.41<br>**Cost of combined therapy:**<br>• Per day: $642.59<br>• Per 28-day course: $17,992.41 |
| Cost of dabrafenib (Tafinlar™)* | • $0.84/mg or $63.33 per 75 mg capsule (oral)<br>• Per day: 150 mg twice daily (300mg/day); $253.33 |

| Table 1. Submitted Economic Model | |
|---|---|
| | • Per 28-day course: 150 mg twice daily (4*75mg capsule) for 28 consecutive days (112 capsules total); $7,093.33 |
| Cost of trametinib (Mekinist™)* | • $145/mg or $290.00 per 2 mg tablet (oral)<br>• Per day: 2 mg once daily; $290.00<br>• Per 28-day course: 2 mg once daily for 28 consecutive days (28 tablets total); $8,120.00 |
| Model Structure | *A three-state model was built including progression-free, progression and death states with a 10-year follow-up. This was achieved by using progression-free and overall survival estimates directly from the coBRIM trial[1] and using parametric survival models for extrapolation beyond the trial duration. The costs of adverse events and supportive care were considered in the model. The costs of 2nd line therapies after progression were not considered. Both CEA and CUA were conducted.* |
| Key Data Sources | *Progression-free and overall survival, actual time on treatment, adverse events, baseline utility, and medication costs were obtained from the coBRIM trial;[1] post-progression utility values were taken from a single UK study,[2] other healthcare (supportive care) utilization was obtained from expert opinion with costing coming from a Canadian costing study in lung cancer.[3]* |
| **Drug costs for all comparators in this table (vemurafenib, dabrafenib, and trametinib) are based on costing information under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc.* | |

## 1.2 Clinical Considerations

**According to the pCODR Clinical Guidance Panel (CGP)**, this comparison is appropriate. The CGP concluded that based on the coBRIM trial with supportive evidence from the BRIM-7 trial, there is an overall net clinical benefit in using cobimetinib plus vemurafenib in BRAF600-mutation positive patients with unresectable locally advanced (stage IIIC) or metastatic melanoma (stage IV). However, the economic model was built using data from the coBRIM trial that enrolled previously untreated patients while the submitter made conclusions on all patients in this group irrespective of prior treatment history.

**Summary of patient input relevant to the economic analysis**
**Patients** considered the oral form of the drugs as an advantage as the medications can be taken at home and will save time and cost to travel to clinics. In the context of comparing vemurafenib versus vemurafenib and cobimetinib combination therapy this has limited effect as both drugs are taken orally. Patients expected that the combination therapy would improve their quality of life. However, study-based patient utility values were only used in obtaining baseline utility in the economic evaluation. Post-progression utilities reflected general societal preferences. Patients considered the adverse event burden of the combination therapy significant but manageable, and gave a higher value to having an additional choice in treatment selection.

**Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis**
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for cobimetinib plus vemurafenib combination therapy that are relevant to the economic analysis:

- The combination therapy of trametinib plus dabrafenib will be a more appropriate comparator for the cobimetinib plus vemurafenib combination therapy. Although the former has not been approved in any of the provinces at the time of application, the treatment landscape of advanced melanoma is rapidly changing. The submitter attempted to provide cost-effectiveness results for comparison of these two combination therapies, using network meta-analysis (NMA) and indirect comparisons. However, the CGP considered that the NMA carried too high a level of uncertainty to rely on in the results.
- PAG considered the oral forms of the drugs are an enabler to access in some provinces and a potential barrier in others. Patients may require applications to their pharmacare programs to be filled for the two drugs separately and face different co-payments and deductibles for each. This was not addressed by the submitter as province-specific analysis was not the aim of the submitted economic evaluation.
- PAG considered the cost of combination therapy as another barrier to implementation. Table 1 shows the costs of vemurafenib and cobimetinib per day and per 28-day course. The cost of the combined therapy is $732 per day and $17,991 per 28-day cycle.

## 1.3 Submitted and EGP Reanalysis Estimates

| Table 2. Submitted and EGP Estimates | | |
|---|---|---|
| Estimates | Submitted | EGP Reanalysis |
| ICER estimate ($/QALY), range/point | $317, 648 | $314,268/QALY - $426,815/QALY |
| ΔE (QALY), range/point | 0.495 | 0.367 - 0.500 |
| ΔE (LY), range/point | 0.535 | 0.361 - 0.535 |
| ΔC ($), range/point | $157,117 | $156,853 - $157,117 |

According to the submitted economic analysis the extra cost of cobimetinib plus vemurafenib compared with vemurafenib is $157,117 and the extra QALY is 0.495, resulting in an ICER of $317,648/QALY. Costs included drug costs, drug administration costs (physician visits and pharmacy dispensing fee), and costs of supportive care. The major cost driver was drug cost accounting for 98% of cost difference between the comparators. Eighty eight percent of the extra QALY of 0.495 came from the difference in progression-free survival (higher in the combined treatment arm). Both progression-free and overall survival estimates came from the coBRIM trial.

**The main assumptions and limitations with the submitted economic evaluation were:**

- The submitted PE model used a partitioned survival model approach that limits the ability to evaluate the effect of uncertainty of survival estimates on the ICER.
- The model's target population includes patients with unresectable locally advanced (stage IIIC) or metastatic melanoma (stage IV), irrespective of history of prior treatment. The coBRIM trial, however, was conducted among previously untreated patients. As such, the conclusions of this economic evaluation may not be applicable to previously treated patients. This has not been further evaluated by the EGP as it requires making assumptions about the costs and effectiveness, and is beyond the scope of this review.
- The selection of grade 3 or more AEs considered for the inclusion in the model were selected based on expert opinion (3 people) and a review article. The probability of these events came from the coBRIM trial.
- Baseline utilities were obtained from the coBRIM trial using EQ-5D and applying UK weights. Post-progression utilities, however, were taken from a study that evaluated societal preferences using the standard gamble approach.[2]

- Post-progression treatment costs were not considered in the model because of lack of data, and this was considered to be a major limitation of this analysis. The high-level description of these treatments provided by the submitter showed that there are some differences between the groups, especially in the use of ipilimumab (higher in the vemurafenib monotherapy arm).
- The unit costs of adverse events were not accurate and reflected treatment costs of these conditions in an acute care (hospital) setting.

## 1.4 Detailed Highlights of the EGP Reanalysis

**The EGP made the following changes to the submitted economic model:**

1. **Costs of second line treatments**: We only considered the cost of the ipilimumab as the utilization was notably different between the groups. Based on the pCODR final economic guidance report on Ipilimumab, the recommended dose of this drug in the 2nd line setting is 3 mg/kg intravenously every three weeks for four doses, with a total cost of $97,400 assuming a body mass of 70 kg and no wastage.[4] After adding the cost of ipilimumab to other costs, the ICUR becomes $32,640/QALY less from the original. For this calculation, we assumed all patients who received ipilimumab would get all four doses, which may not be true considering the AE profile of the drug and its use as a second-line therapy. In addition, the lower number of patients getting ipilimumab in the combination arm may reflect administrative censoring rather than the reality (of 10 years of follow up). The overall effect of second (and potentially third) line treatments is still highly unclear considering the lack of information provided on other treatments (i.e., drug name, dose, duration) and the fact that therapeutic approaches are changing rapidly in the management of this disease.
2. **Health utility values**: the EGP reviewed the systematic review document provided by the submitter which was conducted to inform the selection of the source and values for post-progression utility states.[5] A comprehensive peer-reviewed and grey literature search was conducted including the time period up to March 2015. None of the studies that were found used EQ-5D in melanoma (non-treatment specific) patients to elicit utilities for post-progression states. As mentioned, the submitter used SG utility values obtained from the general public in the UK.[2] A similar study was also conducted among the Canadian general public with results not very different from those in the UK.[6] These values will be tested in the EGP reanalysis. No new relevant studies were identified by the EGP at the time of writing this report.
3. **AE unit costs:** this reanalysis addresses the concern that AE treatment unit costs in the model used acute hospital admission codes, which may not be accurate in estimating the costs of AEs that could be treated in an ambulatory setting. We could not locate one single source to verify the unit costs of such AEs but did find a few studies that provided more reasonable and justified cost estimates. A recent Canadian study, for example, evaluated the cost-effectiveness of dabrafenib versus dacarbazine and VM in BRAF V600 positive unresectable or metastatic melanoma, and obtained AE treatment costs from a survey of 14 Canadian physicians who considered the unit costs of physician and ED visits for the AE, medications, laboratory tests and other specialist assessments as needed.[7] The costs of treating rash, pyrexia, and neutropenia in 2012 CAD were $368.23, $1706.85, and $6,432.45 respectively, which were all less than those used in the submitted model. A Canadian study, conducted among breast cancer patients receiving adjuvant therapy, used the cost of diarrhea equal to $2,760.30 referring to OCCI 2005 (less than in the submitted model, which used OCCI 2010/11).[8] Another Canadian study among breast cancer patients on hormone therapies calculated the cost of arthralgia or myalgia to be $341, which was also less than that used in the submitted model.[9] Conducting a more comprehensive search

and finding the most appropriate estimates for each modeled AE was beyond the scope of this critical appraisal. Instead, we can conclude that the submitter should have considered other sources for AE unit costs as the sources used overestimated the cost of these AEs. However, when the AE unit costs described above are introduced into the model, the impact on ICUR is non-significant considering the rarity of these events.

| EGP's One-way and multi-way sensitivity analyses | | | | | |
|---|---|---|---|---|---|
| Description of Reanalysis | ΔC | ΔE QALYs | ΔE LYs | ICUR (QALY) | Δ from baseline submitted ICER |
| **PFS:** log-normal distribution | $152,154 | 0.497 | 0.535 | $306,121 | -$11,527 |
| **PFS:** log-logistic distribution | $149,357 | 0.498 | 0.535 | $299,759 | -$17,889 |
| **OS extrapolation:** Log-logistic | $156,929 | 0.431 | 0.447 | $363,728 | $46,080 |
| **OS extrapolation:** Gamma | $156,905 | 0.384 | 0.387 | $408,959 | $91,311 |
| **OS extrapolation:** Weibull | $156,853 | 0.364 | 0.361 | $430,584 | $112,936 |
| **EGP's Reanalysis for the Best Case Estimate** | | | | | |
| Description of Reanalysis | ΔC | ΔE QALYs | ΔE LYs | ICUR | Δ from baseline submitted ICER |
| Baseline (Submitter's best case) (Log-Normal OS extrapolation) | $157,117 | 0.495 | 0.535 | **$317,648/QALY** | -- |
| **2nd line treatments:** adding cost of ipilimumab | $140,972 | 0.495 | 0.535 | $285,008 | -$32,640/QALY |
| **Utilities:** progression health state (<5 years) = 0.55 | $157,117 | 0.497 | 0.535 | $315,975 | -$1,673/QALY |
| **Utilities:** stable disease (≥ 5 years) = 0.79 | $157,117 | 0.497 | 0.535 | $315,923 | -$1,725/QALY |
| **Utilities:** use Canadian data for both progressive health state and stable disease | $157,117 | 0.500 | 0.535 | $314,268 | -$3,380/QALY |
| **AE unit costs changed to:** *$368.23 for rash, $1706.85 for pyrexia, $6432.45 for neutropenia, $2,760 for diarrhea, and $341 for arthralgia* | $157,159 | 0.495 | 0.535 | $317,734 | $86/QALY |
| **Best case estimate of above parameters:** | | | | | |
| Using Canadian utility values and Log-Normal OS extrapolation | $157,117 | 0.500 | 0.535 | $314,268/QALY | -$3,380/QALY |
| Using Canadian utility values and Weibull OS extrapolation | $156,853 | 0.367 | 0.361 | $426,815/QALY | $109,167/QALY |

**Fitting OS distributions for extrapolations:** As part of one-way sensitivity analysis, the submitter showed that the selection of a survival distribution for OS in a cure-mixture rate parametric model has a significant impact on the ICER that could vary from $317,648 to $430,584 if lognormal (base-case), log-logistic, gamma and Weibull distributions are considered. The AICs under these distributions are quite close, and the visual inspection of observed and estimated survival curves

are also not very different. The EGP concluded that the large uncertainty around the extrapolation of survival probabilities (uncertainty that is impossible to evaluate under current model structure) is the main reason for seeing this large difference in ICER.

The EGP concludes that based on the provided information the ICER is between the **$314,268/QALY** (using Canadian utility values and log-normal distribution) and **$426,815/QALY** (using Canadian utility values and OS with Weibull distribution) range.

### 1.5 Evaluation of Submitted Budget Impact Analysis

Budget impact analysis (BIA) were most sensitive to changes in percent positive after BRAV600 testing (BIA increasing with more patients testing positive), market share assumptions (increasing with increasing shares), and the dose of combination therapy. In the latter case if per trial (actual) use is replaced by per label use, the 3-year BIA is higher than the Submitter's estimate.

BIA calculations considered only incident cases that will occur from 2017 to 2018. Each year, there will be a certain proportion of patients who will become metastatic from the past years' incident stage I/II patients, ultimately increasing the BI over years. Another limitation was the use of treatment dose as per trial ('real-world' estimate) for the cobimetinib plus vemurafenib and vemurafenib monotherapy only. For more accurate BIA calculations per label use should have been assigned to all comparators (considering that actual use is not available for all comparators). So, if we assign per label use to cobimetinib plus vemurafenib and vemurafenib monotherapy, the 3-year BIA is higher than the Submitter's estimate.

### 1.6 Conclusions

**The EGP's best estimate of ΔC and ΔE for COBI plus VM when compared to VM monotherapy is:**

- Between $314,268/QALY and $426,815/QALY where $317,648/QALY corresponds to the results of base case analysis by the submitter.
- The extra cost of COBI plus VM is between $156,853 and $157,117 with 98% of cost difference attributed to drugs costs.
- The extra clinical effect of COBI plus VM is between 0.367QALY and 0.500QALY with 88% of difference attributed to higher progression-free survival.

**Overall conclusions of the submitted model:**

Based on the EGP evaluation of the submitted model, the ICER of treating patients with COBI plus VM compared to VM in stage IIIC/IV previously untreated patients EGP is between $314,268/QALY and $426,815/QALY. The large uncertainty around the extrapolation of survival probabilities is the main reason for this large difference in the ICER. In addition, the current model structure limited the possibility of evaluating uncertainty around the cost-effectiveness estimates. Another major limitation that adds uncertainty to the current estimates is the lack of data on second line treatment after disease progression.

# 2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

# 3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Melanoma Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of cobimetinib and vemurafenib for metastatic melanoma. A full assessment of the clinical evidence of cobimetinib and vemurafenib for metastatic melanoma is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

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

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

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

# REFERENCES


1. Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med.* 2014;371(20):1867-1876.
2. Beusterien KM, Szabo SM, Kotapati S, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. *Br J Cancer.* 2009;101(3):387-389.
3. Cressman S, Lam S, Tammemagi MC, et al. Resource utilization and costs during the initial years of lung cancer screening with computed tomography in Canada. *J Thorac Oncol.* 2014;9(10):1449-1458.
4. pan-Canadian Oncology Drug Review. Ipilimumab (Yervoy) for Advanced Melanoma. Final Economic Guidance Report. April 18, 2012
5. Abacus International. Evidence synthesis for metastatic or unresectable melanoma: systematic review of health state utility value evidence. Report (Version 2, Date prepared: 23/07/2015, Abacus reference: 5178).
6. Hogg D, Osenenko K, Szabo SM, et al. Standard gamble utilities for advanced melanoma health states elicited from the Canadian general public. Pigment Cell and Melanoma Research. 2010 December;23 (6):957.
7. Delea TE, Amdahl J, Wang A, Amonkar MM, Thabane M. Cost effectiveness of dabrafenib as a first-line treatment in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma in Canada. *Pharmacoeconomics.* 2015;33(4):367-380.
8. Mittmann N, Verma S, Koo M, Alloul K, Trudeau M. Cost effectiveness of TAC versus FAC in adjuvant treatment of node-positive breast cancer. *Curr Oncol.* 2010;17(1):7-16.
9. Djalalov S, Beca J, Amir E, Krahn M, Trudeau ME, Hoch JS. Economic evaluation of hormonal therapies for postmenopausal women with estrogen receptor-positive early breast cancer in Canada. *Curr Oncol.* 2015;22(2):84-96.
10. Checkpoint Meeting Questions (pCODR). Responses to questions from January 26th, 2016 7. Cotellic for Metastatic Melanoma. February 9, 2016 12.
11. Welsh SJ, Corrie PG. Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Ther Adv Med Oncol.* 2015;7(2):122-136.
12. Canadian Institute for Health Information (CIHI). Patient cost estimator. Accessed March 28, 2016. Available at: https://www.cihi.ca/en/spending-and-health-workforce/spending/patient-cost-estimator.
13. National Institute for Health and Clinical Excellence. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. NICE technology appraisal guidance [TA319}, UK NHS. 2014.
14. Beale S, Dickson R, Bagust A, et al. Vemurafenib for the treatment of locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma: a NICE single technology appraisal. *Pharmacoeconomics.* 2013;31(12):1121-1129.
15. Curl P, Vujic I, van 't Veer LJ, Ortiz-Urda S, Kahn JG. Cost-effectiveness of treatment strategies for BRAF-mutated metastatic melanoma. *PLoS One.* 2014;9(9):e107255.
16. Norwegian Knowledge Centre for the Health Services. A health technology assessment of the new drugs for inoperable or metastatic malignant melanoma patients. Report from Kunnskapssenteret (Norwegian Knowledge Centre for the Health Services), No 22–2015, Health Technology Assessment.