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CADTH Reimbursement Recommendation

# Encorafenib (Braftovi) in Combination With Binimetinib (Mektovi)

**Indication:** For the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation

**Sponsor:** Pfizer Canada

**Final Recommendation:** Reimburse with conditions

CADTH

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

# Summary

CADTH

## What Is the CADTH Reimbursement Recommendation for Braftovi With Mektovi?

CADTH recommends that Braftovi in combination with Mektovi should be reimbursed by public drug plans for the treatment of unresectable or metastatic melanoma with a *BRAF* V600 mutation if certain conditions are met.

### What Are the Conditions for Reimbursement?

Braftovi and Mektovi should only be reimbursed if used in combination and prescribed and monitored by clinicians with expertise in diagnosis and management of melanoma who are familiar with the toxicity profile associated with the Braftovi with Mektovi regimen and if it does not cost more than the least costly BRAF inhibitor and MEK inhibitor (BRAFi/MEKi) combination treatment.

### Which Patients Are Eligible for Coverage?

Braftovi with Mektovi should only be covered to treat adult patients with advanced or metastatic melanoma who have a *BRAF* V600 gene mutation that has been identified through a validated test. Patients who have not received previous treatment and patients whose disease has progressed after first-line immunotherapy are eligible for coverage.

### Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that treatment with Braftovi with Mektovi was associated with an improvement in progression-free survival compared with vemurafenib monotherapy and had manageable side effects.
- Evidence suggested that Braftovi with Mektovi may meet patients' needs by offering them an alternative oral targeted therapy that may have a positive impact on survival.
- There is no evidence to suggest treatment with Braftovi with Mektovi is more effective than other reimbursed therapies used to treat the indicated population under review. Therefore, it should be priced no more than the least costly BRAFi/MEKi to ensure cost-effectiveness.
- Based on public list prices for all therapies reimbursed by public drug plans, the 3-year budget savings is expected to be approximately $15 million.

## Additional Information

Melanoma is a cancer that occurs in skin cells that produce melanin. It is estimated that 1 in 42 males and 1 in 56 females will develop melanoma over their lifetime. Melanoma that cannot be removed by surgery or that has spread to other parts of the body (metastatic disease) is associated with a low survival rate. The most common gene mutation in melanoma is a *BRAF* mutation, which may lead to an aggressive metastatic cancer. *BRAF* mutations may also determine how a patient will respond to treatment.

### Unmet Needs in Unresectable or Metastatic Melanoma With a *BRAF* V600 Mutation

Current treatments may be associated with a number of side effects that may lead to treatment interruptions, delays, or discontinuation. The Braftovi and Mektovi combination offers an alternative oral treatment option with a different toxicity profile.

### How Much Does the Braftovi and Mektovi Combination Cost?

Treatment is expected to cost approximately $14,574 per patient per 28-day cycle.

## Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that encorafenib in combination with binimetinib should be reimbursed for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation only if the conditions listed Table 1 are met.

## Rationale for the Recommendation

Evidence from 1 phase III, randomized, open-label trial (COLUMBUS; N = 577) that included adult patients with histologically confirmed locally advanced unresectable or metastatic *BRAF* V600 mutant cutaneous melanoma or unknown primary melanoma suggested that encorafenib in combination with binimetinib (encorafenib-binimetinib) was associated with a statistically significant progression-free survival (PFS) benefit over vemurafenib monotherapy (hazard ratio [HR] = 0.54; 95% CI, 0.41 to 0.71; P < 0.0001). However, there was no statistically significant difference between patients who received encorafenib-binimetinib compared with those who received encorafenib monotherapy (HR = 0.75; 95% CI, 0.56 to 1.00; P = 0.051). At the time of the primary analysis, the median overall survival (OS) was greater in patients receiving encorafenib-binimetinib (median = 33.6 months; 95% CI, 24.4 to 39.2) than those treated with vemurafenib monotherapy (median = 16.9 months; 95% CI, 14.0 to 24.5) or encorafenib monotherapy (median = 23.5 months; 95% CI, 19.6 to 33.6). Input from patient advocacy groups indicated that patients value timely access to effective treatment options with reduced toxicity, ease of use, improved quality of life (QoL), and improved survival. Considering the totality of evidence, pERC concluded that encorafenib-binimetinib may offer patients an alternative oral targeted therapy that may have a positive impact on survival.

The clinical experts consulted during this review noted that both vemurafenib and encorafenib monotherapies were not considered as relevant comparators in the current standard practice in Canada. Combination therapies with BRAF and mitogen/extracellular signal-regulated kinase (MEK) inhibitors (BRAFi/MEKi) and immunotherapy agents were identified as the key comparators for encorafenib-binimetinib for the treatment of unresectable or metastatic melanoma in patients with *BRAF* V600 mutations. In the absence of head-to-head trials, pERC considered indirect evidence from 4 network meta-analyses (NMAs). Despite limitations and uncertainty in the NMAs, including differences in trial methodology, the results of the NMAs suggested that the efficacy of encorafenib-binimetinib is similar to the combination therapies dabrafenib-trametinib and vemurafenib-cobimetinib in terms of OS and PFS.

Based on an analysis that used the sponsor-submitted prices for encorafenib and binimetinib and publicly listed prices for all other drug costs, encorafenib in combination with binimetinib was less costly and had similar efficacy relative to other BRAFi/MEKi combinations (e.g., dabrafenib in combination with trametinib and vemurafenib in combination with cobimetinib) for patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation. To ensure cost-effectiveness, the cost of reimbursing encorafenib in combination with binimetinib should be no higher than the least costly BRAFi/MEKi combination.

## Table 1: Reimbursement Conditions and Reasons

| Reimbursement condition | Reason |
|---|---|
| **Initiation** | |
| 1. Treatment with encorafenib-binimetinib should be initiated only in adults who have the following characteristics:<br>1.1. Histologically confirmed locally advanced unresectable or metastatic *BRAF* V600E and/or V600K–mutant cutaneous melanoma or unknown primary melanoma (stage IIIB, IIIC, or IV per AJCC)<br>1.2. No previous treatment received (treatment naive) or must have progressed on or after prior first-line immunotherapy for advanced or metastatic disease<br>1.3. Performance status defined as:<br>1.3.1. ECOG PS 0 to 1<br>1.3.2. adequate organ, bone marrow and cardiac function, including left ventricular ejection fraction ≥ 50% by cardiac imaging and laboratory parameters. | The Health Canada indication specifies that encorafenib should be used in combination with binimetinib for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation.<br>Health Canada has not authorized use of this product in a pediatric population.<br>Conditions 1.1, 1.2, and 1.3 reflect the eligibility criteria of the COLUMBUS trial. |
| 2. Eligible patients should be identified through *BRAF* mutational analysis. | In the COLUMBUS trial, patients were required to have a *BRAF* V600 mutation confirmed by a validated test. |
| 3. Treatment with the encorafenib-binimetinib combination should not be initiated in patients with:<br>3.1. untreated CNS lesions<br>3.2. uveal or mucosal melanoma<br>3.3. known positive serology for HIV, or an active hepatitis B or hepatitis C infection, or both<br>3.4. history of leptomeningeal metastases. | These conditions reflect the eligibility criteria of the COLUMBUS trial. |
| **Renewal** | |
| 1. Treatment with encorafenib-binimetinib may be continued unless any of the following occurs:<br>1.1. clinical or radiographic disease progression<br>1.2. intolerable side effects that are not responsive to dose reductions or dose delays. | These conditions reflect the eligibility criteria of the COLUMBUS trial. |
| 2. Patients should be assessed for a response (as per RECIST 1.1) to treatment with encorafenib and binimetinib combination every 2 to 3 months. | In the COLUMBUS trial, tumour assessments were performed after 8 weeks during the first 24 months after randomization and every 12 weeks thereafter. |
| **Discontinuation** | |
| 1. Treatment with the encorafenib and binimetinib combination should be discontinued upon the occurrence of any of the following:<br>1.1. clinical or radiographic disease progression<br>1.2. unacceptable toxicity<br>1.3. development of adverse reactions that do not resolve despite dose delays or dose reductions. | These conditions correspond to the criteria used to determine whether treatment with encorafenib-binimetinib should be discontinued in the COLUMBUS trial, and also correspond to the dosing instructions within the product monographs. |

| Reimbursement condition | Reason |
|---|---|
| 2. If 1 component of the combination therapy is discontinued for toxicity or intolerance, the other drug in the combination should also be discontinued. | The product monographs for encorafenib and binimetinib specify that during combination therapy with encorafenib-binimetinib, if 1 of the drugs is temporarily interrupted, the other drug should also be interrupted; if 1 drug is permanently discontinued, the other drug should also be discontinued. |
| **Prescribing** | |
| 1. Encorafenib in combination with binimetinib should only be prescribed by clinicians who:<br>1.1. have expertise in diagnosis and management of patients with melanoma<br>1.2. are familiar with the toxicity profile associated with the encorafenib and binimetinib regimen. | This condition is required to ensure that the encorafenib and binimetinib combination is prescribed only for appropriate patients and that patients receive optimal care for toxicity management. |
| 2. Dosing of the encorafenib and binimetinib combination should be as follows:<br>2.1. encorafenib 450 mg once daily<br>2.2. binimetinib 45 mg twice daily. | As per eligibility for COLUMBUS trial and recommended dose by Health Canada. |
| **Pricing** | |
| 1. Encorafenib in combination with binimetinib should not be more costly than the least costly BRAFi/MEKi combination regimen. | Evidence from indirect comparisons (NMAs) suggest that there is no statistically significant difference in efficacy among the 3 BRAFi/MEKi combination treatments in patients with unresected or metastatic melanoma. |

AJCC = American Joint Committee on Cancer; BRAFi/MEKi = BRAF and MEK inhibitors; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; NMA = network meta-analysis; RECIST = Response Evaluation Criteria in Solid Tumours Version 1.1.

# Implementation Guidance

## Other Patient Characteristics for Eligibility

- The COLUMBUS trial enrolled patients with *BRAF* V600 E and K mutations. However, the clinical experts consulted by CADTH noted, based on limited data, that encorafenib-binimetinib may have varying degrees of effect on *BRAF* V600 K, V600D, and V600E mutations. The clinical experts acknowledged that, in practice, most clinicians would consider BRAF inhibitors for patients with non-canonical *BRAF* V600 mutations (i.e., V600 D or R). pERC agreed that the trial results can be generalized to patients with all types of *BRAF* mutations.
- pERC discussed that the benefit for patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) greater than 1 cannot be formally concluded from the COLUMBUS trial because these patients were excluded from the trial. The clinical experts consulted by CADTH noted that similar BRAF inhibitors (such as dabrafenib-trametinib) are routinely prescribed for patients with an ECOG PS greater than 1. pERC agreed that it would be reasonable to offer encorafenib-binimetinib to patients with ECOG PS greater than 1.
- Patients with active central nervous system lesions were excluded from the COLUMBUS trial. pERC acknowledged that there is an ongoing trial evaluating effects of encorafenib-binimetinib in patients with *BRAF* V600-mutant melanoma who have brain metastases. However, no data are available to draw any conclusions regarding the clinical benefit

and safety of the encorafenib and binimetinib combination in these patients. The clinical experts consulted by CADTH noted the evidence from studies of combination therapy with dabrafenib-trametinib showed an intracranial response rate of 50% for these patients. pERC agreed with the clinical experts that the available evidence supports offering encorafenib-binimetinib to patients with treated or asymptomatic brain metastases. However, these patients may have more severe disease and are more likely to have an unfavourable prognosis.

### Optimal Sequencing With Other Treatments

- pERC agreed that encorafenib-binimetinib can be used either in the first-line or second-line setting. However, the optimal sequencing of encorafenib-binimetinib with immunotherapy options available for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation is currently unknown. pERC was therefore unable to make an evidence-informed recommendation on optimal sequencing.
- PERC noted that patients with a *BRAF* V600 mutation who have demonstrated disease progression during treatment on another BRAFi regimen should not be treated with encorafenib in combination with binimetinib.
- pERC agreed that encorafenib-binimetinib is an appropriate alternative BRAFi/MEKi therapy for patients with documented *BRAF* V600 mutation who are intolerant of currently available BRAFi/MEKi regimens. pERC noted that the toxicity profiles between encorafenib in combination with binimetinib and dabrafenib in combination with trametinib are different; therefore, jurisdictions might find encorafenib in combination with binimetinib to be a suitable replacement for dabrafenib in combination with trametinib in cases of intolerance.

### Eligibility for Re-Treatment

- pERC agreed with the clinical experts consulted by CADTH that re-initiating treatment with encorafenib-binimetinib when the treatment is temporarily interrupted due to toxicity would likely occur in clinical practice, although there is a lack of data to inform this decision. Clinical experts indicated that the treatment may be re-initiated in the form of reduced doses or a customized drug holiday.
- pERC discussed the benefit of encorafenib-binimetinib in patients who previously received BRAFi/MEKi in the adjuvant setting. The Committee noted that patients who had received prior adjuvant BRAFi/MEKi were excluded from the COLUMBUS trial and that there are no data available to support the use of encorafenib-binimetinib in these patients. However, pERC agreed with the clinical experts consulted by CADTH that encorafenib-binimetinib could be considered as a treatment option if the disease relapse occurs more than 6 months after the completion of adjuvant treatment with BRAFi/MEKi.

## Discussion Points

- pERC discussed the results of the phase III COLUMBUS trial and noted that combination therapy with encorafenib and binimetinib demonstrated PFS and OS benefits compared with vemurafenib monotherapy. While acknowledging that treatment with a single-agent BRAF inhibitor was the standard of care when COLUMBUS was initiated, pERC noted that neither of the comparators used in the trial (i.e., vemurafenib monotherapy and encorafenib monotherapy) were relevant comparators to current standard of practice in Canada.

According to the clinical experts consulted by the CADTH review team, vemurafenib monotherapy is administered to less than 5% of patients with metastatic melanoma in current practice. Relevant comparators would include other BRAF and MEK inhibitor combinations, such as dabrafenib with trametinib or vemurafenib with cobimetinib, or immunotherapies such as ipilimumab, nivolumab plus ipilimumab, nivolumab, or pembrolizumab.

- In the absence of head-to-head comparative trials, pERC considered indirect evidence from 4 NMAs. Despite differences in methodologies and data cuts used, the results of the NMAs suggest that encorafenib in combination with binimetinib may have comparable efficacy to dabrafenib with trametinib and vemurafenib with cobimetinib in terms of OS and PFS outcome. However, pERC noted that these results were associated with considerable uncertainty due to several limitations of these NMAs, including incomplete reporting of NMA methods, small network size, imprecision in results, and the unknown influence of effective post-progression treatments on the observed results for the OS outcome.
- pERC discussed inputs from patient advocacy groups that indicated patients value effective treatment options with reduced toxicity, ease of use, improved QoL, and improved survival. The Committee agreed that encorafenib in combination with binimetinib offers patients an alternative, oral, targeted therapy that has a positive impact on survival compared with vemurafenib monotherapy; however, it was not clear to pERC how the encorafenib and binimetinib combination compared to other relevant treatments. pERC discussed that a convenient oral option would likely contribute to a better QoL for both patients and caregivers but was unable to reach a conclusion on the effect of combination therapy with encorafenib and binimetinib on QoL due to the exploratory nature of patient-reported measures in the COLUMBUS trial, lack of statistical testing, limitations of data collection methods, and the lack of a relevant comparator. Patients also expressed concern that while the required diagnostic testing is funded, timely access to results varies across Canada.
- pERC discussed the toxicity profile of encorafenib in combination with binimetinib and agreed that the toxicities associated with this combination therapy were manageable. pERC agreed that combination therapy with encorafenib and binimetinib can provide an additional BRAFi/MEKi option with a different toxicity profile for patients who are not tolerating current therapies. It can also be considered as oral targeted therapy option for patients who are not able to travel to a treatment centre.

## Background

Encorafenib and binimetinib, in combination, are approved by Health Canada for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation. Encorafenib is a selective BRAF inhibitor and is available as 75 mg capsules. Binimetinib is a reversible MEK inhibitor and is available as 15 mg tablets. In patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation, the recommended dose of encorafenib is 450 mg (six 75 mg capsules) once daily, and the recommended dose of binimetinib is 45 mg (three 15 mg tablets) twice daily, both administered orally.

## Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- a review of 1 phase III randomized, open-label trial in patients with locally advanced unresectable or metastatic melanoma with *BRAF* V600 mutation
- patients' perspectives gathered by 2 patient groups: Save Your Skin Foundation (SYSF) and Melanoma Network of Canada (MNC)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with locally advanced or metastatic melanoma
- input from 2 clinician groups, including the SYSF Medical Advisory Group and Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Patient Input

Two patient groups — SYSF and MNC — provided input for this submission. Patients explained that pain, fatigue, depression, and disfigurement were common symptoms of metastatic disease that affect day-to-day life. Patients also indicated significant fear and anxiety associated with living with melanoma. They further noted that the disease can significantly impact the ability to work, strain relationships with other family members, and affect their ability to form new relationships. Other difficulties reported were travelling to treatment centres, accessing treatments, financial costs of treatments, emotional hardships of dealing with the disease, and impact on family.

Patients had experience with a variety of treatments, such as surgery, immunotherapies, radiation, and targeted therapies, and reported side effects such as fatigue, fever, chills, rashes, gastrointestinal issues, arthritis, and autoimmune issues. Most patients reported that their current treatments were tolerable and offered benefits that outweighed side effects. Patients who had experience with encorafenib in combination with binimetinib seemed to experience fewer side effects compared with previously used therapies and reported slower disease progression. Patients expressed a need for options that would allow them to choose therapies. They also desired timely access to treatment, fewer side effects, access to oral targeted medications, and communication between physicians and surgeons regarding each patient's treatment plan. Patients further stated that oral therapies require less travel, are associated with fewer costs (e.g., parking and gas), and reduce caregiver burden. This is of utmost importance given the current COVID-19 pandemic because many patients have indicated that the ongoing pandemic has led to more fear and anxiety about visiting the hospital. Patients stated that if these outcomes were achieved, they would experience less anxiety and fear and would have an improved QoL. Overall, both patient group inputs seemed to indicate that treatment with encorafenib in combination with binimetinib would provide patients and caregivers with prospects of prolonged survival and better QoL.

# Drug Plan Input

Input was obtained from drug programs (Ministries of Health and/or cancer agencies) participating as part of the CADTH pan-Canadian Oncology Drug Review Provincial Advisory Group (PAG). PAG identified the following as factors that could impact the implementation:

- eligible population
- sequencing with other therapies for *BRAF*-mutated unresectable or metastatic melanoma
- eligibility for re-treatment.

# Clinical Evidence

## Clinical Trials

The CADTH systematic review included 1 phase III randomized, open-label trial (COLUMBUS; N = 577). COLUMBUS was a multi-centre trial that included adult patients (aged ≥ 18 years) with histologically confirmed locally advanced unresectable or metastatic *BRAF* V600 mutant cutaneous melanoma or unknown primary melanoma (stage IIIB, IIIC, or IV per AJCC). Patients were required to be previously untreated (treatment naive) or to have progressed on or after prior first-line immunotherapy for unresectable locally advanced or metastatic melanoma. Prior adjuvant therapy (e.g., interferon, interleukin-2 therapy, any other immunotherapy, radiotherapy, or chemotherapy) was permitted. Patients were excluded if they had any untreated central nervous system lesions, uveal and mucosal melanoma, history of leptomeningeal metastases, retinal vein occlusion, prior therapy with BRAF inhibitors and/or MEK inhibitors, any previous systemic chemotherapy, extensive radiotherapy, or more than 1 line of immunotherapy.

Eligible patients were randomized in a 1:1:1 ratio to 3 treatment arms: a combination of encorafenib 450 mg once daily and binimetinib 45 mg twice daily, monotherapy with encorafenib 300 mg once daily, and monotherapy with vemurafenib 960 mg twice daily. Dose modifications and interruptions were permitted for patients who were unable to tolerate the protocol-specified dose(s). Anticancer treatments (chemotherapy, radiation, or surgery) and strong inhibitors of the CYP3A4 substrate were prohibited.

The key limitations of the COLUMBUS trial are related to a lack of comparison to other BRAFi/MEKi combination therapies (current standard of care) and the open-label nature of the study that introduced bias in the assessment of subjective outcomes, such as adverse events (AEs) and health-related quality of life (HRQoL). The study is also limited by the exploratory nature of the HRQoL data, lack of statistical testing, and data collection methods that make it difficult to detect the magnitude of the improvement with encorafenib with binimetinib and to assess the influence of effective post-progression treatments on the observed results, particularly on OS.

## Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, pERC discussed the following: PFS, OS, overall response rate (ORR), time to objective response, disease control rate, duration of response, and HRQoL.

- **PFS** was defined as the time from the date of randomization to the date of the first documented progression (according to RECIST 1.1) or death due to any cause, whichever occurred first. PFS was assessed centrally by a blinded independent review committee (BIRC) for the primary efficacy analysis.
- **OS** was defined as the time from the date of randomization to the date of death due to any cause. If a death was not observed by the date of analysis cut-off, OS was censored at the date of last contact. Survival time for patients with no post-baseline survival information was censored on the date of randomization.
- **ORR** was defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR).
- **Time to objective response** was defined as the time between the date of randomization until first documented response of CR or PR.
- **Duration of response** was calculated as the time from the date of first documented response (CR or PR) to the first documented progression or death due to underlying cancer.
- **Disease control rate** was calculated as the proportion of patients with a best overall response of CR, PR, stable disease, or non-CR/non-PD for patients with no target lesions) as per RECIST 1.1.
- **HRQoL** was assessed using the Functional Assessment of Cancer Therapy-Melanoma (FACT-M, version 4), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30, version 3.0), and EuroQoL5-Dimension 5-Levels (EQ-5D-5L, version 4.0). EORTC QLQ-C30 consists of both multi-item scales and single-item measures, which include 5 functional scales (physical, role, emotional, cognitive, and social functioning), 3 symptom scales (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact), and a global health status/QoL scale. EQ-5D-5L is a standardized measure of health utility that provides a single index value for one's health status. EQ-5D-5L measurement properties have not been identified in melanoma patients.

## Efficacy

The primary efficacy outcome of the COLUMBUS trial was PFS by BIRC. At the time of primary analysis (May 2016 data cut), the median PFS was significantly higher in the encorafenib-binimetinib combination arm (median = 14.9 months; 95% CI, 11.0 to 18.5) compared with the vemurafenib monotherapy arm (median = 7.3 months; 95% CI, 5.6 to 8.2), with an HR of 0.54 (95% CI, 0.41 to 0.71; P < 0.0001).The median PFS for the encorafenib-binimetinib combination was nominally higher than that for the encorafenib monotherapy arm (median = 9.6 months; 95% CI, 7.5 to 14.8); however, this difference was not statistically significant. The PFS results from November 2017 and November 2018 updated analyses were consistent with those from the primary analysis. At both data cut-off dates, the median PFS remained consistent at 14.9 months (95% CI, 11.0 to 20.2) in the encorafenib-binimetinib arm compared with 9.6 months (95% CI, 7.4 to 14.8) in the encorafenib monotherapy arm and 7.3 months (95% CI, 7.4 to 14.8) in the vemurafenib monotherapy arm.

At the November 2017 data cut, the median OS was 33.6 months in the encorafenib-binimetinib arm (95% CI, 24.4 to 39.2) versus 23.5 months (95% CI, 19.6 to 33.6) in the encorafenib monotherapy arm and 16.9 months (95% CI, 14.0 to 24.5) in the vemurafenib monotherapy arm. The estimates of OS at 12 months and 24 months were 75.5% (95% CI, 68.8% to 81.0%) and 57.6% (95% CI, 50.3% to 64.3%) for encorafenib in combination

with binimetinib compared with 74.6% (95% CI, 67.6% to 80.3%) and 49.1% (95% CI, 41.5% to 56.2%) for encorafenib. The updated OS analysis (November 2018) demonstrated consistent results.

At the time of primary analysis, ORR was 63% (95% CI, 55.8% to 69.9%) in the encorafenib-binimetinib arm compared with 50.5% (95% CI, 43.3% to 57.8%) in the encorafenib monotherapy arm and 40% (95% CI, 33.3% to 47.6%) in the vemurafenib monotherapy arm. Time to objective response by BIRC was similar across all treatment arms (2 months each). It was noted that this timing was due to the protocol design because the first tumour assessment was at cycle 3 day 1. Disease control rate was 92.2% in the encorafenib-binimetinib arm compared with 84.0% in the encorafenib arm and 81.7% in the vemurafenib arm. The median duration of response for confirmed responses was 16.6 months for the encorafenib-binimetinib arm (95% CI, 12.2 to 20.4) and 14.9 months in the encorafenib arm (95% CI, 11.1 to not estimable).

## HRQoL

HRQoL was a secondary outcome in the COLUMBUS trial and was measured using 3 scales: FACT-M, EORTC QLQ C30, and EQ-5D-5L. FACT-M (version 4) is a melanoma-specific QoL questionnaire.

The HRQoL instruments were administered every 8 weeks from randomization during the first 24 months (until week 105) and every 12 weeks after until disease progression per BIRC. Compliance rates that were calculated for patients who were still receiving treatment on the assessment date were reported to be 82% to 90%. The baseline mean scores were similar for all 3 instruments across treatment groups. Evaluation of changes in FACT-M and EORTC QLQ-C30 scores over time showed slightly more favourable results for the encorafenib and binimetinib combination arm. EQ-5D-5L scores showed slight improvement in the encorafenib-binimetinib combination arm or remained unchanged (in the vemurafenib and encorafenib monotherapy arms) at cycle 3 day 1 from baseline and then scores decreased over time in all treatment groups. Despite small improvements in QoL across all 3 scales (0.1 to 4 points), no treatment arm reached the minimal important difference (between 5 and 9 points for FACT-M, greater than 10 points for EORTC QLQ-C30, and 4.5 for EQ-5D-5L).

It should be noted that HRQoL assessment results are considered exploratory due to a lack of type I error pre-specified in the testing hierarchy. In addition, collecting data from only those patients who remained in studies introduces bias and will inflate the observed benefit. Further, there is added uncertainty from 2 of the scales used (EORTC QLQ-C30 and EQ-5D-5L), which are not validated for melanoma patients.

## Harms

The majority (> 98%) of patients in the COLUMBUS trial experienced at least 1 AE. The most commonly reported AEs in the encorafenib in combination with binimetinib arm (all grades) were nausea (41.1%), diarrhea (36.5%), fatigue (28.6%), and arthralgia (25.5%). Nausea and diarrhea occurred more frequently in the encorafenib in combination with binimetinib arm (41.1% and 36.5%, respectively) compared with encorafenib monotherapy (38.5% and 13.5%, respectively) and the vemurafenib arm (33.9% and 33.9%, respectively). Further, most patients experienced a skin and subcutaneous tissue disorder (encorafenib: 95.8%; vemurafenib: 91.4%); however, this AE was less common in the encorafenib in combination with binimetinib arm (65.1%). The incidence of grade 3 or 4 AEs was lower in the encorafenib

in combination with binimetinib arm (57.8%) compared with the those in the encorafenib arm (66.1%) and the vemurafenib arm (63.4%). The most commonly reported grade 3 or 4 AEs in the encorafenib in combination with binimetinib arm were diarrhea (2.6%), fatigue (2.1%), and nausea (1.6%). The most common grade 3 or 4 serious AE was pyrexia, which occurred more frequently in the encorafenib in combination of binimetinib arm (2.6%) versus the encorafenib (1%) and vemurafenib (0%) monotherapy arms. Overall, 12.5% of patients in the encorafenib in combination with binimetinib arm, 14.1% in the encorafenib arm, and 16.7% in the vemurafenib arm withdrew from treatment due to AEs. The most commonly cited reason in the encorafenib in combination with binimetinib arm was increased alanine transaminase and aspartate transaminase (2.6%). Mortality was comparable across treatment arms. The encorafenib-binimetinib arm had a total of 17 deaths (8.9%) compared with 14 (7.3%) in the encorafenib and 19 (10.2%) in the vemurafenib arms. The majority of deaths (80%) were attributable to disease progression.

## Indirect Evidence

The CADTH review team identified other BRAFi/MEKi combination treatments and immunotherapy agents as the key comparators for encorafenib in combination with binimetinib for the treatment of unresectable or metastatic melanoma in patients with *BRAF* V600 mutations. The other BRAFi/MEKi combination treatments identified were dabrafenib in combination with trametinib and vemurafenib in combination with cobimetinib. The key immunotherapy agents identified as comparators were pembrolizumab, nivolumab, ipilimumab, and the combination of nivolumab and ipilimumab. In the absence of head-to-head trials comparing the efficacy and safety between encorafenib plus binimetinib and these comparators, 4 indirect treatment comparisons were reviewed and critically appraised: an unpublished Bayesian NMA submitted by the sponsor that was focused on the BRAFi/MEKi combination therapy trials and reported on OS and PFS outcomes; an adjusted indirect treatment comparison (Bucher method) that was focused on the BRAFi/MEKi combination therapy trials and reported ORR and grade 3 to 4 AEs in addition to OS and PFS; a Bayesian NMA that compared dabrafenib in combination with trametinib to other BRAFi/MEKi combinations (including encorafenib in combination with binimetinib), monotherapy with BRAF inhibitors, immunotherapy agents, and chemotherapy agents; and a Bayesian NMA that compared a pooled chemotherapy group to various immunotherapy agents, targeted agents, and other chemotherapy treatments.

- Despite differences in methodologies and data cuts used, all the NMAs reached a similar conclusion that there were no statistically significant differences between the 3 BRAKi/MEKi combination treatments for unresected or metastatic melanoma for OS and PFS outcomes. Overall, the limited data suggest that encorafenib in combination with binimetinib likely has comparable efficacy to dabrafenib in combination with trametinib and vemurafenib in combination with cobimetinib, for both OS and PFS outcomes. However, this conclusion is associated with considerable uncertainty due to unclear and/or incomplete reporting on NMA methods, small or sparse networks, imprecision in results, and the unknown influence of effective post-progression treatments on the observed results, particularly for the OS outcome.
- One of the NMAs assessed ORR and showed no statistically significant differences between the combination therapies for the ORR outcome.
- One NMA included an indirect comparison of grade 3 or 4 toxicities across the BRAFi/MEKi combination therapy treatments. The NMA found that toxicities differed between the 3 combination therapy regimens. When compared with encorafenib-binimetinib, combination

therapy with vemurafenib-cobimetinib was associated with a significantly higher incidence of grade 3 and 4 liver toxicity, rash, arthralgia, basal cell carcinomas, and diarrhea, but lower incidence of decreased left ventricular ejection fraction. When compared to dabrafenib-trametinib, combination therapy with encorafenib-binimetinib demonstrated few statistically significant differences in grade 3 and 4 toxicities. Only hypertension occurred more frequently with dabrafenib-trametinib, whereas only squamous cell carcinoma occurred more frequently with encorafenib-binimetinib. It should be noted that confidence intervals were wide, reflecting uncertainty in the results.

- One NMA included comparisons of a BRAFi/MEKi combination therapy (dabrafenib-trametinib combination) with immunotherapy agents which are key comparators for BRAFi/MEKi combinations for the first-line treatment of unresectable or metastatic melanoma. Comparisons between agents within these 2 classes are of high clinical interest. However, results for comparisons between dabrafenib in combination with trametinib and immunotherapy agents were difficult to interpret due to inconsistency between results for OS and PFS outcomes for the same comparisons.

# Economic Evidence

## Cost and Cost-Effectiveness

Encorafenib is supplied as 75 mg capsules at a submitted price of $50.25 per capsule while binimetinib is supplied as 15 mg tablets at a submitted price of $36.50 per tablet. The recommended dosage regimen is 450 mg of encorafenib once daily in combination with 45 mg of binimetinib twice daily. At the sponsor's submitted price, the 28-day drug cost of encorafenib in combination with binimetinib is $14,574 per patient.

The sponsor submitted a cost-utility analysis based on a 3-state partitioned survival model comparing encorafenib in combination with binimetinib to targeted therapies such as vemurafenib monotherapy, dabrafenib in combination with trametinib, and vemurafenib in combination with cobimetinib for the treatment of *BRAF* V600 mutation–positive unresectable or advanced melanoma. The analysis was undertaken from the perspective of a Canadian publicly funded health care payer with costs and quality-adjusted life-years (QALYs) modelled over a 20-year time horizon. Patients entered the model in the progression-free health sate and, the proportion of patients who were progression-free, experienced progressive disease, or were dead at any time over the model time horizon was derived from non-mutually exclusive survival curves. Clinical efficacy of encorafenib with binimetinib and vemurafenib monotherapy was informed by the COLUMBUS trial with OS further adjusted based on the American Joint Committee on Cancer Melanoma Registry and CheckMate 066 trial. The HRs for dabrafenib plus trametinib and for vemurafenib plus cobimetinib were obtained from the sponsor-commissioned NMA in which vemurafenib monotherapy was the anchor treatment. The HRs were then applied to the extrapolated OS and PFS curves for encorafenib plus binimetinib. In deriving treatment acquisition costs, drug costs were adjusted by the relative dose intensity (RDI) observed in their respective clinical trials.

The following key limitations were identified:

- Concerns were raised by the clinical experts consulted by CADTH regarding the choice of comparators. Vemurafenib monotherapy is only prescribed approximately 5% of the

time in Canadian practice given the improved response and patient tolerability of targeted combination therapy, while immunotherapy, a first-line treatment for *BRAF* mutation–positive unresectable or metastatic melanoma, was excluded as a comparator from the submitted economic evaluation.

- Comparative efficacy of encorafenib plus binimetinib to other BRAFi/MEKi targeted combination treatments is uncertain because concerns remain with the internal validity of the sponsor's submitted NMA.
- As the subsequent therapies that patients received in the trials were not reflective of Canadian clinical practice, there is high uncertainty in the predicted QALYs accrued post-progression.
- Costs of oral medications were underestimated given inappropriate adjustments to account for RDI.

CADTH undertook re-analyses to address the identified limitations, including removing vemurafenib monotherapy as a comparator, assuming equal efficacy and time-to-discontinuation across the BRAFi/MEKi combination treatments, and setting 100% RDI for all oral medications. Based on CADTH re-analyses, encorafenib in combination with binimetinib dominated other BRAFi/MEKi targeted combination treatments at available list prices because this regimen is associated with lower total costs ($633,406; vemurafenib in combination with cobimetinib: $675,449; dabrafenib in combination with trametinib: $684,588) and produced similar QALYs (5.16). CADTH was unable to address the lack of comparative clinical data to inform a comparison between encorafenib plus binimetinib and immunotherapies. Based on the sponsor's submitted price, most immunotherapy regimens are less expensive than encorafenib in combination with binimetinib in terms of their average annual drug costs.

## Budget Impact

The sponsor estimated an incremental budget savings associated with reimbursing encorafenib in combination with binimetinib to be $21,470,467 over 3 years. CADTH identified limitations with the submitted budget impact analysis and undertook a reanalysis to adjust the RDI to 100% for oral treatments. Based on this reanalysis, the estimated incremental budget savings associated with reimbursing encorafenib in combination with binimetinib was $15,733,868 over 3 years. CADTH could not address limitations related to the included comparators and uncertainty regarding population size. If negotiated prices are used for the comparator treatments, encorafenib in combination with binimetinib may not be associated with the budget savings reported.

## Members of the pCODR Expert Review Committee

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Winson Cheung, Dr. Michael Crump, Dr. Avram Denburg, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

**Meeting Date**: May 13, 2021

**Regrets:** None

**Conflicts of Interest:** One pERC member did not vote due to a conflict of interest.