Encorafenib (BRAFTOVI) in combination with Binimetinib (MEKTOVI)

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

Recommendation: Reimburse with Conditions
ENCORAFENIB IN COMBINATION WITH BINIMETINIB (BRAFTOVI & MEKTOVI — PFIZER CANADA)

Therapeutic Area: unresectable or metastatic melanoma with a BRAF V600 mutation

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 one 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 (33.6 months, 95% CI: 24.4 to 39.2) than those treated with vemurafenib monotherapy (16.9 months, 95% CI: 14.0 to 24.5) or encorafenib monotherapy (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, 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 four network meta-analyses (NMAs). Despite limitations and uncertainty in the NMAs, including differences in trial methodology, the results of 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

<table>
<thead>
<tr>
<th>Reimbursement Condition</th>
<th>Reason</th>
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<tr>
<td><strong>Initiation</strong></td>
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<tr>
<td>1. Treatment with encorafenib-binimetinib should be initiated only in adults who have the following characteristics:</td>
<td>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 V600E mutation. Health Canada has not authorized use of this product in a pediatric population. Conditions 1.1, 1.2, and 1.3 reflect the eligibility criteria of the COLUMBUS trial.</td>
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<td>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)</td>
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<td>1.2. No previous treatment received (treatment naïve) or must have progressed on or after prior first-line immunotherapy for advanced or metastatic disease</td>
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<td>1.3. Performance status defined as:</td>
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<td>1.3.1. ECOG PS 0 to 1</td>
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<td>1.3.2. Adequate organ, bone marrow and cardiac function, including left ventricular ejection fraction ≥ 50% by cardiac imaging and laboratory parameters</td>
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<td>2. Eligible patients should be identified through BRAF mutational analysis.</td>
<td>In the COLUMBUS trial, patients were required to have a BRAF V600 mutation confirmed by a validated test.</td>
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<td>3. Treatment with the encorafenib-binimetinib combination should not be initiated in patients with:</td>
<td>These conditions reflect the eligibility criteria of the COLUMBUS trial.</td>
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<td>3.1. Untreated CNS lesions</td>
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<td>3.2. Uveal or mucosal melanoma</td>
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<td>3.3. Known positive serology for human immunodeficiency virus (HIV), or an active hepatitis B or hepatitis C infection, or both</td>
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<td>3.4. History of leptomeningeal metastases</td>
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<td><strong>Renewal</strong></td>
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<td>1. Treatment with encorafenib-binimetinib may be continued unless any of the following occurs:</td>
<td>These conditions reflect the eligibility criteria of the COLUMBUS trial.</td>
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<td>1.1. Clinical or radiographic disease progression</td>
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<td>1.2. Intolerable side effects that are not responsive to dose reductions or dose delays</td>
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<td>2. Patients should be assessed for a response (as per RECIST v1.1) to treatment with encorafenib and binimetinib combination every 2 to 3 months.</td>
<td>In the COLUMBUS trial, tumour assessments were performed after eight weeks during the first 24 months after randomization and every 12 weeks thereafter.</td>
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<td><strong>Discontinuation</strong></td>
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<tr>
<td>1. Treatment with the encorafenib and binimetinib combination should be discontinued upon the occurrence of any of the following:</td>
<td>These conditions correspond to the criteria used to determine whether treatment with encorafenib and binimetinib should be discontinued in the COLUMBUS trial, and also correspond to the dosing instructions within the Product Monographs.</td>
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<tr>
<td>1.1. Clinical or radiographic disease progression</td>
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<td>1.2. Unacceptable toxicity</td>
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<td>1.3. Development of adverse reactions that do not resolve despite dose delays or dose reductions</td>
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### Reimbursement Condition

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<td>2. If one component of the combination therapy is discontinued for toxicity or intolerance, the other drug in the combination should also be discontinued.</td>
<td>The product monographs for encorafenib and binimetinib specify that during combination therapy with encorafenib-binimetinib, if one of the drugs is temporarily interrupted, the other drug should also be interrupted; if one drug is permanently discontinued, the other drug should also be discontinued.</td>
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### Prescribing

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<tr>
<td>1. Encorafenib in combination with binimetinib should only be prescribed by clinicians who: 1.1. have expertise in diagnosis and management of patients with melanoma 1.2. are familiar with the toxicity profile associated with the encorafenib and binimetinib regimen.</td>
<td>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.</td>
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<td>2. Dosing of the encorafenib and binimetinib should be as follows: 2.1. encorafenib 450 mg once daily 2.2. binimetinib 45 mg twice daily</td>
<td>As per eligibility for COLUMBUS trial and recommended dose by Health Canada.</td>
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### Pricing

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<td>1. Encorafenib in combination with binimetinib should not be more costly than the least costly BRAFi/MEKi combination regimen.</td>
<td>Evidence from indirect comparisons (NMAs) suggest that there is no statistically significant difference in efficacy among the three BRAFi/MEKi combination treatments in patients with unresected or metastatic melanoma.</td>
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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

### 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 and binimetinib may have varying degrees of effect on BRAF V600 K, V600D, 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 as 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 >1. pERC agreed that it would be reasonable to offer encorafenib-binimetinib to patients with ECOG PS >1.

- Patients with active central nervous system (CNS) lesions were excluded from the COLUMBUS trial. pERC acknowledged that there is an ongoing trial evaluating the 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 encorafenib-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 unfavorable 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 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.

- While encorafenib-binimetinib might be considered as adjuvant treatment to surgery where dabrafenib in combination with trametinib is poorly tolerated, it should be noted that there is no evidence for the efficacy of encorafenib in combination with binimetinib in the adjuvant setting.

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 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 the current practice. Relevant comparators would include other BRAF and MEK inhibitor combinations such as dabrafenib and trametinib or vemurafenib and 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 four network meta-analyses (NMAs). Despite differences in methodologies and data cuts used, the results of 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 quality of life, 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 when compared to 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 quality of life for both patients and caregivers; however, pERC was unable to reach a conclusion on the effect of combination therapy with encorafenib and binimetinib on quality of life, 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 one phase III randomized, open-label trial in patients with locally advanced unresectable or metastatic melanoma with BRAF V600 mutation
- Patients’ perspectives gathered by two 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
- Two clinical specialists with expertise diagnosing and treating patients with locally advanced or metastatic melanoma
- Input from two 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 centers, 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, GI issues, arthritis, and auto-immune 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 seem to experience fewer side effects compared to 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, as many patients have indicated that the ongoing pandemic has led to more fear and anxiety of visiting the hospital. Patients stated that if these outcomes were achieved, they would experience less anxiety and fear and would have an improved quality of life. 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 quality of life.
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 one phase III randomized, open-label trial (COLUMBUS; N = 577). COLUMBUS was a multicentre trial that included adult patients (aged ≥ 18 years) with histologically confirmed locally advanced unresectable or metastatic BRAF V600E mutant cutaneous melanoma or unknown primary melanoma (stage IIIB, IIIC or IV per AJCC). Patients were required to be previously untreated (treatment naïve) 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 CNS 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 one line of immunotherapy.

Eligible patients were randomized in a 1:1:1 ratio to three 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 and HRQoL. The study is also limited by the exploratory nature of the HRQoL data and lack of statistical testing and data collection methods that make it difficult to detect the magnitude of the improvement with encorafenib and binimetinib, and difficult to assess influence of effective post-progression treatments on the observed results, particularly on overall survival.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, pERC discussed the following: PFS, OS, ORR, TTR, DOR, DOR, and HRQoL.

- **Progression-free survival (PFS)** was defined as the time from the date of randomization to the date of the first documented progression (according to RECIST v1.1) 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.

- **Overall Survival (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 to be censored at the date of last contact. Survival time for patients with no post-baseline survival information was to be censored on the date of randomization.

- **Overall Response Rate (ORR)** was defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR).

- **Time to Objective Response (TTR)** was defined as the time between the date of randomization until first documented response of CR or PR.

- **Duration of Response (DOR)** 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 (DCR) 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 v1.1.

Health-Related Quality of Life (HRQoL) was assessed using the Functional Assessment of Cancer Therapy-Melanoma (FACT-M, v4), European Organization for Research and Treatment of Cancer’s core quality of life questionnaire (EORTC QLQ-C30, v3.0), and EuroQol-5 Dimension-5 Level (EQ-5D-5L, v4.0). EORTC QLQ-C30 is composed 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 (14.9 months, 95% CI: 11.0 to 18.5) compared to the vemurafenib monotherapy arm (7.3 months, 95% CI: 5.6 to 8.2), with a hazard ratio (HR) of 0.54 (95% CI: 0.41 to 0.71; p <0.0001). The median PFS for encorafenib- binimetinib combination was nominally higher than that for encorafenib monotherapy arm (9.8 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 to 9.6 months (95% CI: 7.4 to 14.8) in the vemurafenib monotherapy arm.

At the November 2017 data cut, the median overall survival 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 to 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 to 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. TTR by BIRC was similar across all treatment arms (2 months each). It was noted that this timing was due to the protocol design as the first tumor assessment was at Cycle 3 Day 1. DCR 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 DOR 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 three scales: FACT-M, EORTC QLQ C30, and EQ-5D-5L. FACT-M (v4) is a melanoma-specific quality of life (QoL) questionnaire.

The HRQoL instruments were administered every eight 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 three instruments across treatment groups. Evaluation of changes in FACT-M and EORTC QLQ-C30 scores over time showed slightly more favorable results for the encorafenib and binimetinib combination arm. EQ-5D-5L scores showed slightly improvement in the encorafenib-binimetinib combination arm or remined 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 quality of life across all three scales (0.1 to 4 points), no treatment arm reached the MID (between 5 to 9 points for FACT-M, over 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 1 error prespecified in the testing hierarchy. In addition, collecting data from only those patients who remain in studies introduces bias and will inflate the observed benefit. Further, there is added uncertainty from two of the scales utilized (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 one adverse event. The most commonly reported adverse events 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 to encorafenib monotherapy (38.5% and 13.5%, respectively) and 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 adverse event was less common in the encorafenib in combination with binimetinib arm (65.1%). The incidence of Grade 3 or 4 adverse events was lower in the encorafenib in combination with binimetinib arm (57.8%) compared to the 66.1% of patients in the encorafenib arm and 63.4% in the vemurafenib arm. The most commonly reported grade 3 and 4 adverse events 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 SAE was pyrexia, which occurred more frequently in the encorafenib in combination with binimetinib arm (2.6%) versus the encorafenib (1%) and (0%) in the vemurafenib monotherapy arm. Overall, 12.5% of patients in the encorafenib in combination with binimetinib arm, 14.1% of patients in the encorafenib arm, and 16.7% of those in the vemurafenib arm withdrew from treatment due to adverse events. The most commonly cited reason in the encorafenib in combination with binimetinib arm was increased ALT and AST (2.6%). Mortality was comparable across treatment arms. The encorafenib-binimetinib arm had a total of 17 deaths (8.9%) compared to 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 efficacy and safety between encorafenib plus binimetinib and these comparators, four indirect treatment comparisons were reviewed and critically appraised: (1) an unpublished Bayesian network meta-analysis (NMA) submitted by the sponsor that was focused on the BRAFi/MEKi combination therapy trials and reported on OS and PFS outcomes, (2) 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 adverse events in addition to OS and PFS, (3) a Bayesian NMA which 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 (4) a Bayesian NMA which compared a pooled chemotherapy group to various I0s, 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 three BRAKi/MEKi combination treatments for unresected or metastatic melanoma for OS and PFS outcomes. Overall, the limited data suggests 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 to 4 toxicities across the BRAFi/MEKi combination therapy treatments. The NMA found that toxicities differed between the three combination therapy regimens. When compared to encorafenib-binimetinib, combination therapy with vemurafenib-cobimetinib was associated with significantly higher Grade 3 to 4 liver toxicity, rash, arthralgia, basal cell carcinomas, and diarrhea, but less decrease of left ventricular ejection fraction. When compared to dabrafenib-trametinib, combination therapy with encorafenib-binimetinib demonstrated few statistically significant differences in Grade 3 to 4 toxicities. Only hypertension occurred more frequently with dabrafenib-trametinib, while 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 IOs which are key comparators for BRAFi/MEKi combinations for the first-line treatment of unresectable or metastatic melanoma. Comparisons between agents within these two classes are of high clinical interest. However, results for comparisons between dabrafenib in combination with trametinib and IOs 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 three-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 healthcare payer with costs and quality-adjusted life years (QALYs) modelled over a 20-year time horizon. All patients entered the model in the progression-free health state 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 in combination with binimetinib and vemurafenib monotherapy was informed by the COLUMBUS trial with OS further adjusted based on American Joint Committee on Cancer– melanoma registry and CheckMate 066 trial. The HRs for dabrafenib + trametinib and vemurafenib + 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 + binimetinib to other BRAFi/MEKi targeted combination treatments is uncertain as concerns remain with the internal validity of the sponsor’s submitted NMA.
- As the subsequent therapies which 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 reanalyses 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 as 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 + 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 three-years. CADTH identified limitations with the submitted budget impact analysis and undertook a reanalysis to adjust the relative dose intensity to 100% for oral treatments which estimated the incremental budget saving associated with reimbursing encorafenib in combination with binimetinib to be $15,733,868 over three-years. CADTH could not address limitations related to 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.
pERC Members
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.

May 13, 2021 Meeting

Regrets
None

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