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CADTH Reimbursement Recommendation

Encorafenib (Braftovi)

Indication: In combination with cetuximab, for the treatment of patients with metastatic colorectal cancer (mCRC) with a *BRAF* V600E mutation, as detected by a validated test, after prior therapy.

Sponsor: Pfizer Canada ULC

Recommendation: Reimburse with conditions

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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?

CADTH recommends that Braftovi should be reimbursed by public drug plans for the treatment of metastatic colorectal cancer (mCRC) if certain conditions are met.

What are the conditions for reimbursement?

Braftovi should only be reimbursed when given in combination with cetuximab, prescribed by clinicians with experience in treating colorectal cancer, and the cost of Braftovi is reduced.

Which patients are eligible for coverage?

Braftovi should only be covered for patients who have *BRAF* V600E–mutated mCRC, have received at least 1 previous systemic treatment for mCRC, have good performance status, and have adequate organ function. Braftovi should not be reimbursed for patients who have had previous treatment with epidermal growth factor receptor (EGFR) inhibitors or BRAF inhibitors.

Why did CADTH make this recommendation?

- Evidence from 1 clinical study demonstrated that Braftovi in combination with cetuximab prolonged life and delayed the progression of the disease by a few months compared to chemotherapy.
- Braftovi in combination with cetuximab may meet some of the needs that are important to patients, including prolonging life, minimizing adverse effects, and improving symptoms.
- Based on public list prices, Braftovi (when used in combination with cetuximab) is not considered cost-effective at a willingness to pay of $50,000 per quality-adjusted life-year (QALY) for the indicated population relative to currently reimbursed alternatives. Economic evidence suggests that a 99% price reduction for Braftovi and a 60% price reduction for cetuximab is needed to ensure Braftovi is cost-effective at a $50,000 per QALY threshold.
- Based on public list prices, the 3-year budget impact of Braftovi (when used in combination with cetuximab) is at least $113M.

Additional Information

What is mCRC with a *BRAF* V600E mutation?

Colorectal cancer is the third most commonly diagnosed cancer in Canada, with an expected 26,900 new cases in 2020; approximately 20% are metastatic at initial diagnosis. *BRAF* mutations account for 10% to 15% of colorectal cancer cases, with the V600E mutation being the most common variant. *BRAF* V600E–mutated mCRC is an aggressive form of colorectal cancer associated with poor prognosis and survival.

Unmet needs in mCRC with a *BRAF* V600E mutation

The treatment of mCRC is based on various chemotherapy regimens, which are associated with fatigue, nausea, and vomiting. There are currently no treatments for mCRC that specifically target the *BRAF* V600E mutation. There is a need for treatments that prolong survival, have an acceptable side effect profile, and a favourable impact on quality of life.

How much does Braftovi cost?

Treatment with Braftovi (when used in combination with cetuximab) is expected to cost approximately $13,203 per person, per 28-day cycle.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that encorafenib should be reimbursed for the treatment of patients with metastatic colorectal cancer (mCRC) with a *BRAF* V600E mutation, as detected by a validated test, after prior therapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 open-label, phase III, randomized controlled trial (RCT) — BEACON — in adult patients with mCRC whose tumours expressed the *BRAF* V600E mutation and whose disease had progressed after 1 or 2 prior regimens in the metastatic setting demonstrated that encorafenib in combination with cetuximab was associated with a statistically significant and clinically meaningful longer median overall survival (OS) (8.41 months, 95% confidence interval [CI], 7.46 to 11.04) compared with the control group, which consisted of treatment with irinotecan plus cetuximab or FOLFIRI (folinic acid plus fluorouracil plus irinotecan) plus cetuximab (5.42 months, 95% CI, 4.76 to 6.57). A 40% lower risk of death was observed in the encorafenib in combination with cetuximab group compared with the control group (hazard ration [HR] = 0.60; 95% CI, 0.45 to 0.79). The median progression-free survival (PFS) was also longer for patients treated with encorafenib in combination with cetuximab (4.21 months) compared to the control group (1.51 months; P < 0.0001). Exploratory analyses assessing health-related quality of life (HRQoL) using a time to deterioration (TTD) analysis indicated encorafenib in combination with cetuximab delayed deterioration of HRQoL compared with the control group. Given the totality of the evidence, pERC concluded that encorafenib in combination with cetuximab potentially addresses some of the unmet needs identified by patients: prolonging life, minimizing adverse effects, providing an alternative treatment option, and improving symptoms. Patients also valued a drug with simpler administration. Encorafenib met this need, as it is an oral drug, and while cetuximab is an IV treatment, it does have a shorter infusion time than other chemotherapies. The other unmet needs identified by patients were either unmet by encorafenib or the evidence was not clear; these unmet needs include providing a cure and promoting good quality of life.

Results from an indirect treatment comparison (ITC) suggested that encorafenib in combination with cetuximab was [redacted] to FOLFIRI based on [redacted] OS [redacted] and PFS [redacted]. While the [redacted] treatment with encorafenib in combination with cetuximab compared to FOLFIRI or FOLFOX (folinic acid plus fluorouracil plus oxaliplatin), the [redacted] remains uncertain because of the many limitations reported with the ITC.

Using the sponsor-submitted price for encorafenib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for encorafenib in combination with cetuximab was $198,779 per QALY compared with FOLFOX. At this ICER, encorafenib is not cost-effective at a $50,000 per QALY willingness to pay threshold for the treatment of patients with mCRC with a *BRAF* V600E mutation as detected by a validated test, after prior therapy. Encorafenib, when used in combination with cetuximab, would not be considered cost-effective at a $50,000 per QALY threshold, even with a 100% price reduction for encorafenib, because of the high cost of cetuximab.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Patients must receive encorafenib in combination with cetuximab.	The Health Canada indication specifies that encorafenib be used in combination with cetuximab. In the BEACON study, patients received encorafenib in combination with cetuximab.
2. Patients must have *BRAF* V600E–mutated mCRC.	The Health Canada indication specifies that encorafenib be used in patients with mCRC with a *BRAF* V600E mutation, as detected by a validated test. The BEACON study only enrolled patients with the *BRAF* V600E mutation.
3. Patients must have received at least 1 previous systemic treatment for mCRC.	The Health Canada indication specifies that encorafenib be used after prior therapy. The BEACON study only enrolled patients whose disease had progressed after 1 or 2 prior regimens in the metastatic setting.
4. Patients must have good performance status.	The BEACON study excluded patients who had an ECOG PS of greater than 1 at baseline.
5. Patients must not have received prior EGFR inhibitors or BRAF inhibitors	The BEACON study excluded patients who received prior EGFR inhibitors or BRAF inhibitors.
6. Patients must have adequate organ function.	The BEACON study only enrolled patients with adequate organ function.
Renewal	
1. Ongoing clinical (and radiographic) evidence of response and tolerance to therapy.	Renewal should be based on demonstration of ongoing response and tolerance to therapy.
2. Patients need to be assessed clinically every 2 to 4 weeks, with radiological assessments performed every 8 to 12 weeks.	The clinical experts' input to pERC noted that clinical response assessments need to be performed every 2 to 4 weeks and radiological assessments need to be performed every 8 to 12 weeks.
Discontinuation	
1. Reimbursement of encorafenib in combination with cetuximab should be discontinued for disease progression based on RECIST criteria or unacceptable toxicity due to encorafenib or cetuximab.	In the BEACON study, unacceptable toxicities from either encorafenib or cetuximab required the discontinuation of both treatments. Treatment was permitted to continue in the BEACON study after disease progression if it was believed that the patient may experience benefit from the treatment and if it was in the patient's best interest (based on physician's discretion). The product monograph noted that if cetuximab is discontinued, encorafenib is also discontinued.
Prescribing	
1. The prescribing of encorafenib in combination with cetuximab should be restricted to clinicians and centres with experience in treating colorectal cancer.	This would ensure that the appropriate patients receive treatment with encorafenib in combination with cetuximab and optimizes toxicity management.

Reimbursement condition	Reason
2. Cetuximab should be administered in an approved oncology infusion clinic.	Cetuximab is administered intravenously.
Pricing	
Price reduction.	The ICER for encorafenib in combination with cetuximab is $198,779 when compared with FOLFOX. Given the cost of cetuximab, there is no price for encorafenib at which an ICER of $50,000 could be achieved. If the price of cetuximab was reduced by more than 60%, encorafenib may be able to achieve an ICER of $50,000 per QALY, with a 99% price reduction.

ECOG = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; FOLFOX = folinic acid plus fluorouracil plus oxaliplatin; ICER = incremental cost-effectiveness ratio; mCR = metastatic colorectal cancer; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year.

Implementation Guidance

1. Within the BEACON study, cetuximab was administered as 400 mg/m^2 intravenously, followed by 250 mg/m^2 every week. The clinical experts' input to pERC noted that cetuximab might be provided to patients at an alternative dosing schedule of 500 mg/m^2 every 2 weeks to address challenges with implementation (i.e., chair time, hospital resources, travel time, and inconvenience to patients).
2. While encorafenib in combination with cetuximab is indicated for the treatment of patients with mCRC, pERC agreed with the clinical expert input that encorafenib in combination with panitumumab may be considered for the treatment of patients with mCRC if the patients experience an allergic reaction to cetuximab, or to decrease chemotherapy resource utilization, or patient preference is for less frequent chemotherapy sessions. The clinical experts noted that, while currently there is no evidence available for encorafenib in combination with panitumumab, it is expected that patients who receive encorafenib in combination with panitumumab would respond in the same manner as patients who receive encorafenib in combination with cetuximab, given that the efficacy of panitumumab is similar to that of cetuximab.
3. While the BEACON study excluded patients who were previously treated with panitumumab or cetuximab, pERC agreed with the clinical expert input that, given the lack of options, some patients who are receiving ongoing treatment with cetuximab or panitumumab in combination with chemotherapy might be treated with encorafenib in combination with cetuximab or panitumumab if they have not yet progressed on the EGFR inhibitors.
4. Some patients might have both *BRAF* mutation-positive and microsatellite instability high (MSI-H)–positive mCRC. pERC agreed with the clinical expert input that patients should be treated for MSI-H with pembrolizumab as first-line treatment and then may be treated with encorafenib in combination with cetuximab or panitumumab as a second-line or third-line treatment.
5. While patients enrolled in the BEACON study had to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, the clinical experts' input to pERC noted that patients with ECOG PS 2 could be considered in some patients for treatment with encorafenib in combination with cetuximab.

6. The sponsor estimated the incremental budget impact of reimbursing encorafenib in combination with cetuximab to be $97,946,588 over 3 years. CADTH identified limitations with the submitted budget impact analysis and undertook reanalyses that estimated the incremental budget impact of reimbursing encorafenib in combination with cetuximab to be $113,661,749 over 3 years. If additional costs are included (e.g., administration, subsequent drug treatment, adverse events, *BRAF* mutation testing), the incremental budget impact may be higher. Due to the magnitude of the budget impact, there may be challenges with implementing the recommendation unless product listing agreements can be established that mitigate the long-term financial risk to public payers.

Discussion Points

- Patient groups and clinician input to CADTH highlighted that *BRAF* V600E–mutated mCRC is an aggressive cancer with poor prognosis and few treatment options.
- pERC discussed that the BEACON study enrolled patients with the *BRAF* V600E mutation and that treatment with encorafenib in combination with cetuximab cannot be generalized to patients with other *BRAF* V600 mutations or whose BRAF status cannot be determined. Therefore, treatment with encorafenib in combination with cetuximab should be limited to patients with a *BRAF* V600E mutation.
- The recommended dose of cetuximab is 400 mg/m^2 followed by 250 mg/m^2 via IV infusions every week. pERC discussed that the administration of cetuximab in Canadian clinical settings may involve a higher dose and a less frequent schedule at 500 mg/m^2 IV every 2 weeks. The less frequent administration schedule for cetuximab may be favourable for patients and clinics, as it reduces the burden on clinic resources and patients (i.e., travel time, cost, chair time). While no evidence comparing the 2 regimens exists to support the conclusion of clinical equivalence, pharmacokinetic studies combined with input from the clinical experts supported the alternative dose of cetuximab at 500 mg/m^2 IV every 2 weeks.
- The indication for encorafenib specifies the use in mCRC patients after having received prior therapy. No subgroup data were available to assess the magnitude of clinical benefit stratified by whether patients receive encorafenib in combination with cetuximab as second-line treatment or third-line treatment. As such, the cost-effectiveness of encorafenib in combination with cetuximab for these subgroups is not known.

Background

Encorafenib has a Health Canada indication to be used in combination with cetuximab for the treatment of patients with mCRC with a *BRAF* V600E mutation, as detected by a validated test, after prior therapy. Encorafenib is a kinase inhibitor. It is available as a 75 mg capsule. The recommended dose of encorafenib in patients with mCRC is 300 mg (4 75 mg capsules) orally taken once daily in combination with cetuximab until disease progression or unacceptable toxicity.

Sources of Information Used by the Committee

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

- a review of 1 phase III randomized controlled trial in adult patients with *BRAF* V600E–mutated mCRC
- patients' perspectives gathered by patient groups, Colorectal Cancer Canada (CCC), Colorectal Cancer Resource & Action Network (CCRAN)
- 2 clinical specialists with expertise diagnosing and treating patients with mCRC
- input from 3 clinician groups: the Canadian Gastrointestinal Oncology Evidence Network (CGOEN), Ontario Health (Cancer Care Ontario), the Gastrointestinal Cancer Drug Advisory Committee (DAC), and 9 clinicians who treat mCRC
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Patient Input

Two patient groups, CCC and CCRAN, submitted input for this submission. Information from CCC was collected via online surveys from 2 patients and 4 caregivers from Canada, the US, the UK, and Turkey. Information from CCRAN about the experience of mCRC was collected via online surveys from 63 patients, 17 caregivers, and 5 patients who were also caregivers. A focus group discussion was held with 7 patients. Phone interviews with 3 patients from Canada and the Netherlands provided insight about direct experiences for encorafenib plus cetuximab.

The patient input indicated symptoms of fatigue, bloody stools, diarrhea, and abdominal cramping as the most commonly occurring colorectal cancer symptoms. Fatigue and pain were symptoms of colorectal cancer, which patients considered most important to control. The patient input identified difficulty with being able to work and being unable to fulfill family obligations because of the disease. Side effects of therapies considered most difficult to tolerate included vomiting, nausea, pain, rash, neuropathy, hair loss, and low platelets. Patients indicated that a cure, prolonged life, an effective treatment option, and improved quality of life were the most important considerations for new therapies.

In general, among patients who had experience with encorafenib plus cetuximab, side effects were reported to be more tolerable compared to previous therapies. However, gastrointestinal side effects, fatigue, emotional drain, and medication management were reported to be the most difficult aspects of treatment with encorafenib plus cetuximab.

Drug Plan Input

The key implementation factors identified by the drug programs were related to eligible population, relevant comparators, generalizability, and prescribing of therapy. The Provincial Advisory Group (PAG) inquired whether encorafenib could be used with either cetuximab or panitumumab. In addition, PAG inquired if encorafenib in combination with cetuximab can be used in patients with ECOG PS greater than 1 as these patients were excluded from

the BEACON study. The PAG also inquired whether there is potential to use encorafenib in patients with other *BRAF* V600 mutations than V600E or in patients whose *BRAF* status cannot be determined.

Clinical Evidence

Clinical Trials

The systematic review included 1 multi-centre, multinational, randomized, open-label, phase III study. The BEACON study evaluated the efficacy and safety of 3 treatment groups: encorafenib in combination with cetuximab (doublet group), encorafenib plus cetuximab plus binimetinib (triplet group), and a control group, which was the investigator's choice of either irinotecan in combination with cetuximab or FOLFIRI in combination with cetuximab. Eligible patients included adults with mCRC whose tumours expressed the *BRAF* V600E mutation and whose disease had progressed after 1 or 2 prior regimens in the metastatic setting. Local assay testing was only accepted via polymerase chain reaction or next-generation sequencing; patients enrolled based on local assays were required to have a confirmation of their *BRAF* mutation status by central laboratories no later than 30 days from the first dose of study treatment.

A total of 220 patients were randomized to the doublet group and 221 patients to the control group. Within the control group, 92 patients (41.6%) received cetuximab plus irinotecan and 129 patients (58.4%) received cetuximab plus FOLFIRI. Randomization was stratified according to baseline ECOG PS (0 versus 1), prior use of irinotecan (yes versus no), and cetuximab source (US-licensed versus EU-approved). Patients randomized to the doublet group received encorafenib at 300 mg daily in combination with cetuximab. Patients randomized to the control group received either irinotecan (180 mg/m^2 every 2 weeks) plus cetuximab, or FOLFIRI plus cetuximab; dosage for FOLFIRI is presented herein; cetuximab was administered at 400 mg/m^2 followed by 250 mg/m^2 every week via IV infusion in all treatment combinations:

- irinotecan at 180 mg/m^2 IV infusion every 2 weeks
- folinic acid at 400 mg/m^2 IV infusion or maximal dose tolerated in a prior regimen every 2 weeks
- 5-fluorouracil at 400 mg/m^2 initial dose bolus, then 1,200 mg/m^2 /day for 2 days of continuous infusion or maximal dose tolerated in a prior regimen every 2 weeks.

The key limitations of the BEACON study are related to the open-label nature of the study which might have introduced bias in the assessment of subjective outcomes, such as adverse events and HRQoL; in addition, the use of subsequent therapies differed across treatment groups and may have influenced observed survival in the BEACON trial. As analyses for OS did not control for subsequent therapies, results for OS could have been over- or underestimated.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, the Committee discussed the following:

Overall Survival: OS was defined as the time from randomization to death due to any cause. Patients who did not die by the data cut-off date were censored for OS at their last contact date.

Objective Response Rate: ORR was defined as the number of patients achieving a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the total number of patients in that treatment group. The BOR (i.e., CR or PR) was assessed by blinded independent central review and the investigator according to RECIST 1.1 criteria.

Progression-Free Survival: PFS was defined as the time from randomization to the earliest documented date of progression per RECIST 1.1 criteria by blinded independent central review and the investigator assessment, or death due to any cause.

Health-Related Quality of Life: HRQoL was an exploratory end point and analyzed using the following questionnaires: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, core 30 items (EORTC QLQ-C30); the Functional Assessment of Cancer Therapy - Colon Cancer (FACT-C); the EuroQuol scale, 5-Dimensions 5-Levels (EQ-5D-5L), and the Patient Global Impression of Change (PGIC).

The primary end points for this trial were based on comparisons between the triplet and control groups. Key secondary end points included analyses of OS, ORR, and PFS between the doublet group and the control group. A statistical hierarchy ensured that key secondary end points were formally tested only if OS between the triplet group and the control group was found to be statistically significant.

Efficacy

An interim analysis was pre-specified in the protocol of the BEACON trial to occur after a minimum of 188 OS events in the triplet and control groups combined and a minimum of 169 OS events in the doublet and control groups combined. The median OS was 8.41 months (95% CI, 7.46 to 11.04) in the doublet group compared to 5.42 months (95% CI, 4.76 to 6.57) in the control group (P = 0.0002, log-rank test). A 40% lower risk of death was observed in the doublet group (HR = 0.60; 95% CI, 0.45 to 0.79).

The median PFS was 4.21 months (95% CI, 3.71 to 5.36) in the doublet group compared to 1.51 months (95% CI, 1.45 to 1.71) in the control group (P < 0.0001, log-rank test). A 60% reduction in progression or death (HR = 0.40; 95% CI, 0.31 to 0.52) was observed in the doublet group compared to the control group.

A greater proportion of patients in the doublet group had a confirmed response (20.4%; 95% CI, 13.4 to 29.0) versus the control group (1.9%; 95% CI, 0.2 to 6.6). Patients treated with encorafenib plus cetuximab showed statistically significantly improved ORR compared to the control group (P < 0.0001, Cochran-Mantel-Haenszel test).

An additional updated analysis that was not pre-specified in the protocol of the BEACON trial was conducted, which added approximately 6 months of data. The results of these post-hoc analyses were generally consistent with primary results in supporting efficacy favouring treatment with encorafenib plus cetuximab over therapies in the control group observed at the interim analysis. However, results from the post-hoc analysis are considered descriptive and should be interpreted with caution.

Quality of life data were assessed using a TTD analysis; a TTD analysis of all HRQoL questionnaires indicated longer TTD (improvement) for patients in the doublet group over the control group. However, analyses of HRQoL are exploratory and should be interpreted with caution.

Harms (Safety)

A similar proportion of any-grade adverse events (AEs), treatment-emergent AEs (TEAEs), serious AEs (SAEs), and Grade ≥ 3 SAEs were observed in similar proportions across the doublet and control groups. Grade ≥ 3 AEs and Grade ≥ 3 TEAEs occurred more frequently in the control group than the doublet group. In general, most AEs observed were Grade 1 or Grade 2. AEs of any grade with a difference of 10% between the doublet and control groups, and which occurred more frequently in the doublet group, included arthralgia (19.0% versus 0.5%, respectively), headache (19.4% versus 2.6%), melanocytic nevus (14.4% versus 0%), myalgia (13.4% versus 2.1%), and musculoskeletal pain (12.5% versus 1.6%). The most commonly occurring any-grade AEs were diarrhea (33.3% in the doublet group versus 48.2% in the control group), dermatitis acneiform (29.2% versus 39.4%), nausea (34.3% versus 41.5%), fatigue (30.1% versus 27.5%), vomiting (21.3% versus 29.0%), decreased appetite (26.9% versus 26.9%), abdominal pain (22.7% versus 24.9%), and asthenia (21.3% versus 35.4%). The most frequently reported TEAEs of any grade included dermatitis acneiform (27.8%), fatigue (22.7%), and nausea (20.4%) in the doublet group; and diarrhea (44.0%), dermatitis acneiform (38.9%), nausea (36.3%), asthenia (22.3%), and stomatitis (21.2%) in the control group. Deaths occurring during treatment or within 30 days of the last administered dose occurred in 7 patients (3.2%) in the doublet group and 8 patients (4.1%) in the control group.

Indirect Evidence

The sponsor provided an ITC evaluating the efficacy of encorafenib in combination with cetuximab to FOLFIRI. The sponsor's ITC compared the efficacy of encorafenib plus cetuximab to FOLFIRI among *BRAF*-mutated patients with mCRC after prior therapy. The results of the sponsor's ITC suggested that encorafenib plus cetuximab was [redacted] to FOLFIRI based on [redacted] OS [redacted] and PFS [redacted]. No comparisons for harms or safety were incorporated in the sponsor's ITC. Little published peer-reviewed literature was available for the assessment of feasibility into the sponsor's ITC. Only 1 trial, NCT00339183, was included in the sponsor's ITC to provide comparison with encorafenib plus cetuximab based on evidence from the BEACON trial. The trial was limited in the number of *BRAF*-mutated patients; therefore, generalizations about baseline characteristics and clinical outcomes for all patients in NCT00339183 were made to the small *BRAF*-mutated subsample included in the trial. Patients in the NCT00339183 trial had received only 1 previous systemic therapy, whereas patients in the BEACON trial could have received 2 treatments. As patients with *BRAF* mutations face poorer prognoses, these generalizations of baseline characteristics and trial results between *BRAF*-mutated and wild type patients may not be appropriate and may have resulted in an underestimation of the benefit of encorafenib plus cetuximab. In addition, a number of assumptions regarding clinical equivalence between different treatments were made; assumptions were considered reasonable by clinicians consulting on this CADTH review. However, without direct evidence, it is not possible to know the comparative efficacy of different treatments with certainty. While the results of the sponsor's ITC, which [redacted] encorafenib plus cetuximab [redacted] FOLFIRI may be true, the magnitude of this [redacted] is uncertain.

Economic Evidence

Cost and Cost-Effectiveness

Encorafenib (Braftovi) is available as a 75 mg capsule at a submitted price of $50.25 per capsule. The proposed dosing regimen for encorafenib is 300 mg daily in combination with cetuximab until disease progression or unacceptable toxicity. The 28-day per patient drug acquisition cost of encorafenib is $5,628 (when in combination with cetuximab: $13,203) assuming no wastage and 100% relative dose intensity.

The sponsor submitted a cost-utility analysis comparing encorafenib in combination with cetuximab with cetuximab plus FOLFIRI or irinotecan, FOLFOX, or FOLFIRI in patients with *BRAF* V600E–mutated mCRC. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer over a 10-year horizon and was based on a partitioned survival model, including 3 health states: progression-free, post-progression, and death. All patients entered the model in the pre-progression health state. PFS and OS in the model was based on OS and PFS observed in the BEACON trial for encorafenib in combination with cetuximab and cetuximab plus FOLFIRI or irinotecan. Relative efficacy for FOLFIRI compared with encorafenib in combination with cetuximab was derived from an ITC; the efficacy of FOLFOX was assumed equivalent to FOLFIRI. In the sponsor's base case, encorafenib in combination with cetuximab was associated with an ICER of $150,682 per QALY gained relative to treatment with FOLFOX.

CADTH identified the following key limitations with the sponsor's pharmacoeconomic analysis:

- Based on CADTH clinical expert opinion, there is no direct head-to-head evidence comparing encorafenib in combination with cetuximab and the regimens considered most relevant (FOLFIRI and FOLFOX).
- Regimens containing cetuximab and irinotecan may only be funded in some jurisdictions for the third-line treatment of mCRC in patients who have failed an oxaliplatin- or irinotecan-based regimen.
- Treatment for mCRC is highly individualized and other relevant comparators were not considered.
- The predicted OS and PFS for encorafenib in combination with cetuximab and cetuximab plus FOLFIRI or irinotecan were overestimated and lacked face validity based on CADTH clinical expert opinion.
- The sponsor incorporated 1-time costs related to AEs, assumed that quality of life effects of AEs would be captured as part of health state utility values, and assumed that all AEs would be managed in hospital.
- Treatment-specific utilities were included in the sponsor's model.
- Different assumptions were incorporated for time on treatment after disease progression across treatments.

CADTH undertook reanalyses to address the identified limitations, including adopting an alternative parametric distribution of OS for encorafenib in combination with cetuximab and cetuximab plus FOLFIRI or irinotecan and using consistent health state utility values across treatments. CADTH was unable to address the lack of head-to-head comparative clinical data, limited generalizability of model comparators, and the impact of AEs. Based

on CADTH reanalyses, the ICER for encorafenib in combination with cetuximab compared to FOLFOX is $198,779 per QALY gained; FOLFIRI and cetuximab plus FOLFIRI or irinotecan were dominated and extendedly dominated, respectively. There is no price for encorafenib at which an ICER of $50,000 per QALY could be achieved. If the price of cetuximab is reduced by more than 60%, encorafenib in combination with cetuximab may achieve an ICER of $50,000 per QALY if a 99% price reduction for encorafenib can be achieved. CADTH did not assess the cost-effectiveness of encorafenib in combination with panitumumab given the lack of clinical evidence available for this combination. The Health Canada product monograph recommends the use of encorafenib in combination with cetuximab exclusively for this population.

Budget Impact

The sponsor estimated the incremental budget impact of reimbursing encorafenib in combination with cetuximab to be $97,946,588 over 3 years. CADTH identified limitations with the submitted budget impact analysis, and undertook reanalyses that estimated the incremental budget impact of reimbursing encorafenib in combination with cetuximab to be $113,661,749 over 3 years. If additional costs are included (e.g., administration, subsequent drug treatment, AEs, *BRAF* mutation testing), the incremental budget impact may be higher. CADTH noted the budget impact is sensitive to the proportion of colorectal cancer cases that are metastatic and the proportion of mCRC cases that carry the *BRAF* V600E mutation.

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 14, 2021

Regrets: None

Conflicts of Interest: One member had a conflict of interest and did not vote.