CADTH

CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: Metastatic colorectal cancer

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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.

Key Messages

- Pembrolizumab can be reimbursed as first-line monotherapy for patients with mismatch repair-deficient metastatic colorectal cancer (mCRC). Subsequent lines of therapy reimbursed for these patients follow the sequence available to patients with mismatch repair-proficient mCRC.
- In the first-line setting, epidermal growth factor receptor inhibitors (EGFRi) combined with chemotherapy should not be reimbursed to patients with *BRAF* V600E or *RAS* gene mutations.
- Encorafenib in combination with an EGFRi can be reimbursed as a second, or subsequent, line of therapy for patients with *BRAF* V600E mutations in mCRC, including those patients who received first-line treatment with pembrolizumab.
- Approximately 5% of patients with mCRC are suitable candidates for first-line treatment with pembrolizumab.
- Approximately 10% of patients with mCRC are suitable candidates to receive encorafenib in combination with an EGFRi as a second, or subsequent, line of therapy.

Background

CADTH has reviewed and issued recommendations for drugs that can be used to treat adults with metastatic colorectal cancer (mCRC).

pERC Recommendation for Encorafenib (Braftovi) in Combination With Cetuximab (Erbitux)

From the 2021 review of encorafenib (Braftovi) in combination with cetuximab (Erbitux) for patients with mCRC, CADTH issued the following reimbursement 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 Table 1 are met.

pERC Recommendation for Pembrolizumab (Keytruda)

Based on the 2021 review of pembrolizumab (Keytruda) for the treatment of metastatic microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) CRC, CADTH:

- The CADTH pCODR Expert Review Committee (pERC) recommends that pembrolizumab should be reimbursed as monotherapy for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer only if the conditions listed in Table 1 are met.

pERC Recommendations for Panitumumab (Vectibix)

Two reviews of panitumumab for first-line treatment of patients with mCRC have been completed. In 2018, CADTH issued the following reimbursement recommendation for panitumumab (Vectibix) for treatment of patients with wild-type *RAS* mCRC:

- pERC does not recommend the reimbursement of panitumumab in combination with chemotherapy for the first-line treatment of mCRC patients with left-sided primary tumours that express wild-type *RAS* and who would otherwise be candidates to receive bevacizumab.

In 2015, CADTH issued the following reimbursement recommendation for panitumumab (Vectibix) for treatment of patients with wild-type *RAS* mCRC:

- The pCODR Expert Review Committee (pERC) recommends funding panitumumab in addition to combination chemotherapy conditional on cost-effectiveness being improved to an acceptable level, for the treatment of patients with WT RAS mCRC in the first-line treatment setting who have a contraindication or intolerance to bevacizumab and who would otherwise be treated only with combination chemotherapy.

Note that in this report, it is assumed that *deficient mismatch repair* (dMMR) and *high microsatellite instability* (MSI-H) refer to the same biomarker and can be used interchangeably. For brevity, "dMMR" will be preferentially used.

Implementation Issues

At the request of the participating drug programs, CADTH convened a panel of clinical experts in Canada to provide advice for addressing the outstanding implementation issues as follows:

- identification of treatment sequences for mCRC based on tumour genetic biomarkers (*RAS*, *BRAF*, MMR)
- anticipated prevalence of treatment sequences for mCRC.

Consultation Process and Objectives

The implementation advice panel comprised 6 specialists in Canada with expertise in the diagnosis and management of patients with mCRC, a representative from a public drug program, and a panel chair. The objective of the panel was to provide advice to the participating drug programs regarding the implementation issues listed in the Background section. A consensus-based approach was used, and input from stakeholders was solicited using questionnaires. Stakeholders, including patient and clinician groups, pharmaceutical manufacturers, and public drug programs, were invited to provide input in advance of the meeting.

The advice presented in this report has been developed based on the experience and expertise of the implementation advice panel members and, as such, represents experience-informed opinion; it is not necessarily based on evidence.

Advice on Funding Algorithm

Summary of Implementation Advice

Implementation advice regarding the optimal sequencing of treatments is summarized in Table 1. For each implementation issue, a summary of the relevant panel discussion is provided for additional context.

Table 1: Summary of Advice for Addressing Implementation Issues

Issue	Advice
Identification of treatment sequences for mCRC based on tumour genetic biomarkers (*RAS*, *BRAF*, MMR)	The panel advises that patients with mCRC receive the following treatment sequences based on the indicated tumour genetic biomarkers: • ***RAS*-mutated tumours:** Patients should be treated with multi-agent chemotherapy in combination with bevacizumab as first-line therapy, followed by alternate chemotherapies for second and third lines of therapy. • ***RAS* and *BRAF* wild-type tumours:** Patients should be treated with multi-agent chemotherapy in combination with bevacizumab as first-line therapy. If bevacizumab cannot be given, an EGFRi such as cetuximab or panitumumab (where available) can be used instead in combination with chemotherapy. This can be followed by alternate chemotherapy, with bevacizumab if a biologic was not combined with chemotherapy previously, as second-line therapy. A third-line treatment option of an EGFRi with or without chemotherapy can be available to patients who did not receive an EGFRi in a previous line of therapy. • ***BRAF* V600E–mutated tumours:** Patients should be treated with multi-agent chemotherapy in combination with bevacizumab as first-line therapy. On progression, they would be eligible for encorafenib in combination with an EGFRi. Alternate chemotherapy can be offered subsequently. • **dMMR:** Regardless of other tumour genetic biomarkers, these patients are eligible to receive pembrolizumab monotherapy as first-line therapy. For patients with disease progression following pembrolizumab, the subsequent treatment sequence follows sequences available to patients with pMMR starting at first line. Additionally, patients with *BRAF* V600E–positive tumours should be offered encorafenib in combination with an EGFRi after pembrolizumab in the next line of therapy.
Anticipated prevalence of treatment sequences for mCRC	The panel advises that jurisdictions should anticipate that approximately 5% of all patients with mCRC will receive pembrolizumab treatment and approximately 10% will receive encorafenib in combination with an EGFRi. Patients who will be eligible for both pembrolizumab first-line treatment and subsequent treatment with encorafenib in combination with an EGFRi are estimated to comprise less than 2% of all patients with mCRC.

dMMR = deficient mismatch repair; EGFRi = epidermal growth factor receptor inhibitor; mCRC = metastatic colorectal cancer; MMR = mismatch repair; pMMR = proficient mismatch repair.

In addition to the preceding advice, the panel indicated that all reimbursement recommendations were contingent upon ensuring improved cost-effectiveness so that the relevant sequences are affordable to public payers.

Panel Discussion

Treatment Sequences for mCRC Based on Tumour Genetic Biomarkers (*RAS*, *BRAF*, MMR)

The panel discussed the available evidence for possible treatment sequences, in the context of their expertise and experience, for patients with mCRC. The panel emphasized that mCRC treatment sequences should offer the highest probability of clinical benefit as early as possible since patients can deteriorate rapidly and may not be eligible for later lines of treatment. The *RAS*, *BRAF*, and MMR genetic biomarkers are predictors of mCRC treatment efficacy and therefore dictate treatment eligibility and sequences. Timely genetic biomarker assessment was unanimously raised as a concern by the panel. Biomarker

assessment of mCRC will be required to accurately implement this provisional funding algorithm and provide the evidence-based treatment to patients as intended by the panel.

In addition to the timely assessment of mCRC genetic biomarkers, the panel had concerns regarding pre-treated patients with dMMR mCRC. The panel highlighted an unmet therapeutic need in patients with dMMR mCRC previously treated with chemotherapy for mCRC but who have not yet received immunotherapy. The panel emphasized the need for access to pembrolizumab due to the unmet need for more efficacious and tolerable options for this population, and highlighted that evidence for efficacy of pembrolizumab in pre-treated patients is available.[1] According to the panel, this prevalent population of patients with mCRC will decrease over time as newly diagnosed patients are treated with pembrolizumab in the first-line setting. The concern about pre-treated patients with dMMR mCRC was also raised from patient and clinician groups that provided input on the proposed project scope. However, the panel was unable to issue implementation advice on this subject since pembrolizumab therapy for a treatment-experienced mCRC population was not reviewed through the CADTH Reimbursement Review process and is therefore outside the scope of this project. The panel indicated that, pursuant to CADTH procedures, a distinct submission for pembrolizumab monotherapy in the second or subsequent line setting would be required to inform funding.

Additionally, the panel clarified that the scope of this implementation advice would not cover patients who were candidates for surgical intervention with curative intent and who received induction chemotherapy for tumour debulking. Such induction treatment is not part of the provisional funding algorithm for mCRC and should not impact eligibility to first-line therapies outlined in this report.

No Relevant Genetic Marker

For patients with mCRC harbouring no abnormal genetic biomarkers (i.e., wild-type *RAS*, wild-type *BRAF*, proficient MMR), the panel consensus was that multi-agent chemotherapy regimens (i.e., FOLFIRI, FOLFOX, or FOLFIXIRI) with or without bevacizumab would be the standard of care. In cases of intolerance or contraindication to the latter, an EGFRi combined with multi-agent chemotherapy could be offered instead. An alternate chemotherapy regimen could be offered in the second line of therapy, with bevacizumab if the latter or another biologic (e.g., EGFRi) has not been received previously in combination with chemotherapy. Third-line therapy for this tumour genetic profile consists of an EGFRi with or without a chemotherapeutic agent if an EGFRi was not part of a previous line of therapy.

RAS Mutation

For patients with mutant *KRAS* or *NRAS* (*RAS*m) mCRC, the panel agreed that any treatment regimen employing an EGFRi is unlikely to provide benefit. Therefore, patients with *RAS*m mCRC should be eligible to receive multi-agent chemotherapy in combination with bevacizumab as first-line therapy. Subsequent lines of therapy consist of alternate chemotherapy regimens. According to the panel, *RAS*m mCRC tumours that are also positive for *BRAF* V600E are highly unlikely.

BRAF V600E Mutation

First-line treatment for patients with *BRAF* V600E–mutated pMMR mCRC would consist of multi-agent chemotherapy with the option of combining with bevacizumab. The panel was aware of robust evidence and rationale that EGFRi combined with chemotherapy would provide limited benefit and should not be used for this tumour profile. Current evidence and

CADTH recommendations support EGFRi with encorafenib treatment in second or later lines of therapy, with the panel agreeing that use in the second line would be preferred.[4] However, the panel also felt patients who had disease progression subsequent to first-line EGFRi plus chemotherapy should have access to subsequent EGFRi plus encorafenib treatment. The panel suggested that this would represent a small and declining prevalent population of patients with *BRAF* V600E mCRC who were not identified as such in the first-line setting but may still respond adequately to this new treatment option despite the lack of evidence.[4] Following treatment with EGFRi plus encorafenib, patients are eligible for treatment with alternative chemotherapies to those received in first-line therapy, with or without bevacizumab (if not received previously).

dMMR/MSI-H

The panel consensus supported pembrolizumab as first-line treatment of dMMR mCRC regardless of any other biomarker status. There was limited evidence to inform sequencing of therapies for patients who experience disease progression following pembrolizumab. Nevertheless, the panel mentioned a strong biological rationale for providing multi-agent chemotherapy in combination with a biologic agent for wild-type *BRAF* dMMR mCRC[5] or EGFRi with encorafenib treatment of *BRAF* V600E–mutated dMMR mCRC.[4] Other previously mentioned sequencing parameters would apply in this setting.

Anticipated Prevalence of Tumour Genotypes (*RAS*, *BRAF*, MMR) and Treatment Sequence Utilization

The panel did not identify evidence on the frequency of mCRC tumour genetic profiles encountered in the Canadian health care setting; however, their experience combined with data from clinical trials provided an estimate of anticipated prevalence.[4-8] Approximately half of mCRC tumours have no relevant mutations in *RAS* or *BRAF* genes and are pMMR. In approximately half of cases of mCRC with genetic biomarker status relevant to the project scope, more than half (> 25% overall) have *RAS*m. These patients are unlikely to benefit from EGFRi therapy. Only a very small percentage of *RAS*m tumours also have a *BRAF* V600E mutation. Approximately 15% of patients with mCRC tumours have a *BRAF* V600E mutation; however, not all patients with these tumours will progress and be suitable candidates for encorafenib in combination with an EGFRi. Approximately 5% of patients with mCRC have tumours with a mismatch repair deficiency and are suitable candidates for first-line pembrolizumab regardless of *RAS* mutational status. According to data from the KEYNOTE-177 trial, approximately 26% of patients with dMMR mCRC also harbour a *BRAF* V600E mutation.[9]

The panel estimated that 70% to 80% of patients with mCRC would be eligible for first-line therapy, with some variation depending on the local population. The patients who would be ineligible for subsequent treatment lines following mCRC disease progression was estimated to be approximately 20% to 25%. Taken together, the implementation of the CADTH Reimbursement Recommendation for the treatment of dMMR mCRC with pembrolizumab will result in first-line pembrolizumab treatment of approximately 5% of all patients with mCRC. The implementation of the CADTH Reimbursement Recommendation for encorafenib will result in second- and third-line treatment of *BRAF* V600E mCRC representing approximately 10% of patients with mCRC. It can then be estimated that less than 2% of patients with mCRC would have both *BRAF* V600E and dMMR and would be eligible to receive encorafenib in combination with an EGFRi following disease progression after first-line pembrolizumab therapy.

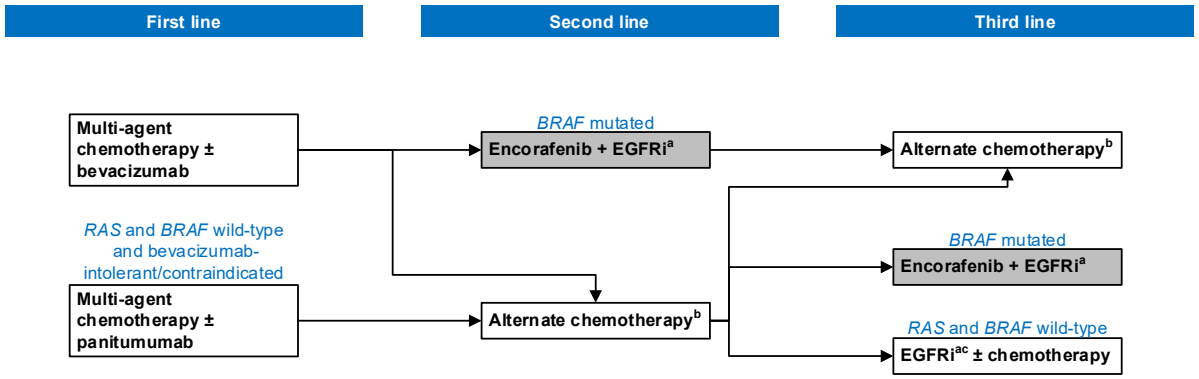
Some patients with mCRC may be eligible for treatment options that include biologic inhibitors of the epidermal growth factor receptor (EGFRi), such as panitumumab or cetuximab, for different tumour genetic biomarkers and lines of treatment. To better anticipate drug utilization patterns, drug programs were interested in knowing EGFRi preferences by clinicians. If given the choice, the panel expressed their preference for panitumumab in the majority of circumstances, including when used in combination with encorafenib for *BRAF* V600E mCRC. Although no evidence was identified that compared EGFRi specifically in combination with encorafenib or in BRAF-mutated cancers, the panel cited evidence for the non-inferiority and unique safety profile of panitumumab as compared to cetuximab, either used as a monotherapy or in combination with irinotecan.[2,3] It was further mentioned that cetuximab has been associated with a higher risk of severe infusion reaction compared with panitumumab. The preference of the panel for panitumumab was also based on their collective experience of comparative safety, stability, and ease of preparation and administration.

Provisional Funding Algorithm

Figure 1 depicts the provisional funding algorithm proposed by the panel. Note that this diagram is a summary representation of the drug funding options for the condition of interest. It is not a treatment algorithm; it is not meant to detail the full clinical management of each patient or the provision of each drug regimen. The diagram may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain jurisdictions. All drugs are subject to explicit funding criteria, which may also vary between jurisdictions. Readers are invited to refer to the individual drug entries on the CADTH website for more details.

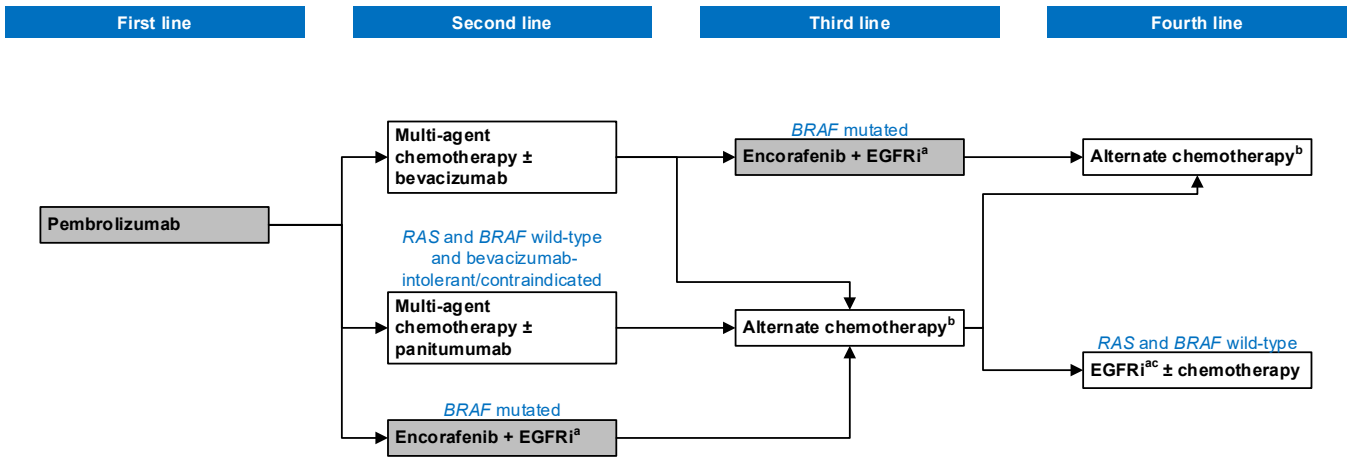
Figure 1: Provisional Funding Algorithm Diagram for mCRC

A. MSI-L/MSS/pMMR



Notes:
[a] EGFRi include cetuximab and panitumumab, where available
[b] Bevacizumab may be available in some provinces in this setting, if not received a biologic combined with chemotherapy in previous lines
[c] If not received EGFRi in previous lines

B. MSI-H/dMMR



Notes:
[a] EGFRi include cetuximab and panitumumab, where available
[b] Bevacizumab may be available in some provinces in this setting, if not received a biologic combined with chemotherapy in previous lines
[c] If not received EGFRi in previous lines

Legend

Therapy funded across most jurisdictions	Therapy under review for funding (pCPA or province/cancer agency)

dMMR = deficient mismatch repair; EGFRi = epidermal growth factor receptor inhibitor; mCRC = metastatic colorectal cancer; MSI-H = high microsatellite instability; MSI-L = low microsatellite instability; MSS = microsatellite stable; pMMR = proficient mismatch repair.

References

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