CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: Metastatic Colorectal Cancer

This report supersedes the CADTH Provisional funding algorithm report for Metastatic Colorectal Cancer dated November 2021.

Please always check CADTH Provisional Funding Algorithms | CADTH to ensure you are reading the most recent algorithm report.

Service Line:	CADTH Reimbursement Review
Version:	Draft
Publication Date:	Date
Report Length:	10 Pages

CADTH

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

Background

Following a request from jurisdictions, CADTH may design or update an algorithm depicting the sequence of funded treatments for a particular tumour type. These algorithms are proposals for the jurisdictions to implement and adapt to the local context. As such, they are termed "provisional." Publishing of provisional algorithms is meant to improve transparency of the oncology drug funding process and promote consistency across jurisdictions.

Provisional funding algorithms are based on 3 principal sources of information:

- CADTH pCODR Expert Review Committee (pERC) reimbursement recommendations and/or implementation guidance regarding drug place in therapy and sequencing
- implementation advice from panels of clinicians convened by CADTH concerning sequencing of drugs in the therapeutic space of interest
- existing oncology drug reimbursement criteria and legacy funding algorithms adopted by jurisdictional drug plans and cancer agencies.

Note that provisional funding algorithms are not treatment algorithms; they are neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagrams 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 cited sources of information on the CADTH website for more details.

Provisional funding algorithms also delineate treatment sequences available to patients who were never treated for the condition of interest (i.e., incident population). Time-limited funding of new options for previously or currently treated patients (i.e., prevalent population) is not detailed in the algorithm.

Provisional funding algorithms may contain drugs that are under consideration for funding. Algorithms will not be dynamically updated by CADTH following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a CADTH provisional funding algorithm on Metastatic Colorectal Cancer, no outstanding implementation issues were identified, and no additional implementation advice is provided in this report. The algorithm depicted herein is meant to reflect the current and anticipated funding landscape based on the previously mentioned sources of information.

History and Development of the Provisional Funding Algorithm

In the November 2021 panel algorithm, CADTH developed the first provisional funding algorithm for metastatic colorectal cancer (mCRC), incorporating recommendations for the following, which can be found in Table 1:

- pembrolizumab (Keytruda)
- encorafenib (Braftovi) in combination with cetuximab (Erbitux)
- panitumumab (Vectibix)

The first algorithm for mCRC addressed the following implementation issues, which have been summarised in Table 2:

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

In March 2024, jurisdictional cancer drug programs have requested an update to this algorithm report to incorporate the latest CADTH recommendations for:

- trifluridine-tipiracil (Lonsurf) in combination with bevacizumab, for the treatment of adult patients with mCRC who have previously been treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if RAS wild-type, anti-EGFR agents, and
- panitumumab in combination with chemotherapy for the treatment of previously untreated patients with non-mutated (wild-type) RAS mCRC.

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Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and Guidance on Treatment Sequencing
Panitumumab (Vectibix)	March 2024	The CADTH Formulary Management Expert Committee (FMEC) recommends that panitumumab, in combination with chemotherapy, be reimbursed for patients with wild-type RAS left-sided metastatic colorectal cancer, only if the following conditions are met: 1. Panitumumab, in combination with chemotherapy, should be reimbursed for the first-line treatment in adult patients with: 1.1. previously untreated mCRC that is left-sided and RAS wild-type; and 1.2. good performance status (ECOG 0-1); and 1.3. no active brain metastases. 2. Panitumumab, in combination with chemotherapy, should be continued until: 2.1. evidence of progression of disease; or 2.2. patient intolerance; or 2.3. withdrawal of consent. 3. Panitumumab, in combination with chemotherapy, must be initiated by a clinician with expertise in the treatment of mCRC. 4. A price reduction is required. FMEC highlighted the importance of timely testing that must be done for KRAS/NRAS/BRAF, with RAS status known, in order to access treatment with panitumumab. Reimbursement of panitumumab should also be limited to patients who have BRAF wild-type disease.
Trifluridine-tipiracil	March 2024	The CADTH pCODR Expert Review Committee (pERC) recommends that

(Lonsurf)		trifluridine-tipiracil in combination with bevacizumab be reimbursed for the treatment of metastatic colorectal cancer (mCRC) in adults who have been previously treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-vascular endothelial growth factor (anti-VEGF) biological agents, and, if rat sarcoma virus (RAS) wild-type, anti-epidermal growth factor receptor (anti-EGFR) agents, only if the following conditions are met: 1. Adult patients with all of the following 1.1. histologically confirmed adenocarcinoma with either unresectable or metastatic disease 1.2. disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer. 1.2.1. Prior treatment must include fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody and/or an anti-EGFR monoclonal antibody for RAS wild type. 1.2.2. Patients who had received adjuvant/neoadjuvant chemotherapy and had recurrence during or within 6 months of completion could count the adjuvant/neoadjuvant therapy as one of the maximum of 2 required prior chemotherapy regimens to qualify. 2. Patients should have good performance status. 3. Treatment with trifluridine-tipiracil, in combination with bevacizumab, should not be reimbursed in patients with either of the following: 3.1. symptomatic central nervous system metastases that are neurologically unstable, 3.2. those requiring increasing doses of steroids to control CNS disease. 4. Treatment with trifluridine-tipiracil, in combination with bevacizumab, should be discontinued upon the occurrence of any of the following: 4.1. Disease progression (clinical or radiological) 4.2. Intolerable toxicity 5. The trifluridine-tipiracil and bevacizumab regimen should only be prescribed by a clinician with expertise in the diagnosis and management of patients with mCRC. 6. Trifluridine-tipiracil, in combination with bevacizumab, should not be used with other systemic therapy. 7. A reduction in price. 8. The feasibility of adoption of trifluridine-tipiracil, in combination with bevacizumab, must be addressed. Guidance on sequencing: • pERC acknowledged the need for a new treatment option for patients with mCRC who experience disease progression after second-line therapy. pERC noted that currently available treatment options are limited for this patient population and that these therapies have limited efficacy with considerable toxicity. Based on the evidence reviewed, trifluridine-tipiracil, in combination with bevacizumab fills a current treatment gap. • The clinical experts consulted by CADTH reported that patients with advanced metastatic colorectal have limited treatment options after they have exhausted all prior lines of therapy. For patients who currently have access to trifluridine-tipiracil (alone) or regorafenib, the clinical experts consulted by CADTH remarked that trifluridine-tipiracil in combination with bevacizumab may replace either drug, as the last line of therapy. The clinical experts consulted by CADTH agreed with the sponsor's proposed place in therapy for trifluridine-tipiracil in combination with bevacizumab to replace best supportive care as a

		new treatment option. • pERC agreed with the clinical experts that if trifluridine-tipiracil in combination with bevacizumab were to be reimbursed, it would replace trifluridine-tipiracil as well as regorafenib, which would remain available privately. • pERC acknowledged that clinicians and patients may want access to trifluridine-tipiracil in combination with bevacizumab for use in the third line setting and beyond.
Pembrolizumab (Keytruda)	July 27, 2021	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 and patients should have good performance status at the start of treatment with pembrolizumab.
Encorafenib (Braftovi) in combination with Cetuximab (Erbitux)	July 26, 2021	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, have good performance status, and have adequate organ function. Encorafenib should not be reimbursed in patients who have had previous treatment with epidermal growth factor (EGFR) inhibitors or BRAF inhibitors.
Panitumumab (Vectibix)	March 29, 2018 December 3, 2015	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.

Table 2: CADTH Implementation Advice Panels on Metastatic Colorectal Cancer

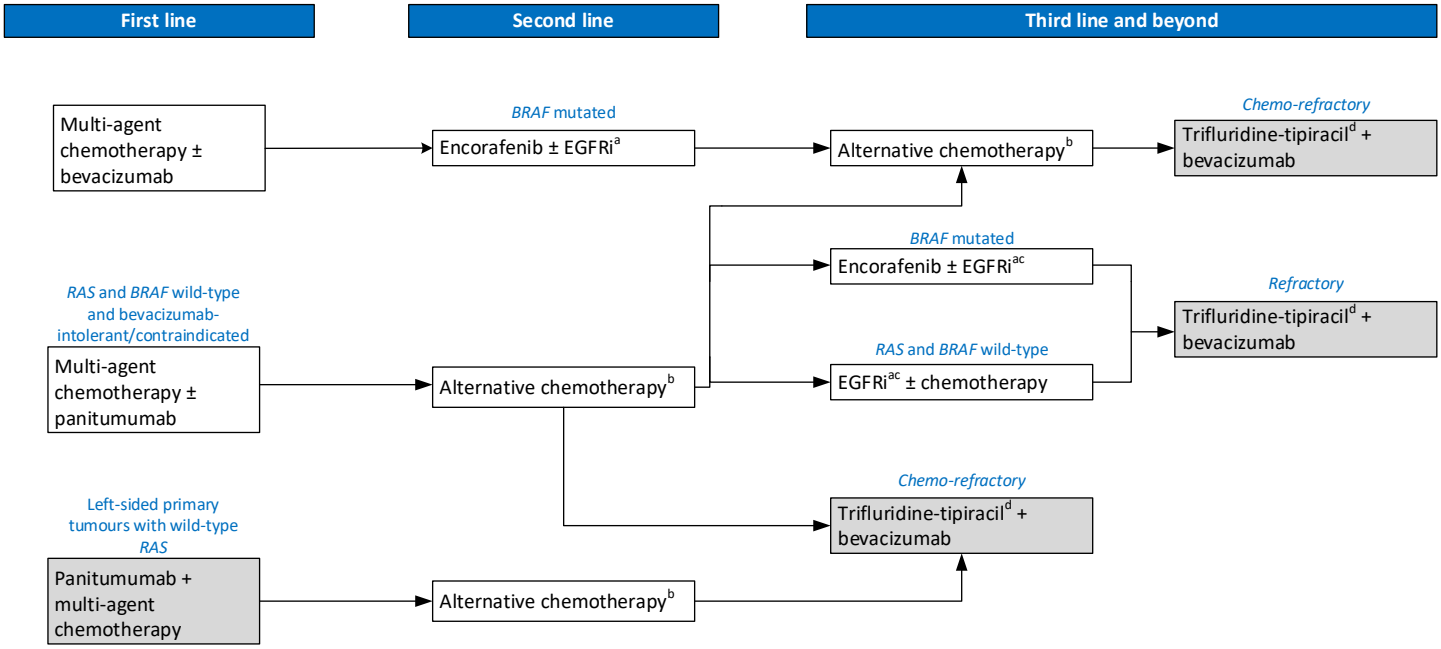
Date of publication	Implementation Advice
November 2021	**Identification of treatment sequences for mCRC based on tumour genetic biomarkers (*RAS, BRAF, MMR*)** The panel advises that patients with mCRC receive the following treatment sequences based on the indicated tumour genetic biomarkers: • ***RAS*-mutated 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.
November 2021	**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.

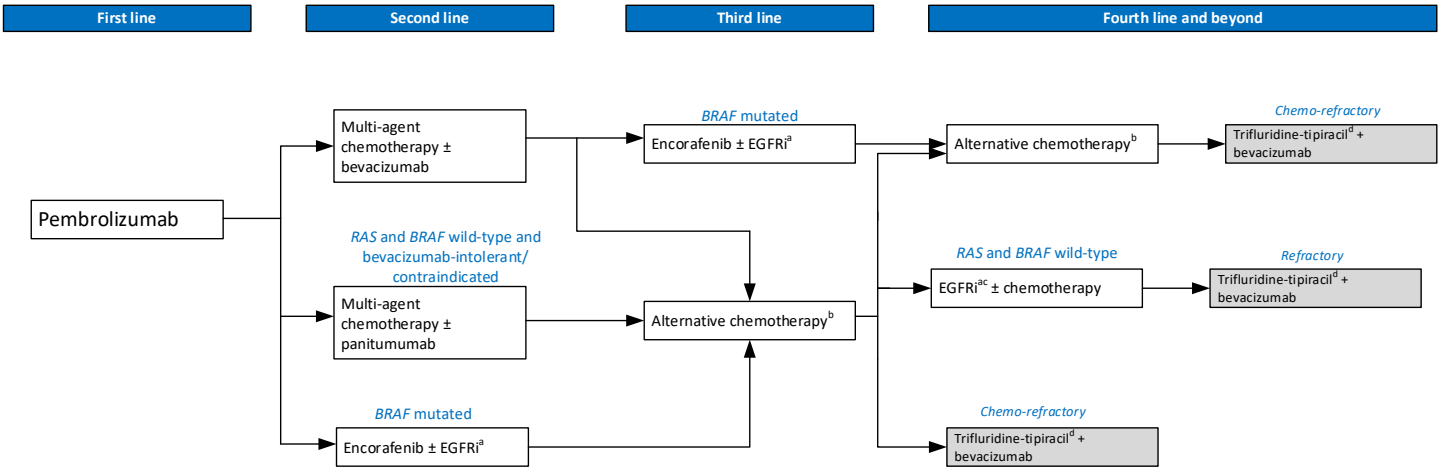
Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for mCRC (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
[d] Trifluridine-tipiracil in combination with bevacizumab is for chemo-refractory patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VGEF biological agents, and, if RAS wild-type, anti-EGFR agents and have disease progression or demonstrated intolerance to a **maximum of 2 prior chemotherapy regimens** for the treatment of advanced colorectal cancer .

Figure 2: Provisional Funding Algorithm Diagram for mCRC (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
[d] Trifluridine-tipiracil in combination with bevacizumab is for chemo-refractory patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VGEF biological agents, and, if RAS wild-type, anti-EGFR agents and have disease progression or demonstrated intolerance to a **maximum of 2 prior chemotherapy regimens** for the treatment of advanced colorectal cancer.

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.

Description of the Provisional Funding Algorithm

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

In November 2021, a panel discussed treatment sequences for metastatic colorectal cancer (mCRC) based on genetic biomarkers. Emphasizing the importance of early intervention, the panel considered RAS, BRAF, and MMR genetic biomarkers as crucial predictors of treatment efficacy, necessitating timely assessment. Concerns were raised regarding pre-treated patients with dMMR mCRC previously treated with chemotherapy for mCRC but who have not yet received immunotherapy, highlighting the need for access to pembrolizumab due to an unmet therapeutic need. Additionally, the panel clarified that the implementation advice scope explicitly excluded patients eligible for surgical intervention with curative intent who underwent induction chemotherapy, ensuring it did not impact eligibility for the outlined first-line therapies.

No Relevant Genetic Marker

For patients with mCRC harbouring no abnormal genetic biomarkers (i.e., wild-type RAS, wild-type BRAF, proficient MMR), 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. Patients with mCRC would be considered eligible for treatment with trifluridine-tipiracil, in combination with bevacizumab, in third-line setting and beyond if they have been previously treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, and anti-vascular endothelial growth factor (anti-VEGF) biological agents and have disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer.

RAS Mutation

For patients with mutant KRAS or NRAS (RASm) mCRC, multi-agent chemotherapy in combination with bevacizumab can be offered as first-line therapy. For adult patients with left-sided RAS wild-type mCRC, panitumumab in combination with chemotherapy can be offered as first-line therapy. Subsequent lines of therapy consist of alternate chemotherapy regimens. Patients are eligible for trifluridine-tipiracil in combination with bevacizumab if they have been previously treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-vascular endothelial growth factor (anti-VEGF) biological agents, and, if RAS wild-type, anti-epidermal growth factor receptor (anti-EGFR) agents **and have** disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer.

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. In subsequent lines of therapy, EGFRi with encorafenib treatment can be offered in the second line but can also be used in later lines of therapy. Patients who had disease progression subsequent to first-line EGFRi plus chemotherapy are also eligible for subsequent EGFRi plus encorafenib treatment. 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). Patients are eligible for trifluridine-tipiracil in combination with bevacizumab if they have been previously treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-vascular endothelial growth factor (anti-VEGF) biological agents, and, if RAS wild-type, anti-

epidermal growth factor receptor (anti-EGFR) agents and have disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer.

MSI-H/dMMR

For adult patients, panel consensus supported pembrolizumab as the 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 or EGFRi with encorafenib treatment of BRAF V600E–mutated dMMR mCRC. Patients are eligible for trifluridine-tipiracil in combination with bevacizumab if they have been previously treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-vascular endothelial growth factor (anti-VEGF) biological agents, and, if RAS wild-type, anti-epidermal growth factor receptor (anti-EGFR) agents and have disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer.