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 Provisional Funding Algorithms to ensure you are reading the most recent algorithm report.

May 2024

Background

Following a request from jurisdictions, we 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:

- pCODR Expert Review Committee (pERC) reimbursement recommendations and/or implementation guidance regarding drug place in therapy and sequencing
- implementation advice from panels of clinicians we convened 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 our 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. We will not be dynamically updating algorithms following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a 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 summarized 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 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–vascular endothelial growth factor (VEGF) biological agents, and, if *RAS* wild-type, anti- epidermal growth factor (EGFR) agents
- panitumumab in combination with chemotherapy for the treatment of previously untreated patients with wild-type *RAS* left-sided mCRC.

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Panitumumab (Vectibix)	April 2024	The CADTH Formulary Management Expert Committee (FMEC) recommends that panitumumab, in combination with chemotherapy, be reimbursed for previously untreated 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 of adult patients with all of the following: 1.1. mCRC that is left-sided and *RAS* wild-type 1.2. good performance status (ECOG 0 to 1) 1.3. no active brain metastases. 2. Panitumumab, in combination with chemotherapy, should be continued until any of the following: 2.1. evidence of progression of disease 2.2. patient intolerance 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, to access treatment with panitumumab. Reimbursement of panitumumab should also be limited to patients who have *BRAF* wild-type disease.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Trifluridine-tipiracil (Lonsurf)	March 2024	The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that trifluridine-tipiracil plus bevacizumab be reimbursed for the treatment of mCRC in adults who have been previously treated with, or are not candidates for, available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if positive for *RAS* wild-type disease, 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 disease. 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: 3.1. with symptomatic CNS metastases that are neurologically unstable, and/or 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 plus bevacizumab regimen should only be prescribed by a clinician with expertise in the diagnosis and management of patients with mCRC. 6. Trifluridine-tipiracil, plus bevacizumab, should not be used with other systemic therapy. 7. A reduction in price. 8. The feasibility of adoption of trifluridine-tipiracil, plus bevacizumab, must be addressed. Guidance on sequencing: • For condition 1.2, pERC acknowledged that clinicians and patients may want access to trifluridine-tipiracil plus bevacizumab for use in the third-line setting and beyond.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		• For condition 1.2.1, patients would be eligible for trifluridine-tipiracil plus bevacizumab regardless of prior bevacizumab exposure. • The clinical experts consulted by CADTH anticipated that trifluridine-tipiracil plus bevacizumab would be used in patients with small bowel or appendiceal adenocarcinoma based on extrapolation of findings from the SUNLIGHT trial, as they represent a very small number of patients, and therefore precludes a randomized trial exclusively in this subpopulation. The clinical experts consulted by CADTH commented that the ECOG is subjective, and for patients who have exhausted all previous lines of therapy and are highly motivated, their oncologist would likely advocate for them to access trifluridine-tipiracil plus bevacizumab, as long as they are otherwise eligible (e.g., criteria for laboratory assessments are met). For patients with MSI-H/dMMR or with *BRAF* V600E mutation, the clinical experts reiterated that they would be considered eligible for treatment with trifluridine-tipiracil plus bevacizumab if all other lines of therapy have been exhausted. In the SUNLIGHT enrolled population (N = 492), there were 21 (6.8%) patients with MSI-H/dMMR and 19 (5.6%) patients with a *BRAF* mutation. • pERC agreed with the clinical experts that patients with small bowel or appendiceal adenocarcinoma, ECOG PS > 1, MSI-H/dMMR, and *BRAF* V600E mutation would be considered eligible for treatment with trifluridine-tipiracil plus bevacizumab if all other lines of therapy have been exhausted. • 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 plus 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 plus bevacizumab to replace BSC as a new treatment option. • pERC agreed with the clinical experts that if trifluridine-tipiracil plus 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 plus bevacizumab for use in the third-line setting and beyond. • pERC agreed with the clinical experts that trifluridine-tipiracil alone (without bevacizumab) could be continued in patients who develop contraindication to bevacizumab. pERC would not recommend using bevacizumab alone if trifluridine-tipiracil is discontinued.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
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	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.
Panitumumab (Vectibix)	December 3, 2015	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.

CNS = central nervous system; dMMR = deficient mismatch repair; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor; FMEC = Formulary Management Expert Committee; mCRC = metastatic colorectal cancer; MSI-H = metastatic microsatellite instability-high; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; VEGF = vascular endothelial growth factor.

Table 2: CADTH Implementation Advice Panels on Metastatic Colorectal Cancer

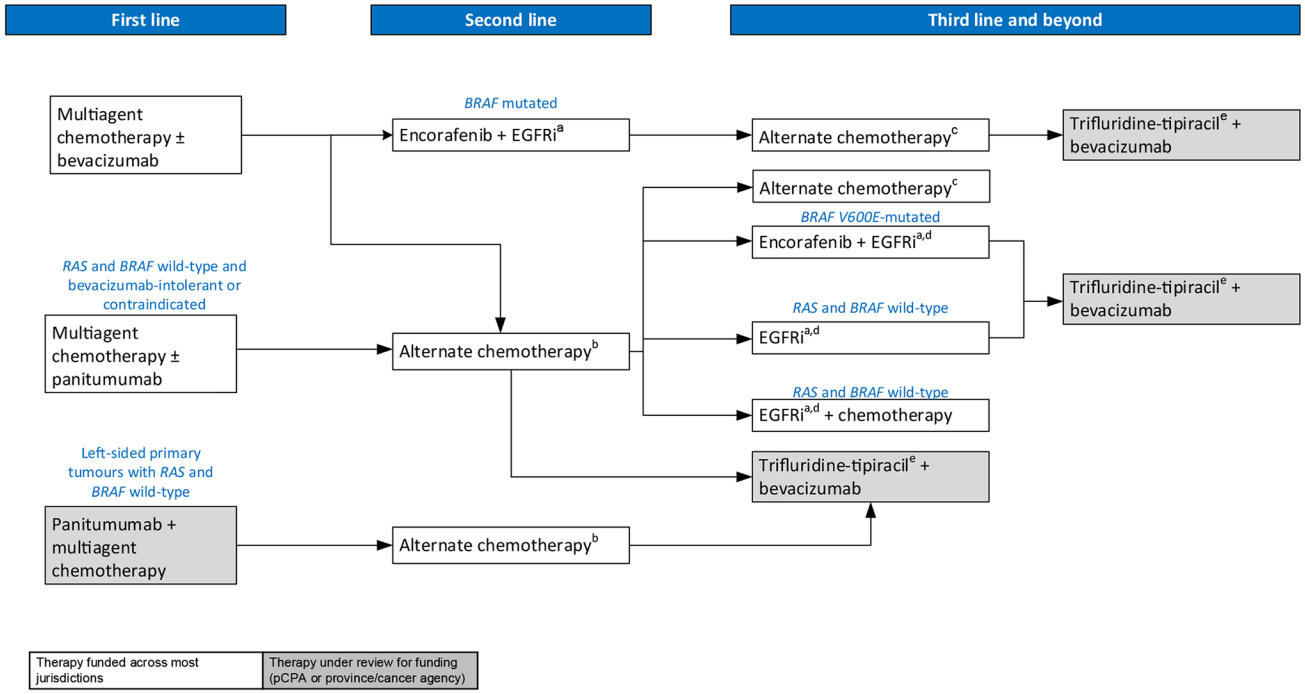
Indication	Date of publication	Implementation advice
Colorectal cancer	November 2021	**Identification of Treatment Sequences for mCRC Based on Tumour Genetic Biomarkers (*RAS, BRAF, MMR*)** The panel advises that patients with mCRC receive the following treatment sequences based on the indicated tumour genetic biomarkers:

Indication	Date of publication	Implementation advice
		• ***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.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for mCRC (MSI-L, MSS, pMMR)



EGFR = epidermal growth factor receptor; EGFRi = epidermal growth factor receptor inhibitor; mCRC = metastatic colorectal cancer; MSI-L = low microsatellite instability; MSS = microsatellite stable; pMMR = proficient mismatch repair; VEGF = vascular endothelial growth factor.

Note: Encorafenib and EGFRi are classified as targeted therapies.

[a] EGFRis include cetuximab and panitumumab, where available.

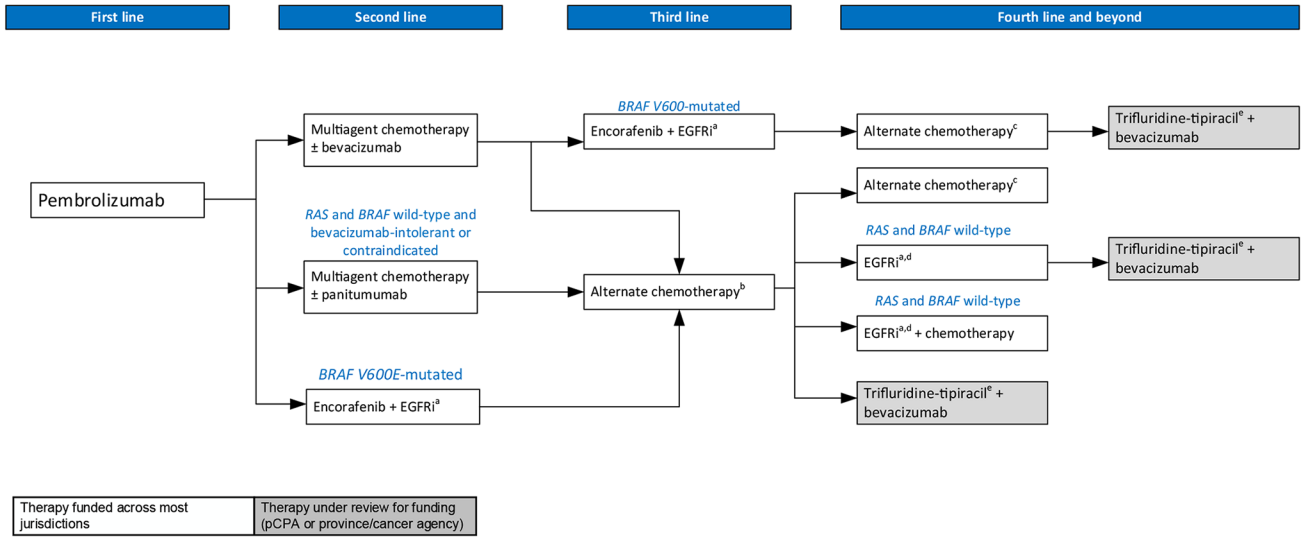
[b] Alternate chemotherapy with or without bevacizumab. Bevacizumab may be available in some provinces in this setting, if the patient did not receive a biologic combined with chemotherapy in previous lines.

[c] Bevacizumab may be available in some provinces in this setting if the patient did not receive a biologic combined with chemotherapy in previous lines.

[d] This would be the option if an EGFRi was not received in previous lines.

[e] Trifluridine-tipiracil in combination with bevacizumab is for patients who are refractory to chemotherapy and have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biologics, and, if they have disease that is *RAS* wild-type, anti-EGFR drugs, and have disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer. Patients who had received adjuvant/neoadjuvant chemotherapy and had recurrence during or within 6 months of completion could count the adjuvant/neoadjuvant therapy as 1 of the maximum of 2 required prior chemotherapy regimens to qualify. Patients with small bowel or appendiceal adenocarcinoma are eligible for treatment with trifluridine-tipiracil in combination with bevacizumab.

Figure 2: Provisional Funding Algorithm Diagram for mCRC (MSI-H, dMMR)



EGFR = epidermal growth factor receptor; EGFRi = epidermal growth factor receptor inhibitor; mCRC = metastatic colorectal cancer; MSI-L = low microsatellite instability; MSS = microsatellite stable; pMMR = proficient mismatch repair; VEGF = vascular endothelial growth factor.

Notes: Pembrolizumab is classified as an immunotherapy. Encorafenib and EGFRis are classified as targeted therapies

[a] EGFRis include cetuximab and panitumumab, where available.

[b] Alternate chemotherapy with or without bevacizumab. Bevacizumab may be available in some provinces in this setting if the patient did not receive a biologic combined with chemotherapy in previous lines.

[c] Bevacizumab may be available in some provinces in this setting if the patient did not receive a biologic combined with chemotherapy in previous lines.

[d] This would be the option if an EGFRi was not received in previous lines.

[e] Trifluridine-tipiracil in combination with bevacizumab is for patients who are refractory to chemotherapy and have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biologics, and, if they have disease that is *RAS* wild-type, anti-EGFR drugs and have disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer. Patients who had received adjuvant/neoadjuvant chemotherapy and had recurrence during or within 6 months of completion could count the adjuvant/neoadjuvant therapy as 1 of the maximum of 2 required prior chemotherapy regimens to qualify. Patients with small bowel or appendiceal adenocarcinoma are eligible for treatment with trifluridine-tipiracil in combination with bevacizumab.

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 mCRC based on genetic biomarkers, including 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 as 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. mCRC biomarker assessment will be required to accurately implement this provisional funding algorithm and provide the evidence-based treatment to patients intended by the panel.

In addition to the timely assessment of mCRC genetic biomarkers, the panel had concerns regarding patients with mismatch repair deficient (dMMR) mCRC who have been pretreated. 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 because of the unmet need for more efficacious and tolerable options for this population, and highlighted that evidence for efficacy of pembrolizumab in patients who have been pretreated is available. According to the panel, this prevalent population of patients with mCRC will decrease over time as patients who have been newly diagnosed are treated with pembrolizumab in the first-line setting. The concern about patients with dMMR mCRC who have been pretreated was also raised from the patient and clinician groups that provided input on the proposed project scope. However, the panel was unable to issue implementation advice on this subject as pembrolizumab therapy for the 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 our procedures, a distinct submission for pembrolizumab monotherapy in the second-line 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 for the first-line therapies outlined in this report.

No Relevant Genetic Marker

The November 2021 panel consensus supported that for patients with mCRC harbouring no abnormal genetic biomarkers (i.e., wild-type *RAS*, wild-type *BRAF*, proficient *MMR*), multidrug chemotherapy regimens (i.e., folinic acid, fluorouracil, and irinotecan [FOLFIRI], folinic acid, fluorouracil, and oxaliplatin [FOLFOX], or folinic acid, fluorouracil, oxaliplatin, and irinotecan [FOLFIXIRI]) with or without bevacizumab can be offered as first-line therapy. In cases of intolerance or contraindication to the latter, an epidermal growth factor receptor inhibitor (EGFRi) combined with multidrug chemotherapy could be offered instead.

An alternate chemotherapy regimen could be offered in the second line of therapy, with bevacizumab if it 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 chemotherapy drug if an EGFRi was not part of a previous line of therapy.

The April 2024 update to the algorithm indicated that patients with mCRC would be considered eligible for treatment with trifluridine-tipiracil in combination with bevacizumab, if they are refractory to chemotherapy and have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biologic drugs, and, if their disease is *RAS* wild-type, anti-EGFR drugs and have disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer. Patients who had received adjuvant/neoadjuvant chemotherapy and had recurrence during or within 6 months of completion could count the adjuvant/neoadjuvant therapy as 1 of the maximum of 2 required prior chemotherapy regimens to qualify. Patients with small bowel or appendiceal adenocarcinoma are eligible for treatment with trifluridine-tipiracil in combination bevacizumab.

RAS Mutation

The November 2021 panel consensus supported multidrug chemotherapy in combination with bevacizumab as first-line therapy for patients with mutant *KRAS* or *NRAS* (*RAS* mutated) mCRC. Subsequent lines of therapy consist of alternate chemotherapy regimens. The April 2024 update to the algorithm indicated that 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-VEGF biologics, and, if their disease is *RAS* wild-type, anti-EGFR drugs and have disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer.

The April 2024 update to the algorithm indicated that in patients with wild-type *RAS* left-sided mCRC, panitumumab in combination with multidrug chemotherapy can be offered as first-line therapy.

The April 2024 update to the algorithm indicated that patients with mCRC would be considered eligible for treatment with trifluridine-tipiracil, in combination with bevacizumab if they are refractory to chemotherapy and have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biologic drugs, and, if their disease is *RAS* wild-type, anti-EGFR drugs and have disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer. Patients who had received adjuvant/neoadjuvant chemotherapy and had recurrence during or within 6 months of completion could count the adjuvant/neoadjuvant therapy as 1 of the maximum of 2 required prior chemotherapy regimens to qualify. Patients with small bowel or appendiceal adenocarcinoma are eligible for treatment with trifluridine-tipiracil in combination bevacizumab.

BRAF V600E Mutation

The November 2021 panel consensus supported multidrug chemotherapy with the option of combining with bevacizumab as first-line treatment for patients with *BRAF* V600E–mutated pMMR mCRC. The panel was aware of robust evidence and rationale that an EGFRi combined with chemotherapy would provide limited benefit and should not be used for this tumour profile. Current evidence and CADTH recommendations support an EGFRi with encorafenib in second or later lines of therapy, with the panel agreeing that use in the second line would be preferred. However, the panel also felt patients who had disease progression subsequent to a 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. Following treatment with an 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).

The April 2024 update to the algorithm indicated that patients with mCRC would be considered eligible for treatment with trifluridine-tipiracil in combination with bevacizumab if they are refractory to chemotherapy and have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biologic drugs, and, if their disease is *RAS* wild-type, anti-EGFR drugs and have disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment

of advanced colorectal cancer. Patients who had received adjuvant/neoadjuvant chemotherapy and had recurrence during or within 6 months of completion could count the adjuvant/neoadjuvant therapy as 1 of the maximum of 2 required prior chemotherapy regimens to qualify. Patients with small bowel or appendiceal adenocarcinoma are eligible for treatment with trifluridine-tipiracil in combination bevacizumab.

MSI-H and dMMR

The November 2021 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 biologic rationale for providing multidrug chemotherapy in combination with a biologic drug for wild-type *BRAF* dMMR mCRC or EGFRi with encorafenib treatment for *BRAF* V600E–mutated dMMR mCRC.

The April 2024 update to the algorithm indicated that patients with mCRC would be considered eligible for treatment with trifluridine-tipiracil in combination with bevacizumab if they are refractory to chemotherapy and have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biologic drugs, and, if their disease is *RAS* wild-type, anti-EGFR drugs and have disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer. Patients who had received adjuvant/neoadjuvant chemotherapy and had recurrence during or within 6 months of completion could count the adjuvant/neoadjuvant therapy as 1 of the maximum of 2 required prior chemotherapy regimens to qualify. Patients with small bowel or appendiceal adenocarcinoma are eligible for treatment with trifluridine-tipiracil in combination bevacizumab.

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

The November 2021 panel did not identify evidence on the frequency of mCRC tumour genetic profiles encountered in the health care setting in Canada; however, their experience combined with data from clinical trials provided an estimate of anticipated prevalence. Approximately half of mCRC tumours have no relevant mutations in *RAS* or *BRAF* genes and are proficient mismatch repair (pMMR). In approximately half of cases of mCRC with genetic biomarker status relevant to the project scope, more than half (> 25% overall) have mutated *RAS*. These patients are unlikely to benefit from EGFRi therapy. Only a very small percentage of *RAS-mutated* 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* mutation status. According to data from the KEYNOTE-177 trial, approximately 26% of patients with dMMR mCRC also harbour a *BRAF* V600E mutation.

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-line and third-line treatment of *BRAF* V600E mCRC representing approximately 10% of patients with mCRC. It can then be estimated that fewer 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 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 noninferiority and unique safety profile of panitumumab as compared to cetuximab, either used as a monotherapy or in combination with irinotecan. 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.

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