Provisional Funding Algorithm

Indication: Metastatic Colorectal Cancer

This report supersedes the CDA-AMC provisional funding algorithm report for metastatic colorectal cancer dated May 2024.

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

Background

Following a request from jurisdictions, Canada's Drug Agency (CDA-AMC) 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:

- pan-Canadian Oncology Drug Review 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 CDA-AMC 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 CDA-AMC 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 CDA-AMC following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a CDA-AMC 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, CDA-AMC 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.

An algorithm report published in May 2024 incorporated the latest CDA-AMC 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
- panitumumab in combination with chemotherapy for the treatment of previously untreated patients with wild-type *RAS*, left-sided mCRC.

In November 2024, jurisdictional cancer drug programs requested an update to this algorithm report to incorporate the latest CDA-AMC recommendation for fruquintinib for the treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available standard therapies.

Table 1: Relevant CDA-AMC Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Fruquintinib (Fruzaqla)	December 2024	The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that fruquintinib be reimbursed for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with or are not considered candidates for available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti–vascular endothelial growth factor (anti-VEGF) agent, an anti–epidermal growth factor receptor (anti-EGFR) agent (if *RAS* wild-type), and either trifluridine-tipiracil or regorafenib only if the following conditions are met: 1. Fruquintinib should only be reimbursed in adult patients (≥ 18 years) who meet all of the following criteria: 1.1. histologically and/or cytologically confirmed metastatic colorectal adenocarcinoma 1.2. previously been treated with all or not considered candidates for any of the following: 1.2.1. standard fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy 1.2.2. an anti-VEGF therapy, and 1.2.3. an anti-EGFR therapy (if *RAS* wild-type) 1.2.4. trifluridine-tipiracil-based therapy 1.3. MSI-H or dMMR tumours must have been treated with an

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		immune checkpoint inhibitor if eligible. 1.4. *BRAF*-mutant positive tumours must have been treated with a *BRAF* inhibitor if eligible. 2. Patients should have good performance status. 3. Treatment with fruquintinib should not be reimbursed in patients with 1 or both of the following: 3.1. symptomatic CNS metastases that are neurologically unstable 3.2. requires increasing doses of steroids to control CNS disease. 4. Treatment with fruquintinib should be discontinued upon the occurrence of any of the following: 4.1. disease progression (clinical or radiological) 4.2. intolerable toxicity. 5. Treatment with fruquintinib should be prescribed by clinicians with expertise in the diagnosis and management of patients with mCRC. 6. Fruquintinib treatment should not be reimbursed for use in combination with other systemic anticancer drugs. 7. A reduction in price. 8. The feasibility of adoption of fruquintinib must be addressed. Guidance on sequencing: • pERC agreed with the clinical experts that it would be reasonable for patients who previously had disease progression to or are not candidates for trifluridine-tipiracil plus bevacizumab be eligible to receive fruquintinib treatment. • For condition 1.2.1: Patients who had received adjuvant or neoadjuvant chemotherapy and had recurrence during or within 6 months of completion could count the adjuvant or neoadjuvant therapy as 1 of the required prior chemotherapy regimens to qualify. • For condition 1.2.4: ◦ Patients who have missed the window of opportunity to receive trifluridine-tipiracil plus bevacizumab are considered eligible for fruquintinib treatment. ◦ Patients who have been previously treated with or are not considered candidates for regorafenib treatment are considered eligible for fruquintinib treatment. Regorafenib treatment is not widely available in Canada, and thus not specified in the reimbursement condition.
Panitumumab (Vectibix)	March 2024	The 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.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		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.
Trifluridine-tipiracil (Lonsurf)	March 2024	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 1 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

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		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. • 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.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		• 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.
Pembrolizumab (Keytruda)	July 27, 2021	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	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 receptor (EGFR) inhibitors or *BRAF* inhibitors.
Panitumumab (Vectibix)	March 29, 2018	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	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.

BSC = best supportive care; CDA-AMC = Canada's Drug Agency; CNS = central nervous system; dMMR = deficient mismatch repair; ECOG PS = Eastern Cooperative Oncology Group performance status; FMEC = Formulary Management Expert Committee; mCRC = metastatic colorectal cancer; MSI-H = high microsatellite instability; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; WT = wild-type.

Table 2: CDA-AMC Implementation Advice Panels on Metastatic Colorectal Cancer

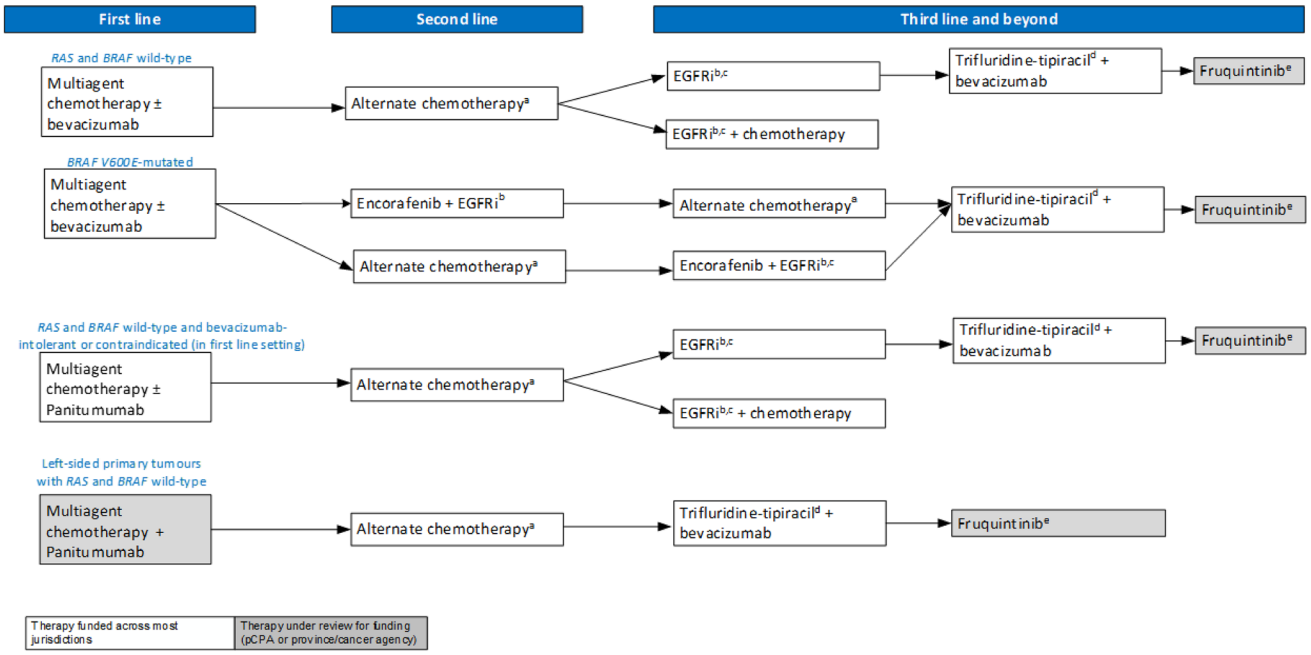
Indication	Date of publication	Implementation advice
Colorectal cancer	November 2021	**Identification of treatment sequences for mCRC based on tumour genetic biomarkers (*RAS, BRAF, MMR*):** The panel advises that patients with mCRC receive the following treatment sequences based on the indicated tumour genetic biomarkers: • ***RAS*-mutated tumours:** Patients should be treated with multiagent 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 multiagent 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

Indication	Date of publication	Implementation advice
		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 multiagent 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.

CDA-AMC = Canada's Drug Agency; dMMR = deficient mismatch repair; EGFRi = EGFR 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)



EGFRi = EGFR inhibitor; mCRC = metastatic colorectal cancer; MSI-L = low microsatellite instability; MSS = microsatellite stable; pMMR = proficient mismatch repair.

Notes: Encorafenib and EGFRis are classified as targeted therapies and are not counted as a chemotherapy regimen. Patients with activating *RAS* mutations would follow the same pathway as *RAS* and *BRAF* wild-type; however, they would not be eligible for an EGFRi.

[a] Bevacizumab may be available in combination with 1 line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy, provided that the patient is bevacizumab naive).

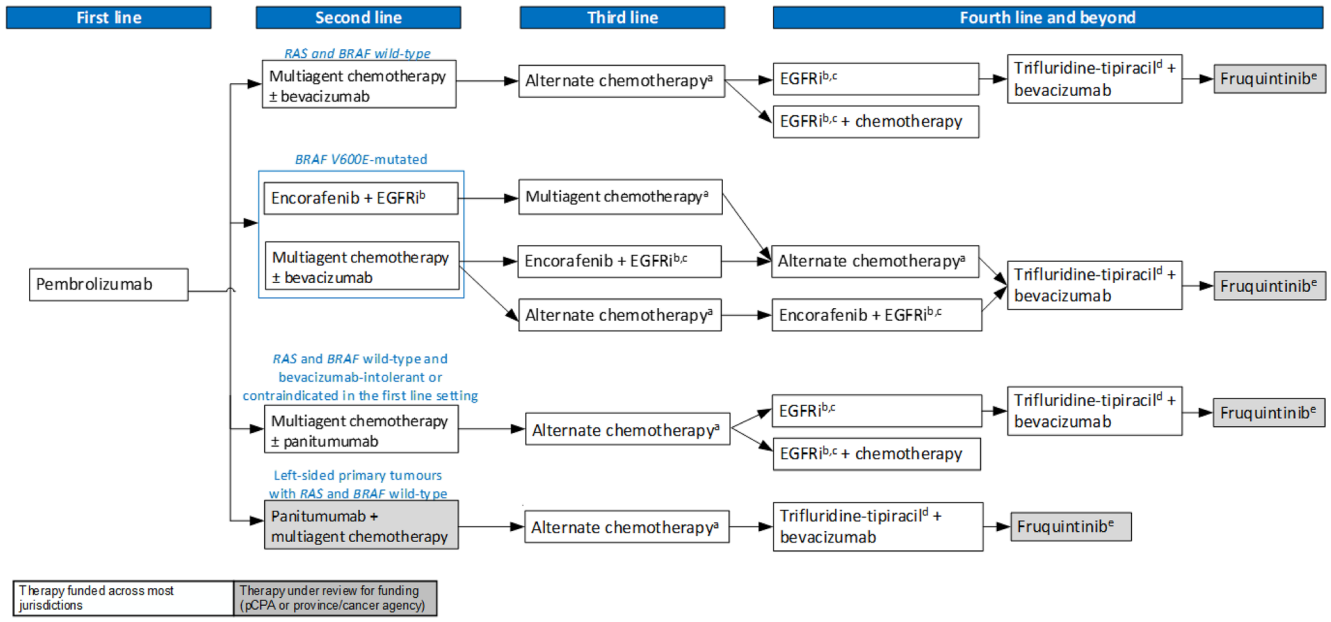
[b] EGFRis include cetuximab and panitumumab, where available.

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

[d] 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 or neoadjuvant chemotherapy and had recurrence during or within 6 months of completion could count the adjuvant or 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.

[e] Fruquintinib should be reimbursed for patients who have been previously treated with or are not considered candidates for available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF agent; an anti-EGFR agent (if *RAS* wild-type); and either trifluridine-tipiracil or regorafenib.

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



dMMR = deficient mismatch repair; EGFRi = EGFR inhibitor; mCRC = metastatic colorectal cancer; MSI-H = high microsatellite instability; MSS = microsatellite stable; pMMR = proficient mismatch repair.

Notes: Pembrolizumab is classified as an immunotherapy. Encorafenib and EGFRis are classified as targeted therapies and not counted as a chemotherapy regimen. Patients with activating *RAS* mutations would follow the same pathway as *RAS* and *BRAF* wild-type; however, they would not be eligible for an EGFRi.

[a] Bevacizumab may be available in combination with 1 line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy, provided that the patient is bevacizumab naive).

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

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

[d] 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 or neoadjuvant chemotherapy and had recurrence during or within 6 months of completion could count the adjuvant or 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.

[e] Fruquintinib should be reimbursed for patients who have been previously treated with or are not considered candidates for available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF agent; an anti-EGFR agent (if *RAS* wild-type); and either trifluridine-tipiracil or regorafenib.

Description of the Provisional Funding Algorithm

Treatment Sequences for mCRC in Patients With Low Microsatellite Instability, Microsatellite Stable, or Proficient Mismatch Repair

Figure 1 depicts the funded options for patients with metastatic colorectal cancer (low microsatellite instability [MSI-L], microsatellite stable [MSS], or proficient mismatch repair [pMMR]).

RAS and *BRAF* Wild-Type

Patients with mCRC with MSI-L, MSS, or pMMR are eligible for first-line treatment with multiagent chemotherapy (e.g., folinic acid, fluorouracil, and irinotecan [FOLFIRI]; folinic acid, fluorouracil, and oxaliplatin [FOLFOX]; or folinic acid, fluorouracil, oxaliplatin, and irinotecan [FOLFOXIRI], with or without bevacizumab).

Following progression, alternate chemotherapy is available as a second-line treatment option. Bevacizumab may be offered in combination with chemotherapy if the patient has not previously received this treatment. EGFRis would be an option in the third-line setting.

In the fourth-line setting, patients may have the option to be treated with trifluridine-tipiracil with bevacizumab. Following treatment with trifluridine-tipiracil with bevacizumab, fruquintinib may be a subsequent treatment option. Fruquintinib is currently under review for funding.

BRAF V600E-mutated

Patients with *BRAF* V600E-mutated mCRC are eligible for first-line treatment with multiagent chemotherapy (e.g., FOLFIRI, FOLFOX, or FOLFIXIRI, with or without bevacizumab). Treatment options in the second-line and third-line settings may depend on when *BRAF* V600E mutations are identified. Patients may be offered encorafenib with an EGFRi (e.g., cetuximab and panitumumab, where available) in the second-line setting, followed by alternate chemotherapy in the third-line setting. Alternatively, second-line treatment may consist of alternate chemotherapy followed by encorafenib with an EGFRi (e.g., cetuximab and panitumumab, where applicable) in the third line. Upon further progression, trifluridine-tipiracil with bevacizumab is available as a subsequent treatment option. Following treatment with trifluridine-tipiracil with bevacizumab, fruquintinib may be an option. Fruquintinib is currently under review for funding.

RAS and *BRAF* Wild-Type and Intolerance or Contraindication to Bevacizumab (in First-Line Setting)

For patients with *RAS* and *BRAF* wild-type disease who are intolerant or contraindicated to bevacizumab, first-line treatment options include multiagent chemotherapy with or without panitumumab. For these patients, the second-line treatment option is alternate chemotherapy. Bevacizumab may be available in combination with chemotherapy with 1 line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy provided the patient is bevacizumab naive) if they are no longer intolerant or contraindicated to bevacizumab.

Following this second-line treatment option, third-line options include EGFRis with or without chemotherapy. An EGFRi would be the option in the third-line setting if an EGFRi (e.g., panitumumab) was not received in previous lines. For patients who have received third-line treatment with encorafenib with an EGFRi, or an EGFRi alone, there is the option to be treated with trifluridine-tipiracil with bevacizumab upon disease progression. Following treatment with trifluridine-tipiracil with bevacizumab, fruquintinib may be a subsequent treatment option. Fruquintinib is currently under review for funding.

Left-Sided Primary Tumours, *RAS* and *BRAF* Wild-Type

In patients with wild-type *RAS,* left-sided mCRC, panitumumab in combination with multidrug chemotherapy can be offered as a first-line therapy option. Following this first-line option, second-line treatment options may include alternate chemotherapy. Bevacizumab may be available in combination with chemotherapy with 1 line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy, provided the patient is bevacizumab naive). Upon disease progression, patients may be treated with trifluridine-tipiracil with bevacizumab in the third-line setting. Following treatment with trifluridine-tipiracil

with bevacizumab, fruquintinib may be a subsequent treatment option. Fruquintinib is currently under review for funding.

Note that, in all of these settings, 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 if they have disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer. Patients who received adjuvant or neoadjuvant chemotherapy and had recurrence during or within 6 months of completion could count the adjuvant or 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. Patients with mCRC would be considered eligible for treatment with fruquintinib if they have been previously treated with, or are not considered candidates for, available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF agent; an anti-EGFR agent (if *RAS* wild-type); and either trifluridine-tipiracil or regorafenib.

Treatment Sequences for mCRC in Patients With High Microsatellite Instability and Deficient Mismatch Repair

Figure 2 depicts the funded options for patients with mCRC (high microsatellite instability [MSI-H] or deficient mismatch repair [dMMR]).

In patients with MSI-H and dMMR tumours, the first-line option is pembrolizumab.

RAS and *BRAF* Wild-Type

Following pembrolizumab, patients with MSI-H and dMMR tumours are eligible for second-line treatment with multiagent chemotherapy (e.g., FOLFIRI, FOLFOX, or FOLFOXIRI, with or without bevacizumab).

Following progression, alternate chemotherapy is available as a third-line treatment option. Bevacizumab may be offered in combination with chemotherapy if the patient has not previously received this treatment. EGFRis with or without chemotherapy would be options in the fourth-line setting.

Following an EGFRi, patients may have the option to be treated with trifluridine-tipiracil with bevacizumab. Following treatment with trifluridine-tipiracil with bevacizumab, fruquintinib may be a subsequent treatment option. Fruquintinib is currently under review for funding.

BRAF V600E-Mutated

Patients with *BRAF* V600E-mutated mCRC are eligible for second-line treatment with multiagent chemotherapy (e.g., FOLFIRI, FOLFOX, or FOLFIXIRI, with or without bevacizumab). Patients may be offered encorafenib with an EGFRi (e.g., cetuximab and panitumumab, where available) or alternate chemotherapy in the third-line and fourth-line settings. Alternatively, the second-line option may consist of encorafenib with an EGFRi (e.g., cetuximab and panitumumab, where applicable) followed by multiagent chemotherapy in the third line. Upon further progression, trifluridine-tipiracil with bevacizumab is available as

a subsequent treatment option. Following treatment with trifluridine-tipiracil with bevacizumab, fruquintinib may be an option. Fruquintinib is currently under review for funding.

RAS and *BRAF* Wild-Type and Intolerance or Contraindication to Bevacizumab (in First-Line Setting)

For patients with *RAS* and *BRAF* wild-type disease who are intolerant or contraindicated to bevacizumab, second-line treatment options include multiagent chemotherapy with or without panitumumab. For these patients, the third-line treatment option is alternate chemotherapy. Bevacizumab may be available in combination with chemotherapy with 1 line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy, provided that the patient is bevacizumab naive) if they are no longer intolerant or contraindicated to bevacizumab.

Following this third-line treatment option, fourth-line options include EGFRis with or without chemotherapy. An EGFRi would be the option in the fourth-line setting if an EGFRi (e.g., panitumumab) was not received in previous lines. For patients who have received fourth-line treatment with an EGFRi alone, there is the option to be treated with trifluridine-tipiracil with bevacizumab upon disease progression. Following treatment with trifluridine-tipiracil with bevacizumab, fruquintinib may be a subsequent treatment option. Fruquintinib is currently under review for funding.

Left-Sided Primary Tumours, *RAS* and *BRAF* Wild-Type

In patients with wild-type *RAS,* left-sided mCRC, panitumumab in combination with multidrug chemotherapy can be offered as second-line therapy. Following this second-line option, third-line therapy may include alternate chemotherapy. Bevacizumab may be available in combination with chemotherapy with 1 line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy, provided that the patient is bevacizumab naive). Upon disease progression, patients may be treated with trifluridine-tipiracil with bevacizumab in the fourth-line setting. Following treatment with trifluridine-tipiracil with bevacizumab, fruquintinib may be a subsequent treatment option. Fruquintinib is currently under review for funding.

Note that, in all of these settings, 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 if they 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 or neoadjuvant chemotherapy and had recurrence during or within 6 months of completion could count the adjuvant or 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. Patients with mCRC would be considered eligible for treatment with fruquintinib if they have been previously treated with or are not considered candidates for available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF agent; an anti-EGFR agent (if *RAS* wild-type); and either trifluridine-tipiracil or regorafenib.

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Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.