CDA-AMC Reimbursement Review

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.

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CADTH

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.

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 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.

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, and
- 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 metastatic colorectal cancer (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 tumors must have been treated with an immune checkpoint inhibitor if eligible. 1.4. BRAF-mutant positive tumors 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 a widely-available in Canada, and thus, not specified in the reimbursement condition.
Panitumumab (Vectibix)	March 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, in order 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	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. • 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.
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.

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

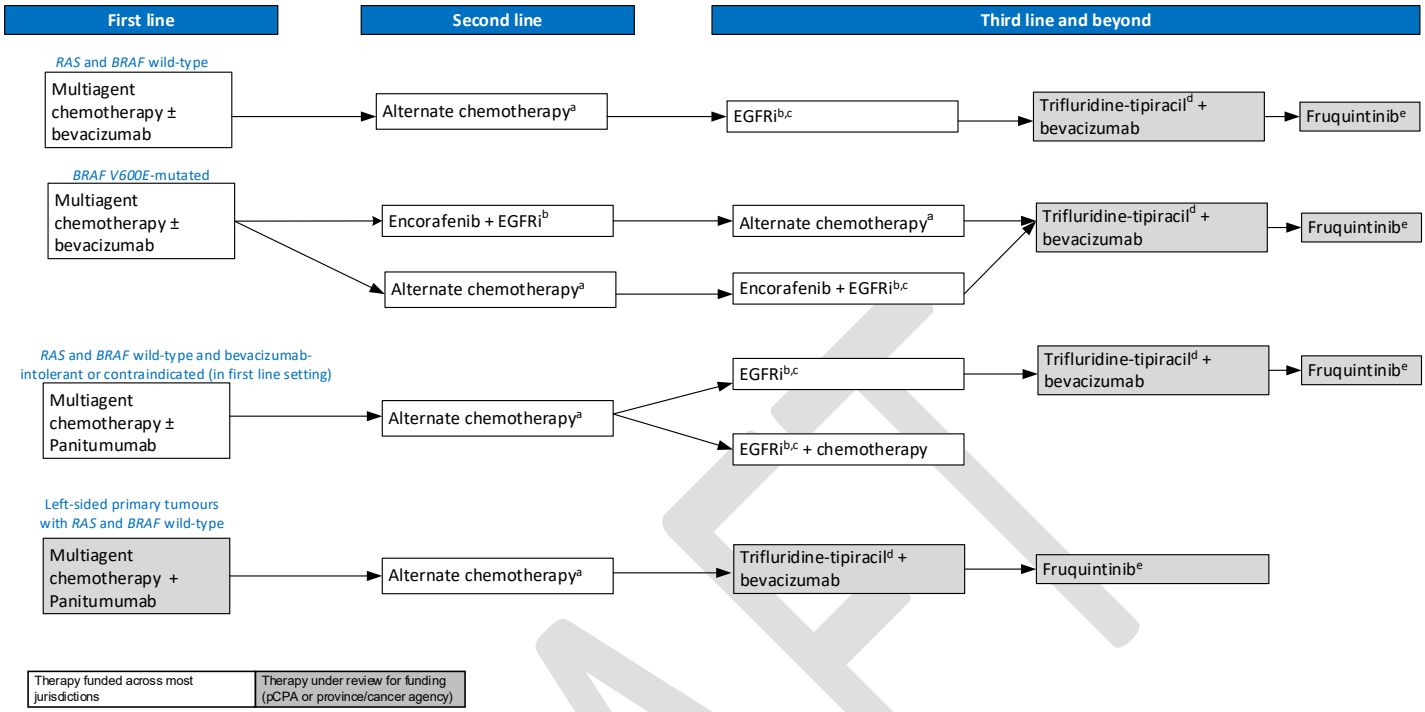
Indication	Date of publication	Implementation Advice
Colorectal Cancer	November 2021	**Identification of treatment sequences for mCRC based on tumour genetic biomarkers (*RAS, BRAF, MMR*)** The panel advises that patients with mCRC receive the following treatment sequences based on the indicated tumour genetic biomarkers: • ***RAS*-mutated tumours:** Patients should be treated with 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 and are not counted as a chemotherapy regimen.

[a] Bevacizumab may be available in combination with one line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy provided bevacizumab naïve).

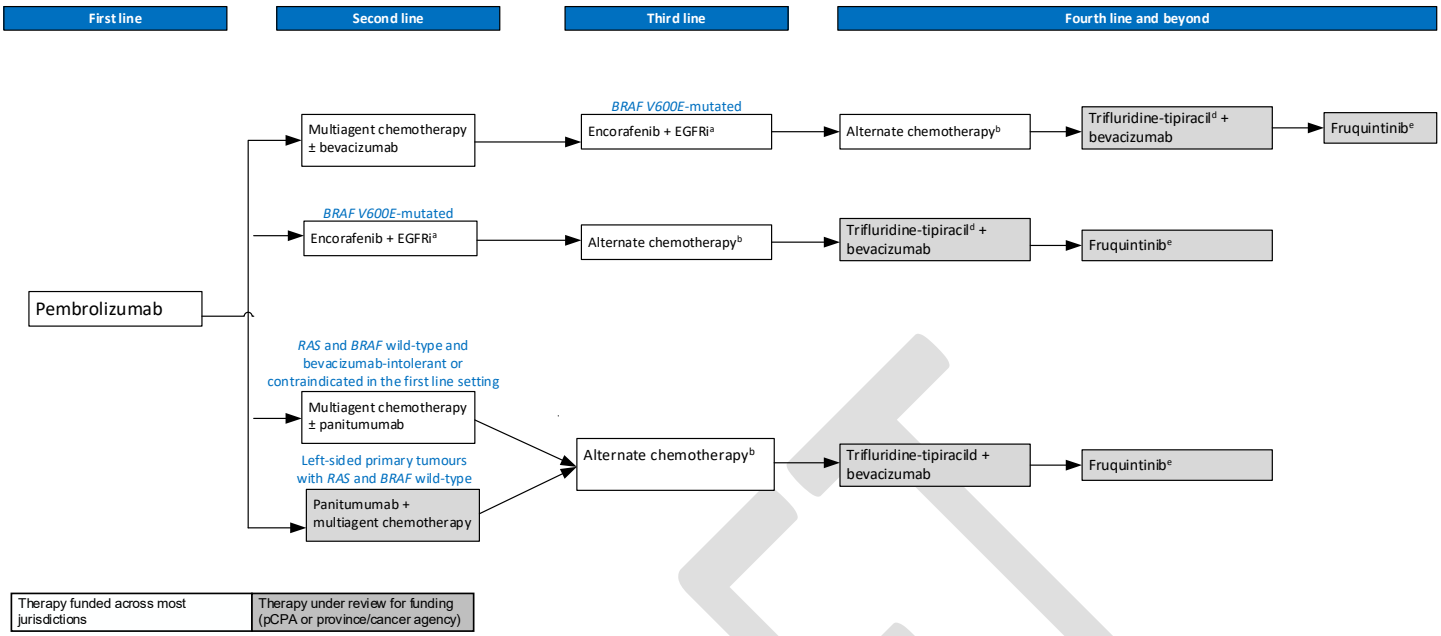
[b] EGFRis include cetuximab and panitumumab, where available.

[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/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.

[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)



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 and not counted as a chemotherapy regimen.
[a] EGFRis include cetuximab and panitumumab, where available.
[b] Bevacizumab may be available in combination with one line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy provided bevacizumab naïve).
[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/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.
[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 MSI-L, MSS, pMMR

(Figure 1)

RAS and BRAF wild-type

For patients with mCRC with MSI-L, MSS, pMMR, they are eligible for first line treatment option with multiagent chemotherapy (e.g., folinic acid, fluorouracil, and irinotecan (FOLFIRI), folinic acid, fluorouracil and oxalipatlin [FOLFOX], or folinic acid, fluorouracil, oxalipatin and irinotecan [FOLFIXIRI] with or without bevacizumab.

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

These patients may have the fourth line 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. Trifluridine-tipiracil with bevacizumab and fruquintinib are currently under review for funding.

BRAF V600E-mutated

For patients with BRAF V600E mCRC, they are eligible for first line treatment option with multiagent chemotherapy (e.g., folinic acid, fluorouracil, and irinotecan (FOLFIRI), folinic acid, fluorouracil and oxalipatlin [FOLFOX], or folinic acid, fluorouracil, oxalipatin and irinotecan [FOLFIXIRI] with or without bevacizumab. The mutations may not be identified in the first-line setting, they may be offered encorafenib with EGFRi (e.g., cetuximab and panitumumab, where available) in second-line setting, followed by alternate chemotherapy in third-line setting. Alternatively, second-line option may consist of alternate chemotherapy followed by encorafenib with EGFRi (e.g., cetuximab and panitumumab, where applicable) in the third line option. 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. Trifluridine-tipiracil with bevacizumab and fruquintinib are currently under review for funding.

RAS and BRAF wild-type and bevacizumab-intolerant or contraindicated (in first line setting)

For patients with RAS and BRAF wild-type mutation as well as intolerant or contraindicated to bevacizumab, their first line treatment option includes multiagent chemotherapy with or without panitumumab. For these patients, their second-line treatment option is alternate chemotherapy. Bevacizumab may be available in combination with chemotherapy with one line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy provided bevacizumab naïve) if they are no longer intolerant or contraindicated to bevacizumab.

Following this second line treatment option, third line options include EGFRi with or without chemotherapy. 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 option with encorfenib with EGFRi or EGFRi alone, they may have 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. Trifluridine-tipiracil with bevacizumab and fruquintinib are currently under review for funding.

Left-sided primary tumours with RAS and BRAF wild-type

In patients with wild-type *RAS* left-sided mCRC, panitumumab in combination with multidrug chemotherapy can be offered as first-line therapy. Following this first line option, second line option may include alternate chemotherapy. Bevacizumab may be available in combination with chemotherapy with one line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy provided bevacizumab naïve). 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. Trifluridine-tipiracil with bevacizumab and fruquintinib are currently under review for funding.

Note that in all 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 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. 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 MSI-H and dMMR

(Figure 2)

In patients with MSI-H and dMMR, their first line option is pembrolizumab. Following pembrolizumab, all patients may receive multiagent chemotherapy with or without bevacizumab in the second-line setting, followed by encorafenib with EGFRi if patients have been found to have BRAF V600E mutation in the third-line setting. EGFRi (e.g., cetuximab or panitumumab, where available) would be an option in the third line setting if an EGFRi (e.g., panitumumab) was not received in previous lines. For these patients, their fourth line and beyond options include alternate chemotherapy followed by trifluridine-tipiracil in combination with bevacizumab and then fruquintinib. Trifluridine-tipiracil with bevacizumab and fruquintinib are currently under review for funding.

Following pembrolizumab, patients with BRAF V600E mutation may receive encorafenib with EGFRi (e.g., cetuximab or panitumumab, where available) in the second-line setting, followed by alternate chemotherapy in the third-line setting. Bevacizumab may be available in combination with chemotherapy with one line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy provided bevacizumab naïve). In the fourth-line and beyond setting, they may be eligible for subsequent treatment with trifluridine-tipiracil in combination with bevacizumab followed by fruquintinib. Trifluridine-tipiracil with bevacizumab and fruquintinib are currently under review for funding.

Following pembrolizumab, patients with RAS and BRAF wild-type and with intolerance or contraindication to bevacizumab may receive multiagent chemotherapy with or without panitumumab in the second line setting. For patients with left-sided primary tumours with RAS and BRAF wild-type, they may receive multiagent chemotherapy with panitumumab. Following these second-line options, alternate chemotherapy may be offered as a third-line option. Bevacizumab may be available in combination one line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy provided bevacizumab naïve). Following progression, these patients may receive trifluridine-tipiracil in combination with bevacizumab followed by fruquintinib in the fourth-line and beyond setting. Trifluridine-tipiracil with bevacizumab and fruquintinib are currently under review for funding.

Note that in all 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 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. 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.