Canada's Drug Agency
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Drugs Health Technologies Health Systems

Provisional Funding Algorithm

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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 (Updated December 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:

- 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 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 by request from jurisdictions.

Jurisdictional cancer drug programs requested a provisional funding algorithm on metastatic colorectal cancer (mCRC); 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, Canadian Agency for Drugs and Technologies in Health (CADTH) developed the first provisional funding algorithm for 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*, and *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 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

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

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.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Bevacizumab (Avastin)	July 21, 2015	In 2015, CADTH issued the following reimbursement recommendation for bevacizumab (Avastin) in combination with a fluoropyrimidine, for the first-line treatment of patients with advanced or metastatic colorectal cancer (CRC): • The pCODR Expert Review Committee (pERC) recommends funding bevacizumab (Avastin) in combination with a fluoropyrimidine, for the first-line treatment of patients with advanced or metastatic colorectal cancer (CRC) for whom combination chemotherapy with oxaliplatin or irinotecan is unsuitable, conditional on cost-effectiveness being improved to an acceptable level.

BSC = best supportive care; CADTH = Canadian Agency for Drugs and Technologies in Health; CNS = central nervous system; dMMR = deficient mismatch repair; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; 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

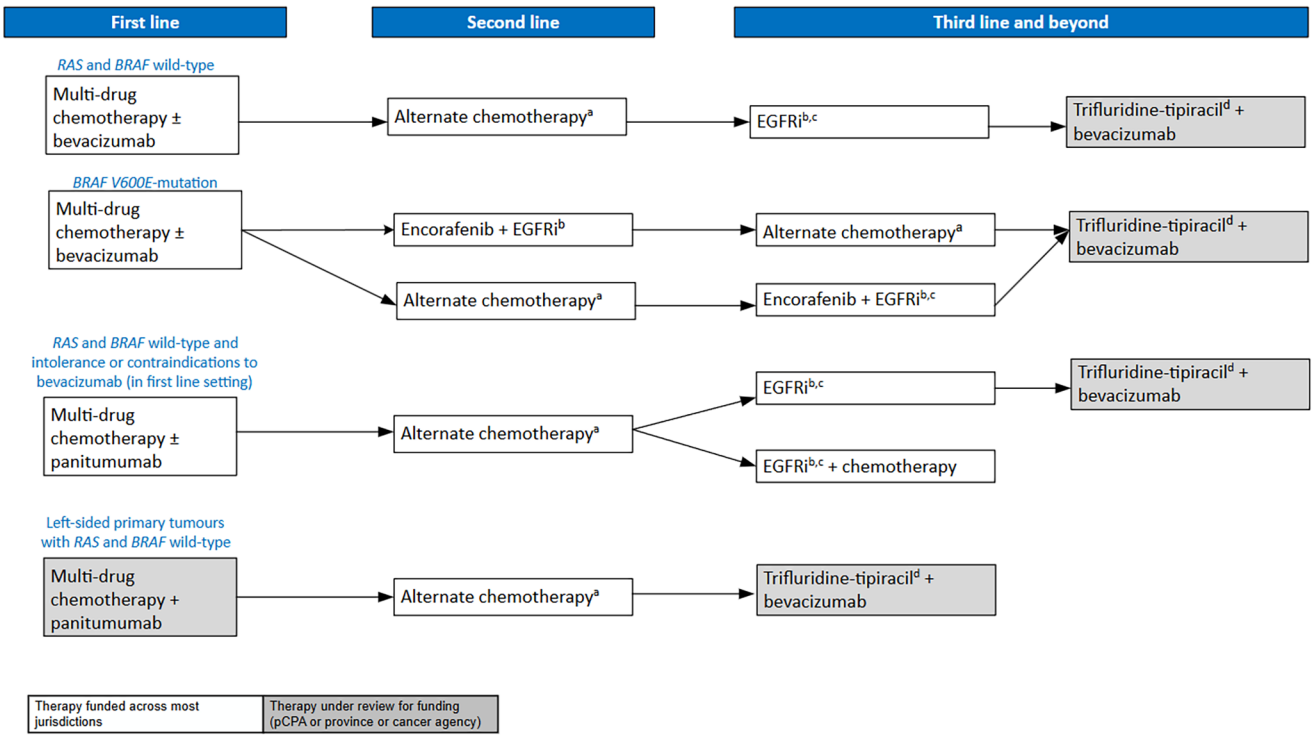
Indication	Date of publication	Implementation advice
Colorectal cancer	November 2021	**Identification of Treatment Sequences for mCRC Based on Tumour Genetic Biomarkers (*RAS, BRAF, MMR*)** The panel advises that patients with mCRC receive the following treatment sequences based on the indicated tumour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

Indication	Date of publication	Implementation advice
		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.

CADTH = Canadian Agency for Drugs and Technologies in Health; 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, and pMMR)



EGFR = epidermal growth factor receptor; EGFRi = epidermal growth factor receptor inhibitor; mCRC = metastatic colorectal cancer; MSI-L = low microsatellite instability; MSS = microsatellite stable; pCPA = pan-Canadian Pharmaceutical Alliance; 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.

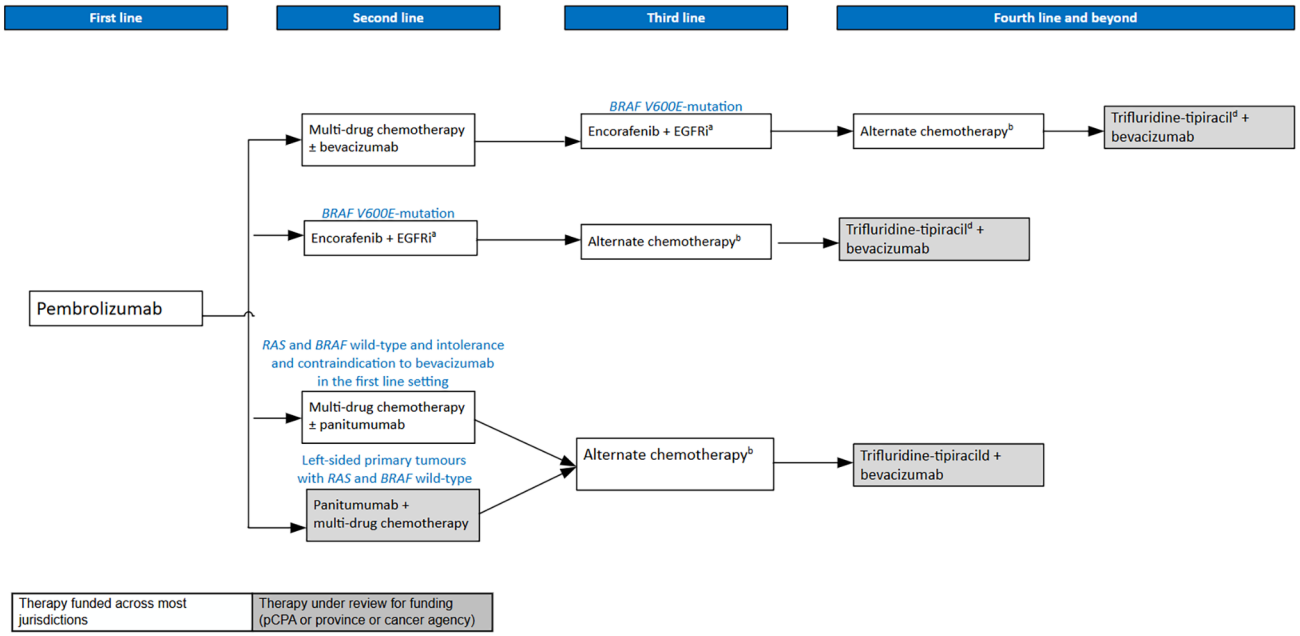
[a]Bevacizumab may be available in combination with 1 line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy provided patients have not received bevacizumab before [e.g., bevacizumab naïve]).

[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 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.

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



dMMR = deficient mismatch repair; EGFR = epidermal growth factor receptor; EGFRi = epidermal growth factor receptor inhibitor; mCRC = metastatic colorectal cancer; MSI-H = high microsatellite instability; MSI-L = low microsatellite instability; MSS = microsatellite stable; pCPA = pan-Canadian Pharmaceutical Alliance; 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 1 line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy provided patients have not received bevacizumab before [e.g., 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 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.

Description of the Provisional Funding Algorithm

Treatment Sequences for mCRC in Patients With MSI-L, MSS, and pMMR (Figure 1)

RAS and BRAF Wild-Type

For patients with mCRC with low microsatellite instability (MSI-L), who are microsatellite stable (MSS), or with proficient mismatch repair (pMMR), they are eligible for a first-line treatment option with multi-drug 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 disease 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. EGFR inhibitors (EGFRis) would be an option in the third-line setting.

Patients may have the fourth-line option to be treated with trifluridine-tipiracil with bevacizumab upon disease progression. Trifluridine-tipiracil with bevacizumab is currently under review for funding.

BRAF V600E Mutation

For patients with BRAF V600E mCRC, they are eligible for a first-line treatment option with multi-drug 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 and patients may be offered encorafenib with EGFRi (e.g., cetuximab and panitumumab, where available) in a second-line setting, followed by alternate chemotherapy in a third-line setting. Alternatively, a 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. With further disease progression, trifluridine-tipiracil with bevacizumab is available as a subsequent treatment option. Trifluridine-tipiracil with bevacizumab 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 mutation as well as intolerance or contraindication to bevacizumab, their first-line treatment option includes multi-drug 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 1 line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy provided patients have not received bevacizumab before [e.g., 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 a 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. Trifluridine-tipiracil with bevacizumab is 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 multi-drug chemotherapy can be offered as a first-line therapy. Following this first-line option, the second-line option 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 patients have not received bevacizumab before [e.g., bevacizumab naïve]). With disease progression, patients may be treated with trifluridine-tipiracil with bevacizumab in the third-line setting. Trifluridine-tipiracil with bevacizumab 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

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. 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 bevacizumab.

Treatment Sequences for mCRC in Patients With MSI-H and dMMR (Figure 2)

In patients with high microsatellite instability (MSI-H) and deficient mismatch repair (dMMR), their first-line option is pembrolizumab. Following pembrolizumab, all patients may receive multi-drug 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. Trifluridine-tipiracil with bevacizumab is 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 1 line of chemotherapy for the treatment of advanced colorectal cancer (indicated for any line of therapy provided patients have not received bevacizumab before [e.g., bevacizumab naïve]). In the third-line setting, they may be eligible for subsequent treatment with trifluridine-tipiracil in combination with bevacizumab. Trifluridine-tipiracil with bevacizumab is currently under review for funding.

Following pembrolizumab, patients with *RAS* and *BRAF* wild-type and with intolerance or contraindication to bevacizumab may receive multi-drug 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 multi-drug chemotherapy with panitumumab. Following these second-line options, alternate chemotherapy may be offered as a third-line option. 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 patients have not received bevacizumab before [e.g., bevacizumab naïve]). Following progression, these patients may receive trifluridine-tipiracil in combination with bevacizumab in the fourth-line setting. Trifluridine-tipiracil with bevacizumab 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 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. 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 bevacizumab.

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