Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Fruzaqla (Fruquintinib)

Indication: For the treatment of adult patients with 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-VEGF agent, an anti-EGFR agent (if RAS wild-type), and either trifluridine-tipiracil or regorafenib

Sponsor: Takeda Canada Inc.

Recommendation: Reimburse with Conditions

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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.

Recommendation

The CADTH pCODR 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 conditions listed in **Error! Reference source not found.** are met.

Rationale for the Recommendation

One phase III, double-blind, randomized controlled trial (FRESCO-2, N = 691) demonstrated that treatment with fruquintinib plus best supportive care (BSC) resulted in statistically significant and clinically meaningful improvements in overall survival (OS) and progression-free survival (PFS), compared with placebo plus BSC in adults patients with mCRC who were previously treated with standard chemotherapy, anti-VEGF agent, an anti-EGFR agent (if RAS wild-type), and had progressed on or been intolerant to treatment with trifluridine-tipiracil or regorafenib. Median OS was 7.4 months (95% confidence interval [CI], 6.7 to 8.2 months) in the fruquintinib plus BSC group and 4.8 months (95% CI, 4.0 to 5.8 months) in the placebo plus BSC group, with a hazard ratio (HR) of 0.66 (95% CI, 0.55 to 0.80; P<0.001). Median PFS was 3.7 months (95% CI, 3.5 to 3.8 months) in the fruquintinib plus BSC group and 1.8 months (95% CI, 1.8 to 1.9 months) in the placebo plus BSC, with a HR of 0.32 (95% CI, 0.27 to 0.39; P<0.001). Fruquintinib plus BSC was associated with a higher frequency of grade 3 or greater side effects (including hand-foot syndrome and hypertension) compared to placebo plus BSC. Nevertheless, pERC considered the safety profile of fruquintinib to be consistent with the known safety of vascular endothelial growth factor receptor inhibitors.

Patients identified a need for accessible and effective treatment options that can be administered orally, prolong survival, improve quality of life, and have fewer side effects. pERC concluded that fruquintinib met some of the needs identified by patients as it offers ease of oral administration, provides improvements in OS and PFS, and has manageable side effects. The evidence suggested that fruquintinib may result in in little or no deterioration in health-related quality of life (HRQoL); however, pERC noted that this was uncertain due to a notable amount of missing data.

Using the sponsor submitted price for fruquintinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for fruquintinib was $325,989 per quality-adjusted life-year (QALY) compared with BSC. At this ICER, fruquintinib is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for adults with metastatic colorectal cancer 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. A price reduction for fruquintinib is therefore required.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
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. Patients with MSI-H or dMMR tumors must have been treated with an immune checkpoint inhibitor if eligible. 1.4. Patients with BRAF-mutant positive tumors must have been treated with a BRAF inhibitor if eligible.	Evidence from the pivotal FRESCO-2 trial showed that treatment with fruquintinib resulted in OS and PFS benefits in patients with these characteristics.	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.
Patients should have good performance status	Patients with an ECOG PS score of 0 or 1 were included in the FRESCO-2 trial.	Patients with an ECOG PS score of greater than 1 may be eligible for fruquintinib treatment at the discretion of the treating physician.
Treatment with fruquintinib should not be reimbursed in patients with untreated CNS metastases.	Patients with untreated CNS metastases were excluded from the FRESCO-2 trial. Therefore, no evidence was reviewed regarding the safety and efficacy of fruquintinib in these patients.	—
Discontinuation		
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	In the FRESCO-2 trial, treatment was discontinued in patients who exhibited disease progression or intolerable toxicity.	—
Prescribing		
Treatment with fruquintinib should be prescribed by clinicians with expertise in the	This is intended to ensure that the treatment is prescribed only for	—

Reimbursement condition	Reason	Implementation guidance
diagnosis and management of patients with mCRC.	appropriate patients and adverse effects are managed in an optimized and timely manner.	
Fruquintinib treatment should not be used in combination with other anticancer drugs.	No evidence was reviewed to demonstrate the safety and potential benefits of combining fruquintinib with any other systemic anticancer therapy.	—
Pricing		
A reduction in price	The ICER for fruquintinib is $325,989 when compared with BSC. A price reduction of approximately 87% would be required for fruquintinib to achieve an ICER of $50,000 per QALY compared to BSC.	—
Feasibility of adoption		
The feasibility of adoption of fruquintinib must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	—

BSC = best supportive care; BRAF = B-raf proto-oncogene; CNS = central nervous system; dMMR = mismatch repair deficient; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; MSI-H = microsatellite instability-high QALY = quality adjusted life year.

Discussion Points

- Aligned with the input from patient and clinicians, pERC acknowledged that there is an unmet need for effective and safe therapy options for patients with mCRC who experience disease progression after third-line therapy. pERC noted that there is currently no approved treatment for these patients. BSC alone is typically offered to provide palliation of symptoms in this patient population, and to maintain or improve patients' quality of life. Based on the evidence reviewed, pERC noted that fruquintinib could address a current treatment gap by improving OS and PFS in the fourth- or later-line setting.

- pERC deliberated on the results of the phase III FRESCO-2 trial that demonstrated statistically significant improvements in OS and PFS with fruquintinib treatment plus BSC compared to placebo plus BSC in the patient population under review. pERC discussed the improvement in median OS (7.4 months in the fruquintinib group versus 4.8 months in the placebo group) was modest but considered it to be clinically meaningful in this population of heavily pre-treated patients.

- Considering that trifluridine-tipiracil was recently recommended by pERC for reimbursement in third or later line of treatment, when used in combination with bevacizumab, the clinical experts consulted for this review anticipated that most patients would receive fruquintinib in the fourth or later lines of treatment subsequent to disease progression on trifluridine-tipiracil plus bevacizumab if this combination therapy becomes publicly funded. In the FRESCO-2 trial, all patients received prior treatment with trifluridine-tipiracil and/or regorafenib (including 52.2% receiving trifluridine-tipiracil alone, and 39.4% receiving both trifluridine-tipiracil and regorafenib). However, the proportion of patients who had previously received trifluridine-tipiracil plus bevacizumab was unknown. pERC noted that this could introduce uncertainty to the generalizability of the study results. Nonetheless, pERC agreed with the clinical experts that patients who have experienced disease progression or demonstrated intolerance to trifluridine-tipiracil in combination bevacizumab would be eligible for fruquintinib treatment. The committee further discussed the eligibility of patients who might have missed the window of opportunity to receive trifluridine-tipiracil plus bevacizumab (e.g., those with more than 2 prior cytotoxic chemotherapy regimens) and agreed that those patients would be eligible to receive fruquintinib treatment.

- pERC discussed the question from the public drug programs regarding the generalizability of the evidence reviewed to patients with small bowel or appendiceal adenocarcinoma. pERC acknowledged that the rarity of small bowel or appendiceal adenocarcinomas may preclude a randomized controlled trial exclusively in this patient population, and agreed with the clinical experts that these patients would be considered eligible for treatment with fruquintinib if all other lines of therapy have been exhausted. pERC further noted that this would be consistent with the reimbursement recommendation for trifluridine-tipiracil plus bevacizumab.

- pERC discussed the health-related quality of life (HRQoL) outcomes from the FRESCO-2 trial, as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) scale. The evidence suggested that fruquintinib plus BSC may result in little to no difference in HRQoL compared with placebo plus BSC; however, it was noted that results were uncertain due to a notable amount of missing data. The committee was unable to draw definitive conclusions on the effect of fruquintinib on HRQoL based on the submitted evidence.

- Caregiver burden was identified as important outcome as per input from patient group and clinical experts. pERC noted that this outcome was not assessed in the submitted trials and the effect of fruquintinib on that is thus unknown. pERC acknowledged that fruquintinib treatment is administered orally, which aligns with patients' preference.

- pERC noted that the sponsor's budget impact analysis was not designed to assess the reimbursement of fruquintinib as a fourth-line therapy, and the assumptions regarding subsequent treatment use in the sponsor's analysis were associated with uncertainty. As a result, CADTH was unable to adequately assess the budget impact of fruquintinib in the fourth-line treatment setting, after trifluridine/tipiracil plus bevacizumab in Canada.

Background

Colorectal cancer refers to malignant tumours that develop in the epithelial lining of the rectum or colon, from polyps that progress into cancer. The 5-year prevalence of CRC in Canada is estimated to be 79,009 (8.3 per 100,000). mCRC results when colorectal cancer cells become invasive and travel to other parts of the body, most commonly the liver, lungs, and bones. The most common symptoms of mCRC include altered bowel habits such as diarrhea or constipation, blood in stool, fatigue, nausea, abdominal pain, loss of appetite, and unintentional weight loss. Prognosis is also typically worse for patients who have progressed on multiple lines of therapy. Clinical trials in patients with mCRC receiving third-line or later treatment reported median OS ranging from 6.4 months to 7.1 months. First-line and second-line treatments for mCRC consist of chemotherapy (including fluoropyrimidine, oxaliplatin, irinotecan) which may be combined with molecular targeted therapies. In patients who have progressed on available chemotherapy, trifluridine-tipiracil and regorafenib have been studied as single agent treatments; their benefits are modest and they are currently not publicly funded in Canada. Trifluridine-tipiracil plus bevacizumab combination therapy is currently under consideration for public funding as a third- or later-line treatment. There is currently no approved treatment for patients with disease that progressed on available standard chemotherapy, and either trifluridine-tipiracil or regorafenib (i.e., fourth- or later-line setting); BSC is available to these patients in clinical practice.

Fruquintinib has been approved by Health Canada for the treatment of adult patients with 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-VEGF agent, an anti-EGFR agent (if RAS wild-type), and either trifluridine-tipiracil or regorafenib. Fruquintinib is a vascular endothelial growth factor receptor inhibitor. It is available as 1 mg and 5 mg oral capsules and the dosage recommended in the product monograph is 5 mg orally once daily for 21 consecutive days, followed by a 7-day rest period to comprise a complete cycle of 28 days. Treatment with Fruquintinib should be continued until disease progression or unacceptable toxicity occurs.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 2 randomized controlled trial (RCT) in adults with mCRC
- patients' perspectives gathered by 2 patient groups, including the Colorectal Cancer Resource & Action Network (CCRAN) and Colorectal Cancer Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from two clinical specialists with expertise diagnosing and treating patients with mCRC
- input from 1 clinician group, the Canadian GI Oncology Evidence Network (CGOEN)
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

CADTH received 2 patient group submissions from Colorectal Cancer Resource & Action Network (CCRAN) and Colorectal Cancer Canada. CCRAN is a national, not-for-profit patient advocacy group championing the health and wellbeing of Canadians touched by colorectal cancer and those at risk of developing the disease, by providing support, education and advocacy to help improve patient outcomes by way of longevity and quality of life. Colorectal Cancer Canada is a not-for-profit colorectal cancer patient organization dedicated to colorectal cancer awareness and education, supporting patients and their caregivers and advocating on their behalf.

CCRAN employed a multi-faceted outreach approach which resulted in 3 patient interviews and a survey of metastatic colorectal cancer patients with 119 respondents from March 21st to April 17th, 2024, 115 patients resided in Canada and the remaining 4 patients were from the US. Data was gathered by Colorectal Cancer Canada via 4 online patient interviews between April 1st and

May 15th, 2024, and 1 online survey with patients in the United States and Canada in August 2023 to which 15 patients and 1 caregiver responded.

Most patients reported that abdominal cramps, gas, bloating, and pain, fatigue, weakness, bloody stools, and diarrhea are common impacts of the disease that affect the quality of life, resulting in inability to work, exercise, participate in social activities, and fulfill family obligations and concentrate. Caregivers also noted significant difficulties caring for patients with mCRC. Fluorouracil-based chemotherapy, capecitabine, bevacizumab and panitumumab were cited to be the most frequently used treatments by the respondents, with the most common side effects being fatigue, hair loss, nausea, peripheral neuropathy, and diarrhea. Both patient groups noted that it is very important for a new therapy to bring about improvement to their physical condition (e.g., tumour shrinkage, tumour stability, reduction of pain and improved breathing), and quality of life. Four respondents from CCRAN's and 3 respondents from Colorectal Cancer Canada's survey had experience with fruquintinib treatment, and the patients' main access to fruquintinib was through clinical trial centre in U.S. Patients reported that fruquintinib treatment helped stabilize their disease and was easy to administer as an oral therapy. Most patients experienced hand-foot syndrome with fruquintinib treatment but noted that it was manageable. Both groups believed that access to fruquintinib for patients in the refractory, mCRC setting is of utmost importance because it could provide these patients with an effective treatment option to stabilize their disease and improve their quality of life (QOL).

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts noted that there is a need for effective mCRC treatments that provide more durable disease control and OS benefit, have fewer adverse effects, and could delay decline in quality of life from the underlying cancer. The clinical experts also noted that comprehensive biomarker profiling and adaptive treatment strategies are required to personalize therapy more effectively. Equitable access to novel treatments remains a key barrier for many patients with mCRC, as per clinical expert input.

The clinical experts expected fruquintinib to be used in patients with mCRC in the fourth- or later-line setting (i.e., have disease refractory to or intolerable toxicity to at least 2 lines of standard chemotherapy [including fluoropyrimidine, irinotecan, and oxaliplatin] and to trifluridine-tipiracil plus bevacizumab).

The clinical experts noted that fruquintinib would be most appropriate for patients with mCRC who have disease that progressed on or intolerable toxicity to all standard approved cytotoxic treatment (fluoropyrimidine, irinotecan, and oxaliplatin), an anti-VEGF, anti-EGFR, as well as trifluridine-tipiracil plus bevacizumab or regorafenib. Patients should also have received prior immune checkpoint inhibitors and BRAF inhibitor targeted therapy, if indicated, as per the clinical experts. The clinical experts noted that patients with ECOG PS score of 0 or 1 are suitable treatment candidates, though patients with a PS score of 2 may be eligible for treatment at the treating physician's discretion. However, for patients with an ECOG PS score of more than 2, the clinical experts felt it was inappropriate to prescribe fruquintinib given the absence of evidence and that the harms would likely outweigh the benefits in these patients. The clinical experts noted that patients with untreated or unstable CNS metastases would not be suitable candidates for fruquintinib treatment.

According to the clinical experts, a clinically meaningful response includes improved survival, significant reduction in the frequency and severity of disease-related symptoms, enhanced ability to perform daily activities, and noticeable improvements in quality of life. The clinical experts noted that patients are generally seen in each cycle (28-days in case of fruquintinib) with blood work and a CT scan of chest, abdomen and pelvis is performed every 2 to 3 cycles (8 to 12 weeks). The clinical experts noted that treatment discontinuation would be considered upon disease progression and/or intolerable toxicity. The clinical experts noted that fruquintinib should be prescribed by an oncologist with expertise in assessing and monitoring of patients with mCRC.

Clinician Group Input

CADTH received 1 clinician group submission from the CGOEN, represented by 16 clinicians across Canada.

In general, CGOEN shared a consistent view on management of mCRC with the clinicians consulted by CADTH. The clinician group stated that the main goals of treatment for mCRC are improvements in overall survival and quality-of-life while minimizing toxicities from treatment. In terms of unmet need, the clinician group noted that there are currently no publicly funded treatment options for

patients with mCRC who have been previously treated with, or are intolerant to, standard chemotherapy. However, with recent a positive reimbursement recommendation for trifluridine-tipiracil in combination with bevacizumab for treatment-refractory colorectal cancer, the clinician group indicated that fruquintinib could be considered in patients who would not be eligible for trifluridine/tipiracil plus bevacizumab or in patients who previously received trifluridine/tipiracil plus bevacizumab, which could provide clinical flexibility required in this specific later-line setting.

Lastly, the clinician group indicated that fruquintinib would be used in patients with mCRC who have been treated with or intolerant of fluoropyrimidine, irinotecan, and oxaliplatin. Furthermore, it would be considered after encorafenib-based therapy in patients with BRAF mutant tumors, immunotherapy in patients with dMMR tumors, anti-EGFR therapies in patients with KRAS wild type tumors, and anti-VEGF therapies as well as patients who have not received previous anti-VEGF therapy. The clinician group further commented that patients would be undergoing clinical evaluations on a regular basis for clinical response and toxicity, and a meaningful response would be patient preference, tolerability of treatment, quality of life, and response on imaging. Moreover, fruquintinib should be discontinued upon disease progression (i.e., radiologic or clinical), toxicity, clinician discretion, or patient's request. The clinician group also mentioned that fruquintinib could be reasonably given in any centre and by any specialist who is currently treating mCRC patients with systemic therapy.

Drug Program Input

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
Given the negative CDA-AMC recommendation for trifluridine-tipiracil monotherapy and the fact regorafenib is not publicly funded, can pERC confirm whether eligible patients must have progressed on or been deemed not a candidate for trifluridine-tipiracil plus bevacizumab?	The clinical experts consulted for this review noted that the results were in favour of fruquintinib plus BSC over placebo plus BSC in the FRESCO-2 trial, in which the majority of patients had previously received trifluridine-tipiracil. 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.
Considerations for discontinuation of therapy	
In the FRESCO-2 trial, patients who experienced progressive disease were able to continue treatment if the investigator deemed that there could be further clinical benefit. What discontinuation criteria should be used for fruquintinib?	In the FRESCO 2 trial, patients could continue receiving fruquintinib beyond RECIST-defined progression if they were receiving clinical benefit based on the investigators' judgement. However, pERC agreed with the clinical experts that treatment discontinuation would be considered upon disease progression, severe or serious AEs despite dose modification, and/or decline in patients' clinical condition.
Generalizability	
Should fruquintinib be used in patients with • small bowel or appendiceal adenocarcinoma? • ECOG PS >1 • MSI-H/dMMR • BRAF V600E mutation	The clinical experts agreed that patients with small bowel or appendiceal adenocarcinoma could be potential candidates for fruquintinib treatment, as could be in patients with MSI-H/dMMR, and BRAF V600E mutation after progression on immunotherapy or BRAF inhibitor, respectively. The FRESCO 2 trial included patients with an ECOG PS score of 0 or 1. pERC agreed with the clinical experts that patients with an ECOG PS more than 1 may be treated at the discretion of the treating physician.
Funding algorithm	
Provisional funding algorithm to be updated to include fruquintinib	This is a comment from the drug plans to inform pERC deliberations.

BSC = best supportive care; BRAF = B-raf proto-oncogene; dMMR = mismatch repair deficient; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MSI-H = microsatellite instability-high; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Clinical Evidence

Systematic Review

Description of Studies

Two studies, FRESCO (N = 416) and FRESCO-2 (N = 691), met the inclusion criteria for the systematic review conducted by the sponsor. FRESCO and FRESCO-2 were multicentre, randomized, double-blind, placebo-controlled phase III trials assessing the efficacy and safety of fruquintinib plus BSC compared to placebo plus BSC in adult patients with metastatic colorectal adenocarcinoma. The FRESCO trial enrolled patients from 28 sites (all in China) who had progressed on, or intolerable toxicity, to at least 2 lines of standard chemotherapy. The FRESCO-2 trial enrolled patients from 124 sites (North America, Europe, Asia Pacific; none from Canada) who were previously treated with all standard chemotherapy, anti-VEGF therapy, and if RAS wild type, an anti-EGFR therapy, and had progressed on, or been intolerant to, treatment with trifluridine-tipiracil or regorafenib. Patients in FRESCO-2 also had received immune checkpoint inhibitors and/or BRAF inhibitors if indicated.

In both trials, patients were randomized in a 2:1 ratio to receive fruquintinib (5 mg by oral once daily for 3 weeks then 1 week off for a 28-day cycle) plus BSC or placebo plus BSC until disease progression or intolerable toxicity. The efficacy outcomes of interest to this review included OS (primary end point), progression-free survival (PFS; secondary end point in FRESCO; key secondary end point in FRESCO-2), EORTC QLQ-C30 Global Health Status/Quality of Life score (FRESCO-2 only, secondary end point).

In FRESCO, at baseline, the majority of patients having received 3 or less lines of prior anticancer treatment for metastatic disease (78.8%); 30.0% of patients received prior anti-VEGF treatment and 14.2% of patients received prior anti-EGFR treatment. The proportion of patients had previously received immune checkpoint inhibitors, BRAF inhibitors, trifluridine-tipiracil, and regorafenib, was not reported. In FRESCO-2, at baseline, most patients had received more than 3 lines of prior anticancer treatment for metastatic disease (72.6%) and prior anti-VEGF treatment (96.4%).All patients received prior treatment with trifluridine-tipiracil and/or regorafenib (including 52.2% receiving trifluridine-tipiracil alone; 39.4% receiving both trifluridine-tipiracil and regorafenib). Approximately one-third of patients had prior anti-EGFR treatment. In both trials, the proportion of patients who received prior trifluridine-tipiracil plus bevacizumab combination therapy was unknown.

Efficacy Results

Results presented below represent the final efficacy analysis at the data cut-off on January 17, 2017 (FRESCO) and June 24, 2022 (FRESCO-2).

Overall Survival

FRESCO

The median duration of follow-up was 13.3 (95% confidence interval [CI], 12.1 to 14.7) months in the fruquintinib plus BSC group and 13.2 (95% CI, 10.6 to 19.6) months in the placebo plus BSC group when a total of 297 deaths occurred. The KM estimate for the median OS (primary end point) was 9.30 (95% CI, 8.18 to 10.45) months in the fruquintinib plus BSC group and 6.57 (95% CI, 5.88 to 8.11) months in the placebo plus BSC group, with a stratified hazard ratio (HR) of 0.65 (95% CI, 0.51 to 0.83; P<0.001). The between-group difference in the probability of survival at 6 months, 12 months, and 18 months was [redacted], respectively. Results of the sensitivity analysis and the subgroup analyses of interest were in general consistent with the primary analysis.

FRESCO-2

The median duration of follow-up was 11.3 (95% CI, 10.6 to 12.4) months in the fruquintinib plus BSC group and 11.2 (95% CI, 9.9 to 12.0) months in the placebo plus BSC group when a total of 490 deaths occurred. The KM estimate for the median OS (primary end point) was 7.4 (95% CI, 6.7 to 8.2) months in the fruquintinib plus BSC group and 4.8 (95% CI, 4.0 to 5.8) months in the placebo plus BSC group, with a stratified HR of 0.66 (95% CI, 0.55 to 0.80; P<0.001). The between-group difference in the probability of

survival at 6 months, 12 months, and 18 months was [redacted], respectively. Results of the sensitivity analysis and the subgroup analyses of interest were in general consistent with the primary analysis. Of note, however, no effect was observed in the subgroup of patients with 3 or less prior lines (not specific to the stage of disease in which they were given) of chemotherapies treatment (HR =0.94; 95% CI, 0.56 to 1.53), whereas treatment effect was consistently observed across subgroups by the number of prior lines of chemotherapies specific to the metastatic setting.

Progression-Free Survival

FRESCO

The KM estimate for the median PFS (secondary end point) was 3.71 (95% CI, 3.65 to 4.63) months in the fruquintinib plus BSC group and 1.84 (1.81 to 1.84) months in the placebo plus BSC group, with a stratified HR of 0.26 (95% CI, 0.21 to 0.34; P<0.001). The majority of PFS event in both treatment groups were attributed to disease progression. The between-group difference in the probability of surviving progression-free at 3 months, 6 months, and 9 months was [redacted] respectively. None of these end points were adjusted for multiplicity. Results of the subgroup analysis were consistent with the primary analysis.

FRESCO-2

The KM estimate for the median PFS (key secondary end point) was 3.7 (95% CI, 3.5 to 3.8) months in the fruquintinib plus BSC group and 1.8 (95% CI, 1.8 to 1.9) months in the placebo plus BSC group, with a stratified HR of 0.32 (95% CI, 0.27 to 0.39; P<0.001); this end point was adjusted for multiplicity. The majority of PFS event in both treatment groups were attributed to disease progression. The between-group difference in the probability of survival at 3 months, 6 months, and 9 months was [redacted], respectively. Results of the subgroup analysis were consistent with the primary analysis.

EORTC QLQ-C30

FRESCO

This outcome was not assessed in this trial.

FRESCO-2

EORTC QLQ-C30 questionnaire-based outcomes were secondary end points and not adjusted for multiplicity in the FRESCO-2 trial.

[redacted] randomized patients in the fruquintinib plus BSC group and [redacted] randomized patients in the placebo plus BSC group were included in the analysis of proportion of patients with minimally important deterioration (i.e., at least a 6.38-point reduction) from baseline in EORTC QLQ-C30 Global Health Status/QoL score at the last on-treatment visit. Of the patients analyzed, [redacted] in the fruquintinib plus BSC group and [redacted] in the placebo plus BSC group achieved this end point; the between-group difference was [redacted].

Caregiver Burden

This outcome was not assessed in the trials.

Harms Results

Treatment-Emergent Adverse Events (TEAEs)

The proportion of patients who reported at least 1 TEAE was higher in the fruquintinib plus BSC group compared to the placebo plus BSC group in both the FRESCO (98.6% versus 88.3%) and the FRESCO-2 (98.9% versus 92.6%) trials. The most commonly reported TEAEs in the fruquintinib plus BSC group of the trials (reported in at least 30% of patients in at least 1 of the trials) were hand-foot syndrome, hypertension, dysphonia, proteinuria, and asthenia; all of which were more commonly reported than in the placebo plus BSC group.

Grade 3 or higher TEAEs were more commonly reported in the fruquintinib plus BSC group than the placebo plus BSC group in both the FRESCO (61.2% versus 19.7%) and the FRESCO-2 (62.7% versus 50.4%) trials. The most commonly reported grade 3 or higher TEAEs in the fruquintinib plus BSC groups were hypertension, asthenia, and hand-foot syndrome. The frequency of grade 3 or higher hypertension and hand-foot syndrome were consistently higher in the fruquintinib plus BSC group compared to the placebo BSC group in both trials (hypertension: 21.6% versus 2.2% in FRESCO, and 13.6% versus 0.9% in FRESCO-2; hand-foot syndrome10.8% versus none in FRESCO, and 6.4% versus none in FRESCO-2).

Serious Adverse Events (SAEs)

SAEs were more commonly reported in the fruquintinib plus BSC group (15.5%) compared to the placebo plus BSC group (5.8%) in the FRESCO trial but were similar between the treatment groups in FRESCO-2 (fruquintinib plus BSC, 37.5%; placebo plus BSC, 38.3%). SAEs were not attributed to any specific TEAEs in both trials.

Withdrawals Due to Adverse Events (WDAEs)

WDAEs were more commonly reported in the fruquintinib plus BSC group (15.1%) compared to the placebo plus BSC group (5.8%) in the FRESCO trial but were similar between the treatment groups in FRESCO-2 (fruquintinib plus BSC, 20.4%; placebo plus BSC, 21.3%). WDAEs were not attributed to any specific TEAEs in both trials.

Mortality

Deaths were less commonly reported in the fruquintinib plus BSC group compared to the placebo plus BSC group in both the FRESCO (67.6% versus 78.8%) and the FRESCO-2 (68.9% versus 75.2%) trials.

Notable Harms

The incidence of thromboembolic events and gastrointestinal perforations were similarly low between the fruquintinib plus BSC group and the placebo plus BSC group in both trials (thromboembolic events, 0.7% in both treatment groups in FRESCO, 4.6% versus 2.2% in FRESCO-2; gastrointestinal perforations, 2.2% versus 1.7% in FRESCO, 3.5% versus 0.4% in FRESCO-2). The proportion of patients with hand-foot syndrome, hemorrhage, hypertension, and proteinuria in the fruquintinib plus BSC group were reported to be between 43.2% and 57.2% in the FRESCO trial, and between 14.3% and 36.8% in the FRESCO-2 trial; these harms were notably more common in the fruquintinib plus BSC group than the placebo plus BSC group.

Critical Appraisal

The trials used adequate methods of randomization and allocation concealment. Baseline patient characteristics were generally balanced between treatment groups, with the exception of gender though it was not expected to impact study results. The trials were adequately blinded; however, there is a risk of bias in measurement of subjective outcomes based on the inferred judgement by patients and investigators regarding treatment assignment due to AEs associated with the interventions (e.g., hypertension, hand-foot syndrome). This could potentially lead to results in favour of fruquintinib plus BSC for HRQoL outcomes and in favour of placebo plus BSC for subjective harms outcomes. No multiplicity adjustment was in place for the HRQoL outcomes in the FRESCO-2 trial and for PFS in the FRESCO trial, so statistically significant results were at an increased risk of type 1 error (false positive results). In FRESCO-2, data were missing from a total of [redacted], fruquintinib plus BSC and placebo plus BSC, respectively) in the analysis of proportion of patients with minimally important deterioration from baseline EORTC QLQ-C30 Global Health Status/QoL score. Missing data could have biased the validity and interpretability of HRQoL results. Sensitivity analyses for the change from baseline in score analysis using the MMRM were conducted to assess the impact of missing data; however, the underlying assumption that data were missing at random may not hold when, for example, missing data were more likely to occur in patients with end-stage disease and poor health status. There is the potential that the impact of the missing data [redacted] could not be negligible in the analysis of proportion of patients with minimally important deterioration from baseline EORTC QLQ-C30 Global Health Status/QoL score, particularly when the between group difference was small [redacted].

Of note, in the FRESCO-2 trial, the treatment exposure as measured by mean duration (4.0 months vs. 2.0 months) and total number of treatment cycles received (4.3 vs. 2.3) were almost doubled in the fruquintinib plus BSC group than placebo plus BSC group. Patients discontinued the treatment largely due to disease progression, AEs or investigator decision, etc., yet the proportion

of patients who discontinued treatment due to disease progression was not substantially different (59% vs 64%) between the two group. According to the protocol, patients in the FRESCO-2 study were allowed to continue the study treatment following disease progression as determined by the RECIST criteria v 1.1 if deemed to be deriving clinical benefit by the investigator. Of the 461 patients randomized to the fruquintinib group, 301 experienced disease progression; among these, 99 patients (32.9%) received at least one dose of fruquintinib after disease progression. It is unclear what proportion of patients in the control group was allowed to continue treatment beyond radiographic progression. The decision to continue treatment beyond disease progression was made by the investigator in a blinded manner, and thus, unlikely to have introduced bias. Subsequent anticancer treatments were lower in the fruquintinib plus BSC group (29.4%) than in the placebo plus BSC group (34.3%) which could have introduced bias to the OS results in favour of the control group.

For the prespecified OS and PFS subgroup analyses, there was a lack of sample size consideration, control for multiplicity, and treatment-by subgroup interaction analysis, which preclude any firm conclusions on subgroup effects.

In terms of external validity, the clinical experts consulted on this review anticipated that patients would have also received anti-VEGF, and if indicated an anti-EGFR, BRAF inhibitor, and immune checkpoint inhibitor (in addition to 2 lines of standard chemotherapy), prior to receiving fruquintinib treatment, as per current treatment approach in Canada. As well, the clinical experts noted that if trifluridine-tipiracil became publicly funded, fruquintinib would be used subsequently in the fourth- or later-line setting in most patients. The FRESCO trial was designed for patients who had failed at least 2 lines of chemotherapy and hence by inclusion criteria, the aforementioned prior therapies were not required. By baseline characteristics, the proportion of patients who had received these treatments were either small or unknown. This does not align with clinical expert input that in clinical practice, most patients eligible for fruquintinib treatment would have received these prior therapies. FRESCO-2 included patients who had been heavily pre-treated and received all standard chemotherapy, anti-VEGF, anti-EGFR, immune checkpoint inhibitor, and BRAF inhibitor, as indicated. Of note, patients were not required to have experienced disease progression on these treatments. This may increase uncertainty on the generalizability of study results to the fourth- or later-line setting. However, in the clinical experts' opinion, the concern was minor since in the clinical practice, typically, treatments are switched upon disease progression or poor tolerance . As well, most patients were expected to receive trifluridine-tipiracil plus bevacizumab combination therapy prior to fruquintinib treatment in clinical practice as per clinical expert input. While the majority of patients in FRESCO-2 previously received trifluridine-tipiracil (91.6%), the sponsor was unable to provide data on the proportion of patients who receive trifluridine-tipiracil in combination with bevacizumab in both trials, which could introduce uncertainty to the generalizability of the study results. The sponsor noted that the trials were completed during a time when there was limited clinical evidence for trifluridine-tipiracil plus bevacizumab therapy and no approved indications for the use of such combination therapy, which limit the ability to accurately characterize the proportion of patients who receive trifluridine-tipiracil in combination with bevacizumab. In consultation with the clinical experts, the CADTH review team considered that compared to FRESCO, patients in FRESCO-2 were more reflective of the patient population eligible for fruquintinib treatment based on the inclusion criteria and baseline characteristics, albeit subject to the aforementioned generalizability concerns. In addition, the clinical experts noted that the use of chemotherapy as a common subsequent treatment in the trials did not align with the clinical practice in Canada given that the trial populations were chemo-refractory at baseline. As well, FRESCO was conducted in China; there is potential for differences in the standard of care and availability of BSC across countries.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and randomized controlled trials (RCTs) identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- OS (probability of OS at 6, 12, and 18 months)

- PFS (probability of PFS at 3, 6, and 12 months)
- HRQoL (EORTC QLQ-C30 Global Health Status/Quality of Life score responder analysis)
- Harms (SAEs)

Table 3 presents the GRADE summary of findings for fruquintinib plus BSC versus placebo plus BSC in patients with mCRC who had progressed on or intolerant to at least 2 lines of standard chemotherapy.

Table 4 presents the GRADE summary of findings for fruquintinib plus BSC versus placebo plus BSC in patients with mCRC who had previously received standard chemotherapy, an anti-VEGF, and an anti-EGFR if RAS wild-type, and had progressed on or been intolerant to trifluridine-tipiracil or regorafenib.

Table 3: Summary of Findings for Fruquintinib plus BSC Versus Placebo plus BSC for Patients With mCRC who had Progressed on or intolerant to at Least 2 Lines of Standard Chemotherapy

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Fruquintinib plus BSC	Placebo plus BSC	Difference		
Overall survival							
Probability of overall survival at 6 months, % (95% CI%) Median follow-up: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[a]	Fruquintinib plus BSC may result in a clinically important increase in the probability of overall survival at 6 months when compared to placebo plus BSC.
Probability of overall survival at 12 months, % (95% CI%) Median follow-up: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[a]	Fruquintinib plus BSC may result in a clinically important increase in the probability of overall survival at 12 months when compared to placebo plus BSC.
Probability of overall survival at 18 months, % (95% CI%) Median follow-up: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Very low[a,b,c]	The evidence is very uncertain about the effect of fruquintinib plus BSC on the probability of overall survival at 18 months when compared to placebo plus BSC.
Progression-free survival							
Probability of progression-free survival at 3 months, % (95% CI%) Median follow-up: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[a]	Fruquintinib plus BSC may result in a clinically important increase in the probability of progression-free survival at 3 months when compared to placebo plus BSC.
Probability of progression-free survival at 6 months, % (95% CI%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[a]	Fruquintinib plus BSC may result in a clinically important increase in the probability of progression-free survival at 6 months when compared to placebo plus BSC.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Fruquintinib plus BSC	Placebo plus BSC	Difference		
Median follow-up: [redacted]							
Probability of progression-free survival at 9 months, % (95% CI%) Median follow-up: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[a,c]	Fruquintinib plus BSC may result in a clinically important increase in the probability of progression-free survival at 9 months when compared to placebo plus BSC.
Health-related quality of life							
Health-related quality of life	NA	No data available	No data available	No data available	No data available	NA	There is no evidence for the effect of fruquintinib plus BSC on health-related quality of life when compared with placebo plus BSC.
Caregiver burden							
Caregiver burden	NA	No data available	No data available	No data available	No data available	NA	There is no evidence for the effect of fruquintinib plus BSC on caregiver burden when compared with placebo plus BSC.
Serious adverse events							
Proportion of patients with serious adverse events, % (95% CI) Follow-up: 4.47 months versus 2.6 months	415 (1 RCT)	NR	155 per 1,000	58 per 1,000	96 more per 1,000 (38 more to 154 more per 1,000)	Low[d]	Fruquintinib plus BSC may result in a clinically important increase in serious adverse events when compared with placebo plus BSC.

BSC = best supportive care; CI = confidence interval; EORTC = European Organization for Research and Treatment of Cancer; mCRC = metastatic colorectal cancer; NR = not reported; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] Rated down 2 levels for very serious indirectness related to trial population and subsequent anti-cancer treatment use. The clinical experts consulted on this review anticipated that patients would have also received anti-VEGF, and if indicated an anti-EGFR, BRAF inhibitor, and immune checkpoint inhibitor (in addition to 2 lines of standard chemotherapy), prior to receiving fruquintinib treatment, as per current treatment approach in Canada. As well, the clinical experts noted that if trifluridine-tipiracil became publicly funded, fruquintinib would be used subsequently in the fourth- or later-line setting in most patients. In the FRESCO trial, by inclusion criteria, these prior treatments were not required. By baseline characteristics, the proportion of patients who had received these treatments was either small or unknown. The clinical experts also noted that in the trial, the use of chemotherapy subsequent to treatment failure of fruquintinib did not align with the current treatment approach in the target population (i.e. chemo-refractory) in Canada.

[b] Rated down 1 level for serious imprecision. Based on clinical expert input, 50 more to 100 more per 1,000 patients surviving could be considered clinically important. The 95% CI included the possibility of benefit and little to no difference.

[c] As per clinical expert input, the findings at later time points (i.e., at 18 months for OS and at 9 months for PFS) were less relevant since survival is generally limited for patients in late-line settings and most patients were expected to have experienced disease progression or died at those time points.

[d] Rated down 1 level for serious imprecision. Based on clinical expert input, 50 more to 100 more per 1,000 patients with serious adverse events could be considered clinically important. The 95% CI included the possibility of important harm and no difference. Rated down 1 level for indirectness. Clinical expert input indicated that patients eligible for fruquintinib treatment in clinical practice were expected to be more treatment experienced (i.e., received more prior anti-cancer treatments) than the trial population of FRESCO and that the trial was conducted in single country with all patients being Asians; both factors could limit the generalizability of the harms results to the patient population in Canada.

Source: FRESCO Clinical Study Report.[16] Details included in the table are from the sponsor's Summary of Clinical Evidence.[17]

Table 4: Summary of Findings for Fruquintinib plus BSC Versus Placebo plus BSC for Patients With mCRC who had Previously Received Standard Chemotherapy, an anti-VEGF, and an anti-EGFR if RAS wild-type, and had Progressed on or been Intolerant to Trifluridine-Tipiracil or Regorafenib

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Fruquintinib plus BSC	Placebo plus BSC	Difference		
Overall survival							
Probability of overall survival at 6 months, % (95% CI%) Median follow-up:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Moderate[a]	Fruquintinib plus BSC likely results in a clinically important increase in the probability of overall survival at 6 months when compared to placebo plus BSC.
Probability of overall survival at 12 months, % (95% CI%) Median follow-up:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[a,b]	Fruquintinib plus BSC may result in little to no clinically important difference in the probability of overall survival at 12 months when compared to placebo plus BSC.
Probability of overall survival at 18 months, % (95% CI%) Median follow-up:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[a,c,d]	Fruquintinib plus BSC may result in little to no clinically important difference in the probability of overall survival at 18 months when compared to placebo plus BSC.
Progression-free survival							
Probability of progression-free survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Fruquintinib plus BSC likely results in a clinically important increase in the probability of progression-free

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Fruquintinib plus BSC	Placebo plus BSC	Difference		
at 3 months, % (95% CI%) Median follow-up: [redacted]							survival at 3 months when compared to placebo plus BSC.
Probability of progression-free survival at 6 months, % (95% CI%) Median follow-up: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Fruquintinib plus BSC likely results in a clinically important increase in the probability of progression-free survival at 6 months when compared to placebo plus BSC.
Probability of progression-free survival at 9 months, % (95% CI%) Median follow-up: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Fruquintinib plus BSC likely results in a clinically important increase in the probability of progression-free survival at 9 months when compared to placebo plus BSC.
EORTC QLQ-C30							
Global health status, proportion of patients with at least a 6.38-point deterioration from baseline at last on-treatment visit, % (95% CI) Median follow-up: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[a,e]	Fruquintinib plus BSC may result in little to no clinically important difference on the proportion of patients with at least a 6.38-point deterioration from baseline in the Global Health Status score when compared to placebo plus BSC
Caregiver burden							
Caregiver burden	NA	No data available	No data available	No data available	No data available	NA	There is no evidence for the effect of fruquintinib plus BSC on caregiver burden when compared with placebo plus BSC.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Fruquintinib plus BSC	Placebo plus BSC	Difference		
Serious adverse events							
Proportion of patients with serious adverse events, % (95% CI) Follow-up: 3.71 months versus 2.6 months	686 (1 RCT)	NR	375 per 1,000	383 per 1,000	8 less per 1,000 (85 less to 69 more per 1,000)	Moderate[f]	Fruquintinib plus BSC likely result in little to no clinically important difference in serious adverse events when compared to placebo plus BSC.

BSC = best supportive care; CI = confidence interval; EGFR = epidermal growth factor receptor; EORTC = European Organization for Research and Treatment of Cancer; mCRC = metastatic colorectal cancer; NR = not reported; OS = overall survival; PFS = progression-free survival; RAS = rat sarcoma proto-oncogene; RCT = randomized controlled trial; VEGF = vascular endothelial growth factor.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] Rated down 1 level for serious indirectness related to trial population and subsequent anti-cancer treatment use. The clinical experts consulted on this review anticipated that in most patients, fruquintinib would be used in the fourth- or later-line setting, subsequent to failure of trifluridine-tipiracil plus bevacizumab combination therapy if this combination therapy becomes publicly funded. The proportion of patients who had previously received trifluridine-tipiracil plus bevacizumab was unknown in the FRESCO-2 trial. The clinical experts also noted that in the trial, the use of chemotherapy subsequent to treatment failure of fruquintinib did not align with the current treatment approach in the target population (i.e. chemo-refractory) in Canada.

[b] Rated down 1 level for serious imprecision. Based on clinical expert input, 50 more to 100 more per 1,000 patients surviving could be considered clinically important. The 95% CI included the possibility of benefit and little to no difference.

[c] Rated down 1 level for serious imprecision. Based on clinical expert input, 50 more to 100 more per 1,000 patients surviving could be considered clinically important. The 95% CI included the possibility of benefit and no difference. Did not rate down further even though the lower bound of the 95% CI indicated the possibility for harm given that it was marginally crossing the threshold of 50 less per 1,000 patients.

[d] As per clinical expert input, the findings at later time points (i.e., at 18 months for OS and at 9 months for PFS) were less relevant since survival is generally limited for patients in late-line settings and most patients were expected to have experienced disease progression or died at those time points.

[e] Rated down 1 level for serious study limitation. There was substantial missing data (18.2%) in the treatment groups that may impact the prognostic balance of the groups. Did not rate down for imprecision. The lower limit of the 95% CI marginally crossed the threshold of 100 less per 1,000 patients with at least a 6.38-point deterioration from baseline in Global health Status score based on clinical expert input. This outcome was not adjusted for multiplicity and was considered as supportive evidence.

[f] Rated down 1 level for serious imprecision. Based on clinical expert input, 50 more to 100 more per 1,000 patients with serious adverse events could be considered clinically important. The 95% CI included the possibility of both benefit and harm based on the threshold of 50 more to 100 more per 1,000 patient threshold. Alternatively, if the threshold of 100 more per 1,000 patients was used, the point estimate and 95% CI would indicate little to no clinically important difference, and therefore, there would not be concerns for imprecision.

Source: FRESCO-2 Clinical Study Report.[18] Details included in the table are from the sponsor's Summary of Clinical Evidence.[17]

Long-Term Extension Studies

No long-term extension studies were submitted for review.

Indirect Comparisons

One sponsor-conducted ITC comparing the efficacy of fruquintinib with alternative third- or later-line treatments in patients with mCRC was included in the sponsor's submission in anticipation of the approval of fruquintinib in the third- or later-line setting. Fruquintinib was subsequently granted an NOC by Health Canada for use in the fourth- or later-line setting (i.e., following failure of at least 2 lines of standard chemotherapy and either trifluridine-tipiracil or regorafenib). Direct evidence between fruquintinib and relevant comparator (BSC) in the fourth- or later-line setting was available from the FRESCO-2 study. The sponsor-conducted ITC, which intended to provide indirect comparative evidence between fruquintinib to trifluridine-tipiracil in combination with bevacizumab in the third- or later- line setting, was therefore considered to have limited relevance for the purpose of this review and will not be further summarized. Refer to Appendix 2 for a summary of the sponsor-conducted ITC, along with a summary of a published ITC (Gao et al., 2023) assessing the same PICO (identified in the sponsor's submission).

Studies Addressing Gaps in the Evidence From the Systematic Review

No additional studies were submitted for review.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Adult patients with mCRC who have been previously treated with or are not considered candidates for available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy.[a]
Treatment	Fruquintinib
Dose regimen	5 mg daily for 21 days, followed by 7 days off treatment to comprise a complete cycle of 28 days. Treatment should be continued until disease progression or unacceptable toxicity.
Submitted price	Fruquintinib • 1 mg: $75.24 per capsule • 5 mg: $301.00 per capsule
Submitted treatment cost	28-day cycle cost: $6,321
Comparators	• Trifluridine/tipiracil plus bevacizumab[a] • BSC: interventions that provide palliation of symptoms and improve quality of life.
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (10 years)
Key data source	FRESCO Phase III Trial, FRESCO-2 Phase III Trial, Sponsor submitted NMA.
Key limitations	• During the review, the indication population was revised from the 3rd line or later setting to the 4th line or later setting. This revised population was narrower than the original indication but is aligned with the population considered in the CADTH base case. The CADTH clinical review of the FRESCO and FRESCO-2 trials found that fruquintinib is associated with

Component	Description
	prolonged OS and PFS relative to BSC, although there were concerns regarding the generalizability of the results to the patients who would use fruquintinib in Canada. • Based on clinical expert input, the population of FRESCO-2 was more reflective of the likely place in therapy of fruquintinib as a fourth- or later-line treatment compared to FRESCO. • The sponsor's methods led to potential inaccuracies with the estimation of the expected costs and benefits associated with all treatment options. This was reflected by: the decision to cap OS by the general population mortality risk; the approach used to characterize parameter uncertainty; and the use of an inappropriate data source to adjust utility values for age.
CADTH reanalysis results	• The CADTH base case reflected several changes to the sponsor's submission. These included: the removal of the cap on OS; corrected treatment acquisition costs; the removal of the age-adjusted utility values; the removal of costs related to treatment switching and using data from the FRESCO-2 trial to inform parameter inputs. • In line with the use of data from FRESCO-2, in whom the majority of patients had previously received trifluridine/tipiracil, trifluridine/tipiracil plus bevacizumab was not considered a relevant comparator. In the fourth-line population, fruquintinib is more costly (incremental costs: $28,076) and more effective (incremental QALYs: 0.09) than BSC, leading to an ICER of $325,989 per QALY gained. To be considered cost effective as fourth-line therapy a price reduction would be required based on the decision maker's willingness to pay.

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; mCRC = metastatic colorectal cancer; NMA = network meta analysis; OS = overall survival; PFS = progression free survival; PSM = partitioned survival model; QALY= quality-adjusted life-year.

[a] The indication was revised during the review process. The target population described here was aligned with the original proposed indication, although the sponsor's economic evaluation was modifiable to consider a target population aligned with the revised indication. This also required a change in the primary comparator, from tipiracil-trifluridine plus bevacizumab to BSC.

Budget Impact

CADTH identified one key limitation with the sponsor's analysis. The number of patients eligible for treatment is uncertain. In the absence of more reliable input values to estimate the eligible population size, the sponsor's base case was maintained. The net budget impact of reimbursing fruquintinib for the treatment of adult patients with metastatic colorectal cancer who have been treated with or are not considered candidates for available therapies including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEFG therapy, and an anti-EGFR therapy was estimated to be $27,142,807 (Year 1: $9,725,263; Year 2: $8,830,251; Year 3: $8,587,293).

The sponsor's BIA was not designed to assess the reimbursement of fruquintinib as a fourth line therapy. As a result, the assumptions regarding subsequent treatment use in the sponsor's analysis were associated with uncertainty. CADTH was unable to assess the budget impact of fruquintinib if it was approved as a fourth-line treatment after trifluridine/tipiracil plus bevacizumab in Canada.

pERC Information

Members of the Committee:

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, Danica Wasney.

Meeting date: October 9, 2024

Regrets:

Three expert committee member(s) did not attend.

Conflicts of interest:

None of the expert committee members who attended the meeting declared conflict of interest.