CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Trifluridine-tipiracil (Lonsurf)

Indication: In combination with bevacizumab, for the treatment of adult patients with metastatic colorectal cancer who have previously been treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if RAS wild-type, anti-EGFR agents.

Sponsor: Taiho Pharma 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 trifluridine-tipiracil in combination with bevacizumab, be reimbursed for the treatment of metastatic colorectal cancer (mCRC) in adults who have been previously treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-vascular endothelial growth factor (anti-VEGF) biological agents, and, if rat sarcoma virus (RAS) wild-type, anti-epidermal growth factor receptor (anti-EGFR) agents, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, open-label, multicentre trial (SUNLIGHT, N = 492) demonstrated that treatment with trifluridine-tipiracil, in combination with bevacizumab, resulted in longer survival in adults with advanced mCRC who had received up to two previous chemotherapy regimens and demonstrated progressive disease or intolerance to their last regimen compared with trifluridine-tipiracil alone. Specifically, trifluridine-tipiracil, in combination with bevacizumab, led to a clinically meaningful and statistically significant improvement in overall survival (OS) and progressive-free survival (PFS) benefit compared with trifluridine-tipiracil alone. After a median follow-up of 14.2 months (interquartile range, 12.6 to 16.4), the median (95% CI) OS in patients treated with trifluridine-tipiracil in combination with bevacizumab was 10.78 months (9.36 to 11.83) versus 7.46 months (6.34 to 8.57) in patients treated with trifluridine-tipiracil alone, HR (95% CI): 0.61 (0.49 to 0.77; P < 0.001). The median (95% CI) PFS was 5.55 months (4.50 to 5.88) versus 2.4 months (2.07 to 3.22), in the groups treated with trifluridine-tipiracil in combination with bevacizumab vs trifluridine-tipiracil alone, respectively, HR (95% CI): 0.44 (0.36 to 0.54; P < 0. 001). In addition, the safety profile of trifluridine-tipiracil, in combination with bevacizumab, was consistent with the known safety profile of trifluridine-tipiracil alone and was considered manageable.

pERC noted a lack of relevant direct comparative evidence given that the comparator in the SUNLIGHT trial (trifluridine-tipiracil alone) is not publicly funded in Canada. Therefore, the committee considered the results of a sponsor-submitted indirect treatment comparison (ITC) comparing trifluridine-tipiracil, in combination with bevacizumab, with best supportive care (BSC). pERC determined that notwithstanding the limitations of the ITC (mainly due to the heterogeneity of the included studies), the results suggest that OS and PFS outcomes with trifluridine-tipiracil, in combination with bevacizumab, were better than with BSC, recognizing the uncertainty of the magnitude of the clinical benefit when comparing with BSC.

pERC concluded that trifluridine-tipiracil, in combination with bevacizumab, met some of the needs identified by patients who have exhausted other publicly funded therapies, such as prolonging life while having manageable treatment side effects.

The committee considered the cost-effectiveness of trifluridine-tipiracil, in combination with bevacizumab relative to BSC based on data from a sponsor-submitted ITC. Using the sponsor-submitted price for trifluridine-tipiracil, in combination with bevacizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for trifluridine-tipiracil, in combination with bevacizumab, was estimated to be $195,000 per quality-adjusted life-year (QALY) compared with best supportive care (BSC). Given the cost of the combination treatment ($7,488 per 28 days based on the recommended dose), the duration of treatment with trifluridine-tipiracil in combination with bevacizumab in the CADTH reanalysis, and the lack of robust evidence to support a post-progression survival benefit, there are no price reductions for trifluridine-tipiracil where a $50,000 per QALY gained threshold could be achieved for the combination regimen.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
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. 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.	Evidence from the pivotal SUNLIGHT trial showed that treatment with trifluridine-tipiracil, in combination with bevacizumab, resulted in OS and PFS benefits in patients with these characteristics. Prior treatment defined in this condition reflects patients' experience in the SUNLIGHT trial and is aligned with how patients are treated in clinical practice in Canada.	—
2. Patients should have good performance status.	Patients with an ECOG performance status of 0 or 1 were included in the SUNLIGHT trial.	Treating patients with ECOG performance status greater than 1 may be at the discretion of the treating clinician
3. Treatment with trifluridine-tipiracil, in combination with bevacizumab, should not be reimbursed in patients with either of the following: 3.1. symptomatic central nervous system metastases that are neurologically unstable, 3.2. those requiring increasing doses of steroids to control CNS disease	Patients with these conditions were excluded from the pivotal SUNLIGHT trial. Therefore, no evidence was reviewed regarding the safety and efficacy of trifluridine-tipiracil, in combination with bevacizumab, in these patients.	—
Discontinuation		
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	In the SUNLIGHT trial, treatment was discontinued in patients who exhibited radiologic progressive disease, clinical progression, or unacceptable toxicity, whichever occurred first. Based on input from clinical experts, this is aligned with clinical practice.	—

Reimbursement condition	Reason	Implementation guidance
Prescribing		
5. The trifluridine-tipiracil and bevacizumab regimen should only be prescribed by a clinician with expertise in the diagnosis and management of patients with mCRC.	To ensure that the treatment is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
6. Trifluridine-tipiracil, in combination with bevacizumab, should not be used with other systemic therapy.	No evidence was reviewed to demonstrate that trifluridine-tipiracil, in combination with bevacizumab, would result in additional benefits when used in addition to other systemic cancer therapy.	—
Pricing		
7. A reduction in price	The ICER for trifluridine-tipiracil in combination with bevacizumab is $195,000 when compared with BSC. Given the cost ($7,488 per 28 days based on the recommended dose) and the duration of treatment for the combination regimen, and the lack of robust evidence to support a post-progression survival benefit, the CADTH reanalysis showed that there are no price reductions for trifluridine-tipiracil where a $50,000 per QALY gained threshold could be achieved for the combination regimen. If a price reduction is applied to both drugs within the combination regimen, a price reduction of at least 77% (i.e., a price reduction of at least 77% for trifluridine-tipiracil and a price reduction of at least 77% for bevacizumab) would be required to achieve an ICER of $50,000 per QALY gained compared to BSC.	—
Feasibility of adoption		
8. The feasibility of adoption of trifluridine-tipiracil, in combination with bevacizumab, must be addressed.	At the submitted price for trifluridine-tipiracil and the public list price of bevacizumab, the incremental budget impact of trifluridine-tipiracil, in combination with bevacizumab,	

Reimbursement condition	Reason	Implementation guidance
	is expected to be greater than $40 million in year 3. At the submitted price for trifluridine-tipiracil and the public list price of bevacizumab, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, as CADTH reanalysis was not possible.	

BSC = best supportive care; CNS = central nervous system; EGFR = epidermal growth factor receptor; ICER = incremental cost-effectiveness ratio; mCRC = metastatic colorectal cancer; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year: RAS = rat sarcoma viral oncogene; VEGF = vascular endothelial growth factor.

Discussion Points

- pERC acknowledged the need for a new treatment option for patients with mCRC who experience disease progression after second-line therapy. pERC noted that currently available treatment options are limited for this patient population and that these therapies have limited efficacy with considerable toxicity. Based on the evidence reviewed, trifluridine-tipiracil, in combination with bevacizumab fills a current treatment gap.

- pERC deliberated health-related quality of life (HRQoL) outcomes from the SUNLIGHT trial, as measured by the EORTC QLQ-C30 and EQ-5D-5L scales. The committee noted that the uncertainty in the outcomes of some assessed domains precludes a definitive conclusion about the HRQoL benefit with trifluridine-tipiracil in combination with bevacizumab compared with trifluridine-tipiracil alone.

- pERC noted that in the SUNLIGHT trial, some patients (29% of patients in the combination and 20% in the trifluridine-tipiracil alone groups) received concomitant G-CSF as prophylaxis and to manage neutropenia. The committee discussed the existing variability in provincial funding of growth factors in the palliative setting and suggested that public plans resolve this potential inequity to ensure that G-CSF is available to support all patients eligible for trifluridine-tipiracil in combination with bevacizumab.

- pERC discussed the potential size of the budget impact associated with the introduction of trifluridine-tipiracil in combination with bevacizumab. The committee noted that the sponsor's estimated 3-year budget impact of $110,993,278 was associated with uncertainty. Inputs such as duration of treatment, market size and the proportion of the population eligible for public coverage, affect the estimated budget impact. pERC noted that price negotiations and implementation of discontinuation criteria could assist in reducing the budget impact.

Background

Colorectal cancer (CRC) collectively refers to malignant tumours that develop in the epithelial lining of the rectum or colon, from polyps that progress into cancer. CRC is the third most prevalent cancer and the second leading cause of cancer-related death (11% of all cancer deaths) in Canada. It is estimated that the Canadian (excluding Quebec) 10-year prevalence of CRC in both sexes of all ages is 343.5 cases per 100,000 in 2018 (or 97,755 cases). mCRC indicates that the cancer has spread beyond the primary tumour site to other organs of the body (i.e., stage IV disease), where the most common location of metastases are the liver, lung, peritoneum and distant lymph nodes. The stage of CRC at diagnosis is strongly associated with survival. Patients with early CRC are usually asymptomatic, whereas patients with advanced disease experience varying symptoms depending on the location of metastasis, including upper-right quadrant pain, abdominal distention, early satiety, supraclavicular adenopathy, and periumbilical nodules. Right-sided (proximal) tumours rarely present with obvious rectal bleeding as the blood becomes admixed with the stool. Left-sided (distal) tumors are more likely to present with bright red blood per rectum and symptoms of bowel obstruction. The majority of patients with mCRC have unresectable (inoperable) disease, for which the mainstay of treatment is systemic multi-agent

chemotherapy. Choice of treatment is dependent on a number of factors, including a patient's fitness (e.g., performance status), organ function, and comorbidities, in addition to tumour characteristics (e.g., tumour location [right versus left], presence of primary tumour, mutation status for RAS and BRAF [v-RAF murine sarcoma viral oncogene homolog B], presence of dMMR [deficient mismatch repair]/MSI-H [microsatellite instability-high]), type and timing of prior therapy, and toxicity profiles of constituent drugs. Trifluridine-tipiracil (Lonsurf®) and regorafenib (Stivarga®) are approved in Canada for the treatment of patients who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if RAS wild-type, anti-EGFR agents; however, these treatments are not publicly funded in Canada (except in Quebec). Following treatment with standard cytotoxic chemotherapy backbone regimens, patients are usually treated with best-supportive care (BSC).

Trifluridine-tipiracil in combination with bevacizumab for the treatment of mCRC in adult patients 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 RAS wild-type, anti-EGFR agents, is an unlabeled indication. It is available as a 35 mg/m^2/dose oral tablet and the dosage recommended in the Product Monograph is twice daily on days 1 to 5 and days 8 to 12 of each 28-day cycle, repeated every 4 weeks, in combination with bevacizumab.

Sources of Information Used by the Committee

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

- A review of 1 randomized controlled trial (RCT) in adults with mCRC 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 RAS wild-type, anti-EGFR agents
- Patients' perspectives gathered by patient groups, 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 2 clinical specialists with expertise diagnosing and treating patients with metastatic colorectal cancer
- Input from 2 clinician groups, including the Canadian Gastrointestinal Oncology Evidence Network (CGOEN) with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) and Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee (OH-CCO)
- A review of the pharmacoeconomic model and report, and indirect treatment comparison submitted by the sponsor

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

CADTH received two patient group submissions from CCRAN and Colorectal Cancer Canada. CCRAN used a multi-faceted outreach approach by emailing clinicians who treat advanced colorectal cancer to help recruit patients or caregivers with experience with Lonsurf (in combination with bevacizumab) and via an online survey of patients' experience of mCRC and prior drug therapies resulting 77 survey respondents (including 60 patients, 13 caregivers, and 4 patients who were also caregivers). Colorectal Cancer Canada conducted an on-line survey of 23 respondents (22 patients and 1 caregiver). Most patients reported that fatigue/weakness, bloody stools, diarrhea, and abdominal cramping/gas/feeling bloated, abdominal pain are common symptoms they experienced and that they felt were important to control. Symptoms of colorectal cancer affected the quality of life for patients and their families, limiting the ability to work, ability to exercise, participate in social activities, or perform daily tasks. According to both patient groups, it is very important for a new therapy to bring about improvement to patients' physical condition (e.g., tumour shrinkage, tumour stability, reduced pain and improved breathing) and quality of life (e.g., improved mobility, improved sense of wellness, relief from side effects). Patients would take a new therapy to bring about improvement in their quality of life even if it does not extend overall survival (e.g., at a modest 3 months to 4 months of survival, 53% of respondents were willing to tolerate significant side effects

including nausea, anemia, and neutropenia). Moreover, patients prefer a drug therapy that is convenient (e.g., orally administered, either at home or with a short infusion duration/chair time at a cancer centre). CCRAN believes that if publicly funded, trifluridine and tipiracil in combination with bevacizumab would be an extremely important third line and beyond therapy for patients whose disease has been deemed to be refractory or ineligible for standard of care therapies. Colorectal Cancer Canada noted that given that Lonsurf® alone is currently reimbursed only in Quebec, there is a strong need for equity of access for patients located elsewhere in Canada. Both patient groups strongly agree that trifluridine-tipiracil aligns well with the identified patient and caregiver need for a new, effective treatment option, that is capable of prolonging life and maintaining quality of life.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Two clinical experts with expertise in the diagnosis and management of mCRC reported that the cornerstone of treatment for patients with mCRC involves sequential use of the best available systemic therapies. Standard of care (SOC) first-line treatment in Canada includes: pembrolizumab immunotherapy (for patients with dMMR/MSI-H mCRC); chemotherapy with a regimen of infusional 5-fluorouracil (5-FU), folinic acid, and oxaliplatin (FOLFOX) or a regimen of infusional 5-FU, folinic acid, and irinotecan (FOLFIRI) in combination with an EGFR inhibitor (for patients with left-sided, extended RAS wild-type CRC); and, chemotherapy with FOLFOX or FOLFIRI in combination with bevacizumab (for patients with right-sided or extended RAS mutated CRC). Patients who progress on or within 6 months of adjuvant therapy (e.g., cancer growth while on adjuvant therapy or within 6 months of adjuvant FOLFOX) would be considered to experience progression on first-line treatment. Following disease progression on first-line therapy, the clinical experts consulted by CADTH indicated that SOC second-line systemic treatment in Canada includes encorafenib plus cetuximab (for patients with BRAF V600E mutations) or switching of the backbone chemotherapeutic regimen (for patients without BRAF V600E mutation) such that patients who were initially treated with FOLFOX would then be switched to FOLFIRI, for example. Anti-angiogenic therapies added to the chemotherapy backbone (e.g., bevacizumab, aflibercept, ramucirumab) for patients without BRAF V600E mutation or dual immunotherapy (e.g., nivolumab plus ipilimumab) for patients with MMR deficient/MSI-high molecular marker, are routinely offered to patients with colorectal cancer and recommended in guidelines for CRC, according to the clinical experts consulted by CADTH. The clinical experts consulted by CADTH noted that following disease progression on 2 lines of prior therapy, a single-agent EGFR inhibitor (cetuximab or panitumumab) or cetuximab plus irinotecan as SOC treatment in Canada is an option for patients with extended RAS wild-type, whereas regorafenib monotherapy or trifluridine-tipiracil is SOC in Canada for patients without the extended RAS wild-type marker (among patients with access through private insurance or out-of-pocket). Importantly, there exists a significant unmet need for effective treatment options for patients with mCRC who experience disease progression following 2 lines of anti-cancer therapy, according to the clinical experts consulted by CADTH.

The clinical experts consulted by CADTH considered trifluridine-tipiracil in combination with bevacizumab to represent a new standard of care treatment for patients with unresectable CRC after progression on 2 prior lines of anti-cancer therapy. According to the clinical experts consulted by CADTH, eligible patients should be able to tolerate both trifluridine-tipiracil (i.e., able to safely swallow pills, have normal bowel transit, have an Eastern Co-operative Oncology Group Performance Status (ECOG PS) of 0 to 1, and have adequate hematologic, hepatic, and renal function) and bevacizumab (i.e., without absolute contraindication to use of a VEGF inhibitor, included but not limited to: uncontrolled hypertension, in situ colonic stent, recent surgery, high-risk for bleeding, risk for or presence of fistula or gastrointestinal tract perforation). The clinical experts consulted by CADTH outlined the following hierarchy for determining treatment response: 1) patient-reported symptoms or side effects, as determined by clinician assessment of patient treatment history, 2) examination and selective use of clinical instruments to evaluate symptoms (e.g., Edmonton Symptoms Assessment System, EQ-5D), and 3) cross-sectional imaging (e.g., CT scan, MRI) and tumour markers (e.g., CEA and CA 19-9). Patients should be assessed after every 2 to 3 cycles of treatment (and more frequently with bothersome symptoms or adverse events [AEs]), with tumour markers completed at least once every 4 weeks and CT scans conducted every 2 to 3 months, according to the clinical experts consulted by CADTH. The clinical experts consulted by CADTH highlighted overall survival, symptom control, and quality of life as clinically meaningful endpoints. Side effects or toxicity were key determinants for discontinuing treatment with trifluridine-tipiracil in combination with bevacizumab, according to the clinical experts consulted by CADTH, particularly for discontinuing bevacizumab in the event of development of an absolute contraindication to further therapy with VEGF inhibitor. The clinical experts consulted by CADTH highlighted the importance of shared and fully informed decision-

making with patients that include discussions regarding treatment effectiveness and symptoms or AEs that significantly impact quality of life.

Clinician Group Input

CADTH received 2 clinician group submissions from the CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) and OH-CCO. CGOEN gathered data and information based on personal experience in treating patients with mCRC and expert evidence-based review by Canadian gastrointestinal cancer specialists of the following information presented at international oncology meetings, and subsequently published in the New England Journal of Medicine, and OH-CCO's Drug Advisory Committees gathered information through videoconferencing and email communication. Both clinician groups highlighted that trifluridine-tipiracil would be placed as a further line of therapy and would be used in patients who received current standard of care options and have experienced disease progression, intolerance or chose to stop for personal reasons. This combination would also be used for those with medical contraindications to earlier line standard of care therapies. CGOEN stated that trifluridine-tipiracil is currently Health Canada approved but received a do not reimburse CADTH recommendation August 2019 from CADTH due to the magnitude of benefit felt to be too small to warrant approval, despite being recognized as addressing the needs of a population with unmet need. It is currently funded in Quebec having received a reimburse recommendation from INESSS. Outside of Quebec, patients have been able to apply to the manufacturer for access to the drug under review through private insurance or direct user pay. Therefore, the majority of mCRC patients in Canada do not have access to publicly funded the drug under review according to CGOEN. OH-CCO's Drug Advisory Committees also echoed this concern highlighted by CGOEN. Therefore, CGOEN felt that findings from the original trial of trifluridine-tipiracil (alone) compared to BSC, should be considered in the current review of trifluridine-tipiracil, in combination with bevacizumab, given the current landscape in Canada.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2. Responses to Questions from the Drug Programs

Drug program implementation questions	Response
Relevant comparators	
SUNLIGHT compared trifluridine tipiracil-bevacizumab against trifluridine tipiracil, which is not funded. The comparator of trifluridine tipiracil was negative pCODR in 2018 and 2019 in which PAG input noted the trifluridine tipiracil had very modest overall survival (1.8 months), short progression free survival (incremental 0.3 months PFS), low objective response rates and occurrence of serious side effects. Regorafenib is indicated in the same group of patients and pERC did not recommend funding regorafenib as it had only a very modest progression free survival and overall survival benefit, moderate but not insignificant toxicities and a similar decline in the quality of life.	The clinical experts consulted by CADTH acknowledged that if trifluridine-tipiracil in combination with bevacizumab were to be recommended for reimbursement, it would replace trifluridine-tipiracil as well as regorafenib. pERC agreed with the clinical experts that if trifluridine-tipiracil in combination with bevacizumab were to be reimbursed, it would replace trifluridine-tipiracil as well as regorafenib, which are not currently publicly reimbursed. Regorafenib may still be available through private payers. pERC noted that for trifluridine-tipiracil, in combination with bevacizumab, to be successfully implemented, access to both the oral and IV components of the regimen should be aligned.
Generalizability	
Should trifluridine-tipiracil bevacizumab be used in patients with - small bowel or appendiceal adenocarcinoma? - ECOG PS >1 - MSI-H/dMMR	The clinical experts consulted by CADTH anticipated that trifluridine-tipiracil, in combination with 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

Drug program implementation questions	Response
- BRAF V600E mutation	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, in combination with 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, in combination with 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 and dMMR and 19 (5.6%) patients with 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, in combination with bevacizumab, if all other lines of therapy have been exhausted.
Funding algorithm	
Drug may change place in therapy of drugs reimbursed in subsequent lines.	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 in combination with 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 in combination with bevacizumab to replace BSC as a new treatment option. pERC agreed with the clinical experts that if trifluridine-tipiracil in combination with 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 in combination with bevacizumab for use in the third line setting and beyond.
Care provision issues	
If bevacizumab is discontinued for reasons other than disease progression, can trifluridine tipiracil be continued as monotherapy and vice-versa? This is a key question as the trifluridine tipiracil without bevacizumab has two negative pCODR recommendations July 6, 2018 and August 29, 2019.	The clinical experts consulted by CADTH indicated that trifluridine-tipiracil alone (as monotherapy) would only be considered to be administered without bevacizumab if a patient had a known contraindication or experienced an absolute contraindication (e.g., gastrointestinal perforation) to bevacizumab. 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.
System and economic issues	
There are confidential negotiated prices for panitumumab, bevacizumab, pembrolizumab, and encorafenib.	*This is a comment from the drug plans to inform pERC deliberations.*

Drug program implementation questions	Response
In Canada, bevacizumab is available as a biosimilar. Therefore, for this indication, bevacizumab in combination with trifluridine-tipiracil will be utilizing a biosimilar bevacizumab as well.	*This is a comment from the drug plans to inform pERC deliberations.*

BRAF = v-RAF murine sarcoma viral oncogene homolog B; BSC = best supportive care; dMMR = deficient mismatch repair; ECOG PS = Eastern Co-operative Oncology Group Performance Status; MSI-H = microsatellite instability-high; pCODR = pan-Canadian Oncology Drug Review; PFS = progression-free survival.

Clinical Evidence

Systematic Review

Description of Studies

One randomized, phase III, open-label, multicentre study (SUNLIGHT) evaluated the efficacy and safety of trifluridine-tipiracil in combination with bevacizumab versus trifluridine-tipiracil (alone). SUNLIGHT enrolled 492 adults with advanced mCRC who had received up to two previous chemotherapy regimens and demonstrated progressive disease or intolerance to their last regimen, and randomized patients to each group with stratification by geographic region (North America, European Union, Rest of the World), time since first metastasis diagnosis (< 18 months, ≥ 18 months), and RAS status (wild type, mutant). The primary objective of SUNLIGHT was to demonstrate superiority of overall survival (OS) and the key secondary objective was to estimate investigator-assessed progression-free survival (PFS). Additional secondary end points included health-related quality of life (HRQoL) assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EQ-5D-5L, and treatment-emergent adverse events (TEAEs).

Patients had a mean age of 61.7 years (standard deviation [SD] = 11.1), and most were enrolled from the European Union (64.0%). Most patients had a primary diagnosis of colon cancer (73%) and stage IV disease (66%), and primary tumour located on the left side (72%). The time from the diagnosis of the first metastasis until randomization was 18 months or longer in 57.5% of the patients, and 30.7% had RAS wild-type disease. Most patients (92.1%) had received two previous treatment regimens for metastatic disease, 2.6% had more than 2 prior regimens and 5.3% had received 1 previous treatment regimen. All patients had received previous fluoropyrimidine-based therapy, 72.0% had received previous anti-VEGF therapy (47.8% had received bevacizumab as part of their first regimen, 43.9% as part of their second regimen, and 20.3% as part of both their first and second regimens), and 93.7% of the patients with RAS wild-type disease had received previous anti-EGFR therapy. Demographic characteristics were generally similar between trifluridine-tipiracil in combination with bevacizumab and trifluridine-tipiracil (alone), with notable (> 5%) between-group differences for patients with age 65 years and older (41% versus 48%, respectively), primary tumour located on the right side (25% versus 31%, respectively), and primary tumour located on the left side (75% versus 69%, respectively).

Efficacy Results

The key efficacy results from the SUNLIGHT trial are summarized, based on the data cut-off date of July 5, 2022 for clinical (non-survival) data and July 19, 2022 for survival data.

OS

At the survival cut-off date of July 19, 2022, the median follow-up was 14.2 months (interquartile range, 12.6 to 16.4) in the trifluridine-tipiracil in combination with bevacizumab group and 13.6 months (interquartile range, 12.7 to 15.9) in the trifluridine-tipiracil (alone) group. OS (95% confidence interval [CI]) at 6 months among patients in the full analysis set (FAS) population was 0.77 (0.72 to 0.82) and 0.61 (0.55 to 0.67) for trifluridine-tipiracil in combination with bevacizumab and trifluridine-tipiracil alone, respectively. OS at 12 months was 0.43 (0.36 to 0.49) and 0.30 (0.24 to 0.36) for trifluridine-tipiracil in combination with bevacizumab and trifluridine-tipiracil alone, respectively. The median (95% CI) OS was 10.78 months (9.36 to 11.83) in the trifluridine-tipiracil in combination with bevacizumab group and 7.46 months (6.34 to 8.57) in the trifluridine-tipiracil (alone) group. The hazard ratio (HR) (95% CI) in the FAS population was 0.61 (0.49 to 0.77; P < 0.001) for trifluridine-tipiracil in combination with bevacizumab when compared with trifluridine-tipiracil alone.

PFS

The PFS (95% CI) at 3 months among patients in the FAS population was 0.73 (0.67 to 0.78) in the trifluridine-tipiracil in combination with bevacizumab group versus 0.45 (0.39 to 0.51) in the trifluridine-tipiracil (alone) group. PFS (95% CI) at 6 months was 0.43 (0.37 to 0.49) and 0.16 (0.11 to 0.21) for trifluridine-tipiracil in combination with bevacizumab and trifluridine-tipiracil alone, respectively. Median (95% CI) PFS was 5.6 months (4.50 to 5.88) in the trifluridine-tipiracil in combination with bevacizumab group and 2.4 months (2.07 to 3.22) in the trifluridine-tipiracil (alone) group. The HR (95% CI) for PFS was 0.44 (0.36 to 0.54; P < 0.001) for trifluridine-tipiracil in combination with bevacizumab when compared with trifluridine-tipiracil alone.

HRQoL

In SUNLIGHT, analyses for the EORTC QLQ-C30 and EQ-5D-5L were performed in patients from the FAS with at least 1 questionnaire item at baseline and during the study period. Higher scores in the EORTC QLQ-C30 Global Health Status and EQ-5D-5L utility and visual analogue scale (VAS) indicated better HRQoL, with positive change from baseline indicating benefit and negative change from baseline indicating deterioration.

In the Global Health Status score, the least squares mean (LSM) change from baseline (95% CI) was –2.85 (–5.92 to 0.22) for trifluridine-tipiracil in combination with bevacizumab and –6.62 (–10.36 to –2.88) for trifluridine-tipiracil alone. The LSM difference (95% CI) in change from baseline for Global Health Status was 3.77 (0.22 to 7.32; P = 0.038) in favour of trifluridine-tipiracil in combination with bevacizumab. The number of patients in the FAS population with 10 points or greater definitive deterioration were 62 (25.2%) and 72 (29.3%) in the trifluridine-tipiracil in combination with bevacizumab and trifluridine-tipiracil (alone) group, respectively. Median time (95% CI) until definitive deterioration in the Global Health Status was 8.54 months (7.49 to 10.94) in the trifluridine-tipiracil in combination with bevacizumab group and 4.70 (4.01 to 5.78) in the trifluridine-tipiracil (alone) group (P < 0.001).

In the EQ-5D-5L utility, the LSM change from baseline (95% CI) was –0.01 (–0.03 to 0.01) for trifluridine-tipiracil in combination with bevacizumab and –0.03 (–0.06 to –0.01) for trifluridine-tipiracil alone. The LSM difference (95% CI) in change from baseline for EQ-5D-5L utility was 0.02 (0.00 to 0.05; P = 0.070). In the EQ-5D-5L VAS, the LSM change from baseline (95% CI) was –0.87 (–3.74 to 2.00) for trifluridine-tipiracil in combination with bevacizumab and –5.34 (–8.75 to –1.92) for trifluridine-tipiracil alone. The LSM difference (95% CI) in change from baseline for EQ-5D-5L VAS was 4.46 (1.11 to 7.81; P = 0.009).

Harms Results

The analysis population for harms included all patients who received at least 1 dose of trifluridine-tipiracil, with patients grouped according to the treatment received. Safety data were performed using the clinical data cut-off of July 5, 2022.

In SUNLIGHT, the number of patients reporting any TEAEs was 98.0% for trifluridine-tipiracil in combination with bevacizumab and 98.0% for trifluridine-tipiracil alone. The most common TEAEs occurring in at least 20% of patients in either treatment group were neutropenia (62.2% versus 51.2%), nausea (37.0% versus 27.2%), anemia (28.9% versus 31.7%), asthenia (24.4% versus 22.4%), fatigue (21.5% versus 16.3%), diarrhea (20.7% versus 18.7%) and decreased appetite (20.3% versus 15.4%).

The proportion of patients who experienced at least 1 serious adverse event (SAE) was 24.8% in the trifluridine-tipiracil in combination with bevacizumab group and 31.3% in the trifluridine-tipiracil (alone) group. SAEs occurring in at least 2% of patients in either treatment group were intestinal obstruction (2.8% versus 2.0%), malignant neoplasm progression (2.4% versus 4.5%), COVID-19 (2.0% versus 2.4%), anemia (0.4% versus 3.3%), febrile neutropenia (0.4% versus 2.4%), jaundice (0.8% versus 2.0%), and hepatic failure (0 versus 2.0%). The proportion of patients who experienced AEs grade 3 or greater were 72.4% in the trifluridine-tipiracil in combination with bevacizumab group and 69.5% in the trifluridine-tipiracil (alone) group. The most common AEs of grade 3 or greater occurring in at least 5% of patients in either treatment group were neutropenia (43.1% versus 32.1%), anemia (6.1% versus 11.0%), neutrophil count decreased (8.9% versus 5.3%), and hypertension (5.7% versus 1.2%).

A total of 12.6% of patients experienced TEAEs that led to treatment withdrawal in each treatment group. Withdrawals due to AEs occurring in at least 1 patient in either treatment group were asthenia (3.3% versus 0.4%), jaundice (0.8% versus 0.8%), decreased appetite (0.8% versus 0.4%), fatigue (0.4% versus 0.8%), anemia (0.4% versus 0.8%), intestinal obstruction (0.4% versus 0.8%), malignant neoplasm progression (0.4% versus 0.8%), biliary dilation (0.8% versus 0), blood bilirubin increased (0.8% versus 0), pain (0.8% versus 0), and metastases to central nervous system (0 versus 0.8%).

At the clinical cut-off date, a total of 323 patients had died, including 59.4% of patients in the trifluridine-tipiracil in combination with bevacizumab group and 72.0% of patients in the trifluridine-tipiracil (alone) group. A total of 37 deaths during the treatment period occurred in 13 (5.3%) patients and 24 (9.8%) patients in the trifluridine-tipiracil in combination with bevacizumab and trifluridine-tipiracil (alone) group, respectively. Deaths which occurred during the follow-up period (54.1% and 62.2%) were mostly due to progressive disease in the trifluridine-tipiracil in combination with bevacizumab and trifluridine-tipiracil (alone) group, respectively.

Notable Harms

Notable harms in the SUNLIGHT trial were conducted post-hoc using lists of predefined preferred terms with similar medical concepts to define the overall terms. The proportion of patients who experienced bone marrow suppression were 80.9% in the trifluridine-tipiracil in combination with bevacizumab group and 73.2% of patients in the trifluridine-tipiracil (alone) group, including neutropenia (62.2% versus 51.2%), anemia (28.9% versus 31.7%), thrombocytopenia (17.1% versus 11.4%), and leukopenia (6.5% versus 8.5%). The proportion of patients who experienced at least 1 TEAE related to infections were 30.9% in the trifluridine-tipiracil in combination with bevacizumab group and 23.2% in the trifluridine-tipiracil (alone) group. Infections of grade 3 or higher were reported for 7.7% of patients and 7.3% of patients in the trifluridine-tipiracil in combination with bevacizumab and trifluridine-tipiracil (alone) group, respectively. The proportion of patients who experienced gastrointestinal symptoms were 48.4% in the trifluridine-tipiracil in combination with bevacizumab group and 41.1% in the trifluridine-tipiracil (alone) group, including nausea (37.0% versus 27.2%), diarrhea (20.7% versus 18.7%), and vomiting (18.7% versus 14.6%). Gastrointestinal symptoms of grade 3 or higher were reported for 2.0% of patients and 4.9% of patients in the trifluridine-tipiracil in combination with bevacizumab and trifluridine-tipiracil (alone) group, respectively, including nausea (1.6% versus 1.6%), diarrhea (0.8% versus 2.4%), and vomiting (0.8% versus 1.6%). The proportion of patients who experienced hypertension was 10.2% in the trifluridine-tipiracil in combination with bevacizumab group and 2.0% in the trifluridine-tipiracil (alone) group. Hypertension events of grade 3 or higher were reported for 5.7% of patients and 1.2% of patients in the trifluridine-tipiracil in combination with bevacizumab and trifluridine-tipiracil (alone) group, respectively.

Critical Appraisal

SUNLIGHT was a phase III, open-label RCT that used stratified randomization that appeared to be appropriate as patients were generally balanced between treatment groups for key prognostic factors, disease characteristics, and prior chemotherapy regimens. The open-label study design has the potential to impact HRQoL for which knowledge of the assigned treatment may bias reporting in favour of the intervention (trifluridine-tipiracil in combination with bevacizumab) group. Trifluridine-tipiracil (alone) was the comparator used in the SUNLIGHT trial. Trifluridine-tipiracil is approved and available in Canada but is not publicly funded such that patients may gain access via private drug coverage or out-of-pocket costs. OS as primary and PFS as key secondary end points were included in statistical hierarchical testing and were appropriate key end points according to treatment guidelines and outcomes identified important by patients and clinicians. Findings for OS and PFS demonstrated a benefit for patients treated with trifluridine-tipiracil in combination with bevacizumab; the proportional hazards assumption was likely valid based on Schoenfeld residuals testing and visual inspection of the K-M curves and log(-log) curves showing crossover early during treatment but clear separation thereafter. For HRQoL, MIDs were identified in the literature among patients with cancer and with mCRC for the cancer-specific EORTC QLQ-C30 tool, and among patients with cancer for the generic preference-based EQ-5D-5L tool. It was unclear whether significant missing data for HRQoL by cycle 3 to 4 may impact findings. Longer treatment duration and higher mean dose of trifluridine-tipiracil in the trifluridine-tipiracil in combination with bevacizumab group may not be fully explained by the relatively small difference in treatment discontinuations between groups and it is unknown whether the open-label study design may have impacted patients' adherence to assigned treatment.

The enrolled population in the SUNLIGHT trial were generally aligned with patients seen in clinical practice according to the clinical experts consulted by CADTH despite there being no patients in Canada enrolled in the trial. Patients who were excluded from eligibility (with more than 2 prior chemotherapy regimens, had prior treatment with trifluridine-tipiracil, with ECOG PS greater than 1) were considered by the clinical experts consulted by CADTH to be eligible for treatment with trifluridine-tipiracil in combination with bevacizumab. The clinical experts consulted by CADTH also considered patients with small bowel or appendiceal adenocarcinoma as eligible to be treated with trifluridine-tipiracil in combination with bevacizumab based on the small number of patients that precludes a trial enrolling patients exclusively in this subpopulation. While the clinical experts consulted by CADTH noted a higher proportion of patients with RAS status expressing mutations (compared with the wild-type), the key prognostic indicators (i.e., age, number of metastatic sites, number of prior chemotherapy regimens, sidedness of tumour, and ECOG PS) appeared to be reflective of patients in clinical practice. The intervention in the SUNLIGHT trial is for an unlabeled indication, as trifluridine-tipiracil (alone) was approved by Health Canada for adult patients with mCRC, but not publicly funded. Acknowledging that this treatment is only available to a small patient population with access (via private insurance or self-funding) among other treatment options (including BSC and regorafenib, the latter available via compassionate access), the clinical experts consulted by CADTH emphasized that trifluridine-tipiracil (alone) is the most relevant comparator for trifluridine-tipiracil in combination with bevacizumab. Outcomes included in SUNLIGHT were identified as important to patients and clinicians, including survival, HRQoL, and TEAEs. OS at 6

months and 12 months were highlighted by the clinical experts consulted by CADTH as important for assessing effects of treatment. Furthermore, PFS (at 3 months and 6 months) was an appropriate end point as supportive evidence for OS. Findings may be limited in generalizability to patients with mCRC in Canada for EQ-5D-5L health utility values derived using a French value set and in the absence of patients enrolled from sites in Canada. A higher proportion of patients who discontinued treatment in the trifluridine-tipiracil (alone) group were not concerning to the clinical experts consulted by CADTH as they noted that they were low with similar between-group rates for discontinuations due to AEs and deaths.

Long-Term Extension Studies

No long-term extension studies were submitted in the systematic review evidence.

Indirect Comparisons

Description of Studies

The sponsor submitted a systematic review and indirect treatment comparison (ITC) report where trifluridine-tipiracil in combination with bevacizumab was compared to BSC, regorafenib and trifluridine-tipiracil alone among patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.

In this ITC, OS, PFS and treatment-related AEs were assessed. The network meta-analyses (NMAs) were conducted within a Bayesian framework.

In total, 10 RCTs were included and contributed evidence. These studies were conducted in Asia, North America, South America, and Europe. There was no information as to whether Canadian patients were enrolled. The mean age of patients ranged from 55.5 years to 67 years. The proportion of male patients ranged from 48.5% to 64.8%. These studies were published between 2007 and 2023. The included RCTs evaluated the efficacy and safety of the following therapies which are relevant to this review: trifluridine-tipiracil in combination with bevacizumab in 2 studies, BSC alone in 7 studies, regorafenib in 2 studies, and trifluridine-tipiracil alone in 6 studies.

Efficacy Results

Based on the results of the sponsor-submitted ITC, treatment of trifluridine-tipiracil in combination with bevacizumab may be associated with prolonged OS and PFS in patients with mCRC, compared to other treatments such as BSC, regorafenib or trifluridine-tipiracil alone.

Harms Results

Treatment of trifluridine-tipiracil in combination with bevacizumab may be associated with increased risk of treatment-related AEs in patients with mCRC, compared to other treatments such as BSC, regorafenib or trifluridine-tipiracil alone. However, results of the NMA for treatment-related AEs were imprecise with wide credible intervals.

Critical Appraisal

In the sponsor-submitted ITC, based on the data presented, potential sources of heterogeneity with respect to the patients' characteristics were identified, such as ECOG performance status (the proportion of patients with ECOG performance status of 0 ranged from 22% to 64%) and RAS status (the proportion of patients with RAS positive status ranged from 27% to 70%) at baseline. Heterogeneities in trial characteristics were observed in study design (such as blinding, definition of BSC across trials and prior lines of therapies). Despite various statistical models being employed to lessen the impact of potential clinical heterogeneity on the estimated comparative treatment effect of trifluridine-tipiracil in combination with bevacizumab, there remains significant uncertainty in the ITC results. In addition, given the lack of closed loops in any of the networks, consistency in the ITC analyses could not be tested. All comparisons are therefore informed only by indirect evidence, which increases the level of uncertainty.

Some important patient characteristics in the included trials were not reported in this ITC, such as treatment duration, timing of study endpoint evaluation, use of subsequent therapies after disease progression, and the length of follow-up. Therefore, adjustment for

their potential treatment effect modification was not feasible, and it is likely that the transitivity assumption (the assumption that if treatment A is preferred to treatment B and treatment B is preferred to treatment C then treatment A is preferred to treatment C) was not met. Furthermore, it is unclear whether the results can provide insight into the long-term effect of the study drug for patients with mCRC due to a lack of data regarding the length of trial follow-up.

Outcomes other than OS and PFS that are important to the patients and clinicians (e.g., HRQoL) were not analyzed in the ITC. A more comprehensive assessment on the safety profile of the study drug is desired.

Studies Addressing Gaps in the Evidence from the Systematic Review

No additional studies addressing important gaps in the systematic review evidence were submitted.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and 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: survival (overall survival, and progression-free survival), HRQoL (measured as LSM change from baseline and the proportion of patients with a 10-point or greater deterioration from baseline in the EORTC QLQ-C30 Global Health Status, and LSM change from baseline in the EQ-5D-5L utility score and VAS), and harms (bone marrow suppression, infections, gastrointestinal symptoms, and hypertension).

When possible, the certainty was rated in the context of the presence or absence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review for survival (overall survival, and progression-free survival), HRQoL (EORTC QLQ-C30 and EQ-5D-5L), and harms (bone marrow suppression, infections, gastrointestinal symptoms, and hypertension).

Table 2: Summary of Findings for Trifluridine-Tipiracil in Combination with Bevacizumab Versus Trifluridine-Tipiracil Alone for Patients With Metastatic Colorectal Cancer

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Trifluridine-tipiracil	Trifluridine-tipiracil plus bevacizumab	Difference		
Survival							
Overall Survival							
Probability of overall survival at 6 months Median follow-up: 14.1 months	492 (1 RCT)	RR 1.26 (1.17 to 1.36)	610 per 1,000	770 per 1,000 (720 to 820 per 1,000)	160 more per 1,000 (80 to 240 more per 1,000)	Moderate[a]	Trifluridine-tipiracil in combination with bevacizumab likely results in a clinically important increase in the probability of overall survival at 6 months when compared with trifluridine-tipiracil alone.
Probability of overall survival at 12 months Median follow-up: 14.1 months	492 (1 RCT)	RR 1.43 (1.31 to 1.57)	300 per 1,000	430 per 1,000 (360 to 490 per 1,000)	130 more per 1,000 (40 to 220 more per 1,000)	Moderate[b]	Trifluridine-tipiracil in combination with bevacizumab likely results in a clinically important increase in the probability of overall survival at 12 months when compared with trifluridine-tipiracil alone.
Progression-Free Survival							
Probability of progression-free survival at 3 months Median follow-up: 14.1 months	492 (1 RCT)	RR 1.62 (1.50 to 1.76)	450 per 1,000	730 per 1,000 (670 to 780 per 1,000)	280 more per 1,000 (200 to 360 more per 1,000)	High[c]	Trifluridine-tipiracil in combination with bevacizumab results in a clinically important increase in the probability of progression-free survival at 3 months when compared with trifluridine-tipiracil alone.
Probability of progression-free survival at 6 months Median follow-up: 14.1 months	492 (1 RCT)	RR 2.69 (2.49 to 2.91)	160 per 1,000	430 per 1,000 (370 to 490 per 1,000)	270 more per 1,000 (190 to 350 more per 1,000)	Moderate[d]	Trifluridine-tipiracil in combination with bevacizumab likely results in a clinically important increase in the probability of progression-free survival at 6 months when compared with trifluridine-tipiracil alone.
Health-Related Quality of Life							
EORTC QLQ-C30 (0 [worse health-related quality of life] to 100 [best health-related quality of life])							
Global Health Status, LSM change from baseline, points (95% CI) Follow-up: cycle 1 to cycle 10[e]	450 (1 RCT)	NA	–6.62	–2.85 (–5.92 to 0.22)	3.77 (0.22 to 7.32)	Very low[f]	The evidence is very uncertain about the effect of trifluridine-tipiracil in combination with bevacizumab on the LSM change from baseline in the Global Health Status score when compared with trifluridine-tipiracil alone.
Global Health Status, patients with at least a 10-point	492 (1 RCT)	RR 0.86 (0.64 to 1.15)	293 per 1,000	252 per 1,000 (NR)	40 fewer per 1,000	Very low[g]	The evidence is very uncertain about the effect of trifluridine-tipiracil in combination with bevacizumab on the proportion of

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Trifluridine-tipiracil	Trifluridine-tipiracil plus bevacizumab	Difference		
deterioration from baseline, % (95% CI) Follow-up: median 8.54 months vs. 4.70 months					(120 fewer to 40 more per 1,000)		patients with at least a 10-point deterioration from baseline in the Global Health Status score when compared with trifluridine-tipiracil alone.
EQ-5D-5L Utility Score (0 [death] to 1 [full health])							
EQ-5D-5L utility score, LSM change from baseline, points (95% CI) Follow-up: cycle 1 to cycle 10[e]	448 (1 RCT)	NA	–0.03	–0.01 (–0.03 to 0.01)	0.02 (0.00 to 0.05)	Very low[h]	The evidence is very uncertain about the effect of trifluridine-tipiracil in combination with bevacizumab on the LSM change from baseline in EQ-5D-5L utility score when compared with trifluridine-tipiracil alone.
EQ-5D-5L VAS (0 [worst health imaginable] to 100 [best health imaginable])							
EQ-5D-5L VAS, LSM change from baseline, points (95% CI) Follow-up: cycle 1 to cycle 10[e]	448 (1 RCT)	NA	–5.34	–0.87 (–3.74 to 2.00)	4.46 (1.11 to 7.81)	Low[i]	Trifluridine-tipiracil in combination with bevacizumab may result in little to no clinically important difference in the LSM change from baseline in EQ-5D-5L VAS score when compared with trifluridine-tipiracil alone.
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 trifluridine-tipiracil in combination with bevacizumab on caregiver burden when compared with trifluridine-tipiracil alone.
Notable Harms							
Proportion of patients with bone marrow suppression, % (95% CI) Follow-up: median 5.0 months vs. 2.1 months	492 (1 RCT)	NA	732 per 1,000	809 per 1,000 (NR)	80 more per 1,000 (0 to 150 more per 1,000)	Low[j]	Trifluridine-tipiracil in combination with bevacizumab may result in little to no clinically important difference in the proportion of patients who experience bone marrow suppression when compared with trifluridine-tipiracil alone.
Proportion of patients with infections, % (95% CI)	492 (1 RCT)	NA	232 per 1,000	309 per 1,000 (NR)	80 more per 1,000 (0 to 160 more per 1,000)	Low[k]	Trifluridine-tipiracil in combination with bevacizumab may result in little to no clinically important difference in the proportion of patients who experience

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Trifluridine-tipiracil	Trifluridine-tipiracil plus bevacizumab	Difference		
Follow-up: median 5.0 months vs. 2.1 months							infections when compared with trifluridine-tipiracil alone.
Proportion of patients with gastrointestinal symptoms, % (95% CI) Follow-up: median 5.0 months vs. 2.1 months	492 (1 RCT)	NA	411 per 1,000	484 per 1,000 (NR)	70 more per 1,000 (10 fewer to 160 more per 1,000)	Low[l]	Trifluridine-tipiracil in combination with bevacizumab on may result in little to no clinically important difference in the proportion of patients who experience gastrointestinal symptoms when compared with trifluridine-tipiracil alone.
Proportion of patients with hypertension, % (95% CI) Follow-up: median 5.0 months vs. 2.1 months	492 (1 RCT)	RR 5.00 (1.95 to 12.85)	20 per 1,000	102 per 1,000 (NR)	80 more per 1,000 (40 to 120 more per 1,000)	Low[m]	Trifluridine-tipiracil in combination with bevacizumab may result in little to no clinically important difference in the proportion of patients who experience hypertension when compared with trifluridine-tipiracil alone.

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LSM = least squares mean; NA = not assessed/not applicable; NR = nor reported; RCT = randomized controlled trial; RR = risk ratio; VAS = visual analogue scale.

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 imprecision. There is no established MID. The clinical experts consulted by CADTH indicated that a between-group difference of 10% to 20% was clinically important. The lower bound of the 95% CI for difference between groups did not reach the identified threshold.

[b] Rated down 1 level for serious imprecision. There is no established MID. The clinical experts consulted by CADTH indicated that a between-group difference of 10% to 20% was clinically important. The lower bound of the 95% CI for difference between groups did not reach the identified threshold.

[c] There is no established MID. The clinical experts consulted by CADTH indicated that a between-group difference of 20% was clinically important.

[d] Rated down 1 level for serious imprecision. There is no established MID. The clinical experts consulted by CADTH indicated that a between-group difference of 20% was clinically important. The lower bound of the 95% CI for difference between groups did not reach the identified threshold.

[e] A repeated measures mixed effects model that included terms for treatment, baseline stratification factors, baseline score, time to visit prior to any procedure (at each cycle including the withdrawal visit), and treatment groups by time to visit interaction, was used to compare change from baseline sub-scales scores longitudinally (cycle 1 to cycle 10) over time between treatment groups.

[f] Rated down 2 levels for very serious study limitations. The open-label study design and patients' and caregivers' knowledge of assigned treatment may have biased reporting of HRQoL questionnaires. There was substantial missing data from treatment cycle 1 to cycle 10 that may impact the prognostic balance of the treatment groups. Rated down 1 level for serious imprecision. An MID of 5.53 to 6.36 (weighted 5.86) for improvement, and –9.21 to –6.81 (weighted –8.13) for deterioration was identified in the literature. The point estimate suggests little to no difference and the 95% CI included the possibility of important benefit. Statistical testing for EORTIC QLQ-C30 were not conducted; therefore, results are considered as supportive evidence.

[g] Rated down 2 levels for very serious study limitations. The open-label design and patients' and caregivers' knowledge of assigned treatment may have biased reporting of HRQoL questionnaires. There was substantial missing data from cycle 1 to cycle 10 that may impact the prognostic balance of treatment groups. Rated down 1 level for serious imprecision. The clinical experts consulted by CADTH indicated that a between-group difference of 10% was clinically important. The lower bound of the 95% CI for difference between groups included possible important benefit Statistical testing for EORTIC QLQ-C30 were not conducted; therefore, results are considered as supportive evidence.

[h] Rated down 2 levels for very serious study limitations. The open-label study design and patients' and caregivers' knowledge of assigned treatment may have biased reporting of HRQoL questionnaires. There was substantial missing data across and up to treatment cycle 10 that may impact the prognostic balance of the treatment groups. Rated down 1 level for serious

indirectness due to utility values that were derived from a French population set. No MID was identified in the literature for patients with mCRC. An MID of 0.08 based on literature for patients with cancer was identified by the clinical experts consulted by CADTH. Statistical testing for EQ-5D-5L were not conducted; therefore, results are considered as supportive evidence.

[i] Rated down 2 levels for serious study limitations. The open-label study design and patients' and caregivers' knowledge of assigned treatment may have biased reporting of HRQoL questionnaires. There was substantial missing data across and up to treatment cycle 10 that may impact the prognostic balance of the treatment groups. No MID was identified in the literature for patients with mCRC. An MID of greater than 7 points to 10 points was identified by the clinical experts consulted by CADTH, based on literature for patients with cancer. Statistical testing for EQ-5D-5L were not conducted; therefore, results are considered as supportive evidence.

[j] Rated down 1 level for post-hoc analyses of adverse events of risk of bias in the selection of outcomes reported in the results. Rated down 1 level for serious imprecision. The clinical experts consulted by CADTH indicated that a between-group difference of 10% was clinically important. The point estimate suggests little to no difference and the 95% CI included the possibility of important harm.

[k] Rated down 1 level for post-hoc analyses of adverse events of risk of bias in the selection of outcomes reported in the results. Rated down 1 level for serious imprecision. The clinical experts consulted by CADTH indicated that a between-group difference of 10% was clinically important. The point estimate suggests little to no difference and the 95% CI included the possibility of important harm.

[l] Rated down 1 level for post-hoc analyses of adverse events of risk of bias in the selection of outcomes reported in the results. Rated down 1 level for serious imprecision. The clinical experts consulted by CADTH indicated that a between-group difference of 10% was clinically important. The point estimate suggests little to no difference and the 95% CI included the possibility of important harm.

[m] Rated down 1 level for post-hoc analyses of adverse events of risk of bias in the selection of outcomes reported in the results. Rated down 1 level for serious imprecision. The clinical experts consulted by CADTH indicated that a between-group difference of 10% was clinically important. The point estimate suggests little to no difference and the 95% CI included the possibility of important harm.

Source: SUNLIGHT Clinical Study Report. Details included in the table were provided from sponsor in response to additional data request.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Adult patients with metastatic colorectal cancer 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 RAS wild-type, anti-EGFR agents.
Treatment	Trifluridine-tipiracil with bevacizumab
Dose regimen	The recommended dose is 35 mg/m^2 of trifluridine-tipiracil (to a maximum of 80 mg/dose based on the trifluridine component) twice daily on Days 1 to 5 and Days 8 to 12 every 28 days as long as benefit is observed or until unacceptable toxicity occurs, plus 5 mg/kg of bevacizumab every 14 days.
Submitted price	Trifluridine 15 mg trifluridine/ tipiracil 6.14 mg: $76.25 per tablet Trifluridine 20 mg/ tipiracil 8.19 mg: $78.54 per tablet
Submitted treatment Cost	The 28-day cost of trifluridine-tipiracil with bevacizumab is $8,191. The 28-day average weighted cost of trifluridine-tipiracil alone and bevacizumab alone is $5,405 and $2,786, respectively.
Comparator	BSC (interventions required to provide palliation of symptoms and improve quality of life as needed)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (28.3 years)
Key data sources	SUNLIGHT trial, RECOURSE trial, and network meta-analyses.
Key limitations	• The comparative efficacy and safety of trifluridine-tipiracil with bevacizumab relative to BSC is uncertain owing to a lack of head-to-head trials and limitations with the sponsor's NMA. Indirect evidence submitted by the sponsor suggests that trifluridine-tipiracil with bevacizumab may be associated with prolonged OS and PFS compared to BSC, but the magnitude of these differences is associated with substantial uncertainty. Clinical expert input indicated that the sponsor's projections of OS and PFS for trifluridine-tipiracil with bevacizumab were likely overestimated based on the natural history of disease and available trial evidence. • Treatment duration was modelled inappropriately. The sponsor assumed that all patients would discontinue trifluridine-tipiracil with bevacizumab after cycle 5, creating a misalignment between treatment costs and efficacy as patients continued to receive the benefits of treatment but did not incur the corresponding treatment cost. Clinical expert input indicated treatment duration would be closely aligned with PFS. • The use of a PSM introduces structural assumptions about the relationship between PFS and OS that likely do not accurately reflect causal relationships within the disease pathway. In the sponsor's base case, these assumptions produced a post-progression survival benefit that favored trifluridine-tipiracil with bevacizumab for which there was no evidence to support. • The impact of adverse events on patient quality of life is uncertain. Disutilities were not included in the sponsor's base case and the values available for inclusion in a scenario analysis lacked face validity. Additionally, the rate of adverse events was based on naïve comparisons of trifluridine-tipiracil with bevacizumab, without adjustment or accounting for differences in patient characteristics.
CADTH reanalysis results	• CADTH incorporated the following changes to address the identified limitations for the base case: Use of full parametric survival curves for OS and PFS; use of a Generalized Gamma distribution to extrapolate OS; treatment duration equal to PFS; and alternative health state utility values from the CORRECT trial. • In the CADTH base case, trifluridine-tipiracil with bevacizumab is associated with higher costs (incremental: $100,657) and higher QALYs (incremental: 0.54) compared with BSC over a lifetime time horizon, resulting in an ICER of $195,000 per QALY gained.

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; PSM = partitioned survival model; QALY= quality-adjusted life-year; OS = overall survival; PFS = progression-free survival; KM = Kaplan Meier; NMA = network meta-analysis; EGFR = epidermal growth factor receptor; RAS = rat sarcoma virus; VEGF = vascular endothelial growth factor.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the number of eligible patients is uncertain, the treatment duration for trifluridine-tipiracil with bevacizumab is uncertain, the estimated proportion of patients that would be eligible for public coverage is uncertain, and market uptake is uncertain.

In the absence of more reliable input values to estimate the eligible population size and the proportion of patients eligible for public coverage, the sponsor's base case was maintained. The net budget impact of reimbursing trifluridine-tipiracil with bevacizumab for the treatment of adult patients with metastatic colorectal cancer 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 RAS wild-type, anti-EGFR agents, was estimated to be $31,235,958 in Year 1, $37,485,914 in Year 2, and $42,271,406 in Year 3. The net budget impact over the 3-year time horizon was $110,993,278.

pERC Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: January 10, 2024

Regrets:

1 of expert committee member did not attend.

Conflicts of interest:

1 expert committee member did not participate due to considerations of conflict of interest.