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CADTH Reimbursement Review

Trifluridine-Tipiracil (Lonsurf)

Sponsor: Taiho Pharma Canada, Inc.
Therapeutic area: Metastatic colorectal cancer

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Abbreviations

AE	adverse event
anti-EGFR	anti–epidermal growth factor receptor
anti-VEGF	anti–vascular endothelial growth factor
BSA	body surface area
BSC	best supportive care
CCRAN	Colorectal Cancer Resource & Action Network
CEA	carcinoembryonic antigen
CGOEN	Canadian Gastrointestinal Oncology Evidence Network
CI	confidence interval
CRC	colorectal cancer
CrI	credible interval
dMMR	deficient mismatch repair
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-5L	5-Level EQ-5D
EQ VAS	EQ visual analogue scale
FAS	full analysis set
FOLFIRI	folinic acid, fluorouracil, and irinotecan
FOLFOX	folinic acid, fluorouracil, and oxaliplatin
G-CSF	granulocyte colony-stimulating factor
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
HRQoL	health-related quality of life
ITC	indirect treatment comparison
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LSM	least squares mean
mCRC	metastatic colorectal cancer
MID	minimal important difference
MSI-H	microsatellite instability–high
NMA	network meta-analysis

OH-CCO	Ontario Health (Cancer Care Ontario)
OR	odds ratio
OS	overall survival
PFS	progression-free survival
RCT	randomized controlled trial
RECIST 1.1	Response Evaluation Criteria in Solid Tumours Version 1.1
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
SOC	standard of care
TEAE	treatment-emergent adverse event
VEGF	vascular endothelial growth factor

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Background Information of Application Submitted for Review

Item	Description
Drug product	Trifluridine-tipiracil (Lonsurf), 15 mg trifluridine/6.14 mg tipiracil (as tipiracil hydrochloride) and 20 mg trifluridine/8.19 mg tipiracil (as tipiracil hydrochloride), oral tablets
Sponsor	Taiho Pharma Canada, Inc.
Approved Health Canada indication	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
Reimbursement request	Unlabelled indication: Trifluridine-tipiracil plus 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
Health Canada approval status	Not applicable; unlabelled indication
Health Canada review pathway	Not applicable; unlabelled indication
NOC date	Not applicable; unlabelled indication
Recommended dosage	Recommended dosage for the treatment of 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 (as per SUNLIGHT trial): 35 mg/m^2 per dose twice daily, 5 days on/2 days off, over 2 weeks, followed by a 14-day rest; bevacizumab (5 mg/kg, IV) every 2 weeks (day 1 and day 15). This treatment cycle is repeated every 4 weeks.

Anti-EGFR = anti–epidermal growth factor receptor; anti-VEGF = anti–vascular endothelial growth factor; NOC = Notice of Compliance.

Introduction

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.[1] CRC is the third most prevalent cancer[2] and the second leading cause of cancer-related death (11% of all cancer deaths) in Canada.[3] 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 population in 2018 (or 97,755 cases in total).[4] Metastatic colorectal cancer (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.[5] The stage of CRC at diagnosis is strongly associated with survival.[6] 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.[7] Right-sided (proximal) tumours rarely present with

obvious rectal bleeding as the blood becomes admixed with the stool. Left-sided (distal) tumours are more likely to present with bright red blood per rectum and symptoms of bowel obstruction.[8,9] The majority of patients with mCRC have unresectable (inoperable) disease, for which the mainstay of treatment is systemic multidrug chemotherapy.[10,11] The 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*, presence of deficient mismatch repair [dMMR] or microsatellite instability–high [MSI-H]), type and timing of prior therapy, and toxicity profiles of constituent drugs.[5,10,12-15] 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–vascular endothelial growth factor (anti-VEGF) biological agents, and, if *RAS* wild-type, anti–epidermal growth factor receptor (anti-EGFR) agents;[16,17] however, these treatments are not publicly funded in Canada, except in Quebec.[18,19] Following treatment with standard cytotoxic chemotherapy backbone regimens, patients are usually treated with best supportive care (BSC).

The objective of CADTH's Clinical Review Report is to review and critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of trifluridine-tipiracil (15 mg trifluridine and 6.14 mg tipiracil [as tipiracil hydrochloride] and 20 mg trifluridine and 8.19 mg tipiracil [as tipiracil hydrochloride]) plus bevacizumab for the treatment of mCRC in adults who have been previously treated with, or are not candidates for, available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if *RAS* wild-type, anti-EGFR agents, which is an unlabelled indication. Trifluridine-tipiracil alone was previously reviewed by CADTH.

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 experts consulted by CADTH for the purpose of this review.

Patient Input

CADTH received 2 patient group submissions from Colorectal Cancer Resource and Action Network (CCRAN) and Colorectal Cancer Canada. CCRAN used a multifaceted outreach approach by emailing clinicians who treat advanced CRC 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 in 77 survey respondents (including 60 patients, 13 caregivers, and 4 patients who were also caregivers). Colorectal Cancer Canada conducted an online survey of 23 respondents (22 patients and 1 caregiver). Most patients reported that fatigue/weakness, bloody stools, diarrhea, and abdominal cramping/gas/feeling bloated and abdominal pain are common symptoms they experienced and that they felt were important to control. Symptoms of CRC affected quality of life for patients and their families, limiting the ability to work, to exercise, to participate in social activities, or to 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, 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 (OS) (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 or chair time at a cancer centre). CCRAN believes that if publicly funded, trifluridine-tipiracil plus 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 (SOC) 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. SOC first-line treatment in Canada includes pembrolizumab immunotherapy (for patients with dMMR or MSI-H mCRC); chemotherapy with a regimen of folinic acid, fluorouracil, and oxaliplatin (FOLFOX) or a regimen of folinic acid, fluorouracil, and irinotecan (FOLFIRI) in combination with an epidermal growth factor receptor (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 have experienced 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 the switching of the backbone chemotherapeutic regimen (for patients without a *BRAF* V600E mutation) such that patients who were initially treated with FOLFOX would then be switched to FOLFIRI, for example. Antiangiogenic 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 dMMR or MSI-H molecular marker are routinely offered to patients with CRC 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-drug 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 who pay 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 anticancer therapy, according to the clinical experts consulted by CADTH.

The clinical experts consulted by CADTH considered trifluridine-tipiracil plus bevacizumab to represent a new SOC treatment for patients with unresectable CRC after progression on 2 prior lines of anticancer 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 Cooperative Oncology Group Performance Status [ECOG PS] score of 0 to 1, and have adequate hematologic, hepatic, and renal function) and bevacizumab (i.e., without absolute contraindication to the use of a vascular endothelial growth factor [VEGF] inhibitor, including but not limited to uncontrolled hypertension, in situ colonic stent, recent surgery, a high risk for bleeding, and a 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 Symptom Assessment System, EQ-5D), and 3) cross-sectional imaging (e.g., CT scan, MRI) and tumour markers (e.g., carcinoembryonic antigen [CEA], CA 19 to 9). Patients should be assessed after every 2 cycles 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 months to 3 months, according to the clinical experts consulted by CADTH. The clinical experts consulted by CADTH highlighted OS, symptom control, and quality of life as clinically meaningful end points. Side effects or toxicity were key determinants for discontinuing treatment with trifluridine-tipiracil plus bevacizumab, according to the clinical experts consulted by CADTH, particularly for discontinuing bevacizumab in the event of the development of an absolute contraindication to further therapy with a VEGF inhibitor. The clinical experts consulted by CADTH highlighted the importance of shared and fully informed decision-making with patients that includes 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 Canadian Gastrointestinal Oncology Evidence Network (CGOEN) with the Medical Advisory Board of Colorectal Cancer Canada (and other Colorectal Cancer Canada treating physicians) and the Ontario Health (Cancer Care Ontario) (OH-CCO) Gastrointestinal Cancer Drug Advisory Committee. CGOEN gathered data and information based on personal experience in treating patients with mCRC and expert evidence-based review by gastrointestinal cancer specialists in Canada of the following information presented at international oncology meetings and subsequently published in *The New England Journal of Medicine*; 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 SOC options and have experienced disease progression, have experienced intolerance, or have chosen to stop for personal reasons. This combination would also be used for those with medical contraindications to earlier-line SOC therapies. CGOEN stated that trifluridine-tipiracil is currently Health Canada–approved but received a do not reimburse recommendation in August 2019 from CADTH due to the fact that the magnitude of benefit was felt to be too small to warrant approval, despite being recognized as addressing the needs of a population with an unmet need. It is currently funded in Quebec, having received

a reimburse recommendation from the Institut national d'excellence en santé et en services sociaux. Outside Quebec, patients have been able to apply to the sponsor for access to the drug under review through private insurance or direct user pay. Therefore, the majority of patients with mCRC in Canada do not have access to a publicly funded version of 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 plus bevacizumab, given the current landscape in Canada.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially affect the implementation of a CADTH recommendation for trifluridine-tipiracil plus bevacizumab: relevant comparators, generalizability, a funding algorithm, care provision issues, and system and economic issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs. Refer to Table 5 for more details.

Clinical Evidence

Systematic Review

Description of Studies

One randomized, phase III, open-label, multicentre study (the SUNLIGHT trial) evaluated the efficacy and safety of trifluridine-tipiracil plus bevacizumab versus trifluridine-tipiracil alone. The SUNLIGHT study enrolled 492 adults with advanced mCRC who had received up to 2 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, the rest of the world), time since first metastasis diagnosis (< 18 months, ≥ 18 months), and *RAS* status (wild-type, mutant). The primary objective of the SUNLIGHT study was to demonstrate the superiority of 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 5-Level EQ-5D (EQ-5D-5L), and treatment-emergent adverse events (TEAEs).

Patients had a mean age of 61.7 years (standard deviation [SD] = 11.1 years), 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 a 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% of patients had *RAS* wild-type disease. Most patients (92.1%) had received 2 previous treatment regimens for metastatic disease, 2.6% of patients had received more than 2 prior regimens, and 5.3% of patients had received 1 previous treatment regimen. All patients had received previous fluoropyrimidine-based therapy, 72.0% of patients had received previous anti-VEGF therapy (47.8% of patients had received bevacizumab as part of their first regimen, 43.9% of patients had received bevacizumab as part of their second regimen, and 20.3%

of patients had received bevacizumab 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 the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, with notable (> 5%) between-group differences for patients aged 65 years and older (41% versus 48%, respectively), with primary tumour located on the right side (25% versus 31%, respectively), and with primary tumour located on the left side (75% versus 69%, respectively).

Efficacy Results

The key efficacy results from the SUNLIGHT trial are summarized in Table 2, based on the data cut-off date of July 5, 2022, for clinical (nonsurvival) data and July 19, 2022, for survival data.

Overall Survival

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

Progression-Free Survival

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

Health-Related Quality of Life

In the SUNLIGHT trial, 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 the EQ visual analogue scale (EQ 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 was −2.85 (95% CI, −5.92 to 0.22) for the trifluridine-tipiracil plus bevacizumab group and −6.62 (95% CI, −10.36 to −2.88) for the trifluridine-tipiracil alone group. The LSM difference in change from baseline for global health status was 3.77 (95% CI, 0.22 to 7.32; P = 0.038) in favour of the trifluridine-tipiracil plus bevacizumab group. The number of patients in the FAS population with 10 points or greater definitive deterioration was 62 (25.2%) patients and 72 (29.3%) patients in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively. The median time until definitive deterioration in the global health status was 8.54 months (95% CI, 7.49 months to 10.94 months) in the trifluridine-tipiracil plus bevacizumab group and 4.70 months (95% CI, 4.01 months to 5.78 months) in the trifluridine-tipiracil alone group (P < 0.001).

In the EQ-5D-5L utility, the LSM change from baseline was −0.01 (95% CI, −0.03 to 0.01) for the trifluridine-tipiracil plus bevacizumab group and −0.03 (95% CI, −0.06 to −0.01) for the trifluridine-tipiracil alone group. The LSM difference in change from baseline for the EQ-5D-5L utility was 0.02 (95% CI, 0.00 to 0.05; P = 0.070). In the EQ VAS, the LSM change from baseline was −0.87 (95% CI, −3.74 to 2.00) for the trifluridine-tipiracil plus bevacizumab group and −5.34 (95% CI, −8.75 to −1.92) for the trifluridine-tipiracil alone group. The LSM difference in change from baseline for the EQ VAS was 4.46 (95% CI, 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 date of July 5, 2022.

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

The proportion of patients who experienced at least 1 serious adverse event (SAE) was 24.8% in the trifluridine-tipiracil plus bevacizumab group and 31.3% in the trifluridine-tipiracil alone group. SAEs occurring in at least 2% of patients in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group were intestinal obstruction (2.8% versus 2.0%, respectively), malignant neoplasm progression (2.4% versus 4.5%, respectively), COVID-19 (2.0% versus 2.4%, respectively), anemia (0.4% versus 3.3%, respectively), febrile neutropenia (0.4% versus 2.4%, respectively), jaundice (0.8% versus 2.0%, respectively), and hepatic failure (0 versus 2.0%, respectively). The proportion of patients who experienced AEs of grade 3 or greater were 72.4% in the trifluridine-tipiracil plus 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 the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group were neutropenia (43.1%

versus 32.1%, respectively), anemia (6.1% versus 11.0%, respectively), decreased neutrophil count (8.9% versus 5.3%, respectively), and hypertension (5.7% versus 1.2%, respectively).

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 the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group were asthenia (3.3% versus 0.4%, respectively), jaundice (0.8% versus 0.8%, respectively), decreased appetite (0.8% versus 0.4%, respectively), fatigue (0.4% versus 0.8%, respectively), anemia (0.4% versus 0.8%, respectively), intestinal obstruction (0.4% versus 0.8%, respectively), malignant neoplasm progression (0.4% versus 0.8%, respectively), biliary dilation (0.8% versus 0, respectively), increased blood bilirubin (0.8% versus 0, respectively), pain (0.8% versus 0, respectively), and metastases to central nervous system (0 versus 0.8%, respectively).

[redacted].

Notable Harms

Analyses of 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 events was 80.9% in the trifluridine-tipiracil plus bevacizumab group and 73.2% in the trifluridine-tipiracil alone group, including neutropenia (62.2% versus 51.2%, respectively), anemia (28.9% versus 31.7%, respectively), thrombocytopenia (17.1% versus 11.4%, respectively), and leukopenia (6.5% versus 8.5%, respectively). The proportion of patients who experienced at least 1 TEAE related to infections was 30.9% in the trifluridine-tipiracil plus 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 plus bevacizumab group and the trifluridine-tipiracil alone group, respectively. The proportion of patients who experienced gastrointestinal symptoms was 48.4% in the trifluridine-tipiracil plus bevacizumab group and 41.1% in the trifluridine-tipiracil alone group, including nausea (37.0% versus 27.2%, respectively), diarrhea (20.7% versus 18.7%, respectively), and vomiting (18.7% versus 14.6%, respectively). Gastrointestinal symptoms of grade 3 or higher were reported for 2.0% of patients and 4.9% of patients in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively, including nausea (1.6% versus 1.6%, respectively), diarrhea (0.8% versus 2.4%, respectively), and vomiting (0.8% versus 1.6%, respectively). The proportion of patients who experienced hypertension was 10.2% in the trifluridine-tipiracil plus 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 plus bevacizumab group and the trifluridine-tipiracil alone group, respectively.

Critical Appraisal

The SUNLIGHT study was a phase III, open-label, randomized controlled trial (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 plus bevacizumab) group. Trifluridine-tipiracil alone was the comparator used in the SUNLIGHT trial. Trifluridine-tipiracil is approved and available in Canada but is not universally publicly funded, so the majority of patients must gain access via private drug coverage or out-of-pocket costs. OS as the primary end point and PFS as a key secondary end point were included in statistical hierarchical testing and were appropriate key end points according to treatment guidelines and outcomes identified as important by patients and clinicians. Findings for OS and PFS demonstrated a benefit for patients treated with trifluridine-tipiracil plus bevacizumab; the proportional hazards assumption was likely valid based on Schoenfeld residuals testing and visual inspection of the Kaplan-Meier (KM) 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 cycle 4 could impact findings. Longer treatment duration and a higher mean dose of trifluridine-tipiracil in the trifluridine-tipiracil plus 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 was 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 (those with more than 2 prior chemotherapy regimens, those who had prior treatment with trifluridine-tipiracil, or those with an ECOG PS score greater than 1) were considered by the clinical experts consulted by CADTH to be eligible for treatment with trifluridine-tipiracil plus bevacizumab. The clinical experts consulted by CADTH also considered patients with small bowel or appendiceal adenocarcinoma as eligible to be treated with trifluridine-tipiracil plus 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 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 unlabelled indication, as trifluridine-tipiracil alone was approved by Health Canada for adult patients with mCRC but is not universally 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 of which is available via compassionate access), the clinical experts consulted by CADTH emphasized that trifluridine-tipiracil alone is the most relevant comparator for trifluridine-tipiracil plus bevacizumab. Outcomes included in the SUNLIGHT trial were identified as important to patients and clinicians, including survival, HRQoL, and TEAEs. OS at 6 months and 12 months was highlighted by the clinical experts consulted by CADTH as important for assessing the 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 was not concerning to the clinical experts consulted by CADTH as they noted that the proportions were low with similar between-group rates for discontinuations due to AEs and deaths.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool 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.[20,21] 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, the imprecision of effects, and publication bias.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, on consultation with clinical experts, and on 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 (OS and PFS), 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 EQ 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 was 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 (OS and PFS), 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 Plus Bevacizumab Versus Trifluridine-Tipiracil Alone for Patients With mCRC

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 plus 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[a]	Trifluridine-tipiracil plus 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[b]	Trifluridine-tipiracil plus 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[c]	Trifluridine-tipiracil plus bevacizumab likely results in a clinically important increase in the probability of progression-free survival at 6 months when compared with trifluridine-tipiracil alone.

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		
HRQoL							
EORTC QLQ-C30 (0 [worst HRQoL] to 100 [best HRQoL])							
Global health status, LSM change from baseline, points (95% CI) Follow-up: Cycle 1 to cycle 10[d]	450 (1 RCT)	NA	−6.62	−2.85 (−5.92 to 0.22)	3.77 (0.22 to 7.32)	Very low[e]	The evidence is very uncertain about the effect of trifluridine-tipiracil plus 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 deterioration from baseline, % (95% CI) Follow-up: Median 8.54 months vs. 4.70 months	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 (120 fewer to 40 more per 1,000)	Very low[f]	The evidence is very uncertain about the effect of trifluridine-tipiracil plus bevacizumab on the proportion of 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[d]	448 (1 RCT)	NA	−0.03	−0.01 (−0.03 to 0.01)	0.02 (0.00 to 0.05)	Very low[g]	The evidence is very uncertain about the effect of trifluridine-tipiracil plus bevacizumab on the LSM change from baseline in EQ-5D-5L utility score when compared with trifluridine-tipiracil alone.
EQ VAS (0 [worst health imaginable] to 100 [best health imaginable])							
EQ VAS, LSM change from baseline, points (95% CI)	448 (1 RCT)	NA	−5.34	−0.87 (−3.74 to 2.00)	4.46 (1.11 to 7.81)	Low[h]	Trifluridine-tipiracil plus bevacizumab may result in little to no clinically important difference in the LSM change from baseline in EQ

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: Cycle 1 to cycle 10[d]							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 plus 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[i]	Trifluridine-tipiracil plus 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) Follow-up: Median 5.0 months vs. 2.1 months	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[i]	Trifluridine-tipiracil plus bevacizumab may result in little to no clinically important difference in the proportion of patients who experience 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[i]	Trifluridine-tipiracil plus bevacizumab may result in little to no clinically important difference in the proportion of patients who experience gastrointestinal symptoms when compared with trifluridine-tipiracil alone.

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		
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[i]	Trifluridine-tipiracil plus 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; EQ-5D-5L = 5-Level EQ-5D; EQ VAS = EQ visual analogue scale; HRQoL = health-related quality of life; LSM = least squares mean; mCRC = metastatic colorectal cancer; MID = minimal important difference; NA = not applicable; NR = not reported; RCT = randomized controlled trial; RR = risk ratio; vs. = versus.

Notes: Details included in Table 2 were provided from the sponsor in response to additional data request.[23]

Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, the 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]There is no established MID. The clinical experts consulted by CADTH indicated that a between-group difference of 20% was clinically important.

[c]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.

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

[e]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 have impacted 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 EORTC QLQ-C30 was not conducted; therefore, results are considered as supportive evidence.

[f]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 have impacted 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 EORTC 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 study design and patients' and caregivers' knowledge of assigned treatment may have biased the reporting of HRQoL questionnaires. There was substantial missing data across and up to treatment cycle 10 that may have impacted 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 was not conducted; therefore, results are considered as supportive evidence.

[h]Rated down 2 levels for serious study limitations. The open-label study design and patients' and caregivers' knowledge of assigned treatment may have biased the reporting of HRQoL questionnaires. There was substantial missing data across and up to treatment cycle 10 that may have impacted 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 was not conducted; therefore, results are considered as supportive evidence.

[i]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.[22]

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 plus bevacizumab was compared to BSC, regorafenib, and trifluridine-tipiracil alone among patients with mCRC who had been previously treated with, or were not considered candidates for, available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.[24]

In this ITC, OS, PFS, and treatment-related AEs (defined as any AEs that were considered related to treatment received) 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 patients living in Canada 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 plus 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, the treatment of trifluridine-tipiracil plus 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

The treatment of trifluridine-tipiracil plus bevacizumab may be associated with an 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 (CrIs).

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 PS (the proportion of patients with an ECOG PS score 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, the 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 plus 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 were therefore informed only by indirect evidence, which increased the level of uncertainty.

Some important patient characteristics in the included trials were not reported in this ITC, such as treatment duration, the timing of study end point evaluation, the 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 was not met (the transitivity assumption is 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). 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.

Conclusion

The SUNLIGHT study was a randomized, phase III, open-label trial in adults with mCRC who had been previously treated with, or were not candidates for, available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if *RAS* wild-type, anti-EGFR agents. Evidence from the SUNLIGHT study demonstrated that trifluridine-tipiracil plus bevacizumab likely results in a clinically important increase in the proportion of patients with OS at 6 months and 12 months (moderate certainty). The evidence demonstrated that trifluridine-tipiracil plus bevacizumab results in a clinically important increase in the proportion of patients with PFS at 3 months (high certainty) and likely results in a clinically important increase in the proportion of patients with PFS at 6 months (moderate certainty) when compared with trifluridine-tipiracil alone. Trifluridine-tipiracil plus bevacizumab may result in little to no clinically important difference in the change from baseline in EQ VAS (low certainty) when compared with trifluridine-tipiracil alone. However, the evidence is very uncertain about the effect of trifluridine-tipiracil plus bevacizumab in the change from baseline in EORTC QLQ-C30 global health status score, the proportion of patients with at least a 10-point deterioration from baseline in the global health status score, and the change from baseline in EQ-5D-5L health utilities (very low certainty) when compared with trifluridine-tipiracil alone. Trifluridine-tipiracil plus bevacizumab may result in little to no clinically important difference in bone marrow suppression, infections, gastrointestinal symptoms, and hypertension (low certainty) when compared with trifluridine-tipiracil alone. Patients treated with trifluridine-tipiracil plus bevacizumab experienced similar frequencies of TEAEs, SAEs, treatment discontinuations due to AEs, and deaths, and no new safety signals were identified. Confidence in the effect estimates in the SUNLIGHT trial were limited due to imprecision from wide CIs for survival and harms outcomes, the potential of the open-label design to bias patient-reported outcomes, and significant missing data for HRQoL.

There is a lack of head-to-head direct evidence between trifluridine-tipiracil plus bevacizumab and other treatments for advanced mCRC. A sponsor-submitted ITC indicated that the treatment of trifluridine-tipiracil plus bevacizumab may be associated with prolonged OS and PFS, but with an increased risk of treatment-related AEs in patients with mCRC compared to other treatments such as BSC, regorafenib, or trifluridine-tipiracil alone. However, there was substantial uncertainty due to limitations, including significant between-trial heterogeneity, potential intransitivity, and the absence of HRQoL outcomes of importance to patients and clinicians.

Introduction

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of trifluridine-tipiracil (15 mg/6.14 mg and 20 mg/8.19 mg) oral tablets in combination with bevacizumab in the treatment of mCRC in adults who have been previously treated with, or are not candidates for, available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biological agents, and if *RAS* wild-type, anti-EGFR agents. The submission is not a Health Canada–approved indication; rather, it has been accepted under review as an unlabelled indication.

Disease Background

Content in this section has been informed by materials submitted by the sponsor and clinical expert input. The following has been summarized and validated by the CADTH review team.

CRC collectively refers to malignant tumours that develop in the rectum or colon, due to their similar tissue type and continuity. Most CRC cases develop in the epithelial lining of the colon or rectum from polyps that progress into cancer.[1] Metastatic CRC 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 locations of metastases are the liver, lung, peritoneum, and distant lymph nodes.[5]

Patients with early CRC are usually asymptomatic.[7] In patients with advanced disease, common clinical presentation includes iron-deficiency anemia, rectal bleeding, abdominal pain, change in bowel habits, and intestinal obstruction or perforation. Right-sided (proximal) tumours rarely present with obvious rectal bleeding as the blood becomes admixed with the stool.[9] Left-sided (distal) tumours are more likely to present with bright red blood per rectum and symptoms of bowel obstruction.[8,9] In mCRC, symptoms may vary depending on the location of metastasis, and may include upper-right quadrant pain, abdominal distention, early satiety, supraclavicular adenopathy, and periumbilical nodules.[7] In its early stages, CRC is a subtle disease; resultantly, most CRCs are diagnosed after symptom onset, although population-based screening is increasing the number of asymptomatic cases identified.[7]

The cause of CRC is dependent on a number of factors. People with a family history of CRC (first-degree relatives) are at a higher risk for CRC.[1,7,11] Lynch syndrome is the most common hereditary factor in CRC predisposition, accounting for 2% to 4% of all CRC cases.[1,7,11,25] People with inflammatory bowl disease are also at an increased risk for CRC.[1,7,11] Other risk factors include smoking, dietary factors (consumption of

red and processed meats), heavy alcohol consumption, diabetes mellitus, low levels of physical activity, metabolic syndrome, and obesity and/or high body mass index.[1,7,11]

CRC is the third most prevalent cancer in Canada overall and the second most prevalent cancer by sex, accounting for 12.7% and 10.0% of all 25-year prevalent cancers among males and females, respectively.[2] It is estimated that the Canadian (excluding Quebec) 10-year prevalence of CRC in both sexes of all ages was 343.5 cases per 100,000 population in 2018 (or 97,755 cases in total).[4] CRC is also the fourth most commonly diagnosed cancer (10% of all new cancer cases) as well as the second leading cause of cancer-related death (11% of all cancer deaths) among Canadians.[3] In 2022, it was estimated that 13,500 men and 10,800 women were diagnosed with CRC and 5,200 men and 4,200 women died from it.[3]

Data from the Canadian Cancer Registry database at Statistics Canada shows that approximately one-fifth (19.9%) of CRC cases are stage IV at diagnosis. The stage of CRC at diagnosis is strongly associated with survival.[6] The 5-year relative survival for colon cancer is estimated to be 92% for cancers diagnosed at stage I compared with only 11% for those diagnosed at stage IV disease; similarly, the 5-year survival for rectal cancer is estimated to be 87% for stage I compared with only 12% for those diagnosed at stage IV disease.[6]

Diagnostic testing is not required for the indication under review, as patients eligible for trifluridine-tipiracil will have already been diagnosed with metastatic disease (stage IV) and would be considered refractory to all existing treatment options. As previously noted, trifluridine-tipiracil plus bevacizumab is an unlabelled indication, and while the approved indication is for trifluridine-tipiracil alone, no specific diagnostic technology is recommended in the product monograph.[17] In general, diagnostic testing is required to confirm a diagnosis of CRC and pathologic confirmation of CRC is required before treatment. Typically, colonoscopy-guided biopsy confirms the primary cancer, and biopsy of the liver, lung, or lymph node confirms metastases.[11,12,26] Diagnostic staging should include contrast-enhanced CT imaging of the chest, abdomen, and pelvis.[11,12,26] At the time of diagnosis, patients will also undergo testing for activating mutations of *RAS* (*KRAS* and *NRAS*), *BRAF*, and the evaluation of microsatellite instability or mismatch repair deficiency in tumour tissue, which guides the overall treatment plan for an earlier line of therapy.[26] Additional baseline imaging is appropriate if symptoms are suggestive of metastases (e.g., CT head, bone scan). While on systemic therapy, imaging should be done every 2 months to 3 months depending on the clinical scenario.[26]

Standards of Therapy

Content in this section has been informed by materials submitted by the sponsor and clinical expert input. The following has been summarized and validated by the CADTH review team.

Place in Therapy and Comparators

Current Treatment Paradigm

For patients with advanced CRC or mCRC, the main goals of treatment are to improve quality of life by controlling or delaying the onset of tumour-related symptoms and, if possible, to prolong life;[26,27] treatment intent is palliative rather than curative.[27] The majority of patients with mCRC have unresectable (inoperable) disease, for which the mainstay of treatment is systemic multidrug chemotherapy.[10,11] The 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 [*RAS*, *BRAF*], presence of dMMR or MSI-H), type and timing of prior therapy, and toxicity profiles of constituent drugs.[5,10,12-15] External beam radiation therapy — either conventional or stereotactic — may be also offered to suitable patients with mCRC to palliate symptoms or control disease, according to the clinical expert consulted by CADTH.

Management of mCRC is increasingly driven by tumour biology and gene expression analysis of individual tumours.[10,27] Multiple different classes of drugs with antitumour activity in mCRC may be appropriate, although the optimal combination and sequence of available drugs is evolving and is focused on individualized treatment along a continuum of care.[10] Systemic fluorouracil-based chemotherapy, especially when combined with regimens containing irinotecan or oxaliplatin, produce meaningful improvements in survival now consistently approaching 2 years.[27] FOLFIRI and FOLFOX are the standard initial chemotherapy regimens.[11,27] Anti-VEGF and anti-EGFR drugs can be added to chemotherapy regimens to further increase survival for patients with mCRC. Anti-EGFR drugs only benefit a subpopulation of patients with mCRC with wild-type *RAS* tumours (approximately 52% of patients with CRC[28,29]).[5,11,13-15] There is also a small subset of patients with mCRC with MSI-H status (approximately 3.5% to 6.5% of patients[27]) for whom pembrolizumab (an immune checkpoint inhibitor) would be an initial treatment option. For a small population of patients with *BRAF* mutations (approximately 5% to 12% of patients with mCRC[27]), encorafenib (a kinase inhibitor) is funded for use in combination with cetuximab or panitumumab (an anti-EGFR drug) after disease progression on initial chemotherapy with or without bevacizumab.[5,10,11,13-15]

The duration of chemotherapy for unresectable mCRC is dependent on the patient and regimen used, where intermittent therapy rather than continuous therapy has the potential to reduce treatment-related toxicity (e.g., cumulative neurotoxicity has been observed in oxaliplatin-containing regimens).[27] Importantly, the initiation of chemotherapy before patients become symptomatic is ideal.

Response to chemotherapy is typically assessed by a periodic assay of serum CEA levels, if initially elevated, and radiographic evaluation (every 8 weeks to 12 weeks, or as prompted by rising CEA levels), quantified using Response Evaluation Criteria in Solid Tumours.[27]

Regimens containing fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies are broadly funded and comprise the most frequently used cytotoxic regimens for patients with mCRC.[5,11,13-15] In Canada, oncologists often follow well-accepted international treatment guidelines, including the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, the American Society of Clinical Oncology guidelines, and the European Society for Medical Oncology Clinical Practice Guidelines.[5,11,12,14,15] Across Canada, provincial cancer agencies have also developed treatment guidelines that align with international guidelines.[26,30,31]

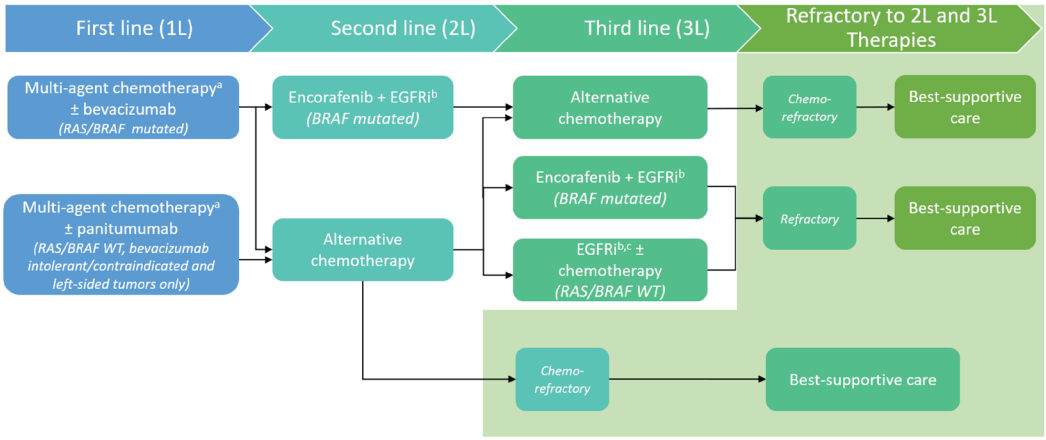
Following treatment with standard cytotoxic chemotherapy backbone regimens, there are few efficacious options in later lines of therapy. Both trifluridine-tipiracil (Lonsurf) and regorafenib (Stivarga) are approved in Canada for the treatment of patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if *RAS* wild-type, anti-EGFR agents;[16,17] however, these treatments are not publicly funded in Canada (except in Quebec)[18,19] Patients

with mCRC who have already been treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if *RAS* wild-type, anti-EGFR agents, they are usually treated with BSC, for whom median survival is approximately 5 months to 6 months.[27]

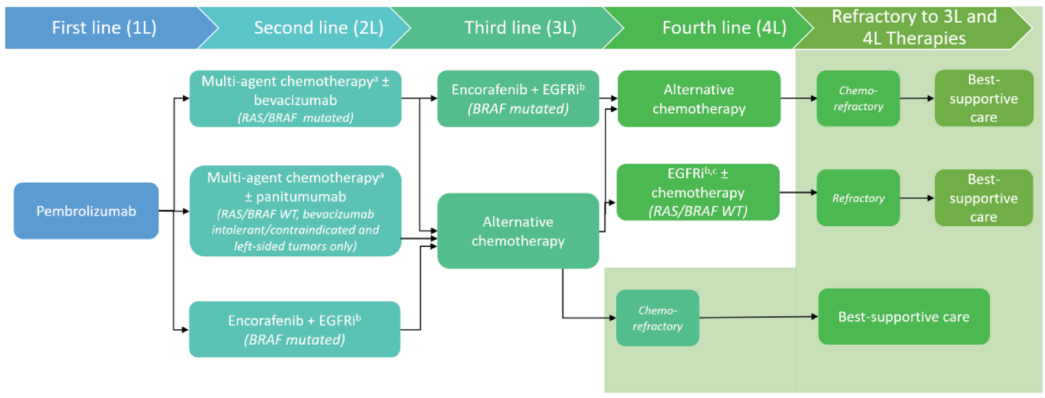
The overall treatment algorithm for mCRC is summarized in Figure 1.

Figure 1: Metastatic Colorectal Cancer Funding Algorithm (Current)

(A) Patients with metastatic colorectal cancer that is microsatellite instability–low, microsatellite stable, or proficient mismatch repair



(B) Patients with metastatic colorectal cancer that is microsatellite instability–high or deficient mismatch repair



1L = first-line; 2L = second-line; 3L = third-line; 4L = fourth-line; EGFR = epidermal growth factor receptor; EGFRi = epidermal growth factor receptor inhibitor; ESMO = European Society for Medical Oncology; FOLFIRI = folinic acid, fluorouracil, and irinotecan, FOLFOX = folinic acid, fluorouracil, and oxaliplatin; FOLFOXIRI = folinic acid, fluorouracil, oxaliplatin, and irinotecan; NCCN = National Comprehensive Cancer Network; WT = wild-type.

Note: Figure 1 presents information from the CADTH provisional algorithm,[13] Cancer Care Alberta guidelines,[26] NCCN guidelines,[11,12] and ESMO guidelines.[32] The clinical experts consulted by CADTH generally agreed with the algorithm submitted by the sponsor; however, they noted that among patients who are treated with EGFRi (e.g., FOLFIRI plus panitumumab) in the 1L setting, there is limited to no funding to rechallenge with this therapy in the 3L setting.

[a] Multidrug chemotherapy consists of doublet therapy (FOLFOX, FOLFIRI, or capecitabine + oxaliplatin) and triplet therapy (FOLFOXIRI).

[b] EGFRi includes cetuximab and panitumumab, where available.

[c] If had not received EGFR in previous lines.

Source: Sponsor's Summary of Clinical Evidence.[33]

Drug Under Review

Key characteristics of trifluridine-tipiracil (Lonsurf) plus bevacizumab are summarized in Table 3 with other treatments available for the treatment of adult patients 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.

Table 3: Key Characteristics of Trifluridine–Tipiracil Plus Bevacizumab, Lonsurf Alone, and Regorafenib

Characteristic	Trifluridine-tipiracil plus bevacizumab	Trifluridine-tipiracil monotherapy	Regorafenib
Mechanism of action	An antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase inhibitor tipiracil (as tipiracil hydrochloride), with the VEGF-A monoclonal antibody bevacizumab	An antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase inhibitor tipiracil (as tipiracil hydrochloride)	A multikinase inhibitor that targets angiogenic, stromal, and oncogenic RTK
Indication[a]	Unlabelled indication: In combination with bevacizumab, for the treatment of adult patients 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	For the treatment of adult patients 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	For the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy, and, if *RAS* wild-type, an anti-EGFR therapy
Route of administration	Orally and IV	Orally	Orally
Recommended dosage	Twice daily, 35 mg/m^2 of body surface area, within 1 hour after completion of morning and evening meals, on day 1 to day 5 and day 8 to day 12 of each 28-day cycle, repeated every 4 weeks with bevacizumab given as an IV infusion 5 mg/kg of body weight once every 14 days on day 1 and day 15	Twice daily, at a starting dose of 35 mg/m^2 of body surface area, on day 1 through day 5 and day 8 through day 12 every 28 days	Once daily, 160 mg (4 tablets, each containing 40 mg regorafenib), for 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks
Serious adverse effects or safety issues	Neutropenia, nausea, fatigue, anemia, and leukopenia	Neutropenia, nausea, fatigue, anemia, and leukopenia	Severe hepatic impairment, hemorrhage, hand-foot skin reaction, infections, and infestations

Characteristic	Trifluridine-tipiracil plus bevacizumab	Trifluridine-tipiracil monotherapy	Regorafenib
Other	NA	Do not reimburse recommendation from CADTH, not universally publicly funded (except in Quebec)	Do not reimburse recommendation from CADTH, not universally publicly funded

Anti-EGFR = anti–epidermal growth factor receptor; anti-VEGF = anti–vascular endothelial growth factor; mCRC = metastatic colorectal cancer; NA = not applicable; RTK = receptor tyrosine kinase; VEGF-A = vascular endothelial growth factor A.

[a]Health Canada–approved indication.

Source: Product monographs for Stivarga, Lonsurf, and Avastin.[16,17,34]

Dosing and Administration

Note: As this is an unlabelled indication, the individual dosing of trifluridine-tipiracil and bevacizumab have been taken from their respective product monographs for their CRC indications.[17,34] Both dosing regimens align with the dosing used in the SUNLIGHT trial.[22]

Trifluridine-Tipiracil Dosing

The recommended starting dose of trifluridine-tipiracil for adults is 35 mg/m^2 per dose administered orally with water, twice daily, within 1 hour after completion of morning and evening meals, on day 1 to day 5 and day 8 to day 12 of each 28-day cycle. This treatment cycle is repeated every 4 weeks as long as benefit is observed or until unacceptable toxicity occurs. Refer to Table 4 for dose calculation based on body surface area (BSA). The dosage must not exceed 80 mg per dose based on the trifluridine component.[17]

Dosing adjustments may be required based on individual safety and tolerability. A maximum of 3 dose reductions is permitted to a minimum dose of 20 mg/m^2 twice daily. Dose escalation is not permitted after it has been reduced.[17]

In the event of hematologic and/or nonhematologic toxicities, patients should follow the dose interruption, resumption, and reduction criteria, as detailed in the product monograph.[17]

Bevacizumab Dosing

As per the product monograph for the mCRC indication, the recommended dose of bevacizumab is 5 mg/kg of body weight given once every 14 days as an IV infusion.[34]

In a 28-day treatment cycle with trifluridine-tipiracil, bevacizumab would be administered on day 1 and day 15.[22]

Mechanism of Action

Trifluridine-tipiracil comprises an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase inhibitor tipiracil (as tipiracil hydrochloride).[22]

Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to and neutralizes the biologic activity of human VEGF. Bevacizumab contains human framework regions with antigen binding regions of a humanized murine antibody that binds to VEGF. Bevacizumab is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system and is purified by a process that

includes specific viral inactivation and removal steps. Bevacizumab consists of 214 amino acids and has a molecular weight of approximately 149,000 daltons.[34]

Combination regimens of different chemotherapeutic drugs (e.g., fluorouracil, oxaliplatin, irinotecan, molecularly targeted drugs) have prolonged survival in patients with mCRC compared to treatment with fluorouracil alone. Blood vessels in tumour tissues, including mCRC, tend to be poorly organized as well as hyperpermeable, resulting in a diminished blood supply, which may limit the accumulation of trifluridine-tipiracil in tumours. Since bevacizumab inhibits angiogenesis and normalizes tumour vasculature, tumour blood supply is improved, allowing an increase in the accumulation of trifluridine-tipiracil in the tumour and subsequent phosphorylation of trifluridine in the tumour. The phosphorylated forms of trifluridine are active components, responsible for the inhibitory effect on tumour DNA.[35,36]

Prescribing

Both trifluridine-tipiracil and bevacizumab should only be prescribed by a doctor with experience in the use of anticancer drugs for mCRC.[17,34]

Table 4: Trifluridine–Tipiracil Starting Dose Calculation According to Body Surface Area

Trifluridine-tipiracil dose	BSA (m^2)	Dose in mg (twice daily)	Tablets per dose		Total daily dose (mg)
			15 mg trifluridine/ 6.14 mg tipiracil	20 mg trifluridine/ 8.19 mg tipiracil	
35 mg/m^2	< 1.07	35	1	1	70
	1.07 to 1.22	40	0	2	80
	1.23 to 1.37	45	3	0	90
	1.38 to 1.52	50	2	1	100
	1.53 to 1.68	55	1	2	110
	1.69 to 1.83	60	0	3	120
	1.84 to 1.98	65	3	1	130
	1.99 to 2.14	70	2	2	140
	2.15 to 2.29	75	1	3	150
	≥ 2.30	80	0	4	160

BSA = body surface area.

Sources: Lonsurf product monograph[17] and SUNLIGHT Clinical Study Report.[22]

Stakeholder Perspectives

Patient Group Input

This section was prepared by the CADTH review team based on the input provided by patient groups. The full original patient input received by CADTH has been included in the Stakeholder section of this report.

CADTH received 2 patient group submissions from CCRAN and Colorectal Cancer Canada. CCRAN is a national, not-for-profit patient advocacy group championing the health and well-being of Canadians touched by CRC 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 organization for patients with CRC dedicated to CRC awareness and education, supporting patients and their caregivers and advocating on their behalf.

CCRAN used a multifaceted outreach approach by emailing clinicians who treat advanced CRC to help recruit patients or caregivers with experience with Lonsurf (plus bevacizumab) and via an online survey of patients' experience of mCRC and prior drug therapies. Five patients who had experience with the therapy under review participated in a telephone interview from June 12 to July 26, 2023, and 77 survey respondents (including 60 patients, 13 caregivers, and 4 patients who were also caregivers) provided input from June 13 to August 5, 2023. Colorectal Cancer Canada conducted an online survey of 23 respondents (22 patients and 1 caregiver) from July 19 to August 17, 2023.

Most patients reported that fatigue/weakness, bloody stools, diarrhea, and abdominal cramping/gas/feeling bloated, and abdominal pain are common symptoms they experienced and that they felt were important to control. Symptoms of CRC affected the quality of life for patients and their families, limiting the ability to work, to exercise, to participate in social activities, or to undertake daily tasks. Furthermore, patients cited feeling consistently worried, nervous, or uneasy and with a persistent fear of the cancer getting worse or recurring (coming back) as the most common psychological impacts. For some patients with mCRC, there were no symptoms before diagnosis and the diagnosis was the result of incidental findings. Caregivers also reported challenges with caring for patients with CRC, including loss of lifestyle, inability to work outside the home, difficulty managing treatment-induced side effects, loss of income and/or financial strain, time spent at medical appointments, and feelings of inadequacy or helplessness.

In terms of current therapy options, FOLFOX, FOLFIRI, capecitabine, and bevacizumab were cited most frequently. According to Colorectal Cancer Canada's survey, 5% of respondents said "no," 45% said "somewhat," and 50% said "yes" when asked whether these drug therapies had been effective at controlling the progression of the disease. Moreover, when patients and caregivers were asked whether they believed their needs were not being met by current drugs available to treat the cancer, 30% of respondents replied "yes." In general, all patients from both patient groups reported debilitating side effects while undergoing treatments for their mCRC, which compromised their quality of life. According to CCRAN's survey, all interviewed patients and 1 caregiver reported debilitating side effects while undergoing treatments for mCRC, which compromised their quality of life. While patients may have derived a clinical benefit in terms of response, that response was accompanied by incapacitating side effects such as fatigue, nausea, lack of energy, diarrhea, neuropathy, skin rash, lethargy, and flu-like symptoms that prevented them from engaging in life on any meaningful level. Patients were quite emphatic about their experience with combination chemotherapies that compromised their well-being some or most of the time, resulting in the need to take time off work, the inability to care for children, a lack of self-care, and less time spent enjoying life in general. Normal daily activities could not be resumed nor could quality time with friends and family be spent, permitting them the freedom to "live life again".

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, improved breathing) and quality of life (e.g., improved mobility, improved sense of wellness, relief from side effects) such that patients would take a new therapy to bring about improvement in their quality of life even if it does not extend OS (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 preferred a drug therapy that is convenient (e.g., orally administered, either at home or with a short infusion duration or chair time at a cancer centre).

A total of 5 respondents from CCRAN's survey and 1 respondent from Colorectal Cancer Canada's survey indicated having experience with the drug under review, and the primary method of access to the drug under review was through private insurance and the sponsor's Patient Support Program. According to the CCRAN survey, all 5 patients demonstrated excellent tolerance with Lonsurf plus bevacizumab, with a reduced incidence of AEs, and maintained quality of life despite having experienced significant side effects with SOC therapies. One respondent from Colorectal Cancer Canada's survey rated trifluridine-tipiracil plus bevacizumab as being similar to their experiences with other drugs in effectiveness (i.e., able to partially shrink or control their CRC and/or metastasis) and side effects (i.e., neutropenia, loss of appetite, diarrhea, and nausea), being easy to administer or receive, and enabling them to continue daily activities while undergoing treatment.

CCRAN believes that if publicly funded, trifluridine-tipiracil plus bevacizumab would be an extremely important third-line and beyond therapy for patients whose disease has been deemed to be refractory or ineligible for SOC 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 this combination under review 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

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of mCRC.

Unmet Needs

The cornerstone of treatment for patients with mCRC involves the sequential use of the best available systemic therapies, according to the clinical experts consulted by CADTH. For patients with dMMR or MSI-H mCRC, SOC first-line treatment in Canada includes pembrolizumab immunotherapy, based on findings of

the KEYNOTE-177 phase III RCT according to input from clinical experts consulted by CADTH.[37] For patients with left-sided, extended *RAS* wild-type CRC, SOC first-line treatment in Canada includes chemotherapy with FOLFOX or FOLFIRI in combination with an EGFR inhibitor (panitumumab or cetuximab), based on the findings of the PARADIGM phase III RCT according to the clinical experts consulted by CADTH.[38] For patients with right-sided or extended *RAS*-mutated CRC, the clinical experts consulted by CADTH reported that SOC first-line treatment in Canada is chemotherapy with FOLFOX or FOLFIRI in combination with bevacizumab, based on results from a retrospective analysis of 6 RCTs.[39] 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 have experienced 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 for patients with *BRAF* V600E mutations includes encorafenib plus cetuximab, based on findings of the BEACON phase III RCT,[40] whereas patients without the *BRAF* V600E mutation are switched on the backbone chemotherapeutic regimen (e.g., patients initially treated with FOLFIRI would be switched to FOLFOX, patients initially treated with FOLFOX would be switched to FOLFIRI), based on findings of the GERCOR phase III RCT.[41] According to the clinical experts consulted by CADTH, other therapies in addition to the chemotherapy backbone are not routinely used in Canada; conversely, the addition of antiangiogenic therapies to the chemotherapy backbone (e.g., bevacizumab, aflibercept, ramucirumab) for patients without a *BRAF* V600E mutation or dual immunotherapy (e.g., nivolumab plus ipilimumab) for patients with a dMMR or MSI-H molecular marker are routinely offered to patients with CRC outside Canada and are listed in the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines, respectively.[11,12,15]

Following disease progression on 2 lines of prior therapy, patients with extended *RAS* wild-type CRC who have not been previously treated with an EGFR inhibitor are eligible for a single-drug EGFR inhibitor (cetuximab or panitumumab) or cetuximab plus irinotecan as SOC treatment in Canada, based on the findings of several phase III RCTs,[42,43] according to the clinical experts consulted by CADTH. The clinical experts noted that other patients (without an extended *RAS* wild-type marker) are treated with either regorafenib monotherapy or trifluridine-tipiracil as SOC treatment in Canada, based on the results of the CORRECT and RECOURSE phase III RCTs, respectively.[44,45]

According to the clinical experts consulted by CADTH, the selection of systemic therapy in all lines of treatment is dependent on the patient's performance status, the sidedness (for treatment decision-making in the first-line setting) and molecular features of the tumour, symptoms, values, and preferences. Notably, the clinical experts consulted by CADTH reported that BSC without anticancer therapy is a treatment option in all lines of treatment and is often given higher consideration, taking into account the limited efficacy of therapies after progression on second-line treatments. The clinical experts consulted by CADTH indicated that for patients with mCRC who experience disease progression following 2 lines of anticancer therapy, there exists a significant unmet need for effective treatment options that improve OS, decrease symptom burden, and improve quality of life. Additionally, given that there are patients diagnosed with de novo CRC presenting with more aggressive disease, and that there are higher rates of CRC diagnoses in a younger

demographic, the clinical experts consulted by CADTH highlighted an important need for novel and effective treatment options.

Place in Therapy

The clinical experts consulted by CADTH considered trifluridine-tipiracil plus bevacizumab to represent a new SOC treatment for patients with mCRC after disease progression on 2 prior lines of anticancer therapy.

Patient Population

According to the clinical experts consulted by CADTH, trifluridine-tipiracil plus bevacizumab would be an appropriate treatment option for patients with unresectable CRC who experience disease progression on 2 prior lines of anticancer systemic therapy. Among patients with mCRC, the clinical experts consulted by CADTH noted that those eligible for treatment should be able to tolerate both trifluridine-tipiracil (i.e., able to safely swallow pills, have normal bowel transit, have an ECOG PS score of 0 to 1, and have adequate hematologic, hepatic, and renal function) and bevacizumab (i.e., without absolute contraindication to the use of a VEGF inhibitor, including but not limited to uncontrolled hypertension, in situ colonic stent, recent surgery, a high-risk for bleeding, and a risk for or presence of fistula or gastrointestinal tract perforation). The clinical experts consulted by CADTH indicated that a companion diagnostic is not required for treatment with trifluridine-tipiracil plus bevacizumab.

Assessing the Response Treatment

According to the clinical experts consulted by CADTH, 3 key factors are used to determine response to treatment among patients with mCRC, in the following hierarchy: 1) patient-reported symptoms or side effects, as determined by clinician assessment of patient treatment history, 2) the examination and selective use of clinical instruments to evaluate symptoms (e.g., Edmonton Symptom Assessment System, EQ-5D), and 3) cross-sectional imaging (e.g., CT scan, MRI) and tumour markers (e.g., CEA, CA 19 to 9). Patients should be assessed after every 2 cycles to 3 cycles of treatment (and more frequently with bothersome symptoms or AEs), with tumour markers completed at least once every 4 weeks and CT scans conducted every 2 months to 3 months, according to the clinical experts consulted by CADTH. Overall, the clinical experts consulted by CADTH emphasized that OS, symptom control, and quality of life are clinically meaningful end points; all other end points (e.g., response rate, CEA response, PFS) may be considered surrogates if they predict better OS or quality of life.

Discontinuing Treatment

Patient-reported symptoms and well-being, including side effects or toxicity, were key determinants for discontinuing treatment with trifluridine-tipiracil plus bevacizumab, according to the clinical experts consulted by CADTH. In the event of the development of an absolute contraindication to further therapy as noted previously (e.g., the development of uncontrolled hypertension, the requirement for surgery or having had recent surgery, uncontrollable bleeding, the risk for or presence of fistula or gastrointestinal perforation), the clinical experts consulted by CADTH indicated that treatment with bevacizumab should be discontinued. Overall, the clinical experts highlighted the importance of shared and fully informed decision-making with patients that includes discussions regarding treatment effectiveness (e.g., incorporating results of imaging and serum tumour markers for context) and symptoms or AEs that significantly impact quality of life.

Prescribing Considerations

The clinical experts consulted by CADTH agreed that trifluridine-tipiracil plus bevacizumab should be prescribed by or be administered under the supervision of an oncologist with expertise in the prescription and management of chemotherapy-related side effects in an inpatient clinic or an outpatient setting.

Clinician Group Input

This section was prepared by the CADTH review team based on the input provided by clinician groups. The full original clinician group input received by CADTH has been included in the Stakeholder section of this report.

CADTH received 2 clinician group submissions from the CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other Colorectal Cancer Canada treating physicians) and the OH-CCO Gastrointestinal Cancer Drug Advisory Committee. CGOEN is a virtual and inclusive network of gastrointestinal oncology clinicians in Canada who contribute to the knowledge of gastrointestinal cancer and its treatments, including by participating in clinical trials, by conducting observational research, and by being involved in local, provincial, and national clinical guideline developments and Health Technology Assessments. OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of OH-CCO's mandate, including the Provincial Drug Reimbursement Programs and the Systemic Treatment Program.

CGOEN gathered data and information based on personal experience in treating patients with mCRC and expert evidence-based review by gastrointestinal cancer specialists in Canada of the following information presented at international oncology meetings and subsequently published in *The New England Journal of Medicine*; OH-CCO's Drug Advisory Committees gathered information through videoconferencing and email communication.

Both CGOEN and OH-CCO's Drug Advisory Committees emphasized that the treatment of mCRC is limited to fluoropyrimidine plus irinotecan and fluoropyrimidine plus oxaliplatin chemotherapy backbones with the use of bevacizumab and anti-EGFR monoclonal antibody therapy (either panitumumab or cetuximab) in tumours without an *RAS* mutation. Treatment of MSI-H mCRC includes the use of checkpoint inhibitor pembrolizumab. In tumours that have a *BRAF* V600E variant, treatment would include the use of encorafenib with anti-EGFR monoclonal antibody therapy.

CGOEN stated that trifluridine-tipiracil is currently Health Canada–approved but received a do not reimburse recommendation in August 2019 from CADTH due to the fact that the magnitude of benefit was felt to be too small to warrant approval, despite being recognized as addressing the needs of a population with an unmet need. It is currently funded in Quebec, having received a reimburse recommendation from the Institut national d'excellence en santé et en services sociaux. Outside Quebec, patients have been able to apply to the sponsor for access to the drug under review through private insurance or direct user pay. Therefore, the majority of patients with mCRC in Canada do not have access to a publicly funded version of 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 compared to

BSC should be considered in the current review of trifluridine-tipiracil plus bevacizumab, given the current landscape in Canada.

CGOEN indicated that there is an unmet need for patients with advanced CRC whose disease progresses on currently available and/or funded therapies. Many of these patients have a reasonable ECOG PS score of 0 or 1. Moreover, the primary goal for therapy in this population is OS. Response rates and quality of life are also goals for minimizing symptoms and the ability to maintain independence.

CGOEN expressed that a clinical assessment would be done before each cycle, with radiographic restaging generally performed every 8 weeks to 12 weeks with the primary goal being to extend survival. The goal is to improve current symptoms by shrinking tumour burden and delaying further progression and the associated decrease in quality of life and increased symptom burden that comes with that. It is also important to focus on patient functioning and impact on caregivers.

Both clinician groups highlighted that the drug under review would be placed as a further line of therapy and would be used in patients who received current SOC options and have experienced disease progression, have experienced intolerance, or have chosen to stop for personal reasons. This combination would also be used for those with medical contraindications to earlier-line SOC therapies. Patients suitable for treatment would include those who are refractory or intolerant of fluoropyrimidine, irinotecan, oxaliplatin, bevacizumab, EGFR monoclonal antibody therapy (if *KRAS* wild-type), encorafenib (if *BRAF* V600E), and immunotherapy (if dMMR or MSI-H). CGOEN stated patients should have an ECOG PS score of 0 or 1 and adequate hematologic and biochemical parameters for therapy; there is no biomarker for this therapy and therefore a companion diagnostic is not required. There is not a subgroup that did not show a benefit; it should be noted that the majority of patients had previously received bevacizumab and a benefit is seen with re-treatment with bevacizumab in combination with the drug under review. Both groups agreed that treatment would be discontinued due to disease progression, toxicity, clinician discretion, or patient request.

CGOEN mentioned that it would be reasonable for trifluridine-tipiracil plus bevacizumab to be given in any centre and by any specialist who is currently giving systemic therapy for patients with mCRC. OH-CCO's Drug Advisory Committees noted that this treatment should be given in OH-CCO–approved cancer facilities that have qualified staff, lab facilities, and infusion facilities (level 1 to level 4 cancer centres).

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 5.

Table 5: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation question	Clinical expert response
Relevant comparators	
The SUNLIGHT study compared trifluridine-tipiracil plus bevacizumab against trifluridine-tipiracil, which is not universally funded in Canada. The comparator of trifluridine-tipiracil received a negative recommendation from CADTH in 2018 and 2019, in which PAG input noted that trifluridine-tipiracil had very modest overall survival (1.8 months), short PFS (incremental gain of 0.3 months in PFS), low objective response rates, and 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 PFS rate and overall survival benefit, moderate but not insignificant toxicities, and a similar decline in quality of life.	The clinical experts consulted by CADTH acknowledged that since trifluridine-tipiracil alone and regorafenib are not universally funded due to neither drug being recommended for reimbursement, the only way for patients to obtain access to either drug currently is via private drug coverage or out-of-pocket payments. The clinical experts noted that regorafenib is available through a compassionate access program. If trifluridine-tipiracil plus bevacizumab was to be recommended for reimbursement, it would replace trifluridine-tipiracil as well as regorafenib, according to the clinical experts consulted by CADTH.
Generalizability	
Should trifluridine-tipiracil plus bevacizumab be used in patients with: • small bowel or appendiceal adenocarcinoma? • ECOG PS > 1? • MSI-H or dMMR? • *BRAF* V600E mutation?	The clinical experts consulted by CADTH anticipated that trifluridine-tipiracil plus bevacizumab would be used in patients with small bowel or appendiceal adenocarcinoma based on the extrapolation of findings from the SUNLIGHT trial, as they represent a very small number of patients; therefore, this precludes a randomized trial exclusively in this subpopulation. The clinical experts consulted by CADTH commented that ECOG PS is subjective, and for patients who have exhausted all previous lines of therapy and are highly motivated, their oncologist would likely advocate for them to access trifluridine-tipiracil plus bevacizumab as long as they are otherwise eligible (e.g., meet the criteria for laboratory assessments). For patients with MSI-H or dMMR or with *BRAF* V600E mutation, the clinical experts reiterated that they would be considered eligible for treatment with trifluridine-tipiracil plus bevacizumab if all other lines of therapy had been exhausted. In the SUNLIGHT trial's enrolled population (N = 492), there were 21 (6.8%) patients with MSI-H and dMMR and 19 (5.6%) patients with *BRAF* mutation.
Funding algorithm	
The drug may change place in the therapy of drugs reimbursed in subsequent lines.	The clinical experts consulted by CADTH reported that patients with advanced metastatic colorectal cancer have limited treatment options after they have exhausted all prior lines of therapy. For patients who currently have access to trifluridine-tipiracil alone or regorafenib, the clinical experts consulted by CADTH remarked that trifluridine-tipiracil plus bevacizumab may replace either drug as the last line of therapy. The clinical experts consulted by CADTH agreed with the sponsor's proposed place in therapy for trifluridine-tipiracil plus bevacizumab to replace best supportive care as a new treatment option (refer to Appendix 1, Figure 12).

Drug program implementation question	Clinical expert response
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 trifluridine-tipiracil without bevacizumab has 2 negative CADTH recommendations: from 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.
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.
Bevacizumab in this combination will be a biosimilar bevacizumab as the Canadian oncology formulary has all bevacizumab used as biosimilars.	This is a comment from the drug plans to inform pERC deliberations.

dMMR = deficient mismatch repair; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MSI-H = microsatellite instability–high; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; PFS = progression-free survival.

Clinical Evidence

The objective of CADTH's Clinical Review Report is to review and critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of trifluridine-tipiracil (15 mg trifluridine and 6.14 mg tipiracil [as tipiracil hydrochloride] and 20 mg trifluridine and 8.19 mg tipiracil [as tipiracil hydrochloride]) plus bevacizumab in the treatment of mCRC 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. The focus will be placed on comparing trifluridine-tipiracil plus bevacizumab to relevant comparators and identifying gaps in the current evidence.

A summary of the clinical evidence included by the sponsor in the review of trifluridine-tipiracil plus bevacizumab is presented in 4 sections with CADTH's critical appraisal of the evidence included at the end of each section. The first section, the systematic review, includes pivotal studies and RCTs that were selected according to the sponsor's systematic review protocol. CADTH's assessment of the certainty of the evidence in this first section using the GRADE approach follows the critical appraisal of the evidence. The third section includes indirect evidence from the sponsor. There were no long-term extension studies or additional studies that were considered by the sponsor to address important gaps in the systematic review evidence.

Included Studies

Clinical evidence from the following is included in the CADTH review and appraised in this document:

- One pivotal study identified in the systematic review
- One ITC.

Systematic Review

Content in this section has been informed by materials submitted by the sponsor. The following has been summarized and validated by the CADTH review team.

Description of Studies

Characteristics of the included studies are summarized in Table 6.

Table 6: Details of Studies Included in the Systematic Review

Detail	SUNLIGHT study
Designs and populations	
Study design	Multicentre, open-label, active-controlled, randomized controlled trial
Locations	Patients were enrolled in 87 study sites in the following 13 countries: Spain (115 patients), Russia (77 patients), Brazil (63 patients), Hungary (47 patients), Italy (39 patients), Poland (34 patients), France (28 patients), Ukraine (21 patients), Denmark (20 patients), the US (16 patients), Austria (15 patients), Germany (10 patients), and Belgium (7 patients).
Patient enrolment dates	**Start date:** November 25, 2020 **End date:** February 18, 2022 **Data cut-off date:** July 5, 2022 (nonsurvival data); July 19, 2022 (survival data)
Randomized (N)	Total = 492 Trifluridine-tipiracil plus bevacizumab group = 246 Trifluridine-tipiracil alone group = 246
Inclusion criteria	• Male or female patient aged ≥ 18 years • Had histologically confirmed unresectable adenocarcinoma of the colon or rectum (all other histological types were excluded) • *RAS* status had been previously determined (mutant or wild-type) based on local assessment of tumour biopsy. Wild-type was defined as *KRAS* (exons 2, 3, and 4) and *NRAS* (exons 2, 3, and 4) wild-type. Mutant was defined as at least a *KRAS* or *NRAS* mutant (any exon, any mutation). • Had received a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer and had demonstrated progressive disease or intolerance to their last regimen: ◦ prior treatment regimens for the treatment of advanced colorectal cancer had included fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody, and/or an anti-EGFR monoclonal antibody for patients with *RAS* wild-type disease ◦ patients who had received adjuvant or neoadjuvant chemotherapy and had recurrence during or within 6 months of completion of the adjuvant or neoadjuvant chemotherapy could count the adjuvant or neoadjuvant therapy as 1 regimen of chemotherapy for advanced disease. • Had measurable or nonmeasurable disease as defined by RECIST 1.1 • Was able to swallow tablets • Had an estimated life expectancy ≥ 12 weeks • Had an ECOG PS ≤ 1; ECOG PS had to remain ≤ 1 during all of the screening period (from screening visit to randomization) • Had an adequate organ function as defined by the following laboratory values obtained within 7 days before the randomization: ◦ ANC ≥ 1.5×10^9/L

Detail	SUNLIGHT study
	◦ hemoglobin ≥ 9 g/dL; in case of blood transfusion, the hemoglobin assessment had to be performed 2 weeks or more after the transfusion ◦ platelet count ≥ 100 × 10^9/L ◦ creatinine clearance ≥ 50 mL per minute assessed using the Cockcroft-Gault formula ◦ total serum bilirubin < 1.5 × ULN (unless Gilbert disease confirmed) ◦ AST (SGOT) and ALT (SGPT) ≤ 2.5 × ULN (unless if liver function abnormalities were due to underlying liver metastasis, in which case AST and ALT ≤ 5 × ULN) ◦ adequate coagulation function for all patients; for patients receiving anticoagulant therapy (except platelet antiaggregates), adequate therapeutic levels of INR had to be confirmed. Note: Prior anti-VEGF monoclonal antibody was optional except in France, where it was mandated.
Exclusion criteria	• More than 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer • Pregnant or lactating person or person facing a possibility of becoming pregnant during the study • Receiving or having received anticancer therapies within 4 weeks before randomization • Had not recovered from clinically relevant nonhematologic CTCAE grade ≥ 3 toxicity of previous anticancer therapy before the randomization (excluding alopecia and skin pigmentation) • Had symptomatic CNS metastases that were neurologically unstable or required increasing doses of steroids to control CNS disease • Had major surgery within 4 weeks before randomization (the surgical incision should have been fully healed before study drug administration), had not recovered from side effects of previous surgery, or might have required major surgery during the study • In the investigator's opinion, patient had chronic gastrointestinal disorders that could have significantly interfered with proper absorption of the study treatments • Had hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption • Had severe or uncontrolled active acute or chronic infection • Had active interstitial lung disease or a history of it • Known HBV infection determined as HBsAg positive and/or known HCV infection determined as detection of HCV RNA in serum or plasma by a sensitive quantitative molecular method • Known carrier of HIV antibodies • In the investigator's opinion, had uncontrolled diabetes mellitus even under treatment • Had confirmed uncontrolled arterial hypertension (defined as systolic blood pressure ≥ 150 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg) or uncontrolled or symptomatic arrhythmia • Had a deep arterial thromboembolic event, including a cerebrovascular accident or myocardial infarction within the 6 months before randomization • Had severe or unstable angina, symptomatic congestive heart failure NYHA class III or class IV • Had drainage for ascites, pleural effusion, or pericardial fluid within 4 weeks before randomization • Had other malignancies, including those that were radically treated and for which the remission period at the time of screening was less than 5 years • Had treatment with systemic immunosuppressive therapy (except steroids given in a prophylactic setting or at a chronic low dose [≤ 20 mg per day prednisone equivalent]) • Prior radiotherapy if completed less than 4 weeks before randomization, except if provided as a short course for symptoms palliation only; tumour lesions if previously irradiated should not have

Detail	SUNLIGHT study
	been chosen as target lesions for response evaluation • Had any clinically significant medical condition (e.g., organ dysfunction) or laboratory abnormality likely to jeopardize the patient's safety or to interfere with the conduct of the study, in the investigator's opinion • Had previously received trifluridine-tipiracil • History of allergic reactions attributed to compounds of similar composition as trifluridine-tipiracil or any of its excipients • Any contraindication present in the EU product information on trifluridine-tipiracil • History of allergic reactions or hypersensitivity to bevacizumab or any of its excipients • History of hypersensitivity to Chinese hamster ovary cells products or other recombinant human or humanized antibodies • Serious nonhealing wound, nonhealing ulcer, or nonhealing bone fracture • Deep venous thromboembolic event within 4 weeks before randomization • Known coagulopathy that increases risk of bleeding, bleeding diathesis; any other hemorrhage or bleeding event of CTCAE grade ≥ 3 within 4 weeks before randomization • Any contraindication present in the EU product information on bevacizumab • History of any life-threatening VEGF-related adverse event • Proteinuria ≥ 1 g per 24 hours or 2 or more by dipstick
Drugs	
Intervention	Trifluridine-tipiracil (35 mg/m^2 per dose, twice daily, on day 1 to day 5 and day 8 to day 12 of each 28-day cycle) plus bevacizumab (5 mg/kg as an IV infusion on day 1 and day 15 of each 28-day cycle)
Comparator(s)	Trifluridine-tipiracil alone (35 mg/m^2 per dose, twice daily, on day 1 to day 5 and day 8 to day 12 of each 28-day cycle)
Study duration	
Screening phase	Up to 28 days before randomization
Treatment phase	Patients received the first dose of study treatments within 3 days after randomization and continued until they met a discontinuation criterion, which included radiologic progressive disease, clinical progression, unacceptable toxicity, treatment delay of at least 28 days, withdrawal of consent by patient, physician decision, or death, whichever occurred first.
Follow-up phase	Patients were followed up every 8 weeks for radiologic progression and/or survival status.
Outcomes	
Primary end point	Overall survival, defined as the time elapsed between the date of randomization and the date of death due to any cause
Secondary and exploratory end points	**Key secondary:** Progression-free survival, based on investigator assessment, defined as the time elapsed between randomization and the date of radiologic tumour progression according to RECIST 1.1 or death from any cause **Secondary:** • Objective response rate, based on the investigator's assessment of tumour response and defined as the proportion of patients with objective evidence of CR or PR according to RECIST 1.1 criteria • Disease control rate, based on the investigator's assessment of tumour response and defined as the proportion of patients with objective evidence of CR, PR, or stable disease according to RECIST 1.1 criteria

Detail	SUNLIGHT study
	• EORTC QLQ-30 • EQ-5D-5L • Safety and tolerability (adverse events, laboratory tests, physical examinations, vital signs, and the time from randomization to worsening of the ECOG PS score from 0 or 1 to 2 or more) **Exploratory:** None
Publication status	
Publications	SUNLIGHT trial (NCT04737187) Prager et al. (2023){Prager, 2023 #77} Tabernero et al. (2021){Tabernero, 2021 #118} Prager et al. (2023){Prager, 2023 #76}

ALT = alanine aminotransferase; ANC = absolute neutrophil count; anti-EGFR = anti–epidermal growth factor receptor; anti-VEGF = anti–vascular endothelial growth factor; AST = aspartate aminotransferase; CNS = central nervous system; CR = complete response; CTCAE = *Common Terminology Criteria for Adverse Events*; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = 5-Level EQ-5D; EU = European Union; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; NYHA = New York Heart Association; PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1; RNA = ribonucleic acid; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal; VEGF = vascular endothelial growth factor.

Note: Details included in Table 6 are from the sponsor's Summary of Clinical Evidence.[33]

Source: SUNLIGHT Clinical Study Report.[22]

The SUNLIGHT trial was a randomized, double-arm, phase III, open-label, multicentre study that evaluated the safety and efficacy of trifluridine-tipiracil plus bevacizumab versus trifluridine-tipiracil alone among adult patients with refractory mCRC who had received no more than 2 previous chemotherapy regimens. The primary objective was to estimate OS of patients in the trifluridine-tipiracil plus bevacizumab group compared with trifluridine-tipiracil alone group. The key secondary objective was to estimate PFS of patients in the trifluridine-tipiracil plus bevacizumab group compared with trifluridine-tipiracil alone group, based on investigator assessment. Following screening, patients were enrolled from November 25, 2020, to February 18, 2022, at 87 study sites (there were no study sites in Canada).

A total of 492 patients were randomized 1:1 via an Interactive Web Response System (IWRS) using central randomization to the trifluridine-tipiracil plus bevacizumab group or the trifluridine-tipiracil alone group. Randomization was stratified by geographic region (North America, European Union, the rest of the world), time since first metastasis diagnosis (< 18 months, ≥ 18 months), and the *RAS* status (wild-type, mutant). The data cut-off dates were July 5, 2022, for clinical data (i.e., nonsurvival) and July 19, 2022 (occurrence of the 331st death), for survival data.

Populations

Inclusion and Exclusion Criteria

The study included adult patients (aged 18 years or older) with refractory mCRC who had received no more than 2 previous chemotherapy regimens and had progressive disease or whose last regimen had caused unacceptable adverse effects. Previous treatment must have included fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody (not necessarily bevacizumab), or an anti-EGFR monoclonal antibody (for patients with *RAS* wild-type disease), and the treatment could have included neoadjuvant or adjuvant chemotherapy if disease had recurred during treatment or within 6 months after the last

administration of neoadjuvant or adjuvant therapy. Eligibility required knowledge of *RAS* status. Patients had to have adequate organ function and an ECOG PS score of 0 or 1.

Interventions

Pretreatment Phase

Blood and urine tests are required before starting trifluridine-tipiracil. Blood and urine tests are routine procedures that are ordered by a physician and are typically performed at an outpatient laboratory clinic. Complete blood cell counts must be obtained before the initiation of therapy with trifluridine-tipiracil and as needed to monitor blood counts, but at a minimum, they must be obtained before each treatment cycle. Treatment with trifluridine-tipiracil must not be started if the absolute neutrophil count is below 1.5 multiplied by 10^9/L, if the platelet counts are below 75 multiplied by 10^9/L, or if the patient has unresolved grade 3 or grade 4 nonhematologic clinically relevant toxicity from prior therapies and/or prior trifluridine-tipiracil cycles. Monitoring of proteinuria by dipstick urinalysis is recommended before starting therapy and during therapy.

Treatment Phase

Trifluridine-tipiracil is administered orally and can be taken at home or in a community setting. As noted earlier, complete blood cell counts must be obtained before each treatment cycle along with the monitoring of proteinuria by dipstick urinalysis.

Trifluridine-tipiracil was administered orally, twice daily, at a starting dose of 35 mg/m^2 of BSA, on day 1 through day 5 and on day 8 through day 12 every 28 days. If doses were missed or held on those days, the patient was not to make up for missed doses. The extension of study treatment into day 6 to day 7 or into the rest period (day 13 through day 28) was not permitted. The patient's weight at screening (baseline) was used to calculate the initial dose (based on BSA); however, if at the beginning of a new treatment cycle, the patient's weight changed by at least 10%, the dose was recalculated based on the updated weight and the adjusted dose was provided to the study site by the IWRS. Table 7 shows the number of tablets that are needed per calculated BSA for a dose of 35 mg/m^2 and for a reduced dose (30 mg/m^2, 25 mg/m^2, and 20 mg/m^2).

Table 7: Number of Tablets of Trifluridine-Tipiracil per Dose (Reduced Dose)

Trifluridine-tipiracil dose	BSA (m^2) (calculate to 2 decimal places)	Dose in mg (twice daily)	Tablets per dose		Total daily dose (mg)
			15 mg trifluridine/ 6.14 mg tipiracil	20 mg trifluridine/ 8.19 mg tipiracil	
Level 1 dose reduction: From 35 mg/m^2 to 30 mg/m^2					
30 mg/m^2	< 1.09	30	2	0	60
	1.09 to 1.24	35	1	1	70
	1.25 to 1.39	40	0	2	80
	1.40 to 1.54	45	3	0	90
	1.55 to 1.69	50	2	1	100
	1.70 to 1.94	55	1	2	110

Trifluridine-tipiracil dose	BSA (m^2) (calculate to 2 decimal places)	Dose in mg (twice daily)	Tablets per dose		Total daily dose (mg)
			15 mg trifluridine/ 6.14 mg tipiracil	20 mg trifluridine/ 8.19 mg tipiracil	
	1.95 to 2.09	60	0	3	120
	2.10 to 2.28	65	3	1	130
	≥ 2.29	70	2	2	140
Level 2 dose reduction: From 30 mg/m^2 to 25 mg/m^2					
25 mg/m^2	< 1.10	25[a]	2[a]	1[a]	50[a]
	1.10 to 1.29	30	2	0	60
	1.30 to 1.49	35	1	1	70
	1.50 to 1.69	40	0	2	80
	1.70 to 1.89	45	3	0	90
	1.90 to 2.09	50	2	1	100
	2.10 to 2.29	55	1	2	110
	≥ 2.30	60	0	3	120
Level 3 dose reduction: From 25 mg/m^2 to 20 mg/m^2					
20 mg/m^2	< 1.14	20	0	1	40
	1.14 to 1.34	25[a]	2[a]	1[a]	50[a]
	1.35 to 1.59	30	2	0	60
	1.60 to 1.94	35	1	1	70
	1.95 to 2.09	40	0	2	80
	2.10 to 2.34	45	3	0	90
	≥ 2.35	50	2	1	100

BSA = body surface area.

[a]At a total daily dose of 50 mg, patients should take one 20 mg/8.19 mg tablet in the morning and two 15 mg/6.14 mg tablets in the evening.

Source: SUNLIGHT Clinical Study Report.[22]

Bevacizumab was administered intravenously by study site personnel at a dose of 5 mg/kg of body weight on day 1 and day 15. At each visit, the IWRS provided the study site with the adjusted bevacizumab dose based on the patient's actual weight. The study site could round this dose at the nearest 0.5 mL. The initial dose was to be delivered over 90 minutes as an IV infusion. If the first infusion was well tolerated, the second infusion could be administered over 60 minutes. If the 60-minute infusion was well tolerated, all subsequent infusions could be administered over 30 minutes. If a medical condition developed that required bevacizumab to be permanently withdrawn, the patient could continue with trifluridine-tipiracil alone. Bevacizumab was not to be administered alone in case of dose delay due to trifluridine-tipiracil toxicities. The cycle was to be delayed and bevacizumab was to be restarted at the same time as trifluridine-tipiracil. Bevacizumab infusions should be prepared by a health care professional using an aseptic technique and would be administered at an outpatient infusion clinic or outpatient hospital setting.

There are no concomitant drugs required or recommended for patients receiving trifluridine-tipiracil plus bevacizumab. However, as trifluridine-tipiracil has emetogenic potential, a single antiemetic drug, such as dexamethasone, a 5-HT3 receptor antagonist, or a dopamine receptor antagonist such as metoclopramide hydrochloride may be considered for prophylaxis. For patients who experience anticipatory nausea and vomiting, benzodiazepines are recommended.

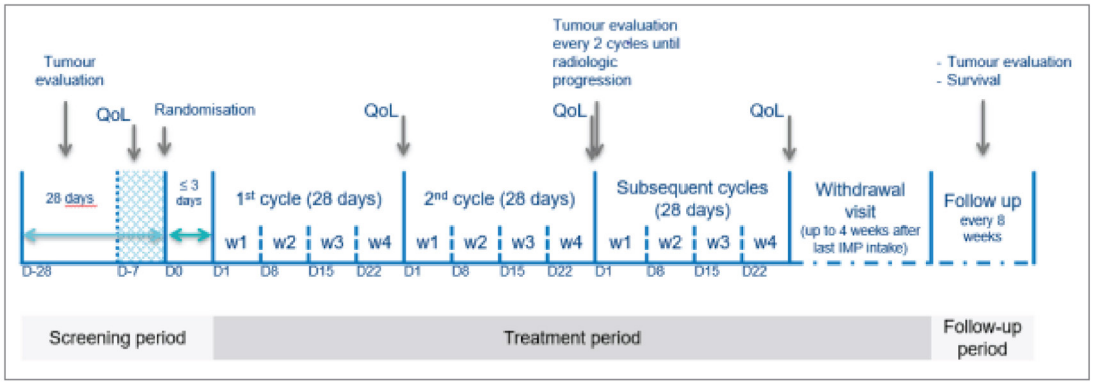
Post-Treatment Phase

After treatment, medications may be used for the management of AEs and can include the following.

- Loperamide hydrochloride may be used for diarrhea at an initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool (not to exceed 16 mg per day). For patients with complicated diarrhea, treatment includes IV fluids, octreotide at a starting dose of 100 mcg to 150 mcg, subcutaneously 3 times daily or IV (25 mcg per hour to 50 mcg per hour) if the patient is severely dehydrated, with dose escalation up to 500 mcg until diarrhea is controlled, plus the administration of antibiotics (e.g., fluoroquinolone).
- Sodium bicarbonate mouthwash, anesthetic mouthwashes, topical analgesic or anti-inflammatory drugs, topical anesthetics, and alternative mouthwashes may be used for mucosal injury.
- Hematologic support may be used as medically indicated (e.g., blood transfusions, granulocyte colony-stimulating factor [G-CSF], erythropoietin) for febrile neutropenia and anemia.

The treatment schema for the SUNLIGHT trial is depicted in Figure 2. Each treatment cycle was 28 days in duration for each group.

Figure 2: Schematic of Study Design for SUNLIGHT Study



D = day; QoL = quality of life; w = week; IMP = investigational medicinal product.

Source: SUNLIGHT Clinical Study Report.[22]

One treatment cycle of the trifluridine-tipiracil plus bevacizumab group consisted of the following:

- day 1 to day 5 — oral intake of trifluridine-tipiracil and bevacizumab IV infusion on day 1
- day 6 to day 7 — rest
- day 8 to day 12 — oral intake of trifluridine-tipiracil
- day 13 to day 14 — rest

- day 15 — bevacizumab IV infusion
- day 16 to day 28 — rest.

One treatment cycle of the trifluridine-tipiracil alone group consisted of the following:

- day 1 to day 5 — oral intake of trifluridine-tipiracil
- day 6 to day 7 — rest
- day 8 to day 12 — oral intake of trifluridine-tipiracil
- day 13 to day 28 — rest.

The 28-day treatment cycles continued until disease progression occurred, unacceptable toxic effects occurred, or consent was withdrawn. Patients were considered to be receiving treatment for as long as they continued to receive trifluridine-tipiracil; bevacizumab monotherapy was not allowed.

Dose Modifications of Trifluridine-Tipiracil Due to Toxicities

All toxicities related to trifluridine-tipiracil had to be resolved to grade 1 or baseline before the start of a new treatment cycle. In the event of hematologic and/or nonhematologic toxicities, rules for trifluridine-tipiracil dose interruption and resumption, and rules for dose modifications are provided (refer to Appendix 1, Figure 13). A new treatment cycle with trifluridine-tipiracil could be started only if the neutrophils count was equal to or greater than 1.5 multiplied by 10^9/L and the platelets count was equal to or greater than 75 multiplied by 10^9/L.

If the patient recovered from toxicities requiring treatment interruption, the following occurred.

- During the 2-week active treatment intake period of a cycle (treatment day 1 to day 12):
  - if no dose reduction was required, trifluridine-tipiracil could be resumed during that cycle
  - if a dose reduction was required, trifluridine-tipiracil had to be resumed at the start of the next cycle at the appropriate dose level.
- During the rest period (day 13 to day 28):
  - the next cycle was to be started on schedule at the appropriate trifluridine-tipiracil dose level.

If the toxicities did not resolve during the given cycle to grade 1 or baseline, the start of the next cycle had to be delayed for a maximum of 28 days from the scheduled start date of the next cycle. If more than 28 days were needed to recover, the patient had to be withdrawn from treatment.

Dose Discontinuation of Bevacizumab Due to Toxicities

Dose reduction for adverse reactions was not recommended. If indicated, therapy had either to be permanently discontinued or suspended temporarily. If a medical condition developed that required bevacizumab to be permanently withdrawn, the patient could continue with trifluridine-tipiracil alone.

Concomitant Treatments

Concomitant treatments that were permitted during the study treatment included palliative radiotherapy (irradiation of target lesions was to be avoided), effective contraception methods, and the management of toxicities of the study treatment (e.g., antiemetic regimen, antidiarrheal therapy, G-CSF use). Concomitant

G-CSF treatment was permitted for primary prophylaxis (i.e., G-CSF at cycle 1, with or without neutropenia at cycle 1), secondary prophylaxis (i.e., G-CSF at any subsequent cycle to cycle of neutropenia), and therapeutic use (i.e., G-CSF on or 1 day after neutropenia onset date); patients with both secondary prophylaxis and therapeutic use of G-CSF were defined only as therapeutic use. Patients treated with anti–vitamin K were strongly recommended to be switched to low–molecular weight heparin. Caution was directed when using drugs that were human thymidine kinase substrates (e.g., zidovudine), which could have competed with the effector, trifluridine, for the activation of thymidine kinases.

Intercurrent Events

The following were considered intercurrent events in the SUNLIGHT study: the administration of further anticancer therapy, treatment discontinuation, or treatment switch (from trifluridine-tipiracil plus bevacizumab to trifluridine-tipiracil alone, and vice versa).

Withdrawal Criteria

Patients could discontinue treatment for the following reasons: AEs that were incompatible with the continuation of study treatment as judged by the investigator, protocol deviation that interfered with study evaluations and/or the patient's safety, radiologic progressive disease documented by CT scan or MRI, clinical progressive disease evident by symptomatic deterioration, a nonmedical reason (e.g., consent withdrawal, patient's removal), and other reasons, including physician decision. A withdrawal visit was to take place within 4 weeks after the date of study treatment withdrawal and before the start of a new anticancer therapy.

Outcomes

Summarized end points are based on outcomes included in the sponsor's Summary of Clinical Evidence as well as any outcomes identified as important to this review, according to the clinical experts consulted by CADTH and stakeholder input from patient and clinician groups and public drug plans. Using the same considerations, the CADTH review team selected end points that were considered the most relevant to inform CADTH's expert committee deliberations and finalized this list of end points in consultation with members of the expert committee. All summarized efficacy end points in Table 8 were assessed using GRADE. Select notable harms outcomes considered important for informing CADTH's expert committee deliberations were also assessed using GRADE.

Overall Survival

In the SUNLIGHT trial, the primary efficacy end point was OS, defined as the time elapsed between the date of randomization and the date of death due to any cause. For patients without documentation of death, the OS was censored at the last contact date the patient was known to be alive. Based on the consensus from Colorectal Cancer Canada, an improvement of 2 months or more in median OS or an HR for survival of 0.75 or lower (or both) are the threshold for a clinically meaningful benefit.[46]

Progression-Free Survival

In the SUNLIGHT trial, the key secondary end point was PFS based on investigator assessment. PFS was defined as the time elapsed between the date of randomization and the date of radiologic tumour

progression according to Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) or death from any cause.

Health-Related Quality of Life

In the SUNLIGHT trial, HRQoL was measured using the EORTC QLQ-C30 and the EQ-5D-5L.

The EORTC QLQ-C30 is a multidimensional, cancer-specific, self-administered measure of HRQoL consisting of 30 questions across 5 multi-item functional scales, 3 multi-item symptom scales, 6 single-item symptom scales, and a 2-item global health status scale. Each item is evaluated using 4-point and 7-point Likert scales, raw scores for each scale are computed as the average of the items that contribute to a particular scale, and each raw scale score is converted to a standardized score that ranges from 0 to 100 using a linear transformation. Higher scores in the global health status and functioning scales indicate better HRQoL, whereas higher scores in the symptom scales indicate poorer HRQoL.[47-50] The change in score from baseline in the global health score was the primary HRQoL end point. In the SUNLIGHT trial, an absolute change from baseline greater than 10 points in the EORTC QLQ-C30 was considered a clinically meaningful difference.[22,51,52] A study of 21 European Organisation for Research and Treatment of Cancer phase III trials of patients across 9 cancer types estimated that for CRC (1,491 patients), most MIDs were approximately 5 points to 10 points, with larger MIDs for improvements than for deterioration across most scales in within-group and between-group analyses.[53] A between-group difference of 10 points was identified by the sponsor to be a MID.[52,54]

The EQ-5D-5L is a generic, preference-based measure of HRQoL consisting of 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; index scores range from 0 to 1, with 0 and 1 representing the health states “dead” and “perfect health,” respectively, while EQ VAS scores range from 0 to 100, with 0 and 100 representing “worst imaginable health” and ”best imaginable health,” respectively.[55] No MID for the EQ-5D-5L utility or EQ VAS was identified by the sponsor.

In the SUNLIGHT trial, HRQoL data (i.e., EORTC QLQ-C30 and EQ-5D-5L) were collected at baseline (within 7 days before randomization), at every cycle before any study procedure, and at the withdrawal visit. Questionnaires were completed on an electronic patient-reported outcomes tablet by patients (independent of study personnel) or by a caregiver who read the questions to the patient and recorded responses. No MID for the EQ-5D-5L utility or EQ VAS was identified by the sponsor.

Harms

In the SUNLIGHT trial, safety end points included AEs, SAEs, concomitant treatments, the assessment of laboratory tests, physical examinations, vital signs, and the time from randomization to worsening of the ECOG PS score from 0 or 1 to 2 or more. AEs were defined as any untoward medical occurrence in a patient, whether or not there was a causal relationship with the study treatments and/or experimental procedures, occurring or detected from the date the patient signed the information and consent form, irrespective of the period of the study. An AE could include any unfavourable and unintended sign (e.g., abnormal finding from an additional examination such as lab tests, X-rays, electrocardiogram) deemed clinically relevant by the investigator, any symptom or disease, and any worsening during a study visit at an additional examination

or that had occurred since the previous study visit. SAEs included any AE that at any dose resulted in death, was life-threatening, required inpatient hospitalization, or required the prolongation of existing hospitalization, was medically significant, resulted in persistent or significant disability or incapacity, or was a congenital anomaly or birth defect. A data safety monitoring board was responsible for reviewing the safety data on a regular basis and providing written recommendations to the sponsors regarding the conduct of the study.

Table 8: Outcomes Summarized From the Studies Included in the Systematic Review

Outcome measure	Time point	SUNLIGHT study
Overall survival	Time from date of randomization to date of death due to any cause	Primary end point[a]
Progression-free survival	Time from date of randomization to radiologic tumour progression according to RECIST 1.1 or death from any cause, based on investigator assessment	Key secondary end point[a]
EORTC QLQ-C30	Baseline, every 4 weeks before any study procedure, and at the withdrawal visit	Secondary end point
EQ-5D-5L	Baseline, every 4 weeks before any study procedure, and at the withdrawal visit	Secondary end point
Treatment-emergent adverse events	Throughout study	Secondary end point
Caregiver burden	NA	Not measured[b]

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = 5-Level EQ-5D; NA = not applicable; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1.

Note: Details included in Table 8 are from the sponsor's Summary of Clinical Evidence.[33]

[a]Statistical testing for these end points was adjusted for multiple comparisons (e.g., hierarchical testing).

[b]This outcome was identified as important by input from patient groups and clinical experts consulted by CADTH but was not measured in the SUNLIGHT trial.

Source: SUNLIGHT Clinical Study Report.[22]

Considerations that informed the selection of efficacy outcomes to be summarized and assessed using GRADE included the following.

- Survival outcomes were identified by patient input (as OS, including tumour shrinkage and tumour stability), clinician group input (as extending survival, delaying further progression, and shrinking tumour burden), clinical experts consulted by CADTH (as OS at 6 months and 12 months, and PFS at 3 months and 6 months), and in the sponsor's pharmacoeconomic model (as OS and PFS). OS and PFS were also identified as relevant in a previous CADTH review of trifluridine-tipiracil.[56] PFS was acknowledged by the clinical experts to provide supportive evidence of OS as a primary end point in the SUNLIGHT trial. The clinical experts identified an MID of 10% between treatment groups to be clinically important.
- HRQoL measured using the EORTC QLQ-C30 was identified by patients (as improved mobility, improved sense of wellness), clinician group input (as minimizing symptoms and symptom burden and being able to maintain independence), and clinical experts consulted by CADTH, and was identified as relevant in a previous CADTH review of trifluridine-tipiracil.[56] In the EORTC QLQ-C30,

functioning scales (physical and emotional) and symptom scales (fatigue, nausea and vomiting, pain, dyspnea, appetite loss, and diarrhea) were identified by patient input and clinical experts consulted by CADTH to be important. Given the breadth of subscales, the CADTH review team focused on the global health status scale, to be assessed using GRADE to encompass the broad range of functioning and symptoms identified by stakeholders. Anchor-based MIDs for between-group differences in change on the global health status were estimated to range from 5.53 to 6.36 (weighted value of 5.86) for improvement and range from −9.21 to −6.81 (weighted value of −8.13) for deterioration among patients with advanced CRC treated with chemotherapy.[57]

- HRQoL measured using the EQ-5D-5L was a key input in the sponsor's pharmacoeconomic model and was identified as relevant in a previous CADTH review of trifluridine-tipiracil.[56] Acknowledging the lack of an MID for EQ-5D-5L in the published literature for patients with mCRC, the clinical experts identified a greater than 0.08-point difference between groups for the EQ-5D-5L utility score and a greater than 7-point difference between groups for the EQ VAS score based on MIDs reported for patients with cancer.[58]
- Caregiver burden was identified as important by patient input and the clinical experts consulted by CADTH. No data on caregiver burden were collected in the SUNLIGHT trial.
- Harms of treatment were identified as important by patient input, clinician group input, and the clinical experts consulted by CADTH. Bone marrow suppression was identified by patient input (as nausea, anemia, neutropenia), by the clinical experts consulted by CADTH, and by the product monograph[17] for trifluridine-tipiracil (including grade 3 or grade 4 neutropenia, leukopenia, anemia, thrombocytopenia, and febrile neutropenia). Gastrointestinal symptoms (including nausea, vomiting, and diarrhea) were identified by patient input, by the clinical experts consulted by CADTH (including gastrointestinal perforation), and by the product monograph[17] for trifluridine-tipiracil. Infections were also identified as important by clinical experts consulted by CADTH. Hypertension was identified as important by the CADTH pan-Canadian Oncology Drug Review Expert Review Committee. The clinical experts identified an MID of 10% between treatment groups to be clinically important for bone marrow suppression, gastrointestinal symptoms, infections, and hypertension.

Statistical Analysis

Sample Size and Power Calculation

The sample size considerations for OS were based on a maximum of 331 events (deaths for any cause) for the primary analysis to detect an HR of 0.70 with 90% power using a log-rank test at a 1-sided cumulative 2.5% level of significance. Based on the data from the RECOURSE study,[44] the median OS in the control group was expected to be around 7.1 months. An HR of 0.70 translates into a 3-month increase of the median OS in the experimental group (10.1 months) compared to the control group. Based on the assumption that enrolment would have continued for approximately 12 months, and that an estimated 5% per year of the patients would drop out, a total of 490 patients randomized in a 1:1 ratio was needed to observe the 331st OS event approximately 9 months after the last patient randomization.

No interim analyses were planned for the primary end point of OS.

Statistical Testing

Statistical analysis of efficacy outcomes in the SUNLIGHT trial were controlled for overall type I error rate by using a hierarchical testing strategy. PFS was to be statistically evaluated and interpreted only if the primary efficacy end point of OS was significantly different between the 2 treatment groups.

Analysis of OS

The primary efficacy end point was the effect of the randomized treatments on OS in all patients regardless of whether or not intercurrent events occurred. In line with the intention-to-treat principle, further anticancer therapies were assumed to represent clinical practice and therefore, intercurrent events were considered to be part of the treatments being compared. All data collected during the trial, regardless of occurrence of an intercurrent event, were used.

The distribution of OS was compared between the 2 treatment groups using a stratified log-rank test at a 1-sided 2.5% level of significance (stratification factors were based on IWRS data). OS for each group was estimated using KM curves and further characterized in terms of the median and survival probabilities at 6 months, 12 months, and 18 months with the corresponding 2-sided 95% CIs. The HR of OS with its 95% CI was estimated with a stratified Cox proportional hazards model (stratification factors were based on IWRS data). Underlying assumptions of proportional hazards were checked using a Schoenfeld residuals test and graphical methods (i.e., log cumulative hazard curve): if the curve of the estimated treatment effect at each time and its CI deviate away from the horizontal, a time dependent effect is present. A statistical test using the Grambsch and Therneau (1994){GRAMBSCH, 1994 #119} test based on Schoenfeld residuals was performed. If the P value of the test was below 0.05, the null hypothesis (proportional hazards) was rejected and the proportional hazards assumption was not validated.

Analysis of PFS

The key secondary end point was the effect of the randomized treatments on PFS in all patients regardless of whether or not intercurrent events occurred (treatment policy strategy). The PFS was based on the investigator's judgment and was defined as the time elapsed between the date of randomization and the date of radiologic tumour progression (according to RECIST 1.1) or death from any cause. All data collected during the trial, regardless of the occurrence of an intercurrent event, were used.

A hierarchical testing strategy, where PFS was to be statistically evaluated and interpreted only if the primary efficacy estimand OS was significantly different between the 2 treatment groups, was used to control the overall type I error rate. The distribution of PFS was compared between the 2 treatment groups using a stratified log-rank test at a 1-sided 2.5% level of significance (stratification factors were based on IWRS data). PFS for each group was estimated using KM curves and further characterized in terms of median and survival probabilities at 3 months, 6 months, 9 months, and 12 months with the corresponding 2-sided 95% CIs. The HR of PFS with its 95% CI was estimated with a stratified Cox proportional hazards model (stratification factors were based on IWRS data).

Censoring

For missing OS data not linked to intercurrent events (i.e., patients without documentation of death [lost to follow-up, withdrawal of consent, or administrative end of study]), OS was censored on the last contact date the patient was known to be alive or the survival cut-off date, whichever was earlier.

For missing PFS data not linked to intercurrent events (i.e., patients who were lost to follow-up or who had withdrawn their consent without radiologic progression or had reached the time point of analysis without a known record of death or radiologic progression), PFS was censored at the date of the last evaluable tumour assessment or the survival cut-off date, whichever was earlier.

Subgroup Analyses

Subgroup analyses for OS and PFS were performed in the FAS using an unstratified Cox-regression model with treatment group as predictor variable fitted separately for each subgroup category. The HR for treatment and associated 95% CIs were reported. No statistical testing was conducted to evaluate differences in effects between subgroups, and analyses were not adjusted for multiplicity. Prespecified subgroups included the following:

- region (North America, European Union, the rest of the world)
- time since diagnosis of first metastasis (< 18 months, ≥ 18 months)
- *RAS* status (wild-type, mutant)
- location of primary disease (right, left)
- ECOG PS (0, ≥ 1)
- sex (female, male)
- age (< 65, ≥ 65 years)
- prior surgical resection (yes, no)
- number of metastatic sites (1 to 2, ≥ 3)
- neutrophils to lymphocytes ratio (< 3, ≥ 3)
- number of prior metastatic drug regimens (1, ≥ 2)
- *BRAF* status (wild-type, mutant)
- microsatellite instability status (MSI-H, microsatellite stable, or microsatellite instability–low)
- prior bevacizumab (yes, no)
- subsequent regorafenib (yes, no).

Sensitivity Analyses

The following sensitivity analyses of OS were performed.

- The distribution of OS was compared between the treatment groups using an unstratified log-rank test and the HR (together with associated 95% CI) resulting from an unstratified Cox model.
- The distribution of OS excluding patients not fulfilling 1 of the following criteria was compared between the treatment groups using a stratified log-rank test (stratification factors were based on

IWRS data) and the HR (together with associated 95% CI) resulting from a stratified Cox proportional hazards model (stratification factors were based on IWRS data):

- has histologically confirmed unresectable adenocarcinoma of the colon or rectum
- has received a maximum of 2 prior chemotherapy regimens for the treatment of advanced CRC and had demonstrated progressive disease or intolerance to their last regimen
- has measurable or nonmeasurable metastatic lesion(s) as defined by RECIST 1.1
- has an ECOG PS of 1 or less
- has more than 2 prior chemotherapy regimens for the treatment of advanced CRC
- has previously received trifluridine-tipiracil
- was not undergoing or has not received anticancer therapies within 4 weeks before randomization.

- The restricted mean survival time for OS was reported with its 95% CI in each treatment group. The difference in restricted mean survival time between treatment groups was tested.

The following sensitivity analyses of PFS were performed.

- The distribution of PFS was compared between treatment groups using an unstratified log-rank test and the HR (with associated 95% CI) resulting from an unstratified Cox model.
- Analysis was conducted including clinical progression and the administration of further anticancer therapy as PFS events in addition to the radiologic progression or death.
- Analysis was conducted censoring the PFS duration at the date of last evaluable tumour assessment before or on the day of administration of further anticancer therapy and censoring patients with radiologic progression or who die after 2 or more consecutive missing radiological assessments at the latest evaluable assessment before the missing assessments. Based on the time interval between the last evaluable tumour assessment date and the event date, if the interval was greater than (2 multiplied by 8) plus 2 equals 18 weeks (protocol-specified threshold), then the analysis would assume 2 missing assessments.

Secondary End Points

No non–key secondary end points were adjusted for multiplicity.

Health-Related Quality of Life

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30:
Patients in the FAS who have completed at least 1 questionnaire item at baseline and during the study period were analyzed in the group they were assigned at randomization. The raw data were scored according to the European Organisation for Research and Treatment of Cancer scoring manual. Descriptive statistics (number of patients, mean, SD, median, range) were used to summarize values at baseline and at postbaseline, and the change from baseline in the global health status and subscale scores at each scheduled assessment time point and by classes (benefit [large, moderate, small], no change, and deterioration [small, moderate, large]) for each treatment group. A mixed model of repeated measures that included terms for treatment,

baseline stratification factors, baseline score, time to visit before any procedure (at each cycle, including the withdrawal visit), and treatment groups by time to visit interaction was used to compare change from baseline subscale scores longitudinally over time between treatment groups. The most suitable covariance structure was chosen according to Akaike's information criterion and Schwartz's Bayesian Criterion between unstructured, compound symmetric, and autoregressive of order 1.

Time until definitive deterioration was defined as the interval between baseline and the first worsening in HRQoL score of 10 points or greater compared to the baseline HRQoL score with no later improvement above this threshold observed during the study. Time until definitive deterioration of 10 points for each subscale was compared between the treatment groups using the stratified log-rank test at a 2-sided 5% level of significance. Distributions were described using KM curves, including the median time to a definitive 10 points' deterioration with 95% CIs. Death was considered as deterioration of HRQoL. Patients who received any further antitumoural treatment before worsening were censored at the date of their last HRQoL assessment before starting such therapy. Patients who did not definitively worsen as of the cut-off date for the analysis were censored at the date of their last assessment before the cut-off date. Patients with a missing scale score at baseline were censored at the randomization date plus 1 day.

5-Level EQ-5D: Patients in the FAS with an evaluable EQ-5D-5L assessment at baseline and at least 1 evaluable assessment postbaseline were analyzed in the group they were assigned at randomization. For data from all countries, the EQ-5D-5L index utility score was derived according to the French value set. Descriptive statistics (number of patients, mean, SD, median, range) were used to summarize values at baseline and the change from baseline in EQ-5D-5L index utility and EQ VAS by treatment group at each scheduled assessment time point before any study procedure. A mixed model of repeated measures that included terms for treatment, baseline stratification factors, baseline score, time to visit before any procedure (at each cycle, including the withdrawal visit), and treatment groups by time to visit interaction was used to compare change from baseline scores between treatment groups. The most suitable covariance structure was chosen according to Akaike's information criterion and Schwartz's Bayesian Criterion between unstructured, compound symmetric, and autoregressive of order 1.

Safety Analyses

Descriptive statistics (number of events, number and percentage of patients reporting at least 1 event) were summarized for each treatment group for emergent AEs, SAEs, withdrawals due to AEs, and deaths. Emergent AEs were to be described for each treatment group according to worst grade, severity, relationship to treatment (related to trifluridine-tipiracil, related to bevacizumab, or related to trifluridine-tipiracil plus bevacizumab), relationship to disease progression, whether they led to death, or whether they required added therapy. The seriousness and relationship with trifluridine-tipiracil and/or bevacizumab were based on investigator opinion and included sponsor decision to upgrade seriousness and/or relationship. Reasons for deaths were to be reported during the treatment and follow-up periods.

Analysis Populations

Analysis sets included in the SUNLIGHT trial are summarized in Table 10.

Table 9: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
SUNLIGHT study				
Overall survival	KM method with treatment comparison using stratified log-rank test. Estimates of treatment effect: HRs using a Cox proportional hazards analysis with 95% CIs	Stratified by the same stratification factors employed in randomization: • geographic region (North America, European Union, the rest of the world) • time since first metastasis diagnosis (< 18 months, ≥ 18 months) • *RAS* status (wild-type, mutant)	Censored on the last contact date the patient was known to be alive or the cut-off date, whichever was earlier	• Unstratified log-rank test and HR with 95% CI from an unstratified Cox model • Excluded patients not fulfilling relevant eligibility criteria • RMST with 95% CI in each treatment group and tested for difference between groups
PFS (key secondary end point)	KM method with treatment comparison using stratified log-rank test. Estimates of treatment effect: HRs using a Cox proportional hazards analysis with 95% CIs	Stratified with the same stratification factors as the primary efficacy analysis	Censored at the date of last evaluable tumour assessment or the cut-off date, whichever was earlier	• Unstratified log-rank test and HR with 95% CI from an unstratified Cox model • Analysis that considered clinical progression and administration of further anticancer therapy as PFS events in addition to radiologic progression or death • Analysis censoring the PFS duration at the date of the last evaluable tumour assessment before or on the day of administration of further anticancer therapy and censoring patients with radiologic progression or who died after 2 or more consecutive missing radiological assessments at the latest evaluable assessment before the missing assessments
EORTC QLQ-C30	An MMRM compared treatment groups on change from baseline scores. Distributions were	None	**Censored:** Patients receiving any further antineoplastic therapy before definitive worsening were censored at the	None

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
	described using KM curves, including median time to definitive 10 points' deterioration.		date of their last QoL assessment before starting this therapy. Patients who had not worsened as of the cut-off date for the analysis were censored at the date of their last assessment (questionnaire) before the cut-off date. Patients without an evaluable questionnaire at baseline were censored at their randomization date + 1 day.	
EQ-5D-5L health utility index and EQ VAS	An MMRM compared treatment groups on change from baseline scores.	None	**Censored:** Patients receiving any further antineoplastic therapy before definitive worsening were censored at the date of their last QoL assessment before starting this therapy. Patients who had not worsened as of the cut-off date for the analysis were censored at the date of their last assessment (questionnaire) before the cut-off date. Patients without an evaluable questionnaire at baseline were censored at their randomization date + 1 day.	None

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = 5-Level EQ-5D; EQ VAS = EQ visual analogue scale; HR = hazard ratio; KM = Kaplan-Meier; MMRM = mixed model of repeated measures; PFS = progression-free survival; QoL = quality of life; RMST = restricted mean survival time.

Note: Details included in Table 9 are from the sponsor's Summary of Clinical Evidence.[33]

Source: SUNLIGHT Clinical Study Report.[22]

Table 10: Analysis Populations in the SUNLIGHT Trial

Study	Population	Definition	Application
SUNLIGHT trial	FAS	All patients to whom a therapeutic unit was randomly assigned using IWRS. Patients in the FAS were analyzed in the group they were assigned by randomization.	All efficacy analyses
	SAS	All patients who had taken at least 1 dose of trifluridine-tipiracil. Patients were analyzed according to the treatment actually received.	All safety analyses

FAS = full analysis set; IWRS = Interactive Web Response System; SAS = safety analysis set.

Note: Details included in Table 10 are from the sponsor's Summary of Clinical Evidence.[33]

Source: SUNLIGHT Clinical Study Report.[22]

Results

Patient Disposition

A summary of patient disposition is presented in Table 11.

Of 659 patients screened, 167 (25.3%) patients did not pass screening, resulting in 492 patients being randomized into the SUNLIGHT trial. Most (24.3%) patients did not pass screening due to eligibility criteria not being met. By the cut-off date of July 5, 2022, for clinical (nonsurvival) data, all randomized patients had received study treatment; of these, 456 (92.7%) patients had discontinued treatment and 36 (7.3%) patients were still on treatment. The proportion of patients who discontinued randomized treatment was lower in the trifluridine-tipiracil plus bevacizumab group (87.0%) compared with the trifluridine-tipiracil alone group (98.4%). The most common reason for patients to discontinue study treatment was clinical and/or radiological progressive disease in the trifluridine-tipiracil plus bevacizumab (77.6%) group and the trifluridine-tipiracil alone (88.6%) group. Reasons for study discontinuation occurred with similar frequencies between groups, except for lower frequencies in the trifluridine-tipiracil plus bevacizumab group versus the trifluridine-tipiracil alone group for radiological and clinical progressive disease (10.6% versus 21.1%, respectively). The number of patients in the FAS and safety analysis set were identical (246 patients each in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group).

Table 11: Summary of Patient Disposition in the SUNLIGHT Trial — Full Analysis Set

Patient disposition	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
Screened, N	659	
Reason for not passing screening, n (%)		
Eligibility criteria not met, n (%)	160 (24.3)	
Withdrawal of consent, n (%)	7 (1.1)	
Randomized, N	246	246
Discontinued treatment, n (%)	214 (87.0)	242 (98.4)
Reason for treatment discontinuation, n (%)		
Adverse events	16 (6.5)	16 (6.5)
Radiological progressive disease	145 (58.9)	146 (59.4)
Clinical progressive disease	20 (8.1)	20 (8.1)
Radiological and clinical progressive disease	26 (10.6)	52 (21.1)
Consent withdrawn	5 (2.0)	8 (3.3)
Other, physician decision	2 (0.8)	0
[redacted]	[redacted]	[redacted]
Discontinued study, n (%)	145 (NR)	169 (NR)

Patient disposition	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
Reason for study discontinuation, n (%)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Ongoing study treatment, n (%)	32 (13.0)	4 (1.6)
FAS, N	246	246
SAS, N	246	246

FAS = full analysis set; NR = not reported; SAS = safety analysis set.
Source: SUNLIGHT Clinical Study Report.[22]

Baseline Characteristics

The baseline characteristics outlined in Table 12 are limited to those that are most relevant to this review or were felt to affect the outcomes or interpretation of the study results.

Table 12: Summary of Baseline Characteristics in the SUNLIGHT Trial — Full Analysis Set

Characteristic	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
Age, years		
Mean (SD)	61.0 (11.1)	62.4 (11.2)
Median (range)	62 (20 to 84)	64 (24 to 90)
< 65 years, n (%)	146 (59.3)	129 (52.4)
≥ 65 years, n (%)	100 (40.7)	117 (47. 6)
Male sex, n (%)	122 (49.6)	134 (54.5)
Weight, kg		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Body surface area (m^2)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Region of enrolment, n (%)		
North America	8 (3.3)	8 (3.3)

Characteristic	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
European Union	158 (64.2)	157 (63.8)
Rest of the world	80 (32.5)	81 (32.9)
Race or ethnic group, n (%)		
White	215 (87.4)	220 (89.4)
Black	4 (1.6)	3 (1.2)
Asian	NR	1 (0.4)
American Indian or Alaska Native	1 (0.4)	NR
Other	8 (3.3)	5 (2.0)
Unknown	18 (7.3)	17 (6.9)
Primary diagnosis, n (%)		
Colon cancer	180 (73.2)	181 (73.6)
Rectal cancer	66 (26.8)	65 (26.4)
Location of primary tumour, n (%)		
Right side	62 (25.2)	77 (31.3)
Left side	184 (74.8)	169 (68.7)
Duration of disease, years		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Time from diagnosis of first metastasis to randomization, n (%) (per IWRS)		
< 18 months	104 (42.3)	105 (42.7)
≥ 18 months	142 (57.7)	141 (57.3)
Number of sites of metastasis, n (%)		
1 or 2	152 (61.8)	141 (57.3)
≥ 3	94 (38.2)	105 (42.7)
Metastasis site		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Characteristic	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
ECOG PS		
0	119 (48.4)	106 (43.1)
1	127 (51.6)	139 (56.5)
2	NR	1 (0.4)
***RAS* status, n (%) (per IWRS)**		
Mutated	171 (69.5)	170 (69.1)
Wild-type	75 (30.5)	76 (30.9)
***BRAF* status, n (%)**		
Mutated	8 (3.3)	11 (4.5)
Wild-type	159 (64.6)	156 (63.4)
Unknown or missing	79 (32.1)	79 (32.1)
MMR and MSI status, n (%)		
Deficient MMR and high MSI	13 (5.3)	8 (3.3)
Proficient MMR and stable or low MSI	139 (56.5)	145 (58.9)
Unknown or missing	94 (38.2)	93 (37.8)
Stage at diagnosis, n (%)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Previous metastatic disease drug		
Fluoropyrimidine	246 (100)	246 (100)
Irinotecan	246 (100)	245 (99.6)
Oxaliplatin	241 (98.0)	243 (98.8)
Anti-VEGF	178 (72.4)	176 (71.5)
Anti-EGFR (patients with *RAS* wild-type)	67 (94.4)	66 (93.0)

Anti-EGFR = anti–epidermal growth factor receptor; anti-VEGF = anti–vascular endothelial growth factor; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IWRS = Interactive Web Response System; MMR = mismatch repair; MSI = microsatellite instability; NR = not reported; SD = standard deviation.

Note: Details included in Table 12 are from the sponsor's Summary of Clinical Evidence.[33]

Source: SUNLIGHT Clinical Study Report.[22]

The demographic characteristics were similar between the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group. However, there was a higher proportion of patients aged younger than 65 years in the trifluridine-tipiracil plus bevacizumab group compared with the trifluridine-tipiracil alone group (59% versus 52%, respectively). More patients were aged 65 years and older in the trifluridine-tipiracil alone group (48%) versus the trifluridine-tipiracil plus bevacizumab group (41%). A slightly higher proportion of patients had a primary tumour located on the right side in the trifluridine-tipiracil alone group (31%) compared with the trifluridine-tipiracil plus bevacizumab group (25%). Conversely, more patients had a left-sided tumour in the trifluridine-tipiracil plus bevacizumab group compared with the trifluridine-tipiracil alone group (75% versus 69%, respectively).

The mean age was 61.7 years (SD = 11.1 years) with 217 of 492 (44.1%) patients aged 65 years and older and 58 (11.8%) patients aged 75 years and older. Overall, 52.0% of patients were males and most patients enrolled were from the European Union (64.0%) and white (95.2%). Most patients had a primary diagnosis of colon cancer (73%) and stage IV disease (66%). 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% of the patients had *RAS* wild-type disease. Most patients (92.1%) had received 2 previous treatment regimens for metastatic disease; however, 4.5% of the patients in the trifluridine-tipiracil plus bevacizumab group and 6.1% of the patients in the trifluridine-tipiracil alone group had received only 1 first-line triplet regimen, and 2.6% of the patients in the trial had received 3 or more previous drug regimens for metastatic disease. All patients had received previous fluoropyrimidine-based therapy, 72.0% of patients had received previous anti-VEGF therapy (47.8% of patients had received bevacizumab as part of their first regimen, 43.9% of patients as part of their second regimen, and 20.3% of patients as part of both their first and second regimens), and 93.7% of patients with *RAS* wild-type disease had received previous anti-EGFR therapy.

Exposure to Study Treatments

Treatment exposure in the SUNLIGHT trial is summarized in Table 13. The median duration of treatment was 5.0 months (range = 0.1 months to 18.5 months) in the trifluridine-tipiracil plus bevacizumab group and 2.1 months (range = 0.6 months to 14.3 months) in the trifluridine-tipiracil alone group. [redacted] In the trifluridine-tipiracil plus bevacizumab group, the median relative dose intensities of trifluridine-tipiracil was 88.3% and the median relative dose intensities of bevacizumab was 87.6%. The median relative dose intensity of trifluridine-tipiracil in the trifluridine-tipiracil alone group was 90.4%.

Table 13: Summary of Patient Exposure in the SUNLIGHT Trial

Exposure	Trifluridine-tipiracil plus bevacizumab (N = 246)		Trifluridine-tipiracil (N = 246)
Treatment duration, months			
Mean (SD)	6.1 (4.3)		3.4 (2.5)
Median (range)	5.0 (0.1 to 18.5)		2.1 (0.6 to 14.3)
Cumulative dose	**Trifluridine-tipiracil (mg/m^2)**	**Bevacizumab (mg/kg)**	**Trifluridine-tipiracil (mg/m^2)**
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Dose intensity	**Trifluridine-tipiracil (mg/m^2 per week)**	**Bevacizumab (mg/kg per week)**	**Trifluridine-tipiracil (mg/m^2 per week)**
Mean (SD)	148.7 (23.1)	2.17 (0.68)	152.69 (24.78)
Median (range)	154.59 (27.8 to 180.8)	2.19 (0.9 to 11.6)	158.13 (34.4 to 277.1)
Relative dose intensity,[a] %	**Trifluridine-tipiracil**	**Bevacizumab**	**Trifluridine-tipiracil**
Mean (SD)	85.0 (13.2)	86.9 (27.3)	87.25 (14.2)
Median (range)	88.3 (15.9 to 103.3)	87.6 (36.4 to 463.0)	90.4 (19.7 to 158.4)

SD = standard deviation.

Note: Details included in Table 13 are from the sponsor's Summary of Clinical Evidence.[33]

[a]Treatment adherence was assessed using the relative dose intensity, defined as the ratio of the dose intensity to the planned starting dose intensity at inclusion.

Source: SUNLIGHT Clinical Study Report.[22]

Concomitant Medications and Cointerventions

A summary of concomitant medications by pharmacological class is presented in Table 14.

In the FAS, 84.3% of patients reported at least 1 concomitant treatment at inclusion, with similar frequency in the 2 treatment groups. Most patients (95.5%) received at least 1 concomitant treatment during the treatment period. The most frequent pharmacological classes (≥ 30%) were analgesics (49.0%), drugs for acid-related disorders (38.4%), and drugs acting on the renin-angiotensin system (35.2%). Among other concomitant treatments, the frequency of the therapeutic class "Other viral vaccines" was higher in the trifluridine-tipiracil plus bevacizumab group than in the trifluridine-tipiracil group (28.0% versus 11.8%, respectively); all were COVID-19 vaccines. Of note, 72 (29.3%) patients in the trifluridine-tipiracil plus bevacizumab group and 48 (19.5%) patients in the trifluridine-tipiracil group received at least 1 concomitant G-CSF, including for primary prophylaxis (0.8% and 1.2%, respectively), secondary prophylaxis (22.0% and 9.8%, respectively), therapeutic use (i.e., neutropenia) (16.3% and 11.8%, respectively), and for another indication (3.3% and 2.9%, respectively). There was no relevant between-group difference for the other classes of concomitant treatments at inclusion.

Table 14: Concomitant Medications in the SUNLIGHT Trial

Pharmacological class	Trifluridine-tipiracil plus bevacizumab (N = 246)		Trifluridine-tipiracil (N = 246)	
	n	%	n	%
Patients with at least 1 treatment				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
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[redacted]				
[redacted]				

Pharmacological class	Trifluridine-tipiracil plus bevacizumab (N = 246)		Trifluridine-tipiracil (N = 246)	
	n	%	n	%
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: SUNLIGHT Clinical Study Report.[22]

Subsequent Treatment

[redacted]

Table 15: Summary of Subsequent Treatment in the SUNLIGHT Trial

Exposure	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Note: Details included in Table 15 are from the sponsor's Summary of Clinical Evidence.[33]

[a]Includes detoxifying drugs for antineoplastic treatment (including any of folinic acid, calcium folinate, calcium levofolinate, levofolinate sodium, levofolinic acid, or sodium folinate).

[b]Not specified.

Source: SUNLIGHT Clinical Study Report.[22]

Efficacy

Findings for key efficacy outcomes in the SUNLIGHT trial are summarized in Table 16.

Overall Survival

At the survival cut-off date of July 19, 2022, the median follow-up was 14.2 months (interquartile range = 12.6 months to 16.4 months) in the trifluridine-tipiracil plus bevacizumab group and 13.6 months (interquartile range = 12.7 months to 15.9 months) in the trifluridine-tipiracil group (Figure 3). The number of patients who had died was 148 of 246 (60.2%) patients in the trifluridine-tipiracil plus bevacizumab group and 183 of 246 (74.4%) patients in the trifluridine-tipiracil alone group. The number of patients who were censored (alive at the time of data cut-off) was 98 (39.8%) patients and 63 (25.6%) patients in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively. OS at 6 months among patients in the FAS population was 0.77 (95% CI, 0.72 to 0.82) and 0.61 (95% CI, 0.55 to 0.67) for the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively. OS

at 12 months was 0.43 (95% CI, 0.36 to 0.49) and 0.30 (95% CI, 0.24 to 0.36) for the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively. OS at 18 months was 0.28 (95% CI, 0.19 to 0.37) and 0.15 (95% CI, 0.09 to 0.22) for the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively. The median OS was 10.78 months (95% CI, 9.36 months to 11.83 months) in the trifluridine-tipiracil plus bevacizumab group and 7.46 months (95% CI, 6.34 months to 8.57 months) in the trifluridine-tipiracil alone group. The HR was 0.61 (95% CI, 0.49 to 0.77), corresponding to a 39% reduction (P < 0.001) in the risk of death for trifluridine-tipiracil plus bevacizumab when compared with trifluridine-tipiracil alone.

Sensitivity Analyses

[redacted]

Subgroup Analyses

A forest plot of the HRs and associated 95% CIs for subgroup analyses of OS are presented in Figure 4 and Figure 5. The CADTH review focused on the subgroups of location of primary disease, ECOG PS, age, number of metastatic sites, and number of prior metastatic drug regimens.

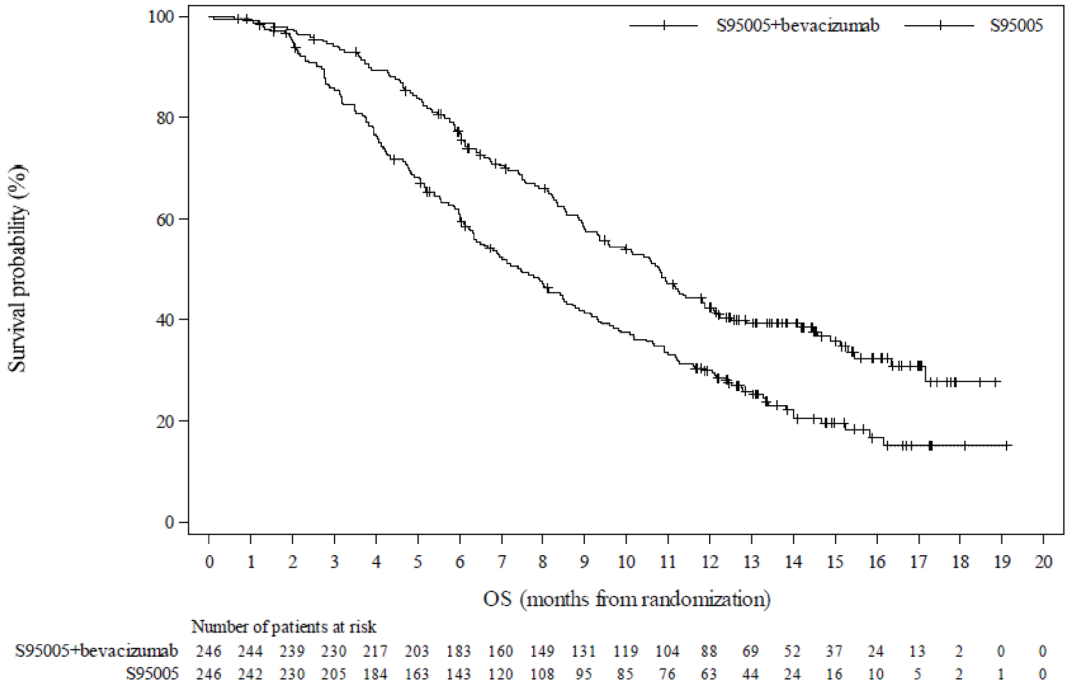
The HRs for primary OS favoured treatment with trifluridine-tipiracil plus bevacizumab compared with trifluridine-tipiracil alone among patients with:

- left-sided primary disease (n = 108 of 184 versus n = 120 of 169, respectively; unstratified HR = 0.65 [95% CI, 0.50 to 0.85]) and right-sided primary disease (n = 40 of 62 versus n = 63 of 77, respectively; unstratified HR = 0.59 [95% CI, 0.40 to 0.87])
- ECOG PS of 1 or greater (n = 78 of 127 versus n = 109 of 140, respectively; unstratified HR = 0.54 [95% CI, 0.41 to 0.73])
- age younger than 65 years (n = 89 of 146 versus n = 94 of 129, respectively; unstratified HR = 0.65 [95% CI, 0.48 to 0.87]) and age 65 years and older (n = 59 of 100 versus n = 89 of 117, respectively; unstratified HR = 0.59 [95% CI, 0.42 to 0.81])
- One to 2 metastatic sites (n = 83 of 152 versus n = 97 of 141, respectively; unstratified HR = 0.62 [95% CI, 0.46 to 0.83]) and 3 or more metastatic sites (n = 65 of 94 versus n = 86 of 105, respectively; unstratified HR = 0.66 [95%CI, 0.47 to 0.91])
- Two or more prior metastatic drug regimens (n = 142 of 235 versus n = 172 of 231, respectively; unstratified HR = 0.64 [95% CI, 0.51 to 0.80]).

Additional Analyses

[redacted]

Figure 3: Kaplan-Meier Curves of Overall Survival in the SUNLIGHT Trial, Data Cut-Off Date of July 19, 2022 — Full Analysis Set



OS = overall survival; S95005 = trifluridine-tipiracil.

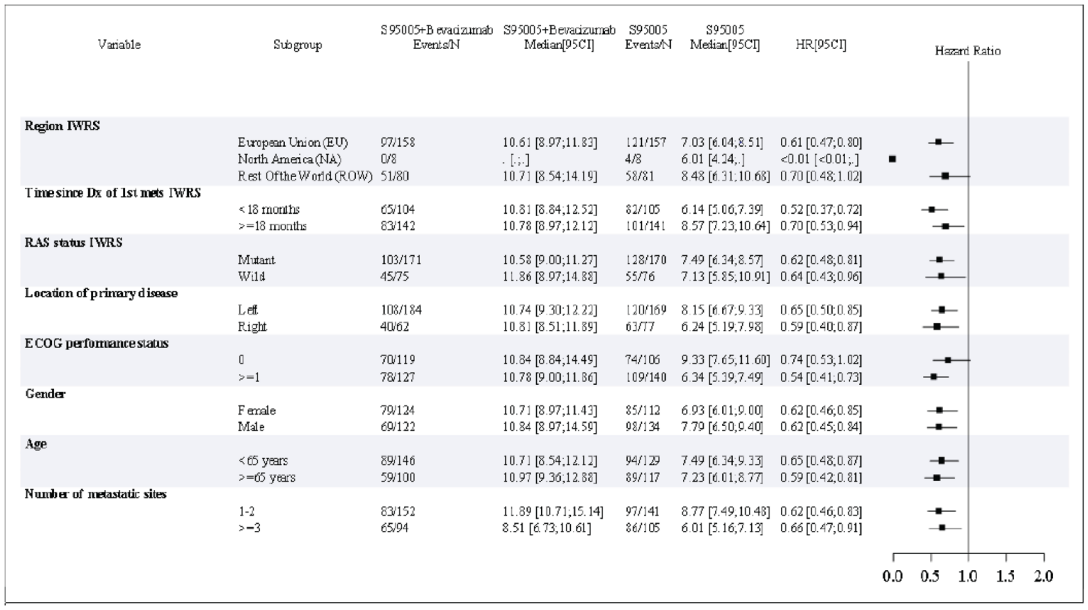
Source: SUNLIGHT Clinical Study Report.[22]

Progression-Free Survival

At the survival cut-off date of July 19, 2022, the number of patients with events (those who had radiological progressive disease or had died) were 206 of 246 (83.7%) patients and 236 of 246 (95.9%) patients in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively. The following are the number of patients who were censored in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively, due to being alive without radiological disease progression (38 [15.5%] patients versus 5 [2.0%] patients, respectively), lost to follow-up (2 [0.8%] patients versus 4 [1.6%] patients, respectively), or without baseline or postbaseline tumour assessment (0 versus 1 [0.4%] patient, respectively). PFS among patients in the FAS at 3 months was 0.73 (95% CI, 0.67 to 0.78) in the trifluridine-tipiracil plus bevacizumab group versus 0.45 (95% CI, 0.39 to 0.51) in the trifluridine-tipiracil alone group. PFS at 6 months was 0.43 (95% CI, 0.37 to 0.49) and 0.16 (95% CI, 0.11 to 0.21) for the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively. PFS at 9 months was 0.28 (95% CI, 0.22 to 0.34) and 0.05 (95% CI, 0.03 to 0.09) for the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively. PFS at 12 months was 0.16 (95% CI, 0.12 to 0.21) and 0.01 (95% CI, 0.00 to 0.03) for the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively. Median PFS was 5.6 months (95% CI, 4.50 months to 5.88 months) in the trifluridine-tipiracil plus bevacizumab group and 2.4 months (95% CI, 2.07 months to 3.22 months) in the trifluridine-tipiracil alone group (Figure 6). The HR for PFS was 0.44 (95% CI, 0.36 to 0.54)

for the trifluridine-tipiracil plus bevacizumab group when compared with the trifluridine-tipiracil alone group (P < 0.001).

Figure 4: Forest Plot of Hazard Ratios for Treatment Effect on Overall Survival by Selected Subgroups in the SUNLIGHT Trial, Data Cut-Off Date of July 19, 2022 — Full Analysis Set



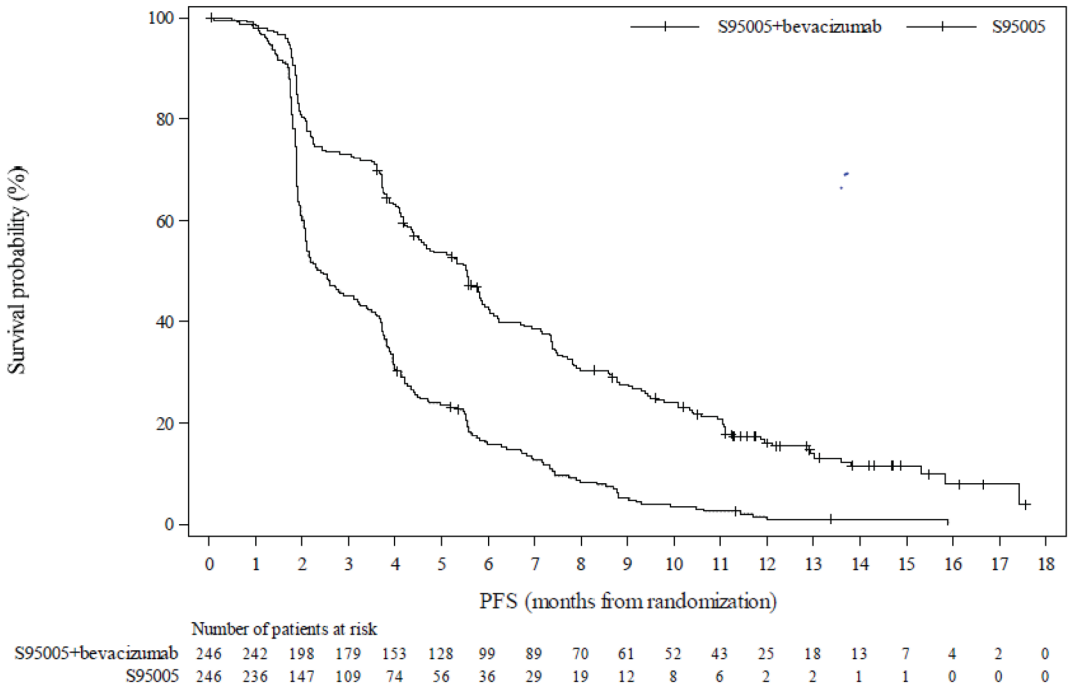
CI = confidence interval; Dx = diagnosis; ECOG = Eastern Cooperative Oncology Group; IWRS = Interactive Web Response System; mets = metastasis; S95005 = trifluridine-tipiracil.

Source: SUNLIGHT Clinical Study Report.[22]

Figure 5: Forest Plot of Hazard Ratios for Treatment Effect on Overall Survival by Selected Subgroups in the SUNLIGHT Trial, Data Cut-Off Date of July 19, 2022 — Full Analysis Set (Continued) [Redacted]

Source: SUNLIGHT Clinical Study Report.[22]

Figure 6: Kaplan-Meier Curves of PFS in the SUNLIGHT Trial, Data Cut-Off Date of July 19, 2022 — Full Analysis Set



PFS = progression-free survival; S95005 = trifluridine-tipiracil.

Source: SUNLIGHT Clinical Study Report.[22]

Sensitivity Analyses

[redacted].

Subgroup Analyses

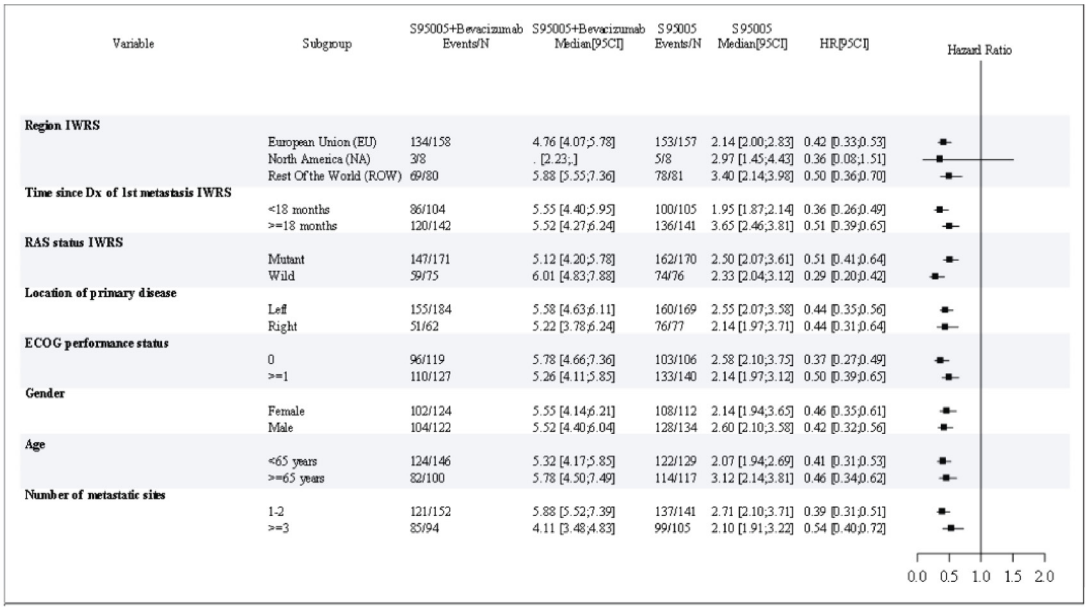
A forest plot of the HRs and associated 95% CIs for subgroup analyses of PFS are presented in Figure 7 and Figure 8.

The HRs (95% CIs) for primary PFS favoured treatment with trifluridine-tipiracil plus bevacizumab compared with trifluridine-tipiracil alone among patients with:

- left-sided disease (n = 155 of 184 versus n = 160 of 169, respectively; unstratified HR = 0.44 [95% CI, 0.35 to 0.56]) and right-sided primary disease (n = 51 of 62 versus n = 76 of 77, respectively; unstratified HR = 0.44 [95% CI, 0.31 to 0.64])
- ECOG PS of 0 (n = 96 of 119 versus n = 103 of 106, respectively; unstratified HR = 0.37 [95% CI, 0.27 to 0.49]) and ECOG PS of 1 or greater (n = 110 of 127 versus n = 133 of 140, respectively; unstratified HR = 0.50 [95% CI, 0.39 to 0.65])

- age younger than 65 years (n = 124 of 146 versus n = 122 of 129, respectively; unstratified HR = 0.41 [95% CI, 0.31 to 0.53]) and age 65 years and older (n = 82 of 100 versus n = 114 of 117, respectively; unstratified HR = 0.46 [95% CI, 0.34 to 0.62)]
- One to 2 metastatic sites (n = 121 of 152 versus n = 137 of 141, respectively; unstratified HR = 0.39 [95% CI, 0.31 to 0.51]) and 3 or more metastatic sites (n = 85 of 94 versus n = 99 of 105, respectively; unstratified HR = 0.54 [95% CI, 0.40 to 0.72])
- One prior metastatic drug regimen (n = 8 of 11 versus n = 13 of 15, respectively; unstratified HR = 0.37 [95% CI, 0.15 to 0.93]) and 2 or more prior metastatic drug regimens (n = 198 of 235 versus n = 223 of 231, respectively; unstratified HR = 0.44 [95% CI, 0.36 to 0.54]).

Figure 7: Forest Plot of Hazard Ratios for Treatment Effect on Progression-Free Survival by Selected Subgroups in the SUNLIGHT Trial, Data Cut-Off Date of July 19, 2022 — Full Analysis Set



CI = confidence interval; Dx = diagnosis; ECOG = Eastern Cooperative Oncology Group; IWRS = Interactive Web Response System; S95005 = trifluridine-tipiracil.
Source: SUNLIGHT Clinical Study Report.[22]

Figure 8: Forest Plot of Hazard Ratios for Treatment Effect on Progression-Free Survival by Selected Subgroups in the SUNLIGHT Trial, Data Cut-Off Date of July 19, 2022 — Full Analysis Set (Continued) [Redacted]

Source: SUNLIGHT Clinical Study Report.[22]

Time to Worsening of ECOG PS

In the FAS population, the number of patients with worsening of ECOG PS of 2 or greater postbaseline (from 0 to 1 at baseline) was 31 of 246 (20.0%) patients in the trifluridine-tipiracil plus bevacizumab group compared with 43 of 246 (23.4%) patients in the trifluridine-tipiracil alone group, including death for 124 (80.0%) patients and 141 (76.6%) patients in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively. The median time to worsening of ECOG PS of 2 or greater was 9.3 months (95% CI, 8.34 months to 10.61 months) and 6.3 months (95% CI, 5.55 months to 7.23 months) in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively.

Table 16: Summary of Primary and Key Efficacy Results in the SUNLIGHT Trial, Data Cut-Off Date of July 19, 2022 — Full Analysis Set

Outcome	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
Overall survival		
Events (death), n (%)	148 (60.16)	183 (74.39)
Censored, n (%)	98 (39.84)	63 (25.61)
Overall survival, months, median[a] (95% CI[b])	10.78 (9.36 to 11.83)	7.46 (6.34 to 8.57)
P value[c]	< 0.001[d]	Reference
Survival probability at 6 months[a] (95% CI[e])	0.77 (0.72 to 0.82)	0.61 (0.55 to 0.67)
Difference in survival probability at 6 months (95% CI)	0.16 (0.08 to 0.24)	Reference
Survival probability at 12 months[a] (95% CI[e])	0.43 (0.36 to 0.49)	0.30 (0.24 to 0.36)
Difference in survival probability at 12 months (95% CI)	0.13 (0.04 to 0.22)	Reference
Survival probability at 18 months[a] (95% CI[e])	0.28 (0.19 to 0.37)	0.15 (0.09 to 0.22)
Difference in survival probability at 18 months (95% CI)	0.13 (0.02 to 0.24)	Reference
HR (95% CI)[f]	0.61 (0.49 to 0.77)	Reference
Progression-free survival		
Events (death or disease progression), n (%)	206 (83.74)	236 (95.93)
Censored, n (%)	40 (16.26)	10 (4.07)
Progression-free survival (months), median[a] (95% CI[b])	5.55 (4.50 to 5.88)	2.40 (2.07 to 3.22)
P value[c]	< 0.001[d]	Reference
Survival probability at 3 months[a] (95% CI[e])	0.73 (0.67 to 0.78)	0.45 (0.39 to 0.51)
Difference in survival probability at 3 months (95% CI)	0.28 (0.20 to 0.36)	Reference

Outcome	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
Survival probability at 6 months[a] (95% CI[e])	0.43 (0.37 to 0.49)	0.16 (0.11 to 0.21)
Difference in survival probability at 6 months (95% CI)	0.27 (0.19 to 0.35)	Reference
Survival probability at 9 months[a] (95% CI[e])	0.28 (0.22 to 0.34)	0.05 (0.03 to 0.09)
Difference in survival probability at 9 months (95% CI)	0.23 (0.16 to 0.30)	Reference
Survival probability at 12 months[a] (95% CI[e])	0.16 (0.12 to 0.21)	0.01 (0.00 to 0.03)
Difference in survival probability at 12 months (95% CI)	0.15 (0.10 to 0.20)	Reference
HR (95% CI)[f]	0.44 (0.36 to 0.54)	Reference

CI = confidence interval; HR = hazard ratio; IWRS = Interactive Web Response System.
Note: Details included in Table 16 are from the sponsor's Summary of Clinical Evidence.[33]
[a]Kaplan-Meier estimate.
[b]Methodology of Brookmeyer and Crowley.
[c]Stratified log-rank test at 1-sided 2.5% level of significance using IWRS stratification factors (geographic region, time since diagnosis of first metastasis, and *RAS* status).
[d]P value has been adjusted for multiple testing.
[e]Using the log-log transformation methodology of Kalbfleisch and Prentice.
[f]Stratified Cox proportional hazards model using IWRS stratification factors (geographic region, time since diagnosis of first metastasis, and *RAS* status).
Source: SUNLIGHT Clinical Study Report.[22]

Health-Related Quality of Life

Findings for HRQoL outcomes in the SUNLIGHT trial at the data cut-off date of July 5, 2022, are summarized in Table 17.

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

EORTC QLQ-C30 and EQ-5D-5L analyses were performed in patients from the FAS with at least 1 questionnaire item at baseline and during the study period. In the EORTC QLQ-C30, higher scores in the global and functioning scales indicated better HRQoL, with positive change from baseline indicating benefit and negative change from baseline indicating deterioration. Conversely, for the symptom scales, lower scores indicated better HRQoL, with positive change from baseline indicating deterioration, and negative change from baseline indicating benefit. In the EQ-5D-5L utility and EQ VAS, higher scores indicated better HRQoL, with positive change from baseline indicating benefit and negative change from baseline indicating deterioration.

Global Health Status: The LSM change from baseline in the global health status was −2.85 (95% CI, −5.92 to 0.22) for trifluridine-tipiracil plus bevacizumab and −6.62 (95% CI, −10.36 to −2.88) for trifluridine-tipiracil alone. The LSM difference in change from baseline for global health status was 3.77 (95% CI, 0.22 to 7.32; P = 0.038) in favour of trifluridine-tipiracil plus bevacizumab. The number of patients with 10 points or

greater definitive deterioration was 62 (25.2%) patients and 72 (29.3%) patients in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively. The number of patients who died was 58 (23.6%) patients and 69 (28.1%) patients in the trifluridine-tipiracil plus bevacizumab group versus the trifluridine-tipiracil alone group, respectively. A total of 126 of 246 (51.2%) patients and 105 of 246 (42.7%) of patients in the trifluridine-tipiracil plus bevacizumab group versus the trifluridine-tipiracil alone group, respectively, were censored, including patients with the following: new anticancer therapy (83 [33.7%] patients versus 89 [36.2%] patients, respectively); 10 points or greater deterioration followed by an improvement, fewer than 10 points deterioration from baseline, or no deterioration in 10 points or greater (40 [16.3%] patients versus 13 [5.3%] patients, respectively); and being alive without a baseline or postbaseline evaluable questionnaire (3 [1.2%] patients versus 3 [1.2%] patients, respectively). Median survival based on time until definitive deterioration in the global health status was 8.54 months (95% CI, 7.49 months to 10.94 months) in the trifluridine-tipiracil plus bevacizumab group and 4.70 months (95% CI, 4.01 months to 5.78 months) in the trifluridine-tipiracil alone group (P < 0.001).

Functioning: [redacted]

[redacted]

Caregiver Burden

Caregiver burden was not assessed in the SUNLIGHT trial.

Table 17: Summary of Health-Related Quality of Life Results in the SUNLIGHT Trial, Data Cut-Off Date of July 5, 2022 — Full Analysis Set

Outcome	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
EORTC QLQ-C30		
Global health status, change from baseline		
Baseline, n	[redacted]	[redacted]
Score at baseline, mean (SD)	[redacted]	[redacted]
Change from baseline to cycle 1, n	[redacted]	[redacted]
Change from baseline to cycle 1, score, mean (SD)	[redacted]	[redacted]
Change from baseline to cycle 10, n	[redacted]	[redacted]
Change from baseline to cycle 10, score, mean (SD)	[redacted]	[redacted]
Change from baseline, LSM (95% CI)	[redacted]	[redacted]
Change from baseline, difference of LSM (95% CI)[a]	[redacted]	[redacted]
P value	[redacted]	[redacted]
Global health status, time until definitive deterioration		
Number of patients contributing to the analysis, n	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Number of patients with ≥ 10 points of deterioration, n (%)	[redacted]	[redacted]
Number of patients with ≥ 10 points of deterioration, risk difference, % (95% CI)	[redacted]	[redacted]
Survival, months, median[b] (range)	[redacted]	[redacted]

Outcome	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
Survival, months, median (95% CI)[c]	[redacted]	[redacted]
P value[d]	[redacted]	[redacted]
Physical functioning, change from baseline		
Baseline, n	[redacted]	[redacted]
Score at baseline, mean (SD)	[redacted]	[redacted]
Change from baseline to cycle 1, n	[redacted]	[redacted]
Change from baseline to cycle 1, score, mean (SD)	[redacted]	[redacted]
Change from baseline to cycle 10, n	[redacted]	[redacted]
Change from baseline to cycle 10, score, mean (SD)	[redacted]	[redacted]
Change from baseline, LSM (95% CI)	[redacted]	[redacted]
Change from baseline, difference of LSM (95% CI)[a]	[redacted]	[redacted]
P value	[redacted]	[redacted]
Physical functioning, time until definitive deterioration		
Number of patients contributing to the analysis, n	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Number of patients with ≥ 10 points of deterioration, n (%)	[redacted]	[redacted]
Survival, months, median[b] (range)	[redacted]	[redacted]
Survival, months, median (95% CI)[c]	[redacted]	[redacted]
P value[d]	[redacted]	[redacted]
Emotional functioning, change from baseline		
Baseline, n	[redacted]	[redacted]
Score at baseline, mean (SD)	[redacted]	[redacted]
Change from baseline to cycle 1, n	[redacted]	[redacted]
Change from baseline to cycle 1, score, mean (SD)	[redacted]	[redacted]
Change from baseline to cycle 10, n	[redacted]	[redacted]
Change from baseline to cycle 10, score, mean (SD)	[redacted]	[redacted]
Change from baseline, LSM (95% CI)	[redacted]	[redacted]
Change from baseline, difference of LSM (95% CI)[a]	[redacted]	[redacted]
P value	[redacted]	[redacted]
Emotional functioning, time until definitive deterioration		
Number of patients contributing to the analysis, n	[redacted]	[redacted]

Outcome	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
Censored, n (%)		
Number of patients with ≥ 10 points of deterioration, n (%)		
Survival, months, median[b] (range)		
Survival, months, median (95% CI)[c]		
P value[d]		
Symptoms scale (fatigue), change from baseline		
Baseline, n		
Score at baseline, mean (SD)		
Change from baseline to cycle 1, n		
Change from baseline to cycle 1, score, mean (SD)		
Change from baseline to cycle 10, n		
Change from baseline to cycle 10, score, mean (SD)		
Change from baseline, LSM (95% CI)		
Change from baseline, difference of LSM (95% CI)[a]		
P value		
Symptoms scale (fatigue), time until definitive deterioration		
Number of patients contributing to the analysis, n		
Censored, n (%)		
Number of patients with ≥ 10 points of deterioration, n (%)		
Survival, months, median[b] (range)		
Survival, months, median (95% CI)[c]		
P value[d]		
Symptoms scale (nausea and vomiting), change from baseline		
Baseline, n		
Score at baseline, mean (SD)		
Change from baseline to cycle 1, n		
Change from baseline to cycle 1, score, mean (SD)		
Change from baseline to cycle 10, n		
Change from baseline to cycle 10, score, mean (SD)		
Change from baseline, LSM (95% CI)		
Change from baseline, difference of LSM (95% CI)[a]		

Outcome	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
P value	[redacted]	[redacted]
Symptoms scale (nausea and vomiting), time until definitive deterioration		
Number of patients contributing to the analysis, n	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Number of patients with ≥ 10 points of deterioration, n (%)	[redacted]	[redacted]
Survival, months, median[b] (range)	[redacted]	[redacted]
Survival, months, median (95% CI)[c]	[redacted]	[redacted]
P value[d]	[redacted]	[redacted]
Symptoms scale (pain), change from baseline		
Baseline, n	[redacted]	[redacted]
Score at baseline, mean (SD)	[redacted]	[redacted]
Change from baseline to cycle 1, n	[redacted]	[redacted]
Change from baseline to cycle 1, score, mean (SD)	[redacted]	[redacted]
Change from baseline to cycle 10, n	[redacted]	[redacted]
Change from baseline to cycle 10, score, mean (SD)	[redacted]	[redacted]
Change from baseline, LSM (95% CI)	[redacted]	[redacted]
Change from baseline, difference of LSM (95% CI)[a]	[redacted]	[redacted]
P value	[redacted]	[redacted]
Symptoms scale (pain), time until definitive deterioration		
Number of patients contributing to the analysis, n	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Number of patients with ≥ 10 points of deterioration, n (%)	[redacted]	[redacted]
Survival, months, median[b] (range)	[redacted]	[redacted]
Survival, months, median (95% CI)[c]	[redacted]	[redacted]
P value[d]	[redacted]	[redacted]
Symptoms scale (dyspnea), change from baseline		
Baseline, n	[redacted]	[redacted]
Score at baseline, mean (SD)	[redacted]	[redacted]
Change from baseline to cycle 1, n	[redacted]	[redacted]
Change from baseline to cycle 1, score, mean (SD)	[redacted]	[redacted]
Change from baseline to cycle 10, n	[redacted]	[redacted]

Outcome	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
Change from baseline to cycle 10, score, mean (SD)		
Change from baseline, LSM (95% CI)		
Change from baseline, difference of LSM (95% CI)[a]		
P value		
Symptoms scale (dyspnea), time until definitive deterioration		
Number of patients contributing to the analysis, n		
Censored, n (%)		
Number of patients with ≥ 10 points of deterioration, n (%)		
Survival, months, median[b] (range)		
Survival, months, median (95% CI)[c]		
P value[d]		
Symptoms scale (appetite loss), change from baseline		
Baseline, n		
Score at baseline, mean (SD)		
Change from baseline to cycle 1, n		
Change from baseline to cycle 1, score, mean (SD)		
Change from baseline to cycle 10, n		
Change from baseline to cycle 10, score, mean (SD)		
Change from baseline, LSM (95% CI)		
Change from baseline, difference of LSM (95% CI)[a]		
P value		
Symptoms scale (appetite loss), time until definitive deterioration		
Number of patients contributing to the analysis, n		
Censored, n (%)		
Number of patients with ≥ 10 points of deterioration, n (%)		
Survival, months, median[b] (range)		
Survival, months, median (95% CI)[c]		
P value[d]		
Symptoms scale (diarrhea), change from baseline		
Baseline, n		
Score at baseline, mean (SD)		

Outcome	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
Change from baseline to cycle 1, n	[redacted]	[redacted]
Change from baseline to cycle 1, score, mean (SD)	[redacted]	[redacted]
Change from baseline to cycle 10, n	[redacted]	[redacted]
Change from baseline to cycle 10, score, mean (SD)	[redacted]	[redacted]
Change from baseline, LSM (95% CI)	[redacted]	[redacted]
Change from baseline, difference of LSM (95% CI)[a]	[redacted]	[redacted]
P value	[redacted]	[redacted]
Symptoms scale (diarrhea), time until definitive deterioration		
Number of patients contributing to the analysis, n	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Number of patients with ≥ 10 points of deterioration, n (%)	[redacted]	[redacted]
Survival, months, median[b] (range)	[redacted]	[redacted]
Survival, months, median (95% CI)[c]	[redacted]	[redacted]
P value[d]	[redacted]	[redacted]
EQ-5D-5L		
EQ-5D-5L utility score		
Baseline, n	[redacted]	[redacted]
Score at baseline, mean (SD)	[redacted]	[redacted]
Change from baseline to cycle 1, n	[redacted]	[redacted]
Change from baseline to cycle 1, mean (SD)	[redacted]	[redacted]
Change from baseline to cycle 1, mean difference, points (95% CI)	[redacted]	[redacted]
Change from baseline to cycle 10, n	[redacted]	[redacted]
Change from baseline to cycle 10, score, mean (SD)	[redacted]	[redacted]
Change from baseline, LSM (95% CI)	[redacted]	[redacted]
Change from baseline, difference of LSM (95% CI)[a]	[redacted]	[redacted]
P value	[redacted]	[redacted]
EQ VAS		
Baseline, n	[redacted]	[redacted]
Score at baseline, mean (SD)	[redacted]	[redacted]
Change from baseline to cycle 1, n	[redacted]	[redacted]
Change from baseline to cycle 1, mean (SD)	[redacted]	[redacted]

Outcome	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
Change from baseline to cycle 1, mean difference, points (95% CI)	[redacted]	[redacted]
Change from baseline to cycle 10, n	[redacted]	[redacted]
Change from baseline to cycle 10, score, mean (SD)	[redacted]	[redacted]
Change from baseline, LSM (95% CI)	[redacted]	[redacted]
Change from baseline, difference of LSM (95% CI)[a]	[redacted]	[redacted]
P value	[redacted]	[redacted]

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = 5-Level EQ-5D; EQ VAS = EQ visual analogue scale; IWRS = Interactive Web Response System; LSM = least squares mean; SD = standard deviation.

[a]A mixed model of repeated measures that included terms for treatment, baseline stratification factors, baseline score, time to visit before any procedure (at each cycle, including the withdrawal visit), and treatment groups by time to visit interaction was used to compare change from baseline subscale scores longitudinally over time between treatment groups.

[b]Kaplan-Meier estimate.

[c]Methodology of Brookmeyer and Crowley.

[d]Stratified log-rank test using IWRS stratification factors (geographic region, time since diagnosis of first metastasis, and *RAS* status).

Source: SUNLIGHT Clinical Study Report.[22]

Harms

Harms data for the SUNLIGHT trial were based on the clinical data cut-off date of July 5, 2022, and are summarized in Table 18.

Adverse Events

The number of patients reporting any TEAEs was 241 of 246 (98.0%) patients for the trifluridine-tipiracil plus bevacizumab group and 241 of 246 (98.0%) patients for the trifluridine-tipiracil alone group. The most common TEAEs occurring in at least 20% of patients in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group were neutropenia (62.2% versus 51.2%, respectively), nausea (37.0% versus 27.2%, respectively), anemia (28.9% versus 31.7%, respectively), asthenia (24.4% versus 22.4%, respectively), fatigue (21.5% versus 16.3%, respectively), diarrhea (20.7% versus 18.7%, respectively), and decreased appetite (20.3% versus 15.4%, respectively).

Serious Adverse Events

The proportion of patients who experienced at least 1 SAE was 24.8% in the trifluridine-tipiracil plus bevacizumab group and 31.3% in the trifluridine-tipiracil alone group. SAEs occurring in at least 2% of patients in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group were intestinal obstruction (2.8% versus 2.0%, respectively), malignant neoplasm progression (2.4% versus 4.5%, respectively), COVID-19 (2.0% versus 2.4%, respectively), anemia (0.4% versus 3.3%, respectively), febrile neutropenia (0.4% versus 2.4%, respectively), jaundice (0.8% versus 2.0%, respectively), and hepatic failure (0 versus 2.0%, respectively).

The proportion of patients who experienced AEs of grade 3 or greater were 72.4% in the trifluridine-tipiracil plus 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 the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group were neutropenia (43.1% versus 32.1%, respectively), anemia (6.1% versus 11.0%, respectively), decreased neutrophil count (8.9% versus 5.3%, respectively), and hypertension (5.7% versus 1.2%, respectively).

Withdrawals Due to Adverse Events

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 the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group were asthenia (3.3% versus 0.4%, respectively), jaundice (0.8% versus 0.8%, respectively), decreased appetite (0.8% versus 0.4%, respectively), fatigue (0.4% versus 0.8%, respectively), anemia (0.4% versus 0.8%, respectively), intestinal obstruction (0.4% versus 0.8%, respectively), malignant neoplasm progression (0.4% versus 0.8%, respectively), biliary dilation (0.8% versus 0, respectively), increased blood bilirubin (0.8% versus 0, respectively), pain (0.8% versus 0, respectively), and metastases to the central nervous system (0 versus 0.8%, respectively).

Mortality

[redacted]

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 for trifluridine-tipiracil (bone marrow suppression, infections, and gastrointestinal symptoms) and bevacizumab (hypertension, proteinuria, bleeding or hemorrhage, embolic and thrombotic events, gastrointestinal perforation, and wound healing complication). Peripheral neuropathy was identified by patient group input to be an important and difficult-to-tolerate side effect.

Bone Marrow Suppression Events

The proportion of patients who experienced bone marrow suppression events was 80.9% in the trifluridine-tipiracil plus bevacizumab group and 73.2% in the trifluridine-tipiracil alone group, including neutropenia (62.2% versus 51.2%, respectively), anemia (28.9% versus 31.7%, respectively), thrombocytopenia (17.1% versus 11.4%, respectively), and leukopenia (6.5% versus 8.5%, respectively).

Infections

The proportion of patients who experienced at least 1 TEAE related to infections was 30.9% in the trifluridine-tipiracil plus 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 plus bevacizumab group and the trifluridine-tipiracil alone group, respectively.

Gastrointestinal Events

The proportion of patients who experienced gastrointestinal events was 48.4% in the trifluridine-tipiracil plus bevacizumab group and 41.1% in the trifluridine-tipiracil alone group, including nausea (37.0% versus 27.2%, respectively), diarrhea (20.7% versus 18.7%, respectively), and vomiting (18.7% versus 14.6%, respectively). Gastrointestinal events of grade 3 or higher were reported for 2.0% of patients and 4.9% of patients in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively, including nausea (1.6% versus 1.6%, respectively), diarrhea (0.8% versus 2.4%, respectively), and vomiting (0.8% versus 1.6%, respectively).

Hypertension

The proportion of patients who experienced hypertension was 10.2% in the trifluridine-tipiracil plus 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 plus bevacizumab group and the trifluridine-tipiracil alone group, respectively.

Proteinuria

The proportion of patients who experienced proteinuria was 6.1% in the trifluridine-tipiracil plus bevacizumab group and 1.2% in the trifluridine-tipiracil alone group. Proteinuria events of grade 3 or higher were reported for 0.8% of patients in the trifluridine-tipiracil plus bevacizumab group.

Hemorrhage

The proportion of patients who experienced at least 1 TEAE related to hemorrhage was 11.8% in the trifluridine-tipiracil plus bevacizumab group and 3.7% in the trifluridine-tipiracil alone group. Hemorrhage events of grade 3 or higher were reported for 1.2% of patients and 0.8% of patients in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively.

Embolic and Thrombotic Events

The proportion of patients who experienced embolic and thrombotic events was 4.9% in the trifluridine-tipiracil plus bevacizumab group and 3.7% in the trifluridine-tipiracil alone group. Embolic and thrombotic events of grade 3 or higher were reported for 1.6% of patients and 3.3% of patients in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively.

Gastrointestinal Perforation

Among the 6 (2.4%) patients in the trifluridine-tipiracil plus bevacizumab group who experienced gastrointestinal perforation, 4 (1.6%) patients experienced gastrointestinal perforation of grade 3 or higher.

Peripheral Neuropathy

Three (1.2%) patients and 1 (0.4%) patient experienced peripheral sensory neuropathy in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively. One patient experienced peripheral neuropathy in the trifluridine-tipiracil plus bevacizumab group.

Table 18: Summary of Harms Results in the SUNLIGHT Trial, Data Cut-Off Date of July 5, 2022 — Safety Analysis Set

AE	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
Most common AEs		
Patients with ≥ 1 TEAE, n (%)	241 (98.0)	241 (98.0)
TEAEs in ≥ 20% of patients in either group, n (%)		
Neutropenia	153 (62.2)	126 (51.2)
Nausea	91 (37.0)	67 (27.2)
Anemia	71 (28.9)	78 (31.7)
Asthenia	60 (24.4)	55 (22.4)
Fatigue	53 (21.5)	40 (16.3)
Diarrhea	51 (20.7)	46 (18.7)
Decreased appetite	50 (20.3)	38 (15.4)
SAEs		
Patients with ≥ 1 SAE, n (%)	61 (24.8)	77 (31.3)
SAEs in ≥ 2% of patients in either group, n (%)		
Intestinal obstruction	7 (2.8)	5 (2.0)
Malignant neoplasm progression	6 (2.4)	11 (4.5)
COVID-19	5 (2.0)	6 (2.4)
Anemia	1 (0.4)	8 (3.3)
Febrile neutropenia	1 (0.4)	6 (2.4)
Jaundice	2 (0.8)	5 (2.0)
Hepatic failure	NR	5 (2.0)
Patients with grade ≥ 3 AEs, n (%)	178 (72.4)	171 (69.5)
Grade 3 or grade 4 AEs in 5% of patients in either group, n (%)		
Neutropenia	106 (43.1)	79 (32.1)
Anemia	15 (6.1)	27 (11.0)
Neutrophil count, decreased	22 (8.9)	13 (5.3)
Hypertension	14 (5.7)	3 (1.2)
Patients who stopped treatment due to AEs		
Patients who stopped study treatment due to a TEAE[a], n (%)	31 (12.6)	31 (12.6)
Withdrawals due to AEs in at least 1 patient in either group, n (%)		
Asthenia	8 (3.3)	1 (0.4)

AE	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
Jaundice	2 (0.8)	2 (0.8)
Decreased appetite	2 (0.8)	1 (0.4)
Fatigue	1 (0.4)	2 (0.8)
Anemia	1 (0.4)	2 (0.8)
Intestinal obstruction	1 (0.4)	2 (0.8)
Malignant neoplasm progression	1 (0.4)	2 (0.8)
Biliary dilation	2 (0.8)	0
Blood bilirubin, increased	2 (0.8)	0
Pain	2 (0.8)	0
Metastases to central nervous system	0	2 (0.8)
Deaths		
Any death, n (%)	146 (59.4)	177 (72.0)
Death during the treatment period, n (%)	13 (5.3)	24 (9.8)
Death during the follow-up period,[b] n (%)	133 (54.1)	153 (62.2)
Number of deaths during the follow-up period, n	132	149
Due to progressive disease, n (%)	127 (96.2[c])	139 (93.3[c])
Due to another reason, n (%)	5 (3.8[c])	10 (6.7[c])
TEAEs leading to death during treatment or follow-up period, n (%)	13 (5.3)	27 (11.0)
AESIs[d]		
Bone marrow suppression events, n (%)	199 (80.9)	180 (73.2)
Bone marrow suppression events, risk difference (95% CI)	−0.08 (−0.15 to 0.00)	Reference
Neutropenia	153 (62.2)	126 (51.2)
Anemia	71 (28.9)	78 (31.7)
Thrombocytopenia	42 (17.1)	28 (11.4)
Leukopenia	16 (6.5)	21 (8.5)
Myelosuppression	1 (0.4)	0
Infections, n (%)	76 (30.9)	57 (23.2)
Infections, risk difference (95% CI)	−0.08 (−0.16 to 0.00)	Reference
Gastrointestinal events, n (%)	119 (48.4)	101 (41.1)
Gastrointestinal events, risk difference (95% CI)	−0.07 (−0.16 to 0.01)	Reference
Nausea	91 (37.0)	67 (27.2)

AE	Trifluridine-tipiracil plus bevacizumab (N = 246)	Trifluridine-tipiracil (N = 246)
Diarrhea	51 (20.7)	46 (18.7)
Vomiting	46 (18.7)	36 (14.6)
Hypertension, n (%)	25 (10.2)	5 (2.0)
Hypertension, risk difference (95% CI)	−0.08 (−0.12 to −0.04)	Reference
Proteinuria	15 (6.1)	3 (1.2)
Hemorrhage	29 (11.8)	9 (3.7)
Embolic and thrombotic events	12 (4.9)	9 (3.7)
Gastrointestinal perforation	6 (2.4)	0
Peripheral sensory neuropathy	3 (1.2)	1 (0.4)
Neuropathy, peripheral	1 (0.4)	0

AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; NR = not reported; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: Details included in Table 18 are from the sponsor's Summary of Clinical Evidence.[33]

[a]Patients who stopped study treatment due to a TEAE corresponded to trifluridine-tipiracil withdrawal since bevacizumab monotherapy was not permitted.

[b]The follow-up period as defined for safety analysis occurred more than 30 days after the last study treatment intake.

[c]Percentages are based on the number of deaths during the follow-up period (132 deaths vs. 149 deaths).

[d]Analyses of AESIs were conducted post hoc. Lists of predefined preferred terms of similar medical concept were used to define the overall AESI terms.

Source: SUNLIGHT Clinical Study Report.[22]

Critical Appraisal

Internal Validity

The SUNLIGHT study was a phase III, randomized, open-label RCT. Patients were randomized 1:1 to trifluridine-tipiracil plus bevacizumab or trifluridine-tipiracil alone based on stratification factors (geographic region, time since first metastasis diagnosis, and *RAS* status) using a centralized IWRS. Baseline characteristics were generally balanced between treatment groups for key prognostic factors, disease characteristics (e.g., tumour biology, gene expression, number of and site of the primary tumour), and prior chemotherapy regimens. However, the open-label study design has the potential to impact patient-reported outcomes — including HRQoL, for which knowledge of the assigned treatment may bias reporting in favour of the intervention group (trifluridine-tipiracil plus bevacizumab).

Trifluridine-tipiracil alone was the comparator used in the SUNLIGHT trial. Trifluridine-tipiracil is approved and available in Canada but is not universally publicly funded; therefore, the majority of patients must obtain access via private drug coverage or out-of-pocket costs.

The duration of treatment for patients in the trifluridine-tipiracil plus bevacizumab group was a median of 5.0 months whereas the duration of treatment among patients in the trifluridine-tipiracil alone group was a median of 2.1 months. The mean (SD) cumulative dose was 3,907 mg/m^2 versus 2,247 mg/m^2 in the trifluridine-tipiracil plus bevacizumab group versus the trifluridine-tipiracil alone group, respectively. It is

important to note that the differential treatment duration and dose may not be fully explained by the relatively small difference (11%) in treatment discontinuations between groups. Additionally, in the absence of data, it is unknown whether the open-label nature of the trial may have impacted patients' adherence to treatment assignment. A significant proportion of patients had missing data (without imputation) for HRQoL by cycle 3 of treatment in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group (68% versus 41%, respectively) and cycle 4 of treatment (60% versus 33%, respectively); it is unclear how the missing data may impact findings for HRQoL. Moreover, it is unknown whether there is an impact of higher rates of G-CSF use in the trifluridine-tipiracil plus bevacizumab group on HRQoL.

A significant number of censored patients and differences in censoring between groups was observed relatively early for both OS and PFS. For OS, the number of patients who were at risk in the trifluridine-tipiracil plus bevacizumab group (n = 246) versus the trifluridine-tipiracil alone group (n = 246) was 230 patients versus 205 patients at 3 months, respectively, 183 patients versus 143 patients at 6 months, respectively, and 88 patients versus 63 patients at 12 months, respectively. For PFS, the number of patients who were at risk in the trifluridine-tipiracil plus bevacizumab group versus the trifluridine-tipiracil alone group was 179 patients versus 109 patients at 3 months, respectively, and 99 patients versus 36 patients at 6 months, respectively. There were more patients who were censored due to being alive without radiological disease progression in the trifluridine-tipiracil plus bevacizumab group compared with the trifluridine-tipiracil alone group (15.5% versus 2.0%, respectively). A positive correlation has been associated between early censoring and the experience of the event of interest, leading to an overestimation of the survival probability in both study groups.[59] The SUNLIGHT trial did not provide data on the number of patients with missing follow-up data who were censored, so it is unknown whether this may have impacted survival findings.

OS was a primary end point in the SUNLIGHT study and statistical analyses employed a hierarchical testing strategy with the aim to demonstrate superiority of trifluridine-tipiracil plus bevacizumab over trifluridine-tipiracil alone. Analyses met the prespecified sample size and statistical significance in the primary estimand to subsequently assess the effect of treatment on PFS. OS and PFS were estimated using stratification factors employed at randomization, which is appropriate for minimizing bias due to potential effect modifiers. The stratified Cox proportional hazards model was checked for underlying assumptions; KM and log(-log) curves (crossing over early in the first month of treatment but with clear separation thereafter) suggested that the proportional hazards assumption likely holds for OS or PFS. Additionally, P values (0.0883 for OS and 0.568 for PFS) from a Schoenfeld residuals test did not appear to have been violated based on a prespecified P value of lower than 0.05 to suggest rejection of the null hypothesis, according to data submitted from the sponsor.[23]

While appropriate statistical testing was conducted to adjust for multiplicity for the primary and key secondary end points, HRQoL was a secondary end point that was not adjusted for multiple testing and, therefore, is at risk of inflated type I error. 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.

External Validity

Approximately 24% of patients did not pass screening due to eligibility not being met. This is indicative of the challenge in selecting suitable patients for treatment, suggesting the possibility of a highly selected population who may derive the greatest benefit from treatment and who may not be fully representative of patients in clinical practice. However, the enrolled population in the SUNLIGHT trial was generally aligned with patients seen in clinical practice according to the clinical experts consulted by CADTH. Patients with unresectable adenocarcinoma of the colon and rectum were included; the clinical experts agreed that patients with metastatic disease and unresectable CRC were considered eligible for treatment with trifluridine-tipiracil, noting that patients with resectable disease undergo a different treatment pathway. Although patients with more than 2 prior chemotherapy regimens and those with prior treatment with trifluridine-tipiracil were excluded, the clinical experts consulted by CADTH considered these patients to be eligible for treatment with trifluridine-tipiracil plus bevacizumab. Patients who had an ECOG PS score of greater than 1 and those with small bowel or appendiceal adenocarcinoma were also considered to be eligible for treatment with trifluridine-tipiracil plus bevacizumab, according to the clinical experts consulted by CADTH. Among patients randomized in the SUNLIGHT study, the clinical experts consulted by CADTH noted a higher proportion of patients with *RAS* status expressing mutations (compared with wild-type) than would be expected in the population in Canada; however, the clinical experts acknowledged that subgroup analyses on *RAS* status did not appear to demonstrate an impact on treatment effects. Overall, the key prognostic indicators outlined by the clinical experts consulted by CADTH (i.e., age, number of metastatic sites, number of prior chemotherapy regimens, sidedness of the tumour, and ECOG PS) appeared to be reflective of patients in clinical practice. This included some with between-group imbalances of approximately 5%, which may have been due to chance rather than systematic differences based on appropriate randomization via IWRS. Since a small proportion of the patients enrolled were from North America (3.3%) with no patients enrolled from sites in Canada, the clinical experts consulted by CADTH considered the findings to be mainly applicable to the included population and limited in generalizability to patients with mCRC in Canada. Notably, the low number of non-white patients (e.g., Black, Asian) who comprised fewer than 2% of the trial population and the absence of Indigenous Peoples signify an important gap in the population and limited the applicability of findings.

The clinical experts consulted by CADTH noted that most patients had discontinued treatment in the SUNLIGHT study, with a greater proportion who stopped treatment due to clinical and/or progressive disease in the trifluridine-tipiracil alone group. This was unsurprising as many patients with advanced disease were likely to have exhausted 2 or more prior lines of therapies and the experts consulted did not consider the imbalance to be concerning given that a low rate of discontinuations due to AEs (6.5%) occurred at the same frequency in both groups and the proportion of patients who discontinued the study due to death was balanced between groups.

The intervention in the SUNLIGHT trial is for an unlabelled indication, as trifluridine-tipiracil alone was approved by Health Canada for adult patients with mCRC who have previously been treated with, or are not candidates for, available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if *RAS* wild-type, anti-EGFR agents. The clinical

experts consulted by CADTH considered trifluridine-tipiracil to be the most relevant comparator (among other treatment options, including BSC and regorafenib) for trifluridine-tipiracil plus bevacizumab, while acknowledging that this treatment is only available to a small patient population with access as it is not currently universally funded in Canada.

Approximately 29% of patients in the trifluridine-tipiracil plus bevacizumab group and 20% of patients in the trifluridine-tipiracil alone group received at least 1 concomitant G-CSF, for primary and secondary prophylaxis, therapeutic use (i.e., management of neutropenia) (16% and 12%, respectively), and for another indication (3.3% and 2.9%, respectively). The clinical experts consulted by CADTH commented that G-CSF prophylaxis was employed variably across clinical settings in Canada. According to the clinical experts, all patients treated with trifluridine-tipiracil (with or without bevacizumab) at their institution are given prophylactic G-CSF and that the proportions of patients in the SUNLIGHT trial who received G-CSF appeared to be reasonable.

Outcomes included in the SUNLIGHT study were identified as important to patients, including survival, HRQoL, and TEAEs. The clinical experts considered OS to be the key efficacy end point, which was examined as a primary outcome. The trial also included PFS as a key secondary end point, which the clinical experts consulted by CADTH identified as less desirable than OS as the presence or absence of measurable disease was not considered to be directly associated with patient survival. According to the clinical experts consulted by CADTH, PFS was appropriately included as supportive evidence for OS. Patients were followed for a median of 14.1 months in the trifluridine-tipiracil plus bevacizumab group and a median of 13.6 months in the trifluridine-tipiracil alone group. This duration appeared to be sufficient according to the clinical experts consulted by CADTH, who indicated that patients with advanced mCRC have limited efficacious treatment options and that OS at 6 months and 12 months is important for assessing the effects of treatment. EQ-5D-5L utility values derived according to a French value set (not calculated using a population health dataset for North America or Canada) was highlighted by the clinical experts consulted as being a limitation for the generalizability of these results to patients in Canada. Caregiver burden was identified as important by patient input and clinical experts consulted by CADTH; however, this was not assessed in the SUNLIGHT trial.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the 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.[20,21]

- **High certainty:** "We are very confident that the true effect lies close to that of the estimate of the effect."
- **Moderate certainty:** "We are moderately confident in the effect estimate — The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. We use the word 'likely' for evidence of moderate certainty (e.g., 'X intervention likely results in Y outcome')."

- **Low certainty:** "Our confidence in the effect estimate is limited — The true effect may be substantially different from the estimate of the effect. We use the word 'may' for evidence of low certainty (e.g., 'X intervention may result in Y outcome')."
- **Very low certainty:** "We have very little confidence in the effect estimate — The true effect is likely to be substantially different from the estimate of effect. We describe evidence of very low certainty as 'very uncertain'."

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, the imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence 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 a clinically important effect for survival rates (OS, PFS), HRQoL (EORTC QLQ-C30, EQ-5D-5L), and notable harms (bone marrow suppression, infections, gastrointestinal symptoms, and hypertension) based on a threshold informed by the clinical experts consulted by CADTH for this review.

Results of GRADE Assessments

Table 2 presents the GRADE summary of findings for trifluridine-tipiracil plus bevacizumab versus trifluridine-tipiracil alone.

Long-Term Extension Studies

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

Indirect Evidence

Content in this section has been informed by materials submitted by the sponsor. The following has been summarized and validated by the CADTH review team.

Objectives for the Summary of Indirect Evidence

As there was limited direct evidence comparing trifluridine-tipiracil plus bevacizumab versus other relevant comparators for the treatment of adult 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, a review of indirect evidence was undertaken and submitted by the sponsor.[24]

The objective of this section is to summarize and critically appraise the sponsor-submitted ITC, and to inform the pharmacoeconomic model.

Description of Sponsor-Submitted ITC

Objectives

The objective of this ITC was to compare the treatment efficacy and safety of trifluridine-tipiracil plus bevacizumab relative to currently existing therapies for the treatment of mCRC.

The ITC included a systematic review of the literature to identify trials investigating trifluridine-tipiracil plus bevacizumab or comparator interventions in patients with mCRC who have been previously treated with, or are not considered candidates for, currently available therapies; a feasibility assessment of conducting an NMA of trifluridine-tipiracil plus bevacizumab versus other relevant comparators in mCRC; and an NMA that compared trifluridine-tipiracil plus bevacizumab to other relevant treatments on both efficacy and safety outcomes. The other treatments examined in this ITC were trifluridine-tipiracil alone, chemotherapy, EGFR inhibitors or anti-VEGF drugs, *BRAF* inhibitors, immune checkpoint inhibitors, regorafenib, and BSC.

Study Selection Methods

Multiple databases were searched for relevant clinical trials in this ITC with a time frame of 2004 to the present. Studies were selected by 2 independent reviewers according to prespecified criteria for patient population, intervention, comparator, outcome measures, and study design. Any disagreements were resolved by discussion between reviewers, including a third researcher if needed. RCTs were included. Efficacy outcomes, safety outcomes, and HRQoL outcomes relevant to the treatment of mCRC were evaluated in this ITC. Data were extracted by a single reviewer and independently validated by a second reviewer. Any discrepancies were resolved by discussion between reviewers, including a third researcher if needed. All included studies in the ITC were evaluated according to a Cochrane risk-of-bias tool for RCTs.

Details of patient population, intervention, comparator, outcome measures, and study design for study selection in the systematic literature review of the ITC are provided in Table 19.

Table 19: Study Selection Criteria and Methods for ITC Submitted by the Sponsor

Characteristic	Indirect comparison
Population	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, regardless of *BRAF* and *RAS* mutation status (wt or *BRAF*-mutated, wt or *RAS*-mutated)
Intervention	• Trifluridine-tipiracil alone • Trifluridine-tipiracil + bevacizumab • Chemotherapy (fluorouracil-, irinotecan-, or oxaliplatin-based) • EGFR inhibitors or anti-VEGF drugs (i.e., cetuximab, panitumumab, and bevacizumab) • *BRAF* inhibitors (i.e., encorafenib) • Immune checkpoint inhibitors (i.e., pembrolizumab and nivolumab) • BSC • Regorafenib
Comparator	Head-to-head comparison of any of the aforementioned interventions, placebo, or BSC

Characteristic	Indirect comparison
Outcome	• Any efficacy outcomes, including OS, PFS, DCR, and ORR • Any safety outcomes, including treatment discontinuation, AEs, treatment-related AEs, grade 3 or grade 4 AEs, or anemia • Any HRQoL outcomes
Study designs	• RCTs • Systematic review and meta-analysis[a]
Publication characteristics	None
Exclusion criteria	• Treatment-naive mCRC • Patients receiving earlier lines of treatment (1L, 2L) • Nonhuman studies • Studies not including comparators listed • Studies not including at least 1 of the outcomes listed in the Inclusion criteria; relevant outcomes are not reported, or data are not extractable (i.e., only available from figures needing to be digitized) • Nonrandomized comparative trials • Single-arm trials • Observational, real-world evidence studies • Editorials, erratums, trial protocols, guidelines, narrative review publications • In vitro, ex vivo, animal, or pharmacokinetic studies • Case studies or case reports
Databases searched	Relevant studies were identified by searching the following databases from inception through the Ovid platform (search date: March 30, 2023): • MEDLINE • Embase • CENTRAL • CDSR Hand searches for relevant materials from the past 2 years of the following scientific conferences were conducted: • ASCO, Annual Meeting • ASCO GI Cancers Symposium, Annual Meeting • ESMO, Annual Meeting • ESMO World Congress on Gastrointestinal Cancer, Annual Meeting Manual searches of the following clinical trial registries were performed: • EU CTR • Health Canada Clinical Trials Database • US National Institutes of Health Clinical Trial Registry • WHO ICTRP
Selection process	Study selection followed a 2-stage screening process based on the review of titles and abstracts (stage I) and then full-text articles (stage II). During both stages, each publication was assessed by 2 independent investigators. Any disagreements were resolved by discussion between investigators, including a third more senior researcher, if needed.

Characteristic	Indirect comparison
Data extraction process	Data from the included studies were extracted into a standardized table template developed in Microsoft Excel. Data were captured by a single investigator and independently validated by a second investigator. Any discrepancies were resolved by discussion between investigators, including a third more senior researcher, if needed. Prior to data extraction, publications reporting on the same trial were grouped together to avoid double-counting trial populations. The most comprehensive publication (e.g., reporting detailed methods and results for all or most outcomes of interest in the target populations) was designated as the "principal" publication and remaining publications were designated as "related." The related publications reported either additional or duplicative data. Relevant additional data were extracted with the data source tracked. Duplicative data were extracted only once. If conflicting data were reported, these were considered on a case-by-case basis. Generally, values from more recently published full-text articles were prioritized.
Quality assessment	All RCT publications included in the analysis were evaluated according to the Cochrane risk-of-bias tool for randomized trials as described in the *Cochrane Handbook for Systematic Reviews of Interventions*.[60]

1L = first-line; 2L = second-line; 3L = third-line; 4L = fourth-line; AE = adverse event; anti-EGFR = anti–epidermal growth factor receptor; anti-VEGF = anti–vascular endothelial growth factor; ASCO = American Society of Clinical Oncology; ASCO GI = American Society of Clinical Oncology Gastrointestinal; BSC = best supportive care; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; DCR = disease control rate; EGFR = epidermal growth factor receptor; ESMO = European Society for Medical Oncology; EU CTR = European Union Clinical Trials Register; HRQoL = health-related quality of life; HTA = Health Technology Assessment; ICTRP = International Clinical Trials Registry Platform; IQWiG = Institute for Quality and Efficiency in Health care; mCRC = metastatic colorectal cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; wt = wild-type.

Note: Details included in Table 19 are from the sponsor's Summary of Clinical Evidence.[33]

[a]In studies where outcomes are not stratified by line of treatment (2L vs. 3L vs. 4L+), a population threshold will be applied to determine if the majority of patients represent the 3L or beyond indication. A threshold of 80% is considered acceptable by other HTA bodies, such as IQWiG.[61]

Source: Sponsor-submitted indirect treatment comparison.[24]

ITC Analysis Methods

After conducting the feasibility assessment, 4 outcomes were deemed feasible for the NMA, from both a methodological and clinical standpoint: OS, PFS, disease control rate, and treatment-related AEs. Note that for the outcome of any AEs, 4 studies did not report the incidence of patients with at least 1 AE. In 1 study, the BSC arm was an outlier, with only 51.9% of patients experiencing AEs, versus more than 85% of patients for BSC arms from 2 other studies. In addition, multiple studies reported a rate of 100% AEs, leading to issues of modelling underlying any ITC and the associated uncertainty of estimates. Therefore, an NMA on any AEs was not performed. Authors of this ITC stated that treatment-related AEs instead of any AEs was considered to be more helpful in modelling and allowed for a better estimation of the associated uncertainty in the safety profile.

All NMA models were conducted using a Bayesian framework. All univariate analyses involved a 10,000 run-in iteration phase and a 10,000-iteration phase for parameter estimation. All calculations were performed via the program Just Another Gibbs Sampler 3.2.3 using 3 chains initiated under 3 main paradigms: "negative," meaning that treatment is better than BSC; "equal," meaning that treatment is equivalent to BSC; and "positive," meaning that treatment is worse than BSC.[62] Fixed-effects and random-effects models were conducted for each outcome of interest and per analysis type (base-case or sensitivity analysis). The random-effects NMAs used a vaguely informative normal prior with a uniform SD, the value of which was equivalent to 1.0 for all binary outcomes, and U(0,2X) for continuous outcomes, where X was the median SD of the outcome within the study. The choice of prior was somewhat arbitrary by nature, and in these cases

was chosen to allow for a moderate to large amount of random-effects variation and to discourage the estimation of extreme values of random-effects variation. Sensitivity to priors was investigated in sensitivity analyses, generally by shortening the internal by 50%. Unconstrained parameters, such as treatment effects, had a prior of N (0, 10,000), though this was decreased to N (0, 1,000) in cases where convergence was imperfect. For each model, model fit was assessed based on deviance, the effective number of parameters, deviance information criterion, and an estimate of random-effects dispersion for random-effects models only. The best model was chosen based on the values of deviance information criterion.

The assessment of consistency was not performed due to the absence of a closed loop in the available networks. Convergence was confirmed through inspection of the ratios of Monte Carlo error to the SDs of the posteriors.

Due to the differences in study design across all included studies, such as population (mCRC or refractory mCRC), blinding (open-label or double-blind), specific ethnic groups (multinational, Asian countries, or European countries), and the definition of BSC, sensitivity analyses were conducted to account for these heterogeneities. These analyses included only multinational trials for each outcome of interest.

Detailed statistical methods of ITC for OS, PFS, and treatment-related AEs are provided in Table 20.

Results of Sponsor-Submitted ITC

Summary of Included Studies

Among the 15 RCTs identified from the systematic review, 5 RCTs were excluded (the reasons for exclusion were not provided) and 10 RCTs were included in the NMA. All 10 studies were RCTs in patients with mCRC or refractory mCRC. The included RCTs evaluated the efficacy and safety of the following therapies, which are relevant to this review: trifluridine-tipiracil plus bevacizumab in 2 studies, BSC alone in 7 studies, regorafenib in 2 studies, and trifluridine-tipiracil alone in 6 studies. Other active treatments included panitumumab, cetuximab, panitumumab with BSC, cetuximab with BSC, and trifluridine-tipiracil plus panitumumab.

Table 20: ITC Analysis Methods

Method	Description
Analysis methods	All NMA models were conducted using a Bayesian framework.
Priors	The random-effects NMAs used a vaguely informative prior with a uniform SD, the value of which was equivalent to 1.0 for all binary outcomes, and U(0,2X) for continuous outcomes, where X was the median SD of the outcome within the study.
Assessment of model fit	Two models were conducted for each outcome of interest and per analysis type (base-case or sensitivity analysis): • fixed effects • random effects. For each of the 2 models, model fit statistics were reported, including: • deviance • pD

Method	Description
	• DIC • estimate of random-effects dispersion (for random-effects models only). Selection between random effects vs. fixed effects: If the DIC of the random-effects model was lower than the DIC of the fixed-effects model by at least 3, the random-effects model was selected; otherwise, the fixed-effects model was selected (following advice from NICE TSD 2[62]).
Assessment of consistency	Not possible due to the absence of a closed loop in any of the networks
Assessment of convergence	Convergence was confirmed through inspection of the ratios of Monte Carlo error to the SDs of the posteriors; values > 5% are strong signs of convergence issues.

Outcomes	A complete feasibility assessment was carried out on the following outcomes and is presented per outcome.
	• Efficacy outcomes:
	  ○ OS
	  ○ PFS
	  ○ DCR
	  ○ ORR
	• Safety outcomes:
	  ○ Discontinuation
	  ○ AEs
	  ○ TAEs
	  ○ grade 3 and grade 4 AEs
	  ○ anemia (all grades)
	Efficacy outcomes
	OS: All included studies except the VELO study reported an OS HR or a Kaplan-Meier curves plot to allow for an NMA to be fitted over, allowing for the comparison of trifluridine-tipiracil + bevacizumab vs. 4 other active comparators (PAN, trifluridine-tipiracil alone, CET, and REGO).
	PFS: All 10 studies reported PFS. In addition, definitions across studies were consistent with a PFS being defined as from time to randomization until progression or death, due to any cause or censoring. However, the CORRECT and CONCUR studies were unclear if they used investigator judgment for progression or IRC. Most studies also reported median PFS with a full confidence interval, allowing for confidence that the data were mature enough for ITC.
	DCR: Only 8 of 10 studies reported a DCR rate, with the Yoshino (2012) and Jonker (2007) trials being the 2 studies not reporting a DCR. In addition, definitions across the studies were similar. However, timing of the tumour assessment varied from 6 weeks (in the CORRECT and CONCUR trials) to 8 weeks (in the SUNLIGHT[22] and RECOURSE trials), meaning that a DCR rate could be slightly biased in favour of treatment with longer time duration. However, the effect would impact similarly both the comparator and treatment arm, and therefore not introduce bias into the relative treatment and subsequently the NMA. No information could be found on whenever DCRs were based on investigator assessment or IRC assessment; however, standard practice suggests those assessments are likely based on investigator assessment. As DCR event rates are much higher than the ORR rate, it is recommended that the NMA be carried out on the DCR rate rather than ORR rate.
	ORR: All studies reported ORR. Definitions across studies are consistent with the use of

Method	Description
	RECIST 1.1. However, the CORRECT and CONCUR trials used investigator judgment in case radiographic progression could not be assessed using radiology. In addition, ORR rates across the networks were very low, creating an issue in estimating associated uncertainty with the ORR rate. The CONCUR trial had a 0-events record for the BSC arm that will require adjustment. For the following reason, we recommend **not** conducting an ITC on ORR due to the lack of power and need for adjustment that could introduce bias in the ITC. **Safety outcomes** **Discontinuation:** Only 2 active comparators could be compared to trifluridine-tipiracil for a discontinuation rate. In addition, upon review of the reason for discontinuation, it was discovered most discontinuations were related to progression. However, 1 of several issues noted was that multiple studies reported a discontinuation rate of 100%, making them **unsuitable** for any NMA. **AEs:** The Yoshino et al. (2012), Jonker et al. (2007), Pfeiffer et al. (2020), and VELO studies did not report the incidence of patients with at least 1 AE. The TERRA study's BSC arm is an outlier with only 51.85% of patients experiencing AEs vs. more than 85% of patients experiencing AEs for the BSC arms from the CORRECT and CONCUR studies. In addition, multiple studies reported 100% AEs, leading to issues of modelling underlying any ITC and the associated uncertainty of estimates. **Treatment-related AEs:** The Yoshino et al. (2012), Jonker et al. (2007), NCT00113763 (open-label, phase III trial of panitumumab plus BSC), and VELO studies did not report the incidence of patients with at least 1 TAE. The rate between the RECOURSE and SUNLIGHT trials' trifluridine-tipiracil arms (81.3% vs. 85.74%, respectively) are homogeneous. Additionally, the list of specific TAEs is available for the SUNLIGHT, RECOURSE, and CORRECT studies. Given the rate was below 100%, using TAEs instead of AEs could help modelling and allow for a better estimation of the associated uncertainty across TAE-associated rates. **Grade 3 and grade 4 AEs:** The SUNLIGHT, RECOURSE, NCT00113763, and CORRECT studies reported grade 3 and grade 4 AE rates. While feasible, the rate between the RECOURSE and SUNLIGHT studies' trifluridine-tipiracil arms (5.82% vs. 60.57%, respectively) were very heterogeneous. Given the low number of studies, it was unlikely that any RE could be fitted on the data to acknowledge population difference. An investigation into using serious AEs to reduce the discrepancy between the SUNLIGHT and RECOURSE trials showed that the NMA was not feasible. **Anemia:** Only the SUNLIGHT, RECOURSE, and CORRECT studies reported treatment-related AEs. An NMA was not recommended due to the low number of events and the lack of multiple studies allowing for a random-effects model to be fitted. For example, the anemia rate in the CORRECT trial was only 5.7% for the regorafenib arm, leading to a very low number of events to be used for inference. After conducting the feasibility assessment, 4 outcomes were deemed feasible for the NMA from both the methodological and clinical standpoint — namely, OS, PFS, DCR, and TAE. To account for the heterogeneity between multinational trials and trials focused on specific ethnic groups, the sponsor performed a sensitivity analysis. This analysis included only multinational trials for each outcome of interest.
Follow-up time points	For efficacy outcomes, as selected outcomes were time-to-event, publications with the longest follow-up or that were most recently published were always selected to allow the integration of a maximum amount of information. For safety outcomes, as the aim of the analysis was to present an unbiased estimation of the safety profile across the whole treatment period, the latest publication was always selected.

Method	Description
Construction of nodes	Each node represented a separate treatment in respect to their duration, type, or dosage. BSC was the only node for which different definitions were allowed, after all definitions were reviewed and deemed similar by a clinician.
Sensitivity analyses	Only multinational trials were kept for the sensitivity analysis. This sensitivity analysis was carried out for all outcomes.
Subgroup analysis	No subgroup analyses were carried out.

AE = adverse event; BSC = best supportive care; CET = cetuximab; DCR = disease control rate; DIC = deviance information criterion; HR = hazard ratio; IRC = independent review committee; ITC = indirect treatment comparison; NICE TSD 2 = National Institute for Health and Care Excellence Technical Support Document 2; NMA = network meta-analysis; ORR = objective response rate; OS = overall survival; PAN = panitumumab; Pd = effective number of parameters; PFS = progression-free survival; RCT = randomized controlled trial; RE = random effect; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1; REGO = regorafenib; SD = standard deviation; TAE = treatment-related adverse event; vs. = versus.

Note: Details included in Table 20 are from the sponsor's Summary of Clinical Evidence.[33]

Source: Sponsor-submitted indirect treatment comparison.[24]

Across the included studies, patients' baseline characteristics were similar in age (mean age = 61.6 years [range = 56 years to 67 years]) and the proportion of colon as the primary site of mCRC. The dosages, frequency of administration, and dosage cycles of commonly investigated drugs (trifluridine-tipiracil plus bevacizumab, trifluridine-tipiracil alone, and regorafenib) were consistent across the included studies and reflective of the clinical practice. Definitions of OS, PFS, and treatment-related AEs were similar across the included studies.

Significant heterogeneities were observed across the included studies for ECOG PS (ECOG PS of 0 ranged from 22.2% to 64.3%) and the incidence of *RAS* wild-type tumour (range = 26.5% to 69.5%).

Patients in 1 study (the SUNLIGHT trial) had received no more than 2 prior lines of therapy while patients in 4 studies had received at least 2 prior lines of therapy and patients in another 5 studies had received at least 3 prior lines of therapy for mCRC.

In the majority of the included studies, BSC was defined as clinically indicated interventions that were required to provide palliation of symptoms and improve quality of life as needed, such as hematologic support and the management of gastrointestinal symptoms, excluding antineoplastic drugs. There were still differences in the definition of BSC across all included studies, though. For example, BSC was defined as any interventions excluding other investigational antitumour drugs or antineoplastic chemotherapy, hormonal therapy, or immunotherapy in 3 trials. The quality of the included studies was evaluated using the Cochrane risk-of-bias tool for randomized trials as described in the *Cochrane Handbook for Systemic Reviews of Interventions*. In general, most studies were considered to have a low risk of bias for "deviations from intended interventions," "missing outcome data," "measurement of the outcome," "selection of the reported result," and "overall bias;" however, 6 of 10 RCTs were considered to have some concerns related to "randomization process."

A description of important differences across trials for key characteristics is provided in Table 21.

The current review presents the results of OS, PFS, and treatment-related AEs, which were identified as the most relevant clinical outcomes for patients with mCRC by the patients and the clinical experts consulted by CADTH.

Table 21: Assessment of Homogeneity for Sponsor-Submitted ITC

Characteristic	Description and handling of potential effect modifiers
Risk of bias	All RCTs' publications included in the analysis were evaluated according to the Cochrane risk-of-bias tool for randomized trials as described in the *Cochrane Handbook for Systemic Reviews of Interventions*. Most studies had a low risk of bias, with the only concerns being related to the randomization process. Given the investigated outcome, the randomization process is not expected to introduce bias on the outcomes.
Study design and line of treatment	Overall, differences exist between the trials, with the TERRA, CONCUR, Jonker (2007), Pfeiffer (2020), and Yoshino (2012) studies being on specific populations. In addition, BSC was defined in different ways across the included trials, such as hematologic support, therapies for gastrointestinal tract discomfort, or any measures with the exception of antineoplastic drugs. However, it is unlikely that these differences would have introduced bias in the assessment of effect on OS or PFS given that actual anticancer ingredients were not included in BSC (refer to the following details in this table).
Baseline characteristics of the included trials population	Baseline characteristics were systematically extracted. If the baseline characteristics were reported by at least 50% of the studies, they were selected for investigation of heterogeneity of trial population on them. **Age:** • Nine of 10 studies were reporting age. • The mean age across studies was 61.6 years, with a minimum of 55.5 years from the CONCUR study and a maximum of 67 years from the Pfeiffer (2020) study. • Heterogeneity across studies was relatively low. **Sex:** • Nine of 10 studies were reporting sex. • The average proportion of males across studies was 59%, with a maximum of 64.8% from the Jonker (2007) study and a minimum of 48.5% from the CONCUR study. • The CONCUR trial had a large discrepancy between the regorafenib treatment arm and the placebo + BSC arm (62.5% vs. 48.5%, respectively). • While heterogeneity was high between studies, a subgroup analysis of the SUNLIGHT trial showed that sex was not associated with a difference in treatment effect. **ECOG PS score across studies:** • Nine of 10 studies were reporting an ECOG PS score. • The average proportion of patients with an ECOG PS score of 0 was 41%, ranging from 22.2% in the TERRA study to 64.3% in the Yoshino (2012) study. • Significant heterogeneity was observed between treatment arms in the NCT00113763 study (the proportion of patients with an ECOG PS score of 0 was 46.3% in the panitumumab and BSC arm and 34.5% in the BSC alone arm) and the Pfeiffer (2020) study (the proportion of patients with an ECOG PS score of 0 was 50.0% in the trifluridine-tipiracil plus bevacizumab arm and 31.9% in the trifluridine-tipiracil alone arm); in addition, a large degree of heterogeneity exists between studies. • However, the sponsor indicated that a score of ECOG PS of 0 or 1 does not impact significantly patient survival and among studies reporting a few patients with an ECOG PS score of 2, ECOG PS and patient progression were not found to be significantly correlated.

Characteristic	Description and handling of potential effect modifiers
	Primary site of the tumour: • Eight of 10 studies were reporting the primary site for tumour. • A relatively large imbalance in the proportion of colon as the primary site of the tumour was observed in the CONCUR study between treatment arms (61% in the regorafenib arm and 72% in the BSC arm). • Heterogeneity in the proportion of either colon or rectum as the primary site between studies was observed, ranging from 56.0% to 78.1%. ***RAS* biomarker status:** • Nine of 10 studies were reporting *RAS* status. • No study had any major imbalance between arms. • The average proportion of patients with *RAS*-positive status was 46%, with a minimum of 26.5% of patients with *RAS*-positive status from the CONCUR study and a maximum of 69.5% of patients from the SUNLIGHT study. • Heterogeneity between studies remained low. However, a notable finding was the difference in *RAS* status between the SUNLIGHT and CONCUR trials. Such a difference was partially explained by the preferential referral of *RAS*-positive patients to clinical trials of anti-EGFR therapy. Differences in *RAS* status may be related to the differential treatment effect of the study drug in this patient population.
Dosage of studies comparing the same treatment	Three treatments included in the network had more than 1 trial assessing efficacy of the respective drug: regorafenib, trifluridine-tipiracil alone, and trifluridine-tipiracil + bevacizumab. In all cases, it was possible to pool the arms with common comparators for the NMA as dosages, the frequency of administration, and dosage cycles were consistent for different trials. Treatment compliance and treatment exposure of the study drugs in the included RCTs were not reported in the sponsor-submitted ITC. A summary of dose definitions for such trials is provided in Table 23 in Appendix 1.
Definitions of end points	• OS was defined as the time from randomization until death or censoring. • PFS was defined as the time from randomization until progression or death, whichever occurred first, as defined by investigator assessment using RECIST 1.1. • TAEs were defined as any adverse events according to the National Cancer Institute's CTCAE v5.0 related to treatment, as per investigator assessment.
Timing of end point evaluation	This was not reported in the sponsor's ITC report.

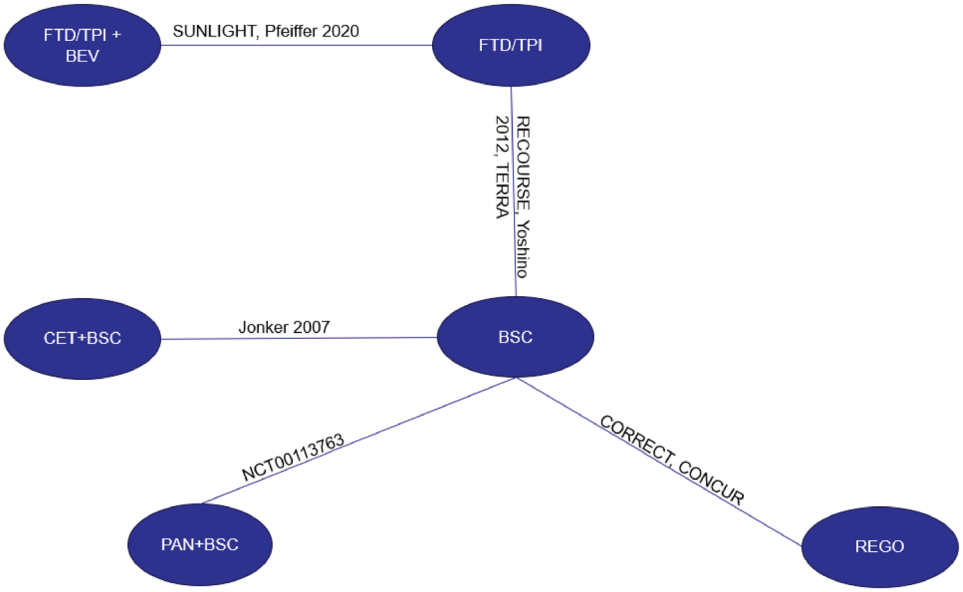
Anti-EGFR = anti–epidermal growth factor receptor; BSC = best supportive care; CTCAE v5.0 = *Common Terminology Criteria for Adverse Events* Version 5.0; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ITC = indirect treatment comparison; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1; TAE = treatment-related adverse event; vs. = versus.

Note: Details included in Table 21 are from the sponsor's Summary of Clinical Evidence.[33]

Source: Sponsor-submitted indirect treatment comparison.[24]

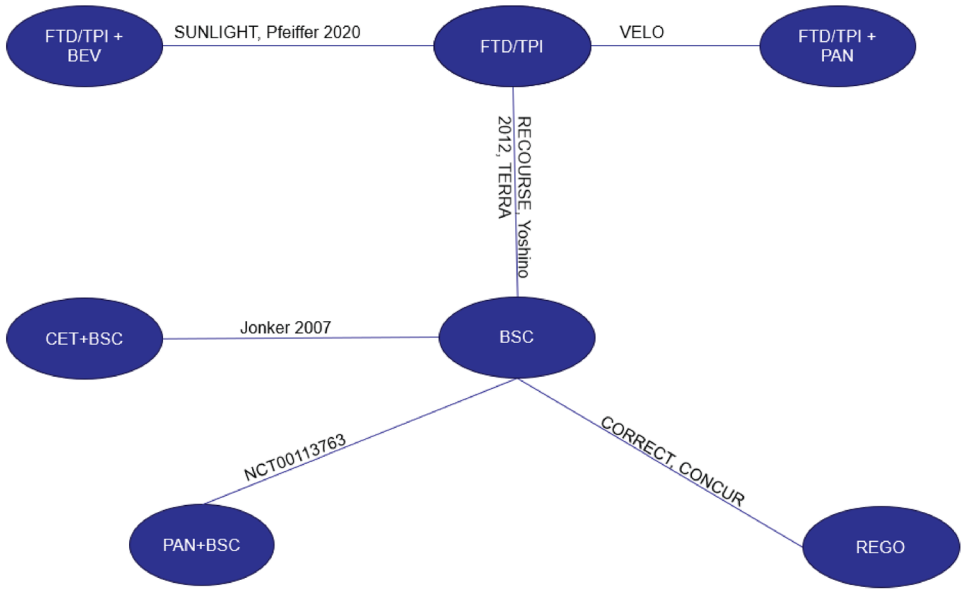
Figure 9 to Figure 11 present the networks of evidence for base-case analysis of OS, PFS, and treatment-related AEs in the included studies.

Figure 9: Network Diagram for OS



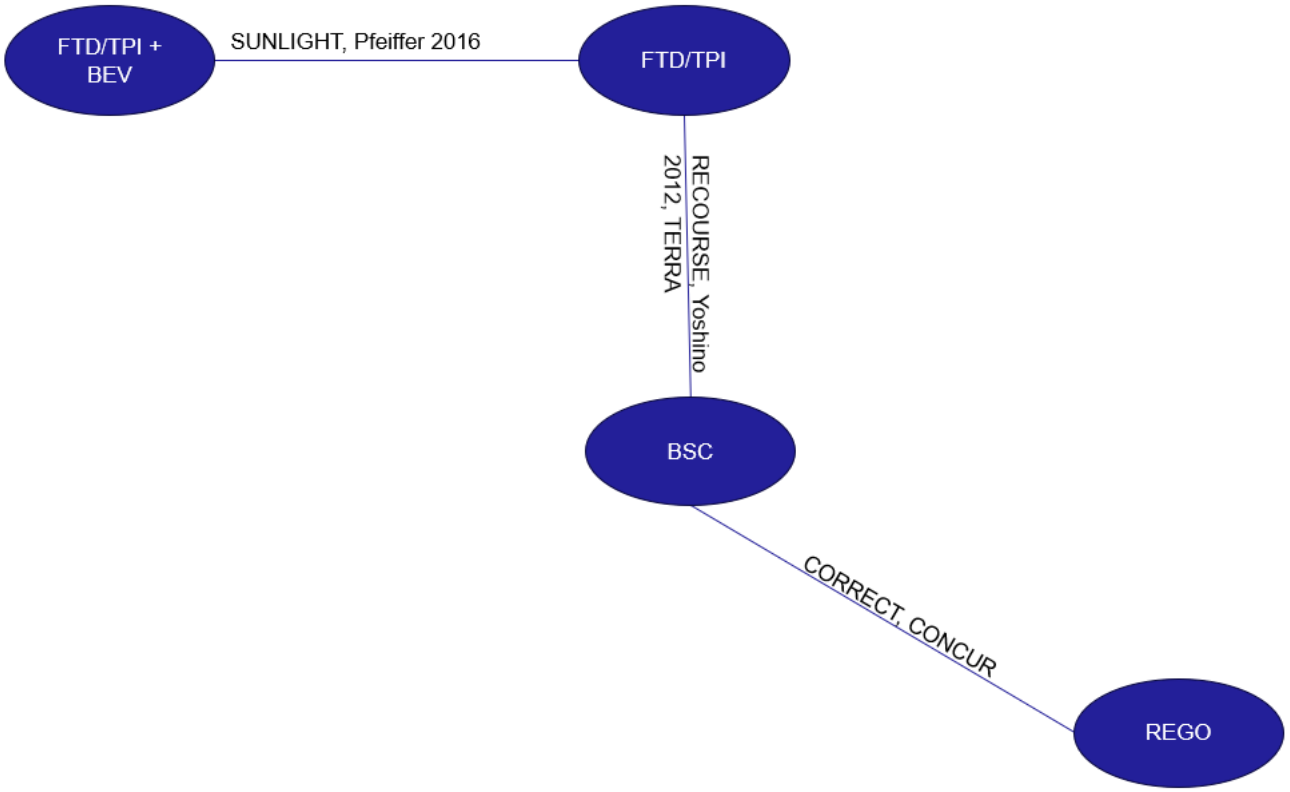
BEV = bevacizumab; BSC = best supportive care; CET = cetuximab; FTD/TPI = trifluridine-tipiracil; OS = overall survival; PAN = panitumumab; REGO = regorafenib.
Source: Sponsor-submitted indirect treatment comparison.[24]

Figure 10: Network Diagram for PFS



BEV = bevacizumab; BSC = best supportive care; CET = cetuximab; FTD/TPI = trifluridine-tipiracil; PAN = panitumumab; PFS = progression-free survival; REGO = regorafenib.
Source: Sponsor-submitted indirect treatment comparison.[24]

Figure 11: Network Diagram for Treatment-Related AEs



AE = adverse event; BEV = bevacizumab; BSC = best supportive care; FTD/TPI = trifluridine-tipiracil; REGO = regorafenib.
Source: Sponsor-submitted indirect treatment comparison.[24]

Results

Detailed efficacy and safety results are presented in Table 22. Only the results for trifluridine-tipiracil plus bevacizumab versus relevant comparators for this review (trifluridine-tipiracil alone, regorafenib, and BSC) are summarized in this section.

Overall Survival

In total, 9 studies were included in the network for OS. All studies presented mature OS data. All studies but 1 reported OS HR or a KM curves plot. Trifluridine-tipiracil plus bevacizumab was compared with 4 other active treatments: BSC, panitumumab, cetuximab, regorafenib, and trifluridine-tipiracil alone. The fixed-effects model was found to be the best fitting model for the analysis of OS.

Overall, results from fixed-effects models showed that the HR for OS was 0.42 (95% CrI, 0.33 to 0.55), 0.60 (95% CrI, 0.44 to 0.81), and 0.60 (95% CrI, 0.49 to 0.73) for the comparisons of trifluridine-tipiracil plus bevacizumab versus BSC, regorafenib, and trifluridine-tipiracil alone, respectively, in favour of trifluridine-tipiracil plus bevacizumab. A larger treatment effect was observed for trifluridine-tipiracil plus bevacizumab versus BSC, compared to the other 2 comparators.

A sensitivity analysis for OS was carried out that included 4 studies to investigate the findings in a network on only multinational trials. Results from fixed-effects models were consistent with those in the primary analysis: HR was 0.42 (95% CrI, 0.32 to 0.55) versus BSC, 0.55 (95% CrI, 0.39 to 0.77) versus regorafenib, and 0.61 (95% CrI, 0.49 to 0.77) versus trifluridine-tipiracil alone.

Progression-Free Survival

PFS was defined consistently across all included studies. Ten studies were included in the network for PFS. All studies presented mature PFS data. Trifluridine-tipiracil plus bevacizumab was compared with trifluridine-tipiracil alone, BSC, cetuximab, regorafenib, panitumumab, and trifluridine-tipiracil plus panitumumab. The fixed-effects model was found to be the best fitting model for the analysis of PFS.

Results from fixed-effects models showed that the HR for PFS was 0.20 (95% CrI, 0.16 to 0.25), 0.44 (95% CrI, 0.34 to 0.58), and 0.44 (95% CrI, 0.36 to 0.53) for the comparisons of trifluridine-tipiracil plus bevacizumab versus BSC, regorafenib, and trifluridine-tipiracil alone, respectively, in favour of trifluridine-tipiracil plus bevacizumab. A larger treatment effect was observed for trifluridine-tipiracil plus bevacizumab versus BSC compared to the other 2 comparators.

A sensitivity analysis for PFS was carried out that included 4 studies to investigate the findings in a network on only multinational trials. Results from fixed-effects models were consistent with those in the primary analysis: HR was 0.21 (95% CrI, 0.16 to 0.27) versus BSC, 0.43 (95% CrI, 0.32 to 0.58) versus regorafenib, and 0.44 (95% CrI, 0.36 to 0.54) versus trifluridine-tipiracil alone.

Treatment-related AEs

Seven studies were included in the network for the incidence of patients with at least 1 treatment-related AE. Trifluridine-tipiracil plus bevacizumab was compared to trifluridine-tipiracil alone, BSC, and regorafenib. Treatment-related AEs were defined consistently across all included studies using the National Cancer Institute's *Common Terminology Criteria for Adverse Events*, Version 5.0. Based on a deviance information criterion value of 58.3 in the random-effects model and 78.3 in the fixed-effects model, the random-effects model was determined to be the most suitable model for the analysis of treatment-related AEs. However, considering that the prior given to the between-study heterogeneity significantly impacted its posterior distribution and the range of treatment effects' posterior distribution was heavily influenced by the between-study heterogeneity, which spanned from 0.01 to 100, the fixed-effects model was chosen to facilitate evidence-driven decision-making.

Results from fixed-effects models showed that the odds ratio (OR) was 11.0 (95% CrI, 5.8 to 21.3), 1.1 (95% CrI, 0.5 to 2.3), and 2.22 (95%CrI, 1.3 to 3.9) for the comparisons of trifluridine-tipiracil plus bevacizumab versus BSC, regorafenib, and trifluridine-tipiracil alone, respectively, in favour of the comparators. A larger effect was observed for trifluridine-tipiracil plus bevacizumab versus BSC compared to the other 2 comparators.

A sensitivity analysis for the incidence of treatment-related AEs was carried out that included 3 studies to investigate the findings in a network on only multinational trials. Results from fixed-effects models were consistent with those in the primary analysis: OR of 1.45 (95% CrI, 0.70 to 3.12) versus regorafenib, OR

of 2.22 (95% CrI, 1.32 to 3.81) versus trifluridine-tipiracil alone, and OR of 11.15 (95% CrI, 5.95 to 20.98) versus BSC.

Table 22: Summary of Efficacy and Safety Outcome Measures in the Sponsor-Submitted ITC

Trifluridine-tipiracil + BEVA vs. comparator	Efficacy or safety outcome		
	OS HR (95% CrI) from fixed-effects models	PFS HR (95% CrI) from fixed-effects models	Treatment-related AEs OR (95% CrI) from fixed-effects models
Number of included studies	9	10	7
BSC	0.42 (0.33 to 0.55)	0.20 (0.16 to 0.25)	11.02 (5.82 to 21.31)
Regorafenib	0.60 (0.44 to 0.81)	0.44 (0.34 to 0.58)	1.07 (0.52 to 2.25)
Trifluridine-tipiracil (alone)	0.60 (0.49 to 0.73)	0.44 (0.36 to 0.53)	2.22 (1.31 to 3.87)

AE = adverse event; BEVA = bevacizumab; BSC = best supportive care; CrI = credible interval; HR = hazard ratio; ITC = indirect treatment comparison; OR = odds ratio; OS = overall survival; PFS = progression-free survival; vs. = versus.

Source: Sponsor-submitted indirect treatment comparison.[24]

Critical Appraisal of Sponsor-Submitted ITC

In the ITC, studies were identified by searching multiple databases based on prespecified inclusion and exclusion criteria. The error and bias in the study selection process are minimized. The reviewers of this ITC used appropriate methods for study selection and data extraction. The quality of the included studies was assessed using a validated tool. However, there was no discussion on how any potential biases in the included trials could have an impact on the validity of the ITC and there were no sensitivity analyses being conducted to assess the impact of trials with poor quality. In this ITC, results were derived from random-effects or fixed-effects models. Reasons for model selection were justified by the authors and based on statistical and clinical considerations.

A significant concern with the ITC presented is that the trials included in the analyses were highly heterogeneous in terms of both study design and patient characteristics. Among the 10 RCTs, 5 were open-label trials and 5 were blinded. However, OS is an objective measurement of the treatment effect. Having or not having the knowledge of treatment allocation (blinding or not) is less likely to have a large impact on OS among patients with cancer.[63] The SUNLIGHT trial enrolled patients who had received no more than 2 previous chemotherapy regimens while the other trials enrolled patients who had received 2 or more lines of therapy for mCRC. Significant heterogeneities in patient characteristics included ECOG PS (the proportion of patients with an ECOG PS score 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. Despite various statistical models being employed to lessen the impact of potential clinical heterogeneity on the estimated treatment effect of trifluridine-tipiracil plus bevacizumab, there is still 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 were therefore informed only by indirect evidence, which increases the level of uncertainty.

The efficacy outcomes and safety outcomes were defined consistently across the included trials. BSC was defined somewhat differently. According to the clinical experts consulted by CADTH, BSC generally includes any interventions other than chemotherapy or immunotherapy — for example, medications for gastrointestinal symptoms and hematologic support, blood transfusion, or radiation for palliative care. The experts noted that it is less likely that the varied definitions for BSC would have an impact on study result interpretation.

Some important patient characteristics in the included trials were not reported in this ITC, such as treatment duration, the timing of study end point evaluation, the 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 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.

In the NMA, safety data were sparse and only the analysis on treatment-related AEs was deemed feasible by the sponsor. Even though the authors of this ITC indicated that using treatment-related AEs instead of any AEs could help modelling and allow for better estimation of the uncertainty across associated rates of treatment-related AEs, it would be desirable to understand the risk of any adverse effect in patients with mCRC during the study, no matter if they were considered drug-related or not.

In this ITC, several efficacy and safety outcomes were analyzed, such as OS, PFS, and treatment-related AEs. However, other efficacy end points of interest to patients and clinicians, such as HRQoL, were not investigated. Therefore, the relative treatment effect of trifluridine-tipiracil plus bevacizumab versus other active treatments on patients' HRQoL remains unknown.

Summary

Based on the results of the sponsor-submitted ITC, treatment of trifluridine-tipiracil plus bevacizumab may be associated with prolonged OS and PFS but also an increased risk of treatment-related AEs in patients with mCRC compared to other treatments such as BSC, regorafenib, or trifluridine-tipiracil alone. However, the magnitude of these differences was uncertain due to substantial uncertainty related to a number of limitations that impact the internal and external validity of this study, such as significant clinical heterogeneities between the included trials, potential intransitivity, reliance solely on indirect data, and a lack of other important outcomes that are important to patients and clinicians (e.g., HRQoL).

Studies Addressing Gaps in the Systematic Review Evidence

Content in this section has been informed by materials submitted by the sponsor. The following has been summarized and validated by the CADTH review team.

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

Discussion

Summary of Available Evidence

One randomized, phase III, open-label, multicentre study evaluated the efficacy and safety of trifluridine-tipiracil plus bevacizumab versus trifluridine-tipiracil alone. The SUNLIGHT study enrolled 492 adults with advanced mCRC who had received up to 2 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, the rest of the world), time since first metastasis diagnosis (< 18 months, ≥ 18 months), and *RAS* status (wild-type, mutant). The primary objective of the SUNLIGHT study was to demonstrate superiority of OS and the key secondary objective was to estimate investigator-assessed PFS. Additional secondary end points included HRQoL assessed with the EORTC QLQ-C30 and EQ-5D-5L, and TEAEs.

In the SUNLIGHT trial, patients had a mean age of 61.7 years (SD = 11.1 years), and most patients were male (52%), white (95.2%), and enrolled from the European Union (64.0%). Most patients had a primary diagnosis of colon cancer (73%) and stage IV disease (66%). 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% of patients had *RAS* wild-type disease. Most patients (92.1%) had received 2 previous treatment regimens for metastatic disease, 2.6% of patients had more than 2 prior regimens, and 5.3% of patients had received 1 previous treatment regimen. All patients had received previous fluoropyrimidine-based therapy, 72.0% of patients 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 patients with *RAS* wild-type disease had received previous anti-EGFR therapy. Demographic characteristics were generally similar between the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, with notable (> 5%) between-group differences for patients aged 65 years and older (41% versus 48%, respectively), for patients whose primary tumour was located on the right side (25% versus 31%, respectively), and for patients whose primary tumour was located on the left side (75% versus 69%, respectively).

One ITC was submitted by the sponsor to compare the treatment efficacy and safety of trifluridine-tipiracil plus bevacizumab with active therapies for the treatment of mCRC. Studies included relevant therapies for the drug under review, including BSC, regorafenib, and trifluridine-tipiracil alone. Outcomes included OS, PFS, and treatment-related AEs.

Interpretation of Results

Efficacy

Patients with mCRC highlighted their need for new therapy to prolong survival while maintaining or improving quality of life, with tolerable side effects. Clinicians also identified a significant need for treatment to improve OS, decrease symptom burden, and improve quality of life among patients with mCRC who experience disease progression following 2 lines of anticancer therapy. The pivotal SUNLIGHT trial assessed OS as the primary end point and PFS as a key secondary end point, which aligned with stakeholder inputs and guidelines for clinical trials. While the clinical experts consulted by CADTH considered OS to be the key

efficacy outcome among patients with mCRC, they acknowledged that PFS may provide added value as being predictive of OS. HRQoL was also assessed in the SUNLIGHT trial, which aligned with stakeholder inputs, especially for patients who emphasized that they would undertake new treatments for modest gains in OS if improvements in HRQoL could be achieved to enable them to engage in normal activities of daily living. However, HRQoL outcomes related to caregiver burden identified as important by patient and clinician inputs were not captured in the SUNLIGHT trial.

Findings for OS demonstrated the superiority of trifluridine-tipiracil plus bevacizumab when compared with trifluridine-tipiracil alone. Visual inspection of the KM curves and log(-log) plots and Schoenfeld residuals testing for OS were examined to evaluate the validity of the proportional hazards assumption; the P value supported the underlying assumption whereas the curves suggested a violation of the assumption. The clinical experts consulted by CADTH agreed that a 39% reduction in the risk of death with a median OS gain of greater than 3 months was clinically meaningful in demonstrating benefit for treatment with trifluridine-tipiracil plus bevacizumab. Findings for OS at 6 months and 12 months were consistent with the primary OS results and clinically meaningful according to the clinical experts consulted by CADTH. While the effect estimates for each time point showed a direction of benefit, the lower bound of the CIs did not reach the threshold identified for clinical significance, which reduced the certainty of the magnitude of benefit.

Findings for PFS were consistent with OS for demonstrating the benefit of trifluridine-tipiracil plus bevacizumab when compared with trifluridine-tipiracil alone, and were also supported by Schoenfeld residuals testing (P value of 0.568) and the KM curves and log(-log) plots. Nevertheless, the clinical experts consulted by CADTH considered that findings for PFS at 3 months and 6 months demonstrated a clinically meaningful difference in favour of treatment with trifluridine-tipiracil plus bevacizumab. As with OS, there was reduced certainty in the magnitude of benefit due to wide CIs.

Subgroup analyses for OS and PFS were conducted for 15 subgroups; these analyses included factors important for patient prognosis of advanced mCRC as identified by the clinical experts consulted by CADTH (i.e., age, number of metastatic sites, number of prior regimens, sidedness of tumour, and ECOG PS). Acknowledging that subgroup analyses were unstratified and unadjusted for multiplicity with a relatively small number of patients and events for each subgroup category, findings are considered exploratory, especially in the absence of known treatment-effect modifiers for trifluridine-tipiracil plus bevacizumab according to the clinical experts consulted by CADTH.

Patients reported having experienced side effects of treatments for mCRC (e.g., fatigue, nausea, diarrhea, neuropathy) that significantly impacted their quality of life. In the SUNLIGHT study, HRQoL was assessed using a disease-specific tool (EORTC QLQ-C30) and a generic measure (EQ-5D-5L). Analyses of the EORTC QLQ-C30 subscales included LSM change from baseline from a mixed model of repeated measures with terms including treatment and baseline stratification factors longitudinally over time. Analyses also included time until definitive deterioration of at least 10 points or greater on the subscales. The sponsor identified a 10-point difference between groups to be important based on literature for patients with cancer.[52,54] Based on literature-identified anchor-based MIDs among patients with CRC for within-group differences (7 to 10 for improvement and −8 to −5 for deterioration) and between-group differences (6 for improvement and −9 to

–7 for deterioration),[57] the clinical experts consulted by CADTH used a between-group treatment difference of 10 points (for the LSM change from baseline) and 10% (for the proportion of patients with a 10-point or greater deterioration) on the global health status subscale. Employing a relatively conservative threshold for a clinically meaningful difference between groups, effect estimates were affected by wide CIs. For patients, it may be worthwhile to note that there was a prolonged time to deterioration (of ≥ 10 points) on subscales of functioning (physical, emotional) and symptoms (fatigue, nausea and vomiting, pain, diarrhea, dyspnea, and appetite loss) of approximately 4 months when treated with trifluridine-tipiracil plus bevacizumab compared with trifluridine-tipiracil alone. Findings for EQ VAS appeared to show improved quality of life among patients treated with trifluridine-tipiracil plus bevacizumab, although the magnitude of difference when compared with trifluridine-tipiracil alone may not have been clinically meaningful according to thresholds used for patients with various cancers. According to the clinical experts consulted by CADTH, utility metrics derived and standardized for the population in Canada were an identified gap in the SUNLIGHT trial as EQ-5D-5L utility values were calculated using a French population. All HRQoL outcomes were affected by concerns related to risk of bias due to the open-label design and knowledge of assigned treatment, and due to missing data over the treatment duration that exceeded 20% at cycle 3 and 40% at cycle 4, with significant losses by cycle 10.

Overall, the patients enrolled in the SUNLIGHT study were representative of patients in clinical practice, according to the clinical experts consulted by CADTH; however, patients who were excluded (having more than 2 lines of prior therapy, an ECOG PS score of greater than 1, and/or small bowel or appendiceal adenocarcinoma) would be considered eligible for treatment with trifluridine-tipiracil plus bevacizumab. Additionally, the clinical experts consulted by CADTH outlined an unmet need for novel and effective therapies among patients with CRC diagnosed in a younger demographic or with de novo metastatic disease who have more aggressive presentations, which were not subpopulations or subgroups examined in the SUNLIGHT trial.

Input from clinician groups identified that BSC is a relevant and important comparator for trifluridine-tipiracil plus bevacizumab given that trifluridine-tipiracil alone is not universally funded or available in Canada. The clinical experts consulted by CADTH also identified BSC among other treatments but indicated trifluridine-tipiracil to be the most appropriate comparator for assessing the efficacy of trifluridine-tipiracil plus bevacizumab among patients with mCRC. While treatment of trifluridine-tipiracil plus bevacizumab may be associated with prolonged OS and PFS compared to other treatments in the sponsor-submitted ITC, there was substantial uncertainty in the magnitude of the differences due to significant heterogeneities between the included trials and an absence of evidence for HRQoL.

Harms

Overall, the safety profile of trifluridine-tipiracil plus bevacizumab showed similar proportions in patients with TEAEs, SAEs, treatment discontinuations due to AEs, and deaths. Input from a patient with experience using trifluridine-tipiracil plus bevacizumab reported side effects of neutropenia, loss of appetite, diarrhea, and nausea. The product monograph for trifluridine-tipiracil alone included serious warnings and precautions for myelosuppression (including neutropenia, leukopenia, anemia, thrombocytopenia, and febrile neutropenia) and gastrointestinal toxicity (including nausea, vomiting, and diarrhea), which were included as AEs of

special interest in the SUNLIGHT trial. Patients in the SUNLIGHT trial commonly experienced neutropenia, nausea, anemia, and diarrhea. A higher proportion of patients in the trifluridine-tipiracil plus bevacizumab group compared with the trifluridine-tipiracil alone group experienced myelosuppression (80.9% versus 73.2%, respectively), including neutropenia (62.2% versus 51.2%, respectively) and thrombocytopenia (17.1% versus 11.4%, respectively). More patients in the trifluridine-tipiracil plus bevacizumab group compared with the trifluridine-tipiracil alone group experienced gastrointestinal symptoms (48.4% versus 41.4%, respectively), including nausea (37.0% versus 27.2%, respectively) and decreased appetite (20.3% versus 15.4%, respectively). Gastrointestinal symptoms of grade 3 or higher were reported for 2.0% of patients and 4.9% of patients in the trifluridine-tipiracil plus bevacizumab group and the trifluridine-tipiracil alone group, respectively, including nausea (1.6% versus 1.6%, respectively), diarrhea (0.8% versus 2.4%, respectively), and vomiting (0.8% versus 1.6%, respectively). In the trifluridine-tipiracil plus bevacizumab group compared with the trifluridine-tipiracil alone group, a higher proportion of patients also experienced infections (30.9% versus 23.2%, respectively) and hypertension (10.2% versus 2.0%, respectively). Fewer patients died in the trifluridine-tipiracil plus bevacizumab group compared with patients treated with trifluridine-tipiracil alone (5.3% versus 9.8%, respectively). Evidence from the ITC submitted by the sponsor demonstrated an increased risk of treatment-related AEs with trifluridine-tipiracil plus bevacizumab. This finding was limited by the lack of specification of AEs as well as by the distinguishing of treatment-related AEs from treatment-emergent AEs (without attribution) and the sparse safety data in the NMA.

Overall, the clinical experts consulted by CADTH expressed that the AEs reported in the SUNLIGHT trial were supported by their observations in clinical practice and noted that patients with advanced mCRC are managed with respect to toxicities experienced during treatment, including the use of G-CSF if available. The clinical experts consulted by CADTH indicated that treatment with trifluridine-tipiracil plus bevacizumab should be well informed by patients' symptoms, side effects, and quality of life as well as treatment effectiveness.

Conclusion

The SUNLIGHT study was a randomized, phase III, open-label trial 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. Evidence from the SUNLIGHT study demonstrated that trifluridine-tipiracil plus bevacizumab likely results in a clinically important increase in the proportion of patients with OS at 6 months and 12 months (moderate certainty). The evidence demonstrated that trifluridine-tipiracil plus bevacizumab results in a clinically important increase in the proportion of patients with PFS at 3 months (high certainty) and likely results in a clinically important increase in the proportion of patients with PFS at 6 months (moderate certainty) when compared with trifluridine-tipiracil alone. Trifluridine-tipiracil plus bevacizumab may result in little to no clinically important difference in the change from baseline in EQ VAS (low certainty) when compared with trifluridine-tipiracil alone. However, the evidence is very uncertain about the effect of trifluridine-tipiracil plus bevacizumab in the change from baseline in EORTC QLQ-C30 global health status score, the proportion of

patients with at least a 10-point deterioration from baseline in the global health status score, and the change from baseline in EQ-5D-5L health utilities (very low certainty) when compared with trifluridine-tipiracil alone. Trifluridine-tipiracil plus bevacizumab may result in little to no clinically important difference in bone marrow suppression, infections, gastrointestinal symptoms, and hypertension (low certainty) when compared with trifluridine-tipiracil alone. Patients treated with trifluridine-tipiracil plus bevacizumab experienced similar frequencies of TEAEs, SAEs, treatment discontinuations due to AEs, and deaths, and no new safety signals were identified. Confidence in the effect estimates in the SUNLIGHT trial was limited due to imprecision from wide CIs for survival and harms outcomes, the potential of the open-label design to bias patient-reported outcomes, and significant missing data for HRQoL.

There is a lack of head-to-head direct evidence between trifluridine-tipiracil plus bevacizumab and other treatments for advanced mCRC. A sponsor-submitted ITC indicated treatment of trifluridine-tipiracil plus bevacizumab may be associated with prolonged OS and PFS but also an increased risk of treatment-related AEs in patients with mCRC, compared to other treatments such as BSC, regorafenib, or trifluridine-tipiracil alone. However, there was substantial uncertainty due to limitations, including significant between-trial heterogeneity, potential intransitivity, and the absence of HRQoL outcomes of importance to patients and clinicians.

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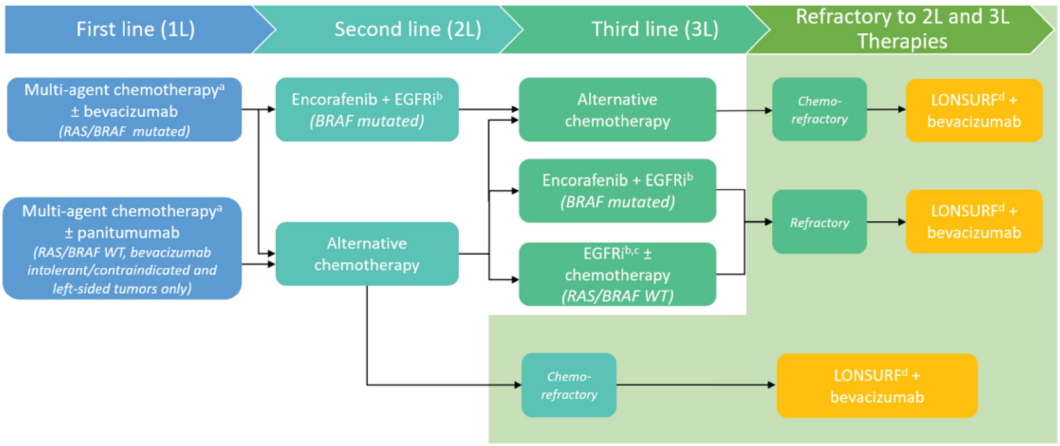
Appendix 1: Detailed Outcome Data

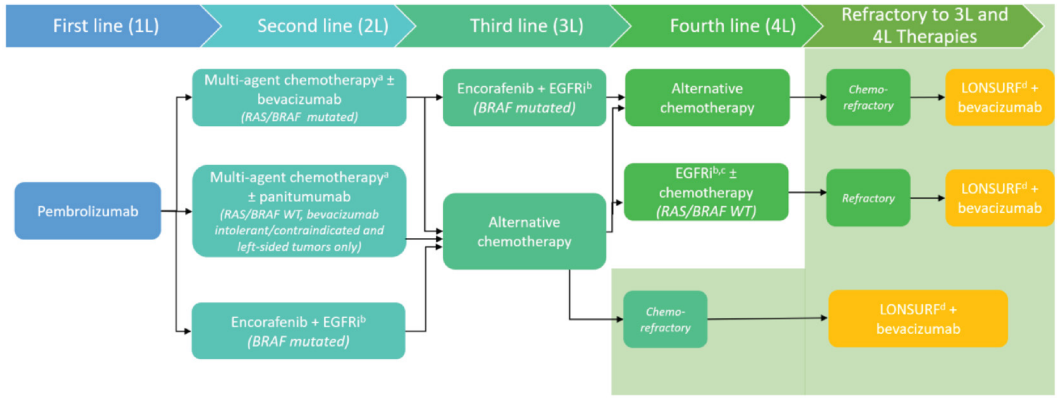
Note that this appendix has not been copy-edited.

Figure 12: mCRC Funding Algorithm (Proposed by Sponsor)

(A) MSI-L/MSS/pMMR mCRC



(B) MSI-H or dMMR mCRC



dMMR = deficient mismatch repair; EGFR = epidermal growth factor receptor; EGFRi = epidermal growth factor receptor inhibitor; FOLFIRI = folinic acid, fluorouracil, and irinotecan; FOLFOX = folinic acid, fluorouracil, and oxaliplatin; FOLFOXIRI = folinic acid, fluorouracil, oxaliplatin, and irinotecan; mCRC = metastatic colorectal cancer; MSI-H = microsatellite instability–high; MSI-L = microsatellite instability–low; MSS = microsatellite stable; pMMR = proficient mismatch repair; VEGF = vascular endothelial growth factor; WT = wild-type

[a] Multidrug chemotherapy: doublet therapy: FOLFOX, or FOLFIRI, or capecitabine plus oxaliplatin; triplet therapy: FOLFOXIRI.

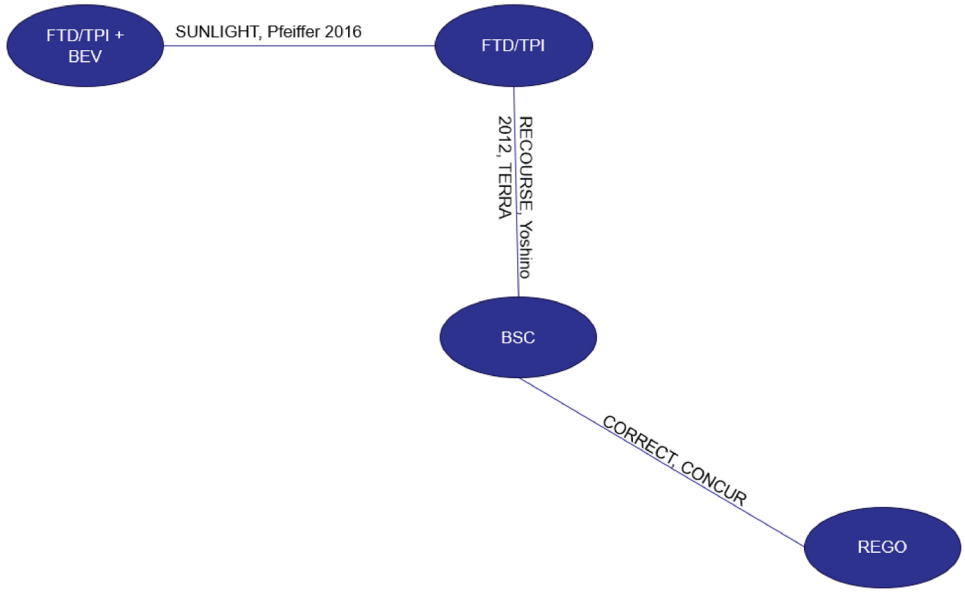
[b] EGFRis include cetuximab and panitumumab, where available.

[c] If had not received EGFR in previous lines.

[d] Lonsurf plus bevacizumab would be for chemo-refractory patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biological drugs, and, if *RAS* wild-type, anti-EGFR drugs.

Source: Sponsor's Summary of Clinical Evidence.[33]

Figure 13: Dose Modifications of Trifluridine-Tipiracil Due to Toxicities



CTCAE = *Common Terminology Criteria for Adverse Events*; D = day; FTD/TPI = trifluridine-tipiracil.
Source: SUNLIGHT Clinical Study Report.[22]

Table 23: Drug Therapies Used in Trials Included in Sponsor-Submitted ITC

Treatment	Trial	Dosage and administration as reported in publication	Cycle length	Summary of dosage received in 1 cycle
Regorafenib	CORRECT trial	160 mg once daily for the first 3 weeks of each 4-week cycle until disease progression, death, unacceptable toxic effects, withdrawal of consent by the patient, or decision by the treating physician that discontinuation would be in the patient's best interest.	28 days	160 mg once daily for 3 weeks, 1 week rest
	CONCUR trial	Once daily on days 1 to 21 of each 28-day cycle until disease progression, death, unacceptable toxic effects, withdrawal of consent by the patient, or decision by the treating physician that discontinuation would be in the patient's best interest.		
Trifluridine-tipiracil	SUNLIGHT trial	Day 1 to day 5: oral intake of trifluridine-tipiracil twice daily. Day 6 to day 7: rest. Day 8 to day 12: oral intake of trifluridine-tipiracil twice daily. Day 13 to day 28: rest.	28 days	35 mg/m^2 per dose twice daily for 5 days consecutively, 2 days off for 2 weeks followed by 2 weeks rest

Treatment	Trial	Dosage and administration as reported in publication	Cycle length	Summary of dosage received in 1 cycle
	RECOURSE trial	Day 1 through day 5: trifluridine-tipiracil (35 mg/m^2 per dose) orally 2 times daily with the first dose administered in the morning of day 1 of each cycle and the last dose administered in the evening of day 5. Day 6 through day 7: rest. Day 8 through day 12: trifluridine-tipiracil (35 mg/m^2 per dose) orally 2 times daily with the first dose administered in the morning of day 8 of each cycle and the last dose administered in the evening of day 12. Day 13 through day 28: rest.		
	TERRA trial	One treatment cycle of trifluridine/ tipiracil (35 mg/m^2 per dose) involved administration of dose twice per day, after morning and evening meals, for 5 days a week, with 2 rest days, for 2 weeks, followed by a 14-day rest period.		
	Pfeiffer (2020)	Trifluridine/tipiracil orally twice daily on day 1 to day 5 and day 8 to day 12 every 28 days		
	VELO trial	Trifluridine/tipiracil was administered at 35 mg/m^2 orally twice daily, 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period.		
	Yoshino (2012)	Day 1 through day 5: trifluridine-tipiracil (35 mg/m^2 per dose) orally 2 times daily with the first dose administered in the morning of day 1 of each cycle and the last dose administered in the evening of day 5. Day 6 through day 7: Rest. Day 8 through day 12: Trifluridine-tipiracil (35 mg/m^2 per dose) orally 2 times daily with the first dose administered in the morning of day 8 of each cycle and the last dose administered in the evening of day 12. Day 13 through day 28: Rest.		
Trifluridine-tipiracil + bevacizumab	SUNLIGHT trial	Oral intake of trifluridine-tipiracil twice daily and bevacizumab IV infusion on day 1. Day 6 to day 7: Rest. Day 8 to day 12: Oral intake of trifluridine-tipiracil twice daily. Day 13 to day 14: Rest. Day 15: Bevacizumab IV infusion. Day 16 to day 28: Rest.	28 days	35 mg/m^2 per dose of trifluridine-tipiracil twice daily for 5 days consecutively, 2 days off for 2 weeks followed by 2 weeks rest, 5 mg/kg bevacizumab intravenously on day 1 and 15

Treatment	Trial	Dosage and administration as reported in publication	Cycle length	Summary of dosage received in 1 cycle
	Pfeiffer (2020)	Trifluridine/tipiracil orally twice daily on day 1 to day 5 and day 8 to day 12 every 28 days + bevacizumab intravenously on day 1 and day 15 every 28 days		

ITC = indirect treatment comparison.

Pharmacoeconomic Review

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Abbreviations

anti-EGFR	anti–epidermal growth factor receptor
anti-VEGF	anti–vascular endothelial growth factor
BIA	budget impact analysis
BSA	body surface area
BSC	best supportive care
EQ-5D-5L	5-Level EQ-5D
G-CSF	granulocyte colony-stimulating factor
ICER	incremental cost-effectiveness ratio
KM	Kaplan-Meier
mCRC	metastatic colorectal cancer
NIHB	Non-Insured Health Benefits
NMA	network meta-analysis
OS	overall survival
PFS	progression-free survival
QALY	quality-adjusted life-year
WTP	willingness-to-pay

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Trifluridine-tipiracil (Lonsurf), 15 mg trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil, oral tablets
Submitted price	Trifluridine-tipiracil, 15 mg/6.14 mg: $76.25 per tablet Trifluridine-tipiracil, 20 mg/8.19 mg: $78.54 per tablet
Indication	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 drugs, and, if *RAS* wild-type, anti-EGFR drugs
Health Canada approval status	Not applicable; unlabelled indication
Health Canada review pathway	Not applicable; unlabelled indication
NOC date	Not applicable; unlabelled indication
Reimbursement request	Unlabelled indication: Trifluridine-tipiracil plus 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 drugs, and, if *RAS* wild-type, anti-EGFR drugs
Sponsor	Taiho Pharma Canada, Inc.
Submission history	Previously reviewed: Yes **Gastric cancer** Indicated for the treatment of adult patients with metastatic gastric cancer or adenocarcinoma of the gastroesophageal junction who have been previously treated with at least 2 prior lines of chemotherapy, including a fluoropyrimidine, a platinum, and either a taxane or irinotecan and if appropriate, with *HER2/neu*-targeted therapy Recommendation date: March 24, 2020 Recommendation: Reimburse with clinical criteria and/or conditions **Metastatic colorectal cancer** Indicated 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 drugs, and, if *RAS* wild-type, anti-EGFR drugs Recommendation date: July 6, 2018, and August 29, 2019 (resubmission) Recommendation: Do not reimburse

Anti-EGFR = anti-epidermal growth factor receptor; anti-VEGF = anti-vascular endothelial growth factor; NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

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 drugs, and, if *RAS* wild-type, anti-EGFR drugs
Treatment	Trifluridine-tipiracil plus bevacizumab
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 NMAs
Submitted results	ICER = $60,879 per QALY gained (incremental costs = $55,270; incremental QALYs = 0.98)
Key limitations	• The comparative efficacy and safety of trifluridine-tipiracil plus 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 plus 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 plus 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 plus 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 that treatment duration would be closely aligned with PFS. • The use of a PSM introduced 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 postprogression survival benefit that favoured trifluridine-tipiracil plus bevacizumab, for which there was no supporting evidence. • 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 naive comparisons of trifluridine-tipiracil plus 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: the use of full parametric survival curves for OS and PFS, the 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 plus bevacizumab is associated with higher costs (incremental costs = $100,657) and higher QALYs (incremental QALYs = 0.54) compared with BSC over a lifetime time horizon, resulting in an ICER of $195,000 per QALY gained.

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

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Conclusions

Based on the CADTH clinical review, trifluridine-tipiracil (Lonsurf) plus bevacizumab may be associated with prolonged overall survival (OS) and progression-free survival (PFS) but also an increased risk of treatment-related adverse events in patients with metastatic colorectal cancer (mCRC), compared to best supportive care (BSC). This is based on an assessment of a sponsor-submitted network meta-analysis (NMA), as there are no direct head-to-head trials comparing trifluridine-tipiracil plus bevacizumab with BSC. The CADTH clinical review noted that the indirect evidence submitted by the sponsor is associated with substantial uncertainty due to limitations, including significant between-trial heterogeneity, potential intransitivity, and the absence of health-related quality of life outcomes of importance to patients and clinicians.

In the CADTH base case, trifluridine-tipiracil plus bevacizumab was associated with an incremental cost-effectiveness ratio (ICER) of $195,000 per quality-adjusted life-year (QALY) gained, compared with BSC. The estimated ICER was higher than the sponsor's estimate, driven primarily by using alternative parametric distributions to extrapolate the OS of trifluridine-tipiracil alone and the revised approach for modelling treatment duration. As a result of the longer time to discontinuation for both drugs within the trifluridine-tipiracil plus bevacizumab regimen in the CADTH reanalysis, and the removal of a postprogression survival benefit that is unsupported by available evidence, there are no price reductions for trifluridine-tipiracil where a $50,000 per QALY gained threshold could be achieved. For trifluridine-tipiracil plus bevacizumab to be considered cost-effective at a $50,000 per QALY gained threshold, all components of the regimen would need to be reduced by 77.2%. The feasibility of obtaining a price reduction for bevacizumab is uncertain. Were a decision-maker to consider other willingness-to-pay (WTP) thresholds, a price reduction for trifluridine-tipiracil might be reached that could achieve cost-effectiveness for the trifluridine-tipiracil plus bevacizumab regimen.

There remains uncertainty in the magnitude of the benefit of trifluridine-tipiracil plus bevacizumab on PFS and OS when compared to BSC, as well as the impact of adverse events from treatments on quality of life.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process (specifically, information that pertains to the economic submission).

Patient and caregiver input was received from Colorectal Cancer Resource and Action Network via a survey and Colorectal Cancer Canada via interviews and a survey from residents in Canada. Patients stated that mCRC-induced symptoms most certainly interfere with their quality of life and their daily activities, with the most common symptoms being fatigue/weakness, bloody stools, abdominal cramping/gas/feeling bloated, and diarrhea. Fatigue resulting from the cancer was reported to be the most important symptom to control, according to patients and caregivers. Patients and caregivers noted that while previous treatments may have provided a clinical benefit in terms of response, that response was accompanied by incapacitating side effects such as fatigue, nausea, lack of energy, diarrhea, neuropathy, skin rash, lethargy, and flu-like

symptoms that prevented patients from engaging in life on any meaningful level. Patient input expressed the desire for a treatment that was orally administered or required minimal chair time, had minimal to no side effects, and could improve their physical condition, quality of life, and survival. Both groups highlighted that it was very important for a new therapy to improve quality of life if it does not extend OS. Patients who had experience with trifluridine-tipiracil plus bevacizumab noted that in comparison to previous treatments, the drug under review was more tolerable, reduced the incidence of adverse events with subjective symptoms, and improved quality of life and physical condition.

Clinician input was received from the Canadian Gastrointestinal Oncology Evidence Network with the Medical Advisory Board of Colorectal Cancer Canada (and other Colorectal Cancer Canada treating physicians) and the Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee. Clinician group input emphasized that treatment of mCRC is limited to fluoropyrimidine and irinotecan as well as fluoropyrimidine and oxaliplatin chemotherapy backbones with the use of bevacizumab and anti–epidermal growth factor receptor (anti-EGFR) monoclonal antibody therapy (either panitumumab or cetuximab) in tumour without a *RAS* mutation. Treatment of microsatellite instability–-high mCRC includes the use of checkpoint inhibitor pembrolizumab. In tumours that have a BRAF V600E variant, treatment would include the use of encorafenib with anti-EGFR monoclonal antibody therapy. Clinician group input noted that there are currently no funded treatment options for patients who received the therapies outlined previously following progression. It was noted that the combination of trifluridine-tipiracil plus bevacizumab would be a third-line therapy and would be used in patients who received the current standard of care options as outlined earlier and have experienced disease progression, have experienced intolerance, or have chosen to stop for personal reasons. Moreover, trifluridine-tipiracil plus bevacizumab would also be used for those with medical contraindications to earlier-line standard of care therapies.

CADTH-participating drug plans commented on trifluridine-tipiracil alone and regorafenib receiving do not reimburse recommendations from CADTH due to very modest OS gains, short PFS, low objective response rates, and the occurrence of serious side effects. Given the negative recommendation for trifluridine-tipiracil alone, drug plans queried whether patients who discontinued bevacizumab for reasons other than disease progression could still continue trifluridine-tipiracil as a monotherapy. Drug plans noted that there are confidential negotiated prices for bevacizumab.

Several of these concerns were addressed in the sponsor's model.

- Quality of life was incorporated into the sponsor's model through the use of the 5-Level EQ-5D (EQ-5D-5L) data captured in the SUNLIGHT trial to inform health state utilities.
- OS was incorporated into the sponsor's model and captured as an outcome (i.e., life-years).

CADTH was unable to address the following concerns raised from stakeholder input.

- While the sponsor's model permitted the inclusion of disutilities associated with adverse events, they were excluded from the sponsor's base case. Upon review, the values provided by the sponsor lacked face validity and thus were not included in CADTH reanalyses.

Economic Review

The current review is for trifluridine-tipiracil plus bevacizumab for adult patients with mCRC 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 drugs, and, if *RAS* wild-type, anti-EGFR drugs.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis of trifluridine-tipiracil plus bevacizumab compared with BSC.[1] The model population comprised adult patients 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 drugs, and, if *RAS* wild-type, anti-EGFR drugs,[1] based on the SUNLIGHT and RECOURSE trials.[2,3] The modelled population was aligned with the unlabelled indication of interest and the reimbursement request.

Trifluridine-tipiracil is available as 15 mg trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil at a submitted price of $76.25 and $78.54, respectively, per oral tablet.[1,4] The recommended dosage is 35 mg/m^2 (to a maximum of 80 mg per dose based on the trifluridine component) twice daily on day 1 to day 5 and day 8 to day 12 every 28 days as long as benefit is observed or until unacceptable toxicity occurs.[4] Trifluridine-tipiracil is to be used in combination with bevacizumab, which is available in 100 mg and 400 mg vials at a price of $347.00 and $1,388.00, respectively.[5] Bevacizumab has a recommended dosage of 5 mg/kg every 14 days.[6] In the sponsor's model, the estimated 28-day cost for trifluridine-tipiracil alone and bevacizumab alone, and trifluridine-tipiracil plus bevacizumab is $5,405, $2,786, and $8,191, respectively, assuming a patient weight of 74.01 kg and body surface area (BSA) of 1.83 m^2.[1] As trifluridine-tipiracil is an oral therapy with dose varying by BSA, the average number of tablets per dose was based on a log-normal probability density function of the BSA from the SUNLIGHT trial to determine the number of tablets required for each dosing strength formulation as specified in the product monograph.[2,4] Wastage was assumed for IV drugs (i.e., no vial sharing). As BSC is assumed to consist of interventions that focus on alleviating symptoms, improving quality of life, and addressing the physical, emotional, and psychosocial needs of patients, the sponsor assumed drug acquisition costs were $0.

The analysis was conducted from the perspective of the Canadian public health care payer. Costs and clinical outcomes (life-years and QALYs) were estimated over a lifetime time horizon of 28.3 years (28-day cycle length), discounted at a rate of 1.5% per annum.[1]

Model Structure

The sponsor submitted a partitioned survival model with 3 health states: progression-free, progressed disease, and death (Appendix 3, Figure 1).[1] The proportion of patients in each health state was from nonmutually exclusive survival curves. All patients entered the model in the preprogression health state,

where they received either trifluridine-tipiracil plus bevacizumab or BSC, with state occupancy defined by PFS.[7] During each cycle, patients either remained progression-free, transitioned to the progressive disease state, or progressed to death. The proportion of patients in the progressive disease state was calculated by subtracting the proportion of patients alive and progression-free (based on the PFS curve) from the proportion of patients alive (based on the OS curve). Patients in the postprogression state could either remain in the same state or move to death. Death was modelled as an absorbing state.

Model Inputs

Baseline patient characteristics in the model were reflective of the SUNLIGHT trial population (i.e., average age = 61.68 years; average weight = 74.01 kg; BSA = 1.83 m^2; proportion male = 52%).[2] Age and the proportion of the population who was male were used to assign age-specific and sex-specific mortality. Additionally, age was used to adjust utilities for aging. Weight and BSA were used to calculate treatment costs for treatments with weight-based or BSA-based dosing.

Key clinical efficacy inputs (i.e., OS and PFS) for trifluridine-tipiracil plus bevacizumab and BSC were based on the results of the sponsor's NMA.[7] The sponsor estimated PFS and OS for trifluridine-tipiracil alone from the SUNLIGHT trial and extrapolated the curves to derive PFS and OS for trifluridine-tipiracil plus bevacizumab and BSC by assuming proportional hazards and applying the hazard ratio for each outcome from the NMA to the reference trifluridine-tipiracil curve. Trifluridine-tipiracil alone was linked to trifluridine-tipiracil plus bevacizumab and BSC via the SUNLIGHT and RECOURSE clinical studies, respectively. Furthermore, the sponsor used a piecewise extrapolation approach, modelling survival using the clinical study Kaplan-Meier (KM) up to the point of cut-off and parametric estimation only thereafter. The chosen parametric survival distribution for OS and PFS for trifluridine-tipiracil alone was KM plus log-logistic and KM plus generalized gamma, respectively. Several parametric survival functions were fitted to the PFS and OS data to determine the best-fitting distribution based on the Akaike information criterion and Bayesian information criterion, and visual inspection. Treatment waning was explored by the sponsor. The sponsor's base case assumed no waning of the treatment effect. However, the sponsor submission included the option for no effect beyond trial duration and a decline in effect up to a prespecified time.

The sponsor modelled treatment duration based on the average of the median durations of treatment as reported in the studies that contributed to the NMA for each treatment of interest.[7] Furthermore, the sponsor assumed the proportion of patients receiving treatment was equal to OS until the average of the median treatment durations was reached. After this point, patients were assumed to no longer be on treatment and did not incur treatment costs.

Health state utility values applied in the economic model were based on the results of the EQ-5D-5L questionnaire administered to the population in the SUNLIGHT trial.[2] Disutilities were assumed to be captured by the health state utility values. However, the sponsor included the option to include disutilities sourced from the SUNLIGHT trial for anemia, neutropenia, and hypertension and the literature for hand foot skin reaction, diarrhea, fatigue, and rash.[2,8,9]

The sponsor's base case included costs for drug acquisition, drug administration, supportive medication, health care resource use, adverse event care, and mortality. Drug acquisition costs for trifluridine-tipiracil were based on the sponsor-submitted price and the price of biosimilar bevacizumab was sourced from a previous CADTH reimbursement review report.[1,10] Drug administration costs for treatments being administered in a hospital setting were estimated based on workload time specified in the Cancer Care Ontario regimen monographs[11] and chair costs estimated by Tam et al. (2013).[9] Supportive medication was calculated based on Cancer Care Ontario guidelines, with emesis risk assigned to each comparator as outlined in their respective Cancer Care Ontario regimen monographs.[11,12] Health care resource use was estimated based on an internal survey of 5 physicians conducted by the sponsor.[13] Unit costs for resources were sourced from provincial fee manuals, the Government of Canada Job Bank, and the Canadian Institute for Health Information.[14-18] Grade 3 and grade 4 adverse event care costs were sourced from the Canadian Institute for Health Information and the Ontario *Schedule of Benefits: Physician Services Under the Health Insurance Act (June 29, 2023 (effective July 24, 2023))*.[14,17,19] The sponsor assumed that 10% of adverse events would be treated in an inpatient setting, 21% would be treated in an emergency department, and 69% would be treated by a clinician visit. Incidence rates for adverse events were sourced from the SUNLIGHT and RECOURSE trials for trifluridine-tipiracil plus bevacizumab and BSC, respectively.[2,3] Lastly, a 1-time terminal care cost was included, encompassing expenses related to end-of-life care based on estimates from the literature.[20,21]

Summary of Sponsor's Economic Evaluation Results

All analyses were run probabilistically (5,000 iterations for the base case and scenario analyses). The deterministic and probabilistic results were similar. The probabilistic findings are presented as follows.

Base-Case Results

In the sponsor's base case, trifluridine-tipiracil plus bevacizumab was more costly (incremental cost = $55,270) and more effective (incremental QALYs = 0.98) than BSC, resulting in an ICER of $60,879 per QALY gained over a lifetime horizon (Table 3). Approximately 73.7% of incremental QALYs were gained in the extrapolated portion of the model (i.e., after the first 19 cycles for which there was observed data from the SUNLIGHT trial). In the sponsor's analysis, trifluridine-tipiracil plus bevacizumab had a 28% probability of being cost-effective at a WTP threshold of $50,000 per QALY gained. Results were driven by the drug acquisition costs of trifluridine-tipiracil plus bevacizumab (incremental drug acquisition costs = $50,485). The submitted analysis is based on the publicly available list prices of all treatments other than trifluridine-tipiracil.

Sensitivity and Scenario Analysis Results

The sponsor conducted various scenario analyses, encompassing considerations such as additional comparators (regorafenib and trifluridine-tipiracil alone), alternative time horizons, discount rates, treatment waning effects, alternative parametric survival curve distributions for the reference treatment for PFS and OS, comparing trifluridine-tipiracil plus bevacizumab to BSC using a naive comparison of the best fit parametric curves instead of NMA, excluding health care resource use costs, adjusting the proportion of patients who

receive bevacizumab in a hospital setting, adopting utility values estimated from the CORRECT trial, and removing the age-adjustment applied to utility values.

The sponsor conducted a scenario analysis from a societal perspective. This analysis included lost wages using a friction cost approach that accounted for the employment rate, average annual salary, and friction period. In this analysis, relative to BSC, trifluridine-tipiracil plus bevacizumab was associated with an ICER of $55,518 per QALY gained. This result was similar to the sponsor's base-case analysis using a health care payer perspective.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. BSC ($/QALY)
BSC	31,141	Reference	0.58	Reference	Reference
Trifluridine-tipiracil plus bevacizumab	86,411	55,270	1.55	0.98	60,879

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.
Source: Sponsor's pharmacoeconomic submission.[1]

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the economic analysis.

- **The comparative clinical efficacy (OS and PFS) of trifluridine-tipiracil plus bevacizumab versus BSC is uncertain.** There is a lack of direct head-to-head evidence comparing trifluridine-tipiracil plus bevacizumab to BSC. To estimate PFS and OS for trifluridine-tipiracil plus bevacizumab and BSC, the sponsor first extrapolated the available PFS and OS data for trifluridine-tipiracil alone from the SUNLIGHT trial. The sponsor then applied the findings of an NMA, assuming proportional hazards and applying the relevant hazard ratio for each outcome and treatment from the NMA to the reference trifluridine-tipiracil curve to derive PFS and OS for trifluridine-tipiracil plus bevacizumab and BSC. The CADTH Clinical Review Report noted that trifluridine-tipiracil plus bevacizumab may be associated with prolonged OS and PFS compared to BSC, but the magnitude of these differences is associated with substantial uncertainty due to several limitations (refer to the CADTH Clinical Review Report for details) that impact the internal and external validity of the sponsor's NMA, such as significant clinical heterogeneities between the included trials. Moreover, the sponsor's approach to modelling OS and PFS relies on the proportional hazards assumption being valid. Additional information was requested from the sponsor to support this approach. Although CADTH's assessment of the additional information found that the proportional hazards assumption may hold, there is some uncertainty with this assumption. Extrapolating the proportional hazards assumption across different comparisons (i.e., comparators from the NMA) has a lack of statistical foundation.

  Additionally, the sponsor's estimates for OS and PFS in the extrapolation period for trifluridine-tipiracil plus bevacizumab and BSC did not align with clinical expert feedback elicited from CADTH for this

review. The sponsor's selected extrapolations for trifluridine-tipiracil plus bevacizumab projected OS estimates of approximately 13.3%, 7.3%, and 3.17% at year 3, year 5, and year 10, respectively. For patients who received BSC, approximately 0.9%, 0.2%, and 0.03% of patients were projected to remain alive at year 3, year 5, and year 10, respectively. In the sponsor's model, long-term survival occurs due to OS approaching an asymptote in which the hazard rate for mortality decreases to the point where there is only a small rate of death by year 10 (0.9% and 2.2% by year 10 for trifluridine-tipiracil plus bevacizumab and BSC, respectively). Clinical experts indicated that the mortality rate would likely increase over time rather than decrease. Moreover, input indicated that based on the natural history of disease in the indicated population, it is unlikely that patients on BSC would remain alive after 3 years and that trifluridine-tipiracil plus bevacizumab estimates should be at least halved beyond 3 years. Input further indicated that the PFS for trifluridine-tipiracil plus bevacizumab is likely overestimated. The sponsor estimates PFS to be approximately 4.8%, 2.4%, and 0.9% in year 3, year 5, and year 10, respectively. Experts commented that PFS should be approximately 2%, 1% or less, and 0% in year 3, year 5, and year 10, respectively.

Lastly, the sponsor employed a piecewise extrapolation approach, modelling survival using the clinical study KM data up to cycle 19 (approximately 1.5 years) and using parametric estimation exclusively thereafter. By fitting the parametric curve to all observed data, a more realistic hazard rate was derived by effectively mitigating the "stepped" characteristic observed in a KM curve, which is generally preferred. CADTH notes that the sponsor applied a hazard ratio to the trifluridine-tipiracil alone curve to extrapolate data for both trifluridine-tipiracil plus bevacizumab and BSC, rather than independently modelling the KM data. Consequently, the adoption of a fully parametric curve in the sponsor's base case has marginal influence.

  - In the CADTH base case, CADTH changed the OS base curve for trifluridine-tipiracil alone to the gamma distribution. This was based on fit and clinical expert opinion regarding the changing mortality rate over time and the expectation of survival at 3 years, 5 years, and 10 years. CADTH notes that this change also resolved the limitation pertaining to the postprogression survival benefit discussed as follows. CADTH was unable to address clinical expert feedback received for PFS as changing the distribution to align with their input resulted in a postprogression benefit for which there was no supporting evidence.
  - Additionally, the full parametric survival curve was used to estimate OS and PFS in the CADTH base case.

- **Treatment duration was underestimated in the sponsor's base case.** The sponsor estimated treatment duration by using the median treatment duration reported in the studies for each treatment of interest included in the NMA.[7] As the submitted model did not include a treatment discontinuation curve, the sponsor assumed that the proportion of patients receiving treatment was equal to OS until the average of the median treatment durations was reached. After this point, it was assumed that all patients would discontinue treatment such that no patients received trifluridine-tipiracil plus bevacizumab after cycle 5. First, clinical expert input received by CADTH noted that treatment duration should closely align with PFS. Therefore, the sponsor's approach, which aligns the proportion

of patients on treatment with OS, likely overestimates the proportion of patients receiving treatment in clinical practice until cycle 5. For example, at cycle 5, the sponsor assumes that 82% of patients receiving trifluridine-tipiracil and bevacizumab are on treatment, while PFS indicates that 53% of patients are progression-free. Second, there is a misalignment between costs and efficacy as patients continue to receive the benefits of treatment but do not incur the corresponding treatment cost. Patients receiving trifluridine-tipiracil plus bevacizumab were assumed to cease treatment after cycle 5 but efficacy is modelled based on the SUNLIGHT trial in which patients may have continued to receive treatment beyond 5 months (maximum duration of treatment = 18.5 months). For example, in cycle 6, 0% of patients were actively receiving trifluridine-tipiracil plus bevacizumab (treatment cost = $0) but 48% of patients were progression-free; in cycle 25, 10% of patients were progression-free but 0% were incurring treatment costs.

Lastly, clinical expert input suggests that PFS may still slightly overestimate the proportion of patients receiving treatment as patients may discontinue treatment due to other reasons such as toxicity. Data from the SUNLIGHT trial supports the notion that the vast majority of patients who discontinued trifluridine-tipiracil plus bevacizumab discontinued due to progression (77.6%).[2] CADTH notes that the product monographs for trifluridine-tipiracil and bevacizumab do not specify treatment duration and do not explicitly state to discontinue treatment upon progression.[4,6]

  - In the CADTH base case, the proportion of patients on treatment was set equal to PFS. CADTH conducted an exploratory analysis to investigate the impact of reducing treatment duration by estimating the proportion of patients who discontinued treatment for reasons related to progression (i.e., those who discontinued due to other reasons such as adverse events not being included), multiplied by the proportion in PFS.

- **Model structure may overestimate comparative efficacy.** Results from the sponsor's model suggested that trifluridine-tipiracil plus bevacizumab was associated with additional survival benefits after progression (i.e., life-years for trifluridine-tipiracil plus bevacizumab in the progressed disease health state were nearly 2 times greater than those for BSC). However, clinical experts consulted by CADTH noted that there is no rationale to support this as there is no clear mechanism by which trifluridine-tipiracil plus bevacizumab would continue to provide a survival benefit after progression versus BSC. The sponsor's use of a partitioned survival model introduced structural assumptions about the relationship between PFS and OS that likely do not accurately reflect causal relationships within the disease pathway — for example, that PFS and OS are assumed to be independent. These assumptions may produce a biased postprogression survival benefit that favours trifluridine-tipiracil plus bevacizumab, as observed in the sponsor's base case.
  - The postprogression benefit was largely removed while addressing the limitations outlined previously and therefore was addressed in the CADTH base case.
- **Health state utility values are associated with uncertainty.** The sponsor derived health state utility estimates from an analysis of EQ-5D-5L index data collected in the SUNLIGHT trial with Canadian tariffs applied. Additionally, the sponsor adjusted baseline utilities for age.[22] However, in selecting this approach, patients receiving trifluridine-tipiracil plus bevacizumab and BSC experience a

preprogression quality of life (0.829) that closely mirrors the average quality of life reported by the typical person in Canada (0.863).[1,23] Moreover, there is only a marginal decrease in quality of life (0.784) for those with progressed disease. Clinical expert input obtained by CADTH noted that the quality of life for those who have not progressed is higher than expected. It was noted that while patients need to be relatively healthy to proceed to third-line therapy, the quality of life is higher than expected due to a patient's progressing cancer and preceding treatments. Second, the incremental difference between the progression-free and progressed disease health states was noted to be significantly smaller than expected, as the patient population from the SUNLIGHT trial were heavily pretreated, while those who experience progression have very few, if any, remaining effective anticancer therapy options. The sponsor provided alternative utility values sourced from the CORRECT trial (progression-free = 0.81; progressed disease = 0.71). Clinical expert input found the incremental difference between the 2 health states to be more reasonable for the indicated patient population.

  - In the CADTH base case, CADTH adopted alternative utility values derived from the CORRECT trial.[1]

- **The impact of adverse events on the cost-effectiveness of trifluridine-tipiracil plus bevacizumab is uncertain.** The sponsor did not include disutilities related to the occurrence of adverse events in the base-case analysis but, rather, assumed that disutilities were captured by the health state utility values. This approach was not aligned with CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada — 4th Edition*, which recommends the adjustment of the utility for a specific health state by applying a disutility for an adverse event to allow the utility for the health state with an adverse event to be estimated. While the sponsor's model permitted the inclusion of disutilities for grade 3 and grade 4 anemia, neutropenia, hypertension, hand foot skin reaction, diarrhea, fatigue, and rash, the reported disutilities lacked face validity. For example, rash was associated with a utility gain of 0.09 as included in the sponsor's model.[1] While the sponsor cited Tam et al.[9] as the source for this value, CADTH was unable to validate the sponsor's claim of a health benefit in the reference provided and is unable to ascertain how quality of life is improved for patients who have a grade 3 or grade 4 rash.[9] Clinical expert input highlighted the importance of including grade 4 adverse events in the economic model as these events are more likely to require hospital treatment and have a negative impact on a patient's quality of life.

  Additionally, the incidence rate of grade 3 and grade 4 adverse events for trifluridine-tipiracil plus bevacizumab and BSC was based on naive comparisons, without adjustment or accounting for differences in patient characteristics. The rate of adverse events is used to calculate adverse event costs in the sponsor's base case. Owing to the direct use of clinical trial data, it is not possible to determine if any observed differences between the therapies are solely due to the treatment or, rather, due to bias or confounding factors. CADTH notes that adverse events were included in the sponsor's NMA.[7] The CADTH Clinical Review Report notes that based on the results of the sponsor-submitted NMA, patients receiving trifluridine-tipiracil plus bevacizumab may be associated with an increased risk of treatment-related adverse events, compared to BSC. However, the magnitude of these

differences was uncertain due to substantial uncertainty related to several limitations (refer to the CADTH Clinical Review Report for details), such as significant clinical heterogeneities between the included trials.

- This limitation could not be addressed by CADTH owing to the sponsor's model flexibility and lack of clinical data. The magnitude of the impact of this limitation is unknown given that the comparative rate of adverse events between trifluridine-tipiracil plus bevacizumab and BSC is uncertain and as CADTH was unable to stratify by adverse event grade. CADTH notes that adjusting the proportion of adverse events managed by a clinician visit has minimal impact on results.

- **The model was cumbersome and lacked transparency.** CADTH noted that the sponsor's submission was overly complex, making simple validation checks time-consuming. The Model Parameters and Results sheets unnecessarily relied on macros. For example, the Results' sheet contained both deterministic and probabilistic results but automatically reset to view probabilistic results if the sheet was exited. Additionally, the sponsor's submitted model included numerous IFERROR statements, which lead to situations in which the parameter value is overwritten with an alternative value without alerting the user to the automatic overwriting. The systematic use of IFERROR statements makes thorough auditing of the sponsor's model impractical, as it remains unclear whether the model is running inappropriately by overriding errors.
  - CADTH was unable to address this limitation and notes that a thorough validation of the sponsor's model was not possible.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (refer to Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
A lifetime horizon (28.3 years) was adopted by the sponsor.	According to CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada — 4th Edition*, the time horizon selected in the economic model should be long enough to capture the costs and effects of treatment. Clinical expert input received by CADTH noted that based on the natural history of disease in the indicated population, it is unlikely that patients would remain alive beyond 10 years. In the sponsor's base case, the time horizon has a notable impact on the results due to OS having a long tail that projects survival beyond 10 years. However, shortening the time horizon in the CADTH base case has minimal impact as the selected OS curve no longer predicts extended survival beyond 10 years.
Bevacizumab will only be administered in a hospital setting.	Reasonable. Clinical expert input received by CADTH noted that nearly 100% of bevacizumab administration would occur in a hospital setting.

Sponsor's key assumption	CADTH comment
All treatments are administered at a dose intensity of 100%.	Reasonable. Assuming a dose intensity of 100% is a conservative assumption that only impacts treatment acquisition costs. CADTH notes that the product monograph for trifluridine-tipiracil outlines dose interruption, resumption, and reduction criteria for patients experiencing hematological and/or nonhematological toxicities.[4] Per the product monograph, there are no recommended dose reductions for bevacizumab.[6]
10% of adverse events will be treated in an inpatient setting, 21% in an emergency department, and 69% by a clinician visit.	Uncertain. Clinical expert input received by CADTH noted that grade 4 adverse events pertaining to toxicity would be treated in hospital. However, CADTH was unable to stratify adverse events by severity. Without this stratification, clinical expert input noted that a greater proportion of adverse events may be managed by a clinician visit. However, the proportion treated via a clinician visit would vary depending on the type of practice (i.e., academic vs. community) and the resources in place (e.g., nurse practitioner, physician assistant, oncology urgent care clinic).

OS = overall survival; vs. = versus.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH undertook reanalyses that addressed key limitations within the submitted economic model, as summarized in Table 5. The CADTH base case was derived by making changes in model parameter values and assumptions in consultation with clinical experts. CADTH was unable to address the other limitations of the model, including the magnitude of the benefit of trifluridine-tipiracil plus bevacizumab on PFS and OS and the impact of adverse events on patient quality of life.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH base case		
1. Use of KM data when modelling OS and PFS	Applied KM data until cycle 19 (approximately 1.5 years)	No KM data applied; full parametric survival analysis curve used
2. Choice of parametric distribution for OS	Log-logistic	Generalized gamma
3. Treatment duration	Equal to OS until the average of the median treatment durations was reached, after which it is assumed that all patients discontinue treatment	Equal to PFS
4. Health state utility values	Sourced from the SUNLIGHT trial	Sourced from the CORRECT trial
CADTH base case	Reanalysis 1 + 2 + 3 + 4	

KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival.

CADTH undertook a stepped analysis, incorporating each change proposed in Table 5 into the sponsor's base case to highlight the impact of each change (refer to Table 6; disaggregated results are presented in Appendix 4, Table 11). All CADTH probabilistic reanalyses were based on 5,000 iterations.

Results from the CADTH base case suggest that trifluridine-tipiracil plus bevacizumab was associated with higher costs (incremental costs = $100,657) and higher QALYs (incremental QALYs = 0.54) compared with BSC over a lifetime time horizon, resulting in an ICER of $195,000 per QALY gained. In the CADTH base case, trifluridine-tipiracil plus bevacizumab had a 0% probability of being cost-effective at a WTP threshold of $50,000 per QALY.

In the CADTH base case, results were driven by predicted differences in QALYs between trifluridine-tipiracil plus bevacizumab and BSC and drug acquisition costs. Drug acquisition costs represent 73% of total costs for trifluridine-tipiracil plus bevacizumab. The CADTH base case predicts that trifluridine-tipiracil plus bevacizumab will generate 1.05 QALYs over a lifetime horizon; of these, 48.9% of the incremental benefits were accrued after the first 19 cycles (i.e., beyond the duration of the SUNLIGHT trial).

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis[a]	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Sponsor's base case	BSC	31,139	0.56	Reference
	Trifluridine-tipiracil plus bevacizumab	85,421	1.55	55,198
CADTH reanalysis 1: Use of KM data when modelling OS and PFS	BSC	31,147	0.57	Reference
	Trifluridine-tipiracil plus bevacizumab	85,399	1.57	54,172
CADTH reanalysis 2: Choice of parametric distribution for OS	BSC	31,105	0.55	Reference
	Trifluridine-tipiracil plus bevacizumab	84,464	1.09	97,546
CADTH reanalysis 3: Treatment duration	BSC	31,156	0.56	Reference
	Trifluridine-tipiracil plus bevacizumab	138,632	1.55	109,289
CADTH reanalysis 4: Health state utility values	BSC	31,139	0.53	Reference
	Trifluridine-tipiracil plus bevacizumab	85,421	1.46	58,191
CADTH base case (1 + 2 + 3 + 4) Probabilistic	BSC	31,106	0.52	Reference
	Trifluridine-tipiracil plus bevacizumab	131,763	1.05	195,000

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; QALY = quality-adjusted life-year; OS = overall survival; PFS = progression-free survival.

[a]Deterministic analysis, unless otherwise stated. The probabilistic and deterministic results of the sponsor's base case were similar.

Scenario Analysis Results

CADTH undertook price reduction analyses based on the sponsor's results and CADTH's reanalyses, applying price reductions to trifluridine-tipiracil only. The results of CADTH reanalysis suggested that there is no price reduction upon which trifluridine-tipiracil plus bevacizumab would be considered cost-effective relative to BSC at the WTP threshold of $50,000 per QALY gained (refer to Table 7). When reducing the price of trifluridine-tipiracil alone by 100%, the drug acquisition cost of the bevacizumab component of the combination regimen represents 86% of the incremental cost. CADTH notes that a price reduction of approximately 74% is required to achieve an ICER of $100,000 per QALY gained.

Table 7: CADTH Price Reduction Analyses

Analysis	ICERs for trifluridine-tipiracil plus bevacizumab vs. BSC ($/QALY)	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
No price reduction	55,198	186,642
10%	51,867	174,948
20%	48,537	163,258
30%	45,206	151,564
40%	41,877	139,873
50%	38,545	128,180
60%	35,216	116,489
70%	31,855	104,796
80%	28,555	93,105
90%	25,224	81,411
100%	21,895	69,721

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Although, based on the CADTH base case, there is no price reduction upon which trifluridine-tipiracil plus bevacizumab would be considered cost-effective at the WTP threshold of $50,000 per QALY gained, CADTH acknowledges that a 100% price reduction could not be expected to be practically implemented by decision-makers. CADTH explored an analysis to determine the price reduction required for the full regimen of trifluridine-tipiracil plus bevacizumab to be cost-effective at a WTP threshold of $50,000 per QALY gained. In this scenario, a 77.2% price reduction for both trifluridine-tipiracil and bevacizumab is required. CADTH presented this analysis to further highlight pricing considerations for bevacizumab in this setting, acknowledging that there are different manufacturers responsible for the treatment, and as such, implementing this approach may not be feasible.

CADTH undertook an exploratory analysis to assess the impact of multiplying the proportion of patients on trifluridine-tipiracil plus bevacizumab by 77.6% to approximate a value for the proportion of patients who discontinued for reasons related to progression. Results from this exploratory analysis are presented in Table 12. The results align with the CADTH base case in that there is no price reduction upon which

trifluridine-tipiracil plus bevacizumab would be considered cost-effective at the WTP threshold of $50,000 per QALY gained.

Issues for Consideration

- Trifluridine-tipiracil may be self-administered and is the only oral advanced therapy drug currently available for the indicated population. Ease of administration was noted as an important aspect of treatment for patients.
- CADTH has previously reviewed trifluridine-tipiracil alone and regorafenib for mCRC.[24,25] The cost-effectiveness results of the trifluridine-tipiracil alone evaluation may not be directly comparable to those in the current review, owing to differences in model structure, clinical effectiveness parameters, health state utility values, and cost inputs. Both treatments received a do not reimburse recommendation from the CADTH pan-Canadian Oncology Drug Review Expert Review Committee.
- Clinical expert input noted that concomitant use of granulocyte colony-stimulating factor (G-CSF) should be considered as it is current clinical practice in some jurisdictions to receive G-CSF concomitantly with trifluridine-tipiracil alone. However, concomitant use of G-CSF was not considered in the submitted analysis.

Overall Conclusions

Based on the CADTH clinical review, trifluridine-tipiracil plus bevacizumab may be associated with prolonged OS and PFS but also an increased risk of treatment-related adverse events in patients with mCRC compared to BSC. This is based on an assessment of a sponsor-submitted NMA, as there are no direct head-to-head trials comparing trifluridine-tipiracil plus bevacizumab versus BSC. The CADTH clinical review noted that the indirect evidence submitted by the sponsor has substantial uncertainty in the findings of the NMA due to limitations, including significant between-trial heterogeneity, potential intransitivity, and the absence of health-related quality of life outcomes of importance to patients and clinicians.

CADTH identified several limitations with the sponsor's economic submission that could be addressed through reanalyses. For the CADTH base-case analysis, CADTH used the full parametric survival curve for OS and PFS, applied a generalized gamma distribution to extrapolate OS, set treatment duration equal to PFS, and adopted alternative health state utility values from the CORRECT trial. In the CADTH base case, trifluridine-tipiracil plus bevacizumab was associated with an ICER of $195,000 per QALY gained, compared with BSC. The estimated ICER was higher than the sponsor's estimate, driven primarily by using alternative parametric distributions to extrapolate the OS of trifluridine-tipiracil alone and the revised approach for modelling treatment duration.

As a result of the longer time to discontinuation for both drugs within the trifluridine-tipiracil plus bevacizumab regimen in the CADTH reanalysis, and the removal of a postprogression survival benefit that is unsupported by available evidence, there are no price reductions for trifluridine-tipiracil where a $50,000 per QALY gained threshold could be achieved. Were a decision-maker to consider other WTP thresholds, a price reduction for trifluridine-tipiracil might be reached that could achieve cost-effectiveness for the trifluridine-tipiracil plus bevacizumab regimen. For example, using the CADTH base case, a 74% price reduction

could achieve an ICER of $100,000 per QALY gained. CADTH explored an analysis to determine the price reduction required for the full regimen of trifluridine-tipiracil plus bevacizumab to be cost-effective at a WTP threshold of $50,000 per QALY gained. In this scenario, a 77.2% price reduction for both trifluridine-tipiracil and bevacizumab is required. CADTH presented this analysis to further highlight pricing considerations for bevacizumab in this setting, acknowledging that there are different manufacturers responsible for the treatment, and as such, implementing this approach may not be feasible.

There remains uncertainty in the magnitude of the benefit of trifluridine-tipiracil plus bevacizumab on PFS and OS when compared to BSC, as well as the impact of adverse events from treatments on quality of life.

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Appendix 1: Cost Comparison Table

Note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s) and drug plan. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for Third-Line or Later-Line Treatment of Metastatic Colorectal Cancer

Treatment	Strength/ concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	28-day cost ($)
Trifluridine-tipiracil (Lonsurf)	**15 mg trifluridine/ 6.14 mg tipiracil** **20 mg trifluridine/ 8.19 mg tipiracil**	**Tablet**	**76.2500** **78.5385**	**35 mg/m^2 (to a maximum of 80 mg per dose based on the trifluridine component) twice daily on Days 1 to 5 and Days 8 to 12 every 28 days[a]**	**168.30**	**4,712**
Bevacizumab	25 mg/mL	100 mg vial 400 mg vial	347.0000 1,388.0000	5 mg/kg every 14 days	99.14	2,776
Trifluridine-tipiracil plus bevacizumab					321.90	7,488

Note: All prices are from the Delta PA IQVIA database (accessed September 2023), unless otherwise indicated, and do not include dispensing fees. For dosing that depends on weight or body surface area, CADTH assumed 75 kg or 1.80 m^2. Total cost estimates per regimen are based on the cheapest combination of the component drugs, with wastage considered for single-use vials.

[a]The product monograph details the number of tablets and tablet strength required per dose, based on a patient's BSA. As such, cost calculations assume three 20 mg tablets are required per dose according to the assumed patient BSA noted previously.

Appendix 2: Submission Quality

Note that this appendix has not been copy-edited.

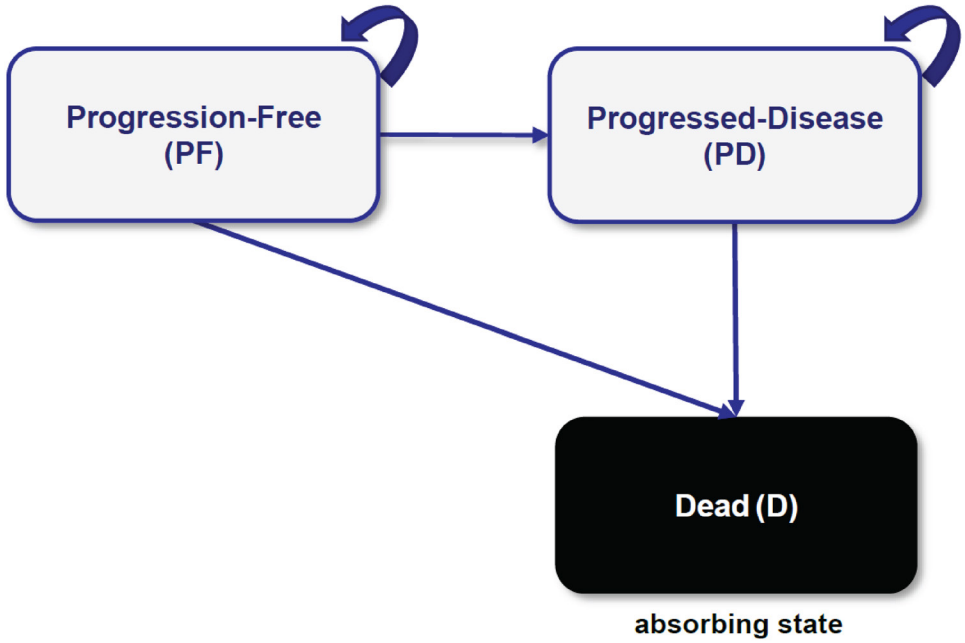
Table 9: Submission Quality

Description	Yes/no	Comment
Population is relevant, with no critical intervention missing, and no relevant outcome missing	Yes	No comment.
Model has been adequately programmed and has sufficient face validity	No	Refer to key limitations.
Model structure is adequate for decision problem	No	The PSM further introduces structural assumptions about the relationship between PFS and OS (i.e., nonmutually exclusive curves), which is potentially problematic since they are likely dependent outcomes. Clinical expert input suggested that survival is linked to the occurrence of progressive disease and thus the transition probability to death should vary for patients within the progression-free state compared to those in the progressed disease state.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	Yes	No comment.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	Yes	No comment.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	No	Refer to key limitations.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Note that this appendix has not been copy-edited.

Figure 1: Model Structure



Source: Sponsor's pharmacoeconomic submission.[1]

Table 10: Disaggregated Summary of the Sponsor's Economic Evaluation Results

Parameter	Trifluridine-tipiracil plus bevacizumab	BSC	Incremental
Discounted LYs			
Total	1.92	0.72	1.20
Progression-free	1.03	0.25	0.78
Progressed disease	0.89	0.48	0.41
Discounted QALYs			
Total	1.55	0.58	0.98
Progression-free	0.85	0.20	0.65
Progressed disease	0.70	0.37	0.33
Discounted costs ($)			
Total	86,411	31,141	55,270

Parameter	Trifluridine-tipiracil plus bevacizumab	BSC	Incremental
Treatment acquisition costs	50,485	0	50,485
Supportive medication costs	7	0	7
Administration costs	1,398	0	1,398
Health care resource use costs	2,945	1,288	1,657
Adverse event costs	2,761	414	2,347
Mortality costs	28,814	29,439	625
ICER ($/QALY)	60,879		

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note that this appendix has not been copy-edited.

Table 11: Disaggregated Summary of CADTH's Economic Evaluation Results

Parameter	Trifluridine-tipiracil plus bevacizumab	BSC	Incremental
Discounted LYs			
Total	1.36	0.69	0.67
Progression-free	0.88	0.25	0.63
Progressed disease	0.48	0.44	0.03
Discounted QALYs			
Total	1.05	0.52	0.54
Progression-free	0.72	0.20	0.51
Progressed disease	0.34	0.32	0.02
Discounted costs ($)			
Total	131,763	31,106	100,657
Treatment acquisition costs	95,602	0	95,602
Supportive medication costs	14	0	14
Administration costs	2,658	0	2,658
Health care resource use costs	1,982	1,239	742
Adverse event costs	2,353	415	1,938
Mortality costs	29,154	29,451	297
ICER ($/QALY)	195,000		

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

Scenario Analyses

Table 12: Summary of Exploratory Analyses Conducted on CADTH Base Case

Analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALYs)
CADTH base case	BSC	31,106	0.52	Reference
	Trifluridine-tipiracil plus bevacizumab	131,763	1.05	195,000
CADTH exploratory analysis: reduction in the proportion of patients receiving trifluridine-tipiracil plus bevacizumab relative to PFS	BSC	31,155	0.52	Reference
	Trifluridine-tipiracil plus bevacizumab	110,462	1.06	154,178

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Note that this appendix has not been copy-edited.

Table 13: Summary of Key Takeaways

Key takeaways of the BIA
• CADTH identified the following key limitations with the sponsor's analysis: the number of eligible patients is uncertain, the treatment duration for trifluridine-tipiracil plus 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 plus 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 drugs, and, if *RAS* wild-type, anti-EGFR drugs, 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.

Summary of Sponsor's Budget Impact Analysis

In the submitted budget impact analysis (BIA), the sponsor assessed the budget impact of reimbursing trifluridine-tipiracil plus bevacizumab for use by adult patients 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 drugs, and, if *RAS* wild-type, anti-EGFR drugs.[26] The BIA was undertaken from the perspective of a Canadian public payer over a 3-year time horizon (2024 to 2026) using an epidemiologic approach. The sponsor's pan-Canadian estimates reflect the aggregated results from provincial budgets (excluding Quebec), as well as the Non-Insured Health Benefits (NIHB) program. Data informing the model were obtained from various sources, including the published literature, the sponsor's internal data, and input from clinical experts consulted by the sponsor.

The sponsor's analysis included drug acquisition costs, assuming wastage. Costs pertaining to drug administration, adverse events, health care resource utilization, pharmacy markups, co-payments, and end-of-life care were included in scenario analyses. Key inputs to the BIA are documented in Table 14.

The sponsor's BIA also included the following key assumptions:

- The price of bevacizumab was based on publicly available sources.
- 70% of the population in Ontario, New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador were assumed to be publicly insured. 100% of residents in all other provinces and the NIHB population were assumed to be publicly insured.
- Time on treatment estimates from clinical trials were assumed to represent treatment duration patterns in Canada.

Table 14: Summary of Key Model Parameters

Parameter	Sponsor's estimate (year 1/year 2/year 3)
Target population	
Incidence of colorectal cancer per 100,000 people[27]	Males = 61.3; females = 49.3
Average annual percent change in incidence[28]	Males = −0.8%; females = −1.1%
New cases diagnosed as metastatic (stage IV)[29]	25.5%
Proportion of all incident CRC cases that are recurrent[29]	30.5%
Proportion of incident stage IV CRC cases among recurrent[29]	65.6%
Proportion of patients with mCRC receiving first-line treatment[30]	93%
Proportion of patients with mCRC receiving second-line treatment after first-line treatment[30]	72%
Proportion of patients with mCRC receiving third-line treatment after second-line treatment[30]	58%
Proportion of patients receiving third-line treatment that are *KRAS* mutant[30]	32%
Proportion of patients with mCRC receiving fourth-line treatment after third-line treatment[30]	29%
Proportion of patients with mCRC treated with third-line treatment that receive fourth-line treatment that are *KRAS* wild-type[30]	70%
Number of patients eligible for drug under review	1,059 / 1,066 / 1,073
Market uptake (3 years)	
Uptake (reference scenario) Trifluridine-tipiracil plus bevacizumab BSC	 0% / 0% / 0% 100% / 100% / 100%
Uptake (new drug scenario) Trifluridine-tipiracil plus bevacizumab BSC	 64.7% / 77.1% / 86.2% 35.3% / 22.9% / 13.8%
Cost of treatment (per patient)	
Annual cost of treatment Trifluridine-tipiracil plus bevacizumab BSC	 $106,482 $0

BSC = best supportive care; CRC = colorectal cancer; mCRC = metastatic colorectal cancer.

Summary of the Sponsor's BIA Results

The sponsor estimated that the 3-year budget impact of reimbursing trifluridine-tipiracil plus bevacizumab for the treatment of adult patients with mCRC would be $110,993,278 (Year 1: $31,235,958; Year 2: $37,485,914; Year 3: $42,271,406).

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **The number of patients eligible to receive trifluridine-tipiracil plus bevacizumab is uncertain:** The sponsor estimated the number of eligible patients based on estimates from a variety of sources, including based on data from Cerner Enviza.[30] It was estimated that 93% of patients with mCRC receive first-line therapy (1L) and, of those, 72% receive second-line therapy (2L). Of those who have received 2L therapy, 58% receive third-line (3L) therapy, of which, 32% are *KRAS* mutant and would be eligible for trifluridine-tipiracil plus bevacizumab. Additionally, of those who have received 3L therapy, 29% receive fourth-line (4L) therapy and 70% are *KRAS* wild-type and eligible for trifluridine-tipiracil plus bevacizumab. Clinical expert input received by CADTH noted that there are uncertainties in the sponsor's estimates. First, clinical expert input obtained by CADTH noted that the proportion of patients who receive 2L may be closer to 80% based on their experience. Additionally, the proportion of patients eligible for trifluridine-tipiracil plus bevacizumab as a 3L therapy may be overestimated as there are currently no publicly funded 3L therapies for *KRAS* mutant colorectal cancer. Clinical input suggests that this proportion may be closer to 15% to 20%. Moreover, clinical input noted that 50% to 60% of patients who are *KRAS* wild type and did not receive first-line anti-EGFR (e.g., panitumumab or cetuximab with or without irinotecan) would be treated with an anti-EGFR drug. Lastly, clinical expert input obtained by CADTH noted that there are no funded 4L therapies for colorectal cancer, and thus the proportion of eligible patients who receive trifluridine-tipiracil as a 4L therapy may be between 5% to 10%. Overall, there is uncertainty with the inputs used by the sponsor in their base case, however, there is a lack of evidence to support more robust estimates.
    - CADTH was unable to address this limitation owing to a lack of robust data to support alternative inputs. The population size is a key parameter in estimating the anticipated budget impact of trifluridine-tipiracil plus bevacizumab.
- **The treatment duration for trifluridine-tipiracil plus bevacizumab is uncertain:** The sponsor estimated treatment duration in the BIA by averaging the median time on treatment from the relevant studies in the NMA.[7] The sponsor reports the median treatment duration from the SUNLIGHT trial to be 5.4 months. However, this does not align with the clinical evidence (mean = 6.12; median 4.96) submitted.[2] Moreover, clinical expert input suggests that treatment duration should closely align with PFS. The sponsor conducted a scenario analysis with the treatment duration calculated based on median PFS (5.6 months) and the budgetary impact increase was approximately $5 million over 3 years. As such, if the average duration of trifluridine-tipiracil plus bevacizumab deviates from 5.37 months in clinical practice, the budget impact will be affected.
    - CADTH was unable to address this limitation.
- **The estimated proportion of patients that would be eligible for public coverage is uncertain:** The sponsor assumed that 70% of the eligible population in Ontario, New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador and 100% of residents in all other provinces and

the NIHB population were publicly insured. As the regimen includes both an oral (trifluridine-tipiracil) and IV (bevacizumab) treatment, the coverage rates may differ between trifluridine-tipiracil and bevacizumab within a jurisdiction. Generally, IV treatments have 100% coverage, but take-home oncology medications (e.g., oral medications) are not covered using a consistent approach. [31] For example, in Ontario and the Atlantic provinces, these medicines are funded for the portion of the population eligible for public covered and eligibility may depend on things like age and income.[31] Of note, NIHB does not fund IV oncology products. It is unclear whether any of these factors were considered in the sponsor's assumption.

    - CADTH was unable to address this owing to model structure and a lack of data. The sponsor's model does not permit different coverage rates for the different regimen components and the sponsor did not detail the proportion of the population that is within key age groups (i.e., under 25, between 25 and 64, and 65+). To address uncertainty around these estimates a scenario was conducted assuming 100% of the eligible population were publicly insured.

- **The market uptake of trifluridine-tipiracil plus bevacizumab is uncertain:** The sponsor's submitted base case assumed that 64.7%, 77.1%, and 86.2% of eligible patients would receive trifluridine-tipiracil plus bevacizumab in year 1, year 2, and year 3, respectively, based on the sponsor's internal forecasting and market research.[26] Clinician input received by CADTH for this review suggests that the sponsor's estimates are reasonable but that uptake of trifluridine-tipiracil plus bevacizumab may vary depending on patient preference.
    - CADTH was unable to address this limitation.

CADTH Reanalyses of the BIA

In the absence of more reliable estimates to inform the key parameters of the BIA, the sponsor's submitted base case was maintained. CADTH expects that the budget impact of reimbursing trifluridine-tipiracil plus bevacizumab for the treatment of adult patients with mCRC who have been previously treated with, or are not candidates for, available therapies described previously will be sensitive to more reliable inputs which may affect the duration of treatment, market size, and the proportion of the population eligible for public coverage.

CADTH undertook a scenario analysis to explore the impact of increasing the proportion of patients who are eligible for public drug coverage to 100% in all CADTH participating jurisdictions.

Table 15: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	3-year total
Submitted base case	BSC	$0	$0	$0	$0	$0
	Trifluridine-tipiracil plus bevacizumab	$0	$31,235,958	$37,485,914	$42,271,406	$110,993,278
	Budget impact	$0	$31,235,958	$37,485,914	$42,271,406	$110,993,278
CADTH scenario analysis: 100% public coverage	Reference	$0	$0	$0	$0	$0
	New drug	$0	$38,173,020	$45,797,166	$51,624,842	$135,595,029
	Budget impact	$0	$38,173,020	$45,797,166	$51,624,842	$135,595,029

BIA = budget impact analysis.

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Colorectal Cancer Resource and Action Network

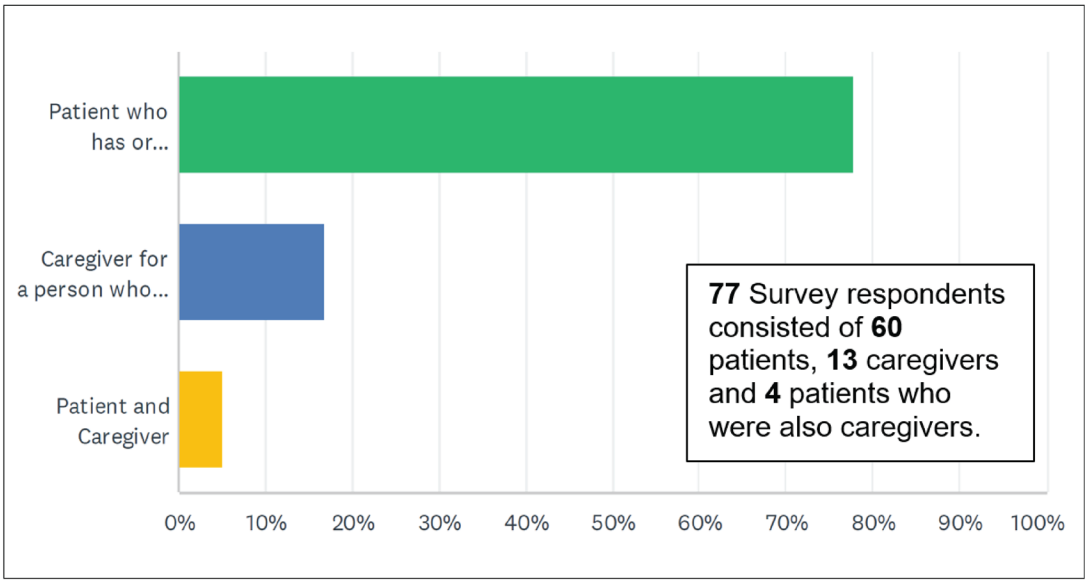
About Colorectal Cancer Resource and Action Network

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. We have an expanded mandate to serve cancer patients outside of the colorectal cancer space through HTA patient evidence submissions, educational events and advocacy initiatives. Our mission is to reduce the burden of cancer in Canada.

Information Gathering

To ensure the metastatic colorectal cancer patient perspective was captured for this therapeutic under review, CCRAN employed a multi-faceted outreach approach. On **June 3rd, 2023**, we reached out to 27 Canadian Clinicians and 6 U.S.-based Clinicians (via email) who treat advanced colorectal cancer patients requesting their assistance in helping to identify patients (or caregivers) who had/have experience with Lonsurf in combination with Bevacizumab for the purposes of participating in a telephone interview. They would participate in the telephone interview to share that experience in an HTA patient input submission to help inform the deliberations of an expert drug review committee in Canada. In that email, we attached a patient flyer (Appendix 3) which we kindly requested be shared with patients who had experience with the therapy under review to encourage participation in the telephone interview process to help capture the patient perspective for this submission. That same email was then followed up 3 and 5 weeks later, resulting in 5 high quality patient interviews, whose data is captured and summarized in Appendix 1.

Figure 1: Input of Metastatic Colorectal Cancer Patients



Additionally, an online survey was developed to help capture the **metastatic colorectal cancer patient's:**

- Experience with respect to the diagnosis of their cancer, cancer journey and drug therapies administered prior to the therapy under review.

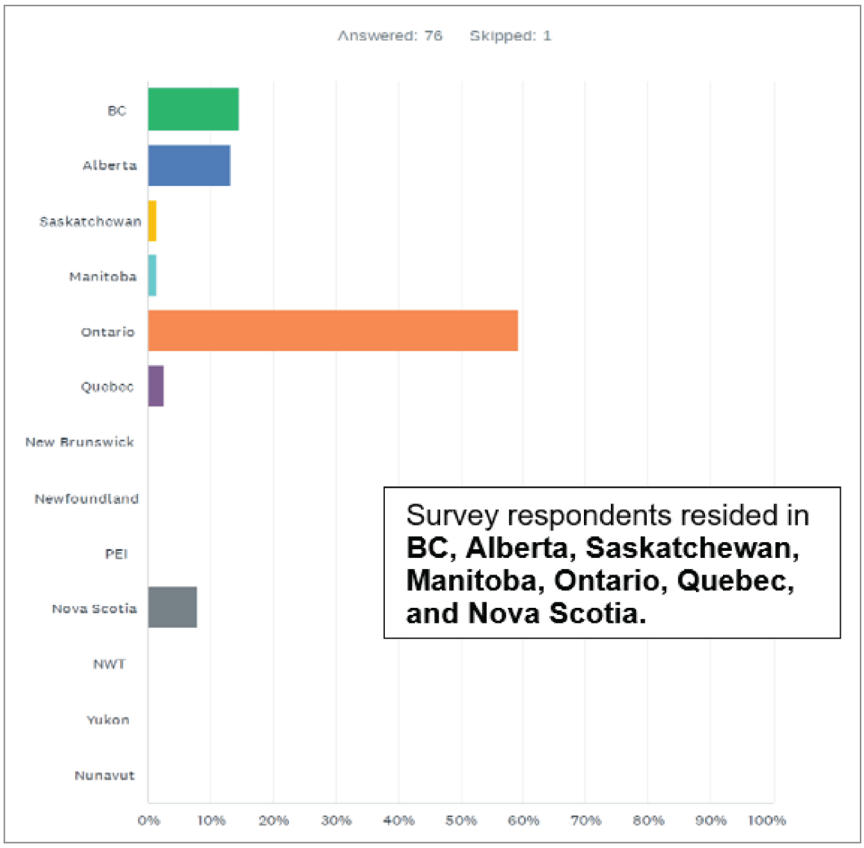
The online survey (targeting metastatic colorectal cancer patients **only**) was administered from **June 13 – August 5, 2023,** and was promoted through CCRAN's email blasts, social media channels and support groups. **77 metastatic survey respondents** replied to the outreach by providing input, whose survey findings are herein attached and labelled as Appendix 2.

The survey findings will be referenced throughout this submission for they reflect the perspectives of the advanced colorectal cancer patients who completed the survey.

Telephone interviews were conducted by CCRAN between **June 12th and July 26th, 2023, inclusive,** with each patient or caregiver providing firsthand, compelling, relevant and high-quality input regarding their:

- Experience with respect to the diagnosis of their cancer
- Disease experience
- Experience with respect to previously administered therapies prior to the therapy under review and

Figure 2: Provinces Where Metastatic Colorectal Cancer Patients Reside



- Experience with respect to Lonsurf + bevacizumab

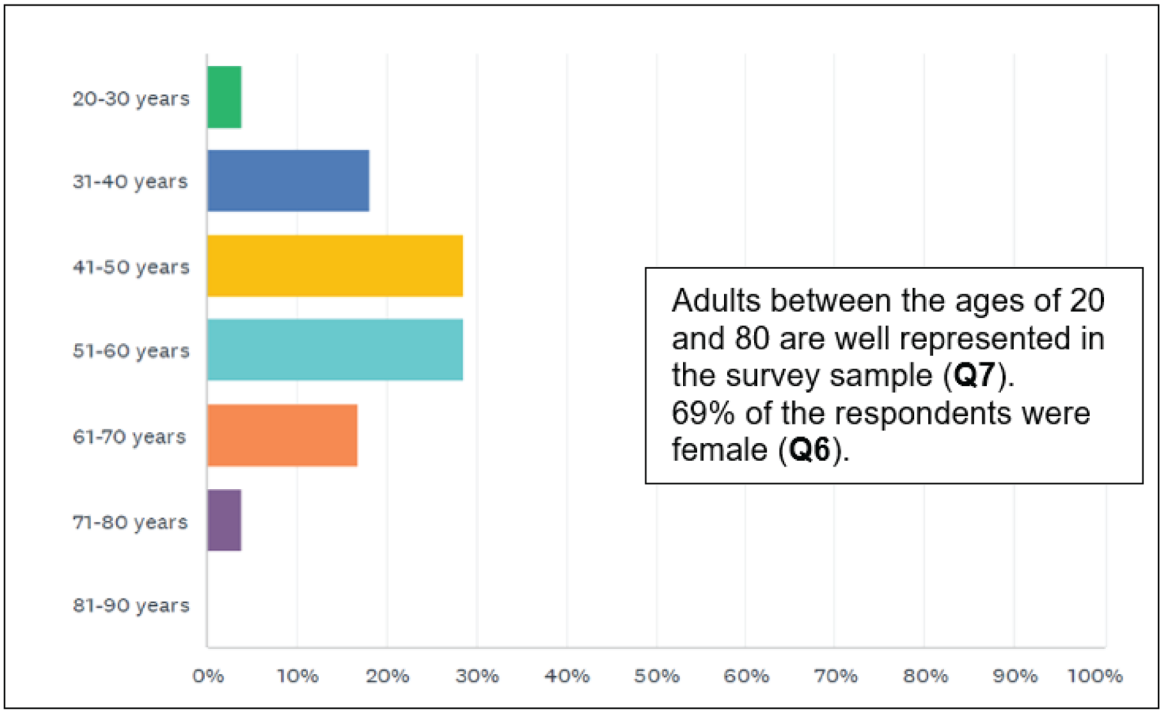
The mean age of the interviewed patients is **47.4** years and median age of the patients at the time of their diagnosis is **51** years. The qualitative data from the interviews is summarized and represented entirely in Appendix 1, which is attached, and will serve for the most part, as the basis for this qualitative submission, in addition to the objective survey findings.

Finally, a focus group was conducted via zoom on **Friday, August 4th, 2023,** between 7:30 and 9:00 p.m. ET with nine metastatic colorectal cancer patients (**Patient F-N**) across Canada to ensure CCRAN captured their perspectives on the disease journey, specifically, relating to metastatic disease-induced symptoms. The patients who participated were tasked with answering the question: "**What symptoms, if any, did you experience from your metastatic colorectal cancer?**" Their thoughtful replies were captured and entered into Table 1 appearing within the second part of the document entitled Appendix 1 and will be referenced herein in the Improved Outcomes section of this submission.

Disease Experience

Colorectal cancer is the third most common cancer and the second leading cause of cancer related death in Canada. Despite optimized surgical procedures and adjuvant combination chemotherapy, many of our patients will experience a disease recurrence, often with a fatal course. And when relapsed, the prognosis is poor, with a median overall survival of approximately 30 months from initiation of first line systemic therapy and a relative 5-year survival of 15% (NCI SEER Program 2022). While systemic treatments such

Figure 3: Demography of Metastatic Colorectal Cancer Patients



as combination chemotherapies, targeted therapy, immunotherapy, and their combinations have improved overall survival in the metastatic colorectal cancer patient population over the past ten years, there is an urgent, unmet clinical need to identify new and more effective treatment options to improve the survival and **quality of life** for patients diagnosed with metastatic disease – a need that is repeatedly reported by our patients. More effective therapeutic approaches are required for this patient population because a subset of our patients is currently not benefiting from standard of care therapies while being exposed to and experiencing substantial toxic side effects, nevertheless.

The online survey results identified **fatigue, bloody stools, and diarrhea** as the most prevalent colorectal cancer-induced symptoms as per **Question 9** (**Q9**). Fatigue resulting from the cancer was reported to be the most important symptom to control according to patients and caregivers (**Q10**). In **Q11**, patients relayed that their colorectal cancer-induced symptoms most certainly interfere with their quality of life (**QoL**) and their daily activities. They are unable to function "normally" in their family or work setting: **87%** are unable to work and **60%** are unable to exercise, while **27%** are unable to concentrate and **25%** are no longer able to drive. These are daily functions or tasks that prevent our patients from leading a semi-normal life. There are limitations that are imposed upon them resulting directly from their cancer. Limitations such as:

> "Mental well-being: depression, anxiety, frustration and scared of what is to come."
>
> "Not knowing when I can leave my house due to bowel irregularity."

The top three limitations that had a psychological impact from patients' colorectal cancer (**Q12**) were:

- An inability to experience joy (72%)
- Chemo brain making me feel forgetful (46%)
- Constant fatigue makes it difficult to function normally – can't think straight (43%)

And some of the open-ended replies to this question included:

> "Anxiety, flashbacks"
>
> "Tired having cancer on my mind all the time and worry about it…"
>
> "Want more children but can't."

It is important to note that not all metastatic patients experience cancer-induced symptoms. 13% of the survey respondents did not experience any symptoms at all prior to their diagnosis: their diagnosis was a result of an incidental finding.

Hence, to that end, three of the five interviewed patients had not experienced cancer-induced symptoms prior to their diagnosis (**Patients A, B, and C**). For the patients who did experience symptoms prior to their diagnosis, interviewed patients reported the following:

> "In most of 2020, I was not feeling well. I had been complaining of breathing issues, because I had picked up a cold the previous winter and I still could not shake it, nor could I shake the cough, it just would not resolve." — **Patient D**
>
> "[…] had pain on my right-hand side which led me to go to the ER and they performed a CT scan. I had

that pain for about a few weeks but was getting worse which led me to go to the ER." — **Patient E**

Patient A was a longstanding Crohn's patient, diagnosed with the pathology at a young age, who underwent annual colonoscopies starting at the age of 14. At the age of 28, his colonoscopy identified a primary tumor and a subsequent colectomy revealed metastatic disease to the peritoneum.

A trip to the Emergency Room (ER) for what was believed to be food poisoning revealed an obstructed bowel and liver metastases for **Patient B**. And a positive Fecal Occult Blood Test (FOBT) is what led to **Patient C's** diagnosis whose workup revealed an obstructed sigmoid colon, metastatic disease to both lobes of the liver and mesentery tissue. **Patient C** relayed:

> "I was really surprised. Because when the colonoscopy was done, I was actually awake, I couldn't believe it, how could this be happening to me? The survival for stage 4 is about 30% after 5 years. I was so healthy and not symptomatic and secondly, what can I do to fight and get rid of this… (became tearful). Once I was diagnosed, it got easier to cope with it than not knowing what was happening to me. I was so lucky to have tests done in an expedited manner and have found it so fast." — **Patient C**

All five interviewed patients were diagnosed with stage 4 disease at time of diagnosis. Metastatic colorectal cancer patients who participated in the focus group, **Patients F through N** (Table 1) identified the following metastatic colorectal cancer-induced symptoms:

- Anemia, bloody stools, abdominal and low back pain
- Difficulty breathing, poor appetite, fatigue
- Abdominal cramping, migraines, dizziness, breaing, all of which were due to a brain metastasis
- Gas, bloating, occasional diarrhea, daily multiple bowel movements, and the feeling as though bowels had not been completely emptied.

One **focus group member** (**Patient M**) provided the following input:

> "Yes, I sure was symptomatic. I just wasn't feeling well. I experienced bloody stools, abdominal pain, gas and bloating, occasional diarrhea, daily multiple bowel movements and a feeling as though I wasn't done emptying my bowels. This went on for a couple of years till I finally was sent for colonoscopy which revealed a massive tumour in my sigmoid colon that had almost completely blocked my colon. And then they discovered 23 tumours in both lobes of my liver. I was pretty devastated, but I suffered for many, many months – 2 years actually - with those symptoms and it's symptoms that were due to an advanced case of colorectal cancer – Stage 4. My family doctor really should have listened to me but failed to do so, I think because of my young age." — **Patient M**

And interviewed **Patient F** thoughtfully relayed:

> "Oh, there was so much going on with me. I had been experiencing anemia and bloody stools for about 10 years before I was actually diagnosed with metastatic colon cancer. I was so young, and this was part of the problem. I had low back pain that I kept complaining about to my GP for well over 2 years, but nothing was done about it, I think because of my young age. My upper right abdomen hurt, and this was due to the 20 metastatic tumours in my liver. It felt like pressure, deep pressure that

just kept gnawing constantly in my right side. And with every passing day, it hurt more and more."

As for the toll the disease has taken on caregivers, caregivers who responded to the online survey identified the following as the top three difficulties when caring for colorectal cancer patients (**Q34**):

- Loss of lifestyle (70.6%)
- Difficulty managing treatment-induced side effects (54.9%)
- Loss of income (45.1%)

These challenges merely underscore the impact of the disease on the caregiver as they struggle with the emotional turmoil of the diagnosis, but as one survey respondent states, "try to run the household on their own while also working and being a full-time caregiver" is a considerable ongoing challenge imposed upon the caregiver from which there is little to no reprieve. (**Q34**)

Experiences With Currently Available Treatments

Patients with metastatic disease who completed the online survey generally received treatment with fluorouracil-based chemotherapy (with oxaliplatin and irinotecan – **65%**), vascular endothelial growth factor (VEGF)-based therapy (mainly bevacizumab – **50%**), and epidermal growth factor receptor (EGFR)-targeted therapies in confirmed RAS wild type disease (either Cetuximab or Panitumumab – **8%** and **17%** respectively). For patients whose disease was identified to be Microsatellite Instability-High (MSI-High), Pembrolizumab was accessed by **3.4%** of the survey respondents and in patients identified to have a BRAF V600E mutation, Encorafenib in combination with an anti-EGFR therapy was accessed by **5.1%** of respondents. One patient accessed Regorafenib. Open ended replies revealed additional systemic therapies were also accessed: Opdivo in combination with Yervoy for the treatment of a patient's metastatic disease; and Raltitrexed in combination with Oxaliplatin was also identified as a prescribed treatment for a patient (**Q15**).

Q16 highlighted the additional non-systemic therapies utilized in the management of the patients' metastatic disease.

The three weighted averages of **3.43, 3.30 and 3.35** each reflect the profound impact the treatment-induced side effects had/have on the patients' daily lives, regardless of the side effects selected: the majority of the respondents selected "**significant impact**" for **Side Effect #1** and the majority then proceeded to select either "**significant impact**" and/or "**moderate impact**" for **Side Effect #2** and **Side Effect #3**.

Medications were prescribed to help address the treatment-induced side effects which included (**Q21**):

> "Emend and Zofran for vomiting, iron for anemia, ondansetron for nausea/fatigue, and CBD, acupuncture and physiotherapy for neuropathy".

Survey respondents relayed they were required to pay out of pocket for some of the medications prescribed to help address the treatment-induced side effects (**Q22**):

> "Mouthwash was $50, not covered, required 4x."
>
> "I paid a lot prior to trillium kicking in."

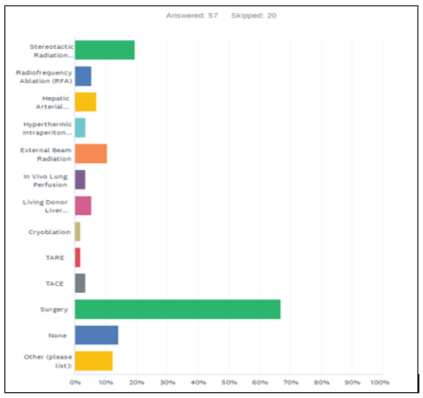
"Hundreds, in the deductibles."

"$500 per year."

Four patients and one caregiver participated in the telephone interviews that allowed CCRAN to capture a significant amount of qualitative data with respect to their treatment journeys. Interviewees provided thoughtful and at times heart wrenching input regarding their treatment journeys, describing the treatments accessed, the impact on their quality of life and the amount of time to disease progression. By way of summary, all five patients received a minimum of two previous fluorouracil-based chemotherapy treatment regimens for metastatic disease (FOLFOX/FOLFIRI); one of whom received the anti-VEGF therapy - Bevacizumab (**Patient E**) as part of their second line therapy in combination with FOLFIRI and thee patients received anti-EGFR therapy as part of third line (**Patient B**), fourth line (**Patient C**) and first line (**Patient D**) therapy. **Patient A** accessed Stivarga in fourth line.

Caregiver A summarized her 28-year-old husband's treatment journey as quite "*hellish*" having been diagnosed with metastatic disease at such an early age. Having been a Crohn's patient most of his life, **Patient A** was diagnosed with colon cancer in December 2015 through an annual colonoscopy and his peritoneal metastases were discovered through his colectomy. He subsequently underwent 12 rounds of FOLFOX, cytoreductive surgery (CRS) plus HIPEC in the U.S., followed by 12 months of FOLFIRI in combination with Avastin, a rechallenge of FOLFOX, SBRT, short course of STIVARGA, and then finally Lonsurf in combination with bevacizumab for almost two years. The only time he was declared No Evidence

Figure 4: Additional Non-Systemic Therapies Utilized in The Management of the Patients' Metastatic Disease



Additional non-systemic therapies included Surgery, SBRT, External Beam Radiation, HAIP, Living Donor Liver Transplant, and In Vivo Lung Perfusion, to mention a few. Complimentary Therapies were included in the open-ended replies.

Patients cited fatigue, peripheral neuropathy, hair loss, diarrhea, and nausea as the most commonly induced side effects from their colorectal cancer treatments (**Q17**). The three treatment induced side effects that were most difficult to tolerate as identified in the survey findings were ***fatigue*** (52%), ***neuropathy*** (48%), and ***nausea*** (40%) (**Q19**).

In **Question 20**, patients were asked to rate those three side effects across a scale of "***No impact***" to "***Significantly impacting***" their daily life, the results of which appear below:

	NO IMPACT	SMALL IMPACT	MODERATE IMPACT	SIGNIFICANT IMPACT	TOTAL	WEIGHTED AVERAGE
Side Effect #1:	3.77% 2	5.66% 3	33.96% 18	56.60% 30	53	3.43
Side Effect #2:	4.00% 2	8.00% 4	42.00% 21	46.00% 23	50	3.30
Side Effect #3:	4.35% 2	4.35% 2	43.48% 20	47.83% 22	46	3.35

of Disease (NED) was immediately after the CRS + HIPEC which lasted nine months. The balance of the therapies he accessed never allowed him to achieve complete remission and according to the patient's caregiver, the therapies were quite toxic:

> "While he was on the FOLFOX, he had a difficult time. It was one of the worst therapies he endured. Probably the worst. He had trouble eating and sleeping, he had bad neuropathy, was brutal, not working, weak, lost weight, and generally unhappy. When he accessed FOLFIRI, that wasn't too bad; he was pretty functional and able to work on that treatment on his off week only, about 15-20 hours per week. The STIVARGA gave him a bad acne/rash and fatigue which he did not appreciate so the med onc lowered the dose and meds were prescribed to help with that. None of the therapies really worked for him. They just tried to buy him time." — **Caregiver A**

Patient B is a 53-year-old female diagnosed at 51 years of age and had no symptoms consistent with colorectal cancer. Were it not for an episode she believed to be food poisoning which led to an ER visit, her metastatic sigmoid cancer (liver) would not have been discovered in May 2021. Surgical resection ensued to address the partially obstructed bowel, followed by 6 months of FOLFIRI, 7 months of FOLFOX (February 2022-August 2022), followed by the introduction of Panitumumab in September 2022 to February 2023. She was happy to have a treatment holiday for 2.5 months which then resulted in surgical resection in April 2023. She then commenced Lonsurf plus bevacizumab in May 2023. She relayed that each therapy would elicit a response of approximately 6-7 months and then she would be required to switch to another therapeutic because of disease progression. Two of the treatments were problematic for her:

> "I would say that for the FOLFIRI and FOLFOX, the nausea was the worst for me on those two treatments. I found it difficult to eat and nothing would work in terms of anti-nausea meds. So, I lost a lot of weight. I would lie down all the time on the couch and close my eyes and do nothing. I would barely do anything every day that I was on those two therapies. I did try my best to work on my off days when I was not on treatment, but I could barely keep up because of lingering effects. With respect to Panitumumab, …. it caused a rash, and I ended up with an infection on my face for which I required additional meds to treat it. It lasted so long. Right up until I came off of the treatment. Nothing worked even though I saw a dermatologist. The med he wanted to put me on wreaked havoc on my liver so I couldn't take it." — **Patient B**

Patients C, D, and E have similar accounts of their treatment journeys:

> "The FOLFIRI: That was the most problematic, I was weak and lethargic, I couldn't recover so fast, so tired and feeling low, constipated, I suffered abdominal pain, sensitivity to smells so I couldn't cook, and I love to cook but I couldn't be in the kitchen when my husband was cooking." — **Patient C**
>
> "So, the FOLFIRI plus the PANI gave me acne from the top of my head to my waist because of the PANI. That was really the worst. I was on the Pani plus FOLFIRI for 16 months and I was actually NED but then once I was off it for 4 months, my cancer came back. And when I went on the FOLFOX, it didn't take very long to progress on that treatment, only 4 months. So that's when I went on the Lonsurf + BEV." — **Patient D**

> "I found the folfiri to be worse than the folfox and it wasn't even close. The folfiri was way worse than the folfox… but the second year was hard for me. I had extreme nausea, vomiting, it's like having the flu for 4 days every two weeks." — **Patient E**

Of note: Patient E experienced a one-year disease free interval after his adjuvant therapy, 28 months on FOLFIRI plus Avastin and 1.5 months on a rechallenge of FOLFOX.

Generally, all interviewed patients and one caregiver reported debilitating side effects while undergoing treatments for their metastatic colorectal cancer, which compromised their quality of life. While patients may have derived a clinical benefit in terms of response, that response was accompanied by incapacitating side effects such as fatigue, nausea, lack of energy, diarrhea, neuropathy, skin rash, lethargy and flu like symptoms that prevented them from engaging in life on any meaningful level. Patients were quite emphatic about their experience with combination chemotherapies which compromised their well-being some or most of the time which necessitated time off work, inability to care for children, lack of self-care, and time spent enjoying life in general. Normal daily activities could not be resumed nor could quality time with friends and family be spent, permitting them the freedom to "live life again".

Improved Outcomes

Patients treated for their advanced stage colorectal cancer, along with their families, are faced with an ongoing challenge: the prognosis for these patients continues to be poor and as such the goal is to provide these patients with additional therapeutics to manage their disease to ensure improved longevity and quality of life is achieved. Hence, when asked "**What improvements would you like to see in new treatments that are not available in current treatments**?", online survey respondents clearly highlighted their desire to access therapies that will effectively control their disease with respect to improvements in their **physical condition** (for example, tumour shrinkage, tumour stability, reduction of pain and improved breathing – **Q38**). Patients found these improvements to be of utmost importance, as reflected in the weighted average score of **9.78** out of a possible 10. However, the survey results revealed therapies that provide improvements in a patient's quality of life (i.e. improvement in mobility, sense of wellness, relief from side effects) **are also important to patients and caregivers** and scored equally as high, with a weighted score of **9.50** (**Q39**). 87.1% of patients would take a therapy that could provide better quality of life during their lifetime even if it does not extend survival (**Q41**). And after being told there is no other available treatment for their cancer, patients would be prepared to access a toxic therapy provided an appropriate survival benefit is realized for them: the greater the survival benefit (**2 months, 6 months, 1 year**), the more likely the patient was willing to access a toxic therapy and endure the treatment's toxic side effects (**Qs 42, 43 and 44**), generating the following weighted scores: **5.02 (2 months), 6.59 (6 months) and 7.53 (1 year)** respectively. Patients provided the following open-ended replies.

> "Oral drugs… and we need access to as many drugs as possible and we need to know the ones that will work for our cancer beforehand (i.e. biomarker testing)."
>
> "Meaningful improvement in survival time."
>
> "Develop a drug that does not involve hair loss. Give me something to treat metal mouth other than sucking on lemon drops or rinsing with salt water – avoid these…"

> "The chemo available will not cure me. There needs to be more options."

The interviewed patients provided their perspective on the improvements they would like to see in a drug therapy, which they believe is currently not available in other previously accessed therapies. They maintain a therapy should regress disease with minimal to no side effects. They prefer a therapy that is designed to cure a patient's cancer. And while the therapy is destroying the cancer, it should not be destroying the balance of the body's healthy tissues, rendering the patient debilitated and unwell. The patient's quality of life should be maintained at all times to ensure they are living their best life **and not a former glimpse of what used to be their life**. If a therapy cannot provide a cure, it should indeed provide a significant extension in survival. A drug therapy should also be conveniently administered: it should be an **orally administered therapy** in the comfort of a patient's home. This would eliminate considerable travel and stress for the patient, their caregiver and the entire family, such that travel costs are avoided and precious time spent away from home is spared. And if the therapy must be infused at a cancer centre, then it should be infused in the shortest amount of time possible with minimal chair time for the patient. Additionally, they emphasized the need for treatments that could provide a durable, longstanding response. When these patients were asked if their life would be any different if the drug therapies had these desired improvements, an emphatic and overwhelming "**yes**" was their reply. **Caregiver A** summarized these points quite articulately:

> "I think we want good quality of life, want to be able to extend longevity while we are able to have a good quality of life, and of course, let's try to avoid infusions as best we can, but if we can't avoid infusions at the cancer centre, then let's make them short infusions. We don't want any side effects from treatments because that will impact our quality of life: it doesn't help if you're living longer but you have no quality of life, right?" — **Caregiver A**

All five interviewees maintained that Lonsurf plus bevacizumab possessed the desired improvements. According to the patients and caregiver, it is capable of regressing disease, prolonging life while providing improved quality of life, with minimal to no side effects. This is a protocol that can allow patients to resume daily activities, some of whom were able to become gainfully employed again, engage in life by spending time with family and friends, good quality time, raise their young children, and permit them the freedom to appreciate life despite the horrors they have endured through toxic treatments. In **Patient's B** words:

> "Absolutely. It has the oral part covered, and it is convenient for me. And it's a better treatment for sure. I am not debilitated like I used to be. Pharma companies need to take into consideration what they are doing to patients' lives when developing drug therapies, especially elder patients. This drug company, Taiho, did that with Lonsurf. It's a great pill. And the Bev is good too."

Experience With Drug Under Review

As evidenced by the input provided by our 5 interviewees, patients with mCRC who have progressed following fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and anti-EGFR antibodies (in confirmed RAS Wild type disease) have limited treatment options but do have a good performance status and should be considered for further treatment. Appendix 1 (**Q10-26**) captured the treatment-related experiences for 5 interviewed Canadian patients, (one of whom is represented by their caregiver – **Caregiver A**) who have or

are currently undergoing the therapy under review. **Patients A, B and E** had their treatments covered through private insurance ± compassionate care as part of **5th, 4th and 3rd** line treatment respectively and **Patient E** also received some assistance from the manufacturer's Patient Support Program; **Patient C** accessed Lonsurf through the manufacturer's Patient Support Program as part of **5th line** treatment and **Patient D** had their treatments covered through RAMQ as part of **3rd line** treatment.

Caregiver A described her late husband's journey with great care and pain. Her husband accessed Lonsurf + bevacizumab as part of 5th line therapy at the young age of 32 years in March 2020 – August 2021 as an mCRC patient, whose metastatic disease was confined to his peritoneum and pelvic lymph nodes. After having received, FOLFOX, CRS + HIPEC, FOLFIRI + Avastin, FOLFOX, SBRT, Stivarga, he received 18 months of the therapy under review which not only regressed his disease but allowed him to achieve an excellent quality of life, capable of engaging him in his life once again. In **Caregiver A's** words:

> "He was able to work on a modified schedule, able to drive longer distances and went to work longer distances, did housekeeping chores, performed tasks such as vacuuming, cleaned the bathrooms and kitchen, walked the dog every day, he had a great appetite, so he ate well, and was able to put on weight. I used to make fun of him, because he was bigger than he ever was. He would cook one or two times per month something requiring time and effort. He was able to do family activities, day trips during the pandemic. He had a really good life with this therapy. Yes. His CEA was a good indicator and it just kept going down. His CT scans were showing regression as well. Apparently, right off the bat, there was a 50% response rate and then the disease had disappeared altogether. It was so wonderful."

It is worth noting that **Patient A** experienced no side effects, according to **Caregiver A,** which accounts for the excellent quality of life and **Caregiver A** rated her husband's experience with the therapy as a **10 out of a possible 10**, which she maintains her husband would most certainly concur were he alive today.

Patient B received her diagnosis of mCRC (liver and ovarian) in May 2021 through an ER visit. She underwent surgical resection of her primary sigmoid tumour followed by FOLFIRI (June-December 2021), FOLFOX (February-August 2022) and Panitumumab (September 2022-February 2023), in confirmed RAS WT disease. Surgical resection of Krukenberg tumours ensued in April 2023. Lonsurf + bevacizumab therapy was initiated in May 2023. **Patient B** is delighted to be on the therapy. She claims to be experiencing only one side effect: "itchiness" throughout her body, predominantly at night, which she attributes to the Lonsurf, and some "mild abdominal cramping two days post avastin infusion, but then it subsides." She claims, "this is a great therapy in comparison to what I have been on previously" and rates her quality of life while on the therapy a **10**.

Patient B shared what she is able to do now that she is on this therapy which she could not otherwise do on previous therapies (**Q23**):

> "Shopping which I love! Freedom to live my life like I used to! That is huge for me. I get to go to lunch all the time now, and I couldn't do that before. I join my friend Elizabeth all the time socially. I am working towards going back to school because of this therapy. Isn't that great? I get to go to church on Sundays now. I couldn't do that before. Just being able to go for walks, do gardening and

household chores, take day trips, all this because of the therapy. It's fantastic. And I am so happy."

Patient C was diagnosed with metastatic disease to liver, lungs, mesentery, spinal and 9th rib and initiated Lonsurf + bevacizumab on December 26, 2022, as part of **5th line** therapy. The patient reports no side effects while undergoing the therapy and, therefore, rates her quality of life while undergoing treatment as a **9-10** out of a possible 10. The patient had cancer induced symptoms before starting Lonsurf + bevacizumab that included: vague pain, constipation, nausea, lack of appetite, etc and according to **Patient C**: "[…] all of the previous symptoms have resolved because of the therapy." And her most recent CT scan has confirmed response to the therapy and her CEA is trending downwards. In her words:

> "I had a CT scan one month ago which confirmed response. My lung and liver have continued to regress! And my CEA is trending downwards. Since December 2022, it has dropped 400 points! And clinically, I feel wonderful. It is incomparable to what I used to feel like back in December of 2022. So, all around, I am really happy with where I am at today because of this terrific therapy."

Patients D and E were diagnosed in August 2020 (liver and lungs) and February 2018 (liver, lungs, chest wall and peritoneum) respectively. They initiated Lonsurf + bevacizumab therapy in February 2023 (bevacizumab only, then added Lonsurf in June 2023) and April 2023 respectively, as part of 3rd line treatment. Neither experienced any side effects and both rated their quality of life while on the protocol as a **9** and **9 or 10**, respectively. **Patient D** reports:

> "[…] this is the best I have felt all year! Before the Lonsurf plus Bev, I was feeling a pressure in my lungs and on my side, which was due to cancer progression. But now, that pressure has literally decreased overnight. Everything feels like it is moving in the right direction at the moment. I am so happy and grateful." And **Patient E** relayed: "[…] cuz you would never know; I feel completely normal. I don't know if it's the nature of stopping the other treatments or my cancer shrinking."

When asked what has the therapy allowed you to do, **Patient D** thoughtfully replied:

> "There are hydrangea bushes that have to be torn out on my property so I am finally going to do that cuz I can finally feel well enough to do it. I haven't been able to do it in the past cuz I haven't felt well enough to do due to silly chemo, but I do now because of this therapy that gives me really good quality of life. It's stuff like this that I am able to do, everyday stuff like this that is meaningful and relevant in the average every day Canadian."

All five patients have shown excellent tolerance to Lonsurf + bevacizumab despite having suffered so terribly with standard of care therapies. None of the 5 patients experienced interruptions in their Lonsurf + bevacizumab treatments and all five interviewees maintained it was well worth accessing the therapy under review (**Q22**) because compared to previously accessed regimens, Lonsurf plus bevacizumab reduced the incidence of adverse events with subjective symptoms and clearly maintained their quality of life:

> "Yes, his quality of life was the best on this therapy." — **Caregiver A**
>
> "Oh, ya, for sure. It gives me, like, I am not stuck at the hospital having to receive long infusions of toxic therapy. When was on the other treatments, I could never go out. Now with this therapy, I am on

> treatment, you would never know it! I am good. It offers me hope to continue my life." — **Patient B**
>
> "Of course it was worth it. For sure. It is giving me length of life and quality of life. That's a lot." — **Patient C**
>
> "The fact that within the first week taking it, it reduced the pain in my side and the pressure in my chest, this is wonderful. The results so far seem to be so positive, so definitely worth it for me!" — **Patient D**
>
> "Of course it was! Of course, of course, it's gonna keep me going. I am out of options. Something that is relatively easy to take and endure. Some people can keep going on this for quite some time, I hope it's me." — **Patient E**

Caregiver A shared what she and her family were able to experience in life because of Lonsurf + bevacizumab therapy:

> "We got to take one last vacation to a cottage as a family up north. It was so precious for us. We did again with friends too. We would not have been able to do that if he was on toxic chemo. He would have been too sick. He also got to stay at home taking care of his daughter while I worked, and he continued to work from home. He was a structural engineer able to contribute in such a meaningful way to society and his family. He was such a good guy. A good human, a good husband and father. Wonderful friend and son. The therapy allowed him to do what he wanted to do which is raise his daughter, work from home and live his life to the fullest. Isn't that what we want from a therapy?"

Patients clearly expressed what they perceived to be a survival benefit and enhanced quality of life in respect of Lonsurf + bevacizumab; and while our sample size is small, the clinical response and improved quality of life being observed is quite remarkable and is irrespective of age, gender, location of primary tumour, treatment line, number of metastatic sites, prior therapy received with bevacizumab and RAS mutational status. This clearly indicates, according to the data provided herein, that Lonsurf + bevacizumab is a viable treatment option for all clinically relevant subgroups of metastatic colorectal cancer.

Anything Else?

Interviewed patients provided thoughtful and compelling examples of why Lonsurf + bevacizumab was worth accessing. Their values, preferences and priorities were captured in Appendix 1, the majority of which have already been highlighted throughout this submission. We would, however, like to summarize the astounding benefits experienced by all interviewed patients by providing one last quote from **Caregiver A** which speaks to the therapy's benefits in terms of: ease of use, oral administration, extension in life, amelioration of symptoms and preferred toxicity profile:

> "You know, since the Lonsurf was an oral medicine, it was significantly easier to use than the previous infusions which were long and tedious. This oral medicine was administered in the comfort of his home and didn't require any effort, travel, cost, nothing. As for the BEV, it was a short infusion and not too time consuming. Chair time was minimal. It was good. His life was not impacted in the same way his life was impacted by the other therapies he had in the past. It really did make a difference. It was time he got to spend with me and his daughter – 18 months. Therein lies the difference. Time with

family, vs time at the cancer centre." — **Caregiver A**

Our interviewed patients accessed the therapy under review in third (2), fourth (1) and fifth (2) line therapy and were happy to report what they believed to be a therapeutic benefit, which suggests this protocol could be applicable not only in third line but later line therapy as well, in patients with refractory disease. It is important to note that therapeutic benefits were observed irrespective of gender, location of primary tumour, age, number of metastatic sites, number of tumours and RAS mutational status. Patients who had previously accessed bevacizumab in an earlier line of therapy, also experienced a clinical benefit, which merely supports a role for continued anti-vegf therapy with bevacizumab beyond progression in this patient population. This is certainly encouraging because it allows patients who were heavily pretreated, such as **Patient A** with bevacizumab, to access a therapy with minimal to no side effects while experiencing a durable response, not only to Lonsurf but to previously administered bevacizumab as well. And as previously noted, responses were experienced by all clinically relevant subgroups: RAS Wild type and RAS Mutated colorectal cancer alike. As it relates to the **RAS mutated colorectal cancer** patient population, the administration of Lonsurf + bevacizumab in third line and beyond is helping to address **an unmet need** in our refractory colorectal cancer patients for there are currently no approved therapies targeting this relevant subgroup. It will provide a new treatment option for these patients with superior quality of life due to fewer and less severe side effects.

It was made abundantly clear by our interviewed patients that the treatment protocol under review allowed them to maintain their physical function – a highly sought-after benefit by cancer patients and caregivers alike. In **Patient C's** words: "**I get to live more in a good way. This is a big accomplishment to live in a better way, a good life**". The therapy under review certainly managed to preserve interviewed patients' performance status as they recalled their compromised selves on combination chemotherapies previously received, living a grueling and "*less than*" life. When compared to another drug therapy administered in third line (Stivarga), **Patient A** experienced no response and his caregiver described the experience as "*hellish*" with respect to adverse events, which necessitated not only a dose reduction, but eventually a treatment termination.

All interviewed patients had failed previous treatment for their colorectal cancer, including surgery, chemotherapy, biologic therapy and radiation therapy and were desperately in need of another therapeutic to help manage their metastatic disease. Each patient was beyond delighted to have accessed what they described as a non-toxic therapy, demonstrating a level of benefit unlike any other previously accessed therapy with respect to quality-of-life maintenance. Additionally, to have observed, in some, the magnitude of response in our interviewed patients who had progressed so quickly following prior treatments confirms that Lonsurf + bevacizumab is effective and amenable for long term administration.

If publicly funded, Lonsurf + 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. Funding this therapy aligns well with the patient perspectives captured within this submission. We, therefore, strongly support and urge that a positive funding recommendation be issued for Lonsurf + bevacizumab for the treatment of metastatic colorectal cancer in adult patients who have been 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. We believe it aligns

well with the identified patient need for a new, effective, quickly administered, oral, less toxic treatment option that is capable of maintaining a **high quality of life for the patient**. This should become the new standard of care for this subset of the patient population.

Conflict of Interest Declaration — Colorectal Cancer Resource & Action Network

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission?

No.

Did you receive help from outside your patient group to collect or analyze data used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures for Colorectal Cancer Resource and Action Network

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Taiho	–	–	X	–

Colorectal Cancer Canada

About Colorectal Cancer Canada

Colorectal Cancer Canada is the nation's not for profit colorectal cancer patient organization dedicated to colorectal cancer awareness and education, supporting patients and their caregivers and advocating on their behalf.

Colorectal Cancer Canada is registered with CADTH. www.colorectalcancercanada.com

Information Gathering

To capture the patient and caregiver perspective on the drug under review, Colorectal Cancer Canada (CCC) launched an online survey in English and French from July 19, 2023, to August 17, 2023, to which 22 patients and 1 caregiver on behalf of a patient responded, for a total of 23 respondents. One patient (patient 5) had experience with the combination under review. Data was gathered from respondents across Canada. The survey was disseminated through CCC's monthly newsletter and posted on CCC's social media platforms (Twitter, Linkedin, Instagram and Facebook) as well as on those of international colorectal cancer organizations. CCC's patient support specialists also reached out to patients in CCC's monthly support groups to complete the survey. Additionally, CCC reached out to the physicians on its Medical Advisory Board

who have experience prescribing this combination and asked them to share with their patients. A copy of the survey questions as well as the survey results by section are attached in this submission.

Disease Experience

Survey data regarding disease experience is summarized in the PDF attached, entitled: "Summary graphs – Disease Experience."

Patients and caregivers were asked about which symptoms of colorectal cancer (CRC) they experienced (Q9). 90.5% of respondents experienced CRC symptoms, with bloody stools, fatigue/weakness, abdominal cramping/gas/feeling bloated cited as the most common symptoms. When asked what the top CRC symptoms were the most important to control (Q10), respondents selected abdominal cramping/gas/feeling bloated, abdominal pain, fatigue/weakness and diarrhea. 22 out of 23 patients/caregivers indicated that CRC symptoms limited their quality of life. Respondents were asked to select the three most important ways the CRC symptoms they experienced impacted their quality of life (Q11), with ability to work, ability to participate in social activities, and ability to exercise cited as the most important. Respondents added the following open-ended responses:

> "I no longer work; I have to be careful not to overdo it."
>
> "Not able to work, not able to volunteer, can't travel."
>
> "Can't really fulfill any part of life, family, exercise, work, etc."

When asked about the psychological impact of CRC (Q12), patients cited feeling consistently worried, nervous or uneasy and persistent fear of [the] cancer getting worse or recurring (coming back) as the most common impacts.

Caregivers were uniquely questioned on the difficulties they faced while caring for the individual living with CRC (Q36-39). The one caregiver who responded to the survey indicated that the main difficulties they faced included being unable to work outside the home, loss of income/financial strain, the time spent at medical appointments, and the feelings of helplessness or inadequacy. The respondent added the following open-ended response: *"Physically draining. More home duties. My inability to help make it better makes me feel helpless*." They indicated that an average of 11-25 hours were dedicated per week to managing the patient's side effects, and an average of 11-25 hours a week were dedicated to managing the patient's treatment including taking them to appointments, administration of medication, and hospital/clinic visits.

Table 2: Demographics of Patients and Caregiver Surveyed

Demographics	Patients							
—	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 7**	**Patient 8**
Country and Region	Canada, Quebec	Canada, Newfoundland & Labrador	Canada, Quebec	Canada, Ontario	Canada, Ontario	Canada, Ontario	Canada, Ontario	Canada, British Columbia
Gender, Age	Male, 61-70 years	Female, 51-60 years	Female, 41-50 years	Female, 61-70 years	Male, 71-80 years	Female, 41-50 years	Male, 51-60 years	Female, 51-60 years
Stage at Dx	IV	III	IV	IV	IV	IV	III	III
—	**Patient 9**	**Patient 10**	**Patient 11**	**Patient 12**	**Patient 13**	**Patient 14**	**Patient 15**	**Patient 16**
Country and Region	Canada, Alberta	Canada, Ontario	Canada, Ontario	Canada, Ontario	Canada, Ontario	Canada, Ontario	Canada, Newfoundland & Labrador	Canada, Quebec
Gender, Age	Male, 71-80 years	Female, 71-80 years	Female, 31-40 years	Female, 51-60 years	Female, 51-60 years	Female, 51-60 years	Male, 61-70 years	Female, 41-50 years
Stage at Dx	IV	III	IV	IV	IV	IV	III	IV
—	**Patient 17**	**Patient 18**	**Patient 19**	**Patient 20**	**Patient 21**	**Patient 22**	**Caregiver 1**	—
Country and Region	Canada, Quebec	Canada, Quebec	Canada, Quebec	Canada, Alberta	Canada, Quebec	Canada, Quebec	Canada, Quebec	—
Gender, Age	Female, 41-50 years	Female, 41-50 years	Female, 61-70 years	Male, 51-60 years	Female, 41-50 years	Male, 80+	Female, 71-80 years	—
Stage at Dx	III	IV	III	III	IV	I	III	—

Experiences With Currently Available Treatments

Survey data regarding experience with currently available treatments is summarized in the "Summary graphs – Experiences with Currently Available Treatments."

Patients and caregivers were asked to indicate which drug therapies they have accessed to treat their CRC (Q17). FOLFOX, FOLFIRI, capecitabine, and bevacizumab were cited most frequently. Fatigue, brain fog, diarrhea, loss of appetite, hair loss and nausea were cited as the most common side effects experienced with drug therapies (Q21), while the most difficult side effects to tolerate were diarrhea, Hand and Foot syndrome, and fatigue (Q23). When asked whether these drug therapies have been effective at controlling the symptoms of the cancer, such as pain (Q18), 11% of patients/caregivers said "no", 37% said "somewhat", and 53% said "yes".

When asked whether these drug therapies have been effective at controlling the progression of the disease, 5% said "no", 45% said "somewhat", and 50% said "yes".

One patient stated that they received:

> "A left hemicolectomy removed tumour. Underwent 6 months of FOLFOX. Have been in remission for 1 year so far, but long-term side effects from chemo continue to affect my quality of life".

Another patient stated that:

> "Panitumumab worked well at first, but then my cancer [grew] aggressively".

Respondents also indicated (Q20) that they accessed other therapies such surgery and radiation therapy to treat their cancer. When patients/caregivers were asked whether they believed their needs are not being met by current drugs available to treat their cancer (Q35), 30% replied "yes", with the following open-ended responses:

> "Yes, while existing drugs have a certain efficacy in prolonging life, the challenge is still what can I do to shrink the tumour to make surgery possible [and] be cured."
>
> "While I am hoping I'm in remission, there may be microscopic cancer cells floating around. Obviously, fighting cancer is the priority. That being said, there was not a choice. I was told Folfox was the treatment. I was not informed about long-term neuropathy & muscle pain caused by these drugs prior to treatment. Microscopic cancer cells are a mystery. Did I need Folfox or not? It was what I was prescribed. So, I trusted. But not it seems there is no support for my long-term effects of chemo".
>
> "Studies are not moving fast enough."

Improved Outcomes

Survey data regarding improved outcomes is summarized in the PDF attached, entitled: "Summary graphs – Improved Outcomes."

Patients/caregivers were asked to rate how important it is to them for a new therapy to bring about improvement to their physical condition and quality of life (Q40 and Q41). 89% of respondents replied 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 72% indicated that it was very important for a new therapy to bring about improvement in their quality of life. 83% of patients/caregivers indicated that they would be willing to take a drug that has been proven to provide better quality of life even if it does not extend overall survival (Q42).

The series of questions Q43-46 aimed to understand patient and caregiver trade-offs with respect to tolerating significant side effects associated with the combination under review (nausea, anemia, neutropenia) if overall survival was 10 months; 8 months; 6 months; 4 months; and 3 months.

- 83% of respondents replied that tolerating significant side effects would be acceptable if overall survival was 10 months;
- 76% of respondents replied that significant side effects would be tolerable if overall survival was 8 months;
- 59% of respondents replied that significant side effects would be tolerable if overall survival was 6 months;
- 53% of respondents replied that significant side effects would be tolerable if overall survival was 4 months;
- 53% of respondents replied that significant side effects would be tolerable if overall survival was 3 months.

These results are significant because even when overall survival is modest, at 3-4 months, more than half of patients/caregivers are willing to tolerate significant side effects. In Q48, 72% of patients/caregivers indicated that it is very important to have a choice along with their physicians in deciding which drug would be best suited to them.

Experience With Drug Under Review

For patients with refractory mCRC, limited therapeutic options exist to treat their disease. The therapy under review, Trifluridine and Tipiracil (Lonsurf®) in combination with bevacizumab, could help address this unmet medical need by providing patients with a new therapeutic option that has an acceptable toxicity profile and that can help extend their overall survival. Improved access to Lonsurf® in combination with bevacizumab could make a significant difference in the lives of patients who have exhausted standard of care therapies.

One patient who completed the online survey has experience with the combination under review. The therapy was funded through their provincial health plan (Ontario). Compared to the other therapies that the patient accessed, FOLFOX and FOLFIRI, they indicated that the combination under review was “the same” in terms of side effects (Q55), and they rated their overall experience with the combination therapy as similar to their experiences with other drugs (Q67). They indicated that Lonsurf® in combination with bevacizumab was able to partially shrink/control their CRC and/or metastasis (Q58), with the common side effects being neutropenia, loss of appetite, diarrhea, and nausea (Q59), the last of which was noted to be the most difficult to tolerate (Q60). The patient indicated that the combination under review was easy to administer/receive (Q62), and at no point did they have to stop treatment due to side effects (Q63). The patient indicated that

while the management of side effects was the most difficult aspect of the treatment (Q66), they were still able to continue their daily activities or work while undergoing treatment (Q65).

When asked about whether the combination should be funded for the treatment of metastatic colorectal cancer, the respondent replied "yes", with the following open-ended response:

> "I believe it is a significant advance to have the opportunity to extend my life with as reasonable quality of life as possible so that I can spend more time with my family. Every month gained is a win!"

One patient from Quebec who participates in CCC's support groups had experience with the combination under review but was unable to complete the survey. When asked to comment on the importance of access to this combination, they stated that they:

> "[Are] relieved to know that it's available to control progression until [I'm] able to determine if other more curative treatments are available following genetic sequencing".

From a previous Lonsurf® submission to CADTH completed by CCC, one patient indicated that he had experience with the combination under review. Regarding side effects, he stated:

> "I only had one side effect: generalized fatigue".

With respect to quality of life, he stated that:

> "It was really ok to tolerate – way easier to tolerate compared to others like oxaliplatin, that's for sure."

Although other patient/caregiver respondents did not have direct experience with the combination under review, they were asked to provide any additional comments about the new therapeutic combination:

> "If cancer returns, I'd like it to be available in Ontario."
>
> "Stage IV, CRC mets to liver. Fear of recurrence. Need it to be available."

Anything Else?

If publicly funded, Lonsurf® plus bevacizumab could be an important therapeutic option for the mCRC patient population who have exhausted standard of care therapies or are not considered candidates for those therapies. Given that Lonsurf® monotherapy is currently reimbursed only in Quebec, we believe that there is a strong need for equity of access for patients located elsewhere in Canada. **We, therefore, strongly support and urge that a positive funding recommendation be issued for Trifluridine and Tipiracil (Lonsurf®) in combination with bevacizumab for the treatment of metastatic colorectal cancer.** We believe this combination aligns well with the identified patient and caregiver need for a new, effective treatment option, that is capable of prolonging life and maintaining QoL.

Conflict of Interest Declaration — Colorectal Cancer Canada

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

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Table 3: Financial Disclosures for Colorectal Cancer Canada

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Abbvie Corp.	–	–	X	–
Amgen Canada Inc.	–	–	–	X
Astra Zeneca Canada Inc.	–	–	–	X
Bayer Inc.	–	–	–	X
Boehringer Ingelheim Ltd.	–	–	–	X
Hoffmann-La Roche	–	–	–	X
Innovative Medicines Canada	–	–	–	X
INCYTE	–	–	X	–
Janssen Inc.	–	–	–	X
Pfizer Canada Inc.	–	–	–	X
Taiho Pharma Canada	–	–	X	–
GlaxoSmithKline	–	–	–	X
Novartis	–	–	X	–
Merck Canada Inc.	–	–	–	X
Bristol Myers Squibb Canada	–	–	–	X

Clinician Input

The Canadian Gastrointestinal Oncology Evidence Network with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians)

About The Canadian Gastrointestinal Oncology Evidence Network with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians)

The Medical Advisory Board of Colorectal Cancer Canada works alongside the patient group to ensure its activities and health information are relevant and useful for patients and caregivers. The Canadian GI Oncology Evidence Network (CGOEN) is a virtual and inclusive network of Canadian GI Oncology clinicians

who contribute to the knowledge of GI cancer and its treatments, including participating in clinical trials, conducting observational research, and involvement in local/provincial and national clinical guideline developments and health technology assessment.

https://www.colorectalcancercanada.com/about/staff-board-medical-advisory/

Information Gathering

Information gathered for this submission was based on personal experience in treating patients with metastatic colorectal cancer 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:

Prager GW, Taieb J, Fakih M, Ciardiello F, Van Cutsem E, Elez E, Cruz FM, Wyrwicz L, Stroyakovskiy D, Pápai Z, Poureau PG, Liposits G, Cremolini C, Bondarenko I, Modest DP, Benhadji KA, Amellal N, Leger C, Vidot L, Tabernero J; SUNLIGHT Investigators. **Trifluridine-Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer**. N Engl J Med. 2023 May 4;388(18):1657-1667. doi: 10.1056/NEJMoa2214963. PMID: 37133585.

Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, Yamazaki K, Shimada Y, Tabernero J, Komatsu Y, Sobrero A, Boucher E, Peeters M, Tran B, Lenz HJ, Zaniboni A, Hochster H, Cleary JM, Prenen H, Benedetti F, Mizuguchi H, Makris L, Ito M, Ohtsu A; RECOURSE Study Group. **Randomized trial of TAS-102 for refractory metastatic colorectal cancer**. N Engl J Med. 2015 May 14;372(20):1909-19. doi: 10.1056/NEJMoa1414325. PMID: 25970050.

Current Treatments and Treatment Goals

Treatment of metastatic colorectal cancer(mCRC) is limited to Fluoropyrimidine/Irinotecan and Fluoropyrimidine/Oxaliplatin chemotherapy backbones with the use of Bevacizumab and anti-EGFR monoclonal antibody therapy (either Panitumumab or Cetuximab) in tumor without a RAS mutation. Treatment of MSI-H mCRC includes the use of checkpoint inhibitor pembrolizumab. In tumors that have a BRAF V600E variant, treatment would include the use of encorafenib with anti-EGFR monoclonal antibody therapy. The sequencing and use of biologics are left to the clinician discretion based on patient and tumor-related factors. Beyond these treatments, there are two Health Canada approved options, Trifluridine-Tipiracil (also known as TAS-102) and regorafenib. These drugs are recommended for use by clinical guidelines internationally and are standard comparisons in clinical trials. Both are not recommended by CADTH for funding and are user pay options for patients.

Trifluridine-Tipiracil is currently Health Canada approved but received a negative CADTH recommendation August 2019 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 positive recommendation from INESSS. Outside of Quebec, patients have been able to apply to the manufacturer for access to Trifluridine-Tipiracil through private insurance or direct user pay.

There is an unmet need for patients with advanced colorectal cancer whose disease progresses on currently available/funded therapies. Clinical trials that open in this space often accrue faster than anticipated. Many of these patients have a reasonable ECOG of 0 or 1.

The primary goal for therapy in this population is overall survival. Response rates and quality of life are also goals for minimizing symptoms and the ability to maintain independence.

The data from the SUNLIGHT trial show a significant improvement of overall survival: the median overall survival is 7.5 months for Trifluridine-Tipiracil alone and 10.8 months for Trifluridine-Tipiracil and Bevacizumab. However, in the Canadian context since Trifluridine-Tipiracil is not publicly funded, survival should be compared to the original trial which showed an improvement of overall survival from 5.3 months with best supportive care to 7.1 months with Trifluridine-Tipiracil. It is reasonable to overlap the two trials given that the two treatment populations are similar and the Trifluridine-Tipiracil arms in both trials performed in a similar manner 7.5 months in the SUNLIGHT trial vs 7.1 months in the RECOURSE trial. Therefore, the benefit in overall survival is approximately 10.8 months vs 5.3 months. This improvement in survival was obtained with a minimal increase in toxicity and is clinically meaningful.

Treatment Gaps (Unmet Needs)

Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

Currently outside of Quebec – there are no funded treatment options for patients with mCRC who have been treated with Fluoropyrimidine, Irinotecan, Oxaliplatin, Bevacizumab, anti-EGFR monoclonal antibody therapy (if RAS wild type), and encorafenib for patients with the BRAFV600E variant or pembrolizumab for patients with MSI-H. The current option is to consider user pay for either Trifluridine-Tipiracil or Regorafenib, however it is important to recognize that the option of user pay is not accessible for the majority of Canadian patients with CRC, therefore patients will transition to supportive and palliative care. Therefore, the original trial of Trifluridine-Tipiracil vs best supportive care should be considered in this review to demonstrate that the benefit is actually greater than the current trial given the current landscape in Canada.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

This drug would be placed as a further line of therapy and would be used in patients who received current standard of care options as outlined above 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."

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients suitable for treatment would include refractory or intolerant of Fluoropyrimidine, Irinotecan, Oxaliplatin, Bevacizumab, EGFR monoclonal antibody therapy (if KRAS wild type), encorafenib (if BRAF V600 E), and Immunotherapy (if dMMR or MSI-H). Patients should have an ECOG of 0 or 1 and adequate

hematologic and biochemical parameters for therapy. While the SUNLIGHT trial limited enrolment to patients with an ECOG performance status of 0-1, given the favourable toxicity profile of this combination, from a clinical perspective it would be a safe and reasonable option for those with an ECOG performance status of 2 as well.

There is no biomarker for this therapy and therefore a companion diagnostic is not required. There is not a subgroup that did not show a benefit and it should be noted that the majority of patients had previously received bevacizumab and a benefit is seen with retreatment with bevacizumab in combination with Trifluridine-Tipiracil.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

A clinical assessment would be done before each cycle, with radiographic restaging generally performed every 8-12 weeks.

While the primary goal is to extend survival (which is clearly illustrated as being achieved with the SUNLIGHT survival data compared to best supportive care) it is also improving current symptoms by shrinking tumour burden and delaying further progression (median progression-free survival was 5.6 months in the combination group and 2.4 months in the trifluridine-tipiracil group) and the associated decrease in quality of life and increased symptom burden that comes with that. It is also important to focus on functioning and caregivers. Having an effective treatment to improve symptom burden and delay further deterioration is integral to improving QOL and functioning. This has downstream positive impact on caregivers and translates to a lower burden of health care use for supportive care.

What factors should be considered when deciding to discontinue treatment with the drug under review?

Treatment would be discontinued due to disease progression, toxicity, clinician discretion or patient's request.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

This treatment would be reasonable to be given in any centre and by any specialist who is currently giving systemic therapy for patients with metastatic colorectal cancer.

Additional Information

It is important to note that the majority of Canadian mCRC patients do not have access to publicly funded Trifluridine-Tipiracil. Therefore, when assessing the benefit of therapy – the combination of Trifluridine-Tipiracil with Bevacizumab should be compared to best supportive care.

Conflict of Interest Declarations — The Canadian Gastrointestinal Oncology Evidence Network with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians)

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please refer to the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

Colorectal Cancer Canada provided administrative support in completing this submission, including the collection of, and collation of COI declarations.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. Please note that this is required for *each clinician* who contributed to the input.

Declaration for Clinician 1

Name: Michela Febbraro

Position: Medical Oncologist – Algoma District Cancer Program

Date: 14-07-2023

Table 4: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 1

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 2

Name: Bruce Colwell

Position: Medical Oncologist, director systemic therapy Nova Scotia Cancer Care Program

Date: 03-08-2023

Table 5: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 2

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
Jansen	X	—	—	—
Merck	X	—	—	—
Viatris	X	—	—	—
Seagen	X	—	—	—
Gilead	X	—	—	—
Amgen	X	—	—	—

Declaration for Clinician 3
Name: Francine Aubin

Position: MD

Date: 1 Aug 2023

Table 6: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 3

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
Taiho	X	—	—	—

Declaration for Clinician 4
Name: Frédéric Lemay

Position: Gastroenterologist

Date: 01-08-2023

Table 7: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 4

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 5
Name: Melanie Seal

Position: Medical Oncologist

Date: 04-08-2023

Table 8: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 5

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 6
Name: Shaqil Kassam

Position: Medical oncologist

Date: 10-08-2023

Table 9: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 6

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 7
Name: Alwin Jeyakumar

Position: Medical oncologist

Date: 01-08-2023

Table 10: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 7

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 8
Name: Benoit Samson

Position: Medical oncologist

Date: 07-07-2023

Table 11: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 8

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
Taiho	X	—	—	—
Pfizer	X	—	—	—
BMS	X	—	—	—
Astra Zeneca	X	—	—	—
Merck	X	—	—	—

Declaration for Clinician 9
Name: Callista Phillips

Position: MD

Date: 02-08-2023

Table 12: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 9

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
Taiho	X	—	—	—

Declaration for Clinician 10
Name: Eric Chen

Date: 02-08-2023

Table 13: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 10

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
Taiho	X	—	—	—

Declaration for Clinician 11
Name: Jennifer Lynn Spratlin

Position: Medical Oncology, Cross Cancer Institute; Associate Professor, University of Alberta; Gastrointestinal Oncology and Phase I Clinical Trials/Investigational New Drugs; Wellness Lead, Medical Oncology

Date: 02-08-2023

Table 14: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 11

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 12
Name: Jose Monzon

Date: 01-08-2023

Table 15: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 12

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 13
Name: Ronald Burkes

Position: Medical Oncologist

Date: 04/07/2023

Table 16: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 13

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
AZ	X	–	–	–
Taiho	X	–	–	–
Pfizer	X	–	–	–
Amgen	X	–	–	–

Declaration for Clinician 14
Name: Moustapha Tehfe

Position: Medical oncologist

Date: 02-08-2023

Table 17: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 14

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
Pfizer	–	–	–	X
Taiho	–	–	X	–

Declaration for Clinician 15

Name: Petr Kavan

Position: Medical oncologist

Date: 31-07-2023

Table 18: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 15

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
Education Grant	–	–	X	–

Declaration for Clinician 16

Name: Ravi Ramjeesingh

Position: Medical Oncologist, Department of Medicine, Dalhousie University

Date: 28-06-2023

Table 19: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 16

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
Novartis	X	–	–	–
Pfizer	X	–	–	–
Knight Pharmaceuticals	X	–	–	–
MERCK	X	–	–	–
Roche	X	–	–	–
Amgen	X	–	–	–
Astra-Zeneca	X	–	–	–
Eisai	X	–	–	–
Incyte	X	–	–	–
Ipsen	X	–	–	–

Declaration for Clinician 17
Name: Safiya Karim

Position: Clinical Associate Professor and Medical Oncologist, University of Calgary

Date: 03-Aug-2023

Table 20: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 17

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
Bayer Canada	X	—	—	—
Amgen	X	—	—	—
Ipsen	X	—	—	—
Bristol Myers Squibb	X	—	—	—
Astellas	X	—	—	—

Declaration for Clinician 18
Name: Abdulazeez Salawu

Position: Staff Medical Oncologist

Date: 01-08-2023

Table 21: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 18

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 19
Name: Stephanie Snow

Position: Professor Dalhousie University, Medical Oncologist QEII Health Sciences Centre, Halifax, NS

Date: Aug 1, 2023

Table 22: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 19

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
AstraZeneca	–	–	X	–
Astellas	X	–	–	–
BMS	–	X	–	–
Taiho	X	–	–	–
Roche	–	–	X	–
Merck	–	X	–	–
GSK	X	–	–	–
Janssen	X	–	–	–
Pfizer	X	–	–	–
Sanofi	X	–	–	–
Knight	X	–	–	–
Lilly	X	–	–	–
Takeda	X	–	–	–

Declaration for Clinician 20
Name: Vincent Tam

Position: Medical Oncologist

Date: 01-08-2023

Table 23: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 20

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 21
Name: Ralph Wong

Position: Medical oncologist

Date: 31-07-2023

Table 24: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 21

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 22
Name: Mark Vincent

Position: Medical oncologist

Date: 03-08-2023

Table 25: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 22

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 23
Name: Wendy Lam

Position: Medical oncologist

Date: 04-08-2023

Table 26: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 23

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 24
Name: Brandon Meyers

Position: Medical oncologist

Date: 04-08-2023

Table 27: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 24

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
AstraZeneca	X	–	–	–
Ipsen	–	X	–	–
Roche	–	X	–	–
Incyte	X	–	–	–
Bayer	X	–	–	–

Declaration for Clinician 25
Name: Howard Lim

Position: Medical Oncologist

Date: 22-Aug-2023

Table 28: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 25

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
Roche	X	—	—	—
Bayer	X	—	—	—
Amgen	X	—	—	—
AstraZeneca	—	X	—	—
Astellas	X	—	—	—
BMS	—	X	—	—
Lilly	X	—	—	—
Taiho	X	—	—	—
Eisai	—	X	—	—
Ipsen	X	—	—	—
Varian	X	—	—	—

Declaration for Clinician 26
Name: Dr. Sharlene Gill

Position: Medical Oncologist, Professor of Medicine – BC Cancer, Vancouver

Date: 03-08-2022

Table 29: COI Declaration for CGOEN with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians) — Clinician 26

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	—	—	—	—

Ontario Health Cancer Care Ontario Gastrointestinal Cancer Drug Advisory Committee (GI DAC)

About Ontario Health Cancer Care Ontario Gastrointestinal Cancer Drug Advisory Committee (GI DAC)

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

Information Gathering
Information was gathered through videoconferencing and email communication.

Current Treatments and Treatment Goals
This indication is for mCRC in the third line setting, after patients have received 5-Fluorouracil, Oxaliplatin, Irinotecan in addition to targeted therapy (anti-VEGF therapy and/or anti-EGFR therapy, as appropriate. Currently, Health Canada has approved both Regorafenib and Trifluridine/Tipiracil (as single agents) in this setting; however, neither are currently widely funded by provincial health authorities.

The SUNLIGHT study compared the combination of Trifluridine/Tipiracil and Bevacizumab against Trifluridine/Tipiracil alone (which is a reasonable and widely accepted standard-of-care arm). Also note that most patients on the study were previously treated with Bevacizumab in a previous line of therapy.

Goals of treatment in this indication are improvement of overall survival, minimization of toxicity, and improvement/maintenance of quality of life.

Treatment Gaps (Unmet Needs)
Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

After progression on 5FU, oxaliplatin, irinotecan, bevacizumab, and EGFRi (if indicated), there is no funded treatment option. While Health Canada has approved both regorafenib and Trifluridine/Tipiracil, neither are funded by provincial health authorities. For mutated RAS patients, and even non-mutated this is very meaningful, as sometimes there is only 2 lines of treatment. So, for a patient with a very good performance status, there is nothing else to try that is funded.

Both of those options (Trifluridine/Tipiracil and Regorafenib) have only marginal improvements in overall survival compared to placebo.

Unlike those previous studies, the SUNLIGHT trial compared Trifluridine/Tipiracil + Bev to an active comparator (Trifluridine/Tipiracil alone) and showed a modest benefit.

Place in Therapy
How would the drug under review fit into the current treatment paradigm?

Similar to the trial criteria, patients would be eligible for Trifluridine/Tipiracil + Bevacizumab if they 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.

In Ontario, patients often only receive either EGFRi (if RAS WT) or Bevacizumab, but rarely both due to our current funding algorithms. Therefore, we would suggest that patients should be eligible for Trifluridine/Tipiracil + Bevacizumab for those who have received 5FU, oxaliplatin, irinotecan, and either/both of EGFRi/VEGFi. Also, given DPYD testing, patients with prior raltitrexed should be eligible as well.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Good performance status.

Likely 20-30% of all mCRC patients will be well enough to receive fourth line therapy.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

CEA testing, cross-sectional imaging, symptoms

What factors should be considered when deciding to discontinue treatment with the drug under review?

Progression and intolerance.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

CCO-approved cancer facilities that have qualified staff, lab facilities, infusional facilities (Level 1-4 Cancer Centres)

Note that patients have to be followed closely for neutropenia, thrombocytopenia, bleeding/thrombosis, and proteinuria.

Additional Information

Not applicable.

Conflict of Interest Declarations — Ontario Health Cancer Care Ontario Gastrointestinal Cancer Drug Advisory Committee (GI DAC)

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

OH-CCO provided a secretariat function to the group.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. Please note that this is required for *each clinician* who contributed to the input.

Declaration for Clinician 1
Name: Dr. Erin Kennedy

Position: Lead, Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee

Date: 20-08-2023

Table 30: COI Declaration for Ontario Health Cancer Care Ontario Gastrointestinal Cancer Drug Advisory Committee (GI DAC) — Clinician 1

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 2
Name: Dr. Suneil Khanna

Position: Member, Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee

Date: 23-08-2023

Table 31: COI Declaration for Ontario Health Cancer Care Ontario Gastrointestinal Cancer Drug Advisory Committee (GI DAC) — Clinician 2

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
Taiho	X	—	—	—
Roche	X	—	—	—
Amgen	X	—	—	—
Organon	X	—	—	—

Declaration for Clinician 3
Name: Dr. Rachel Goodwin

Position: Member, Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee

Date: 20-08-2023

Table 32: COI Declaration for Ontario Health Cancer Care Ontario Gastrointestinal Cancer Drug Advisory Committee (GI DAC) — Clinician 3

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
Taiho	X	—	—	—
Roche	X	—	—	—
Amgen	X	—	—	—

Declaration for Clinician 4

Name: Dr Bishal Gyawali

Position: Member, Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee

Date: 21-08-2023

Table 33: COI Declaration for Ontario Health Cancer Care Ontario Gastrointestinal Cancer Drug Advisory Committee (GI DAC) — Clinician 4

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	—	—	—	—

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Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the CADTH Drug Reimbursement Review Confidentiality Guidelines

Stakeholder Input: The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations. As such, they are independent of CADTH and do not necessarily represent or reflect the view of CADTH. No endorsement by CADTH is intended or should be inferred. By filing with CADTH, the submitting organization or individual agrees to the full disclosure of the information. CADTH does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting organization or individual and all conflict of interest information are included in the submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

Accessibility: CADTH is committed to treating people with disabilities in a way that respects their dignity and independence, supports them in accessing material in a timely manner, and provides a robust feedback process to support continuous improvement. All materials prepared by CADTH are available in an accessible format. Where materials provided to CADTH by a submitting organization or individual are not available in an accessible format, CADTH will provide a summary document upon request. More details on CADTH's accessibility policies can be found here.

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.