pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

NOTE: This recommendation supersedes the pERC Final Recommendation for this drug and indication dated July 6, 2018

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Drug: Trifluridine and Tipiracil (Lonsurf)

Submitted Reimbursement Request: For the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies; anti-vascular endothelial growth factor biological agents; and, if RAS wild-type, anti-epidermal growth factor receptor agents.

Submitted By: Taiho Pharma Canada Inc.	**Manufactured By:** Taiho Pharma Canada Inc.
NOC Date: January 25, 2018	**Submission Date:** January 21, 2019
Initial Recommendation: July 5, 2019	**Final Recommendation:** August 29, 2019

pERC Final Recommendation

This pERC Final Recommendation is based on a reconsideration of the 2019 Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Approximate per Patient Drug Costs, per Month (28 Days)	• Trifluridine-tipiracil costs $76.25 per 15 mg tablet and $93.85 per 20 mg tablet. • At the recommended daily dose of 70 mg/m^2, the cost of trifluridine-tipiracil per 28-day treatment cycle is $5,773 for cycle 1, $5,724 for cycle 2, $5,704 for cycle 3, and $5,700 for subsequent cycles. Note: Costs are calculated based on an average body surface area of 1.78 m^2 and have been adjusted to account for dose reduction.

pERC RECOMMENDATION ☐ **Reimburse** ☐ **Reimburse with clinical criteria and/or conditions*** ☒ **Do not reimburse** *If the condition(s) cannot be met, pERC does not recommend reimbursement of the	pERC does not recommend the reimbursement of trifluridine-tipiracil (Lonsurf) for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies, including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies; anti-vascular endothelial growth factor (VEGF) agents, and anti-epidermal growth factor receptor (EGFR) agents. pERC issued its 2018 original recommendation to not reimburse trifluridine-tipiracil because, compared with placebo plus best supportive care (BSC), trifluridine-tipiracil plus BSC had inconsistent results between trials, potentially modest progression-free survival (PFS) and overall survival (OS) benefit, moderate toxicities, and an uncertain impact on quality of life. Submitters may make a resubmission to pCODR if they have new clinical or economic evidence that addresses concerns raised in earlier

drug for the submitted reimbursement request.	recommendations. For this 2019 resubmission, the submitter provided new evidence on health-related quality of life (HRQoL) using validated measures. However, the new observational evidence has significant limitations (non-comparative; no baseline HRQoL data prior to treatment); based on the study designs used, observed outcomes cannot be attributed to treatment with trifluridine-tipiracil nor can it be determined whether trifluridine-tipiracil improves HRQoL relative to BSC. Therefore, based on the new evidence on HRQoL, pERC decided to uphold its original recommendation. pERC concluded that trifluridine-tipiracil aligned with patient values of a new treatment option that offers ease of oral administration, with moderate but manageable toxicities, and a potentially modest clinical effect compared with placebo plus BSC. pERC was uncertain whether the new evidence aligns with patient values for improved HRQoL. The committee noted that at the submitted price, trifluridine-tipiracil plus BSC compared with placebo plus BSC cannot be considered cost-effective in this population.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps were identified.

SUMMARY OF pERC DELIBERATIONS

In Canada, metastatic colorectal cancer (mCRC) is the second most common cause of cancer death in males and the third most common cause of cancer death in females. pERC acknowledged that there are limited effective treatment options for patients with late-stage disease who have exhausted all other standard treatment options. Patients are currently given BSC after being treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, anti-VEGF therapy, and, if their disease is KRAS wild-type, anti-EGFR therapy. The life expectancy of these patients from the time of diagnosis of metastatic disease is approximately two years but is much shorter once all treatment options have been exhausted.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

As part of deliberations, pERC restated its assessment of the evidence that informed the original 2018 recommendation to not reimburse trifluridine-tipiracil for mCRC, which included three randomized controlled trials (RCTs; RECOURSE, TERRA, and J003-100400306). Based on that evidence, pERC issued a negative recommendation for reimbursement as it considered that, compared with placebo plus BSC, trifluridine-tipiracil had only a modest PFS and OS benefit, moderate toxicities, and an uncertain impact on HRQoL. The committee observed variation in the magnitude of clinical benefit among the trials (median improvement in survival and relative risk reduction) and was therefore uncertain how this magnitude of improvement would translate into clinical practice and whether it was clinically meaningful. pERC concluded that trifluridine-tipiracil aligned with patient values because it provides a treatment option that offers ease of oral administration, but it also has moderate toxicities and a modest clinical effect compared with placebo plus BSC. Additionally, pERC highlighted that the impact of trifluridine-tipiracil on HRQoL is unknown, as it was not measured in any of the RCTs, despite their robust sample sizes. While there were two post-hoc analyses of proxy measures for HRQoL (deterioration in performance status, quality-adjusted time without toxicity and symptoms analysis) presented as evidence, pERC agreed with the pCODR Methods Team appraisal that the proxies used were not validated or formally recognized surrogates for HRQoL. pERC indicated that robust data on HRQoL could have been impactful on its recommendation.

During reconsideration of the pERC Initial Recommendation, pERC discussed the feedback received from the submitter on the determination of resubmission eligibility of trifluridine-tipiracil in mCRC and pCODR's decision to focus the resubmission on the outcome of HRQoL. pERC noted that the pCODR Presubmission, Submission, and Resubmission Guidelines (hereinafter referred to as "Guidelines") clearly outline the circumstances under which pCODR may accept resubmissions, and all circumstances are based on the provision of new information. According to the Guidelines, submitters may make resubmissions to pCODR if they have new clinical or economic evidence that addresses concerns raised in earlier recommendations. For the 2019 resubmission of trifluridine-tipiracil the submitter provided new HRQoL data and new efficacy data from real world evidence (RWE) sources for pERC to consider. A pERC panel comprised of three pERC members performed an administrative review of the new information submitted in order to determine if it met the resubmission requirements as outlined in the Guidelines; however, it did not carry out a critical appraisal of the new information, as quality assessment is the purpose and focus of the full drug review process. The pERC panel granted the resubmission on November 2, 2018 based on the new information on HRQoL that was not available at the time of the original drug submission; the lack of HRQoL data from validated measures was an issue identified in the original 2018 pERC recommendation, and therefore, the panel deemed the resubmission eligible in order to assess the new HRQoL information through the full review process. Conversely, the pERC panel concluded that the new efficacy data that were submitted from RWE sources did not address the sources of uncertainty (comparative PFS or OS of trifluridine-tipiracil compared with placebo) that were identified in the original 2018 pERC recommendation and informed the submitter that these data would not be reviewed as part of the resubmission. pERC discussed that most of the stakeholder feedback received (clinicians, patient group, and submitter) on the 2019 Initial Recommendation centred on the evidence contained in the original 2018 submission but they emphasized that since the purpose of the pCODR resubmission process is to evaluate new information, the evidence contained in the original 2018 submission was not re-evaluated by pERC for the 2019 resubmission.

For the resubmission of trifluridine-tipiracil in 2019, pERC deliberated solely on new HRQoL evidence provided by the submitter, as the resubmission to pCODR was granted based on evidence for this outcome. The new evidence on HRQoL comes from two ongoing observational studies (PRECONNECT and a study referred to herein as TAS-102 versus BSC) that report validated measures of HRQoL in pre-treated patients with mCRC who received trifluridine-tipiracil. PRECONNECT is a multi-centred, phase IIIb, single-group, non-comparative, early access study that reports changes in HRQoL from baseline to end of treatment (EOT) using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0 (EORTC QLQ-C30; global health status) and the EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) (utility score and Visual Analogue Scale [VAS]). TAS-102 versus BSC is an open-label, multi-centred, non-randomized study with two cohorts of patients, one treated with trifluridine-tipiracil and the other with BSC, that provides a one-time point comparison of the HRQoL of each cohort using the Rotterdam Symptom Checklist (RSCL), the FACT Colorectal Symptom Index (FCSI), and Numerical Rating Scale for Pain (NRS). pERC noted that neither study has been fully published; preliminary data on PRECONNECT are available in conference form for the first 464 of 1,000 targeted patients, and data from TAS-102 versus BSC were provided by the submitter in a clinical study report that includes results for the first 70 of 100 targeted patients. As the focus of the resubmission was on HRQoL, pERC did not review efficacy and safety data from the PRECONNECT study; and the TAS-102 versus BSC study did not report on the efficacy or safety of trifluridine-tipiracil.

In the PRECONNECT study, data on mean change in HRQoL from baseline to EOT showed that patients treated with trifluridine-tipiracil experienced clinically relevant deterioration for the EQ-5D utility and VAS; and for the QLQ-C30 global health status, the change from baseline was just short of reaching the clinically relevant deterioration threshold. The proportion of patients who experienced improvement or no deterioration in HRQoL at EOT from baseline was 58.5%, 60.3%, and 46.9% according to the QLQ-C30 global health status, EQ-5D utility, and EQ-5D VAS, respectively. While pERC agrees with the Clinical Guidance Panel (CGP) that these data indicate a sizable proportion of patients report improvement or no deterioration in HRQoL after treatment with trifluridine-tipiracil, the non-comparative design of PRECONNECT makes it unclear whether this outcome is better, the same, or worse when compared with BSC. pERC agreed with the CGP's assessment that the TAS-102 versus BSC study is of limited value given its cross-sectional design, the lack of baseline HRQoL data pre-treatment, and other unknown information, including time of outcome assessment in relation to treatment cycle and disease progression. pERC also noted the imbalance in Eastern Cooperative Oncology Group (ECOG) performance status between the cohorts at the start of treatment could significantly bias outcomes in favour of trifluridine-tipiracil.

pERC discussed at length the limitations of the new evidence on HRQoL and unanimously agreed that the observational studies that were submitted fall short of providing a robust assessment of HRQoL outcomes in patients treated with trifluridine-tipiracil relative to BSC. pERC agreed with the pCODR Methods Team that given the studies' non-comparative and cross-sectional design, the HRQoL outcomes observed cannot be attributed to treatment with trifluridine-tipiracil, nor can it be determined whether trifluridine-tipiracil improves HRQoL relative to BSC. For this reason, pERC concluded that the impact of trifluridine-tipiracil on HRQoL remains uncertain. Since the new evidence on HRQoL is insufficient to recommend reimbursement of trifluridine-tipiracil in mCRC, pERC decided to uphold its original negative recommendation.

pERC deliberated patient advocacy group input that indicated patients value additional therapies to help control their disease (with respect to OS and PFS), reduce CRC-induced symptoms, and improve HRQoL even if survival is not extended. pERC appreciated the considerable effort that the patient group made to identify and interview patients and caregivers who have experience with trifluridine-tipiracil and noted that patient input was of high quality and thus very informative in its deliberations. pERC acknowledged that respondents with direct experience with trifluridine-tipiracil reported manageable side effects that were less toxic compared with other therapies but noted issues with fatigue and nausea. pERC agreed with the patient input that there is a need for more options for patients with this disease when all standard treatment options have been exhausted. pERC concluded that trifluridine-tipiracil aligned with patient values because it provides a treatment option that offers ease of oral administration with moderate but manageable toxicities and a potentially modest clinical effect compared with placebo plus BSC; however, pERC was uncertain whether the new HRQoL evidence aligns with patient values for improved HRQoL, as the evidence provided does not demonstrate an improvement over BSC.

pERC agreed with clinician input that currently there are no funded treatment options for patients with chemorefractory mCRC and the only treatment option provided to patients is BSC. pERC was also in agreement that trifluridine-tipiracil would be considered in patients with mCRC who have a preserved ECOG performance status of 0 or 1 and as a last line of therapy in patients who have failed prior therapies, including fluoropyrimidines, irinotecan, oxaliplatin, bevacizumab, and, in patients with KRAS wild-type tumours, prior anti-EGFR therapy. The clinicians identified patients with known dihydropyrimidine dehydrogenase (DPD) deficiency (as trifluridine-tipiracil is not metabolized by DPD), as well as patients who experience 5-fluorouracil/capecitabine-related angina as a small patient subgroup who would also benefit from treatment with trifluridine-tipiracil. pERC noted that the clinician input aligned with patients' experiences with the toxicity profile of trifluridine-tipiracil; the clinicians viewed the toxicity profile of trifluridine-tipiracil to be better tolerated among patients than other therapies, and the toxicities were easily managed by medical oncologists.

pERC deliberated the cost-effectiveness of trifluridine-tipiracil. pERC noted that the pCODR Economic Guidance Panel's (EGP) estimates were higher than the submitter's base-case estimates and also observed that compared with the original economic evaluation, incorporation of utility data from the PRECONNECT study did not improve cost-effectiveness estimates. pERC agreed with the EGP's reanalysis approach of using the same data source (RECOURSE trial) to model outcomes versus using pooled survival data from two sources; this change had the most influential impact on the ICER. The submitter's selection of data sources was raised as a limitation in the original economic evaluation, where pERC noted the TERRA study was not used to inform the economic evaluation, which would likely further increase the ICER estimates due to the less-optimistic efficacy results observed in TERRA. The TERRA trial also did not inform the resubmission economic evaluation. pERC agreed with the EGP's conclusion that the new HRQoL evidence adds little to the economic model. The EGP noted that while point estimates of utility may be improved compared with the original economic evaluation, uncertainty remains in utility estimates (no measure of utility for BSC; no measure of variance for the post-progression health state). pERC concluded that at the submitted price, trifluridine-tipiracil plus BSC cannot be considered cost-effective in patients with mCRC when compared to placebo plus BSC.

pERC discussed the factors that could impact the feasibility of implementing a positive reimbursement recommendation for trifluridine-tipiracil and noted that trifluridine-tipiracil is expected to be an additional sequential therapy in the treatment of patients with mCRC. Given that trifluridine-tipiracil will not likely replace other therapies, overall treatment costs could increase if the regimen were funded. pERC also noted that the submitted budget impact analysis (BIA) excluded second therapies, and likely underestimated treatment duration and market share uptake of trifluridine-tipiracil. Therefore, the potential budget impact is likely underestimated and may be significantly larger given the prevalence of mCRC.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and BIA
- guidance from the pCODR clinical and economic review panels
- input from one patient advocacy group (Colorectal Cancer Canada [CCC])
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, CCC
- One clinician group comprised of nine clinicians, with representation from Alberta, British Columbia, Manitoba, New Brunswick, Ontario, and Quebec
- The PAG
- The submitter Taiho Pharma Canada

The pERC Initial Recommendation was to not recommend reimbursement of trifluridine-tipiracil for mCRC. Feedback on the pERC Initial Recommendation indicated that the manufacturer, patient advocacy group, and registered clinician group disagreed with the Initial Recommendation; and PAG agreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR Review Scope

The purpose of the review is to evaluate the safety and efficacy of trifluridine-tipiracil (Lonsurf) 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.

Based on pERC's negative recommendation for reimbursement in 2018, the submitter resubmitted to pCODR in 2019 with new clinical information on the efficacy and safety of trifluridine-tipiracil. After reviewing the new evidence for resubmission eligibility, pERC granted the resubmission based on new HRQoL evidence only. As such, the RCT evidence contained in the original submission was not comprehensively reviewed again for the resubmission. An updated literature search performed by pCODR did not identify any new RCT evidence evaluating trifluridine-tipiracil in mCRC; the new evidence on HRQoL was excluded from the pCODR systematic review based on non-RCT design and was instead included as supplemental information relevant to the review.

Studies included: Two observational studies (non-comparative early access study; non-randomized cohort study)

The new evidence on HRQoL includes two observational studies: PRECONNECT and a study referred to herein as TAS-102 versus BSC. Both studies reported validated measures of HRQoL in pre-treated patients with mCRC who received trifluridine-tipiracil.

The PRECONNECT study is an ongoing, multi-centre, phase IIIb, single-group, non-comparative, early access study of trifluridine-tipiracil in patients 18 years of age or older 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. The main objective of the PRECONNECT study is to collect additional safety and efficacy data during treatment with trifluridine-tipiracil in patients with pre-treated mCRC. Included patients had received at least two prior regimens of standard chemotherapies and had an ECOG performance status of 0 or 1. To date, study data have only been published in conference form.

The TAS-102 versus BSC study is an ongoing, open-label, multi-centred, non-randomized study with two cohorts of patients, one treated with trifluridine-tipiracil and the other with BSC. The objectives of the study are to quantify the difference in HRQoL, colorectal cancer-related symptoms, and pain in refractory mCRC patients who were treated with TAS-102 versus those treated with BSC in a real-life setting. Included patients were 18 years of age or older who had been previously treated with at least two prior lines of chemotherapy for mCRC. To date, no study data have been published; the study data reported herein come from a clinical study report dated April 3rd, 2019 that was provided by the submitter to pCODR.

Patient populations: ECOG performance status 0 to 1; ≤ 3 prior therapies

As of March 25th, 2019, 832 patients have been enrolled for participation in the PRECONNECT study. The target number of participants is approximately 1,000 in 20 countries. The patient population was selected based on their choice to receive the intervention (trifluridine-tipiracil), and the study inclusion criteria used were similar to the RECOURSE trial. At the time of the most recent data cut-off on May 20, 2018, there were 464 patients enrolled. The baseline characteristics of patients in the PRECONNECT study are similar to the patients in the RECOURSE trial. At cut-off, the median age of patients was 64 years with a range of 28 to 87 years. The majority of patients were male (63.6%), white (87.3%), had an ECOG performance status of 1 (54.1%), had KRAS mutated status (51.9%), had three or fewer prior treatment lines (63.6%), and had a time from diagnosis of metastasis that was 18 months or greater (81.9%). Patients received trifluridine-tipiracil for a mean (± standard deviation [SD]) of 3.8 (± 2.6) months and a median (range) of 3.0 (0.4 to 14.7) months.

As of April 3rd, 2019, a total of 70 patients had been recruited and enrolled for participation in the TAS-102 versus BSC study. The intended number of participants is 100 from centres across Canada. As of April 3rd, the median age of the trifluridine-tipiracil cohort was 63 years with a range of 40 to 77 years, and the majority of patients were male (51%.), had KRAS wild-type status (56%), had an ECOG performance status of 1 (92%), and had three prior therapies (54%). The median age of the BSC cohort was 63 years with a range of 44 to 77 years, and the majority of patients were male (71%), had KRAS wild-type status (52%), had an ECOG performance status of 2 (71%), and had three prior therapies (61%). Information on treatment exposure in patients in the trifluridine-tipiracil cohort was not reported.

Key efficacy results: Not the focus of resubmission

pERC granted the resubmission of trifluridine-tipiracil on the basis of new HRQoL evidence; therefore, efficacy and safety data from PRECONNECT were not reviewed. The TAS-102 versus BSC study did not report on the efficacy or safety of trifluridine-tipiracil.

Patient-reported Outcomes: A proportion of patients experience no deterioration in HRQoL

PRECONNECT

HRQoL was a secondary outcome of the study and was measured using the EORTC QLQ-C30 (global health status) and EQ-5D-3L (utility and VAS) questionnaires. Patients completed both questionnaires at baseline, every four weeks during study treatment, and at the withdrawal visit. Clinically relevant deterioration from baseline thresholds were defined as a 10-point change for the QLQ-C30 global health status, a decrease of nine or more points for the EQ-5D utility score, and a decrease of seven or more points for the EQ-5D VAS score. The completion rate was reported to be greater than 92% for each questionnaire at each treatment cycle. Change in HRQoL from baseline to EOT was reported for 207 patients for the QLQ-C30, 209 patients for the EQ-5D utility, and 205 patients for the EQ-5D VAS. While on treatment there were no clinically relevant differences in mean change from baseline at any assessment time point for either the QLQ-C30 global health status or the EQ-5D (utility and VAS). Data on mean change in HRQoL from baseline to EOT showed clinically relevant deterioration for the EQ-5D utility score (-9.1 ± 23.6) and the VAS (-8.3 ± 19.3). For the QLQ-C30 global health status, the mean change was just short of reaching the clinical deterioration threshold (-9.9 ± 23.3). Clinical deterioration from baseline in QLQ-C30 global health status, EQ-5D utility, and EQ-5D VAS occurred in 41.5%, 39.7%, and 53.1% of patients, respectively. Median time-to-deterioration in QLQ-C30 global health status was 3.7 months (95% confidence interval, 3.2 to 4.6). The percentage of patients who experienced improvement or no deterioration in HRQoL from baseline was 58.5%, 60.3%, and 46.9% according to the QLQ-C30 global health status, EQ-5D utility, and EQ-5D VAS, respectively.

TAS-102 versus BSC

A total of 70 patients have been enrolled in the TAS-102 versus BSC study; 39 in the trifluridine-tipiracil cohort and 31 in the BSC cohort. The questionnaires used to capture patient-reported HRQoL outcomes

included the RSCL, which was used to measure overall HRQoL; the FCSI; and the NRS. In this study no baseline HRQoL data prior to treatment were captured. Patients completed the three questionnaires once on paper (one-time data capture) and therefore the study did not evaluate the change from baseline in HRQoL outcomes. The questionnaire completion date and time in relation to disease progression or after treatment cycles were not reported. For the RSCL, the majority of patients (14 out of 39, 36%) in the trifluridine-tipiracil cohort rated their valuation of life as "good" while the majority of patients (15 out of 31, 48%) in the BSC cohort rated it as "rather poor." For the FCSI, patients treated with trifluridine-tipiracil had a mean score ± SD of 22.2 ± 6.0 that was significantly higher (indicative of less symptoms) compared with BSC patients who had a mean score ± SD of 19.4 ± 4.1 (P = 0.0292). For the NRS (VAS for pain), there was no significant difference in level of pain between patients treated with trifluridine-tipiracil who had a mean score ± SD of 2.5 ± 2.8 and BSC patients who had a mean score ± SD of 3.2 ± 2.0 (P = 0.1421). Biased outcomes are a significant concern in this study due to the cross-sectional design and the imbalance in ECOG performance status at the start of treatment between cohorts (71% of patients in the BSC cohort had an ECOG performance status of 2, versus 0% of patients in the trifluridine-tipiracil cohort).

Need and Burden of Illness: Effective therapies for patients who have exhausted all other treatments

In Canada, mCRC is the second most common cause of cancer death in males and the third most common cause of cancer death in females. Untreated, the median survival of patients ranges from six months to 10 months. With the availability of cytotoxic chemotherapies (fluoropyrimidines, oxaliplatin, irinotecan) and targeted agents (i.e., bevacizumab, cetuximab, panitumumab), median survival times are now estimated to be 30 to 36 months. Despite these significant improvements, long-term survival is rare; the five-year survival rate is less than 10%, and cures are still not anticipated in patients with unresectable mCRC. Therefore, there is a need for new effective therapies in this patient population. These patients are currently treated with BSC when treatment options are exhausted.

Registered Clinician Input: Unmet need for effective therapies

pERC deliberated two clinician inputs, one joint input submission including 31 oncologists, and one individual submission. The joint clinician input indicated that currently there are no funded treatment options for patients with chemorefractory mCRC and the only treatment option provided to patients is BSC, which is difficult for patients to accept. Patients who have KRAS wild-type tumours may be treated with an EGFR inhibitor and regorafenib is a treatment option for patients who have private drug insurance. The clinicians stated that trifluridine-tipiracil would be considered in patients with mCRC who have a preserved ECOG performance status of 0 or 1 and have failed prior therapies, including fluoropyrimidines, irinotecan, oxaliplatin, bevacizumab and, in patients with KRAS wild-type tumours, prior anti-EGFR therapy. Patients with known DPD deficiency (as trifluridine-tipiracil is not metabolized by DPD), as well as patients who experience 5-fluorouracil/capecitabine-related angina (as 5-fluorouracil-related angina is believed to be related to a DPD metabolite) were identified as a small patient subgroup who would also benefit from treatment with trifluridine-tipiracil. Poor performance status and inability to ingest oral therapy were stated by the clinicians as contraindications to trifluridine-tipiracil. The joint clinician input stated that through their collective experience, the toxicity profile of trifluridine-tipiracil is better tolerated among patients with a more predictable toxicity profile compared with regorafenib. The toxicities related to trifluridine-tipiracil (which include a risk of myelosuppression) were stated to be familiar to and easily managed by medical oncologists.

PATIENT-BASED VALUES

Experience of patients with mCRC: Disease symptoms significantly impact HRQoL

One patient group, CCC, provided input on trifluridine-tipiracil for the treatment of patients with mCRC. Input was received from 118 respondents (85 patients, 28 caregivers, and five patients who were also caregivers). From the patient input provided, CCC identified bloody stools, diarrhea, fatigue, constipation, abdominal cramping, and pencil-thin stools as the most prevalent symptoms of CRC. Patients indicated diarrhea and fatigue resulting from the cancer as the most significant and difficult symptoms to control. CRC-induced symptoms were cited as interfering with HRQoL and daily activities as well as having psychological impacts that included depression.

Patient values on treatment: Need for additional treatments

The patient input received indicated patients with mCRC value therapies that will effectively control their disease and reduce CRC-induced symptoms, improve quality of life (even if the therapy does not extend survival), and increase survival (overall and progression-free). CCC provided input from 27 patients (13 through survey and 14 through interviews) who had direct experience with trifluridine-tipiracil. Survey respondents indicated that compared with other drug therapies they had taken, trifluridine-tipiracil was less toxic and they experienced fewer side effects while on the therapy; fatigue and nausea were cited as the most prevalent treatment-induced side effects, with fatigue as the most difficult to tolerate. In addition to nausea and extreme fatigue, interview respondents also reported additional side effects of trifluridine-tipiracil that included low white blood cells, decreased appetite, extreme loose stools, and vomiting. A proportion of survey and interview respondents indicated or rated their HRQoL as better when taking trifluridine-tipiracil.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility and cost-effectiveness analyses

The EGP assessed the cost-utility (clinical effects measured as quality-adjusted life-years [QALYs] gained) and cost-effectiveness (clinical effects measured as life-years gained) of trifluridine-tipiracil plus BSC compared with placebo plus BSC for patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; anti-VEGF biological therapies; and anti-EGFR therapies.

Basis of the economic model: Clinical and economic inputs

The submitted partitioned survival model was comprised of three health states: pre-progression, post-progression, and death. The economic evaluation was based on pooled survival data (Kaplan–Meier survival data extrapolated with exponential tail) from two RCTs (phase III RECOURSE trial and phase II J003-10040030). Utility data for the pre- and post-progression health states were collected directly from the PRECONNECT study, although no measure of variance or spread was available for the post-progression health state. As PRECONNECT was a non-comparative study, the submitted model assumed that utility on BSC is equivalent to trifluridine-tipiracil. The incidence of adverse events, dosing and dose reductions, delay in treatment initiation, and post-progression costs were derived from the RECOURSE trial. The model did not incorporate disutility associated with the occurrence of adverse events.

The costs considered in the economic evaluation included those for drugs and drug administration, medical resource use pre- and post-progression, adverse events, and terminal care.

Drug costs: Treatment until progression

At the submitted price, trifluridine-tipiracil costs $76.25 per 15 mg tablet and $93.85 per 20 mg tablet. At the recommended dose of 35 mg/m^2 of trifluridine-tipiracil orally twice daily (days 1 through 5 and days 8 through 12 of each 28-day cycle), the cost of trifluridine-tipiracil is $5,773 ($186 per day) for cycle 1, $5,724 ($191 per day) for cycle 2, $5,704 ($184 per day) for cycle 3, and $5,700 ($184 per day) for subsequent cycles.

Clinical effect estimates: Choice of data source most influential parameter on estimates

Overall, the EGP considered the structure and execution of modelling appropriate in the submitted base-case model. However, the EGP considered the selection of data sources to model outcomes (pooled data used to inform survival outcomes; RECOURSE data used to inform incidence of adverse events, dosing and dose reductions, delay in treatment initiation, and post-progression costs) a major limitation considering survival is longer when using pooled survival data (and the pooling methods were not described) and the incidence of adverse events is lower in the RECOURSE trial, which may preferentially set the submitted base case to favour treatment with trifluridine-tipiracil. Other important limitations of the submitted model include uncertainty in utility associated with health states (no measure of utility for BSC; no measure of variance for the post-progression health state), lack of disutility associated with adverse events, and the use of triangle distributions for many parameters in probabilistic sensitivity analysis, which results in systematic underestimation of the uncertainty in cost and QALY outcomes.

In EGP reanalysis, the data source to inform survival outcomes was changed to use RECOURSE data alone, which meant the same data source was used for survival outcomes, incidence of adverse events, dosing and dose reductions, delay in treatment initiation, and post-progression costs. Other changes included

adjustment of the inflation rate to reflect the year 2018, and life-years were discounted using an alternate calculation of the discount factor. The most influential change made in the EGP reanalysis was to use RECOURSE data alone to inform modelled outcomes. The other changes made by the EGP had little effect on the ICER. The application of triangle distributions in probabilistic analysis results in underestimation of uncertainty; the EGP was unable to predict the magnitude of this underestimate.

Cost-effectiveness estimates: Trifluridine-tipiracil is not cost-effective at submitted price
The EGP's best-case estimate (deterministic) is between $124,593 per QALY and $131,972 per QALY depending on the medical resource use (high- versus low-cost estimate) in the pre-progression state. The submitter's best-case ICER was $115,507 per QALY; when only the data source was changed to include RECOURSE data, the ICER increased to $124,609 per QALY.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Additional resources required; budget impact is likely underestimated
PAG identified the following factors that could impact the implementation of trifluridine-tipiracil: the additional resources required to monitor and treat severe (grade 3 to 4) myelosuppression, including anemia, neutropenia, thrombocytopenia, and febrile neutropenia, and the cost of supportive therapy (e.g., anti-emetics, granulocyte-colony stimulating factor). PAG noted that given that trifluridine-tipiracil is available in two strengths and dose is based on body surface area, some patients will require two different strengths of tablets to make up their dose and therefore they may have two dispensing fees in those provinces where the access to oral therapies is through Pharmacare. The oral route of administration of trifluridine-tipiracil was considered as an enabler to implementation; however, PAG noted that in some jurisdictions oral medications are not funded in the same mechanism as intravenous cancer medications; in this case patients would first have to file an application to their Pharmacare program, which may limit accessibility of treatment for patients and cause financial burden on patients and their families in the form of co-payments and deductibles. PAG commented that the other coverage options in those jurisdictions that fund oral and intravenous cancer medications differently are private insurance or full out-of-pocket expenses. PAG considered the blister packaging of tablets an enabler to implementation as it would minimize drug wastage and minimize exposure of hazardous drugs to health care providers and caregivers.

The submitter provided a Canada-wide BIA to assess the feasibility of implementing a reimbursement recommendation for trifluridine-tipiracil in mCRC. The factors found to influence the BIA the most included the number of patients treated with trifluridine-tipiracil and the cost of the drug; therefore, increases in these parameters would result in increases to the predicted budget impact. The EGP highlighted that the submitted BIA was informed by a shorter treatment duration (2.2 months) compared with what was referenced in the submission, which was a mean of 12.7 weeks, and that the BIA excluded secondary therapies. Considering these factors and that the EGP considered that the submitters' market share uptake of trifluridine-tipiracil is likely underestimated, it is likely the budget impact of implementing a reimbursement recommendation for trifluridine-tipiracil in mCRC is underestimated.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Winson Cheung, who was excluded from voting due to a conflict of interest
- Daryl Bell, who did not vote due to his role as a patient member alternate.
- Dr. Henry Conter who was absent from the meeting.

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Winson Cheung, who was excluded from voting due to a conflict of interest.
- Daryl Bell, who did not vote due to his role as a patient member alternate.
- Drs. Henry Conter, Avram Denburg, Christian Kollmannsberger, W. Dominika Wranik, and Matt Cheung who were absent from the meeting.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of trifluridine-tipiracil for mCRC, through their declarations, one member had a real, potential, or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, this member was excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and PAG input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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