CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Trifluridine-Tipiracil (Lonsurf) for Metastatic Colorectal Cancer Resubmission

August 29, 2019

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ABBREVIATIONS

AE	Adverse events
AT	As treated
BSC	Best supportive care
CCC	Colorectal Cancer Canada
CGP	Clinical Guidance Panel
CRO	Contract research organization
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	Epidermal growth factor
EOT	End of treatment
FCSL	FACT colorectal symptom index
HRQoL	Health-related quality of life
mCRC	metastatic colorectal cancer
NRS	Numerical rating scale for pain
ORR	Objective tumour response
OS	Overall survival
PAG	Provincial Advisory Group
pCODR	pan-Canadian Oncology Drug Review
pERC	pCODR Expert Review Committee
PFS	Progression-free survival
PRO	Patient-reported outcomes
RCT	Randomized controlled trial
RSCL	Rotterdam Symptom Checklist
TAS-102	Trifluridine-tipiracil
TR	Tumour response
QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
QoL	Quality of life
Q-TWIST	Quality adjusted time without toxicity and symptoms
VAS	Visual analogue scale (for pain)
VEGF	Vascular endothelial growth factor
WDAE	Withdrawal due to adverse events

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding trifluridine-tipiracil (Lonsurf) for metastatic colorectal cancer (mCRC). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding trifluridine-tipiracil (Lonsurf) for mCRC conducted by the Gastrointestinal (GI) Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from Patient Advocacy Groups; input from the Provincial Advisory Group (PAG); input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on trifluridine-tipiracil (Lonsurf) for mCRC, a summary of submitted PAG Input on trifluridine-tipiracil (Lonsurf) for mCRC, and a summary of submitted Registered Clinician Input on trifluridine-tipiracil (Lonsurf)for mCRC, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety 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-vascular endothelial growth factor (VEGF) agents, and anti-epidermal growth factor receptor (EGFR) agents.

Health Canada issued a Notice of Compliance (NOC) for trifluridine-tipiracil (Lonsurf) 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. The funding request under review by pCODR aligns with the patients described in the Health Canada indication.

Trifluridine-tipiracil is comprised of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil (as tipiracil hydrochloride). The recommended dose of trifluridine-tipiracil (tablets) is a starting dose of 35 mg/m^2/dose administered orally with water, twice daily, within one hour after completion of morning and evening meals, on days 1 to 5 and days 8 to 12 of each 28-day cycle. The treatment cycle is repeated every four weeks as long as benefit is observed or until unacceptability toxicity occurs.

1.1.1 Original pERC Recommendation (2018)

On November 6, 2017 pCODR received a drug submission from Taiho Pharma Canada Inc. for trifluridine-tipiracil for the treatment of mCRC. pERC deliberated on the evidence contained in that submission on April 19, 2018; and on May 3, 2018 issued a negative initial recommendation for the reimbursement of trifluridine-tipiracil 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. After receiving and reviewing feedback from relevant stakeholder groups (patient advocacy group, registered clinicians and the submitter) pERC reconsidered their initial recommendation and

deliberated a second time on June 21, 2018. On July 6, 2018 pERC issued their final recommendation and did not recommend reimbursement of trifluridine-tipiracil for mCRC.[1]

pERC stated several reasons for issuing a negative recommendation; they indicated that compared with placebo plus best supportive care (BSC), trifluridine-tipiracil had only a modest progression-free survival (PFS) and overall survival (OS) benefit, moderate toxicities, and an uncertain impact on health-related quality of life (HRQoL).[1] pERC highlighted inconsistencies in the results of the included trials (related to PFS), and concluded that trifluridine-tipiracil partially aligned with patient values because it provides a treatment option that offers ease of oral administration, but it also has moderate toxicities and modest clinical effect compared with placebo plus BSC. pERC also noted that the impact of trifluridine-tipiracil on HRQoL is unknown, as it was not measured in any of the randomized controlled trials (RCTs) reviewed (RECOURSE, TERRA, or J003-100400306; refer to section 6.1.1 for a summary of the trials and results) despite their robust sample sizes. pERC acknowledged there were two post-hoc analyses of proxy measures for HRQoL (deterioration in performance status; quality adjusted time without toxicity and symptoms [Q-TWIST] analysis) presented as evidence; however, they agreed with the pCODR Methods Team appraisal that the proxies used were not validated or formally recognized surrogates for HRQoL. pERC commented that robust data on HRQoL could have been impactful on their recommendation.

1.1.2 Resubmission (2019)

Based on pERC's negative recommendation for reimbursement, the submitter resubmitted to pCODR with new clinical information on the efficacy and safety of trifluridine-tipiracil. After reviewing the new evidence for resubmission eligibility, pERC granted the resubmission on the basis of new HRQoL evidence.[2] As such, the RCT evidence contained in the original submission was not comprehensively reviewed again for this resubmission.

Following the posting of the pERC Initial Recommendation, the Submitter had several questions about the determination of resubmission eligibility of trifluridine-tipiracil in mCRC and pCODR's decision to focus the resubmission on the outcome of HRQoL. The pCODR Presubmission, Submission and Resubmission Guidelines (hereinafter referred to as "guidelines") outline the circumstances under which pCODR may accept resubmissions; in the case of this resubmission, a pERC panel comprised of three pERC members granted the resubmission based on new information on HRQoL that was not available at the time of the original drug submission. The pERC panel performs an administrative review of the new information provided in order to determine if it meets the resubmission requirements as outlined in pCODR's guidelines; it does not, however, carry out a critical appraisal of the new information as that is the purpose and focus of the full drug review process. In pCODR's communication to the Submitter regarding the pERC panel's decision to grant a resubmission (November 2, 2018), the following response and decision were clearly stated:

> "The pERC resubmission eligibility panel (the panel) noted that, while the PRECONNECT study provides new PFS data for patients treated with trifluridine-tipiracil, it does not address the comparative PFS of trifluridine-tipiracil compared with placebo. Furthermore, the Submitter did not provide new OS data to address the uncertainty identified in the original pERC recommendation. However, the Submitter provided new HRQoL information for patients treated with trifluridine-tipiracil using validated measures, information that was not included in the original submission. The lack of HRQoL data from validated measures was an issue identified in the original recommendation, therefore, the panel deemed this resubmission eligible, in order to assess the new HRQoL information through the full review process."

In view of this information, the Submitter was clearly informed of pCODR's intention to focus the resubmission on the new information on HRQoL and could not take into consideration the new data contained in the resubmission relating to non-comparative efficacy data since it did not address the concerns outlined by pERC in the original recommendation.

A total of 12 reports were provided by the Submitter and were cited as providing new clinical information.[3-11] Of these reports, five were included in the resubmission since they provided new evidence on HRQoL using validated measures.[4,5,7,11,12] The remaining seven reports were excluded because they did not report data on HRQoL.[3,8,9,11,13]

The five reports included in the resubmission represent two unique studies: PRECONNECT and a study referred to herein as TAS-102 versus BSC. Both studies were excluded from the pCODR systematic review based on their non-RCT design. A summary and critical appraisal of each study can be found in section 7.1 (PRECONNECT) and 7.2 (TAS-102 versus BSC) of this report.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The original literature search (from the original 2018 pCODR submission; refer to Appendix A) was updated by the pCODR Methods Team. The updated search did not identify any new evidence that met the selection criteria of the systematic review as outlined in section 6.2.1. Therefore, no new evidence was included in the systematic review (section 6).

1.2.2 Additional Evidence

Refer to Sections 3, 4, and 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and registered clinician input, respectively.

Patient Advocacy Group Input

One patient advocacy group, Colorectal Cancer Canada (CCC), provided input on trifluridine-tipiracil for mCRC. For a summary of this input, refer to Section 3.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified clinical and economic factors that could impact the implementation of trifluridine-tipiracil for mCRC. For a summary of this input, refer to Section 4.

Registered Clinician Input

Two clinician input submissions, one joint submission and one individual submission, were provided. In total, the input received captured the perspectives of 32 oncologists. For a summary of this input, refer to Section 5.

Summary of Supplemental Questions

- Critical appraisal of new evidence (since the original 2018 pCODR submission) on the HRQoL of patients with mCRC treated with trifluridine-tipiracil.

PRECONNECT

PRECONNECT is an on-going, phase 3b, single-group, early access study of trifluridine-tipiracil in 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; the primary endpoint is safety and secondary outcomes are PFS and HRQoL assessed using the EORTC QLQ-C30 and EQ-5D-3L (utility and visual analogue scale [VAS]) questionnaires.[14]

PRECONNECT is a non-comparative observational study and therefore was excluded from the pCODR systematic review. Data related to PRECONNECT were obtained through the submitter by pCODR. The four reports presenting data on this study have only been published in conference form. The most recent data reported in Taieb et al.(2019) represent HRQoL data at baseline and post-treatment for the first 464 patients entered into the study with a data cut-off date of May 20, 2018.[4] Change in HRQoL from baseline to end of treatment (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.[4]

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, including functional and symptom scales) or EQ-5D (utility and VAS).[4] Data on mean change in HRQoL from baseline to EOT showed clinically relevant deterioration (score ±SD) for the EQ-5D utility score (-9.1 ±23.6) and VAS (-8.3 ±19.3); and for the QLQ-C30 global health status score, the mean change was just short of reaching the clinically relevant 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.[4] Median time-to-deterioration in QLQ-C30 global health status was 3.7 months (95% CI 3.2-4.6).[4] 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.[4]

The lack of a comparator is the major limitation of the PRECONNECT study. The study design used inhibits comparability of outcomes with other treatments; and therefore, causal effects of trifluridine-tipiracil on HRQoL cannot be inferred based on the PRECONNECT study.

See section 7.1 for more information on the PRECONNECT study.

TAS-102 versus BSC

The TAS-102 versus BSC study is an on-going, open-label, non-randomized study with two cohorts of patients for the study of trifluridine-tipiracil in patients with mCRC who have been previously treated with at least two prior lines of chemotherapy for mCRC.[15] This study was excluded from the pCODR systematic review as it is an observational comparative cohort study where patient population was selected based on the patient and provider choice to receive trifluridine-tipiracil or BSC.[15] The study reports data based on a one-time capture of HRQoL outcomes and therefore does not provide baseline data on the HRQoL of patients prior to treatment or changes in HRQoL from baseline after a period of follow-up.[15] The questionnaires and PRO scales used to collect HRQoL data were the Rotterdam Symptom Checklist (RSCL), the FACT Colorectal Symptom Index(FCSI), and the Numerical Rating Scale for pain (NRS).

To date, no study data have been published and all study data reported herein come from the clinical study report dated April 3rd, 2019 that was obtained through the submitter by pCODR. For the RSCL, a majority of patients (14/39, 36%) in the trifluridine-tipiracil cohort rated their valuation of life at "good" while the majority of patients (15/31, 48%) in BSC cohort rated it as "rather poor".[15] For the FCSI, trifluridine-tipiracil treated patients had a mean score ± SD of 22.2 ± 6.0 that was significantly higher (indicative of less symptoms) compared to BSC patients who had a mean score ± SD of 19.4 ± 4.1 (p=0.0292).[15] For the NRS (VAS for pain), there was no significant difference in level of pain between trifluridine-tipiracil patients 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).[15]

Due to its cross-sectional design, the TAS-102 versus BSC study does not offer any information about the efficacy of trifluridine-tipiracil compared to BSC in patients with mCRC.

See section 7.2 for more information on the TAS-102 versus BSC study.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 1 addresses the generalizability of the evidence from the PRECONNECT study; an assessment of the limitations and sources of bias associated with the study can be found in Section 7. The generalizability table is based on the Taieb et al. 2019 population (N=464) of all patients enrolled in the PRECONNECT study at the data cut-off date of May 20th, 2018.[4]

Table 1: Assessment of generalizability of evidence from the PRECONNECT study.

Domain	Factor	Evidence from the PRECONNECT study	Generalizability Question	CGP Assessment of Generalizability
Population	Antibody	Patients were eligible for participation if they had at least one of the anti-EGFR monoclonal antibodies for RAS (wild-type or mutant) for mCRC.	Is the antibody an effect modifier (i.e., differences in effect based on antibody status)? Are the results applicable to all subgroups equally? Is there a substantial group of patients excluded to whom the results could be generalized?	The study enrolled patients with both wild-type and mutant RAS status. The CGP noted that compared to previous RCTs and Canadian clinical practice, patients with wild-type status were underrepresented in the PRECONNECT study. Since RCTs have demonstrated that the clinical benefit associated with trifluridine-tipiracil is independent of RAS status, the CGP believes evidence from PRECONNECT is also generalizable to patients independent of RAS status.
	Performance Status	Participants had to have an ECOG performance status of 0 or 1 during the screening period.	Does performance status limit the interpretation of results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	Considering its toxicity profile, the CGP believes trifluridine-tipiracil should only be offered to patients who maintain an ECOG performance status of 0 or 1.
	Disease site	The trial included previously treated mCRC patients.	Do trial results apply to patients with small bowel cancer?	Small bowel cancer is extremely rare, and as such there is limited evidence to guide treatment. The CGP believes treatment with trifluridine-tipiracil in patients with small bowel cancer should remain at the discretion of the treating oncologist.
	Line of treatment	The trial required patients to have received at least two standard chemotherapy regimens for mCRC that they were either refractory or intolerant to.	Do the trial results apply to patients who have had only one or two lines of standard chemotherapy regimens? If so, why?	The CGP believes the trial results are generalizable to KRAS mutant patients with contraindications to bevacizumab and to patients with DPD deficiency. The CGP noted these patient groups are small and have fewer treatment options, and

Domain	Factor	Evidence from the PRECONNECT study	Generalizability Question	CGP Assessment of Generalizability
				therefore would benefit from earlier treatment with trifluridine-tipiracil.
	Organ Function	Participants had to have adequate organ function.	Does the exclusion of patients with organ dysfunction limit the interpretation of the results with respect to the target population?	The CGP felt that organ dysfunction would be reflected in patient performance status. The CGP noted that physician discretion could be used in offering trifluridine-tipiracil to those patients with clinically inconsequential organ dysfunction.
	Toxicity	Patients were excluded if they have had unresolved toxicity of greater than or equal to Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity).	Does this restriction limit interpretation of the results with respect to the target population?	The CGP noted that in Canadian clinical practice patients would be offered trifluridine-tipiracil after resolution of toxicity, and therefore, the exclusion of these patients was clinically appropriate and does not limit the generalizability of the results.
Comparator	There was no comparator in the PRECONNECT study.			
Outcomes	Quality of Life	Quality of life outcomes were assessed using the EORTC QLQ-C30 and EQ-5D-3L questionnaires.	Is that an adequate assessment of quality of life outcomes? Are the results relevant in the Canadian setting?	The EORTC QLQ-C30 and EQ-5D-3L are validated measures of HRQol and utility, respectively. However, the non-comparative design of the PRECONNECT study does not permit causal inferences, and therefore the observed results cannot be attributed to trifluridine-tipiracil with certainty. Further, it is unclear if the use of UK utilities used in the EQ-5D-3L assessment fully align with Canadian utilities and preferences.
Setting	Countries participating in the Study	PRECONNECT was conducted in mainly Azienda Ospealiero Universitaria Pisana, Istituto Toscano Tumori. It is not reported if any of the 15	Do results apply to patients from Canadian centres? Are there any known differences in practice patterns between the countries participating in the Study and Canada?	The CGP has no concerns in generalizing the evidence from Italian centres to Canadian practice; however, it is unclear if generalization is appropriate for the other

Domain	Factor	Evidence from the PRECONNECT study	Generalizability Question	CGP Assessment of Generalizability
		study centres includes a location in Canada.		centres of unknown location.

1.2.4 Interpretation

Burden of Illness and Need

Colorectal cancer is a common cancer representing, in 2017, the second most common cancer overall in Canada (26,800 cases) and the second most cause of cancer-related death (9400 deaths).[16] Patients usually present in the early stages of disease that are surgically resected, of which a percentage (approximately 35%) will later develop metastatic disease. Approximately 10% of patients with mCRC present with de novo metastatic disease. A small percentage of patients with metastases will be surgically resectable for curative intent; however, the majority of patients develop unresectable metastases that are considered incurable. Therefore, the goals of therapy for these patients are palliative and include disease control, improvement or maintenance of HRQoL, and delay of death.

Patients who have unresectable mCRC are initially treated with chemotherapy; this includes fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biological agents, and if RAS wild type, anti-EGFR biological agents. When making a recommendation for treatment, medical oncologists consider the evidence of benefit, toxicity of available therapies, patient performance status, relevant comorbidities, primary tumour location, as well as patient preferences. There is, however, a natural attrition from one line of therapy to the next due to several factors that include a decline in performance status (most common), comorbidities, toxicities of therapy and patient preferences. In addition, anti-VEGF therapies have a biomarker that deems this therapy ineffective in about 50% of the patients. Median survival has improved from 12 months to approximately 30 months over the last 15 years with these therapies, however, a percentage of patients are still well enough to be treated if a funded option exists. Owing to the attrition of patients from one systemic line of therapy to the next, the CGP estimates that it's likely up to 20% of the 9,400 Canadians who die with mCRC would be potential candidates for treatment with trifluridine-tipiracil.

Trifluridine-tipiracil (Lonsurf) is an agent used for the treatment of mCRC in patients who have progressed on standard first-, second- and potentially third-line therapies, if eligible. Therefore, its use is indicated after standard chemotherapeutic agents, including fluoropyrimidine, oxaliplatin, and irinotecan, have been exhausted. Untreated, historical series describe survival rates in mCRC in the range of six to ten months.[17,18] Trifluridine-tipiracil is comprised of an antineoplastic thymidine-based nucleoside analogue trifluridine and a thymidine phosphorylase inhibitor, tipiracil. The recommended dose is 35 mg/m^2/dose administered twice daily by mouth within one hour after completion of morning and evening meals on days 1-5 and days 8-12 of a 28-day cycle. This schedule is repeated every four weeks as long as benefit is achieved, and unacceptable toxicity does not occur in patients who have maintained a performance status of 1.

Effectiveness and Safety

pCODR first reviewed the evidence on trifluridine-tipiracil in 2018.[19] The original submission was based on efficacy and safety evidence from three RCTs (RECOURSE, TERRA, and J003-100400306). Based on this evidence, pERC issued a negative recommendation for reimbursement,[1] with the stated reasons being that, compared to BSC, the PFS and OS benefits observed with trifluridine-tipiracil were modest, there were moderate toxicities, and benefit in terms of HRQoL was uncertain. HRQoL data were lacking from the three RCTs, which instead, only provided evidence in the form of post-hoc analyses of proxy measures for HRQoL (i.e., deterioration in performance status, QTWIST). pERC highlighted the importance of formal HRQoL measurement in end of life

treatments and that the proxy measures assessed in the trials are not validated or formally recognized surrogates for HRQoL. As pERC indicated that robust data on HRQoL could have been very impactful on their recommendation, the Submitter resubmitted to pCODR with new evidence that includes data on HRQoL obtained using validated questionnaires. pCODR approved the resubmission based solely on the new HRQoL evidence, which is primarily focused to the PRECONNECT study;[4] a non-comparative single-group phase 3b early access study. As the PRECONNECT study did not meet the selection criteria of the pCODR systematic review due to its non-comparative design, the trial was reviewed and critically appraised as supplemental information (refer to section 7.1) relevant to the review.

Evidence from Original (2018) pCODR Submission

Two randomized phase 3 trials (RECOURSE, TERRA) and one randomized phase 2 trial (J003-100400306) comprised the evidence base for the original submission and were reviewed by pERC.[19] All three trials showed a statistically significant improvement in OS (primary endpoint) with trifluridine-tipiracil over placebo/BSC with hazard ratios (HRs) of 0.68 (RECOURSE), 0.79 (TERRA), and 0.56 (J003-100400306); median OS estimates (versus placebo/BSC) were 7.1 months (versus 5.3), 7.8 months (versus 7.1), and 9.0 months (versus 6.6), respectively. Likewise, the benefits observed in PFS were also statistically significant. The clinical significance of the OS and PFS benefit observed with trifluridine-tipiracil has been raised extensively, with absolute numerical improvements in OS of approximately two months and PFS of approximately 0.2 months. It is the opinion of the CGP that this modest improvement in efficacy outcomes is clinically meaningful in pretreated mCRC patients who have maintained their performance status at a 0 or 1, so long as there is no observed detriment to patient QoL. Although the toxicity of trifluridine-tipiracil is greater compared to placebo/BSC, the frequency of withdrawals due to toxicity in the RCTs were low and not appreciably higher than placebo/BSC.

New Evidence on Health-Related Quality of Life

The PRECONNECT study has not been published and thus available data are limited to conference proceedings in abstract and poster form. The trial assessed patient-reported HRQoL using validated questionnaires that included the EORTC QLQ-C30 and the EQ-5D.[4] The CGP considered the patient population in the PRECONNECT trial reflective of the patient populations included in the RECOURSE and TERRA RCTs, and patients were treated using the same dose and schedule of trifluridine-tipiracil.

The most recent conference data from PRECONNECT is reported by Taieb et al.(2019) and represents HRQoL data at baseline and post-treatment for the first 464 patients entered into the study with a data cut-off date of May 20, 2018;[4] the median follow-up time of patients was not reported. 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. It's notable that 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 EQ-5D.[4] Data on mean change in HRQoL from baseline to EOT showed clinically relevant deterioration for the EQ-5D utility score and VAS but not for the QLQ-C30 global health status; although the mean change was just short of reaching the clinical deterioration threshold. 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;[4] and median time-to-deterioration in QLQ-C30 global health status was 3.7 months (95% CI 3.2-4.6).[4] The percentage of patients who experienced either 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.[4]

Overall, the lack of a comparator group limits the interpretation of the PRECONNECT study data as causality cannot be inferred from a single-group study; thus, the observed HRQoL findings cannot with certainty be attributed to treatment with trifluridine-tipiracil. Data from a second unpublished study, also provided by the submitter, looked at differences in HRQoL using validated measures at one point in time between two cohorts of patients treated with either trifluridine-tipiracil or BSC; however, the cross-sectional design of this study and the fact that no baseline HRQoL data were reported limited its usefulness for evidence-informed clinical decision-making. The CGP concluded that the PRECONNECT study used validated instruments to measure the HRQoL of patients treated with trifluridine-tipiracil and these results appear to align with the results of proxy outcomes for HRQoL assessed in RCTs, as both sources of evidence show there is a sizable proportion of patients who experience no deterioration in their HRQoL during and after treatment with trifluridine-tipiracil. In the PRECONNECT study the percentage of these patients ranged between 46.9% and 60.3% depending on the scale. The CGP acknowledges, however, that a more robust comparative study design is needed in order to definitively determine the effect of trifluridine-tipiracil on HRQoL compared to BSC.

The clinician and patient input received indicates that the toxicities of trifluridine-tipiracil are manageable and patients report that the side effect profile is improved compared to previous therapies they have received. Patients and patient advocacy groups report a strong desire to have trifluridine-tipiracil as a treatment option as it fulfills an unmet need for wanted therapies. Further, the oral route of administration of trifluridine-tipiracil allows patients to remain at home and has minimal impact on cancer facilities and chemotherapy suites.

Following the posting of the pERC Initial Recommendation, the CGP reviewed and discussed the feedback received from stakeholder groups (Clinicians, Patient Group, and Submitter) who all stated they disagree with pERC's Initial Recommendation to not reimburse trifluridine-tipiracil in patients with mCRC. To address the issues raised, the CGP provided the following comments:

- Unmet clinical need – the CGP agrees with the feedback received that trifluridine-tipiracil provides an unmet clinical need for an additional line of therapy in a small proportion of mCRC patients who maintain a performance status of 0 or 1 and have exhausted all available treatment options.
- Meaningful net clinical benefit - the CGP agrees with the feedback that the net clinical benefit of a two-month advantage in OS is modest but clinically meaningful to patients.
- Manageable toxicity profile - in terms of toxicity, the CGP agrees with the clinicians and patient group providing feedback that the toxicity profile associated with trifluridine-tipiracil is acceptable and better tolerated than other prior therapies patients have received.
- New evidence on HRQoL - the CGP acknowledged that the new evidence on HRQoL submitted for the resubmission is not robust, but noted that, despite its limitations, it is consistent with the surrogate evidence for HRQoL reviewed in the original submission. Thus, the CGP agrees with stakeholder feedback that the totality of the evidence on trifluridine-tipiracil (comparative outcomes on efficacy, safety, and available evidence on HRQoL) should be considered, which lead the CGP to conclude that there is a net clinical benefit associated with trifluridine-tipiracil that outweighs the harm.
- Extrapolation of comparative HRQoL data in metastatic gastric cancer to mCRC – regarding clinician feedback that HRQoL evidence from the TAGS randomized trial

in metastatic gastric cancer is generalizable to patients with mCRC, the CGP believe it is not appropriate to extrapolate these data. This opinion is based on evidence from the adjuvant setting where the toxicity of 5FU chemotherapy and radiation was considerably different in gastric patients than a near identical adjuvant treatment protocol for colorectal cancer. Further, the CGP considers this evidence to be out of scope for the current resubmission.

- Inequity in treatment resulting from differing reimbursement decisions – the CGP believes that as an independent drug review body, pERC's decisions on drug reimbursement should not be influenced by the decisions of other drug review processes, including INESS.

1.3 Conclusions

There are a number of patients with mCRC who currently have exhausted standard publicly available treatment options; trifluridine-tipiracil provides an important additional line of therapy for these patients. Evidence from three RCTS has demonstrated that the use of trifluridine-tipiracil in previously treated mCRC patients is associated with a statistically significant although numerically small improvement in OS and PFS; these findings are clinically meaningful and generalizable to the Canadian population with mCRC. The toxicity of therapy is generally considered low and acceptable to patients and clinicians. While the CGP acknowledges that evidence on HRQoL remains limited, it suggests a proportion of patients treated with trifluridine-tipiracil experience no deterioration in aspects of HRQoL. Overall, the totality of evidence suggests that for patients who have had previous treatment with or are intolerant to standard therapies for mCRC, including fluoropyrimidines, oxaliplatin and irinotecan along with, if appropriate, VEGF and EGFR inhibitors, and have maintained their performance status as 0 or 1, there is a net clinical benefit associated with trifluridine-tipiracil that outweighs the harm.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR GI Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Colorectal cancer is, according to the Canadian cancer statistics, the third most common cancer in Canada and the second most common cause of cancer related deaths.[16] Most patients present with early resectable disease however a significant proportion later develops metastatic disease. Some of these patients are successfully resected but most are found to be unresectable and are candidates for palliative chemotherapy. Of the 9400 patients who are potential candidates for this therapy,[16] the vast majority will not be well enough to get this treatment after receiving previous therapies.

Trifluridine is an analogue of thymidine, and when combined with tipiracil, an agent that inhibits its degradation, the drug can be administered as oral therapy. Trifluridine-tipiracil (Lonsurf®) was approved by the US Food and Drug Administration in September 2015 and the European Medicines Agency in April 2016.

2.2 Accepted Clinical Practice

Other than in very specific situations where resection of a liver or lung metastasis is possible, mCRC is considered an incurable condition. Untreated, historical series describe survivals in the range of six to ten months.[17,18] Although the treatment of patients with mCRC continues to evolve, it is a complex process with multiple options depending on patients' performance status, comorbidities, and other patient-related preferences including socioeconomic and geographical factors, tumour related factors such as primary tumour location and biomarkers such as RAS, MSI and RAF.

Table 2: Lines of treatment in patients with RAS wild-type and RAS mutated mCRC.

Patients with unresectable mCRC		
Line of Therapy	**RAS wild type**	**RAS mutated**
1st-Line	FOLFIRI + VEGF inhibitor or EGFR inhibitor	FOLFIRI + VEGF inhibitor
2nd-Line	FOLFOX + VEGF (if not already given)	FOLFOX
3rd line	EGFR inhibitor (if not already given)	Trifluridine-tipiracil or regorafinib
4th line	Trifluridine-tipiracil or regorafinib	-

In Canada, there is regional variability in practice patterns. However, patients with mCRC are often first treated with FOLFIRI or FOLFOX (Table 2). Use and timing of a biologic/targeted therapy (e.g.: bevacizumab, panitumumab, cetuximab) depends on the patient's comorbidities and preferences, a molecular analysis of the tumour for mutations in RAS and BRAF, and the site of the primary tumour (distal versus proximal). Regorafenib is not publicly funded but can still be accessed through private insurance or if patients are willing to pay for it.

With chemotherapy,[20,21] targeted agents,[22] and a favourable cancer biology (e.g.: absence of mutations in RAS or BRAF, distal primary tumor location),[23,24] median survivals are now reliably measured in the 30- to 36- month range. Contemporary systemic therapies are cost

effective,[25-29] delay the onset of tumour-related symptoms, and improve QoL.[30,31] Despite these improvements, however, unfavourable factors (e.g.: mutations in BRAF, proximal primary tumour location) can still be associated with survivals under 18 months.

2.3 Evidence-Based Considerations for a Funding Population

Based on the available data, the CGP estimates that out of the 9400 patients with mCRC who have received prior lines of systemic therapy,[16] no more than 20% or 1880 patients would be potential candidates for treatment with trifluridine-tipiracil.

2.4 Other Patient Populations in Whom the Drug May Be Used

While this resubmission focuses on the use of trifluridine-tipiracil in mCRC, clinical trials are underway to evaluate whether it can be used in earlier lines of therapy and/or in combination with other agents.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy group(s) provided input on the pCODR resubmission of trifluridine-tipiracil (Lonsurf) for metastatic colorectal cancer and their input is summarized below: Colorectal Cancer Canada (CCC).

Colorectal Cancer Canada (CCC) conducted national and international online surveys to gather patient and caregiver perspective on the therapy under review. The online survey was available between January 15, 2019 to February 13, 2019 and surveyed colorectal cancer patients residing in Canada and the United States (US). There was a total of 118 respondents via Survey Monkey, of which 112 were from Canada, 5 were from the US, and one other was unspecified. Of the 118 respondents, 85 were patients, 28 were caregivers, and 5 patients were also caregivers. Of the respondents, 2 (1.74%) were disease stage 0, 6 (5.22%) were disease stage 1, 17 (14.78%) were disease stage II, 32 (27.8%) were disease stage III, and 38 (33.04%) were disease stage IV. Of the disease stage patients, the survey identified 13 patients who were able to provide experience with the therapy under review.

CCC also contacted online colorectal cancer chat groups/ forums in Canada and in the US as well as one CCC support group member making an appeal on behalf of CCC to the Conexus Patient Support Program Lead at Bayshore who identified patients previously having received or are currently receiving the drug under review in Canada. Furthermore, there were 14 stage IV patients and one caregiver who consented to be contacted by CCC and provided telephone interviews. The data are presented below in Table 2.

From a patient perspective, mCRC has significant symptoms; patients noted that diarrhea and fatigue resulting from the cancer were the most significant and difficult to control. Patients who completed the online survey also noted that their “CRC-induced symptoms” interfere with their QoL and their daily activities. Patients reported that current treatments include side-effects such as chemo-induced fatigue, nausea, and diarrhea which are the most difficult to tolerate. CCC also reported that patients desire therapies that will effectively control their disease with respect to OS, PFS, and, promote QoL during their lifetime, even if the therapy does not extend OS. CCC also noted that for patients who had experience with trifluridine-tipiracil, they reported the treatment was less toxic and they experienced fewer side effects while on therapy. Patient respondents also noted that their QoL while on trifluridine-tipiracil was greater than 5, on a scale of 1-10. Patients who rated their QoL as 5 or lower reported their low rating reflected their QoL while on other chemotherapies.

Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Metastatic Colorectal Cancer

CCC reported that though there have been improvements in the treatment of colorectal cancer which has favourably affected patient outcomes and death rates have declined significantly in the past 20 years, a high proportion of patients with advanced stages will still die from the disease. CCC noted that the five-year survival rate for patients with mCRC is less than 11% and that additional treatment options are required for patients with mCRC.

Patients who completed the online survey noted the following:

“I’d like a drug that will cure me of my metastatic disease”

"When current treatment is no longer effective in stabilizing my disease, then limited options are available"

From the online patient survey, CCC identified the following CRC symptoms as the most prevalent: bloody stools, diarrhea, fatigue, constipation, abdominal cramping, and pencil thin stools.

Of the CRC symptoms, CCC noted that diarrhea and fatigue resulting from the cancer were the most important and difficult to control. Patients who completed the online survey also noted that their "CRC-induced symptoms" interfere with their QoL and their daily activities. They are not able to function "normally" in their family or work setting; 60% of patients reported that they are unable to work and 48% are unable to fulfill their family obligations. Patients also provided open-ended replies regarding the limitations resulting from the CRC that have a psychological impact:

"I think your limitations are limited. There are many more that include depression issues, aches and pains, chemo brain making it difficult to drive and remember many things, weight gain, hernias…"

3.1.2 Patients' Experiences with Current Therapy for Metastatic Colorectal Cancer

CCC reported that according to the patient survey results, patients accessed combination chemotherapies such as FOLFOX and/or FOLFIRI with bevacizumab to help reduce the burden of disease. CCC also noted that less than 14% of patients accessed anti-epidermal growth factor receptor (EGFR) therapies such as cetuximab and panitumumab and 4% accessed regorafenib. CCC noted that from the patient survey, most patients cited fatigue, diarrhea, and nausea as being the most common side effects from their current treatments. Of these side-effects, the patients noted that chemo-induced fatigue, nausea, and diarrhea were the most difficult to tolerate. CCC also reported that 24.5% of patients noted some of their needs were not being met with their current therapies. The following open-ended responses were provided:

"Would love to try an immunotherapy drug"

"I'd like a drug that will cure me of my metastatic disease"

"When current treatment is no longer effective in stabilizing my disease, then limited options are available"

3.1.3 Impact of Metastatic Colorectal Cancer and Current Therapy on Caregivers

CRC reported that the disease has a significant impact on the lives of caregivers and that caregivers are fraught with financial, physical, and psychological challenges when caring for their loved ones. Below is a quote from a caregiver:

"Loss of income; dealing with treatment-induced side effects; loss of lifestyle; taking on double the normal household activities i.e. shopping for groceries, household chores, taking care with kids, etc.; feelings of helplessness because I cannot help my loved one feel better."

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Trifluridine-Tipiracil (Lonsurf)

The patients who responded to the online survey noted their desire for therapies that will effectively control their disease with respect to OS, PFS, and, promote QoL during their lifetime, even if the therapy does not extend OS. CCC also reported that approximately 20% of survey patient respondents are willing to endure significant side effects for a two-month survival benefit and almost 60% are willing to endure those same significant toxicities for a one-year survival benefit.

CCC noted that for patients with refractory mCRC, there are limited therapeutic options available to treat their disease, regardless of RAS mutational status. Patients would like an additional therapy that would provide patients with a new therapeutic option which has an acceptable toxicity profile and can help extend their OS. Patients noted that having access to trifluridine-tipiracil would allow for an additional therapy options for patients who have exhausted standard of care therapies. CCC provided survey results of 13 patients who accessed trifluridine-tipiracil for third-, fourth- and fifth-line treatment of mCRC. Patients accessed trifluridine-tipiracil through clinical trials, self-pay, insurance plan or special access program. Of the 13 patients, 77% of respondents noted that compared to other drug therapies, trifluridine-tipiracil was less toxic and they experienced fewer side effects while on therapy. Additionally, 92% of patient respondents indicated that trifluridine-tipiracil was able to shrink/contain their mCRC and that fatigue and nausea were the most prevalent treatment-induced side effects, with fatigue as the most difficult to tolerate. CCC noted that trifluridine-tipiracil is an important treatment option with manageable side effects. Survey respondents rated trifluridine-tipiracil induced side effects as "minimal," easily administered, and were able to achieve a high QoL while on therapy. CCC noted that 100% of the respondents reported that since trifluridine-tipiracil is an oral therapy it is easy to administer and 75% of patient respondents rated their QoL as high while taking trifluridine-tipiracil. In addition, 90% of survey respondents rated their overall experience as "much better" when compared to other treatments accessed for their mCRC and 100% were in favour of the therapy being made available. The following quotes were provided by CCC to support the patients:

"It gives one more option to extend life with ease of use and minimal side effects"

"Lonsurf works. How can you not fund a treatment that is proven to shrink tumors?!!"

"It should be funded as another option for stage 4 patients"

"Lonsurf has been an effective treatment for me, with few and relatively mild side effects compared to other treatments I have experienced. If my experience is similar to that of a significant number of other patients, then yes, public funding would be appropriate, in my opinion"

In addition to the online survey, CCC conducted telephone interviews with fourteen patients and one caregiver who accessed trifluridine-tipiracil in Canada. Table 1 below outlines the detailed demographics and drug experience for each of the 14 patients. In summary, the patients interviewed were between the ages of 40 and 79 years, and five of the patient respondents were female and nine were male. Three patients noted they received trifluridine-tipiracil previously and the remaining 11 patients were currently taking trifluridine-tipiracil for their treatment. The interviewed patients also reported

their previous treatments for mCRC which included 5FU, oxaliplatin, FOLFOX, panitumumab, FOLFIRI, regorafenib, capecitabine, irinotecan and bevacizumab, immunotherapy, and trifluridine-tipiracil. The number of cycles of trifluridine-tipiracil for each patient ranged from 4 to14. Patients were also asked to rate their QoL while on trifluridine-tipiracil on a scale of 1-10. Of the interviewed patients, four patients rated their QoL as 4/5, two patients rated 6/7, six patients rated 8/9 and three patients rated QoL as 10. When asked about side effects of trifluridine-tipiracil, patients reported that side effects included nausea, low white blood cells (WBC), decreased appetite, extreme fatigue, extreme loose stools, and vomiting. Additional comments were provided by patients on why they stopped taking trifluridine-tipiracil. Of the interviewed patients, five patients had to stop treatment and nine were still on treatment. The five patients who stopped noted that they stopped due to disease progression, one had stopped initially and missed one cycle, and one patient had stopped due to hospitalization for another reason. Patients who were currently on trifluridine-tipiracil reported that their treatment was adjusted due to low WBC and fatigue; as well, one patient noted that they had developed an infection. CCC also reported that no patients reported discontinuing the therapy due to drug-related toxicity.

3.3 Additional Information

CCC provided additional information on access to trifluridine-tipiracil. Respondents indicated that there is a need for new treatment options for patients with refractory mCRC. CCC noted that patients and caregivers who responded to the survey identified the following unmet needs: the need for a novel, conveniently administered oral therapy with an acceptable toxicity profile that has the potential to improve OS in the refractory patient population. Patients noted that “having a pill to take at home would be better than going for IV at the Cancer Centre”. CCC noted that trifluridine-tipiracil could be an extremely important therapeutic option for the mCRC patient population who have exhausted standard of care therapies or for patients who are not considered candidates for those same therapies. They further noted that this treatment aligns well with the identified patient and caregiver need for a new, effective treatment option that can maintain a high QoL. One patient also provided the following quote as part of the interview: “... I’ve been able to have a pretty good quality of life and I haven’t really needed much assistance while on the treatment. I can do almost everything around the house and take care of my family. I couldn’t do all that before. So, I hope this is taken into consideration.”

Table 3: Patient and caregiver interviews - demographics and experiences on trifluridine-tipiracil (Lonsurf).

TABLE 3: PATIENT/CAREGIVER INTERVIEWS – DEMOGRAPHICS & EXPERIENCES ON LONSURF®								
	PATIENT #1	**PATIENT #2 /CAREGIVER #1**	**PATIENT #3**	**PATIENT #4**	**PATIENT #5**	**PATIENT #6**	**PATIENT #7**	**PATIENT #8**
INTERVIEW DATE & TIME	Feb.6/19 2 p.m. EST	Feb.7/19 1 p.m. EST	Feb.7/19 2 p.m. EST	Feb 7/19 2:30 p.m. EST	Feb.7/19 3 p.m. EST	Feb 7/19 4 p.m. EST	Feb 8/19 11 a.m. EST	Feb. 8/19 12 p.m. EST
CITY, COUNTRY	Musgrave Harbour, NL, CA	Beaconsfield, QC, CA	Barrie, ON, CA	Scarborough, ON, CA	Calgary, AB, CA	Winnipeg, MB, CA	Lethbridge, AB, CA	Outside Red Deer, AB, CA
GENDER & AGE	Male, **67**	Male, **66**	Female, **56**	Male, **76**	Male, **40**	Male, **54**	Male, **79**	Male, **66**
MARITAL STATUS	Married	Married	Married	Separated	Single	Married	Married	Married
TX CENTRE?	Gander NL: Eastern Health	McGill University Health Centre, Montreal, QC	London Regional Cancer Centre	Rouge Valley Hospital	Tom Baker Cancer Centre	Saint Boniface Hospital	Jack Ady Treatment Centre, Lethbridge	Red Deer Cancer Centre
DATE OF MCRC DX	Dec 2015	April 2017	January 1993	2013	Summer 2013	2016	November 2014	Spring 2015
LOCATION OF METS?	Both sides of pelvic wall, small spot on lung	Peritoneal carcinomatosis (no primary site)	Liver, Lungs, LNs, Pancreas, Clavicle	Liver, Lungs	Lymph Nodes, Bladder	Liver, Lungs	Lungs, Liver, Abdomen	Liver
CURRENTLY OR PREVIOUSLY ON LONSURF?	**Currently**	**Currently**	**Previously**	**Currently**	**Currently**	**Currently**	**Currently**	**Currently**
LINE OF TX RECEIVED/ RECEIVING LONSURF?	**3rd Line** Started in June 2018	**4th Line** Started in June 2018	**9th Line** Feb 2018 – Jan 2019	**4th Line** Started in September 2018	**5th Line** Started in September 2018	**4th Line** Started in December 2018	**4th Line** Started July 2018	**3rd Line** Started December 2018
PREVIOUS TXS RECEIVED FOR MCRC?	-5FU -Oxaliplatin	-FOLFOX -5FU (2 cycles only) -PANI	-5FU -FOLFIRI -5FU + CET -FOLFIRI -Irinotecan -REGORAFENIB -2 others but cannot recall	Cannot recall the treatment names. Had a reaction to the first therapy after the 2nd dose. Changed it, went along and didn't have any problems. Slight increase in lung nodule. Changed again. Then problem with neuropathy.	-Capecitabin -FOLFIRI -Oxaliplatin -Panitumumab	-FOLFOX -FOLFIRI -PANI	-3 Chemos prior to Lonsurf	-Irinotecan + BEV - PANI
# OF CYCLES OF LONSURF?	**9**	**7**	**12**	**6**	**5**	**3**	**7**	**3**

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SIDE EFFECTS OF LONSURF?	- Nausea (meds prescribed to help with the nausea) - "***Low WBC count for which I have to take Neupogen***".	***"I don't have any side effects on this drug."*** ***Wife's statement:*** "*The week that he is on the drug, his appetite goes down. It's going down in general. The doctor says that if he continues to lose weight, he might*	***"Nausea and extreme fatigue. I took meds for the nausea. Overall it was a better fit for me (than the other drugs), with the oral therapy being huge in maintaining a quality of life. It was effective in terms of reducing the tumours, except for the one***	***"I have no side effects of any kind."***	***"I have fatigue and a bit of nausea. I am prescribed medication for the nausea."*** ***"I also experienced low WBC count which resolved after changing cycle schedule."***	***"Lonsurf is not debilitating. I still work. I would say that during the cycle I have a bit of nausea and fatigue, but I can generally live my life as I always have. I take meds for nausea prophylactically while on***	***"I have no side effects whatsoever."***	***"Extremely loose stools, 3-4 times a day. Now I take half Imodium per day. Stools a a bit loose, but not intolerable.***
		have to come off Lonsurf."	in my pancreas. And the side effects were not debilitating at all."			Lonsurf. Fatigue is ongoing, but not severe."		
RATE QoL WHILE ON LONSURF? (1-10)	10 "Towards a 10, because other than setting my alarm to take it, it hasn't really changed much other than I am a little bit tired. Lonsurf is much better than the other two therapies I was on. I was attached to a cannister for a couple of days	***4*** ***"Because Lonsurf doesn't really do anything bad to me. I am able to get around the same way I was before starting the drug. With regards to the side effects, this is definitely an improvement to the other medications. I***	8 "I was grateful to be on this oral drug. Side effects were really manageable and few."	8 "If I don't include the neuropathy from previous treatments, then I would have to say that my QoL would be an 8-9. But if I include the neuropathy from previous treatments from which I am still suffering, then my qualify of	7 "..because I can do most things that I was able to do before… I have a better quality of life on Lonsurf than I did on other treatments and the pill is smaller than the capecitabine pill which is	8 "I still work. I'm continuing my career. There are no real changes outside of having a cancer diagnosis."	***10*** ***"Since originally starting chemo, I have lost my strength, but this chemo is perfectly fine."***	***8-9*** ***"I feel quite good. Am disappointed that I have cancer but extremely glad to be here. I am definitely slowing down, but is it the cancer, the chemo, or my birth certificate? Ecog status I've been told is 0. If the doctor***

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	every couple of weeks. That's such a pain, and it really slows you down. If I want to go someplace, I can always take the pill with me. My wife says I should slow down though….I'm getting old you know…"	***am rating it a 4 because of the bad side effects I am still feeling from the OTHER THERAPIES.***		life is about a 2 or 3 because it's in my hands and feet. It started very mildly but got worse. It is irritating but not painful. Is in the knees now. Can'[t feel things if I pick them up. "	really good."			***hadn't told me I had cancer, I wouldn't know otherwise. I tend to my horses and do work around the farm, even in 40-degree weather. I also travel to my second home in California sometimes during my weeks off Lonsurf treatment."***
DID CEA CONFIRM RESPONSE?	Always told that it has been low so not a good marker for me.	***Unsure***	"Yes, immediately and dramatically. Went from 12.7 to 6.3 and then again to 3.7. "	"Not aware."	"Yes. It has gone down to 5.5 now which is a lot.."	Unsure.	***"It does not appear on the bloodwork that I can see.".***	***"I can't see it on my bloodwork."***

TABLE 3: PATIENT/CAREGIVER INTERVIEWS – DEMOGRAPHICS & EXPERIENCES ON LONSURF®								
	PATIENT #1	**PATIENT #2 /CAREGIVER #1**	**PATIENT #3**	**PATIENT #4**	**PATIENT #5**	**PATIENT #6**	**PATIENT #7**	**PATIENT #8**
DID CT CONFIRM RESPONSE?	Yes. I have a scan every 2 cycles.	***Wife: "Yes. Shortly after Lonsurf to re-evaluate if he should stay on, considering his diffuse peritoneal condition to very accurately say that I has been effective or not. Thera has been no sign of progression. Stability has been achieved."***	"I had a PET/CT which confirmed that the tumours were reducing except the one in my pancreas. They believe that tumour may be a different primary.	"Yes, my oncologist said that I am responding – my tumours are shrinking. The tumour in the lung has not changed in size."	"Yes, I've had 2 CT scans. The first one said that the tumours are not shrinking but also not spreading or growing. Doctor says this is called stability. I will take it"	"Yes. Had a CT scan recently and there were no growth in mets."	***"Last CT scan showed a slight increase (fraction of a mm) in the mets of both liver and lungs."***	***"I just finished cycle of Lonsurf last Sunday. I am waiting for my requisition for my CT scan to see how I am responding. Hopefully soon."***
HAVE YOU HAD TO STOP LONSURF? WHY?	No.	***No***	"Yes, only because of the one tumour in my pancreas that was progressing. Everything else was shrinking due to Lonsurf. So I started FOLFOX now which can help the pancreatic	"Yes, due to hospitalization, not due to Lonsurf. Late Sept. 2018 I broke my hip."	"No, but we adjusted my treatment schedule to increase my time off the meds. It's 5 days on, 9 days off because my WBC count was low. And I had a lot of fatigue."	"No. But am delaying my next cycle because of a low neutrophil count. Would have started cycle 4 on Monday, but it is delayed, giving my WBCs time to recuperate."	***"Thankfully No."***	***"No."***

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			tumour and everything else."					
DID YOUR CANCER SYMPTOMS RESOLVE WHILE ON LONSURF?	Did not have cancer symptoms prior to starting Lonsurf.	***Didn't have any cancer symptoms but did have significant previous treatment-induced side effects which patient is still battling.***	"I didn't really have any before starting Lonsurf."	"Didn't have any cancer symptoms prior to starting Lonsurf."	"I didn't have any."	Patient did not have cancer symptoms prior to starting Lonsurf.	***"I didn't have any symptoms from my cancer before starting Lonsurf."***	***"I've had no cancer symptoms."***
WAS IT WORTH GOING ON LONSURF?	"Yes. I am hoping that it will be a long- term thing to slow the advancement of cancer. I could be on this one for a long, long time. This drug is certainly beneficial for patients, as it has no real harsh side effects. I'd like to see this drug approved. If more people could	***The patient and his wife both agree that Lonsurf would be beneficial for mCRC patients in a similar situation, considering his lack of noticeable side effects.***	"Yes. I feel that the drug is beneficial for metastatic patients. My oncologist doesn't typically use superlatives but when he saw my CEA and CT scan results, he said: 'I don't believe in miracles, but this is in that category – it's awesome!'"	"Yes, definitely. I was scared to try at first because of all the potential side effects. But I am glad I did. " "It has given me more time with my family and that's what access to drugs is all about – time with those we all love."	"Yes I am hoping it will solve the problem. I would recommend it to others if it would help them." I am able to travel (which I really enjoy) on this drug and get out more. The side effects are really tolerable – not like my	"Well, I know that Lonsurf doesn't have the same kind of data to support it as with my earlier treatments. I try to remain hopeful that I will be an outlier that it will keep the tumours under control."	***"Yes. It stopped the progression of the tumours in the abdomen. Also affecting the liver and lungs. Based on the way that things are, I am very, very, pleased with the lack of side effects."***	***"Yes. I would absolutely recommend Lonsurf to anyone in a similar situation, if it is helping them according to the tests. I believe in quality, not quantity. I see some of these people having lots of nausea and then they go back for***

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	PATIENT #1	**PATIENT #2 /CAREGIVER #1**	**PATIENT #3**	**PATIENT #4**	**PATIENT #5**	**PATIENT #6**	**PATIENT #7**	**PATIENT #8**
	have access to it, that would be great!"				others therapies which kept me at home and not able to do much."			***another bout of treatment. But my side effects have been minimal. Other than the diarrhea, absolutely no problems!!"***
DO YOU WISH TO ADD ANYTHING?	"It's a bit costly, but I'm one of the lucky ones that had my group insurance pick that up." "I am happy I got to access it. Please try to get this drug funded, not just for me, but for everyone who will need it in the future."	***Wife:*** ***"My husband and I support the approval of Lonsurf in Canada. It has continued to prolong his life which is why we recommend the funding. It would be heartbreaking for it not to be approved. We vehemently believe every Canadian should be provided access and not denied this drug that provides good quality of life and the ability to prolong life."***	"I appreciate the work that you do. I know that this drug is very expensive, and I would hate for anyone to not have access to the drug because of financial reasons. But as a Canadian from a philosophical standpoint, every possible avenue needs to be pursued to help Canadians access this treatment which can help them from a quality of life perspective and tumor reduction perspective. So please fund this drug. It has helped me, it can help so many more in Canada."	"Late Sept 2018 I broke my hip. 2.5 months in hospital, then therapy. I still have problems with the hip. But it's been good… I feel good, breathe good, no pain, all functions re working properly. No pain, no gain, right? I'm hanging in there, one day at a time. Some things you can do about, some things you can't. It's a shot in the dark. I started Lonsurf in the hospital and it's been just fine for me. Glad I could have it….because	"I'm hoping my input is helpful. I had to change the cycle 5 days on, 9 days off, etc. because my WBC count is low, and I was feeling a lot of fatigue. It's been better since we changed the cycle schedule. So I am able to do things again. It's a great drug. Everyone should have access, not just those who can afford to pay for it. I strongly believe in access for all – especially lifesaving drugs. Please approve Lonsurf. It got	"I would recommend Lonsurf to others in a similar situation…. but it needs to be funded. Please fund this drug for Canadians. Give them extra time too – extra time to work, dance, play, travel or the chance to wait for the next drug that comes along"	***"I would definitely like to see Lonsurf get approved!"***	***"The grim reaper showed up a couple of times, but I said I aint got time for that… I just bought a pontoon boat, actually. Some people tell me that I'm crazy buying boat with my diagnosis, but for the most part, I feel pretty good and I might as well make the most of my time here. The grandkids are going to use the boat for their birthday parties. It has big waterslide and everything. I'm not gonna lie..I wish I didn't have this cancer, but I do. Part of living is***

TABLE 3: PATIENT/CAREGIVER INTERVIEWS – DEMOGRAPHICS & EXPERIENCES ON LONSURF®								
	PATIENT #1	PATIENT #2 /CAREGIVER #1	PATIENT #3	PATIENT #4	PATIENT #5	PATIENT #6	PATIENT #7	PATIENT #8
				what's the alternative? Others should too."	me out of the house and traveling again."			***dying and I wanna live life as much as I possibly can.."***

TABLE 3 CONTINUED: PATIENT/CAREGIVER INTERVIEWS – DEMOGRAPHICS & EXPERIENCES ON LONSURF®						
	PATIENT #9	PATIENT #10	PATIENT #11	PATIENT #12	PATIENT #13	PATIENT #14
INTERVIEW DATE & TIME	Feb 8/19 1:30 p.m. EST	Feb 8/19 2 p.m. EST	Feb 8/19 3:20 p.m. EST	Feb 11/19 1:30 p.m. EST	Feb 11/19 2 p.m. EST	Feb 12/19 1 p.m. EST
CITY, COUNTRY	Ottawa, ON, CA	Guelph, ON, CA	Amherst, NS, CA	Sherbrooke, QC, CA	Victoria, BC, CA	Goose Bay, NL, CA
GENDER & AGE	Male, **65**	Female, **63**	Male, **78**	Female, **69**	Female, **54**	Female, **55**
MARITAL STATUS	Divorced	Married	Married	Divorced, but common law with new partner	Married	Common Law
TX CENTRE?	Ottawa Cancer Centre	Juravinsky Cancer Centre	Moncton City Hospital	Jewish General Hospital, Montreal	Victoria BC Cancer Clinic	Oncologist in St. John's but I generally speak with my doctors via Videocon in Clarinville
DATE OF MCRC DX	May 2013	January 20, 2016	March 2013	2010	October 31, 2013	2016
LOCATION OF METS?	Lungs, Kidneys	Peritoneum	Lungs	Abdomen	Lungs	Spine, Abdomen, LNs
CURRENTLY OR PREVIOUSLY ON LONSURF?	**Currently**	**Currently**	**Previously**	**Previously**	**Currently**	**Currently**
LINE OF TX RECEIVED/ RECEIVING LONSURF?	**4th Line** Started in December 2017	**4th Line** Started December 2018	**Unsure** March 2018 – February 2019	**5th Line** July 30, 2018 – January 27, 2019	**6th Line** Started in April 2018	**4th Line** Started in July 2018

TABLE 3: PATIENT/CAREGIVER INTERVIEWS – DEMOGRAPHICS & EXPERIENCES ON LONSURF®								
	PATIENT #1	**PATIENT #2 /CAREGIVER #1**	**PATIENT #3**	**PATIENT #4**	**PATIENT #5**	**PATIENT #6**	**PATIENT #7**	**PATIENT #8**
PREVIOUS TXS RECEIVED FOR MCRC?	-FOLFOX -FOLFIRI -Regorafenib	-FOLFOX -FOLFIRI -REGORAFENIB		An array of drugs – unsure of the names	-Immunotherapy -FOLFOX -FOLFIRI -FOLFOX -LONSURF -Regorafenib	***"I don't remember all the names of the drugs. They all blend together. But I do remember Stivarga (Regorafenib).***		-FOLFOX -CAPOX -Clinical Trial
# OF CYCLES OF LONSURF?	**14**	**4**		**10**	**7**	**10**		**6**
SIDE EFFECTS OF LONSURF?	***"Not really that I'm aware of. Slight nausea, but I don't take any meds for nausea. My WBC count is a bit low, so I'm now on 5 week cycles to allow for more recovery."***	***"I had a bit of nausea and vomiting, so they gave me dexamethasone. I was also quite fatigued."***		***"I had no side effects until Jan 2019: Nausea, Took 3 days on, 2 days off + 2 normal days off. Thought I had the flu. Then I was prescribed anti-nausea meds. On Lonsurf again for 5 days + anti-nausea. Then the doctor saw the CT scans and took me off Lonsurf.***	***"I just experienced some fatigue while on Lonsurf. "***	***"Low WBC count and fatigue."***		***"I have yet to be extremely sick on Lonsurf. But I do feel nauseated on my days off of Lonsurf, which is weird. Low WBC count, but I self-inject with a drug for this.***
RATE QoL WHILE ON LONSURF? (1-10)	**5** ***"My overall quality of life is about a 5, but since I started chemo it has never been better than that. I feel as good now or better than at any time since I began chemo. I certainly don't feel any worse. Since it's an oral chemo, I am able to do more things rather than 2 hours at hospital and 48 hours at home with a bottle of chemo infusions. I had to wear this bottle at home for 2 days and visit a clinic to get unhooked. Lonsurf is more*** convenient."**	**10** ***"I can do 90% of what I'd like to do on the day to day. I just feel a bit weak right now because I'm just getting over the flu."***		**8** ***"Because I was doing what I wanted to do. I was energetic. I did my housework and yardwork, was able to get around. I even did some logging. I had a guy cut the trees down and I cut them up and helped to take them to our yard."***	**4 or 5** ***"I'm usually a very active woman. The main problem is dizziness. I've had this for the last 10 years and never found out why. I try to do things around the house as well as gardening and cutting the grass, but not like I used to. Right now, I can't walk too much. It's okay. I try to stay positive. "***	**6** ***"Considering the circumstances, I can drive and get out and do things on Lonsurf. I just have to plan things in advance. Time is so precious now, since my energy levels are definitely low.***		**8** ***"I am able to continue with fishing. I am not letting cancer dictate how I am going to live.".***
DID CEA CONFIRM RESPONSE?	***"Not aware of my CEA level."***	***"I'm not aware of CEA level.".***		***"Unsure."***	***"Unsure "***	***"Unsure"***		***"All my bloodwork came back good. Other than my slightly low levels of WBCs."***

TABLE 3: PATIENT/CAREGIVER INTERVIEWS – DEMOGRAPHICS & EXPERIENCES ON LONSURF®								
	PATIENT #1	PATIENT #2 /CAREGIVER #1	PATIENT #3	PATIENT #4	PATIENT #5	PATIENT #6	PATIENT #7	PATIENT #8
DID CT CONFIRM RESPONSE?	"I have a CT after every second cycle. My tumours have responded in the past. I just had a CT on Tuesday. The rectal tumour is stable, but the tumours on the lungs appear to be growing slightly."	"My last CT in December showed that everything was stable. I will have my next one in mid Feb. Lonsurf seems to be doing a good job of keeping things under control."		***"As of last Wednesday, there was no noticeable difference in the result of the treatment. But they found out that my cancer was 5.5 cm and in a month and a half it had grown to 8 cm. Doctor double checked the CT scan and decided to take me off Lonsurf."***	"Last CT scan showed that some lesions increased in the abdomen."	"According to the results of the CT scans, there so far there has been no increase in the tumours since going on Lonsurf."		"I get CT scans every 3 months. No new tumours. 2 of my tumours in the lymph nodes have disappeared. And 2 shrank."
HAVE YOU HAD TO STOP LONSURF? WHY?	"No. Have never had to stop Lonsurf."	"No, but I did stop a couple of pills short because I developed an infection and am on antibiotics."		***"Yes, Stopped Lonsurf because of disease progression."***	"Yes, due to progression."	"Yes, shortly after I started, I was admitted to the hospital. They wanted to make sure that the Lonsurf was not causing the problem. Missed only 1 cycle. ."		"No. Well I had to wait an extra week to start my next cycle once because of those low WBCs.."
DID YOUR CANCER SYMPTOMS RESOLVE WHILE ON LONSURF?	Did not have cancer symptoms prior to starting Lonsurf.	Patient did not have cancer symptoms prior to starting Lonsurf		***"I never had cancer symptoms."***	"Never really had cancer symptoms."	"I didn't have any really."		Patient did not have cancer symptoms prior to starting Lonsurf.
WAS IT WORTH GOING ON LONSURF?	"Yes, it has been effective for me, but I don't know the experiences with others. If it is effective for others, then that's good. I'd like to see it get approved."	"Yes. Absolutely. I think it's a great drug. I think we need to focus on education for public to make them aware to see that there are other types of cancer that impact Canadians."		***"I would really like to see it get approved. I was hoping it would shrink my cancer. It did stop it from growing to some extent. It looked like it was stable initially, so I guess, yes, it was worth going on Lonsurf."***	"Yes, it was not as hard on my body as Regorafenib is. I find Regorafenib stronger and more aggressive. Lonsurf didn't have the same side effects. I would have liked to have stayed on Lonsurf longer, but it wasn't working according to the CT scans."	"Yes, and I feel that it could help others too. "		"To me, it's a miracle drug because it does more than it's supposed to be doing ……2 tumours in lymph nodes disappeared. 2 shrunk, no new ones appeared. It was supposed to enhance diarrhea, nausea, etc, but I actually only have those side effects on my days off from the drug. I was told that this medication was just to prolong treatment, but it's doing good to me. Oh, definitely, definitely! I'd tell anyone in this circumstance to take it."

TABLE 3: PATIENT/CAREGIVER INTERVIEWS – DEMOGRAPHICS & EXPERIENCES ON LONSURF®								
	PATIENT #1	PATIENT #2 /CAREGIVER #1	PATIENT #3	PATIENT #4	PATIENT #5	PATIENT #6	PATIENT #7	PATIENT #8
DO YOU WISH TO ADD ANYTHING?	"I really don't have any expectations with any of the drugs I've been taking. If they work, good. If not, well c'est la vie. Hope for the best and be prepared for the worst."	"Please fund this drug. It's the right thing to do. I've been able to have a pretty good quality of life and I haven't really needed much assistance while on the treatment. I can do almost everything around the house and take care of my family. I couldn't do all that before. So, I hope this is taken into consideration."		***"I was disappointed to go off Lonsurf. I had it pretty good while I was taking the pill – no noticeable side effects really. It was pretty good to tolerate until January. I hope this treatment gets approved for others who need it. it gave me some more time. This is time I wouldn't have had without it – who knows. I would recommend it become available to everyone in Canada for free."***	"I hope others get to use the drug and that it gets funded in the meantime. It's a drug that doesn't make you sick so why wouldn't you want to use this drug if it can help you?"	"Lonsurf stabilized my tumours. That's the name of the game. I went through a very stressful time trying to get coverage for this drug which has worked well for me. I don't want anyone to go through what I went through so I strongly recommend that that this drug, which has shown effectiveness for me and has been relatively side effect free, be funded for ALL Canadians. Others just like me in Canada deserve to access it too without the stress of financial coverage."	"Patients deserve everything they can get their hands on to help them with their cancer especially if it can give them minimal side effects like Lonsurf. In the meantime, who knows, something else can come along and be that magic bullet that everyone hopes for. It's important that Lonsurf is provided to everyone in Canada from coast to coast, giving patients peace of mind."

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The PAG includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of trifluridine-tipiracil in mCRC:

Clinical factors:

- BSC is available for all patients

Economic factors:

- Cost of supportive therapy (e.g. anti-emetics, granulocyte colony-stimulating factor)
- Resources required to monitor and treat serious adverse events

Please see below for more details.

4.1 Currently Funded Treatments

Currently, there are no funded treatment options for mCRC after chemotherapy, although for patients who have RAS wild type tumors, treatment with an EGFR inhibitor is available. BSC is available for all patients, or for patients who have private drug insurance, regorafenib is an option.

4.2 Eligible Patient Population

There is an unmet need for this group of patients and the younger patients often seek further treatments. PAG noted that trifluridine-tipiracil and regorafenib are indicated for the same group of patients. pERC did not recommend funding of regorafenib as it had only a very modest PFS and OS benefit, moderate but not insignificant toxicities, and a similar decline in QoL compared to BSC.

As there is no direct comparison with intravenous chemotherapy, PAG is seeking clarity that trifluridine-tipiracil would be the last line of therapy, after patients have exhausted all treatment options.

PAG noted that the trial included only patients with ECOG performance status of 0 to 1. In practice, there would be many patients who would have ECOG performance status of 2 at this stage. PAG has concerns of extending treatment to patients with performance status of 2, given the number of serious adverse events associated with trifluridine-tipiracil. If trifluridine-tipiracil is recommended for reimbursement, PAG suggests treatment be limited to patients with ECOG performance status of 0 to 1, aligning with trial eligibility.

Patients with metastatic small bowel cancer are often treated similarly to patients with metastatic large bowel cancer. PAG is seeking information on the generalizability of the results to patients with metastatic small bowel cancer.

PAG has concerns for indication creep to trifluridine-tipiracil use in other GI cancers (i.e., GIST) or earlier lines of therapy prior to exhausting all other standard therapies. Some

patients may have a preference for an oral therapy prior to current standard therapies which are intravenously administered.

4.3 Implementation Factors

Additional resources are required to monitor and treat severe (grade 3 to 4) myelosuppression including anemia, neutropenia, thrombocytopenia and febrile neutropenia. The cost of supportive therapy (e.g. anti-emetics, G-CSF) also needs to be considered in implementation.

Trifluridine-tipiracil is available in two strengths and dose is based on body surface area. PAG noted that some patients will require two different strengths of tablets to make up their dose and thus, may have two dispensing fees in those provinces where the access to oral therapies is through Pharmacare.

PAG noted that trifluridine-tipiracil is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home, and no chemotherapy chair time would be required. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their Pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

PAG noted that trifluridine-tipiracil would be the last line of therapy after chemotherapy. For patients who have RAS wild type mCRC, treatment with an EGFR inhibitor is available and PAG is seeking guidance on sequencing of EGFR inhibitors and trifluridine-tipiracil in this group of patients. Regorafenib for mCRC is not funded in any province give the negative pERC recommendation.

4.5 Additional Information

PAG noted that the blister packaging of the tablets is an enabler to implementation as it would minimize drug wastage and also minimize exposure of hazardous drugs to health care providers and caregivers.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician input submissions, one joint submission and one individual submission, were provided, comprising a total of 32 clinicians. The registered clinicians provided input on trifluridine-tipiracil for 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. While some patients may have treatment options, including an EGFR inhibitor for RAS wild type tumours or regorafenib for patients through private insurance, no treatments were identified as being currently funded for patients in this setting. Eligibility criteria from the pivotal trial were stated as being appropriate to apply to clinical practice; specifically, patients with a preserved ECOG performance status of 0 or 1 who have failed prior therapies. Both the single and joint clinician input stated having experience using trifluridine-tipiracil in practice and commented positively on the safety and efficacy of the treatment. Trifluridine-tipiracil was also stated to be a preferred treatment over regorafenib based on toxicity with experience of using both treatments. Poor performance status and an inability to ingest oral therapy were stated as contraindications to treatment with trifluridine-tipiracil by the joint input. The single clinician input highlighted benefits of trifluridine-tipiracil specifically among patients with dihydropyrimidine dehydrogenase (DPD) deficiency and those who have 5-fluorouracil-related angina, as trifluridine-tipiracil is not metabolized by DPD, which is also believed to be related to 5-fluorouracil-related angina.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for Metastatic Colorectal Cancer

The joint clinician input highlighted that there are currently no funded treatment options for patients with chemorefractory mCRC. However, patients who have RAS wild type tumours may be provided with an EGFR inhibitor. Regorafenib may be an option for patients who have private drug insurance.

The individual clinician input identified irinotecan, oxaliplatin, cetuximab, panitumumab, bevacizumab and regorafenib as treatments that have added two to four months of overall survival benefit for patients. Collectively, these drugs have allowed patients' survival to approach 36 months, compared to the six months of overall survival that was common for patients historically. The clinician also mentioned that patients who received treatment with FOLFIRI with or without bevacizumab, FOLFOX, cetuximab, panitumumab or regorafenib currently do not have any treatment options.

5.2 Eligible Patient Population

The joint clinician input indicated that there is currently no established predictive biomarker for trifluridine-tipiracil. 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 RAS wild-type disease, prior anti-EGFR therapy.

The single clinician input stated that the trial population was completely applicable to their clinical practice. No specific group of patients were indicated as needing to be excluded from the pool of eligible patients. Specific patient groups that would benefit from trifluridine-tipiracil include 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. The clinician stated that trifluridine-tipiracil is theoretically much less likely to cause angina and that clinical studies

seem to show this as well. Trifluridine-tipiracil would not replace any current therapies. The single clinician indicated that they could incorporate trifluridine-tipiracil with oxaliplatin and irinotecan as life prolonging agents in patients with DPD deficiency or 5-fluorouracil related angina. The single clinician highlighted patients with DPD deficiency and who are intolerant to 5-fluorouracil, accounting for approximately 1-2% of patients, and those who develop 5-fluorouracil/capecitabine-related angina, accounting for approximately 5% of patients, as the subgroups that would most benefit from trifluridine-tipiracil.

While the individual clinician input did not indicate any subgroups of patients for whom trifluridine-tipiracil should not be used, the joint clinician input highlighted patients with poor performance status, or who are unable to ingest oral therapies.

5.3 Relevance to Clinical Practice

The joint clinician input indicated that trifluridine-tipiracil is available to patients through the manufacturer's special access program. For patients with a preserved ECOG performance status, the only treatment option provided to patients is best supportive care, which the joint clinician input indicated as being difficult for patients to accept. With trifluridine-tipiracil, the input stated that patients would be offered a modest but meaningful benefit in survival. The toxicity profile was stated to be manageable. Regorafenib is an approved but not funded treatment for chemorefractory mCRC; the joint clinician input stated that through their experience, the toxicity profile of trifluridine-tipiracil is better tolerated among patients with a more predictable toxicity profile compared to regorafenib. A risk of myelosuppression was mentioned as part of the toxicity profile of trifluridine-tipiracil. Toxicities related to trifluridine-tipiracil were stated to be familiar to, and easily managed by medical oncologists. The single clinician input also indicated having experience with trifluridine-tipiracil and commented positively regarding the safety and activity of the drug, stating that trifluridine-tipiracil is very well tolerated. The side effects of trifluridine-tipiracil and bevacizumab were comparable to the combination of capecitabine and bevacizumab, and quality of life did not show significant deterioration in a trial comparing the two treatments. The single clinician indicated that one of their patients had to discontinue treatment with trifluridine-tipiracil as it was not included in the provincial formulary, forcing the patient to travel three hours to access treatment. Two other patients responded well to treatment with significant improvements in symptoms from their mCRC and did not experience any treatment emergent side effects.

Poor performance status and an inability to ingest oral therapy were stated as contraindications to trifluridine-tipiracil. Once again, the single clinician input highlighted the benefits of trifluridine-tipiracil specifically for patients who are DPD deficient or who have 5-fluorouracil - related angina. All patient groups were stated to benefit from the drug. As stated in section 5.2, the single clinician input stated that trifluridine-tipiracil may be less likely to cause angina in patients compared to 5-fluorouracil/capecitabine.

5.4 Sequencing and Priority of Treatments with Trifluridine-Tipiracil

Both the individual and joint clinician input stated that patients who are intolerant or refractory to currently available therapies for mCRC, including FOLFIRI, FOLFOX, bevacizumab, EGFR inhibitors and regorafenib, would be offered trifluridine-tipiracil. Based on a more favourable

toxicity profile and clinical experience, trifluridine-tipiracil was also indicated as the preferential treatment compared to regorafenib.

5.5 Companion Diagnostic Testing

Not applicable.

5.6 Additional Information

The single clinician input highlighted the current state of clinical trials and research in Canada, specifically in regard to colorectal cancer. The clinician stated that Canada has "punched above its weight in clinical trials in colon cancer." If patients are not allowed to access trifluridine-tipiracil and regorafenib in the future, the clinician expressed uncertainty about whether Canadian patients would be able to participate in advanced CRC trials in the future. Concern was expressed that Canadian patients would not have access to internationally accepted treatment algorithms, potentially disadvantaging and leaving behind Canadian CRC patients.

5.7 Implementation Questions

5.7.1 In regard to section 5.2 above, if trifluridine-tipiracil was available in clinical practice:

5.7.1.1 Is there a subgroup of patients from the study population that would most benefit?

5.7.1.2 Is there a subgroup of patients from the study population for whom the new treatment should not be used?

Refer to section 5.2.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy of trifluridine-tipiracil (brand name: LONSURF®; referred to as TAS-102 in clinical studies) as a treatment of adult patients with mCRC who have been previously treated with, or are not candidates for, available therapies including fluropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if RAS wild-type, anti-EGFR agents.

A Supplemental Question relevant to the pCODR review was identified while developing the review protocol and is outlined in section 7 of this report:

- Critical appraisal of new evidence (since the 2018 original pCODR submission) on the HRQoL of patients with mCRC treated with trifluridine-tipiracil.

6.1.1 Summary of Evidence from Original 2018 pCODR Submission

A summary of the evidence that comprised the original pCODR submission[32] reviewed by pERC in 2018 is provided below. Please refer to the original clinical guidance report for more detailed information.[19]

A total of three RCTs were included as evidence.[19] All were double-blind, parallel-group, two-armed, and placebo-controlled trials. RECOURSE and TERRA were phase 3 trials and J003-10040030 was a phase 2 trial. All investigated the efficacy and safety of trifluridine-tipiracil in patients who were intolerant to or had failed standard therapies. Study medication was administered orally twice daily in 35mg/m^2/dose for days 1-5 and 8-12 in a 28-day treatment cycle. Patients also received BSC. Patients were randomized in a 2:1 ratio in all trials to receive trifluridine-tipiracil or placebo. Patient characteristics are summarized in Table 4 and key efficacy and safety outcomes for the three trials are summarized in Table 5.

RECOURSE included patients from 13 countries. Overall, 534 patients were assigned to the trifluridine-tipiracil group and 266 were assigned to the placebo group. The median age of patients was 63 years with a range of 27-82 years and the proportion of males was 61% for treatment and 62% for placebo. The majority of patients were white (58%), had 18 months or more from diagnosis of metastasis (79%), and were on their fourth or greater line of treatment (61%). Eastern Cooperative Oncology performance status (ECOG PS) of participants in RECOURSE was limited to 0-1 with approximately half of patients with each status.

TERRA included patients from three countries and all patients were Asian. Overall, 271 patients were assigned to the trifluridine-tipiracil group and 135 were assigned to the placebo group. The median age of patients was 57 years with a range from 24-81 years, and the proportion of males was 63% for treatment and 62% for placebo. The majority of patients were KRAS wild-type (63%) and had an ECOG PS of 1 (77%).

J003-10040030 included patients from Japan and all patients were Japanese. Overall, 112 patients were assigned to the trifluridine-tipiracil group and 57 were assigned to the placebo group. The median age of patients was 63 years with a range of 28-80 years, and the proportion of males was 57% for treatment and 49% for placebo. In J003-10040030 patients with an ECOG PS of 2 were also included, however patients with ECOG PS 2 only made up 2.4% of the patient population and the majority (63%) had an ECOG PS of 0. The majority of patients were on their third or greater line of treatment (82%).

Table 4: Characteristics of patients included in the RECOURSE, TERRA and J003-10040030 trials that comprised the evidence base in the original (2018) pCODR submission of trifluridine-tipiracil in mCRC.

	RECOURSE[19]		TERRA[19]		J003-10040030[19]	
	Trifluridine-tipiracil	Placebo	Trifluridine-tipiracil	Placebo	Trifluridine-tipiracil	Placebo
N randomized	534	266	271	135	112	57
Age (yrs)						
Median	63	63	58	56	63	62
Range	27-82	27-82	26-81	24-80	28-80	39-79
Sex (%)						
Male	61	62	63	62	57	49
Female	39	38	37	38	43	51
ECOG PS (%)						
0	56	55	24	22	64	61
1	44	45	76	78	33	37
2	0	0	0	0	3	2
Primary site of disease (%)						
Colon	63	61	57	63	56	63
Rectum	37	39	43	37	44	37
KRAS mutation (%)						
Wild type	49	49	63	63	55	48
Mutant	51	51	37	37	45	52
Time since cancer diagnosis, median (months)	36	39	22.8	26.3	NR	NR
Time from diagnosis of metastases (%)						
<18 months	21	21	49	39	10	18
≥18 months	79	79	51	62	87	83
Number of metastatic sites (%)						
1-2	58	55	61	61	60	54
≥3	42	45	39	39	39	46
Number of prior regimens (%)						
2	18	17	23	19	15	23
3	22	20	27	27	85	77
≥4	60	63	50	55		
Previous treatment (%)						
Bevacizumab	100	99.6	19	20	78	82
Cetuximab/panitumumab	52.1	54.1	17	19	63*	63*

Abbreviations: ECOG PS - Eastern Cooperative Oncology Group performance status; **NR** - Not reported.

Notes:
*Only cetuximab.

Efficacy analyses were based on intent-to-treat (ITT) populations in RECOURSE and TERRA. J003-10040030 used a population excluding two untreated patients and one patient that had violated study protocol. The disease control rate (DCR) and objective response rate (ORR) analyses were completed using the tumour response (TR) population for each trial. Safety analyses were completed using the as-treated (AT) population in all trials. Missing efficacy data were censored to last confirmable survival date in TERRA and J003-10040030 or clinical progression dates occurred where only the day was missing for RECOURSE.

OS was the primary endpoint of all trials, defined as the time between randomization and death due to any cause. All trials reported statistically significant improvements in OS in favour of trifluridine-tipiracil treatment.

In RECOURSE formal OS analysis occurred once 571 deaths were observed. The median OS was 7.1 months in the trifluridine-tipiracil group and 5.3 months in the placebo group. An absolute improvement in median OS of 1.8 months for treatment was reported (hazard ratio [HR]=0.68, 95% confidence interval [CI]: 0.58-0.81, p<0.001). The median follow-up time for OS analysis was 11.8 months. The ITT population was used for this analysis (n=800).

Updated survival analysis for RECOURSE was reported in a conference abstract. Updated survival data were collected on October 8th, 2014. This was 7.4 months following the original cut-off date of January 24th, 2014 as stipulated in the RECOURSE study protocol. Median OS was 7.2 months in the trifluridine-tipiracil group and 5.2 months in the placebo group. A slightly higher absolute improvement in median OS of 2.0 months in favour of the treatment group was reported (HR=0.69, 95% CI: 0.59-0.81, p<0.0001). Median follow-up time for the updated analysis was 19.1 months. The ITT population was used for this analysis (n=800).

In TERRA, formal OS analysis occurred once 288 deaths were observed. The median OS was 7.8 months in the trifluridine-tipiracil group and 7.1 months in the placebo group. An absolute improvement in median OS of 0.7 months for treatment was reported (HR=0.79, 95% CI: 0.62-0.99, p=0.035). Median follow-up time for OS analysis was 13.8 months and 13.4 months for the trifluridine-tipiracil and the placebo groups, respectively. The ITT population was used for this analysis (n=406).

In J003-10040030, OS analysis occurred once 121 deaths were observed. The median OS was 9.0 months in the trifluridine-tipiracil group and 6.6 months in the placebo group. An absolute improvement in median OS of 2.4 months for treatment was reported (HR=0.56, 95% CI: 0.39-0.81, p=0.0011). Median follow-up time for OS analysis was 11.3 months. The efficacy population was used in this analysis (n=169).

All trials reported statistically significant improvements in PFS in favour of trifluridine-tipiracil treatment.

The median PFS in RECOURSE was 2.0 months for the trifluridine-tipiracil group compared to 1.7 months in the placebo group (HR=0.48, 95% CI: 0.41-0.57, p<0.001). In TERRA, the median PFS was 2.0 months and 1.8 months for the trifluridine-tipiracil and placebo groups, respectively (HR=0.43, 95% CI: 0.34-0.54, p<0.001). In J003-10040030, the median PFS was 2.0 and 1.0 months for the trifluridine-tipiracil and placebo groups, respectively (HR=0.41, 95%CI: 0.28-0.59, p<0.0001).

Direct measures of HRQoL were not reported in any of the included trials.

All three trials provided data on harm outcomes using an AT population. All trials indicated that certain adverse events (AEs) had higher incidence rates in the trifluridine-tipiracil group compared to placebo (e.g. neutropenia, anemia, and

leukopenia). Serious adverse events (SAEs) are AEs that led to death, were life threatening, led to admission or extension of hospital stay, and/or turned into or triggered lasting disabilities or dysfunctions. In RECOURSE and J003-10040030 febrile neutropenia was reported as the SAE of greatest incidence. Incidence of SAEs was similar between treatment groups in RECOURSE and TERRA but was higher in the trifluridine-tipiracil group compared to placebo in the J003-10040030 trial.

Withdrawals due to AEs were similar between treatment groups for all trials. In RECOURSE, 10.3% of patients in the trifluridine-tipiracil group and 13.6% of patients in the placebo group withdrew due to AEs. In TERRA, 10% and 9.6% of patients withdrew from the treatment and placebo groups, respectively; and in J003-10040030, 4% and 2% of patients withdrew from each group due to AEs, respectively.

In the RECOURSE trial, grade ≥ 3 AEs occurred in 69% of patients in the trifluridine-tipiracil group and 52% of patients in the placebo group; incidence of SAEs was 29.6% and 33.6%, respectively. In the TERRA trial, 45.8% of patients in the treatment group experienced an AE compared to 10.4% in the placebo group. Incidence of drug-related SAEs was 23.2% and 23.0% in the trifluridine-tipiracil and placebo groups, respectively. In the J003-10040030 grade ≥ 3 AEs occurred in 69% of patients in the treatment group and 16% of patients in the placebo group. SAEs occurred in 19% of patients treated with trifluridine-tipiracil and 9% of patients in the placebo group.

In all three trials the main AEs that differed between the treatment groups (>10% difference) were neutropenia, leukopenia, and anemia. Vomiting also had a greater than 10% difference between groups in the J003-10040030 trial. One treatment-related death occurred in RECOURSE due to septic shock; no treatment-related deaths occurred in J003-10040030 and TERRA.

A quality assessment was performed of the three trials and all were considered of high quality based on the SIGN-50 quality checklist for RCTs. All trials were double-blind and used appropriate randomization methods; and sample sizes were targeted for sufficient statistical power of primary outcomes. All three trials were funded by the manufacturer of the drug of interest. The manufacturer in collaboration with the trial investigators designed the trials and collected and analyzed the data. None of the trials included measures of HRQoL.

Table 5: Highlights of the evidence included in the original (2018) pCODR submission of trifluridine-tipiracil in patients with mCRC.

	RECOURSE[19]		TERRA[19]		J003-10040030[19]	
	Trifluridine-tipiracil (n=534)	Placebo (n=266)	Trifluridine-tipiracil (n=271)	Placebo (n=135)	Trifluridine-tipiracil (n=112)	Placebo (n=57)
Median OS in months (95%CI)	7.1 (6.5-7.8)	5.3 (4.6-6.0)	7.8 (7.1-8.8)	7.1 (5.9-8.2)	9.0 (7.3-11.3)	6.6 (4.9-8.0)
HR (95%CI)	0.68 (0.58-0.81)		0.79 (0.62-0.99)		0.56 (0.39-0.81)	
p-value	<0.001		0.035		0.0011	
Median PFS in months (95%CI)	2.0 (1.9-2.1)	1.7 (1.7-1.8)	2.0 (1.9-2.8)	1.8 (1.7-1.8)	2.0 (1.9-2.8)	1.0 (1.0-1.0)
HR (95%CI)	0.48 (0.41-0.57)		0.43 (0.34-0.54)		0.41 (0.28-0.59)	
p-value	<0.001		<0.001		<0.0001	
Harms Outcome, n (%)	Trifluridine-tipiracil (n=533)	Placebo (n=265)	Trifluridine-tipiracil (n=271)	Placebo (n=135)	Trifluridine-tipiracil (n=113)	Placebo (n=57)
AEs Grade ≥3	370(69)	137(52)	124(46)	14(10)	78(69)	9(16)
AEs (any grade)	524(98)	247(93)	244(90)	70(52)	111(98)	52(91)
WDAE	21(4)	5(2)	27(10)	13(9.6)	5(5)	1(2)
Abbreviations: AEs = adverse events, CI = confidence interval, HR = hazard ratio, OS = overall survival, PFS = progression free survival, WDAE = withdrawal due to adverse event.						

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 6 below. Outcomes considered most relevant to patients, based on input from the patient advocacy group, are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 6: Selection criteria.

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCT§ published after April 5, 2018†	Adult patients (≥18 years) with recurrent mCRC previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy, and if KRAS wild-type, anti-EGFR therapy. Subgroup: • Patients with rectal cancer who have received pelvic radiation therapy	Trifluridine-tipiracil (Lonsurf)	• BSC • placebo • regorafenib • immunotherapy approaches	• OS • PFS • HRQoL • ORR • Metastases resection rate • AEs • SAEs • WDAE
Abbreviations: AEs - adverse events; BSC- best standard care; EGFR - epidermal growth factor; mCRC - metastatic colorectal cancer; ORR - objective tumour response rate; OS - overall survival; PFS - progression-free survival; RCT-				

randomized controlled trial; **ROA** - route of administration; **SAEs** - serious adverse events; **HRQoL** - health-related quality of life; **VEGF** - vascular endothelial growth factor; **WDAE** -withdrawal due to adverse events.

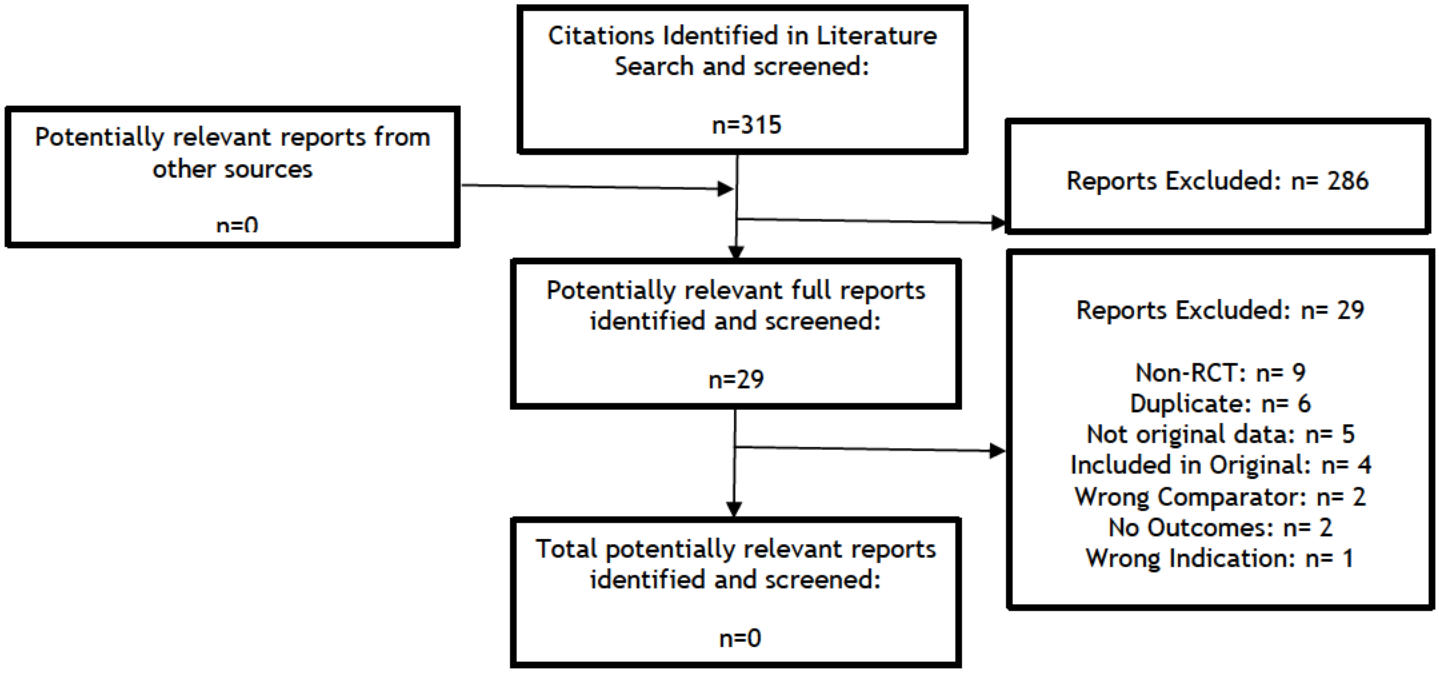
Notes:
* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).
§ Includes retrospective and exploratory analyses from prospective randomized controlled trials.
† This date coincides with the last literature search performed for the original pCODR submission for trifluridine-tipiracil for mCRC.

6.3 Results

6.3.1 Literature Search Results

A total of 315 abstracts were identified by the literature search. Of those, 29 potentially relevant reports were screened as full texts. Based on the selection criteria outlined in section 6.2.1, all 29 reports were excluded for the following reasons: not a RCT (n=9), duplicate publication (n=6), not original data (presentation of previously presented and analysed data (n=5), citation included in the original pCODR submission (n=4), wrong comparator (n=2), no outcomes reported (n=2), and wrong indication (n=1).

Figure 1: PRISMA Flow Diagram for Inclusion and Exclusion of Studies



6.3.2 Summary of Included Studies

The original literature search (from the original 2018 pCODR submission) was updated by the pCODR Methods Team. The updated search did not identify new evidence that met the selection criteria of the review as outlined in section 6.2.1. Therefore, no new studies were included in the systematic review.

6.4 Ongoing Trials

No ongoing clinical trials of trifluridine-tipiracil in mCRC that met the study selection criteria as outlined in section 6.2.1 were identified.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of trifluridine-tipiracil in mCRC:

- Critical appraisal of new evidence (since the 2018 original pCODR submission) on HRQoL of patients with mCRC treated with trifluridine-tipiracil.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 New Evidence on Health-related Quality of Life

7.1.1 Objective

Based on pERC's negative recommendation for reimbursement, the submitter resubmitted to pCODR with new clinical information on the efficacy and safety of trifluridine-tipiracil. After reviewing the new evidence for resubmission eligibility, pERC granted the resubmission on the basis of new HRQoL evidence.[2]

7.1.2 Findings

A total of 12 reports were provided by the submitter and cited as providing new clinical information.[3-11] Of these reports, five were included in the resubmission since they provided new evidence on HRQoL obtained using validated measures.[4,5,7,11,12] The remaining seven reports were excluded because they did not report HRQoL data.[3,8,9,11,13]

The five reports included in the resubmission represent two unique studies: PRECONNECT and a study referred to herein as TAS-102 versus BSC. Both studies were excluded from the pCODR systematic review based on their non-RCT design. A summary and critical appraisal of each study can be found below in sections 7.1 (PRECONNECT) and 7.2 (TAS-102 versus BSC).

7.1.3 PRECONNECT

PRECONNECT is an on-going, phase 3b, single-group, early access study of trifluridine-tipiracil in 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; the primary endpoint is safety and secondary outcomes are PFS and HRQoL.[14]

There are four reports presenting data on the PRECONNECT study, which are summarized in Table 7. Trial data have only been published in conference form.

Table 7: Summary of reports presenting data on the PRECONNECT study.

Author/ Year	Falcone et al. 2018[6]	Taieb et al. 2019[33]	Taieb et al. 2019[4]	Sabater et al. 2019[7]
Report Type	Conference Poster	Conference Abstract	Conference Poster	Conference Poster
Title	QoL at baseline in an international phase 3b, open-label early-access program of trifluridine/tipiracil in	HR-QoL in the early access phase 3b study of trifluridine/tipiracilin in pretreated mCRC:	HR-QoL in the early access phase 3b study of trifluridine/tipiracil in pretreated mCRC: results from PRECONNECT study.	Validation of cost effectiveness of trifluridine/tipiracil vs best supportive care and regorafenib for previously treated

Author/ Year	Falcone et al. 2018[6]	Taieb et al. 2019[33]	Taieb et al. 2019[4]	Sabater et al. 2019[7]
	previously treated mCRC.	results from PRECONNECT study.		mCRC in the UK using phase 3b early access clinical trial data in the real-world setting.
Data Lock Date	March 7, 2017	November 1, 2017	May 20, 2018	May 20, 2018
Number of Patients Enrolled	300	464	464	454[†]
Reported HRQoL Outcomes	- QLQ-C30 - EQ-5D-3L utility - EQ-5D-3L VAS	- QLQ-C30 - EQ-5D-3L utility - EQ-5D-3L VAS	- QLQ-C30 - EQ-5D-3L utility - EQ-5D-3L VAS	- EQ-5D-3L utility converted with UK scoring algorithm

Abbreviations: **ECOS PS** - Eastern Cooperative Oncology Group performance status; **EQ-5D Utility** - EuroQoL Group's standardised measure of health status; **HRQoL** - health-related quality of life; **mCRC** - metastatic colorectal cancer; **QLQ-C30** - European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; **VAS** - visual analogue scale.

Notes:
[†] Only patients with both the QLQ-C30 and progression free survival data were included (10 patients removed).[34]

7.1.3.1 Detailed Study Characteristics

The PRECONNECT study is an on-going, phase 3b, single-group, non-randomized, 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. PRECONNECT is a multi-centred study with a targeted enrollment of 150 sites in 20 countries. There is no indication that early termination has occurred, and study completion date was targeted for May 2019. As of March 25th, 2019, there were 832 patients enrolled from 15 countries;[34] the major patient inclusion and exclusion criteria used in the study are summarized in Table 8.

The purpose of the study is to collect additional safety and efficacy data during treatment with trifluridine-tipiracil in patients with pretreated mCRC. The primary outcome is to measure the incidence of AEs; (safety and tolerability), abnormalities in laboratory assessment (hematology, blood biochemistry, and urinalysis), physical examination and abnormalities in ECOG performance status, and abnormalities in vital signs (blood pressure, heart rate, body temperature, body weight). Secondary outcomes include PFS from date of first study drug intake until the date of investigator-assessed disease progression or death due to any cause, whichever occurs first; and HRQoL measured using the EORTC QLQ-C30 and EQ-5D-3L questionnaires. Only data on HRQoL are presented here as this outcome was the focus of the resubmission.

The funding for PRECONNECT is from Institut de Recherches Internationales Servier (I.R.I.S.).

Table 8: Summary of PRECONNECT study characteristics.

Study Design	Eligibility Criteria	Intervention	Comparator	Outcomes
PRECONNECT Study[14]				
Clinical trial NCT03306394 Open label, single arm, single group assignment, non-randomized, phase 3b study Enrollment: 832 patients enrolled as of March 25, 2019[34] Enrollment Start Date: October 2016[11] Number of centres: Approximately 150 Number of countries: 20 Main Location: Azienda Ospealiero Universitaria Pisana, Istituto Toscano Tumori[11] Study Start Date: October 18, 2016[11] Primary Completion Date: May 2019 Study sponsored by Institut de Recherches Internationales Servier (I.R.I.S.)	<u>Inclusion Criteria:</u> • 18≥ years of age • Has definitive histologically confirmed adenocarcinoma of the colon or rectum • Has metastatic lesion(s) • Has received at least 2 prior regimens of standard chemotherapies (including fluoropyrimidines, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody and at least one of the anti-EGFR monoclonal antibodies for RAS wild-type patients) for mCRC and is refractory or intolerant to those chemotherapies or is not candidate for those chemotherapies • Has ECOG performance status of 0 or 1 during the screening period. • Is able to take medications orally (i.e., no feeding tube) • Has adequate organ function • Women of childbearing potential must have been tested negative in a serum pregnancy test within 7 days prior to first day of test drug administration. Female participants of childbearing potential and male participants with partners of childbearing potential must agree to use a highly effective method of birth control during the study and for 6 months after the discontinuation of study medication. Women and female partners using hormonal contraceptive must also use a barrier method[11] <u>Exclusion Criteria:</u>[11] • Pregnancy, breastfeeding or possibility of becoming pregnant during the study • Eligible for enrolment into another available ongoing clinical study of trifluridine-tipiracil • Has previously received trifluridine-tipiracil or hypersensitivity to the active	Trifluridine-tipiracil hydrochloride 15 mg film-coated tablet of trifluridine and 7.065 mg of tipiracil hydrochloride,[11] or 20 mg of trifluridine and 9.42 mg of tipiracil hydrochloride, taken orally twice a day at 35 mg/m^2/dose. Days 1-5; 8-12: 35mg/m^2/dose bd Days 6-7; 13-28: Rest The treatment is given until progression of disease, unacceptable toxicity, investigator decision, patient refusal or until market authorization or reimbursement has been granted by the relevant authority of the country where that patient is treated or until trifluridine-tipiracil is available by a doctor's prescription or can be accessed from another source or sponsor decision.	None	<u>Primary:</u> • Incidence of AEs [safety and tolerability] • Abnormalities in laboratory assessment • Abnormalities in performance status (ECOG) • Abnormalities in vital signs <u>Secondary:</u> • PFS • HRQoL using EQ-5D-3L • HRQoL using EORTC QLQ-C30

Study Design	Eligibility Criteria	Intervention	Comparator	Outcomes
PRECONNECT Study[14]				
	substances or to any of the excipients of trifluridine-tipiracil • Has rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption • Has certain serious illness or medical condition(s) described in the protocol. • Has had certain other recent treatment e.g. major surgery, anticancer therapy, radiation therapy, participation in another interventional study, within the specified time frames prior to first day of study drug administration • Has unresolved toxicity of greater than or equal to Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity)			
Abbreviations: AEs - Adverse events; ECOG - Eastern Cooperative Oncology Group; HRQoL - health-related quality of life; mCRC - metastatic colorectal cancer; PFS - Progression-free survival.				

a) Populations

A summary of the characteristics of patients included in the PRECONNECT study is provided in Table 9.

As of March 25th, 2019, 832 patients have been recruited and enrolled for participation. 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. The target number of participants is approximately 1,000 in 20 countries.[34] At the time of the most recent data cut-off date on May 20, 2018, there were 464 patients enrolled for participation.[4,7,14] The baseline characteristics of patients in the PRECONNECT study are similar to patients in the RECOURSE trial. The median age of patients was 64 years with a range of 28-87 years, and the proportion of males was 63.6%.[4] The majority of patients were white (87.3%) and had a time from diagnosis of metastasis that was 18 months or greater (81.9%).[4]

Table 9: Characteristics of enrolled patients in the PRECONNECT study (data cut-off date of May 20, 2018).[4]

Characteristics	Patients (N=464)
Median age, years (range)	64 (28-87)
Male	295 (63.6)
Race	
White	405 (87.3)
Black/African American	2 (0.4)
Asian	5 (1.1)
Other/Not reported	52 (11.2)
ECOG PS[1]	
N	453
0/1	207 (45.7)/245 (54.1)
Primary tumour site[2]	
Right colon	113 (24.4)
Left colon	292 (62.9)
Not specified	59 (12.7)
Time from first metastasis, months	
N	463
Median (range)	32.7 (0.8-190.7)
< 18 months	84 (18.1)
≥ 18 months	379 (81.9)
Synchronous metastasis at diagnosis	241 (51.9)
RAS status	
Wild type	140 (30.2)
Mutant	241 (51.9)
Unknown/not collected[3]	83 (17.9)
Number of previous treatment lines[4]	
≤2	159 (34.3)
3	136 (29.3)
4	91 (19.6)
≥5	78 (16.8)
Quality of life and utility	
QLQ-C30 mean (±SD) global health status score at baseline (n=449)	62.8 ± 20.5
QLQ-C30 median global health status score at baseline	66.7
EQ-5D mean (±SD) utility score at baseline (N=447)	73.1 ± 20.7
EQ-5D median utility score at baseline	75.3
EQ-5D mean (±SD) VAS at baseline (N=442)	65.6 ± 20.1
EQ-5D median VAS at baseline	70.0

Abbreviations: ECOG PS - Eastern Cooperative Oncology Group performance status; **SD** - standard deviation; **VAS** - visual analogue scale.

Notes:
Values are reported as n (%), unless otherwise stated.
[1]One patient had an ECOG PS of 2 at inclusion.
[2]Right colon includes transverse location/left colon includes rectum.
[3]Includes patients with at least one evaluation for KRAS or NRAS status missing.
[4]Treatment line is defined by the progression of the disease after first metastasis date.

b) Interventions

All 464 patients received the trifluridine-tipiracil treatment regimen; this included either a 15 mg film-coated tablet and 7.065 mg of tipiracil hydrochloride,[11] or a 20

mg tablet of trifluridine and 9.42 mg of tipiracil hydrochloride,[11] taken orally twice a day at 35 mg/m^2/dose. Each treatment cycle consists of the following: days 1-5 and days 8-12: 35 mg/m^2/dose orally twice daily; days 6-7 and days 13-28: rest. Each treatment cycle is 28 days in duration.[14]

The treatment is given until progression of disease, unacceptable toxicity, investigator decision, patient refusal or until market authorization or reimbursement has been granted by the relevant authority of the country where that patient is treated, or until trifluridine-tipiracil is available by a doctor's prescription or can be accessed from another source, or by sponsor decision.[14]

At the cut-off date for data analysis on May 20, 2018, patients had received treatment for a mean (±standard deviation [SD]) of 3.8 (± 2.6) months and a median (range) of 3.0 (0.4-14.7) months (Table 10).[4] The median relative dose intensity was 88.9% and the median number of cycles was three (range: 1-15). There were 277 patients who completed ≥ 3 treatment cycles.[4] The most common reason for dose reduction was grade ≥3 hematological AEs, i.e. neutropenia and anemia.[34] The specific AEs that led to dose reductions in the PRECONNECT study are summarized in Table 11.[34]

Table 10: Patient exposure to treatment in the PRECONNECT study.[4]

Characteristic	Total (N=464)
Duration of treatment, months*	
Mean ± SD	3.8 ± 2.6
Median (range)	3.0 (0.4–14.7)
Relative dose intensity	
N	457
Median, %	88.9
Median number of cycles (range)	3 (1–15)
≥3 treatment cycles	277 (59.7)
AEs leading to dose reduction	39 (8.4)

Values are reported as n (%), unless otherwise stated. AE, adverse event.

Source: Taieb J, Price TJ, Ciardiello F, et al. Health-related quality of life in the early access phase 3b study of trifluridine/tipiracil in pretreated metastatic colorectal cancer (mCRC): results from PRECONNECT study. In: pan-Canadian Oncology Drug Review manufacturer submission: Lonsurf (trifluridine/tipiracil as tipiracil hydrochloride), 15/6.4 mg, 20/8.18mg tablets [additional manufacturer's information]. 2019 Gastrointestinal Cancers Symposium, San Francisco, CA, USA. Oakville (ON): Taiho Pharma Canada, Inc.; 2019.

c) Patient Disposition

Of the 464 patients, 3 (0.6%) are still on treatment protocol and 461 (99.4%) have withdrawn; 24 withdrawals (5.2%) were due to AEs, 338 (83.6%) were due to progressive disease, 6 (1.3%) were due to a non-medical reason, 10 (2.2%) were due to physician decision, and 33 (7.1%) were due to commercial availability of the drug product.[4]

Table 11: Emergent adverse events leading to dose reduction in the PRECONNECT study (N=464) as of May 20th, 2018.[34]

System Organ Class Preferred Term	NOT GRADED OR MISSING		GRADE 1		GRADE 2		GRADE 3		GRADE 4		GRADE 5		ANY GRADE	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ALL	-	-	1	0.2	11	2.4	17	3.7	10	2.2	-	-	39	8.4
Blood and lymphatic system disorders	-	-	-	-	4	0.9	8	1.7	10	2.2	-	-	22	4.7
Neutropenia	-	-	-	-	3	0.6	6	1.3	8	1.7	-	-	17	3.7
Anaemia	-	-	-	-	2	0.4	1	0.2	1	0.2	-	-	4	0.9
Thrombocytopenia	-	-	1	0.2	1	0.2	-	-	-	-	-	-	2	0.4
Bone marrow toxicity	-	-	-	-	-	-	1	0.2	-	-	-	-	1	0.2
Febrile neutropenia	-	-	-	-	-	-	-	-	1	0.2	-	-	1	0.2
Gastrointestinal disorders	-	-	-	-	3	0.6	5	1.1	-	-	-	-	8	1.7
Diarrhoea	-	-	-	-	1	0.2	3	0.6	-	-	-	-	4	0.9
Abdominal pain upper	-	-	-	-	1	0.2	-	-	-	-	-	-	1	0.2
Enteritis	-	-	-	-	-	-	1	0.2	-	-	-	-	1	0.2
Mouth ulceration	-	-	-	-	-	-	1	0.2	-	-	-	-	1	0.2
Vomiting	-	-	-	-	1	0.2	-	-	-	-	-	-	1	0.2
General disorders and administration site conditions	-	-	-	-	4	0.9	2	0.4	-	-	-	-	6	1.3
Asthenia	-	-	-	-	3	0.6	-	-	-	-	-	-	3	0.6
Fatigue	-	-	-	-	1	0.2	2	0.4	-	-	-	-	3	0.6
Investigations	-	-	1	0.2	1	0.2	1	0.2	-	-	-	-	3	0.6
Alanine aminotransferase increased	-	-	-	-	2	0.4	-	-	-	-	-	-	2	0.4
Aspartate aminotransferase increased	-	-	1	0.2	-	-	-	-	-	-	-	-	1	0.2
Blood alkaline phosphatase increased	-	-	1	0.2	-	-	-	-	-	-	-	-	1	0.2
Gamma-glutamyltransferase increased	-	-	-	-	-	-	1	0.2	-	-	-	-	1	0.2
Weight decreased	-	-	1	0.2	-	-	-	-	-	-	-	-	1	0.2
Renal and urinary disorders	-	-	-	-	1	0.2	1	0.2	-	-	-	-	2	0.4
Acute kidney injury	-	-	-	-	-	-	1	0.2	-	-	-	-	1	0.2
Haematuria	-	-	-	-	1	0.2	-	-	-	-	-	-	1	0.2
Infections and infestations	-	-	-	-	-	-	-	-	1	0.2	-	-	1	0.2
Escherichia sepsis	-	-	-	-	-	-	-	-	1	0.2	-	-	1	0.2
Nervous system disorders	-	-	-	-	-	-	1	0.2	-	-	-	-	1	0.2
Dizziness	-	-	-	-	-	-	1	0.2	-	-	-	-	1	0.2
Headache	-	-	-	-	1	0.2	-	-	-	-	-	-	1	0.2
Product issues	-	-	-	-	-	-	1	0.2	-	-	-	-	1	0.2
Device occlusion	-	-	-	-	-	-	1	0.2	-	-	-	-	1	0.2

N: Number of patients by group
n: Number of patients with at least one event by worst grade / Percentages are based on N
Adverse events were coded using MedDRA 200

d) Limitations/Sources of Bias

A quality assessment of the PRECONNECT study was performed by the pCODR Methods Team using the Risk of Bias Assessment Tool for Non-Randomized Studies (RoBANS).[35] The RoBANS assessment summary is provided below in Table 12. The funding for PRECONNECT is from Taiho Pharmaceutical Inc. Although the study protocol[14] provided some required information regarding the design and intent of the study, the conducted methods and results were reported in poster form only. The limited reporting in the conference publications restricted the ability of the pCODR Methods Team to complete a comprehensive quality assessment.

PRECONNECT is an observational study with no comparator. The lack of comparator is the major limitation of this study. The study design inhibits comparability of outcomes with other treatments; and therefore, causal effects of trifluridine-tipiracil on HRQoL cannot be inferred based on the PRECONNECT study.

The patient population was selected based on their choice to receive the intervention (trifluridine-tipiracil), and the study inclusion criteria used were similar to RECOURSE. Based on the original pCODR submission,[32] there were no limits to generalizability of patients within the RECOURSE study, and thus, the PRECONNECT study is unlikely to suffer from selection bias that limits generalizability. Overall, the measurement of HRQoL for patients enrolled in PRECONNECT is likely valid.

Table 12: RoBANS Assessment[35] for the PRECONNECT study.

Domain	Description	Risk of Bias		
		Low	High	Unclear
Selection of Participants	Selection bias caused by inadequate selection of participants	X		
Confounding Variables	Selection bias caused by inadequate confirmation and consideration of confounding variable	X		
Intervention (exposure) Measurement	Performance bias caused by inadequate measurement of intervention (exposure)	X		
Blinding of Outcome Assessment	Detection bias caused by inadequate blinding of outcome assessment		X	
Incomplete Outcome Data	Attrition bias caused by inadequate handling of incomplete outcome data			X
Selective Outcome Reporting	Reporting bias caused by selective outcome reporting	X		

7.1.3.2 Detailed Outcome Data

Health-related Quality of Life

A secondary outcome of the PRECONNECT study was to measure HRQoL using the EORTC QLQ-C30 and EQ-5D-3L questionnaires. Patients completed the questionnaires at baseline, every four weeks during study treatment and at the withdrawal visit (if not performed within the previous four weeks).[34] Scoring of the questionnaires was completed using the published guideline (EuroQol Group, 1990; Aaronson, 1993; Appendix 1 of appendix).[34] Deterioration thresholds for each questionnaire are defined in Table 13. For the EQ-5D-3L, the tariffs applied were for the UK, based on Dolan et al. (Dolan P. Med Care. 1997;35(11):1095-108); these were applied to all patients who had complete EQ-5D data.[34] Data were considered evaluable when questionnaire responses were completed for at least 20 dimensions on the QLQ-C30 and the EQ-5D utility score or VAS were complete; the completion rate was reported to be >92% for each questionnaire at each treatment cycle.[34]

Table 13: HRQoL questionnaires guide to scoring.

Component	Questionnaire[†]		
	QLQ-C30 Global Health Status	EQ-5D-3L Utility[††]	
		EQ-5D Utility Score	EQ-5D VAS
Description	Patient is asked to answer a list of 30 questions designed to measure their physical, role, social, emotional and cognitive functioning. First 28 questions have four levels: - not at all - a little - quite a bit - very much Last two questions are ranked on a scale between 1 and 7, 1 being very poor, and 7 being excellent	Patient is asked to indicate their health state by assigning a level to each dimension. There are five dimensions: - mobility - self-care - usual activities - pain/discomfort - anxiety and depression Each dimension has three levels: - no problems - some problems - extreme problems	Patient is asked to indicate their self-rated health on a vertical, visual analogue scale where the endpoints are labelled 100 for "Best imaginable health state" and 0 for "Worst imaginable health state".
Improvement	An increase in score from baseline	An increase in score from baseline	An increase in score from baseline
No deterioration	Not defined	Not defined	Not defined
Deterioration (Clinically Deterioration Relevance)	A 10-point threshold for changes from baseline[4]	A decrease of ≥9 points[4]	A decrease of ≥7 points[4]

[†] All scores for each questionnaire are scored on a range from 0-100, where 100 represents "best imaginable health"
[††] Utility score was based on the EQ-5D index and values from Germany, Spain, and the UK.

Falcone et al. 2018

The data reported in Falcone et al. (2018) represent HRQoL data at baseline for the first 300 patients entered into the study with a data cut-off date of March 7, 2017.[6]

Of the 300 patients enrolled, 291 patients were evaluable at baseline for the QLQ-C30 global health status, 289 patients for EQ-5D utility and 285 patients for the EQ-5D VAS. The EORTC QLQ-C30 baseline scores indicated impaired HRQoL in various domains including GI-related AEs (nausea, vomiting, constipation, diarrhea), loss of appetite, insomnia, pain and fatigue.[6] Of the 290 patients for whom EQ-5D data were available, 60% indicated a level of pain that was moderate and 7.2% indicated a level of pain that was extreme.[6]

There were 33.1% of patients who indicated some impact on usual activities.[6] The overall EQ-5D utility (±SD) score was 72.9±20.3. A moderate or extreme level of anxiety or depression was indicated by 42.1% of patients.[6]

Taieb et al. 2019

The data reported in Taieb et al.(2019) represent HRQoL data at baseline and post-treatment for the first 464 patients entered into the study with a data cut-off date of May 20, 2018.[4]

The number of patients who completed each HRQoL questionnaire at baseline and at EOT is summarized in Table 14. At baseline, 449 patients were evaluated using the QLQ-C30 questionnaire.[4] The mean (SD) baseline QLQ-C30 global health status score was 62.75 (20.50) with a median value of 66.67.[4] At baseline, 447 patients were evaluated using the EQ-5D utility score, and 442 patients were evaluated using the EQ-5D VAS. The mean (SD) baseline EQ-5D utility score was 73.11 (20.71) with a median value of 75.27.[4] The mean baseline (SD) EQ-5D VAS score was 65.55 (20.11), which is measured on a scale from 0-100, with 0 being the worst imaginable heath and 100 being the best imaginable health;[4] the median EQ-5D VAS score was 70.00. It was reported that mean baseline scores for all scales were within the range of QLQ-C30 reference values for mCRC.[4]

Change in 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.[4] The baseline patient characteristics including utility for this cohort for whom the EQ-5D utility score was calculated is shown in Table 15.[4]

While on treatment there were no clinically relevant differences in mean change from baseline at any assessment time point for either the QLQ-C30 (including functional and symptom scales) or EQ-5D (utility and VAS).[4] The mean change in HRQoL from baseline to EOT is shown in Table 14; the data show (score ±SD) clinically relevant deterioration (refer to Table 13) for the EQ-5D utility score (-9.1 ±23.6) and VAS (-8.3 ±19.3); and for the QLQ-C30 global health status the mean change was just short of reaching the clinically relevant deterioration threshold (-9.9 ±23.3). Clinical deterioration in QLQ-C30 global health status, EQ-5D utility, and EQ-5D VAS from baseline occurred in 41.5%, 39.7%, and 53.1% of patients, respectively.[4] Median time-to-deterioration in QLQ-C30 global health status was 3.7 months (95% CI 3.2-4.6).[4] 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.[4]

Table 14: HRQoL mean change from baseline to end of treatment in the PRECONNECT study as of May 20, 2018.[4]

All (N=464)	QLQ-C30 Global Health Status	EQ-5D Utility score	EQ-5D VAS
Baseline			
N	N=449	N=447	N=442
Mean (± SD)	62.8 ± 20.5	73.1 ± 20.7	65.6 ± 20.1
Change from baseline to end of treatment			
N	N=207	N=209	N=205
Mean (± SD)	-9.9 ± 23.3	-9.1 ± 23.6	-8.3 ± 19.3
Improvement (>0)	43 (20.8)	52 (24.9)	49 (23.9)
No deterioration[1]	121 (58.5)	126 (60.3)	96 (46.9)
Deterioration[1]	86 (41.5)	83 (39.7)	109 (53.1)

[1] Threshold depending on the nature of the questionnaire. Please refer to methods section.

Source: Taieb J, Price TJ, Ciardiello F, et al. Health-related quality of life in the early access phase 3b study of trifluridine/tipiracil in pretreated metastatic colorectal cancer (mCRC): results from PRECONNECT study. In: pan-Canadian Oncology Drug Review manufacturer submission: Lonsurf (trifluridine/tipiracil as tipiracil hydrochloride), 15/6.4 mg, 20/8.18mg tablets [additional manufacturer's information]. 2019 Gastrointestinal Cancers Symposium, San Francisco, CA, USA. Oakville (ON): Taiho Pharma Canada, Inc.; 2019.

Table 15: Patient characteristics including utility at end of treatment set in whom the EQ-5D utility score was calculated from in Taieb et al. 2019 in Table 14 above.[34]

Characteristics	Patients (N=209)
Median age, years (range)	64 (34-87)
Male	136 (65.1)
Race	
White	183 (87.6)
Black/African American	2 (1.0)
Asian	3 (1.4)
Other/Not reported	21 (10.0)
ECOG PS	
N	206
0/1	102 (49.5)/104 (50.5)
Primary tumour site[2]	
Right colon	44 (21.0)
Left colon	134 (64.1)
Not specified	31 (14.8)
Time from first metastasis, months	
N	209
Median (range)	31.9 (0.8-126.4)
< 18 months	42 (20.1)
≥ 18 months	167 (79.9)
Synchronous metastasis at diagnosis	109 (52.2)
RAS status	
Wild type	65 (31.1)
Mutant	106 (50.7)
Unknown/not collected	38 (18.2)
BRAF status	
N	123
Wild type	114 (92.7)
Mutant	9 (7.3)
Number of previous treatment lines	
≤2	74 (35.4)
3	66 (31.6)
4	41 (19.6)
≥5	28 (13.4)
Quality of life and utility	
QLQ-C30 mean (±SD) global health status at baseline (n=449)	66.7 ± 19.7
QLQ-C30 global health status median score at baseline	66.7
EQ-5D mean (±SD) utility score at baseline (N=447)	76.1 ± 20.0
EQ-5D median utility score at baseline	77.9
EQ-5D mean (±SD) VAS at baseline (N=442)	68.5 ± 18.5
EQ-5D median VAS at baseline	70.0
Abbreviations: ECOG PS - Eastern Cooperative Oncology Group performance status; SD - standard deviation; VAS - visual analogue scale. Values are reported as n (%), unless otherwise stated.	

Sabater et al. 2019

The data reported in Sabater et al. 2019 represent HRQoL data for a population of 454 patients with a data cut-off date of May 20, 2018.[7] Even though there were 464 patients enrolled in the study at the time of data cut-off, only patients with both QLQ-C30 and PFS data were included for analysis (10 patients removed).[7] The unique information presented in this report (in addition to the same outcomes as analysed in Taieb et al) is the relationship between progression status and utility. Sabater et al. 2019 reported that a linear mixed effects model was fitted to the describe the utility data and demonstrated that progression status was predictive of utility, with progression associated with a statistically significant utility decrement of -0.131 (standard error [SE]: 0.016) compared to pre-progression with a utility value of 0.719 (SE: 0.011) (Figure 2).[7]

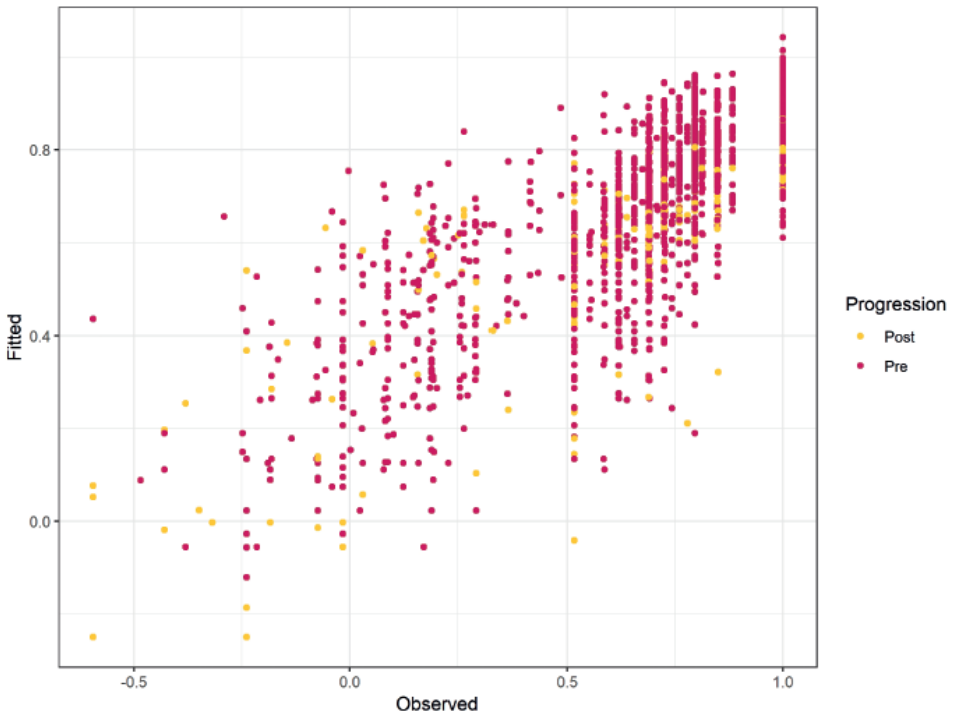


Figure 2: PRECONNECT observed versus predicted utility, separated by progression status.[7]

Source : Sabater J, Ralph L, Batteson R, et al. Validation of cost effectiveness of trifluridine/tipiracil versus best supportive care and regorafenib for previously treated metastatic colorectal cancer in the UK using phase 3b early access clinical trial data in the real-world setting. In: pan-Canadian Oncology Drug Review manufacturer submission: Lonsurf (trifluridine/tipiracil as tipiracil hydrochloride), 15/6.4 mg, 20/8.18mg tablets [additional manufacturer's information]. 2019 Gastrointestinal Cancers Symposium, San Francisco, CA, USA. Oakville (ON): Taiho Pharma Canada, Inc.; 2019.

7.1.4 Summary

PRECONNECT is an on-going, phase 3b, single-group, early access study of trifluridine-tipiracil in 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; the

primary endpoint is safety and secondary outcomes are PFS and HRQoL assessed using the EORTC QLQ-C30 and EQ-5D-3L questionnaires.[14]

PRECONNECT is a non-comparative observational study and therefore was excluded from the pCODR systematic review. Data related to PRECONNECT were obtained through the submitter by pCODR. The four reports presenting data on this study have only been published in conference form. The most recent data reported in Taieb et al.(2019) represent HRQoL data at baseline and post-treatment for the first 464 patients entered into the study with a data cut-off date of May 20, 2018.[4] 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.[4]

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, including functional and symptom scales) or EQ-5D (utility and VAS).[4] Data on mean change in HRQoL from baseline to EOT showed clinically relevant deterioration (score ±SD) for the EQ-5D utility score (-9.1 ±23.6) and VAS (-8.3 ±19.3); and for the QLQ-C30 global health status score, the mean change was just short of reaching the clinically relevant 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.[4] Median time-to-deterioration in QLQ-C30 global health status was 3.7 months (95% CI 3.2-4.6).[4] 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.[4]

The lack of a comparator is the major limitation of the PRECONNECT study. The study design used inhibits comparability of outcomes with other treatments; and therefore, causal effects of trifluridine-tipiracil on HRQoL cannot be inferred based on the PRECONNECT study.

7.2 OTHER REPORTS

7.2.1 Objective

A clinical study report titled, "Patient Reported Quality of Life Impact in Refractory Metastatic Colorectal Cancer Patients Treated with TAS-102 (trifluridine/tipiracil) versus Best Supportive Care (BSC)" was provided to pCODR by the submitter.[15] The pCODR Methods Team reviewed and critically appraised the evidence contained in the clinical study report (referred to herein as TAS-102 versus BSC) as it reports additional HRQoL data in patients with mCRC treated with trifluridine-tipiracil captured using direct validated measures of HRQoL.

7.2.2 Findings

The TAS-102 versus BSC study is an ongoing, open-label, non-randomized study with two cohorts of patients for the study of trifluridine-tipiracil in patients with mCRC who have been previously treated with at least two prior lines of chemotherapy for mCRC.[15]

7.2.3 TAS-102 versus BSC Study

The evidence contained in the clinical study report (April 3, 2019) provided by the submitter is unpublished. pCODR obtained data on patient enrollment from the submitter through an additional request for information.[34]

7.2.3.1 Detailed Study Characteristics

TAS-102 versus BSC is a multi-centred study including eight sites in Ontario, Quebec and Alberta in Canada. The study enrolled 70 patients between March 2017 and November 2018, with 39 patients in the TAS-102 cohort and 31 patients in the BSC cohort.[34] The study was designed to compare patient-reported outcomes (PRO) between the two cohorts of previously treated mCRC patients to determine the difference in HRQoL between TAS-102 versus BSC-treated patients.[15] The primary objective of the study was to quantify the difference in HRQoL in refractory mCRC patients who were treated with TAS-102 versus those treated with BSC in a real-life setting;[15] and secondly, to quantify the difference in colorectal cancer-related symptoms and pain in patients treated with TAS-102 versus those treated with BSC.[15] The questionnaires and PRO scales used were the Rotterdam Symptom Checklist (RSCL), the FACT Colorectal Symptom Index (FCSI), and Numerical Rating Scale for Pain (NRS).

The study was carried out under management by Taiho Canada (the Sponsor), which was delegated to Drug Intelligence Inc. (the Contract Research Organization or CRO).[15] The study was conducted by investigators contracted and directed by the CRO.[15]

a) Population

Characteristics of the patients included in the TAS-102 versus BSC study is summarized in Table 16.

As of April 3rd, 2019, a total of 70 patients have been recruited and enrolled for participation in this study out of an intended 100; 39 patients for TAS-102, and 31 for BSC.[34] The median age of the TAS-102 cohort was 63 years with a range of 40-77 years, and the proportion of males was 51%.[15] The median age of the BSC cohort was 63 years with a range of 44-77 years, and the proportion of males was 71%.[15]

Table 16: Patient characteristics of patients enrolled in the TAS-102 versus BSC study as of report date April 3rd, 2019.[15]

Characteristic	TAS-102 (n=39)	Best Supportive Care (n=31)	Total Patients (n=70)
Age			
Median - years	63	63	63
Range - years	40-77	44-77	40-77
Sex - n (%)			
Male	20 (51)	22 (71)	42 (60)
Female	19 (49)	9 (29)	28 (40)
Number of prior treatments - n (%)			
2 prior therapies	11 (28)	9 (29)	20 (29)
3 prior therapies	21 (54)	19 (61)	40 (57)
4 prior therapies	6 (15)	3 (10)	9 (13)
5 prior therapies	1 (3)	-	1 (1)
KRAS Status - n (%)			
Mutated	17 (44)	15 (48)	32 (46)
Not mutated	22 (56)	16 (52)	38 (54)
Not tested	-	-	-
ECOG performance status at start of current treatment - n (%)			
ECOG 0	3 (8)	-	3 (4)
ECOG 1	36 (92)	8 (26)	44 (63)
ECOG 2	-	22 (71)	22 (31)
ECOG 3	-	1 (3)	1 (1)

Abbreviations: ECOG - Eastern Cooperative Oncology Group.

b) Interventions

In this study, patients in cohort 1 received at least one treatment cycle of trifluridine-tipiracil (TAS-102) () and patients in cohort 2 received BSC only.[15] Information on the dosing, administration and schedule of trifluridine-tipiracil, as well as the total number of treatment cycles received by patients in this cohort was not reported.

c) Limitations/Sources of Bias

TAS-102 versus BSC is an observational comparative cohort study where patient population was selected based on the patient and provider choice to receive trifluridine-tipiracil or BSC.[15] The study reports data based on a one-time capture of HRQoL outcomes and therefore does not provide baseline data on the HRQoL of patients prior to treatment or changes in HRQoL from baseline after a period of follow-up. As a result of its design, the study does not offer any information about the efficacy of trifluridine-tipiracil compared to BSC in patients with mCRC.[15] The funding for this study was from Taiho Pharmaceutical Inc.[15] The conducted methods and preliminary baseline results have only been reported in a confidential clinical study report .

7.2.3.2 Detailed Outcomes

Using the RSCL, the difference between the two study cohorts in overall HRQoL, including physical symptom distress, activity level, psychological distress and overall valuation of QoL was measured.[15] The RSCL has a total of 39 items with most items given on a 4-point Likert-type scale with responses that range from "not at all" to "very much". Each question on the tool refers to the impact on the patient's HRQoL over the previous week.

Using the FCSI, the difference between study cohorts in colorectal cancer symptoms was measured.[15] The FCSI is a colorectal-cancer specific scale designed to capture the clinically-relevant problems associated with this disease; it has 9 items that are given on a 5-point Likert scale from 0 "not at all" to 4 "very much". Each question relates to the patient's HRQoL over the past 7 days.

Difference in pain between cohorts was measured using the NRS (VAS) for pain that ranged from 0 to 10, with 0 indicative of "no pain" and 10 indicative of "worst possible pain".[15] The NRS referred to pain intensity within the previous 24 hours.

In this study, no baseline questionnaire data prior to treatment were captured.[15] Patients who were either on trifluridine-tipiracil or BSC (or their caregivers) completed, once on paper, the three questionnaires listed above, which related to disease-related symptoms, impact on carrying out daily activities, and pain.[15] The questionnaire completion date and time in relation to disease progression or treatment cycles was not reported. The study did not capture the change from baseline in HRQoL as no follow-up of outcomes using the questionnaires was obtained.[15]

The results of the TAS-102 versus BSC study from the April 3rd, 2019 report are summarized below. The data analyses performed (chi-square tests for proportions; Student's t-test for unpaired data for continuous data; two-sided $p<0.05$ considered statistically significant) focused on the differences in mean HRQoL scores between the trifluridine-tipiracil and BSC cohorts.[15]

Rotterdam Symptom Checklist

The results of the RSCL are presented in Table 17. The numerical results across each domain (physical distress, psychological distress, activity level, overall valuation of life) are scored on a scale from 0-100, where 0 indicates no level of impairment and 100 implies highest level of impairment.[15] The mean impairment for all domains was statistically significantly lower for patients receiving trifluridine-tipiracil.[15] Patients rated their "overall valuation of life" across seven domains, from extremely poor to excellent. The results are reported in Table 18, and show a majority of patients (14/39, 36%) in the trifluridine-tipiracil cohort rated their valuation of life at "good" while the majority of patients (15/31, 48%) in BSC cohort rated it as "rather poor.[15]

Table 17: RSCL results of patients enrolled in the TAS-102 versus BSC study as of report date April 3rd, 2019.[15]

Treatment Cohort	Physical Distress	Psychological Distress	Activity Level	Overall Valuation of Life
TAS-102/trifluridine-tipiracil (n=39)				
Mean	23	26	24	35
Standard Deviation	12	22	21	22
Range	0-51	0-67	4-83	0-83
BSC (n=31)				
Mean	28	45	47	62
Standard Deviation	10	18	18	14
Range	12-52	5-76	13-88	33-83
Rotterdam Symptom Checklist: Scale 0 implies a level of no impairment and 100 implies the highest level of impairment				

Table 18: Overall valuation of life based on the RSCL in patients enrolled in the TAS-102 versus BSC study as of report date April 3rd, 2019.[15]

Overall valuation of life n (%)	TAS-102/trifluridine-tipiracil (n=39)	BSC (n=31)	Statistically significant difference
Excellent, good or moderately good	26 (67)	3 (10)	(p <0.0001)
Excellent	2 (5)	-	-
Good	14 (36)	-	-
Moderately good	10 (26)	3 (10)	-
Neither good nor bad	7 (18)	8 (26)	-
Rather poor, poor or extremely poor	6 (15)	20 (65)	-
Rather poor	3 (8)	15 (48)	-
Poor	3 (8)	5 (16)	-
Extremely poor	-	-	-

FACT Colorectal Symptom Index

The results of the FCSI are presented in Table 19. The range of possible scores of the FCSI is from 0 to 36, where a high score indicates less symptomatology.[15] Trifluridine-tipiracil patients had a mean score ± SD of 22.2 ± 6.0 that was significantly higher (less symptoms) compared to BSC patients who had a mean score ± SD of 19.4 ± 4.1 (p=0.0292).[15]

Table 19: Results of the FCSI in patients enrolled in the TAS-102 versus BSC study as of report date April 3rd, 2019.[15]

FCSI*	TAS-102/trifluridine-tipiracil (n=39)	BSC (n=31)	p-value
Mean	22.2	19.4	p=0.0292**
Standard Deviation	6.0	4.1	-
Range	11-34	10-27	-
* FCSI: Higher score indicates less symptomatology. ** p-value is statistically significant.			

Visual Analogue Scale for Pain

The results of the VAS for pain are presented in Table 20. The range of possible scores for the VAS is from 0 to 10, where 0 indicates no pain and 10 indicates worst possible pain.[15] Trifluridine-tipiracil patients had a mean score ± SD of 2.5 ± 2.8 that was not significantly different from BSC patients who had a mean score ± SD of 3.2 ± 2.0 (p=0.1421).[15]

Table 20: Results of the VAS for pain in patients enrolled in the TAS-102 versus BSC study as of report date April 3rd, 2019.[15]

VAS*	TAS-102/trifluridine-tipiracil (n=39)	BSC (n=31)	p-value
Mean	2.5	3.2	p=0.1421**
Standard Deviation	2.8	2.0	-
Range	0-8	0-8.5	-
* VAS Pain: 0 indicates no pain 10 suggests the worst possible pain. **p-value is not statistically significant.			

7.2.4 Summary

The TAS-102 versus BSC study is an ongoing, open-label, non-randomized study with two cohorts of patients for the study of trifluridine-tipiracil in patients with mCRC who have been previously treated with at least two prior lines of chemotherapy for mCRC.[15] This study was excluded from the pCODR systematic review as it is an observational comparative cohort study where patient population was selected based on the patient and provider choice to receive trifluridine-tipiracil or BSC.[15] The study reports data based on a one-time capture of HRQoL outcomes and therefore does not provide baseline data on the HRQoL of patients prior to treatment or changes in HRQoL from baseline after a period of follow-up.[15] The questionnaires and PRO scales used to collect HRQoL data were the RSCL, the FCSI, and the NRS.

To date, no study data have been published and all study data reported herein come from the clinical study report dated April 3rd, 2019 that was obtained through the submitter by pCODR. For the RSCL, a majority of patients (14/39, 36%) in the trifluridine-tipiracil cohort rated their valuation of life at "good" while the majority of patients (15/31, 48%) in BSC cohort rated it as "rather poor".[15] For the FCSI, trifluridine-tipiracil treated patients had a mean score ± SD of 22.2 ± 6.0 that was significantly higher (indicative of less symptoms) compared to BSC patients who had a mean score ± SD of 19.4 ± 4.1 (p=0.0292).[15] For the NRS (VAS for pain), there was no significant difference in level of pain between trifluridine-tipiracil patients 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).[15]

Due to its design, the TAS-102 versus BSC study does not offer any information about the efficacy of trifluridine-tipiracil compared to BSC in patients with mCRC.

8 COMPARISON WITH OTHER LITERATURE

The pCODR GI CGP and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR GI CGP and supported by the pCODR Methods Team. This document is intended to advise the pCODR pERC regarding the clinical evidence available on trifluridine-tipiracil for mCRC. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The GI CGP is comprised of two medical oncologists and one radiation oncologist. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials December 2018, Embase 1974 to 2019 January 31, Ovid MEDLINE(R) ALL 1946 to January 31, 2019
Search Strategy:

#	Searches	Results
1	(Lonsurf* or "Tipiracil / Trifluridine" or Tipiracil Trifluridine or "trifluridine/tipiracil" or trifluridine tipiracil or TAS 102 or TAS102 or Viroptic mixture* or JNJ02).ti,ab,ot,kf,kw,hw,rn,nm.	772
2	(Tipiracil* or MA 1 or MA1 or TPI or 5CIMU or 5 CIMU or tas 1 462 or tas 1462 or tas1462 or NGO10K751P or 4H59KLQ0A4).ti,ab,ot,kf,kw,hw,rn,nm.	6192
3	Trifluridine/	2233
4	(trifluridin* or trifluoridin* or trifluoromethyldeoxyuridine or trifluorothymidine or viroptic* or Triflumann* or Virophta* or TFT Ophtiole* or Viromidin* or aflomin or bephen or ocufridine or tft or thriherpine or trifluor thymidine or trifluoro thymidine or trifluorodeoxythymidine or triherpin or triherpine or Trifluorothymine deoxyriboside or Thilol or TFDU or "BRN 0568095" or BRN0568095 or CCRIS 2348 or CCRIS2348 or EINECS2007228 or EINECS 2007228 or EINECS 200 722 8 or F3DThd or F3T or F3TDR or HSDB 8126 or HSDB8126 or NSC 529182 or NSC529182 or NSC 75520 or NSC75520 or NGO10K751P or RMW9V5RW38).ti,ab,ot,kf,kw,hw,rn,nm.	5427
5	or/3-4	5427
6	2 and 5	774
7	1 or 6	916
8	7 use medall	224
9	7 use cctr	104
10	*tipiracil plus trifluridine/	228
11	(Lonsurf* or "Tipiracil / Trifluridine" or Tipiracil Trifluridine or "trifluridine/tipiracil" or trifluridine tipiracil or TAS 102 or TAS102 or Viroptic mixture* or JNJ02).ti,ab,kw,dq.	766
12	or/10-11	773
13	*tipiracil/	17
14	(Tipiracil* or MA 1 or MA1 or TPI or 5CIMU or 5 CIMU or tas 1 462 or tas 1462 or tas1462 or NGO10K751P or 4H59KLQ0A4).ti,ab,kw,dq.	5789
15	or/13-14	5791
16	*trifluridine/	1087
17	(trifluridin* or trifluoridin* or trifluoromethyldeoxyuridine or trifluorothymidine or viroptic* or Triflumann* or Virophta* or TFT Ophtiole* or Viromidin* or aflomin or bephen or ocufridine or tft or thriherpine or trifluor thymidine or trifluoro thymidine or trifluorodeoxythymidine or triherpin or triherpine or Trifluorothymine deoxyriboside or Thilol or TFDU or "BRN 0568095" or BRN0568095 or CCRIS 2348 or CCRIS2348 or EINECS2007228 or EINECS 2007228 or EINECS 200 722 8 or F3DThd or F3T or F3TDR or HSDB 8126 or HSDB8126 or NSC 529182 or NSC529182 or NSC 75520 or NSC75520 or NGO10K751P or RMW9V5RW38).ti,ab,kw,dq.	3627

18	or/16-17	4140
19	15 and 18	513
20	12 or 19	807
21	20 use oemezd	490
22	21 and conference abstract.pt.	226
23	21 not conference abstract.pt.	264
24	8 or 9 or 23	592
25	remove duplicates from 24	361
26	22 or 25	587
27	limit 26 to yr=2017-current	282
28	limit 27 to english	266

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#13	Search (#11 AND publisher[sb]) Filters: English	4
#12	Search (#11 AND publisher[sb])	4
#11	Search #3 OR #10	226
#10	Search #6 AND #9	144
#9	Search (#7 OR #8)	1706
#8	Search ((trifluridin*[tiab] OR trifluoridin*[tiab] OR trifluoromethyldeoxyuridine[tiab] OR trifluorothymidine[tiab] OR viroptic*[tiab] OR Triflumann*[tiab] OR Virophta*[tiab] OR TFT Ophtiole*[tiab] OR Viromidin*[tiab] OR aflomin[tiab] OR bephen[tiab] OR ocufridine[tiab] OR tft[tiab] OR thriherpine[tiab] OR trifluor thymidine[tiab] OR trifluoro thymidine[tiab] OR trifluorodeoxythymidine[tiab] OR triherpin[tiab] OR triherpine[tiab] OR Trifluorothymine deoxyriboside[tiab] OR Thilol[tiab] OR TFDU[tiab] OR BRN 0568095[tiab] OR BRN0568095[tiab] OR CCRIS 2348[tiab] OR CCRIS2348[tiab] OR EINECS2007228[tiab] OR EINECS 2007228[tiab] OR EINECS 200 722 8[tiab] OR F3DThd[tiab] OR F3T[tiab] OR F3TDR[tiab] OR HSDB 8126[tiab] OR HSDB8126[tiab] OR NSC 529182[tiab] OR NSC529182[tiab] OR NSC 75520[tiab] OR NSC75520[tiab] OR NGO10K751P[rn] OR RMW9V5RW38[rn]))	1706
#7	Search "Trifluridine"[Mesh]	492
#6	Search #4 OR #5	2530
#5	Search (Tipiracil*[tiab] OR MA 1[tiab] OR MA1[tiab] OR TPI[tiab] OR 5CIMU[tiab] OR 5 CIMU[tiab] OR tas 1 462[tiab] OR tas 1462[tiab] OR tas1462[tiab] OR NGO10K751P[rn] OR 4H59KLQ0A4[rn])	2530
#4	Search "tipiracil" [Supplementary Concept]	11
#3	Search (#1 OR #2)	215

Search	Query	Items found
#2	Search (Lonsurf*[tiab] OR "Tipiracil / Trifluridine"[tiab] OR Tipiracil Trifluridine[tiab] OR "trifluridine/tipiracil"[tiab] OR trifluridine tipiracil[tiab] OR TAS 102[tiab] OR TAS102[tiab] OR Viroptic mixture*[tiab] OR JNJ02[tiab])	210
#1	Search "trifluridine tipiracil" [Supplementary Concept]	92

3. Cochrane Central Register of Controlled Trials (Central)
   Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

U.S. NIH ClinicalTrials. gov
http://www.clinicaltrials.gov/

World Health Organization
http://apps.who.int/trialsearch/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Lonsurf/Tipiracil + Trifluridine, mCRC

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Lonsurf/Tipiracil + Trifluridine, mCRC

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

Search: Lonsurf/Tipiracil + Trifluridine, mCRC - last 5 years

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (December 2018) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were lonsurf and tipiracil/ trifluridine and metastatic colorectal cancer.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of June 06, 2019.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov, World Health Organization International Clinical Trials Registry and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

Two members of the pCODR Methods Team independently selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. A quality assessment of the PRECONNECT study was done using the Risk of Bias Assessment Tool for Non-Randomized Studies (RoBANS). Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review

Writing of the Review Report

This report was written by the Methods Team, the CGP and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.

- The pCODR CGP wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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