pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

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

pERC Final Recommendation
This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Trifluridine and Tipiracil (Lonsurf)

Submitted Reimbursement Request:
For the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents

Submitted By: Taiho Pharma Canada, Inc.	**Manufactured By:** Taiho Pharma Canada, Inc.
NOC Date: January 25, 2018	**Submission Date:** November 6, 2017
Initial Recommendation: May 3, 2018	**Final Recommendation:** July 6, 2018

Approximate Per-Patient Drug Costs, per Month (28 Days) Submitted list price of $93.85 per 20 mg tablet and $76.25 per 15 mg tablet	**Trifluridine-tipiracil Regimen Costs:** $5,631.00 per 28-day course Note: Costs are calculated based on an average weight of 70 kg and body surface area of 1.7 m2.

pERC RECOMMENDATION	pERC does not recommend the reimbursement of trifluridine-tipiracil (Lonsurf) for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents. pERC made this recommendation because, compared with placebo plus best supportive care (BSC), trifluridine-tipiracil plus BSC had inconsistent results between trials, potentially modest progression-free survival and overall survival benefit, moderate toxicities, and an uncertain impact on quality of life. pERC concluded that trifluridine-tipiracil aligned with patient values of a treatment option that offers ease of oral administration, with moderate but manageable toxicities and a potentially modest clinical effect compared with placebo plus BSC. The Committee noted that at the submitted price, trifluridine-tipiracil plus BSC compared with placebo plus BSC cannot be considered cost-effective in this population.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps were identified.

SUMMARY OF pERC DELIBERATIONS

In Canada, metastatic colorectal cancer (mCRC) is the second most common cause of cancer death in males and the third most common cause of cancer death in females. pERC noted that there are limited effective treatment options for patients with late-stage disease who have exhausted all other standard treatment options. pERC noted that patients are currently given best supportive care (BSC) after being treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, anti-VEGF therapy, and, if their disease is *KRAS* wild-type, anti-EGFR therapy. Until recently, the life expectancy of these patients from the time of diagnosis of metastatic disease was approximately two years, but was much shorter once all treatment options had been exhausted. pERC agreed that there is a need for additional treatment options that provide a clinically meaningful extension in survival, better symptom control, and maintain or improve quality of life, especially near the end of life. Upon reconsideration of the pERC Initial Recommendation, pERC agreed with the patient group, registered clinicians, and the submitter that there is an unmet need in this setting. However, pERC was uncertain that trifluridine-tipiracil would fulfil this unmet need for patients with mCRC. In 2015, pCODR reviewed regorafenib for a similar indication as trifluridine-tipiracil. At that time, pERC did not recommend regorafenib because, compared with placebo, it offered only a very modest progression-free survival (PFS) and overall survival (OS) benefit, moderate but not insignificant toxicities, and a similar decline in quality of life (QoL). Regorafenib is currently not reimbursed by the provinces; it can be accessed through private drug insurance. pERC acknowledged that while regorafenib was not a formal comparator in the assessment of trifluridine-tipiracil, the pCODR review of regorafenib provided contextual information. pERC noted feedback from the patient group expressing concern that the previous pCODR review of regorafenib contributed negatively to pERC's recommendation with respect to trifluridine-tipiracil. pERC reiterated that the current recommendation was based on the clinical trials that assessed trifluridine-tipiracil versus placebo, and that regorafenib was not a comparator in the assessment of trifluridine-tipiracil.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated on three double-blind randomized controlled trials (RCTs): RECOURSE (phase III, multinational), TERRA (phase III, only Asian countries), and J003-100400306 (phase II, only Japan), all of which compared trifluridine-tipiracil plus BSC with placebo plus BSC. pERC considered placebo plus BSC to be a reasonable comparison in this clinical setting. pERC noted the two larger phase III RECOURSE and TERRA trials were complemented by the evidence from the phase II J003-100400306 trial. Both the RECOURSE and TERRA trials used the same study design; however, pERC observed that the patient populations included in the studies differed. In the RECOURSE trial, prior to commencing the trial, almost all patients had received anti-VEGF therapy (bevacizumab) and more than 50% had received anti-EGFR therapy (cetuximab or panitumumab). In the TERRA trial, only about 20% of patients had received prior anti-VEGF or anti-EGFR therapy. Despite the differences in the patient populations, pERC observed both the TERRA and RECOURSE trials showed OS and PFS advantage compared with placebo. Upon reconsideration of the pERC Initial Recommendation, pERC acknowledged feedback from the submitter and registered clinicians that the results from the RECOURSE trial are more generalizable to the Canadian population. pERC noted that the RECOURSE trial may be more reflective of the Canadian population given patient characteristics and extent of prior therapies; however, they also noted feedback from the submitter that the TERRA trial was considered a "post-marketing" study by Health Canada, which may be more reflective of outcomes in a non-trial setting. pERC acknowledged that the pCODR Clinical Guidance Panel considered that there was a net clinical benefit with trifluridine-tipiracil compared with placebo. The improvement in median OS (the primary outcome) between the trifluridine-tipiracil arm and placebo arm was 2.0 months in the RECOURSE trial and 0.7 months in the TERRA trial. The improvement in median PFS was 0.3 months in the RECOURSE trial and 0.2 months in the TERRA trial. All results were statistically significant in both studies; however, the Committee considered these to be potentially modest improvements in both OS and PFS and acknowledged the relative risk reductions. Upon reconsideration of the pERC Initial Recommendation, pERC noted that the results of the RECOURSE trial were inconsistent with those of the TERRA trial (survival benefit of 2 months and 0.7 months, respectively). The Committee

observed that there was a wide range in the magnitude of clinical benefit observed between the trials as evident in median improvement in survival and relative risk reductions. pERC was uncertain how this improvement would translate into clinical practice and there was considerable discussion by the Committee on whether it was clinically meaningful. Following substantial discussion and despite conflicting opinions, for the majority of pERC members there was considerable uncertainty about the magnitude of benefit, with the potential that the benefit was at most modest. pERC noted that the impact of trifluridine-tipiracil on QoL is unknown, as it was not measured in any of the studies (RECOURSE, TERRA, or J003-100400306) despite their robust sample sizes. pERC values patient QoL outcomes in studies, particularly for end of life treatments, and was very disappointed that the three studies of trifluridine-tipiracil did not include QoL measurements in any of their study designs. pERC acknowledged there were two post hoc analyses of proxies for QoL; however, they agreed with the pCODR Methods Team that the proxies were not validated or formally recognized surrogates for QoL. Upon reconsideration of the pERC Initial Recommendation, pERC discussed and agreed with the pCODR Clinical Guidance Panel that a delay in patients' decline in Eastern Cooperative Oncology Group (ECOG) performance status is clinically meaningful. However, pERC reiterated that no formal measurement of QoL was included in any of the studies and was very disappointed in the lack of QoL measurement in either trial. pERC noted that robust data on QoL could have been very impactful on their recommendation.

pERC discussed the toxicity profile of trifluridine-tipiracil based on the results of the RECOURSE, TERRA, and J003-100400306 studies. pERC noted grade 3 adverse events (AEs) that occurred more frequently in patients treated with trifluridine-tipiracil included neutropenia, leukopenia, anemia, thrombocytopenia, febrile neutropenia, fatigue, vomiting, and diarrhea. pERC acknowledged that these were moderate toxicities with trifluridine-tipiracil. However, pERC noted that these toxicities were likely manageable. Upon reconsideration of the pERC Initial Recommendation, pERC acknowledged the patient group's, registered clinician's, and submitter's feedback that the toxicity profile of trifluridine-tipiracil was manageable.

Therefore, following substantial discussion and expression of various opinions by pERC members, and despite the statistically significant improvement in OS and PFS in patients receiving trifluridine-tipiracil compared with placebo, pERC concluded that there was not a net overall clinical benefit of trifluridine-tipiracil for patients with mCRC. Upon reconsideration of the pERC Initial Recommendation, pERC discussed the feedback received from the patient group, registered clinicians, and submitter regarding the clinical benefit of trifluridine-tipiracil. Stakeholders indicated that the benefit with trifluridine-tipiracil was considered important in this setting. Upon reconsideration of the pERC Initial Recommendation and after substantial discussion, based on the totality of evidence for trifluridine-tipiracil, pERC noted trifluridine-tipiracil had inconsistent results between trials, potentially modest magnitude of survival benefit, uncertain impact on QoL, and moderate but manageable toxicity profile. pERC reiterated the importance of QoL outcomes in studies and that they were very disappointed that the three studies of trifluridine-tipiracil did not include QoL measurements in any of their study designs.

pERC deliberated upon patient advocacy group input, which indicated that there is a need for additional therapeutic options to treat mCRC disease, regardless of *RAS* mutational status, that will help control the disease with respect to OS, PFS, and, in particular, to improve QoL. pERC appreciated the considerable effort that the patient group made to identify and interview 20 patients and caregivers with experience with trifluridine-tipiracil and noted that patient input was informative in their deliberations. pERC acknowledged that respondents with direct experience with trifluridine-tipiracil reported manageable side effects compared to other therapies but noted issues with blood counts and fatigue. pERC agreed with the patient input that there is a need for more options for patients with this disease when all standard treatment options have been exhausted. Upon reconsideration of the pERC Initial Recommendation, pERC acknowledged feedback from the patient group, that the patients interviewed had fewer side effects overall and better QoL. Therefore upon reconsideration, pERC concluded that trifluridine-tipiracil aligned with patient values because it provides a treatment option that offers ease of oral administration, with moderate but manageable toxicities and a potentially modest clinical effect compared with placebo plus BSC. Despite this alignment, pERC maintained that the inconsistent results between trials and potentially modest clinical benefit that was observed with trifluridine-tipiracil were insufficient to recommend reimbursement.

pERC acknowledged and agreed with clinician input that there are no funded treatment options for this specific patient population. Although clinician input stated that regorafenib is not funded in any Canadian jurisdictions due to an unfavourable cost-benefit analysis, the Committee noted that pERC issued a

negative recommendation for regorafenib for this indication due to the very modest PFS and OS benefit, moderate but not insignificant toxicities, and a similar decline in QoL compared to placebo. The Committee acknowledged clinician input that indicated trifluridine-tipiracil prolonged survival and delayed the time to deterioration of performance status, with key side effects including neutropenia or febrile neutropenia. Clinicians also indicated that although trifluridine-tipiracil has not been directly compared with regorafenib, trifluridine-tipiracil appeared to be a more tolerable treatment option.

pERC deliberated upon the cost-effectiveness of trifluridine-tipiracil. pERC noted that the pCODR Economic Guidance Panel (EGP) estimates were higher than the submitter's estimates, and discussed the assumptions upon which the EGP estimates were based. pERC agreed with the EGP's reanalysis, which included a shortened time horizon, medical resource use costs that were equal between treatment groups, and fitted survival curves using Kaplan–Meier curves and extrapolated tails at trial cut-off. pERC noted that these small changes in the estimates of incremental effect and cost increased the incremental cost-effectiveness ratio (ICER) estimates. pERC also noted that the TERRA study was not used to inform the economic evaluation, which would likely further increase the ICER estimates due to the less-optimistic efficacy results observed in TERRA. Overall, pERC noted that at the submitted price, trifluridine-tipiracil plus BSC compared with placebo plus BSC cannot be considered cost-effective in this population. However, pERC also noted that trifluridine-tipiracil's lack of cost-effectiveness was not the main reason for the current recommendation.

pERC discussed factors that could impact the feasibility of implementing a positive reimbursement recommendation for trifluridine-tipiracil, and noted that trifluridine-tipiracil is expected to be an additional, sequential therapy in the treatment of patients with mCRC. It will not likely replace other therapies; overall treatment costs could be expected to increase if it were funded. Therefore, the potential budget impact could be large, given the prevalence of mCRC. pERC acknowledged and agreed with input from the pCODR Provincial Advisory Group that there is an unmet need for this group of mCRC patients, however, the clinical benefits of trifluridine-tipiracil are potentially modest as well the impact on QoL is unknown.

EVIDENCE IN BRIEF

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

- A pCODR systematic review
- Other literature in the *Clinical Guidance Report* that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from pCODR clinical and economic review panels
- Input from one patient advocacy group, Colorectal Cancer of Canada
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, Colorectal Cancer of Canada
- Registered clinicians
- The PAG
- The submitter, Taiho Pharma Canada, Inc.

The pERC Initial Recommendation was to not recommend the reimbursement of trifluridine-tipiracil (Lonsurf) for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents. Feedback on the pERC Initial Recommendation indicated that the PAG agreed with the Initial Recommendation. The patient advocacy group, registered clinicians, and submitter disagreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of trifluridine-tipiracil versus an appropriate comparator for the treatment of adult patients with metastatic colorectal cancer (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.

Studies included: Three high-quality RCTs (two phase III trials and one phase II trial)

The pCODR systematic review included two phase III, double-blind randomized controlled trials (RCTs) — RECOURSE (multinational) and TERRA (only Asian countries) — that evaluated the efficacy and safety of trifluridine-tipiracil versus placebo in previously treated mCRC patients. One phase II, double-blind RCT, J003-100400306 (only Japan), also supported the evidence from the phase III RCTs on trifluridine-tipiracil. Although the studies were multi-centre, no Canadian sites were included in any of the studies. Trifluridine-tipiracil was administered at 35 mg/m^2 twice daily over days 1-5 and 8-12 in a 28-day cycle. All patients received best supportive care (BSC).

RECOURSE and TERRA included patients with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 to 1, while J003-100400306 included patients with ECOG PS 0 to 2. All studies required patients to have received at least two prior standard chemotherapy regimens for mCRC and were refractory, intolerant, or failing these therapies. *KRAS* status was required for inclusion in RECOURSE and TERRA, but not for J003-10040030.

The pCODR review also provided contextual information on a network meta-analysis (NMA) comparing trifluridine-tipiracil with regorafenib in patients with refractory mCRC. The pCODR critique of the NMA concluded that heterogeneity was a limitation of the analysis that restricted the ability to draw conclusions regarding the comparative effectiveness and safety of trifluridine-tipiracil versus regorafenib. No statistically significant differences in efficacy were detected between trifluridine-tipiracil versus regorafenib; regorafenib was associated with greater toxicity. However, pERC noted that regorafenib received a negative reimbursement recommendation from pCODR and is currently not publicly funded in any provinces.

Patient populations: ECOG performance status 0 to 1, some prior anti-VEGF/EGFR therapy use

Patient characteristics appeared to be balanced between treatment groups in all trials. The median age of patients ranged from 56 years to 63 years, with a male population ranging from 49% to 63%. In RECOURSE, the majority of patients had an ECOG PS of 0, with 56% and 55% of patients in the trifluridine-tipiracil and placebo groups, respectively. In TERRA, the majority of patients had an ECOG PS of 1, with 76% and 78% of patients in the trifluridine-tipiracil and placebo groups, respectively. The majority of patients in RECOURSE and TERRA had four or more prior regimens. In the RECOURSE trial, prior to commencing the trial, almost all patients had received anti-VEGF therapy (bevacizumab) and more than 50% had received anti-EGFR therapy (cetuximab or panitumumab). In the TERRA trial, only about 20% of patients had received prior anti-VEGF or anti-EGFR therapy.

Key efficacy results: Modest overall survival and progression-free survival benefit

Key efficacy outcomes deliberated on by pERC included overall survival (OS), the primary end points of the RECOURSE, TERRA, and J003-100400306 studies, and progression-free survival (PFS).

RECOURSE Study: pERC noted that at the cut-off date for OS data analysis, the median OS was 7.1 months and 5.3 months in the trifluridine-tipiracil-plus-BSC and placebo-plus-BSC groups, respectively (hazard ratio 0.68; 95% confidence interval [CI], 0.58 to 0.81). In the updated final analysis, the median OS was 7.2 months and 5.2 months in the trifluridine-tipiracil-plus-BSC and placebo-plus-BSC groups, respectively (hazard ratio 0.69; 95% CI, 0.59 to 0.91). The median PFS was 2.0 months and 1.7 months in the trifluridine-tipiracil-plus-BSC and placebo-plus-BSC groups, respectively (hazard ratio 0.48; 95% CI, 0.41 to 0.57).

TERRA Study: The median OS was higher in the TERRA study compared with the RECOURSE study. In TERRA, the median was 7.8 months and 7.1 months in the trifluridine-tipiracil-plus-BSC and placebo-plus-BSC groups, respectively (hazard ratio 0.79; 95% CI, 0.62 to 0.99). Similarly, the median PFS was 2.0 months and 1.8 months in the trifluridine-tipiracil-plus-BSC and placebo-plus-BSC groups, respectively (hazard ratio 0.43; 95% CI, 0.34 to 0.54).

pERC discussed the magnitude of benefit observed in median PFS and OS and acknowledged that the pCODR Clinical Guidance Panel had concluded that trifluridine-tipiracil conferred a statistically significant and clinically meaningful improvement in OS, and that there was a net clinical benefit to the use of trifluridine-tipiracil compared with placebo. However, pERC discussed the magnitude of the benefit in OS and PFS conferred by trifluridine-tipiracil (2.0 months and 0.3 months, respectively, in the RECOURSE study; 0.7 months and 0.2 months, respectively, in the TERRA study) and considered this benefit to be inconsistent between trials and potentially modest.

Patient-reported outcomes: Not measured; therefore, impact uncertain

Quality of life (QoL) was not measured in any of the studies. Therefore, pERC concluded that the impact of trifluridine-tipiracil on QoL is unknown. However, pERC noted that two post hoc analyses were completed to estimate the effect of trifluridine-tipiracil on QoL in the RECOURSE study. Trifluridine-tipiracil significantly increased the mean time to ECOG PS of 2 or greater compared with placebo. An analysis of quality-adjusted time without symptoms of disease or toxicity (QTWIST) was also conducted. It resulted in a greater QTWIST score for trifluridine-tipiracil compared with placebo. The pCODR Methods Team noted that PS at discontinuation is not a validated or formally recognized surrogate for QoL. Overall pERC reiterated that because QoL was not directly measured in any of the studies, the impact of trifluridine-tipiracil on QoL is unknown.

Safety: Moderate toxicities

pERC deliberated on the safety data available from the RECOURSE, TERRA, and J003-100400306 studies.

RECOURSE Study: Grade 3 adverse events (AEs) occurred in 69% and 52% of patients in the trifluridine-tipiracil-plus-BSC and placebo-plus-BSC groups, respectively. Grade 3 AEs that occurred more frequently in patients treated with trifluridine-tipiracil included neutropenia, leukopenia, anemia, thrombocytopenia, febrile neutropenia, diarrhea, hyperglycemia, and hand-foot syndrome. Serious adverse events (SAEs) occurred in 29.6% and 33.6% of patients in the trifluridine-tipiracil-plus-BSC and placebo-plus-BSC groups, respectively. AEs leading to treatment discontinuation occurred in 10.3% and 13.6% of patients in the trifluridine-tipiracil-plus-BSC and placebo-plus-BSC groups, respectively.

TERRA Study: Grade 3 AEs occurred in 45.8% and 10.4% of patients in the trifluridine-tipiracil-plus-BSC and placebo-plus-BSC groups, respectively. Grade 3 AEs that occurred more frequently in patients treated with trifluridine-tipiracil included neutropenia, leukopenia, anemia, fatigue, vomiting, small intestinal obstruction, thrombocytopenia, increased creatinine, bone marrow failure, and hypoalbuminemia. Drug-related SAEs occurred in 23.2% and 23% of patients in the trifluridine-tipiracil-plus-BSC and placebo-plus-BSC groups, respectively. AEs leading to treatment discontinuation occurred in 10% and 9.6% of patients in the trifluridine-tipiracil-plus-BSC and placebo-plus-BSC groups, respectively.

Need and burden of illness: Effective therapies for patients who have exhausted all other treatments

pERC noted that in Canada, mCRC is the second most common cause of cancer death in males and the third most common cause of cancer death in females. Untreated, the median survival of patients ranged from 6 months to 10 months. With the availability of cytotoxic chemotherapeutics (fluoropyrimidines, oxaliplatin, irinotecan) and targeted agents (i.e., bevacizumab, cetuximab, panitumumab), median survival times are now estimated to be 30 months to 36 months. Despite these significant improvements, long-term survival is rare: the five-year survival rate is less than 10%, and cures are still not anticipated in patients with unresectable mCRC. Therefore, there is a need for new effective therapies in this patient population. These patients are currently treated with BSC when treatment options are exhausted.

Registered clinician input: Unmet need for effective therapies

pERC deliberated on two clinician inputs from a total of 13 oncologists representing two groups. Clinicians indicated that since there are no treatment options (with the exception of clinical trials, as regorafenib is not publicly funded in Canada), trifluridine-tipiracil is the only option for these patients. pERC acknowledged clinician input noting that trifluridine-tipiracil had improved survival, had delayed time to deterioration of performance status, and was associated with key side effects that included neutropenia or febrile neutropenia. Clinician input indicated that although trifluridine-tipiracil has not been directly compared with regorafenib, regorafenib is not widely used due to its side effect profile and is not funded in any province.

PATIENT-BASED VALUES

Values of patients with metastatic colorectal cancer: Need for additional treatments

One patient group, Colorectal Cancer Canada, provided input on trifluridine-tipiracil for the treatment of patients with mCRC. Patient input indicated that there are a number of symptoms associated with mCRC that affect QoL, including fatigue, bloody stools, diarrhea or constipation, anemia, abdominal cramping, and bowel obstruction. pERC acknowledged that patients indicated that there is a need for an additional therapeutic option to treat their mCRC disease, regardless of *RAS* mutational status, that will help control their disease with respect to OS and PFS, and in particular will improve QoL. pERC also acknowledged that there is a considerable caregiver burden associated with this disease because of the financial, physical, and psychological challenges for those caring for loved ones.

Patient values on treatment: Management of toxicities and disease control

pERC noted that 20 survey and interview respondents had direct experience with trifluridine-tipiracil. These patients and caregivers reported manageable side effects that included fatigue, diarrhea, constipation, low blood counts, and abdominal discomfort. Among these, fatigue was considered the most difficult to tolerate. Patient respondents reported that compared with other therapies, trifluridine-tipiracil had fewer side effects overall and better QoL; however, they also noted issues with blood counts and fatigue. Overall, pERC concluded that trifluridine-tipiracil aligned with patient values, as it provides a treatment option that offers ease of oral administration, but with moderate toxicities, and a potentially modest clinical effect compared with placebo.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis, partitioned-survival analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-utility analysis comparing trifluridine-tipiracil plus BSC to placebo plus BSC for patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin-, and irinotecan-

based chemotherapy, anti-VEGF biological therapies, and anti-EGFR therapies. The comparison was based on the results of the RECOURSE and J003-100400306 studies. The submitted model was a partitioned-survival model.

Basis of the economic model: Clinical and economic inputs

Costs included in the model were for treatment, administration, monitoring, AEs, post-progression therapies, and end of life. The key clinical outcomes considered in the model included OS, PFS, and utilities.

Drug costs: Treatment until progression

At the submitted price, trifluridine-tipiracil costs $93.85 per 20 mg tablet (20 mg trifluridine and 8.19 mg tipiracil) and $76.25 per 15 mg tablet (15 mg trifluridine and 6.14 mg tipiracil). At the recommended dose of 35 mg/m^2 of trifluridine-tipiracil orally twice daily on days 1 through 5 and days 8 through 12 of each 28-day cycle, the cost of trifluridine-tipiracil is $201.11 per day and $5,631.00 per 28-day course.

Cost-effectiveness estimates: Not cost-effective at submitted price

pERC discussed the submitter's and the EGP's best estimates of the incremental cost-effectiveness ratio (ICER) of trifluridine-tipiracil plus BSC compared with BSC plus placebo for patients with previously treated mCRC. The main factors found to have the greatest influence on the incremental cost were the drug cost and monitoring costs. The main factors found to have the greatest influence on the incremental effectiveness were the time horizon and the fit of the OS and PFS curves. pERC noted that the EGP estimates were higher than the submitter's estimates, and discussed the assumptions upon which the EGP estimates were based. pERC agreed with the EGP's reanalysis, which included a shortened time horizon, medical resource use costs equal between treatment groups, and fitted survival curves using Kaplan–Meier curves and extrapolated tails at trial cut-off. pERC noted that these small changes in the estimates of incremental effect and cost increased the ICER estimates due to the less-optimistic efficacy results observed in TERRA. pERC also noted that the TERRA study was not used to inform the economic evaluation, which would likely further increase the ICER estimates. In conclusion, pERC determined that trifluridine-tipiracil plus BSC is not cost-effective at the submitted price compared with placebo plus BSC.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Additional therapy

pERC discussed the feasibility of implementing a funding recommendation for trifluridine-tipiracil, and noted that trifluridine-tipiracil is expected to be an additional, sequential therapy for patients with mCRC. As noted in PAG input, there are no funded treatment options for mCRC after chemotherapy, although for patients who have RAS wild-type tumours, treatment with an EGFR inhibitor is available. BSC is available for all patients; for those with private drug insurance, regorafenib is an option. pERC agreed with PAG input that noted an unmet need in this group of patients; however, the clinical benefits of trifluridine-tipiracil are potentially modest as well the impact on QoL is unknown. pERC acknowledged PAG input that indicated that additional resources are required to monitor and treat severe (grade 3 to 4) myelosuppression, including anemia, neutropenia, thrombocytopenia, and febrile neutropenia, as well as supportive therapy (e.g., anti-emetics, G-CSF).

DRUG AND CONDITION INFORMATION

Drug Information	• Composed of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil (as tipiracil hydrochloride) • Recommended dose of trifluridine-tipiracil (tablets) is a starting dose of 35 mg/m^2 administered orally with water twice daily, within 1 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 4 weeks as long as benefit is observed or until unacceptable toxicity occurs.
Cancer Treated	• Metastatic colorectal cancer • After treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-vascular endothelial growth factor agents, and, in the case of KRAS wild-type disease, anti-epidermal growth factor receptor agents
Burden of Illness	• Second most common cause of cancer death in Canadian males and third most common cause of cancer death in Canadian females
Current Standard Treatment	• Best supportive care
Limitations of Current Therapy	• Median survival for patients with untreated metastatic colorectal cancer is in the 6-month to 10-month range. • Long-term survival remains rare; cures are still not anticipated in patients with metastatic colorectal cancer. • There is an unmet need for those patients who retain a good performance status despite exhausting all prior standard therapies.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

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

pERC Membership During Deliberation of the Initial Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)	Leela John, Pharmacist
Dr. Catherine Moltzan, Oncologist (Vice-Chair)	Dr. Anil Abraham Joy, Oncologist
Dr. Kelvin Chan, Oncologist	Dr. Christine Kennedy, Family Physician
Lauren Flay Charbonneau, Pharmacist	Cameron Lane, Patient Member Alternate
Dr. Matthew Cheung, Oncologist	Christopher Longo, Health Economist
Dr. Winson Cheung, Oncologist	Valerie McDonald, Patient Member
Dr. Avram Denburg, Pediatric Oncologist	Carole McMahon, Patient Member
Dr. Craig Earle, Oncologist	Dr. Marianne Taylor, Oncologist

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

- Dr. Craig Earle, who was not present for the meeting
- Cameron Lane, who did not vote due to his role as a patient member alternate.

pERC Membership During Deliberation of the Final Recommendation

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

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

- Drs. Kelvin Chan, Anil Abraham Joy, and Christine Kennedy, who were not present for the meeting
- Cameron Lane, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of trifluridine-tipiracil (Lonsurf) for metastatic colorectal cancer, through their declarations, no members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

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

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. Amgen Canada Inc., as the primary data owner, did not agree to the disclosure of clinical information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

Use of this Recommendation

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

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