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
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Trifluridine-Tipiracil (Lonsurf)	
Submitted Reimbursement Request: For the treatment of adult patients with metastatic gastric cancer or adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior lines of chemotherapy including a fluoropyrimidine, a platinum, and either a taxane or irinotecan and if appropriate, with HER2/neu-targeted therapy	
Submitted By: Taiho Pharma Canada, Inc.	**Manufactured By:** Taiho Pharma Canada, Inc.
NOC Date: November 19, 2019	**Submission Date:** September 3, 2019
Initial Recommendation: March 5, 2020	**Final Recommendation:** March 24, 2020

Approximate per Patient Drug Costs, per Month (28 Days)	• $76.25 per 15 mg tablet or $78.53 per 20 mg tablet • At dose intensity 89.6% (as per the sponsor's submitted model), 28-day cost $4,221.78 • At a dose of 35 mg/m^2 administered orally, twice daily, on days 1 to 5 and days 8 to 12 of each 28-day cycle (10 total days) the average 28-day cycle cost is $4,711.80[a] [a]At 100% dose intensity and based on average body surface area (BSA) of 1.749 m^2 as per the TAGS trial

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends to reimburse trifluridine-tipiracil (Lonsurf) in combination with best supportive care (BSC) for the treatment of adult patients with metastatic gastric cancer or adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior lines of chemotherapy including a fluoropyrimidine, a platinum, and either a taxane or irinotecan and if appropriate, with HER2/neu-targeted therapy if the following condition is met:

- Cost-effectiveness being improved to an acceptable level.

Eligible patients include those with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Treatment should continue until unacceptable toxicity or disease progression.

pERC made this recommendation because it was satisfied that there is a net clinical benefit of trifluridine-tipiracil compared with best supportive care (BSC) in this setting based on a statistically significant and clinically meaningful improvement in overall survival (OS). In addition, trifluridine-tipiracil had a manageable side-effect profile with no detriment to quality of life. pERC noted that trifluridine-tipiracil aligns with the patient values of providing an additional treatment option that offers improved survival.

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	pERC concluded that at the submitted price trifluridine-tipiracil could not be considered cost-effective compared with best supportive care.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Price Arrangement to Improve Cost-Effectiveness** Given that pERC concluded that there is a net clinical benefit of trifluridine-tipiracil compared with best supportive care in this setting, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of trifluridine-tipiracil compared with other treatment options for metastatic gastric cancer or adenocarcinoma of the gastroesophageal junction after two prior lines of chemotherapy. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

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SUMMARY OF pERC DELIBERATIONS

pERC discussed that gastric and cancer of the gastroesophageal junction is the fifth most common cause of cancer mortality. In-2019, 4,100 people were diagnosed, and 1,950 deaths were reported in Canada. pERC also noted that of the 2,300 patients diagnosed with esophageal cancer, half of the patients are diagnosed with adenocarcinomas of the gastroesophageal junction, and about 40% of those patients present with metastatic disease. pERC noted that the most commonly used regimens in Canada contain a combination of a fluoropyrimidine [(FP)] and a platinum (cisplatin or oxaliplatin) or irinotecan with infusional 5FU (FOLFIRI). For patients with HER2 positive disease, the addition of trastuzumab to first-line 5FU/platinum chemotherapy significantly extends survival and is the currently accepted practice for first-line therapy. pERC discussed that **ramucirumab** with paclitaxel is available as second line therapy for patients with ECOG 0-1. pERC commented that duration of disease control with second-line treatment is short, and there are few evidence-based options for third- and later-line therapy. pERC also noted that prognosis in this setting is poor with a median survival of approximately three months with best supportive care (BSC)and that currently approximately 14% of patients receive third-line treatment for which there is currently no standard of care. pERC discussed that there is a significant unmet need for the small percentage of patients who are fit for third-line therapy.

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

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated upon one international phase III, double-blinded, placebo-controlled randomized controlled trial (TAGS) investigating the use of trifluridine-tipiracil plus best supportive care (BSC) for patients with gastric cancer, including those with adenocarcinoma of the gastroesophageal junction (GEJ), who were refractory or were intolerant to at least two prior therapies for their disease. pERC discussed that the TAGS trial was generally well-conducted.

pERC noted that there was an improvement in the median progression-free survival (PFS) in the trifluridine-tipiracil group plus BSC compared with the BSC alone. pERC discussed input from the CGP that for this particular patient population, OS is a more clinically relevant end point. pERC noted there was a statistically significant improvement in median overall survival (OS) with trifluridine-tipiracil plus BSC compared with BSC and agreed with the Clinical Guidance Panel (CGP) that this difference was clinically meaningful. In addition, pERC noted that the one-year OS was 21% in the trifluridine-tipiracil plus BSC group versus 13% in the placebo plus BSC group and considered that this represented a clinically relevant and meaningful improvement in the one-year OS rate. pERC commented that the disease control rate of 44.1% in the trifluridine-tipiracil plus BSC group was high compared to 13% in the placebo plus BSC group and that approximately 40% of patients had stable disease. pERC noted that in a patient population with an anticipated median OS survival of approximately three months and with limited treatment options in the third-line setting, trifluridine-tipiracil was considered an effective additional treatment option. pERC further noted that the median 2.1 month survival advantage and the OS rate at one year with trifluridine-tipiracil was considered clinically meaningful in this patient population.

pERC noted that the patients included in the TAGS trial had to have an ECOG performance status of 0 to 1, and that patients with ECOG PS greater than one were not included in the trial. pERC agreed with the CGP that the trial results cannot be generalized to patients with ECOG status greater than 1. pERC also noted patients in the TAGS trial were previously treated with at least two prior lines of chemotherapy including a fluoropyrimidine, a platinum, and either a taxane or irinotecan and if appropriate with HER2/neu-targeted therapy. pERC agreed with the CGP that some metastatic gastric cancer patients may be unsuitable for first-line therapy with a platinum agent and are treated first-line with FOLFIRI. pERC agreed with the CGP that data from the TAGS trial could be extrapolated to patients who have previously received two lines of systemic therapy regardless of whether it included a platinum-based therapy.

pERC appreciated that the TAGS trial collected quality of life (QoL) data, particularly because the patient group input valued new treatments that offer improved QoL. pERC noted that there was no clinically meaningful change in mean scores from baseline in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 (QLQ-C30) and the EORTC gastric

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cancer module (EORTC-QLQ-STO22) and therefore concluded that trifluridine-tipiracil plus BSC did not result in a detriment to QoL when compared with BSC. Overall, pERC concluded that there is a net clinical benefit of trifluridine-tipiracil plus BSC compared with BSC based on a statistically significant and clinically meaningful improvement in OS, a manageable side-effect profile and no detriment to QoL with trifluridine-tipiracil plus BSC versus BSC alone.

pERC discussed the toxicity profile of trifluridine-tipiracil. pERC noted that the grade 3 or higher adverse events (AEs) were greater in the trifluridine-tipiracil plus BSC group versus the placebo plus BSC group pERC noted that the most frequent AEs in the trifluridine-tipiracil group were anemia neutropenia, nausea, and decreased appetite. pERC also noted that the serious adverse events (SAEs) were similar between treatment groups and pERC commented that the deaths due to AEs were 13.4% in the trifluridine-tipiracil plus BSC group and 11.3% in the placebo plus BSC group. pERC also discussed the use of granulocyte-colony stimulating factor (G-CSF) in the TAGS trial as a supportive treatment for AEs and that its use in clinical practice is uncommon. Based on the toxicity profile, pERC concluded that trifluridine-tipiracil has a manageable side-effect profile.

pERC deliberated on the patient advocacy group input, which indicated that patients with metastatic gastric cancer value improved QoL and manageable side effects. pERC noted that patients were willing to take a therapy that improves their overall daily functioning even if it does not extend survival. pERC discussed the patient values and noted that it was unclear if patients were willing to take trifluridine-tipiracil if it did not improve their QoL. However, pERC also noted that patients presumably value an additional treatment option which offers improved survival. pERC noted that although trifluridine-tipiracil plus BSC did not provide an improvement in QoL in the TAGS study, it provides patients with an additional treatment option in the third-line setting. pERC also considered that there is a statistically significant and clinically meaningful improvement in OS with the addition of trifluridine-tipiracil to BSC. pERC also noted that overall, trifluridine-tipiracil has manageable side effects. pERC discussed that the dosing regimen for trifluridine-tipiracil was complicated and it was unclear how difficult it would be for patients to manage the dosing of the regimen. Therefore, pERC concluded that although the addition of trifluridine-tipiracil may not provide an improvement in QoL, the treatment aligns with patient values as it improves outcomes of interest to patient groups such as overall survival and provides an additional treatment option for patients.

pERC deliberated upon the cost-effectiveness of trifluridine-tipiracil plus BSC compared to BSC alone. pERC noted that the pCODR Economic Guidance Panel (EGP)'s incremental cost-effectiveness ratio (ICER) estimates were less favourable than the sponsor's submitted ICER estimates. The EGP reanalysis was based on setting the dose intensity to 100% to capture the full cost of the dosage, adding institutional costs and dispensing fees for oral medications, shortening the time horizon to five years to reflect the clinical course of patients in this setting, and replacing frequent oncology visits and computed tomography scans with annual visits and diagnostic testing after progression on therapy. pERC also discussed that the incremental costs and ICER were most sensitive to the planned dosage based on body surface area (BSA), dose intensity, and duration of therapy. Overall, pERC agreed with the EGP's best-case estimate for the ICER and concluded that trifluridine-tipiracil plus BSC could not be considered cost-effective when compared to BSC alone at the submitted price.

pERC discussed the feasibility of implementing a positive conditional reimbursement recommendation for trifluridine-tipiracil plus BSC. pERC noted that trifluridine-tipiracil is an oral therapy and although the ease of administration would be an enabler to implementation, in some jurisdictions, oral medications are not reimbursed in the same way as intravenous cancer medication which may limit access to trifluridine-tipiracil. pERC also considered that given that trifluridine-tipiracil is an add-on treatment to BSC, overall treatment costs could increase if the regimen were funded. pERC noted that the budget impact analysis (BIA) was sensitive to the market share of trifluridine-tipiracil and the extent of which trifluridine-tipiracil would replace BSC in the third-line setting as well as duration of therapy, body surface area of the patients for dosing and prevalence of gastric cancer. pERC discussed the key limitations of the BIA, which include the unknown potential of indication creep, the potential of moving the therapy into the larger first- or second-line therapy stages, and unknown market share because of the absence of a currently available active comparator. pERC discussed and noted the EGP's sensitivity analysis of the BIA which explored the market share, duration of therapy, and prevalence of cancer. pERC also noted that the sponsor's BIA did not include supportive care costs for the management of treatment-related AEs, such as G-CSF, and is likely underestimated. pERC discussed the complicated dosing schedule of trifluridine-tipiracil and noted that this may be a potential barrier to implementation as patients would

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need to be monitored closely in the first cycle of administration and potentially in every cycle thereafter. pERC also addressed a number of the implementation questions from PAG that are outlined in Appendix 1.

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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 sponsor's economic model and BIA
- Guidance from the pCODR clinical and economic review panels
- Input from one patient advocacy group(My Gut Feeling [Stomach Cancer Foundation of Canada])
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- Registered clinicians
- The PAG
- The sponsor, Taiho Pharma Canada Inc.

The pERC Initial Recommendation was to conditionally recommend reimbursement of trifluridine-tipiracil (Lonsurf) in combination with best supportive care (BSC) for the treatment of adult patients with metastatic gastric cancer or adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior lines of chemotherapy including a fluoropyrimidine, a platinum, and either a taxane or irinotecan and if appropriate, with HER2/neu-targeted therapy, if the following condition is met:

- cost-effectiveness being improved to an acceptable level.

Feedback on the pERC Initial Recommendation indicated that PAG, the sponsor and the registered clinician agreed with the Initial Recommendation. All three stakeholders supported early conversion of the Initial Recommendation to a Final Recommendation. No feedback was received from patient groups.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of trifluridine-tipiracil in combination with BSC for the treatment of metastatic gastric cancer or adenocarcinoma of the GEJ for patients who have been previously treated with at least two lines of chemotherapy including a fluoropyrimidine, a platinum, and either a taxane or irinotecan, and if appropriate, with HER2/neu-targeted therapy.

Studies included: TAGS trial, an international, placebo-controlled, double-blinded randomized controlled trial (RCT)

The pCODR systematic review included one international, double-blinded, phase III, randomized, placebo-controlled, superiority trial of trifluridine-tipiracil plus BSC versus placebo plus BSC in patients with advanced gastric cancer, including those with adenocarcinoma of the GEJ, who were refractory or intolerant to at least two prior therapies for their disease. Eligible patients were randomized in a 2:1 ratio to receive oral trifluridine-tipiracil at a dose of 35 mg/m2 twice daily or matching placebo twice daily with BSC on days 1 through 5 and days 8 through 12 of each 28-day treatment cycle until disease progression, unacceptable toxicity, or withdrawal due to AEs. There were 337 patients randomized to the trifluridine-tipiracil arm, of which 335 were treated; and 170 patients randomized to the placebo arm, of which 168 were treated.

The primary end point of the TAGS trial was OS, and secondary outcomes included PFS, objective response rate, disease control rate (DCR), and time to deterioration to Eastern Cooperative Oncology Group Performance Status (ECOG PS) greater than or equal to two. Health-related QoL (HRQoL) was also

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explored and assessed using EORTC Quality of Life Questionnaire (QLQ-C30) and the EORTC gastric cancer module (EORTC QLQ-STO22). Safety was monitored regularly throughout the study and included all patients who received at least one dose of the assigned treatment.

Patient populations: Two prior systemic treatments with ECOG Performance Status 0 to 1

The median age was 64 years in the trifluridine-tipiracil arm and 63 years in the placebo arm. Overall, the primary tumour site was gastric for 71% of patients and GEJ for 29% of patients. All patients were previously treated with platinum and 99.8% were previously treated with a fluoropyrimidine. A number of demographic and disease characteristics were imbalanced in the trifluridine-tipiracil arm compared to the placebo arm, including a higher proportion of patients that were male (75% versus 69%), had White ethnicity (72% versus 66%), were ECOG PS 1 (64% versus 60%), had HER2-positive disease (20% versus 16%), and were previously treated with a taxane (92% versus 87%) or immunotherapy (7% versus 4%).. In the placebo arm compared to the trifluridine-tipiracil arm, there were a higher proportion of patients with ≥ 3 metastatic sites (58% versus 54%), ≥ 4 prior chemotherapy regimens (27% versus 23%), and peritoneal metastases (31% versus 26%).

Key efficacy results: Statistically significant improvement in OS and high OS rate at 1 year

The key efficacy outcome deliberated on by pERC included OS, PFS, and DCR.

OS: The median OS was 5.7 months (95% confidence interval [CI], 4.8, 6.2) in the trifluridine-tipiracil treatment arm and 3.6 months (95% CI, 3.1, 4.1) in the placebo arm (hazard ratio [HR]: 0.69; 95% CI, 0.56, 0.86; P = 0.0006).

PFS: The median PFS in the trifluridine-tipiracil arm was 2.0 months (95% CI, 1.9, 2.3) and 1.8 months (95% CI, 1.7 to 1.9) in the placebo arm, with a 43% reduction in the risk of progressive disease or death associated with the trifluridine-tipiracil arm relative to the placebo arm (HR = 0.57; 95% CI, 1.7, 1.9; P < 0.0001).

DCR: The DCR was 44.1% in the trifluridine-tipiracil treatment arm compared to 14.5% in the placebo arm, driven by the large proportion of patients achieving stable disease in the trifluridine-tipiracil treatment arm.

Patient-reported outcomes: No clinically meaningful differences reported for EORTC QLQ-C30 and QLQ-STO22 scores

The mean baseline global health status (GHS) based on the EORTC QLQ-C30 was 58.4 for both treatment arms. There were no clinically relevant changes (≥ 10 points) in GHS from baseline up to cycle 3 in each treatment arm. There were no clinically relevant differences in the mean change in score from baseline for most of the functioning and symptom scales of the EORTC QLQ-C30, except for role functioning at cycle 3, where there was a difference of 10 points favouring placebo; and the pain scale at cycle 2, where there was a difference of 11.3 points favouring trifluridine-tipiracil. There were no clinically relevant changes in mean scores from baseline in the QLQ-STO22 scores.

Limitations: Imbalances in treatment arms leading to potential confounding

There were several imbalanced covariates between treatment arms, some of which may have confounded the efficacy results, including: a slightly higher proportion of patients with an ECOG PS of 1 (64%) and HER2-positive disease (20%) in the trifluridine-tipiracil treatment arm compared to the placebo arm (ECOG PS 1: 60%; HER2-positive disease: 16%); a higher proportion of patients with ≥ 3 metastatic sites (58%) and patients with peritoneal metastases (31%) in the placebo arm compared to the trifluridine-tipiracil arm (≥ 3 metastatic sites: 54%; peritoneal metastases: 26%). It was difficult to determine the impact of the confounding by prior therapies and subsequent therapies post-treatment discontinuation while imbalances in sex, ethnicity, prior taxane, or prior immunotherapy were not considered to confound the results and the exact time of the questionnaires' collection were not recorded in the case report form database, and HRQoL may have been subject to response bias if assessments were conducted following dosing and after significant interactions with study staff.

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Safety: Higher grade ≥ 3 AEs in trifluridine-tipiracil plus BSC group versus BSC alone group

The median total treatment duration was 6.71 weeks in the trifluridine-tipiracil arm and 5.71 weeks in the placebo arm, and less than 50% of patients initiated treatment beyond cycle 2 in either treatment arm (43.3% in the trifluridine-tipiracil arm versus 19.6% in the placebo arm initiated cycle 3). There were 58.2% of patients who required a dose modification (dose delay or dose reduction) in the trifluridine-tipiracil arm compared to 22.0% in the placebo arm. A total of 10.7% and 1.2% of patients required a dose reduction in the trifluridine-tipiracil and placebo arms, respectively.

Any-grade AEs: There were a higher proportion of patients in the trifluridine-tipiracil arm (97.3%) who experienced at least one any-grade AE compared to the placebo arm (93.4%). The most common any-grade AEs included anemia (44.5%), neutropenia (38.5%), nausea (37.0%), and decreased appetite (34.3%) in the trifluridine-tipiracil arm. In the placebo arm, the most common any-grade AEs included nausea (31.5%), decreased appetite (31%), asthenia (23.8%), and fatigue (20.8%).

Grade ≥ 3 AEs: There were a higher proportion of grade ≥ 3 AEs that occurred in the trifluridine-tipiracil arm (79.7%) compared to the placebo arm (57.7%). The most common grade ≥ 3 AEs in the trifluridine-tipiracil arm included neutropenia (23.3%) and anemia (18.8%), whereas in the placebo arm it was general physical health deterioration (8.9%), abdominal pain (8.9%), and anemia (7.7%).

SAEs: SAEs occurred in a similar proportion between treatment arms, occurring in 42.7% of patients in the trifluridine-tipiracil arm and in 41.7% of patients in the placebo arm. In both treatment arms, general deterioration of health (6.3% and 8.9% in the trifluridine-tipiracil arms and placebo arms, respectively) and anemia (3.9% and 2.4%, respectively) were common SAEs.

Withdrawal due to AEs (WDAEs): A total of 43 (12.8%) of patients discontinued treatment due to any AE in the trifluridine-tipiracil arm compared to 28 (16.7%) of patients in the placebo arm.

Deaths: There were a total of 45 (13.4%) deaths due to AEs in the trifluridine-tipiracil arm compared to 19 (11.3%) in the placebo arm. General physical health deterioration was the most common AE in the trifluridine-tipiracil arm (n = 17; 5%) and in the placebo arm (n = 11; 7%) leading to death.

Need and burden of illness: no standard of care — patients need more effective and tolerable systemic therapies

In Canada, it is estimated that in 2019, gastric cancer will be diagnosed in 4,100 people and will lead to death in 1,950. After progression on first- and second-line systemic therapy, there is no standard third-line treatment for gastric cancer. The prognosis in this setting is poor and median survival is just over three months with BSC. Thus, there is significant unmet need in this very small population of patients who are fit for third-line therapy. The oral route of administration is preferred by patients and reduces resource utilization in cancer centres compared to intravenous drugs. It is also advantageous for patients who live outside major urban centres.

Registered clinician input: a significant increase in PFS and OS, and was generally well-tolerated

Two registered clinician input submissions were reviewed on trifluridine-tipiracil for patients with metastatic gastric cancer who have been previously treated with at least two prior systemic treatment regimens. One input was provided by an individual medical oncologist from the Segal Cancer Centre, Jewish General Hospital at McGill University in Quebec, and one joint input submission was provided on behalf of seven clinicians from various institutions in Ontario and British Columbia, including Mount Sinai Hospital, Cross Cancer Institute, London Regional Cancer Program, and the BC Cancer Agency. Based on the favourable results of the TAGS trial, all clinicians agreed that trifluridine-tipiracil is a highly effective treatment for gastric cancer patients for whom two standard treatments have previously failed. The clinicians highlighted that trifluridine-tipiracil was associated with a significant increase in PFS and OS and was generally well-tolerated by patients compared to placebo. Furthermore, both inputs suggested that trifluridine-tipiracil could be an option for patients in earlier lines of treatment who are intolerant to, not candidates for or contraindicated to previous chemotherapies. Clinicians also suggested that the trifluridine-tipiracil could be extended to patients with an ECOG performance status of 2 and to patients who have received prior immunotherapy. Both groups of clinicians highlighted the convenience of trifluridine-tipiracil, as it an oral medication which makes it an effective treatment option for patients who want a low-intensity treatment, such as elderly patients.

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PATIENT-BASED VALUES

Values of patients with gastric cancer: high symptom burden and poor QoL
From a patient's perspective, metastatic gastric cancer has a significant physical and psychological impact on their lives, limiting their ability to carry on with their daily lives. The most common concerns reported by patients included fatigue, loss of appetite, nausea, weight loss, anemia, and the psychological symptoms of anxiety and depression. Caregivers also expressed significant emotional challenges from fulfilling their duties of caring for patients with metastatic gastric cancer, with many reporting that they experience anxiety and depression. Current therapies available include FLOT, FOLFIRI, Capecitabine + cisplatin, Paclitaxel + Ramucirumab, trastuzumab, FOLFOX, Docetaxel, Oxaliplatin, Fluorouracil (5FU), and immunotherapy drugs such as pembrolizumab.

Patient values on treatment: improved outcomes, QoL and improved toxicity profile
Overall, the majority of the 96 patient and caregiver respondents had no knowledge of the drug under review. None of the patient respondents had direct experience with the trifluridine-tipiracil and two caregivers reported that their patients had experience with the drug. Overall, patients and caregivers value an improvement in QoL and better management of side effects. The majority of respondents reported that they are willing to take a drug that improves their overall daily functioning, even if it does not extend OS. Two caregivers reported that their patients had experience with trifluridine-tipiracil. Both of the caregivers who responded noted that they value trifluridine-tipiracil as an additional treatment option to be made available to other patients.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness and cost-utility analysis
The economic analysis submitted to pCODR by Taiho Pharma Canada Inc. compared trifluridine-tipiracil with BSC to placebo plus BSC as per the inclusion criteria of the pivotal study for third-line treatment of adult patients with metastatic gastric cancer or GEJ who have been previously treated with at least two lines of chemotherapy including a fluoropyrimidine, a platinum, and either a taxane or irinotecan and if appropriate with HER2/neu-targeted therapy. The patient population in the economic model is consistent with the reimbursement request.

Basis of the economic model: Markov cohort, partitioned-survival model
The sponsor submitted a partitioned-survival model with escalating health states: progression-free, progressed, and death.

Drug costs: treatment costs of trifluridine-tipiracil plus BSC
Drug dosage for adults is 35 mg/m2 administered orally, twice daily, on days 1 to 5 and days 8 to 12 of each 28-day cycle (10 total days). Average patient BSA (TAGS trial): 1.749 m^2.

Price per tablet (currently approved):
15 mg tablet: $76.25
20 mg tablet: $78.53

At 100% dose intensity, based on average BSA the average 28-day cycle cost is $4,711.80; $471.18 per treatment day; $168.28 per day over 28 days.

At dose intensity 89.6% (as per the sponsor's submitted model) the 28-day cost $4,221.78.

Clinical effect estimates: TAGS trial and literature derived QoL (EuroQol 5-Dimensions [EQ-5D])
Data informing OS, PFS, and (Grade 3+) treatment-emergent AEs were derived from the TAS-102 Gastric Study (TAGS) trial. The economic model projected PFS and OS beyond the trial period for up to 10 years and relies little on extrapolation since a large majority of PFS and OS events occurred during the trial period with a median duration of follow-up for trifluridine-tipiracil of 10.5 months and 10.7 months for placebo. Resource utilization for each health state and for each adverse event was estimated based on a Canadian clinical survey, while unit costs were based on Ontario unit prices for physician services,

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laboratory testing and drug costs (OSB-PS 2019, ODB-Labs 2019, ODB 2019). Rates of AEs were taken from the TAGS trial. QoL estimates for AEs and for health states (progressive-free and progressed) were taken from the literature. The lifetime QoL benefit was driven mostly by extrapolated longer survival data, while AEs had little impact. QoL (such as EQ-5D) was not captured during the trial and instead relied on literature values. In addition, utilities of health states were taken from patients with second-line gastric cancer, which may be different than the values for patients with third-line gastric cancer. UK weights for EQ-5D were used instead of Canadian weights, whereas Canadian utilities are often non-statistically different from UK weights, but the direction varies by disease and AEs.

Cost-effectiveness estimates: not cost-effective compared to BSC at submitted price

pERC considered the uncertainties in the model inputs addressed by the EGP and noted that based on 5,000 iterations, the EGP's probabilistic estimate of the ICER of trifluridine-tipiracil plus BSC is $174,465/quality-adjusted life-year (QALY), which differed from the sponsor's best estimate of $150,529/QALY. The EGP made the following changes to the model to address some of its limitations: setting the dose intensity to 100% to capture the full cost of the dosage, adding the additional institution and dispensing fees costs, selecting a five-year time horizon, and changing the frequency of oncology visits and diagnostic testing to annual visits for those with progressing disease. The EGP conducted price reduction scenarios to assess the impact of a change to the incremental cost-utility ratio based on a change to the price of trifluridine-tipiracil. From these analyses, it was concluded that a price reduction of 50% to 75% would be necessary to achieve an ICER value of below $100,000 QALY.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: potential for indication creep, increased prevalence, and supporting costs for treatment-related AEs

The factors that most influence the BIA include increased duration of therapy since the treatment is to be given until disease progression, unacceptable toxicity or patient withdrawal, increased BSA resulting in higher dosage, increased future market share, and increased prevalence of gastric cancer. Key limitations of the BIA model include the unknown potential of indication creep into the larger first- or second-line therapy stages, and unknown market share of triflurdine-tipiracil because of the absence of a currently available active comparator. The market share, duration of therapy, and prevalence of cancer were explored in the sponsor's sensitivity analysis. The BIA only includes the cost of the drug and does not include costs related to the screening and treatment of AEs; thus, leading to an underestimated BIA.

Factors related to currently funded treatments, the eligible patient population, implementation, and sequencing and priority of treatments are described in Appendix 1.

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ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

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

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

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

- Dr. Maureen Trudeau who did not vote due to her role as the pERC Chair.
- Dr. Winson Cheung who was excluded from voting due to a conflict of interest.

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the 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 for gastric cancer, through their declarations, one member had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, this member was excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and 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*. There was no non-disclosable information in this recommendation document.

Use of this Recommendation

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

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation

Patient Eligibility
 	
• PAG is seeking guidance on whether the following subgroups of patients would be eligible for trifluridine-tipiracil:
  ○ ECOG PS of 2
  ○ CNS metastases
  ○ In earlier lines if patients have contraindication to chemotherapy
  ○ Prior immunotherapy
 	
• PAG noted that patients who are currently receiving BSC or third-line treatment would need to be addressed on a time-limited basis.
	• pERC agreed with the CGP that the results of the trial are not generalizable to patients with ECOG performance status > 1.
	• pERC also noted that the trial excluded patients with brain metastases, and therefore agreed with the CGP that treatment with trifluridine-tipiracil should not be given to patients with CNS metastases.
	• pERC noted that patients must have been refractory or unable to tolerate at least two prior systemic regimens for advanced disease in the TAGS trial. Patients who received preoperative neoadjuvant and/or post-operative adjuvant chemotherapy or chemoradiotherapy and had recurrence during or within 6 months of completion of the adjuvant chemotherapy were allowed to count this therapy as 1 prior regimen for advanced disease (only if the same regimen was administered both pre- and post-operatively). A total of 15 (3.0%) patients met this criterion. pERC noted that a small number of patients had recurrence within 6 months of adjuvant therapy on the TAGS trial, since it was an inclusion criterion, and agreed with the CGP that the data should be generalizable to that specific population. The efficacy of trifluridine-tipiracil in an earlier line of therapy, outside of that specific instance, requires prospective evaluation.
	• pERC agreed with the CGP that the mechanisms of action are different and prior immunotherapy should not influence safety or efficacy of trifluridine-tipiracil. Thus, the results can be applied to patients treated with prior immunotherapy.
	• pERC agreed that patients who are currently receiving BSC or third-line treatment would need to be addressed on a time-limited basis.

Implementation Factors
 	
Barriers to Implementation:
  ○ PAG has concerns with the complex dosing schedule and that multiple dose strengths would be required, as this may lead to dosing or dispensing errors. Additional pharmacy resources would be required for dispensing trifluridine-tipiracil, as well as supports to ensure patient compliance.
  ○ Drug wastage can occur if patients develop AEs (e.g., neutropenia) and need to discontinue treatment. Performance status can decline quickly in these patients.
	• pERC acknowledged that the complex dosing schedule and multiple dose strengths required for trifluridine-tipiracil would require additional pharmacy resources.
	• pERC acknowledged that wastage could be a potential concern in the smaller centres and noted that the EGP's best-case estimates included wastage as well as the associated dispensing fees.
	• pERC noted that in some jurisdictions, oral medications are not reimbursed in the same way as intravenous cancer medication which may limit access to trifluridine-tipiracil.
	• pERC noted that the submitted BIA only includes the cost of the drug and does not

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○ 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. ○ Some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit patients' accessibility to treatment 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 that fund oral and intravenous cancer medications differently are private insurance coverage or full out-of-pocket expenses. • Additional resources (e.g., nursing and clinic visits) are required to monitor and treat severe (grade 3 to 4) myelosuppression, including anemia, neutropenia, thrombocytopenia and febrile neutropenia, as well as to monitor complete blood count. The cost of supportive therapy (e.g., anti-emetics, G-CSF) also needs to be considered in implementation.	include costs related to the screening and treatment of AEs, thus leading to an underestimated BIA.
Sequencing and Priority of Treatments • Pembrolizumab is an option for patients with private drug insurance who have MSI-high metastatic gastric or GEJ adenocarcinomas. • PAG is seeking guidance on sequencing pembrolizumab with trifluridine-tipiracil.	• pERC agreed with the CGP that data reflecting the optimal sequencing of trifluridine-tipiracil and immunotherapy is limited. If patients with MSI-H/dMMR can access immunotherapy, it should not preclude them from treatment with trifluridine-tipiracil if they are deemed suitable for ongoing treatment given the different mechanisms of action of these treatments.

BIA = budget impact analysis; BSC = best supportive care; CGP = Clinical Guidance Panel; EGP = Economic Guidance Panel; G-CSF = granulocyte-colony stimulating factor; GEJ = gastroesophageal junction; ECOG – Eastern Cooperative Oncology Group; PS = Performance Status; CNS = Central Nervous System; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.

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