CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Trifluridine-Tipiracil (Lonsurf) for Metastatic Colorectal Cancer Resubmission

August 29, 2019

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Taiho Pharma Canada, Inc.** compared trifluridine-tipiracil (LONSURF®) to best supportive care (BSC) for patients with metastatic colorectal cancer (mCRC) who have been previously treated with two or more therapies.

Table 1. Submitted Economic Model.

Funding request/patient population modelled	The patient population modelled is identical to that of the RECOURSE clinical trial and included patients with mCRC who have been previously treated with two or more therapies. The manufacturer submitted pharmacoeconomic report suggests that trifluridine-tipiracil will be indicated 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 chemotherapy, anti-VEGF biological therapies, and anti-EGFR therapies.
Type of analysis	*Cost-utility analysis (CUA) and Cost-effectiveness Analysis (CEA)*
Type of model	*Partitioned survival*
Cycle Length	*1 day*
Comparator	*BSC*
Year of costs	*2019*
Time horizon	*5 years*
Perspective	*Canadian public payer perspective*
Cost of trifluridine-tipiracil	• Cost per mg for 15 mg tablet: $5.08; cost of 15 mg tablet is $76.25 • Cost per mg for 20 mg tablet: $4.69; cost of 20 mg tablet is $93.85
Cost of BSC	• None
Model structure	*The partitioned survival model consisted of three health states: pre-progression, post-progression, and death. These health states match the clinical progression of disease and were applied to both treatments being compared (see Figure 1).*
Key data sources	*Survival outcomes:* *Updated RECOURSE trial data (phase III RCT) as cited in (1), pooled with a phase II RCT (2)* *Drug costs:* *Taiho internal pricing database, as cited in (1)* *Utility:* *PRECONNECT phase 3b single group early access study (3) as cited in (1).*

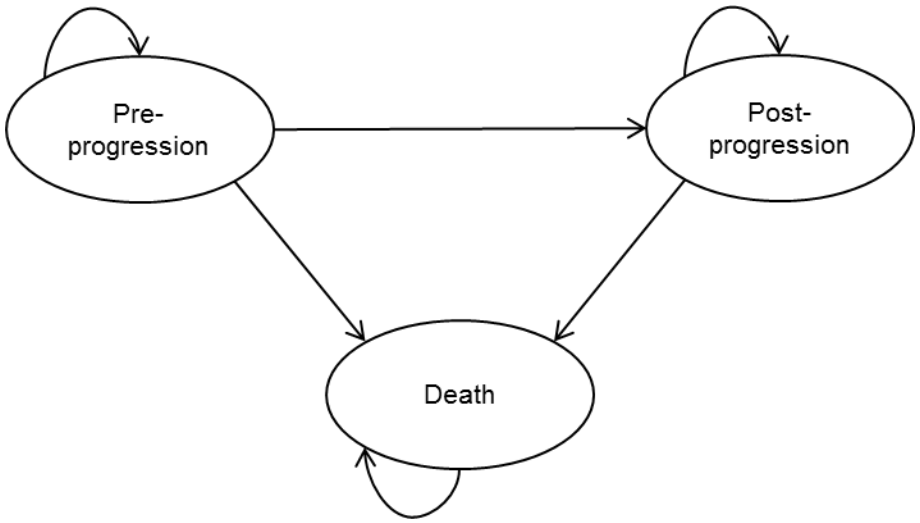

Figure 1: Model diagram, taken from pCODR submission report (1).

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison of BSC and 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 fluoropyrmidine-, oxaliplatin- and irinotecan-based chemotherapy, anti-VEGF biologic therapies, and anti-EGFR therapies, is appropriate. The CGP concluded that trifluridine-tipiracil offers a clinically meaningful benefit over BSC in terms of OS and PFS in patients with a good performance status.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians providing input on trifluridine-tipiracil for adult patients with chemorefractory mCRC suggest that there are no currently funded treatments for these patients. Eligibility criteria considered match clinical practice; specifically, patients with a preserved ECOG status of 0 or 1 who have failed prior therapies. A survival benefit was demonstrated for these patients. Safety and efficacy of trifluridine-tipiracil are thought to be positive, and trifluridine-tipiracil was preferred over regorafenib based on toxicity. Contraindications to treatment include poor performance status and inability to ingest oral therapies. Clinicians note that there are no subgroups of patients for whom trifluridine-tipiracil should not be used.

Registered clinicians considered efficacy, adverse events, and current treatment options as important factors. Efficacy, measured with OS and PFS are included as model inputs, and the survival benefit noted by clinicians is captured. Costs associated with adverse events are also captured. Current supportive treatment options, such as irinotecan, oxaliplatin, cetuximab, panitumumab, bevacizumab, and regorafenib – which were specifically mentioned by clinicians - are considered in the post-progression health state.

Summary of patient input relevant to the economic analysis
Patients considered diarrhea and fatigue resulting from the cancer the most important and difficult to control and noted that current treatments include side-effects such as chemo-induced fatigue, nausea, and diarrhea are the most difficult to tolerate. Patients desire therapies that will increase OS, PFS, or quality of life (QoL) during their lifetime even if OS is not increased.

In the submitted model, OS and PFS are model inputs. Adverse events in the submitted model are not associated with disutility. Consideration of QoL is limited in the submitted model. Utility – which reflects health-related QoL – is from the PRECONNECT study, which is a non-comparative observational study including only patients on trifluridine-tipiracil. In the model, it is assumed that utility on BSC is equivalent to trifluridine-tipiracil. The validity of this assumption is unknown. However, this assumption results in a conservative estimate of the cost-effectiveness of trifluridine-tipiracil unless BSC results in improved utility compared to trifluridine-tipiracil. Furthermore, there is no measure of spread (e.g. variance, standard error, etc.) associated with the post-progression health state. Uncertainty in utility or health-related QoL was noted to be a major limitation of the original submission, and this resubmission is limited by the same uncertainty as the previous submission.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG noted the following relevant economic factors important to consider if implementing a funding recommendation for trifluridine-tipiracil: BSC is available for all patients, cost of supportive therapy, and resources required to monitor and treat serious adverse events.

In the submitted model, it is assumed that BSC is available to all patients and is used as the comparator for trifluridine-tipiracil. Costs of supportive therapy and resources required to monitor and treat serious adverse events are not considered explicitly in the model. However, costs applied to adverse events were sourced from the Ontario Case Costing Initiative (OCCI) -- most frequently from 2015/2016 and inflated to 2019 CAD.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Estimates (deterministic).

Estimates (range/point)	Submitted	EGP Reanalysis, Lower Bound	EGP Reanalysis, Upper Bound
ΔE (LY)	0.22	0.20	0.20
Progression-free	0.15	0.13	0.13
Post-progression	0.07	0.07	0.07
ΔE (QALY)	0.15	0.14	0.14
Progression-free	0.11	0.10	0.10
Post-progression	0.04	0.04	0.04
ΔC ($)	$16,903	$16,879	$17,879
ICER estimate ($/QALY)	$115,507/QALY	$124,593/QALY	$131,972/QALY

The main assumptions and limitations with the submitted economic evaluation were:

- PRECONNECT QoL data are from an ongoing, phase 3b, single-group, early access study; this study was used for the utility associated with the pre-progression and post-progression health states. No measure of spread (e.g. variance, standard error, etc.) was available for the post-progression health state. In addition to incorporation of suggestions made by the EGP with the original submission, the submitter has also incorporated this utility data from PRECONNECT in the resubmission. Other model inputs rely heavily on clinical inputs also present in the original submission.
- In one-way sensitivity analysis, utility of the post-progression health states for trifluridine-tipiracil and BSC were the two variables that affected the ICER most.

- Although costs of adverse events were incorporated into the model, there was no disutility associated with the occurrence of adverse events. The magnitude of this limitation could not be quantified in EGP reanalysis.
- The application of bounded distributions for many parameters in probabilistic sensitivity analysis may result in systematic underestimation of the uncertainty in cost and QALY outcomes. For many parameters, the triangle distribution, which is bounded, was applied in probabilistic sensitivity analysis. This systematically reduces uncertainty in the estimated parameters. CADTH recommends that bounded distributions, such as the triangle distribution, are not used in probabilistic sensitivity analysis (4).
- In the model, incidence of adverse events, dosing and dose reductions, delay in treatment initiation, and post-progression costs are informed by RECOURSE data alone. The incidence of adverse events is lower in RECOURSE than in the pooled data, and survival is greater in the pooled data than RECOURSE alone. Given that pooling methods for RECOURSE data and the phase II trial (2) were not described, the EGP recommends that the most appropriate base-case analysis would use RECOURSE data alone for survival, which would mean the same data source is used for survival outcomes, incidence of adverse events, dosing and dose reductions, delay in treatment initiation, and post-progression costs.

1.4 Detailed Highlights of the EGP Reanalysis

In EGP reanalysis, the data source used to inform survival outcomes was adjusted to use RECOURSE data alone, life years were discounted, and an alternate calculation of the discount factor was implemented. In the submitted analysis, the discount factor was calculated with the following formula:

$$Outcome\ (1 - rate)^{time}$$

The correct formula to be used for discounting, which was applied by the EGP is (5):

$$\frac{outcome}{(1 + rate)^{time}}$$

In the submitted model, regardless of the year costs were measured in, the inflation rate of 1.3% was used. In EGP scenario reanalysis, the inflation rate was adjusted to 1.99% to reflect the inflation rate in 2018.

Overall, the ICER is likely between $124,593 and $131,972/QALY. The most influential change made in EGP reanalysis was to use RECOURSE data alone to inform modelled outcomes. Other changes made by the EGP had little effect on the ICER. Regardless of EGP reanalysis, the application of triangle distributions in probabilistic analysis likely results in underestimation of uncertainty.

The EGP made the following changes to the submitted economic model:

- Data sources informing OS and PFS: In the model, incidence of adverse events, dosing and dose reductions, delay in treatment initiation, and post-progression costs are informed by RECOURSE updated OS data; while OS and PFS are informed by a pooled analysis of data from the RECOURSE trial and a phase II RCT. In EGP reanalysis, RECOURSE data alone are used to inform survival outcomes in the model.
- Discounting rate application: Discount rate was calculated with the following formula:

$$Outcome\ (1 - rate)^{time}$$

The correct formula to be used for discounting, which was applied by the EGP is (5):

$$\frac{outcome}{(1+rate)^{time}}$$

- Discounting of life years: The discount rate of 1.5% was not applied to life years in the model – this was changed in EGP reanalysis.
- In the submitted model, regardless of the year costs were measured in, the inflation rate of 1.3% was used. In EGP scenario reanalysis, the inflation rate was adjusted to 1.99%.

Table 3. Detailed Description of Deterministic EGP Reanalysis.

One-way and multi-way sensitivity analyses					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Data source informing OS and PFS: updated RECOURSE trial data only	$16,877	0.135	0.20	$124,609/QALY	7.9%
Discount rate application	$16,904	0.146	0.22	$115,492/QALY	0%
Discounting of life years	$36,977	0.146	0.22	$115,507/QALY	--
EGP's Reanalysis for the Best-Case Estimate					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$16,903	0.146	0.22	$115,507/QALY	--
EGP Reanalysis					
EGP Reanalysis Lower Bound	$16,879	0.135	0.20	$124,593/QALY	7.9%
EGP Reanalysis Upper Bound	$17,879	0.135	0.20	$131,972/QALY	14.3%
EGP Scenario Reanalysis					
Inflation Rate: 1.99% (lower-bound)	$16,958	0.135	0.20	$125,175/QALY	8.4%
Inflation Rate: 1.99% (upper-bound)	$17,978	0.135	0.20	$132,708/QALY	14.9%

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis (BIA) include the number of patients treated with trifluridine-tipiracil and the cost of the drug. Increases in the number of patients treated with trifluridine-tipiracil and/or increases in cost of the drug result in increases to the predicted budget impact.

Key limitations of the BIA model include the lack of evidence to support treatment duration and the exclusion of secondary therapies. In the citation provided with the submission for mean time on treatment, patients in the trifluridine-tipiracil group received the study drug for a mean (±SD) of 12.7±12.0 weeks (6), rather than the 2.2 months in the submitted BIA. The EGP was unable to estimate additional costs for secondary therapies not included in the submitted BIA.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for trifluridine-tipiracil when compared to BSC is:

- The deterministic ICER is between $124,593/QALY and $131,972/QALY, depending on the medical resource use in the pre-progression state. Given that probabilistic sensitivity analysis used many bounded distributions, probabilistic sensitivity analysis is likely to systematically underestimate uncertainty. The EGP was unable to predict the magnitude of this underestimate.
- The extra cost of trifluridine-tipiracil is between $16,879 and $17,879, which also depends on the medical resource use in the pre-progression state. One-way sensitivity analysis by the submitter shows that the ICER is sensitive to changes in the utility associated with health states for both trifluridine-tipiracil and BSC.
- The extra clinical effect of trifluridine-tipiracil is between 0.14 and 0.15 QALY (ΔE), depending on the data source used to inform survival outcomes in the submitted model.
- The variable that affected the ICER the most in EGP reanalysis was the use of RECOURSE trial data only to inform outcomes. The submitter's best case ICER was $115,507/QALY. When the data source only was changed, the ICER increased to $124,609/QALY.

Overall conclusions of the submitted model:

- *Overall, the structure and execution of modelling is appropriate. In the model, incidence of adverse events, dosing and dose reductions, delay in treatment initiation, and post-progression costs are informed by RECOURSE data alone. The incidence of adverse events is lower in RECOURSE than in the pooled data, and survival is greater in the pooled data than RECOURSE alone. Given that pooling methods for RECOURSE data and the phase II trial (2) were not described, the EGP recommends that the most appropriate base-case analysis would use RECOURSE data alone for survival, which would mean the same data source is used for survival outcomes, incidence of adverse events, dosing and dose reductions, delay in treatment initiation, and post-progression costs.*
- *Other modifications by the EGP, such as correction of discounting, or adjustment of the inflation rate had little impact on the ICER.*
- *Major limitations to this model include a lack of disutility associated with adverse events, and the remaining uncertainty in the utility estimates in this resubmission. One major source of the remaining uncertainty is in the utility associated with health states. PRECONNECT is an observational study that lacks a comparator and adds little to the previous submission. There was no measure of utility for BSC – it was assumed that utility associated with BSC was equal to that of trifluridine-tipiracil. And for the post-progression health state, there was no measure of spread (e.g. variance, standard error, etc.) available.*
- *In one-way sensitivity analysis, utility of the post-progression health states for trifluridine-tipiracil and BSC were the two variables that affected the ICER most.*
- *Another limitation is the application of the triangle distribution in probabilistic sensitivity analysis. This distribution is bounded and may result in systematic underestimation of the uncertainty in the model outcomes.*
- *Results of EGP reanalysis from the original submission are similar to the results of EGP reanalysis from this resubmission (Table 4).*

Table 4. Discounted outcomes from original submission and re-submission to pCODR.

	Original Submission		Resubmission	
	Submitted Estimates	EGP Reanalysis	Submitted Estimates	EGP Reanalysis
Δ Cost Lower Bound	$16,688**	$18,141	$16,903	$16,879
Δ Cost Upper Bound		$19,088	$18,003	$17,879
Δ Effect Lower Bound	0.17**	0.15 QALY	0.15 QALY	0.14 QALY
Δ Effect Upper Bound		0.15 QALY	0.15 QALY	0.14 QALY
ICER Lower Bound	$96,971/QALY**	$123,849/QALY	$115,507/QALY	$125,175/QALY
ICER Upper Bound		$130,314/QALY	$123,024/QALY	$132,708/QALY

**Original submission did not include upper and lower bound scenarios.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Gastrointestinal (GI) Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of trifluridine-tipiracil for mCRC. A full assessment of the clinical evidence of trifluridine-tipiracil for mCRC is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR 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 Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no information redacted from this publicly available Guidance Report.

This Initial Economic Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Economic Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Economic Guidance Report will supersede this Initial Economic Guidance Report.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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