CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Trifluridine-tipiracil (Lonsurf) for metastatic Colorectal Cancer

July 6, 2018

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

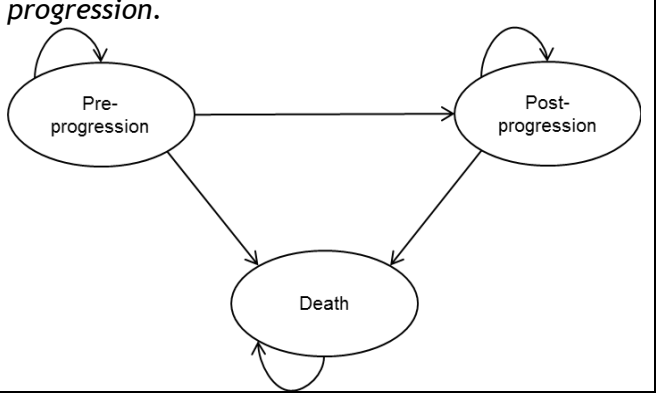
TABLE OF CONTENTS

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 for patients with metastatic colorectal cancer (mCRC) who have previously been treated with two or more therapies.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	*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	*CUA and CEA*
Type of Model	*Partitioned-survival*
Comparator	*Best Supportive Care (i.e., placebo, as defined in RECOURSE trial[1])*
Year of costs	*2017*
Time Horizon	*10-years*
Perspective	*Canadian public payer perspective*
Cost of trifluridine-tipiracil	Trifluridine-tipiracil costs $93.85 per 20 mg tablet dose (20 mg trifluridine/ 8.19 mg tipiracil) and $76.25 per 15 mg tablet dose (15 mg trifluridine/ 6.14 mg tipiracil). At the recommended dose of trifluridine-tipiracil of 35 mg/m^2 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 of Best Supportive Care	*Placebo did not bear any additional drug cost in the model (as defined in RECOURSE trial[1])*
Model Structure	*The model was comprised of 3 health states: pre-progression; post-progression; and death (see Figure below). Model health states were selected in accordance with the clinical pathway. The model structure is identical for patients treated with Trifluridine-Tipiracil or comparator therapies as the structure is based on disease progression.* 

Key Data Sources	*Overall survival and progression-free survival: Mayer et al. (2015) (Phase III RECOURSE trial)[1]; Yoshino et al. (2012) (Phase II trial)[2]* *Health state utilities: Grothey et al. (2013) (CORRECT trial)[3]* *Medical resource use and adverse event costs: Ontario Case Costing Initiative* *Drug Costs: Taiho Pharma Canada*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the published high-quality randomized controlled trials establish that Trifluridine-Tipiracil (LONSURF®) represents a tolerable treatment with a relevant clinical benefit over best supportive care (as mimicked by placebo) and, as such, provides a valuable addition to the armamentarium medical oncologists use to help patients combat their metastatic colorectal cancer.

- Relevant issues identified included:
    - *There are no validated biomarkers identified to limit the population of Canadians with metastatic colorectal cancer eligible for Trifluridine-Tipiracil*
    - *The strength of the evidence comes from the complementary nature of the RECOURSE and TERRA trials; however, both demonstrate statistical superiority in the important end-points and were considered generalizable to the Canadian population of patients with metastatic colorectal cancer.*

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered:

- The number of patients who would be eligible to receive would be small relative to the incident population. *This was considered in the survival analysis inputs for the economic evaluation.*

- Patients should not receive Trifluridine-Tipiracil if they have poor performance status (ECOG 2-4), impaired bone marrow, hepatic or renal functions, or have not progressed on previous chemotherapy as indicated. *This was considered in the economic evaluation as these criteria were applied to the RECOURSE trial, which was the source of the clinical data for the model*

Summary of patient input relevant to the economic analysis
Patients considered:

- With respect to the financial hardship or out of pocket expenses incurred by patients; 40% of respondents (20 out of 50 responses received) indicated they had to pay out of pocket for their medications/drugs. Caregivers were also described as being fraught with enormous financial, physical and psychological challenges when caring for their loved ones. *This was not considered in the economic evaluation as only the Canadian public payer perspective was examined.*

- From a patient's perspective, there are a number of symptoms associated with mCRC that impact quality of life, which include fatigue, bloody stools, diarrhea or constipation, anemia, abdominal cramping, and bowel obstruction. *The economic evaluation addressed this by including all adverse events documented from the RECOURSE trial.*

- Most patients cited fatigue, nausea, diarrhea, hair loss, vomiting, mouth sores, and hand and foot syndrome as being the most common side effects from these CRC treatments, with chemo-induced fatigue, nausea, and diarrhea identified as the most difficult to tolerate. *The economic evaluation addressed this by including all adverse events documented from the RECOURSE trial.*

- There were no survey respondents who rated their quality of life as low/severely impacted by trifluridine-tipiracil; all patients rated a 7 or greater on the 10-point scale (where 10 equates with high/normal living), demonstrating patients were able to achieve a high quality of life while on the therapy. *There was no direct information on patients' health-related quality of life (HRQL) following trifluridine-tipiracil, although it was considered in the economic evaluation by assuming that it was the same for patients treated with regorafenib monotherapy.*

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for LONSURF® which are relevant to the economic analysis:

Clinical factors:

- The value of trifluridine-tipiracil given the very modest overall survival, short progression-free survival, low objective response rates and occurrence of serious adverse events. *The economic evaluation addressed this through scenario analyses of different survival curves and inclusion of all adverse events documented from the CORRECT study.*

Economic factors:

- Cost of supportive therapy (e.g. anti-emetics, granulocyte colony-stimulating factor). *The economic evaluation does not explicitly address this. This was considered in costing of febrile neutropenia when patients receive G-CSF.*
- Resources required to monitor and treat serious adverse events. *The economic evaluation addressed this by including all adverse events documented from the RECOURSE trial.*

1.3 Submitted and EGP Reanalysis Estimates

The main cost drivers in the submitted economic analysis include the drug cost and the pre-progression monitoring or medical resource use costs.

The main drivers of the clinical outcomes (i.e., QALY and Life years) were the overall survival and progression-free survival estimates, the time horizon, and the utility estimates.

Overall the approach taken in the economic evaluation was reasonable and appropriate.

Table 2. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	0.27	0.22	0.22
Progression-free	0.15	0.15	0.15
Post-progression	0.12	0.07	0.07
ΔE (QALY)	0.17	0.15	0.15
Progression-free	0.10	0.11	0.11
Post-progression	0.07	0.04	0.04
ΔC ($)	$16,688	$18,141	$19,088
ICER estimate ($/QALY)	$96,971	$123,849	$130,314

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

- The Clinical Guidance Panel felt that the submitted 10-year time horizon does not align with clinical plausibility for mCRC patients. A 5-year time horizon was thought to be more clinically appropriate (i.e., life expectancy of mCRC patients post-diagnosis closer to 5-years). While the updated CADTH guideline recommends that "the time horizon of the analysis should be conceptually driven, based on the natural history of the condition or anticipated impact of the intervention (Page 31)", the guidelines also state that, in cases where that extrapolation is required to estimate long-term effect, external data sources, biology or clinical expert judgement may be used to justify the plausibility of extrapolation (Page 43).[2]
- Overall survival and progression-free survival were estimated in the model using a stratified log-logistic curve, fitted to the pooled trial data. However, when other curves were fitted there was substantial variability in the ICER. The Clinical Guidance Panel felt that the Kaplan-Meier data from the trials, extrapolated at the trial cut-off, would be more appropriate for the OS and PFS in the model.
- Health-related quality of life (HRQL) for patients treated with LONSURF® was assumed to be the same for patients treated with regorafenib monotherapy because no direct HRQL data was available for patients on LONSURF®.
- Occurrences of medical resource use were informed solely by expert input and were assumed to be greater for the BSC arm. Expert input was used due to the lack of published literature reporting robust estimates of the medical resource use of patients in this setting. With uncertainty in the accuracy of these estimates, the Clinical Guidance Panel was unclear about the validity of the assumption.
- For the uncertainty analyses, a triangular distribution (with +/- 20% upper and lower bounds) was tested for all the parameters derived from expert input (e.g., mean delay in treatment initiation, MRU costs, etc) and this may underestimate the variability in the reported results relative to other distributions.

1.4 Detailed Highlights of the EGP Reanalysis

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

- **Time horizon:** A 5-year time horizon was applied.
- **Medical Resource Use Costs**: These costs were made equal between treatment arms; using either the base case pre-progression MRU costs of BSC or LONSURF®.
- **OS and PFS curves**: Survival data was fitted using Kaplan-Meier curves (from pooled trial data) where the tail was extrapolated using an exponential curve at the trial cut-off.
- **Days of hospitalization pre-progression**: The days of hospitalization were decreased by 50% in both treatment arms.

Table 3. EGP Reanalysis Estimates One-way and multi-way sensitivity analyses					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Time horizon changed to 5-years	$16,552	0.162	0.25	$102,341	+$5,370
Pre-progression MRU costs are equal for both arms - using LONSURF® MRU costs ($1,918)	$18,032	0.172	0.27	$104,908	+$7,937
Pre-progression MRU costs are equal for both arms - using BSC MRU costs ($2,477)	$18,953	0.172	0.27	$110,268	+$13,297
OS and PFS data estimated using Kaplan-Meier curves with exponential tails	$16,835	0.147	0.22	$114,626	+$17,655
Days of hospitalizations pre-progression decreased by 50% for both LONSURF® and BSC arms	$16,336	0.172	0.27	$95,039	-$1,932
EGP's Reanalysis for the Best Case Estimate - Lower Bound					
Description of Reanalysis	ΔC	ΔE (QALY)	ΔE (LYs)	ICUR	Δ from baseline submitted ICER
Time horizon changed to 5-years	$16,552	0.162	0.25	$102,341	+$5,370
Pre-progression MRU costs are equal for both arms - using LONSURF® MRU costs ($1,918)	$18,032	0.172	0.27	$104,908	+$7,937
OS and PFS data estimated using Kaplan-Meier curves with exponential tails	$16,835	0.147	0.22	$114,626	+$17,655
Lower bound best case estimate - modification of all above parameters	$18,141	0.146	0.22	$123,849	+$26,878
EGP's Reanalysis for the Best Case Estimate - Upper Bound					
Description of Reanalysis	ΔC	ΔE (QALY)	ΔE (LYs)	ICUR	Δ from baseline submitted ICER
Time horizon changed to 5-years	$16,552	0.162	0.25	$102,341	+$5,370
Pre-progression MRU costs are equal for both arms - using BSC MRU costs ($2,477)	$18,953	0.172	0.27	$110,268	+13,297
OS and PFS data estimated using Kaplan-Meier curves with exponential tails	$16,835	0.147	0.22	$114,626	+$17,655
Upper bound best case estimate - modification of all above parameters	$19,088	0.15	0.22	$130,314	+$33,343

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include the drug dosing (and resultant drug costs) and the number of the eligible mCRC patients. The latter was examined in a sensitivity analysis and the 3-year budget impact results were moderately sensitive to variations in mCRC incidence.

The budget impact of introducing LONSURF® was also assessed from a Healthcare and a Societal perspective were also examined through scenario analyses. From these perspectives, the results were also most sensitive to variations in mCRC incidence and LONSURF® price.

Key limitations of the BIA model include the maximum treatment horizon of 1-year (i.e., as noted in the submitted BIA report this "may not be entirely the case for all treated patients in the real-world setting"), the assumption that secondary therapy only consisted of best supportive care (i.e., as noted in the submitted BIA report "other possible therapies patients may have received after relapsing on LONSURF® were not included in the model"), and the lack of available real world, Canadian-specific data for market share estimates. These parameters were not able to be modified and explored by the EGP.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for LONSURF® when compared to BSC is:

- Between $123,849/QALY and $130,314/QALY
- Within this range, the best estimate depends on the pre-progression MRU costs. If the costs in both treatment arms were equal to the submitter's estimate of the base case LONSURF® MRU costs, the best case estimate would be near the lower bound. Conversely, if the costs in both treatment arms were equal to the submitter's estimate of the base case BSC MRU costs, the best case estimate would be near the upper bound.
- The extra cost of LONSURF® is between $18,141 (lower bound) and $19,088 (upper bound). The main factors that influence ΔC include the drug cost and monitoring costs.
- The extra clinical effect of LONSURF® is approximately 0.15 QALYs for both the upper and lower bound of the best case estimate. The main factors that influence ΔE are the time horizon and the fit of the OS and PFS curves.

Overall conclusions of the submitted model:

- *The overall structure and conceptualization of the submitted partitioned survival model, including the breadth of incorporated parameters, appear to be sound for the specified patient population, decision-making context, and question of interest.*
- *There were no direct utility estimates available for the HRQL for patients treated with LONSURF® from the RECOURSE trial[1], Phase II trial[2], or the literature. Utility estimates were instead taken from the CORRECT study[3] for regorafenib monotherapy for previously treated mCRC. Regorafenib treatment appeared to lead to more toxicity than LONSURF®, suggesting that this assumption may conservatively estimate the* ΔE.
- *Other limitations and assumptions concerning the parameters values that could underestimate the submitter's base case ICER include the selection of a 10-year time horizon, the selection of the stratified log-logistic curve to estimate OS and PFS, and the difference in pre-progression MRU costs between arms informed solely by expert input.*
- *In addition, relative to other distributions, use of the triangular distribution to examine the variability of parameters informed by expert input may have systematically underestimated the level of uncertainty in the submitter's base case ICER.*
- *If you believe that a 10-year time horizon, that pre-progression MRU costs are greater for BSC, and that the fitted log-logistic curve for OS and PFS are appropriate, then the ICER is $96,971/QALY. However, with a more clinically appropriate time horizon of 5-years, pre-progression MRU costs being equal between arms, and using the Kaplan-Meier curves*

for both OS and PFS (where the tail is extrapolated using an exponential curve), the upper end of this estimate is $130,314/QALY.

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 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 (Lonsurf) for metastatic colorectal cancer. A full assessment of the clinical evidence of trifluridine-tipiracil (Lonsurf) for metastatic colorectal cancer 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 non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

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

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.

REFERENCES

1. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *The New England journal of medicine*. 2015;372(20):1909-1919.
2. Yoshino T, Mizunuma N, Yamazaki K, et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *The Lancet Oncology*. 2012;13(10):993-1001.
3. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet (London, England)*. 2013;381(9863):303-312.
4. Canadian Agency for Drugs and Technologies in Health. Guidelines for the Economic Evaluation of Health Technologies: Canada 4th Edition. 2017; https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf.
5. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal: Trifluridine with tipiracil hydrochloride for treating metastatic colorectal cancer after standard therapy [ID876] - Committee Papers. 2016; https://www.nice.org.uk/guidance/ta405/documents/committee-papers.
6. Scottish Medicine Consortium. Medicine advice: trifluridine/tipiracil (Lonsurf). 2017; https://www.scottishmedicines.org.uk/files/advice/trifluridine_tipiracil_Lonsurf_FINAL_Jan_2017_for_website.pdf.