



**pan-Canadian Oncology Drug Review
Registered Clinician Feedback on a pCODR
Expert Review Committee Initial
Recommendation**

**Trifluridine-Tipiracil (Lonsurf) metastatic
Colorectal Cancer**

July 6, 2018

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s): Trifluridine/Tipiracil
 Eligible Stakeholder Role in Review
 (Submitter and/or Manufacturer, Patient Advisory Group
 Organization Providing Feedback Cancer Care Ontario GI DAC

**The pCODR program may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

___ agrees ___ agrees in part X disagree

Please explain why the Stakeholder agrees, agrees in part or disagrees with the Initial Recommendation. If the Stakeholder agrees in part or disagrees with the Initial Recommendation, please provide specific text from the recommendation and rational. Please also highlight the applicable pERC deliberative quadrants for each point of disagreement. The points are to be numbered in order of significance.

b) Please provide editorial feedback on the Initial Recommendation to aid in clarity. Is the Initial Recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the Stakeholder would support this Initial Recommendation proceeding to Final pERC Recommendation

("early conversion"), which would occur two (2) Business Days after the end of the feedback deadline date.

<input type="checkbox"/> Support conversion to Final Recommendation. Recommendation does not require reconsideration by pERC.	X	Do not support conversion to Final Recommendation. Recommendation should be reconsidered by pERC.
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If the eligible stakeholder does not support conversion to a Final Recommendation, please provide feedback on any issues not adequately addressed in the Initial Recommendation based on any information provided by the Stakeholder in the submission or as additional information during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR program.

Additionally, if the eligible stakeholder supports early conversion to a Final Recommendation; however, the stakeholder has included substantive comments that requires further interpretation of the evidence, the criteria for early conversion will be deemed to have not been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information

The logo for CADTH (Canadian Agency for Drugs and Technologies in Health) is displayed in blue, stylized capital letters.The logo for pCODR (pan-Canadian Oncology Drug Review) is displayed in blue, stylized lowercase letters with a red square above the 'p'. To the right of the letters, there is a small, faint graphic of a grid.

pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

February 2018

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s): Trifluridine and Tipiracil (Lonsurf)
Eligible Stakeholder Role in Review
(Submitter and/or Manufacturer, GI Medical Oncologist
Organization Providing Feedback

**The pCODR program may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

- a) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

agrees agrees in part disagree

We, as medical oncologists who treat advanced colorectal cancer, are disheartened to learn that pCODR did not recommend trifluridine-tipiracil for funding despite the clear evidence of a survival benefit (HR 0.68, $p < 0.001$). For comparison, this drug has been approved by NICE in the UK, in the USA and widely in Europe. From the RECURSE study, there is an early and persistent separation of survival curves in contrast to other studies in this patient population. This improvement is by no means a trivial benefit in these patients who have no other treatment options. While the observed median survival difference in TERRA was less than that observed in RECURSE (despite statistical significance), we feel that this is less generalizable to Canadian practice as it was conducted among Asian countries and only 20% patients received prior anti-VEGF and anti-EGFR therapies (as the committee itself noted). The clinically meaningful median 2-month survival benefit seen in RECURSE is more generalizable for our Canadian population.

In our experience, many patients would eagerly opt for an additional 2 months (median) survival benefit with modest and generally controllable and tolerable toxicities. This is evidenced by the fact that over 300 patients across Canada have been treated with trifluridine-tipiracil since September 2017. Furthermore, this experience is clearly contrary to the committee's statement that it only partly aligns with patient values. In particular it seems unfair to deny patients with RAS mutated tumors a third-line treatment, given the impressive PFS HR in KRAS M+ patients (0.49). Note the PFS benefits are particularly strong in rectal cancer, females, those >65 years and in patients from North America. Lastly, the HR strongly favored trifluridine-tipiracil regardless of the number of prior treatment regimens, showing the consistency of its effectiveness. There are few drugs that are genuinely active in this disease and trifluridine-tipiracil should not so easily be cast aside. Please refer to section 3.2 for further information.

Please note this is a joint clinician feedback submission, all of whom contributed to the original joint clinician input submission:

██████████ Medical Oncologist
██████████ Medical Oncologist

	Medical Oncologist

- b) Please provide editorial feedback on the Initial Recommendation to aid in clarity. Is the Initial Recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the Stakeholder would support this Initial Recommendation proceeding to Final pERC Recommendation (“early conversion”), which would occur two (2) Business Days after the end of the feedback deadline date.

- | | |
|--|--|
| <input type="checkbox"/> Support conversion to Final Recommendation.
Recommendation does not require reconsideration by pERC. | <input checked="" type="checkbox"/> Do not support conversion to Final Recommendation.
Recommendation should be reconsidered by pERC. |
|--|--|

If the eligible stakeholder does not support conversion to a Final Recommendation, please provide feedback on any issues not adequately addressed in the Initial Recommendation based on any information provided by the Stakeholder in the submission or as additional information during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR program.

Additionally, if the eligible stakeholder supports early conversion to a Final Recommendation; however, the stakeholder has included substantive comments that requires further interpretation of the evidence, the criteria for early conversion will be deemed to have not been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
2.	SUMMARY OF pERC DELIBERATIONS	Para 2, line 18	The statement by pERC that “. .the benefits seen in clinical trials often do not translate into clinical practice;..” does not seem to be evidence-based. It seems to license the committee to ignore any data it wishes. One can readily make the contrary case that in fact

			clinical trials may underestimate the benefit by mandating cessation of the drug with clinically insignificant but technical disease progression, and that 'time to failure' is often now reported, and is usually longer than PFS, in those situations where the drug can be continued beyond progression (not the case in the RECOURSE trial).
3	Summary of pERC DELIBERATIONS	Para 5, line 3	<p>In an ideal world, patients with metastatic cancers should be cured of their disease without any toxicity from treatment. However, as the committee is well aware, we are in an imperfect world, and oncologists and patients have to balance potential benefits and toxicities constantly. We strongly believe that the benefits of trifluridine-tipiracil outweigh its toxicities. Canadian medical oncologists are exceptionally capable of choosing wisely, and this statement is supported by the fact that we did not advocate for the funding of regorafenib for this patient population due to its unfavorable toxicity profile.</p> <p>Since September 2017, many of us have treated patients with trifluridine-tipiracil. Our collective experience is that toxicities of this drug are familiar to us (e.g., the risk of neutropenia and the 4% reported rate of febrile neutropenia), and we are comfortable in managing these toxicities.</p>
5	EVIDENCE IN BRIEF	Para 5, line 7	<p>While we agree it is unfortunate that formal QoL analysis was not performed, the delay to ECOG PS 2 or greater, together with the QTWIST, makes a very compelling case that QoL is very likely to have been improved, or at least not diminished. We feel that the prolongation in time to ECOG PS 2 deterioration is reassuring. It seems unreasonable to reject this application given this probable subjective benefit, with the dire situation these patients are in.</p> <p>Since the publication of the committee's initial recommendation, we were spontaneously contacted by many medical oncologists to express their disappointments. Attached for your kind and thoughtful review are 3 Provincial Letters of Support for Trifluridine + Tipiracil/Lonsurf in Appendix A.</p> <p>We strongly urge the committee to re-consider its Initial Recommendation and make this drug available to the 9000+ patients who will die of advanced colorectal cancer in Canada each year.</p>

1 About Stakeholder Feedback

pCODR invites eligible stakeholders to provide feedback and comments on the Initial Recommendation made by the pCODR Expert Review Committee (pERC). (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, pERC makes an Initial Recommendation based on its review of the clinical benefit, patient values, economic evaluation and adoption feasibility for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The Initial Recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation. It should be noted that the Initial Recommendation may or may not change following a review of the feedback from stakeholders.

pERC welcomes comments and feedback from all eligible stakeholders with the expectation that even the most critical feedback be delivered respectfully and with civility.

A. Application of Early Conversion

The Stakeholder Feedback document poses two key questions:

1. Does the stakeholder agree, agree in part, or disagree with the Initial Recommendation?

All eligible stakeholders are requested to indicate whether they agree, agree in part or disagree with the Initial Recommendation, and to provide a rationale for their response.

Please note that if a stakeholder agrees, agrees in part or disagrees with the Initial Recommendation, the stakeholder can still support the recommendation proceeding to a Final Recommendation (i.e. early conversion).

2. Does the stakeholder support the recommendation proceeding to a Final Recommendation (“early conversion”)?

An efficient review process is one of pCODR’s key guiding principles. If all eligible stakeholders support the Initial Recommendation proceeding to a Final Recommendation and that the criteria for early conversion as set out in the *pCODR Procedures* are met, the Final Recommendation will be posted on the CADTH website two (2) Business Days after the end of the feedback deadline date. This is called an “early conversion” of an Initial Recommendation to a Final Recommendation.

For stakeholders who support early conversion, please note that if there are substantive comments on any of the key quadrants of the deliberative framework (e.g., differences in the interpretation of the evidence), the criteria for early conversion will be deemed to have **not** been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting. Please note that if any one of the eligible stakeholders does not support the Initial Recommendation proceeding to a Final pERC Recommendation, pERC will review all feedback and comments received at a subsequent pERC meeting and reconsider the Initial Recommendation.

B. Guidance on Scope of Feedback for Early Conversion

Information that is within scope of feedback for early conversion includes the identification of errors in the reporting or a lack of clarity in the information provided in the review documents.

Based on the feedback received, pERC will consider revising the recommendation document, as appropriate and to provide clarity.

If a lack of clarity is noted, please provide suggestions to improve the clarity of the information in the Initial Recommendation. If the feedback can be addressed editorially this will be done by the pCODR staff, in consultation with the pERC chair and pERC members, and may not require reconsideration at a subsequent pERC meeting.

The Final pERC Recommendation will be made available to the participating federal, provincial and territorial ministries of health and provincial cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

2 Instructions for Providing Feedback

- a) The following stakeholders are eligible to submit Feedback on the Initial Recommendation:
 - The Submitter making the pCODR Submission, or the Manufacturer of the drug under review;
 - Patient groups who have provided input on the drug submission;
 - Registered clinician(s) who have provided input on the drug submission; and
 - The Provincial Advisory Group (PAG)
- b) Feedback or comments must be based on the evidence that was considered by pERC in making the Initial Recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.
- c) The template for providing *Stakeholder Feedback on pERC Initial Recommendation* can be downloaded from the pCODR section of the CADTH website. (See www.cadth.ca/pcodr for a description of the pCODR process and supporting materials and templates.)
- d) At this time, the template must be completed in English. The Stakeholder should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply.
- e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed three pages, only the first three pages of feedback will be provided to the pERC for their consideration.
- f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the Initial Recommendation.
- g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR program.
- h) The comments must be submitted via a Microsoft Word (not PDF) document to pCODR by the posted deadline date.

- i) If you have any questions about the feedback process, please e-mail pcodrsubmissions@cadth.ca

Note: CADTH is committed to providing an open and transparent cancer drug review process and to the need to be accountable for its recommendations to patients and the public. Submitted feedback will be posted on the CADTH website (www.cadth.ca/pcodr). The submitted information in the feedback template will be made fully disclosable.