CADTH

pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Patient Advocacy Group)

Trifluridine-Tipiracil (Lonsurf) for Metastatic Colorectal Cancer Resubmission

August 29, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Trifluridine-tipiracil (Lonsurf)
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient Group, Clinical Group):	Patient Group
Organization Providing Feedback	Colorectal Cancer Canada

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

The Stakeholder disagrees with the pERC recommendation not to recommend the reimbursement of trifluridine-tipiracil (Lonsurf) for the treatment of adults with metastatic *colorectal* cancer who have been previously treated with, or are not considered candidates for, available therapies, including fluoropyrimidine-oxaliplatin, and irinotecan-based chemotherapies; anti-vascular endothelial growth factor (VEGF) agents, and anti-epidermal growth factor receptor (EGFR) agents.

1) The pERC recommendation not to reimburse is not aligned with the conclusions of the *pCODR Initial Clinical Guidance Report Section 1.3 Conclusions p 10 para. 3.* which concluded that:

There are a number patients with chemorefractory mCRC for whom Lonsurf fills an unmet clinical need. *pCODR ICGR (3 Summary of Patient Advocacy Group Input p 13 para. 4 and 3.2.1 Patient Expectations for and Experience to Date with* Trifluridine-tipiracil *(Lonsurf) p 15 para. 2)* states that patients value Lonsurf as a treatment option, the toxicities are acceptable, fewer, more manageable and afforded a better HRQoL than other therapies. Though modest, the impact on OS and PFS is meaningful to patients.

2) Trifluridine-tipiracil provides a net clinical benefit, aligns with patient values for improved HRQoL, and is generalizable to clinical care.

Evidence from all 3 RCTs demonstrated that Lonsurf is associated with small but statistically meaningful improvement in OS and PFS. All trials reported statistically significant improvement in OS and PFS in favor of Lonsurf (ICCR p34 para. 2, line 2 and para. 7 line 1; p 13 para. 6).

pCODR ICGR Conclusions (p 10 para. 3) states that there is a net clinical benefit associated with Lonsurf that outweighs the harm. This magnitude of clinical benefit is

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clinically meaningful and generalizable as it provides a treatment option for who have exhausted available options and for patients with dihydropyridine dehydrogenase (DPD) deficiency and those who have 5-fluorouracil-related angina. (pCODR ICCR p 29 paragraph 1; pCODR ICCR 5.3 Relevance to Clinical Practice p 30 para. 4 and 5).

2 months, though modest improvement in OS and PFS, is significantly meaningful to patients; especially since the toxicities are manageable and do not impact quality of life (*Ko Y.J. et al, What is a clinically meaningful survival benefit in refractory metastatic colorectal cancer? Current Oncology. 2019 Apr; 26(2): e255-e259 published online PMID: 31043834*)

The toxicity is considered low and acceptable to patients and clinicians (pCODR ICGR Conclusions p 10 para. 3), most patients stated that their quality of life, while on Trifluridine-tipiracil was better or no worse, and that they appreciated the ease of administrating a pill rather that having an infusion. *(CADTH Initial Clinical Guidance Report p18 para. 3 and p 24 para. 4)*

This is further supported by patient input (pCORD ICGR p 18 para. and p 24 para. 3) and by registered clinician input (pCORD ICGR Section 5.3 Relevance to Clinical Practice p 30).

3) *We argue that, while the additional evidence provided may not robustly demonstrate improvement in HROoL over BSC, the combination of all evidence and data collected to date indicates that* Trifluridine-tipiracil *does demonstrate evidence of improvement over BSC. It provides low toxicity, tolerable treatment options, valuable- though modest improvement in OS and PFS, ease of administration, and improvement or no deterioration of Quality of Life for a significant proportion of patients.*

Though elements of the robust evidence of the impact of Trifluridine-tipiracil on HRQol remains uncertain – due to research design (lack of baseline and comparators), all evidence presented (new and previous) aligns with patient values and contributes to reducing uncertainty. Data from trials and registered clinician and patient input suggests improvement or no deterioration and a modest improvement in OS and PFS. For a significant proportion of patients, it demonstrates an improvement over BSC in that it offers additional treatment options for those who have exhausted all others, and a treatment option that is more convenient, tolerable, and the side effects can be managed by clinicians. Further, results to date -from the observational studies suggest a definite trend toward improvement or no deterioration of HRQoL with Trifluridine-tipiracil.

While we fully appreciate and value adherence to the integrity of evidence and process, we request that the pERC take into account the quality of the RWE provided by CCC and others, and its alignment with the RCT and observational study findings - in presenting a more complete picture of the impact and value of Trifluridine-tipiracil. We believe that despite the limitations, the RWE and observational studies provide valuable information (trends toward association and biological plausibility) that expand on RCT evidence, *reduces uncertainty from the trials, contributes to understanding and translation,* and therefore adds sufficient weight and justification for a positive recommendation.

Noteworthy to mention: Trifluridine-tipiracil *has been recommended for reimbursement in Quebec.*

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b) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the provisional algorithm: N/A

☐ agrees ☐ agrees in part ☐ disagree

No provisional algorithm provided.

c) Please provide editorial feedback on the Initial Recommendation to aid in clarity.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
1	pERC Recommendation	Para. 1 & 2	pERC recommendation not to reimburse Trifluridine-tipiracil seems not to be in alignment with the conclusion in the Initial Clinical Guidance Report (ICGR) Section 1.3 Conclusions (pCODR July 5, 2019 p 10 para. 3).
3 48 ICGR	pERC Final Recommendation Summary of Deliberations Limitations/Sources of Bias	Para. 4 line 15 Para. 1	"Despite this alignment, pERC maintained that the inconsistent results between the trials …" please clarify what the inconsistent results were considering that: Overall, the measurement of HRQoL for patients enrolled in PRECONNECT is likely valid.
4	pERC Initial Recommendation	Para. 4	Though robust evidence on the impact of Trifluridine-tipiracil compared to placebo or BCS is lacking, there is robust evidence that for many patients Trifluridine-tipiracil represents a treatment option when all others are exhausted; results in modest but meaningful OS and PFS; is convenient (pill vs infusion): and is tolerable with manageable adverse effects. All of these constitute essential elements of HRQoL. Supported by the results of the RECOUSE, TERRA and J003- 10040030, and the patient and clinician input, the results currently available from the PRECONNECT and Tas-102 studies indicate a definite trend supporting positive impact and value of Trifluridine-tipiracil in terms of PFS, OS and HRQoL. Considering all elements, patient and clinician input, and the favorable trends that are apparent from the observational studies we believe that there is ample evidence to support that Trifluridine-tipiracil aligns with patient values for

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			improved HRQoL and that a positive pERC recommendation is warranted.

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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), including the provisional algorithm. (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, including the provisional algorithm 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 disagrees with the Initial Recommendation, and to provide a rational 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), including the provisional algorithm as part of the feasibility of adoption into the health system, 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. If the substantive comments relate specifically to the provisional algorithm, it will be shared with PAG for a reconsideration. 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. Please also note that substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final recommendation.

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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 done by the CADTH staff, in consultation with the pERC chair and pERC members, and may not require reconsideration at a subsequent pERC meeting. Similarly if the feedback relates specifically to the provisional algorithm and can be addressed editorially, CADTH staff will consult with the PAG chair and PAG members.

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) The following stakeholders are eligible to submit Feedback on the provisional algorithm:
   - 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 Board of Directors of the Canadian Provincial Cancer Agencies

c) 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.

d) 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.)

e) 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.

f) 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.

g) 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

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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, and should not contain any language that could be considered disrespectful, inflammatory or could be found to violate applicable defamation law.

h) 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.

i) The comments must be submitted via a Microsoft Word (not PDF) document to pCODR by the posted deadline date.

j) 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.

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