

CADTH

pCODR

PAN-CANADIAN
ONCOLOGY DRUG REVIEW

**pan-Canadian Oncology Drug Review
Submitter or Manufacturer 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): LONSURF® (trifluridine/tipiracil). For the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if RAS wild-type, anti-EGFR agents.

Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient Group, Clinical Group): Submitter/Manufacturer

Organization Providing Feedback: Taiho Pharma Canada, Inc.

**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

Taiho Pharma Canada, Inc. disagrees with the Initial Recommendation. LONSURF fulfills an important unmet medical need in the treatment of mCRC for patients that have exhausted all other standard treatment options (as noted on page 2 of the pCODR Initial Recommendation). LONSURF treatment provides significant and clinically meaningful improvement in OS (CGR page 9) with manageable tolerability (CGR pages 5,9) and LONSURF does not negatively impact QoL (CGR page 43). The clinically meaningful benefit of LONSURF was addressed by INESSS in their embargoed recommendation. Moreover, to ensure availability of LONSURF in Quebec and the rest of Canada, Taiho Pharma is prepared to reduce the cost of LONSURF in a transparent manner through the pCPA process.

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.

_____ Support conversion to Final Recommendation.

Recommendation does not require reconsideration by pERC.

✓

Do not support conversion to Final Recommendation.

Recommendation should be reconsidered by pERC.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
2	Summary of pERC Deliberations pERC deliberative framework: Overall Clinical Benefit and Alignment with Patient Values	Para 2 <i>“Following substantial discussion and despite conflicting opinions, for the majority of pERC members, it was not felt that the magnitude of absolute benefit was clinically meaningful.”</i>	Taiho feels that the clinical significance of the OS benefit of LONSURF from the clinical reviewer assessment (CGR page 9: “....offers a statistically significant and clinically meaningful prolongation of overall survival”) and from the patient group (CGR page 21 and similar: “any chance to prolong a patient’s life with such mild side effects should be allowed”) should be emphasized in pERC deliberations. Moreover, equal weight was given to the RECOURSE (2 months OS) and TERRA studies (0.3 months OS) despite a lack of generalizability of the TERRA study to the Canadian setting as outlined in more detail below. Taiho respectfully asks pERC to recognize the net clinical benefit of LONSURF outlined in the CGR and in Health Canada’s review. In addition, Taiho would also like the committee to notice the differences between the patient populations of the pivotal RECOURSE study (conducted in the United States, Europe, Australia, and Japan) versus TERRA (conducted in China, Thailand, and Korea and deemed a “post-marketing” study by Health Canada) wherein the population included in RECOURSE is more generalizable to the Canadian population. The differences in the patient population contribute to an imbalance in factors known to impact OS as follows: <ul style="list-style-type: none"> • Time since diagnosis of first metastasis, a well-established prognostic factor in mCRC, was not a stratification factor in TERRA. A greater proportion of patients in the placebo arm were ≥18 months from diagnosis of first metastasis vs. the LONSURF arm (61% vs. 51%, respectively), in contrast to RECOURSE where

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
			<p>the groups were matched (79% vs. 79%, respectively); this likely contributed to a longer than expected OS in the placebo arm of TERRA. Adjusting for potential prognostic variables (KRAS status, prior regimens, number of metastatic sites, and time since diagnosis of the first metastasis) resulted in a reduced chance for death in the LONSURF group (HR reduced from 0.79 to 0.72), which is more in line with the RECURSE results (Table 9).</p> <ul style="list-style-type: none"> • In TERRA, only a portion of patients received prior targeted therapies according to KRAS mutation status due to geographic variations in health insurance. Exposure to VEGF- and/or EGFR-targeted biologic therapy was only noted in 45% and 51% of patients in the LONSURF and placebo arms, respectively. In contrast, >99% of patients received targeted therapies according to KRAS mutation status in RECURSE. • A non-planned subgroup analysis in TERRA revealed significantly longer median OS in the LONSURF arm vs. placebo arm (8.0 months [95% CI, 6.8 to 9.3 months] vs 6.0 months [95% CI, 4.4 to 7.4 months] respectively) with a HR for death of 0.67 (95% CI, 0.48 to 0.92) when considering the population of patients who received targeted therapy before enrollment. • Overall post-study anticancer therapies received were imbalanced between treatment groups (37.6% vs 45.2% for LONSURF vs placebo respectively), as placebo patients who stopped study treatment earlier had more chances to receive anticancer therapies after the study (most commonly including investigational drug, LONSURF, and regorafenib), which may have impacted OS.
5	<p>Overall Clinical Benefit</p> <p>pERC deliberative framework: Overall Clinical Benefit</p>	<p>Key efficacy results:</p> <p><i>Modest overall survival and progression-free survival benefit</i></p>	<p>Taiho feels it is important for pERC to understand that while the magnitude of difference in median PFS is small, examination of PFS curves in both RECURSE and TERRA after the median indicate a much greater difference favouring LONSURF treatment. In all three submitted studies, a consistent PFS benefit was demonstrated by the HR (RECURSE: 0.48 [0.41-0.57], TERRA: 0.43 [0.34-0.54], J003-10040030: 0.41 [0.28-0.59]), which is more representative of the treatment effect size. Median PFS is not a representative</p>

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
			measure to assess the treatment performance with respect to delay of disease progression in a heavily pretreated population with such poor disease prognosis (short PFS). Scheduling bias confounds the median PFS estimates since the first assessment is not until about 2 months after initiation of treatment.
5	Overall Clinical Benefit pERC deliberative framework: Overall Clinical Benefit and Alignment with Patient Values	Patient-reported outcomes: <i>Not measured; therefore impact uncertain</i>	Taiho respectfully requests pERC to reassess the consistent impact of LONSURF on patient quality of life (as measured by maintenance or improvement of ECOG status, placebo-like rates of study discontinuation due to AEs, and QTWIST scores (CDR page 43) to the same degree as that acknowledged in the CGR (pages 9-10, 43) and the patient group (CGR, page 18). The surrogate measures presented to pCODR (quality-adjusted time without symptoms of disease or toxicity [QTWIST], mean time to ECOG PS of 2 or greater vs. placebo, and selected adverse events likely to affect QoL) indicate that LONSURF treatment does not result in deterioration of patient QoL versus placebo. LONSURF treated patients remained on study for longer periods of time than placebo patients, despite a higher likelihood of experiencing longer and more severe adverse events that may have impacted their QoL, suggesting that LONSURF treatment is well-tolerated. Both PS and specific QoL instruments have proven good predictors of outcome, especially in mCRC as supported by two recent papers (Mol et al., 2016; Kelly and Shahrokni 2016). In addition, the delay in deterioration in performance status makes the patients eligible for further treatment that can prolong survival.
5	Overall Clinical Benefit pERC deliberative framework: Overall Clinical Benefit and Alignment with Patient Values	Safety: <i>Moderate toxicities</i>	Taiho respectfully requests pERC to further reassess the tolerability and manageability of the AEs as provided by the clinical reviewer (CGR, page 9-10) and the patient group (CGR, page 18). Though LONSURF treated patients were more likely to experience grade 3/4 AEs that affect QoL, the onset of these AEs did not decrease treatment exposure. In fact, as noted in the pERC initial recommendation (page 5, second last paragraph) there were more AEs leading to treatment discontinuation in the placebo group than in the LONSURF group. Clearly patients are well able to tolerate the

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
			"toxicities" with LONSURF treatment.

REFERENCES

1. Mol L, Ottevanger PB, Koopman M, Punt CJA. The prognostic value of WHO performance status in relation to quality of life in advanced colorectal cancer patients. *Eur J Cancer* 2016;66:138-43.
2. Kelly CM, Shahrokni A. Moving beyond Karnofsky and ECOG performance status assessments with new technologies. *J Oncol*. 2016;2016:6186543

About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an “early conversion” of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

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

Instructions for Providing Feedback

- a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.
- 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 *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR 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 Submitter (or the Manufacturer of the drug under review, if not the Submitter) 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. Similarly, the Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

- 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 forwarded to the pERC.
- 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 Secretariat.
- h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.
- i) If you have any questions about the feedback process, please e-mail pcodrsubmissions@cadth.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.