pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

(Manufacturer)

Trifluridine-Tipiracil (Lonsurf) for Metastatic Colorectal Cancer Resubmission

August 29, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Lonsurf (trifluridine/tipiracil): metastatic colorectal cancer in previously treated patients
Eligible Stakeholder Role in Review:	Manufacturer
Organization Providing Feedback	Taiho Pharma 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

Taiho Pharma Canada (TAIHO) disagrees with the initial pERC recommendation for Lonsurf (trifluridine/tipiracil TAS-102) and does not support conversion to a Final Recommendation.

Real-World Data Supports the Overall Body of Evidence for Lonsurf

TAIHO is disappointed and perplexed with the decision of the pERC in the face of new Real-World Evidence (RWE) submitted and the robust clinical experience with Lonsurf across Canada in more than 1,500 treated patients (March 2018 - June 2019). TAIHO is confused why pCODR could accept the resubmission based on RWE demonstrating the health-related quality of life (HRQoL) of patients treated with Lonsurf utilizing validated measures and then recommend to not fund Lonsurf based on the design of the studies. The design of the studies was described in the Resubmission Eligibility Form and an abstract further describing the study design of PRECONNECT was provided in the pre-submission documents. Furthermore, TAIHO undertook the TAS102 vs BSC study only to facilitate the provision of Canadian HRQoL data to pCODR/pERC. It is exceedingly disappointing that the RWE study design and findings have been rejected and have not been taken into context of the overall body of evidence to support the net clinical benefit for Lonsurf.

pERC disregarded the CGP Conclusion, Clinician and Patient Input that Support Net Clinical Benefit and Patient Values

Moreover, TAIHO does not understand the rationale for the pERC decision to not deliberate on any of the other new efficacy, tolerability, and unmet medical need information provided. The pERC has also disregarded the experience and conclusions of the Clinical Guidance Panel (CGP). The totality of evidence also shows that there is a net clinical benefit for Lonsurf as expressed clearly by treating clinicians and patients.

Conflicting Review compared to INESSS/Improved Cost-Effectiveness and Budget Impact

In contrast to pERC's initial recommendation, Quebec's INESSS recognized the clinical benefit for this last-line treatment option for metastatic colorectal cancer (mCRC) patients and accepted the clinical meaningfulness of the submitted Lonsurf data. The pERC Recommendation is in stark contrast to the recommendations of INESSS and NICE in the UK. TAIHO has recently executed the Letter of Intent with the pCPA/Quebec to improve the budget impact and cost-effectiveness of

Lonsurf. Listing of Lonsurf in Quebec will be effective in August 2019. The offer is available to all pCODR jurisdictions to ensure that Lonsurf is affordable and cost-effective.

Deliberative Framework - RWE, Clinician and Patient Input supports a Positive Recommendation

A. Net Clinical Benefit

- TAIHO disagrees with the assessment of the HRQoL evidence submitted (pg. 4, para 1, 2, 3).
- TAIHO presented RWE to demonstrate the HRQoL benefit of Lonsurf in
  i. an international, post-marketing population (PRECONNECT N=464) and;
  ii. a prospective, comparative study (vs BSC) in a Canadian real-world setting.
- pCODR accepted the Lonsurf resubmission based on these 2 studies.
- TAIHO also presented new RWE of efficacy and tolerability and TAIHO believes that this information should have been reviewed. It is unclear why the new RWE on efficacy and tolerability was also not considered during the review.

- **PRECONNECT:** The PRECONNECT trial demonstrates that patients with pretreated mCRC can maintain their HRQoL while on Lonsurf treatment.
- TAIHO agrees with the CGP, that "*the PRECONNECT study used validated instruments to measure the HRQoL of patients treated with trifluridine/tipiracil and these results appear to align with the results of proxy outcomes for HRQoL assessed in RCTs* [pg10, para 1]". Furthermore, "*…the PRECONNECT study is unlikely to suffer from selection bias that limits generalizability. Overall, the measurement of HRQoL for patients enrolled in PRECONNECT is likely valid* [pg 48 para 1]."

- **"TAS-102 vs. BSC" in Canadian patients**: The Canadian RWE PRO study of Lonsurf vs BSC shows that refractory mCRC patients treated with Lonsurf have a better overall HRQoL than patients treated with BSC alone in a real-world post-marketing setting.
- This study was undertaken specifically for pERC to address the need for HRQoL data of Lonsurf. The study design was established with the advice of key treating physicians including a pERC member. While TAIHO acknowledges the cross-sectional design may not provide absolute certainty, this prospective RWE study is supportive of previously-submitted RCT evidence as well as the PRECONNECT trial. TAIHO urges that the totality of the evidence, with all evidence pointing to better overall HRQoL with Lonsurf compared to BSC, be considered.
- In fact, TAIHO believes that the provision of such a prospective RWE study to address pERC initial review concerns should be used as a model of further evidence generation for other pCODR submitted products. Compared to the RCT data, RWE, such as the TAS-102 vs. BSC study, is more generalizable to the treated Canadian population and better reflects the outcomes that can be achieved in Canadian patients.

- **Totality of Evidence:** TAIHO urges the pERC to reassess the totality of all direct and indirect HRQoL, efficacy and tolerability evidence submitted to support the net clinical benefit for Lonsurf. Specifically and namely:
  i. Consistent OS of 2.0 to 2.4 months shown in three trials (RECOURSE, the Japanese Study, and TERRA (patient matched); Mayer et al., 2015, Yoshino et al., 2012, Xu et al., 2018);
  ii. the favourable AE profile of Lonsurf from the RECOURSE trial (Mayer et al., 2015; Abrahao et al., 2018);
  iii. the delay to deterioration of ECOG in RECOURSE (Mayer et al., 2015; Van Cutsem et al., 2016 and 2017);
  iv. favourable QTWIST analysis (Tabernero et al., 2017);
  v. the PRECONNECT RWE study in 484 patients (Taieb et al., 2019a and 2019b);
  vi. the prospective Canadian RWE PRO study of TAS-102 vs BSC (Drug Intelligence Inc., 2019);

vii. HRQoL remained stable for most functional system scales in both arms of a recent TAS-102 vs BSC RCT gastric trial (Alsina, 2019)

- TAIHO also requests that pERC reconsider the totality of all evidence and feedback from clinicians (Ko et al., 2019) and patients (Colorectal Cancer Canada survey) supporting the net clinical benefit and support for patient values that Lonsurf provides.
- TAIHO does not agree with the pERC recommendation and assessment of the Net Clinical Benefit. TAIHO supports the conclusions of the CGP of the original submission [June 21, 2018]
  "*…there is a net overall clinical benefit over best supportive care (as mimicked by placebo) and, as such, provides a valuable and novel addition to the armamentarium medical oncologists use to help patients combat their metastatic colorectal cancer*."
- *AND*, the most recent CGP [June 20, 2019]:
  "*Overall, the totality of the evidence suggests that for patients who have had previous treatment with or are intolerant to standard therapies for mCRC, including fluoropyrimidines, oxaliplatin and irinotecan along with, if appropriate, VEGF and EGFR inhibitors, and have maintained their performance status as 0 or 1, there is a net clinical benefit associated with trifluridine-tipiracil that outweighs the harm*."
- At a minimum, TAIHO requests that the pERC recommend conditional reimbursement pending the final results of both the PRECONNECT and the TAS-102 vs BSC trial.

B. Patient Values

- TAIHO agrees with pERC's conclusion that "*trifluridine-tipiracil aligned with patient values of a new treatment option that offers ease of oral administration, with moderate but manageable toxicities, and a potentially modest clinical effect compared with placebo plus BSC.*" [pg 1, bottom para]

- While pERC remains "*uncertain whether the new evidence aligns with patient values for improved HRQoL*" [pg 2, top], TAIHO is asserts that, based on patients' submitted experience described in the CGR on pages 15-16, the totality of HRQoL evidence provided for Lonsurf does align with the patients' values for improved HRQoL. Some of the patients' verbatim feedback about their direct experience with Lonsurf was described in the CGR:
  - "*….of the 13 patients [who access trifluridine-tipiracil for thir-, fourth, and fifth-line treatment of mCRC], 77% of respondents noted that compared to other drug therapies, trifluridine-tipiracil was less toxic and they experienced fewer side effects while on therapy*."
  - "*Additionally, 92% of patient respondents indicated that trifluridine-tipiracil was able to shrink/contain their mCRC and that fatigue and nausea were the most prevalent treatment-induced side effects, with fatigue as the most difficult to tolerate*."
  - "*CCC noted that trifluridine-tipiracil is an important treatment option with manageable side effects. Survey respondents rated trifluridine-tipiracil induced side-effects as "minimal", easily administered, and were able to achieve a high QoL while on therapy*."
  - "*CCC noted that 100% of the respondents reported that since trifluridine-tipiracil is an oral therapy it is easy to administer and 75% of patient respondents rated their QoL as high while taking trifluridine-tipiraci." In addition, 90% of survey respondents rated their overall experience as "much better" when compared to other treatments accessed for their mCRC and 100% were in favour of the therapy being made available*."

- TAIHO also encourages the pERC to provide further weight to the statements on pages 15-16 of the CGR. "*Of the interviewed patients, four patients rated their QoL as 4/5, two patients rated 6/7, six patients rated 8/9 and three patients rated QoL as 10*."

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

☐ agrees ☐ agrees in part ☐ Disagree

Not applicable

c) 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 or provisional algorithm) clearly worded? Is the intent clear? Are the reasons clear?

Not applicable

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.

References

Abrahao A., Ko YJ., Berry S., Chan K. A Comparison of Regorafenib and TAS-102 for Metastatic Colorectal Cancer: A Systematic Review and Network Meta-analysis. Clinical Colorectal Cancer. 2018 Jun;17(2):113-120

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Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015 May 14;372(20):1909–19.

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Taieb J, Price T, Ciardiello F, Peeters M, Wyrwicz L, Bachet J-B, et al. Abstract #239971 - Health-related quality of life in the early access phase 3b study of trifluridine/tipiracil in pretreated metastatic colorectal cancer (mCRC): results from PRECONNECT study. 2019a Gastrointestinal Cancers Symposium; 2019 Jan 17; San Francisco, California.

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Van Cutsem E, Garcia-Carbonero R, Pastorino A, Zaniboni A, Falcone A, Amellal N, et al. RECOURSE trial: Performance status at discontinuation in patients receiving trifluridine/tipiracil (TAS-102). Ann Oncol [Internet]. 2016 Oct 1 [cited 2019 Jan 3];27(suppl_6). Available from: https://academic.oup.com/annonc/article/27/suppl_6/515P/2799310

Van Cutsem E, Falcone A, Garcia-Carbonero R, Komatsu Y, Pastorino A, Peeters M, et al. Proxies of quality of life in metastatic colorectal cancer: analyses in the RECOURSE trial. ESMO Open. 2017;2(5):e000261.

Xu J, Kim TW, Shen L, Sriuranpong V, Pan H, Xu R, et al. Results of a Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Trifluridine/Tipiracil (TAS-102) Monotherapy in Asian Patients With Previously Treated Metastatic Colorectal Cancer: The TERRA Study. J Clin Oncol. 2018 Feb 1;36(4):350–8.

Yoshino T, Mizunuma N, Yamazaki K, Nishina T, Komatsu Y, Baba H, et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol. 2012 Oct;13(10):993–1001.

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 submissions@pcodr.ca.

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