CADTH

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

Lorlatinib (Lorbrena) for Non-Small Cell Lung Cancer

Cancer Care Ontario Lung DAC

January 16, 2020

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Lorlatinib/ALK+ NSCLC
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Registered Clinician Feedback Cancer Care Ontario Lung 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 the pCODR program.*

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 CCO Lung DAC feels that there is a disappointing lack of faith in phase 2 data. The DAC would like to highlight the ORR and intracranial activity observed in the trial. The ALK mutational coverage and CNS penetration should not be disregarded. This is a very small patient population; however, there is an unmet need and lorlatinib adds an additional line of therapy after alectinib before chemotherapy.

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

☐ agrees ☐ agrees in part ☐ disagree

Please explain why the Stakeholder *agrees, agrees in part or disagrees with the provisional algorithm. Please note that comments should relate* ***only to the proposed place in therapy of the drug under review*** *in the provisional algorithm. If feedback includes New Information or about other therapies that are included in the provisional algorithm, the information will not be considered and will be redacted from the posted feedback. Substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final recommendation.*

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?

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.

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, including the provisional algorithm, 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

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.

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 Sponsor 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 Sponsor 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

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.

CADTH

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

Lorlatinib (Lorbrena) for Non-Small Cell Lung Cancer

Lung Cancer Canada

January 30, 2020

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Lorlatinib (Lobrena). As monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on: crizotinib and at least one other ALK inhibitor, or patients who have progressed on ceritinib or alectinib.
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer,	Clinical Group
Organization Providing Feedback	Lung Cancer Canada

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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 initial recommendation of the pCODR Expert Review Committee regarding funding of lorlatinib as a monotherapy for the treatment of adult patients with ALK +ve metastatic NSCLC was met with concern. We ask that pCODR to reconsider the initial negative funding recommendation.

1. pERC made a comment that phase II studies are considered hypothesis generating and should lead to phase III studies. In the oncogene addicted cancer era, we are increasingly able to accept phase II data because of the high efficacy rates seen, as evidenced by this study. pCODR recently accepted crizotinib for ROS1 lung cancer on the basis of a smaller patient number in a phase II study. Clinicians treating ALK+ lung cancer clearly see the benefits of the response rate and in particular the CNS disease control rate, and we do not believe pCODR should assess this drug differently.

2. We agree that chemotherapy is an alternate option, but there are many lung cancer patients who are not fit enough for chemotherapy, however can receive well

tolerated oral medications like lorlatinib. pERC in their initial response noted that lorlatinib side effects are generally manageable. Therefore by denying access to lorlatinib is in a very tangible way denying access to a drug that has all the benefits that pERC has acknowledged in their initial response. For those who are fit enough for chemotherapy, this can be given post lorlatinib.

3. It is also helpful to look at these results in context with ALK trials in pre-treated populations. Pemetrexed or docetaxel in the ALUR trial demonstrated an mPFS of 1.4 months and in ASCEND 5 it demonstrated an mPFS of 1.5 months. Taking a look at first line cisplatin/pemetrexed in ALK+, the median PFS is consistently about 8 months. It can therefore be argued that even if cisplatin/pemetrexed is equally effective in these heavily pretreated patients with prior TKIs, the mPFS and toxicity will be more favourable.

4. pERC also did not place enough weight to the CNS control offered by lorlatinib, which is a common and devastating consequence of ALK+ NSCLC. Depending on the series, between 20-30% of ALK+ NSCLC patients have brain metastases at initial diagnosis, and some series of pre-treated ALK NSCLC report CNS disease in up to 69-71% of cases (ALTA and ASCEND 2). High intracranial response rates, as outlined in the initial submission, offer a compelling case for approval.

5. The lack of clinical equipoise in terms of conducting a phase III clinical trial of lorlatinib versus another treatment option. We have multiple positive targeted therapy versus chemo trials in this setting. The very point that they make – i.e. that there are completed trials of alectinib and ceritinib versus chemotherapy, while feasible, is not the right thing to do in this situation. We would not use immunotherapy unless a last resort in these patients, so this would not be a reasonable control arm either. We would argue on scientific and ethical grounds that this suggestion "pERC considered that it is possible to conduct a comparative clinical trial in the requested reimbursement patient population" is not reasonable.

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

☐ agrees ☐ agrees in part ☒ disagree

pERC has noted that at the submitted price lorlatinib is not cost effective. However this does not take into account the higher cost of managing chemotherapy related side effects, and also that ultimately pERC does not set the price. pERC has the opportunity to approve an effective drug with the statement, as in previous cases, contingent on 'cost effectiveness is improved to an acceptable level. Lorlatinib is also a preferred option versus immunotherapy – which is expensive and generally ineffective for these patients.

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?

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☐ 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.

Based on the points raised above, we respectfully request that pCODR reconsider its recommendation.

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