CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

Alectinib (Alecensaro) for Non-Small Cell Lung Cancer - Resubmission

March 29, 2018

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Alecensaro™ (alectinib) as monotherapy for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced (non amenable to curative therapy) or metastatic non-small lung cancer (NSCLC) who have progressed or are intolerant to crizotinib until loss of clinical benefit.
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Submitter Hoffmann-La Roche Limited

**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 X agrees in part ____ 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.*

Hoffmann-La Roche (Roche) agrees in part with the initial pERC recommendation for ALK+ non-small cell lung cancer for patients who have failed crizotinib. Roche is in agreement with pERC's clinical assessment and recommendation on the net overall clinical benefit of Alecensaro, based on the statistically significant and meaningful improvement in progression-free survival (PFS) and no appreciable detriment in quality of life (QoL) compared with chemotherapy. In addition, Roche is in agreement regarding Alecensaro's favorable toxicity profile compared with chemotherapy and agreement that Alecensaro aligns with patient values of symptom control, disease control, and the need for an effective treatment option to delay progression and delay subsequent treatment with chemotherapy and radiation. Roche is agreement with pERC's conclusion that Alecensaro is likely to be cost-effective compared with chemotherapy.

Roche disagrees with the initial pERC recommendation that concludes the true ICER for Alecensaro compared to ceritinib is likely near the upper end of the EGP re-analysis. In particular, there is no compelling evidence that points to the extreme OS analysis as being the most likely (where the "true" ICER lies). Choosing a worst case scenario where the OS value is at the upper end of the 95% CI and chemotherapy and ceritinib at the lower end of the 95% CI is an extreme scenario and the likely estimate should be

weighted by their likelihood. This applicable pERC deliberative quadrant for this point disagreement is regarding Economic Evaluation.

Roche supports this initial recommendation proceeding to early conversion to support expediting public access for Alecensaro. However, Roche is highly concerned about several statements made regarding the real world data (RWD) from the Electronic Health Record (EHR) database which was retrospectively analysed to indirectly compare overall survival (OS) in the target population to derive an estimate of treatment effect. Several of the statements appear incorrect, leading to flawed conclusions. These statements directly contradict the literature provided to pCODR. Given these inconsistences, Roche highly suggests that these statements are either corrected or removed from the recommendation so as to align with the currently available literature and information provided to pCODR to ensure that this data is not misrepresented. Statements that are inaccurate and Roche would suggest are corrected or removed are highlighted within the table under section 3.2.

The CGR report states "the reported OS estimate is likely confounded since the effects of important prognostic baseline variables were not controlled for in the analysis" and "however, important limitations in the analysis were noted, including the issues related to relevancy (a substantial proportion of patients in the ceritinib RWD treatment group did not experience crizotinib failure". As 100% of patients in the ceritinib cohort did have prior treatment with crizotinib and the analysis provided did adjust for prognostic variables includes CNS metastases and prior lines of treatment, Roche believes that these statements may have unfairly influenced the EGP re-analysis of the ICER value of alectinib versus ceritinib resulting in a value that is unlikely to be where the "true" ICER lies. This applicable pERC deliberative quadrant for this point of disagreement is regarding Economic Evaluation.

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
Pg. 67 of the CGR Pg. 68 of the CGR	7.2.2 7.2.2	Results Paragraph 2 Critical Appraisal Bullet 1	The CGR states that only 57% of patients treated with ceritinib received first-line crizotinib. This statement is inconsistent with the poster by Davies et al.: Methods A ceritinib real-world cohort comprised patients from Flatiron Health's EHR database. The NP28763 and NP28761 inclusion and exclusion criteria were used to extract patients diagnosed with aNSCLC between January 1, 2011 and December 31, 2014, who received ceritinib treatment following CF. Follow-up data was provided until February

<table>
<tr><th>Page Number</th><th>Section Title</th><th>Paragraph, Line Number</th><th>Comments and Suggested Changes to Improve Clarity</th></tr>
<tr><td></td><td></td><td></td><td>28, 2016.

Table 1
<table>
<tr><th>Prior Lines, n (%)</th><th>Alectinib (n=183)</th><th>Ceritinib RWD (n=67)</th></tr>
<tr><td>1</td><td>52 (28)</td><td>38 (57)</td></tr>
<tr><td>2</td><td>66 (36)</td><td>20 (30)</td></tr>
<tr><td>≥ 3</td><td>65 (36)</td><td>9 (13)</td></tr>
<tr><td>Range</td><td>1-8</td><td>1-5</td></tr>
</table>
To confirm, all patients (100%) in the ceritinib RWD group received crizotinib and not 57% as stated.</td></tr>
<tr><td>Pg. 69 of the CGR</td><td>7.2.2</td><td>Critical Appraisal Bullet 3</td><td>The CGR states that the reported OS estimate is likely confounded since the effects of all important prognostic baseline variables (CNS metastases and previous chemotherapy) were not controlled for in the primary analysis. This statement is incorrect.

Per the manufacturer information provided to pCODR, baseline variable including prognostic baseline variables (CNS metastases and previous chemotherapy) were controlled for as outlined within the methods sections and supplement. It is an incorrect statement that prognostic factors were not included or controlled for.</td></tr>
</table>

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.

X	Support conversion to Final Recommendation.	____	Do not support conversion to Final Recommendation.
	Recommendation does not require reconsideration by pERC.		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
Pg. 12 of CGR	1.2.2	Paragraph 2 Under Bullet #2	"however, important limitations in the analysis were noted, including the issues related to relevancy (a substantial proportion of patients in the ceritinib RWD treatment group did not experience crizotinib failure)"
Pg. 12 of the CGR	1.2.2	Paragraph 2 Under Bullet #2	"and internal validity (important key prognostic variables were left out of the model used to balance treatment groups)"
Pg. 12 of the CGR	1.2.2	Paragraph 2 Under Bullet #2	"Therefore, the reported OS estimate is likely confounded since the effects of important prognostic baseline variables were not controlled for in the analysis"
Pg. 67. - 68 of the CGR	7.2.2	Appraisal Bullet #1	"Although it is implied in the manufacturer's ITC that all patients experienced crizotinib failure, just over half of the patients included in the ceritinib RWD treatment group (57%) received and discontinued treatment with crizotinib"
Pg. 67-68 of the CGR	7.2.2	Critical Appraisal, Bullet #1	"The difference between the two treatment groups in the proportion of patients with crizotinib failure (57% versus 100%) calls into question the relevancy of the analysis performed, and whether or not it aligns to the target population of the pCODR review"
Pg. 68 of the CGR	7.2.2	Critical Appraisal, Bullet #3	"Pre-weighting there were clear imbalances between the treatment groups in proportions of patients with CNS metastases and previous chemotherapy but these variables were not accounted for in the analysis"
Pg. 68 of the CGR	7.2.2	Critical Appraisal, Bullet #3	"A sensitivity analysis did explore the influence of CNS metastases on the result obtained but it did not provide an estimate that incorporated all important variables in the model"
Pg. 68 of the CGR	7.2.2	Summary Paragraph 1	"however, important limitations in the analysis were noted, including the issues related to relevancy (a substantial proportion of patients in the ceritinib RWD treatment group did not experience crizotinib failure)"

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
Pg. 68 of the CGR	7.2.2	Summary Paragraph 1	"and internal validity (important key prognostic variables were left out of the model used to balance treatment groups)"
Pg. 68 of the CGR	7.2.2	Summary Paragraph 1	"Therefore, the reported OS estimate is likely confounded since the effects of important prognostic baseline variables were not controlled for in the analysis"
Pg. 12 of the EGR	1.2	Bullet #2	"However, the reported estimate is likely confounded since the effects of important prognostic baseline variables were not controlled for in the analyses"

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 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), 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 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.

1 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.