pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Alectinib (Alecensaro) for Non-small Cell Lung Cancer

May 4, 2017

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Alecensaro™ (alectinib) as monotherapy for the treatment of patients with ALK-positive locally advanced or metastatic NSCLC who have progressed or are intolerant to crizotinib and who have CNS metastases
Role in Review (Submitter and/or Manufacturer):	Submitter
Organization Providing Feedback	Hoffmann-La Roche Limited

**pCODR 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 Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part _X_ disagree

Please explain why the Submitter (or the Manufacturer of the drug under review, if not the Submitter) *agrees, agrees in part or disagrees with the initial recommendation.*

Hoffmann-La Roche disagrees that the initial recommendation is in the best interest of patients, or the healthcare professionals who treat and manage these patients. Central nervous system (CNS) metastases are common in patients with advanced ALK-positive NSCLC, with over 60% experiencing metastases within the CNS upon progression on initial treatment[1,2]. They are associated with many complications[3], may significantly diminish neurocognitive function and QoL, and carry a poor prognosis[4]. Patient input described brain metastases as a huge additional burden for lung cancer patients, as it significantly diminishes their prognosis[5].

Although the availability of crizotinib has offered ALK-positive patients substantial clinical benefit in first-line, patients typically relapse within a year of treatment initiation[6], with over half progressing in the CNS[7]. Current management of CNS metastases in NSCLC centers on the use of surgery and radiation, particularly whole brain radiation therapy (WBRT). Avoidance of such techniques is increasingly desired by both clinicians and patients, as they can be associated with significant morbidity, including late neuro-toxicity[8]. The pERC agreed with the CGP that there are no effective systemic therapies available and that there is a significant need for effective treatments for ALK-positive NSCLC patients with CNS metastases. Moreover, clinicians providing feedback noted that the current therapeutic approach with either stereotactic radiosurgery (SRS) or WBRT carries significant limitations and risks to patients. The clinicians providing input indicated that alectinib would be used in patients who have progressed on, or are intolerant to, crizotinib and have CNS metastases.

If funded, clinicians indicated that alectinib would replace SRS and WBRT therapies, as well as chemotherapy in second line to avoid potential detrimental side effects and deterioration of quality of life associated with those options[5].

Two independent phase 2 pivotal studies (NP28761 and NP28673) have consistently demonstrated significant and clinically meaningful efficacy for alectinib. At the most updated analysis, the ORR was 52% (95% confidence interval [CI], 40% to 65%) in NP28761 and 51% (95% CI, 42% to 60%) in NP28673. In trial NP28761, median PFS and OS were 8.2 months and 22.7 months, respectively. In trial NP28673, median PFS and OS were 8.9 months and 26 months, respectively. This is in contrast to the 5.4 months median OS observed in patients who received subsequent systemic chemotherapy following progression on crizotinib[9]. Moreover, both pivotal studies demonstrated clinically meaningful CNS efficacy with alectinib therapy in the subset of patients with CNS lesions at baseline. The CNS ORR in patients with *measurable or non-measurable* metastases at baseline was 40% (95% CI, 27% to 55%) and 46% (95% CI, 36% to 58%), in NP28761 and NP28673, respectively. Furthermore, the CNS ORR in patients with *measurable* CNS metastases at baseline was 75% (95% CI, 48% to 93%) and 59% (95% CI, 41% to 75%), in NP28761 and NP28673, respectively[10,11]. The three-member pERC panel concluded that alectinib met priority review criteria for pCODR based on these unprecedented CNS response rates. NCCN and ESMO guidelines recommend alectinib for patients with ALK-positive NSCLC who have progressed or are intolerant to crizotinib based on the results of these two trials[12,13]. Additionally, registered clinicians providing input to pCODR confirmed this trial benefit by describing alectinib as efficacious and well-tolerated in clinical practice[5].

Alectinib demonstrated a manageable safety profile, with the majority of adverse events grade 1 or 2 severity in both NP28761 and NP28673. pERC concluded that alectinib aligned with patient values due to its manageable toxicity profile. This was confirmed through patient feedback, indicating that the safety profile of alectinib did not inhibit life, allowed them to experience milestones and the ability to believe in long-term benefits[5].

We do not agree with pERC that there was a "minimal clinically important difference in quality of life." Although there is no comparative data to chemotherapy or radiation therapy, pERC agreed that "chemotherapy…potential detrimental impact on quality of life…and radiotherapy is also associated with poor quality of life." In contrast, "three symptom scales (fatigue and pain) and two of six single-symptom items (dyspnea, appetite loss) showed improvements from baseline at week 6 that *exceeded the minimal clinically important difference (MCID)*. For the QLQ-LC13, three of 10 lung cancer symptoms (coughing, pain in chest, and pain in other parts) *showed improvements from baseline at week 6 that exceeded the MCID.*" In addition, although patients with CNS metastases may have shorter life expectancy and poorer QoL than patients who do not develop CNS metastases, this was a conclusion drawn generally during a time where treatments had little to no CNS activity. The NP28761 trial evaluated QoL outcomes, and over the course of treatment with alectinib, the mean changes from baseline in overall QoL status were similar between patients with and without CNS metastases[5].

For advanced ALK-positive NSCLC patients previously treated with crizotinib and who have CNS metastases, alectinib addresses the current unmet need for an efficacious and tolerable treatment that improved quality of life. Consistent results observed in the two independent pivotal alectinib studies NP28761 and NP28673, demonstrated significant and consistent systemic efficacy and meaningful CNS activity, a manageable safety profile, and sustained improvement in patient quality of life over time.

References:

1. Shaw AT, Gandhi L, Gadgeel S, Riely GJ, Cetnar J, West H, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. The Lancet Oncology. 2016;17(2):234-42.
2. Mok T. ASCEND-2: A single-arm, open-label, multicenter phase II study of ceritinib in adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) previously treated with chemotherapy and crizotinib (CRZ). 51st American Society of Clinical Oncology Annual Meeting; Chicago, IL2015.
3. Guerin A, Sasane M, Zhang J, Culver KW, Dea K, Nitulescu R, et al. Brain metastases in patients with ALK+ non-small cell lung cancer: clinical symptoms, treatment patterns and economic burden. Journal of medical economics. 2015;18(4):312-22.
4. Kamar FG, Posner JB. Brain metastases. Seminars in neurology. 2010;30(3):217-35.
5. Alecensaro (alectinib). pCODR Expert Review Committee (pERC) Initial Recommendation. 2017.
6. Solomon BJ, Mok T, Kim D-W, Wu Y-L, Nakagawa K, Mekhail T, et al. First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer. New England Journal of Medicine. 2014;371(23):2167-77.
7. Weickhardt AJ, Scheier B, Burke JM, Gan G, Lu X, Bunn PA, Jr., et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2012;7(12):1807-14.
8. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. The Lancet Oncology. 2009;10(11):1037-44.
9. Ou, S. H. et al. Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC. Ann Oncol. 2014;25: 415-422.
10. Barlesi, F., et al. "Updated efficacy and safety from the global phase II NP28673 study of alectinib in patients (pts) with previously treated ALK+ non-small-cell lung cancer (NSCLC)." Annals of Oncology 27.suppl 6 (2016): 1263P.
11. Camidge, D. Ross, et al. "MA07. 02 Updated Efficacy and Safety Data from the Phase 2 NP28761 Study of Alectinib in ALK-Positive Non-Small-Cell Lung Cancer." Journal of Thoracic Oncology 12.1 (2017): S378.
12. Novello, S., et al. "Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up." Annals of Oncology 27.suppl 5 (2016): v1-v27.
13. Ettinger, David S., et al. "NCCN guidelines insights: non–small cell lung cancer, version 4.2017." Journal of the National Comprehensive Cancer Network 14.3 (2017): 255-264.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

____ Support conversion to final recommendation.

Recommendation does not require reconsideration by pERC.

_X_ Do not support conversion to final recommendation.

Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. 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**
18	Clinical Guidance Report, Section 2.3 Evidence-based Considerations for a Funding Population	Paragraph 1, Lines 1-4	The report estimated 650 patients with advanced ALK-positive NSCLC in Canada in 2015. The submitter believes this to be an over estimate as it assumes that 100% of NSCLC patients are tested for the ALK rearrangement. An Ontario linked database study found that of patients diagnosed with advanced NSCLC only 70% have a consultation with a medical oncologist and are considered for ALK testing. (Sacher, A. et al. Cancer. 2015).
30	Clinical Guidance Report, Section 6.3.1 Literature Search Results	Paragraph 1	Pooled exploratory analyses of trial data were not of interest and thus were excluded from the systematic review. Consistent with CADTH's Guidelines for the Economic Evaluation of Health Technologies: Canada, 4th Edition (Draft, p. 44) Hoffmann La-Roche agrees that data from all available sources should be used to inform estimates of effectiveness. This includes pooled quantitative analyses to reflect the totality of the available evidence, and provide best estimates of outcomes and their uncertainties.
5	Economic Guidance Report, Section 1.3, Submitted and EGP Reanalysis Estimates	Last bullet	The EGP suggested that a main limitation of the submitted model was that the unit costs of pemetrexed and cisplatin were too high given the availability of their generic versions, thereby overestimating the chemotherapy costs. Reanalyses by the EGP reduced the unit costs of both pemetrexed and cisplatin by 25, 50 and 75%. The submitted model in fact used the only publicly available generic unit costs (list price) available from QuintilesIMS's Delta PA database.

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
8	Economic Guidance Report, Section 1.4, Detailed Highlights of the EGP Reanalysis	Table 4	A reanalyses by the EGP increased the current unit cost (list price) of alectinib by 25, 50 and 75%. Roche disagrees with this implausible scenario. PMPRB regulates prices and given current guidelines would not permit price increases of that magnitude. Taken together, multiple reanalyses using implausible scenarios unjustly discredits the manufacturer's best estimate of the cost-effectiveness.

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) 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 Secretariat.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
3	Summary of recommendations	Paragraph 2, Lines 7-9	The pERC states that efficacy data on ALK-positive NSCLC patients with CNS metastases were based on unplanned exploratory analyses. This is only the case for efficacy data on patients with measurable or non-measurable CNS metastases. As a result, Roche believes the statement should be revised to: "efficacy data on

Page Number	Section Title	Paragraph, Line Number	Additional Comments
			patients with measurable or non-measurable CNS metastases were based on unplanned exploratory analyses".
4	Summary of recommendations	Paragraph 3, Lines 5-6, 11	The pERC frequently cites considerable uncertainty in the manufacturer's best estimate of the ICER which Roche argues is manufactured using implausible extreme scenarios by the EGP. For instance, the EGP used the lower 95thCI of alectinib OS with the upper 95thCI of chemotherapy OS. The probability of the two 95%CI values or more extreme occurring together is 0.025^2=0.000625. The EGP cannot continue to misrepresent extreme scenarios as plausible, most likely base cases as evidence of large uncertainty to pERC.
4	Summary of recommendations	Paragraph 3, Line 17	Roche is concerned that through a flawed process the pERC is not receiving evidence-based recommendations with regard to the lifetime horizon. The concept of a time horizon for use in an economic model is an economic rather than a clinical one. Therefore, the time horizon recommendation should be based on the estimate of *maximum* survival, rather than, what can only be assumed as, the CGP's anecdotal estimate of *median* survival. For an outcome such as OS, in order to estimate the population mean value (the goal of an economic evaluation), one requires an estimate of the last surviving person. This follows the CADTH draft 4th guidelines which state that the time horizon should capture "*all* relevant differences in the future costs and outcomes" (Guideline 6.1, italics our own). Based on the data collected in the two independent pivotal studies submitted, it is clear that using a 3-year time horizon in the economic model for this patient population treated with alectinib is incorrect, as it falls far short of a lifetime horizon and the CADTH guidelines. Yet based on clinical opinion this was recommended to and accepted by pERC.

Page Number	Section Title	Paragraph, Line Number	Additional Comments
			Even in the absence of complete survival information (100% death observed), "a lack of data is not an appropriate justification for a shorter time horizon" (Guideline 6.3). Anecdotal evidence is a lower level of evidence compared to the prospective study data provided. Moreover, the evidence considered and the process used to synthesize the evidence in developing this clinical opinion was not transparent.
6	Evidence in Brief → Overall Clinical Benefit → Quality of Life: Minimal clinically important differences in quality of life	Sub-title	The sub-title states "Minimal clinically important differences in quality of life". However, in lines 4-8, the following is stated: "Three symptom scales (fatigue and pain) and two of six single-symptom items (dyspnea, appetite loss) showed improvements from baseline at week 6 that exceeded the minimal clinically important difference (MCID). For the QLQ-LC13, three of 10 lung cancer symptoms (coughing, pain in chest, and pain in other parts) showed improvements from baseline at week 6 that exceeded the MCID." As a result, Roche believes the sub-title should state: "Minimal clinically important differences in quality of life exceeded".

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.