



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

**Lorlatinib (Lorbrena) for Non-Small Cell Lung
Cancer**

January 30, 2020

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication: PrLORBRENA® (lorlatinib) 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 and Organization: Manufacturer, Pfizer Canada ULC

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

Pfizer Canada ULC (Pfizer) reviewed the initial negative recommendation and disagrees with the pERC. Pfizer stands strongly behind lorlatinib's net clinical benefit in a rare pre-treated population of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) patients, which has been consistently confirmed by data from multiple sources. Pfizer is also concerned by the pERC's contradictory interpretation of the clinical guidance panel (CGP) and economic guidance panel (EGP) reports and dismissal of clinician and patient input regarding clinical benefit, patient values and cost-effectiveness.

Pfizer disagrees with the pERC's assessment of the need and burden of illness, which emphasizes options with more manageable toxicities. Innocuity of ALK tyrosine kinase inhibitor [TKI], including lorlatinib, are understood, manageable and recognized as favorable compared to chemotherapy (CT). The CGP is unequivocal: "[...] ALK positive disease has a high level of CNS disease and progression, and control is likely to be significantly better with lorlatinib than CT [...]. The intracranial (IC) response rate (ORR) is particularly important, as progression of IC disease can be a devastating outcome – leading to significant cognitive decline, significant neurological debility, and other comorbidities prior to death. Central nervous system (CNS) progression particularly is a meaningful clinical endpoint in this population [...]. Although effective in many patients, there is still a clinical progression rate in the CNS and non-CNS for patients receiving alectinib, or similar non-crizotinib ALK inhibitors (i.e. brigatinib) that requires alternate therapy." Lorlatinib's profile is highly consistent with the need in this patient population.

The CGP acknowledged on multiple occasions lorlatinib's net clinical benefit (e.g.: "lorlatinib is a drug with [...] potential significant health benefit in patients with ALK positive carcinoma of the lung.", "In conclusion, there may be a net clinical benefit for lorlatinib in the treatment of patients who progressed on previous alectinib or ceritinib or crizotinib and at least one other ALK inhibitor.", "In comparison to best supportive care [BSC], it is concluded that lorlatinib does provide and is highly likely to provide an advantage and clinically meaningful benefit in patients with ALK positive cancer [...].", "It can be reasonably inferred from Trial 1001's phase II results of response rate and particularly intracranial response rate that there is likely to be a benefit for patients to have access to this drug at some point after 2nd-gen ALK inhibitor failure.", etc).

The potential next steps for stakeholders are development of additional comparative data (i.e. a randomized controlled trial [RCT]), which contradicts the CGP, and clinician and patient input. To our knowledge, there are no planned studies to compare lorlatinib (or any other ALK TKI) with CT after treatment with a 2nd-gen ALK TKI. Such results would also take several years to become available – time patients do not have. Trial 1001 is, and will remain, the best evidence available in this patient population. The CGP states: "it [a RCT] would not answer whether lorlatinib should be offered at all, and the CGP agrees that a placebo-controlled study would be unethical and non-feasible". "Even without this, it is reasonable to conclude that the drug provides some benefit in comparison to either single agent CT, or BSC [...]."

Overall, statements from the CGP, Canadian clinicians and patients, and multiple national and international treatment guidelines¹⁻⁴ suggest that the pERC may have misinterpreted or overlooked some of the evidence provided as part of the pCODR review:

1) Consistency of results and reasonable expectation of confirmed efficacy:

- a) As a targeted therapy, there is a plausible mechanism of action for lorlatinib. Eligible patient criteria are clearly defined by detection of ALK rearrangements; the median time to response (both intra- and extra-cranial) is rapid, at 1.4 months after lorlatinib initiation.^{5,6}
- a) RCTs of 2nd-gen ALK TKIs^{7,8} versus CT in patients with ALK-positive advanced NSCLC previously treated with crizotinib and CT have all confirmed results of the single-arm trials.^{9,10} ORR, IC ORR and median progression free survival (mPFS) with 2nd-gen ALK TKIs were similar to those of lorlatinib, which were observed in a more heavily pre-treated population.^{7-9,11-15}

Table 1. Naïve comparison of ORR and IC ORR of lorlatinib and 2nd-gen TKIs

Outcome	Lorlatinib (EXP3B-5) ^{5,6}	Alectinib ^{7,10,11}	Ceritinib ^{8,9}	Brigatinib ¹⁶
ORR / IC ORR	40% / 54%	38%-50% / 54%	39% / 35%	45%-54% / 52%
mPFS	7 months	8-10 months	5-7 months	9-13 months

- b) Real world evidence from various jurisdictions (France¹⁷, Austria¹⁸ and Turkey¹⁹) obtained from their respective early access programs have been provided as part of the review and have corroborated the results of the pivotal Trial 1001.
- c) Hashim et al.²⁰ recently evaluated the correlation between surrogate endpoints and overall survival (OS) in advanced NSCLC studies of 2nd- and further-line therapy without crossover or with balanced subsequent treatments. Interventions that are associated with significant treatment effect size of ≥ 41% ORR or a mPFS ≥ 4.15 months are associated with a significant OS benefit.

2) **Strength and breadth of available evidence:**

- a) Lorlatinib efficacy is clinically significant and consistent across treatment settings, including 2nd-line and 3rd-line, patients with or without identified secondary mutations and patients with or without brain metastases; lorlatinib is the only agent with significant in-vivo activity against ALK G1202R, the most common and challenging mutation after treatment with 2nd-gen ALK inhibitors.^{21,22}
- b) The ORR (38%-54%) and IC ORR (35%-54%) for lorlatinib after failure of 2nd-gen ALK TKIs contrasts with the poor responses seen with CT in the 2nd-line ALK-positive setting and beyond (ORR: 3%-7% and IC ORR: 0%-5%).^{7,8}
- c) Lorlatinib has a better mPFS point estimate (6.9 months) than CT (1.6 months) after failure of crizotinib and platinum-based doublet CT (supported by indirect treatment comparisons [ITC]: adjusted PFS HR of 0.35, 95% CI: 0.29-0.43).^{8,23}
- d) Median OS (20.4 months) with lorlatinib in cohorts EXP3B-5 is in the same range as the median OS for alectinib (22.7-26.0 months) and ceritinib (14.9 months) in patients with crizotinib-refractory ALK-positive NSCLC^{13-15,24} and is considerably higher than previously reported real-world OS associated with CT (7.6 months) in ALK-positive Canadian patients post-crizotinib.²⁵
- e) Lorlatinib ORR and PFS were assessed by independent central review⁶; reducing information bias in tumor progression assessment.
- f) A mPFS \geq 6 months scores “3” on the ESMO Magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS v1.1) for single-arm studies of non-curative anti-cancer therapies in “orphan diseases” and diseases with “high unmet need” when primary outcome is PFS or ORR.²⁶ This is the highest score for this category of trials.

The CGP, EGP and pERC also deliberated on the choice of comparator and assessment of relative efficacy. Pfizer submitted an ITC comparing lorlatinib to the historical cohorts based on the comparator arms of the ALUR (alectinib) and ASCEND-5 (ceritinib) trials, which evaluated the efficacy of 2nd-gen ALK TKIs in the post-crizotinib setting. Regarding this comparison, the CGP stated that “[...] a reasonable assumption would be that the standard of care arm would have similar or worse outcomes for disease control than the control arm of platinum doublet CT from earlier line trials with the same disease [...]”. We agree with this assessment.

Pfizer also acknowledges that national and international guidelines recommend the use of platinum doublet CT in the post ALK TKI setting. As a result – and for simplicity in a complex actual treatment sequence mosaic – Pfizer positioned this treatment choice as a valid comparator. However, guidelines are reflective of an ideal situation, whereas, as pointed out by the CGP, “in practice and in implementation, lorlatinib would likely be used prior to doublet platinum CT in some patients, after doublet platinum CT in others, and in patients who would not ever receive or accept doublet platinum CT – similar to the patients enrolled in the clinical trial”. This was also confirmed by clinician input. As a result, we reiterate that our ITC is reflective of actual clinical practice and expected outcomes in the Canadian clinical setting.

The pERC’s recommendation refers to substantial uncertainty on outcomes important to decision making such as PFS and OS. The determination of the *incremental* effectiveness of lorlatinib over CT in the absence of direct evidence is a recognized challenge. Consequently, we included various mechanisms as part of our submission to both quantify and manage any potential uncertainties. We were equally surprised and disappointed that none of these were mentioned in the CGP and EGP guidance reports, or the pERC recommendation:

1) **Quantification of value of information to inform decision making around areas of economic uncertainty:**

- a. Pfizer used best practices to quantify the value of parameter uncertainty, including OS and PFS, outcomes generally considered important for decision making (CADTH Guidelines chapter 13). The expected value of perfect information for the model, and for OS and PFS specifically were low, raising the question whether the pERC’s decision was based on *actual* or on *perceived* uncertainty.

2) **Request to the pERC to consider risk sharing agreements based on real world performance as part of their deliberations:**

- a. Pfizer proposed elaboration of a prospective real-world evidence project based on a successful previous experience that allowed patient to obtain treatment with PRXALKORI® (crizotinib) in Australia, [the details of which are publicly available](#).

Lorlatinib has been the most requested drug across all therapeutic areas through the Pfizer compassionate access program, with well over 2000 requests worldwide. In Canada, 46 Health Canada Special Access Program (SAP) requests were made between 2016 and May 2019. Since May 2019, Pfizer is aware of 64 clinicians requesting lorlatinib through Pfizer’s patient support program. Through this mechanism, a total of 77 ALK-positive NSCLC patients have received drug, 53 of which are currently on therapy. In addition, as of November 2019, lorlatinib is fully reimbursed in the United States, Japan, Germany, Netherlands, Ireland and Sweden. Case-by-case reimbursement is available in France, Spain, Portugal, United Kingdom, Austria, Denmark, Hungary, Slovakia and Czech Republic. These facts reinforce the substantial unmet need in this patient population, as well as the national and international medical community’s confidence in lorlatinib’s clinical profile.

Finally, an analysis of pCODR submissions from 2015 to 2019 identified 18 files based on non-comparative trials. Of these, 9 received positive recommendations, including the recent crizotinib for ROS1-positive NSCLC file. Based on historical reviews, we fail to understand the present decision on lorlatinib, as it shares many of the elements that justified the positive recommendations issued for similar anterior reviews.

As a result of the points mentioned above, we reiterate our request for public funding of lorlatinib for the treatment of adult patients with ALK-positive metastatic NSCLC who have progressed on: crizotinib and at least one other ALK inhibitor, or patients who have progressed on ceritinib or alectinib. We also reiterate our commitment to work collaboratively with jurisdictions in order to address any potential economic or clinical concerns through prospective data collection and risk sharing agreements based on real world performance of the product.

b) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the provisional algorithm: **Not applicable**.

c) Please provide editorial feedback on the Initial Recommendation to aid in clarity: **No comment**.

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. Do not support conversion to Final Recommendation.

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.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
p. 1, 3 & 7	pERC Rec. & Sum. of pERC deliber. & Key efficacy results	Par. 2, L.1 & Par. 2, L. 8 & Par. 5, L. 7	Pfizer disagrees with pERC’s questioning of the validity of ORR as a surrogate endpoint and other difficulties in interpreting outcomes important for decision making such as PFS, OS and QOL for the reasons stated in section 3.1 of this response. Pfizer’s position also aligns with the CGP’s belief “[...] that this situation [absence of proven surrogacy] is somewhat different with ALK positive disease, as it is clear that these patients have historically benefited from targeted agents in comparison to chemotherapy.”
p. 3 & 7	Sum. of pERC deliber. & Limitations	Par. 3, L. 4 & Par. 7 L. 3	Pfizer disagrees with the interpretation that the results of Trial 1001 are only hypothesis generating. The EXP 3B-5 cohorts had the robustness to justify lorlatinib’s conditional approval from Health Canada. The indication was established based on advice from three prominent Canadian experts in the treatment of NSCLC. These cohorts have the highest relevance for the broad patient profile that are being treated in practice. Further, highly specific TKIs blocking a major, single tumor driver have shown that a larger sample size only increased the precision of estimates without significantly changing the outcome in terms of (ORR). ^{7-9,11-15}
p. 4	Sum. of pERC deliber.	Par. 2, L. 2	Pfizer, the CGP, clinicians and patient groups disagree with the pERC about the feasibility and appropriateness of conducting a RCT in the lorlatinib target population. The need for traditional drug development stages (e.g. safety in phase 1, proof of concept in phase 2 and confirmation in phase 3 RCT) is rapidly fading for precision medicines, with emergence of new trial designs to optimize biomarker-drug co-development. Pfizer agrees with the CGP that “with targeted therapy of a known oncogenic mutation in lung cancer, response rates historically have correlated well with patient benefits, when studied in subsequent RCTs.”
p. 4	Sum. of pERC deliber.	Par. 3, L. 10 & Par. 4, L. 12	Pfizer acknowledges the EGP’s reanalysis and believes the best-case estimate to be rationally and sufficiently conservative to reassure the pERC on the cost-effectiveness estimate for lorlatinib. The EGP’s best-case estimate doubled the modeled mPFS for CT from 1.8 months to 3.7 months, reflecting recent results of platinum doublet CT post 2 nd -gen ALK TKI. ²⁷
p. 7	Patient-reported outcomes	Par. 6, L. 7	Pfizer does not agree with the pERC’s suggestion that quality of life (QoL) results are difficult to interpret. A wealth of literature (e.g. Labbé et al., crizotinib Trial 1007 and 1014, etc.) supports higher QoL for patient on TKIs versus CT. ²⁸⁻³⁰ Lorlatinib Trial 1001 is consistent with previous results showing, on average, rapid and sustained QoL improvements. ³¹ The CGP also states that “[...] delaying progression/improving control will improve morbidity and QoL”.
p. 8	Need and burden of illness	Par. 5, L.5	Pfizer disagrees with the pERC’s interpretation of the need and burden of illness. Toxicity profiles of ALK TKIs, including lorlatinib, are understood, manageable and recognized as favorable compared to CT. The CGP is unequivocal, as per statements included in section 3.1 of this response. Lorlatinib’s profile is highly consistent with the need in this patient population.
p. 8	Limitations	Par. 1, L. 4	Pfizer emphasizes that OS comparisons are highly challenging in ALK-positive NSCLC due to the high level of crossover in the available evidence, as pointed out multiple times by the CGP. We did, however, provide results of an exploratory ITC based on the results from Ou et al. ³² , that corroborated the proposed approach (PFS hazard ratio [HR] = OS HR), which was used – and accepted – in previous health technology assessments (HTA), notably the National Institute for Health and Care Excellence (NICE) in the United Kingdom (TA422). ³³
p. 8	Limitations	Par. 2, L. 1	Pfizer believes the critics of the assessment of incremental benefit of lorlatinib versus CT and BSC are overstated. Internal validity for comparison to CT was addressed in section 3.1 of this response. External validity for the submitted BSC meta-analysis is underestimated as survival for ALK-positive NSCLC treated with CT have been shown to be similar to the general NSCLC population. Further, the meta-analysis only included newly diagnosed patient, where survival is likely better than in the heavily pre-treated lorlatinib setting.

4 References (included in the submission or provided during review)

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5. Besse B, Solomon BJ, Felip E, et al. Lorlatinib in patients (Pts) with previously treated ALK+ advanced non-small cell lung cancer (NSCLC): Updated efficacy and safety. *Journal of Clinical Oncology*. 2018;36(15_suppl):9032-9032.
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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 be 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.