pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Lorlatinib (Lorbrena)

Submitted Reimbursement Request: 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.

Submitted By: Pfizer Canada ULC	**Manufactured By:** Pfizer Canada ULC
NOC Date: February 22, 2019	**Submission Date:** June 11, 2019
Initial Recommendation: December 5, 2019	**Final Recommendation:** January 30, 2020

Approximate per Patient Drug Costs, per Month (28 Days)	Cost per 25 mg tablet: $112.44 Cost per 100 mg tablet: $337.33 Cost per day: $337.33 Cost per 28-day cycle: $8,958.38

pERC RECOMMENDATION

☐ **Reimburse**

☐ **Reimburse with clinical criteria and/or conditions***

☒ **Do not reimburse**

* If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC does not recommend reimbursement 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.

The Committee made this Recommendation because it was not confident of the net clinical benefit of lorlatinib given the limitations in the available evidence from the non-randomized clinical trial that was based on an unplanned analysis and an estimation design with no specific hypothesis testing. While pERC was confident that lorlatinib produces a tumour response, the Committee was unable to determine how lorlatinib compares with other available treatments given the lack of robust comparative data on outcomes important to decision-making such as overall survival (OS), progression-free survival (PFS), and quality of life (QoL).

pERC noted that lorlatinib aligned with patient values in that it produces anti-tumour activity with manageable side effects, offers an additional treatment choice and ease of treatment.

pERC concluded that, at the submitted price, lorlatinib was not cost-effective compared with chemotherapy or best supportive care; there was considerable uncertainty in the cost-effectiveness estimates because of a lack of direct comparative data in the submitted economic evaluation.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Possibility of Resubmission to Support Reimbursement

pERC considered that it is possible to conduct a well-designed clinical trial in the requested reimbursement patient population. pERC noted that new clinical data comparing lorlatinib with currently available treatments in Canada for the 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 could form the basis of a resubmission to CADTH if efficacy data important to decision-making such as OS, PFS, and QoL, are available.

SUMMARY OF pERC DELIBERATIONS

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

It is estimated that there will be 29,300 new cases of lung cancer diagnosed and 21,000 deaths associated with lung cancer in 2019. pERC noted that NSCLC represents approximately 85% of all cases of lung cancer and approximately 2% to 5% of patients with NSCLC are expected to have the ALK mutation. pERC acknowledged that central nervous system (CNS) metastases are quite common in ALK-positive lung cancers, presenting in up to 30% of patients at diagnosis, and developing in more than 50% of patients initially treated with crizotinib at some point in their disease course. The standard first-line treatment for patients with ALK-positive advanced NSCLC is crizotinib or alectinib. For those who have disease progression, current treatment in the second-line includes ALK inhibitors (alectinib or ceritinib), and chemotherapy with platinum-based doublet therapy. Third-line options include single-drug chemotherapies or immunotherapies. pERC noted that Clinical Guidance Panel (CGP) also considered best supportive care as a treatment option for this patient population. pERC recognized that even though there are treatment options available for these patients, there is a continued need for effective treatment options with more manageable toxicity profiles.

pERC deliberated on one non-randomized, phase II, ongoing, multicentre, open-label, single-arm study (Trial 1001) that investigated the activity of single-drug lorlatinib in patients with ALK-positive, advanced NSCLC. pERC noted that the trial was composed of several cohorts, of which three cohorts: EXP 3B (one prior second generation ALK TKI ± chemotherapy), EXP 4 (two prior ALK TKIs ± chemotherapy), and EXP 5 (three prior ALK TKIs ± chemotherapy), were considered relevant to the reimbursement request. pERC noted that patients in Trial 1001 were a heavily pretreated patient population (having had previous radiotherapy, previous brain-directed radiotherapy, or more than one line of previous therapy). pERC considered that lorlatinib produced a tumour response. However, pERC noted that overall response rate (ORR) is an uncertain surrogate for survival in NSCLC. pERC also noted that secondary outcomes were reported in the trial including PFS, event-free survival (EFS), OS, and QoL, however, they noted that these are difficult to interpret without direct comparative data.

pERC also discussed in detail the limitations of Trial 1001, particularly the fact that the pooled analysis plan for EXP 3B-5 was not outlined a priori in the protocol and the statistical plan was based on an estimation design with no specific hypothesis testing (and so, the sample size for the cohorts of interest was not powered to detect statistical significance for the primary and secondary end points). As a result, the interpretation of the pooled results for EXP 3B-5 were only hypothesis generating.
Upon reconsideration, pERC discussed the feedback from the sponsor regarding the interpretation of the results of Trial 1001. The sponsor expressed that EXP 3B-5 cohorts had the robustness to justify lorlatinib's conditional approval from Health Canada. pERC noted that the role of regulatory agencies, such as Health Canada, is limited to assessing the safety and activity of a drug. pERC noted that its role as a health technology assessment body is to determine the net clinical benefit of a drug relative to comparators and with consideration of additional factors such as cost-effectiveness, patient perspectives, and clinical evidence; pERC's decision on the net clinical benefit of a drug is greatly influenced by the robustness of the clinical evidence provided. pERC acknowledged and agreed with the Method team's interpretation that the sample size of each cohort was based on an estimation design with no specific hypothesis testing, and that the sample size of EXP 3B, EXP 4, and EXP 5 was not powered to detect statistical significance for the primary and secondary end points. As a result, pERC was not confident of the net clinical benefit of lorlatinib given the limitations in the available evidence.

pERC also discussed the safety of lorlatinib and noted that Grade 3 and Grade 4 adverse events were reported in more than 40% of patients (EXP 3B-5). pERC also noted that the majority of Grade 3 and 4 events were biochemically related (e.g., hypercholesterolemia and hypertriglyceridemia). pERC discussed that there were neurocognitive effects due to the CNS penetration of lorlatinib and noted some concerns as these adverse events have not been commonly observed with other ALK inhibitors. Lastly, pERC acknowledged that there were no treatment-related deaths reported in the trial. Overall, pERC noted

lorlatinib's toxicity profile appeared manageable and was consistent with the safety profile of other ALK inhibitors. However, pERC noted that the non-comparative design of Trial 1001 makes interpreting the safety results challenging.

pERC discussed the input from two patient groups which indicated that patients value having treatment options that control disease, delay progression, prolong survival, have manageable side effects, maintain QoL, have ease of treatment, and avoid out-of-pocket costs to patients. pERC noted that patient and caregiver respondents with experience with lorlatinib indicated that side effects were manageable, although half of respondents reported neuropathy as well as cognitive and memory loss as a side effect of lorlatinib. Patient respondents also reported improved symptoms, stable disease, and increased ability to function with lorlatinib. pERC considered that lorlatinib is an oral treatment that could be administered in the patients' homes and that patients value additional treatment options relevant to their genotype. pERC also noted that Lung Canada Cancer (LCC) recognized that pERC would have concerns with accepting phase II data but asked that pERC issue a conditional approval, in order to enable collection of efficacy, safety and quality of life data while allowing patients who need this treatment to continue to live. pERC concluded that lorlatinib aligned with patient values in that it produces anti-tumour activity with manageable side effects, offers an additional treatment choice and ease of treatment. However, the Committee was unable to make conclusions on the benefit of lorlatinib compared with other treatment options.

In addition, pERC acknowledged the input from the LCC clinicians who noted consistency between phase II and phase III targeted therapy clinical trial results. pERC discussed that phase II trials are mainly hypothesis generating and their intent is to determine whether or not there is sufficient promise to proceed to a phase III confirmatory trial. pERC discussed feedback from the sponsor, patient group (LCC) and registered clinicians noting the consistency of outcomes between phase II and III clinical trials for targeted therapies and discussed whether it is reasonable to expect that the results of the phase II lorlatinib trial would translate into confirmed efficacy. pERC concluded that it is not guaranteed to expect that the results from the lorlatinib phase II trial (Trial 1001) would translate into confirmatory results. Moreover, although pERC has issued positive recommendations for other drugs with phase II data in some circumstances, pERC highlighted that as a principle, it considers every review based on its own merits and on the evidence presented for the drug under consideration. The Committee reiterated that while it was confident that lorlatinib produces a tumour response, given the limitations of the trial design and interpretation of the result, pERC was not confident of the net clinical benefit of lorlatinib

Moreover, pERC discussed the feasibility of conducting a phase III randomized controlled trial (RCT) in this setting and acknowledged that an RCT was feasible for alectinib, ceritinib, and crizotinib in ALK-positive patients. Ultimately, pERC considered that it is possible to conduct a comparative clinical trial in the requested reimbursement patient population. pERC noted that new clinical data comparing lorlatinib with currently available treatments in Canada for the 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 could form the basis of a resubmission to CADTH if comparative efficacy data important to decision-making such as OS, PFS, and QoL, are available. Upon reconsideration, pERC discussed the feedback from the sponsor and registered clinicians regarding the feasibility of conducting a phase III trial. The sponsor noted that the development of additional comparative data (i.e., an RCT), contradicts the CGP, and clinician and patient input. In their feedback, registered clinicians stated that while it may be feasible to conduct an RCT, it is not reasonable to conduct an RCT because of scientific and ethical reasons. pERC acknowledged that the CGP indicated that a phase III trial of lorlatinib versus doublet chemotherapy would answer a sequencing question (whether lorlatinib should ideally be given before doublet chemotherapy or following doublet chemotherapy), but it would not answer whether lorlatinib should be offered at all. pERC also noted that the CGP stated that a placebo-controlled study would be unethical and infeasible. pERC acknowledged that it may be challenging to conduct an RCT, however, pERC felt that this does not negate the fact that pooled results from Trial 1001 were based on an unplanned analysis with no specific hypothesis testing. pERC agreed that it is possible to conduct a well-designed clinical trial in the requested reimbursement patient population and that data from this trial could form the basis of a resubmission to CADTH if efficacy data important to decision-making such as OS, PFS, and QoL are available.

pERC deliberated on the cost-effectiveness of lorlatinib compared with chemotherapy (pemetrexed-platinum chemotherapy [cisplatin or carboplatin]) and compared with best supportive care based on the submitted economic evaluation and the reanalysis provided by the Economic Guidance Panel (EGP). pERC discussed the submitted unanchored match-adjusted indirect comparison which compared lorlatinib to

chemotherapy and also discussed the meta-analysis used to inform the comparison of lorlatinib to best supportive care. pERC agreed with the key limitations noted by the Methods team and CGP including the unanchored match-adjusted indirect comparison, and the fact that patients had previously received doublet platinum chemotherapy, whereas neither the current reimbursement request nor the multiple cohorts in Trial 1001 mandated prior platinum-based chemotherapy. The meta-analysis included patients with NSCLC, whereas the reimbursement request was specific to ALK-positive NSCLC patients. Overall, pERC concluded that the results should be interpreted with caution and that the magnitude of effect of lorlatinib compared with available therapies was uncertain.

pERC noted that the EGP's best-case estimate comparing lorlatinib to chemotherapy and best supportive care consisted of changing the hazard ratio for overall survival using a more plausible assumption for OS (for chemotherapy versus lorlatinib), choosing an appropriate statistical distribution to extrapolate PFS, accounting for treatment cost beyond progression, and assuming equal proportion of patients receiving active therapy after progression. Furthermore, pERC discussed whether the cost of pemetrexed and carboplatin were truly reflective of generic prices and highlighted that a higher cost of pemetrexed and carboplatin could bias the cost-effectiveness in favour of lorlatinib. pERC believed that it may be plausible that the EGP's best-case estimate for lorlatinib compared with chemotherapy and to best supportive care were underestimated and acknowledged that a 75% price reduction could offset the underestimation and the level of uncertainty in the cost-effectiveness estimates. In the end, pERC concluded that, at the submitted price, lorlatinib was not cost-effective compared with chemotherapy or best supportive care; and there was considerable uncertainty in the cost-effectiveness estimates because of a lack of direct comparative data and limitations in the treatment effect estimates from the available phase II clinical trial and the indirect treatment comparison analyses in the submitted economic evaluation.

Lastly, pERC considered the feasibility of implementing a positive recommendation for lorlatinib. Regarding currently reimbursed treatments, pERC noted reimbursement of ceritinib and alectinib in most jurisdictions and acknowledged that there are second-line and beyond treatment options for patients with ALK-positive NSCLC who have failed crizotinib and at least one other ALK inhibitor, or who have progressed on ceritinib or alectinib. In terms of the eligible population, pERC acknowledged that the reimbursement request did not include ALK-positive treatment-naive patients, ROS-1 positive patients with any previous treatment, and ALK-positive patients with disease progression following previous crizotinib only. With regard to the implementation factors, pERC discussed the cost of lorlatinib and the budget impact. As well, pERC discussed the oral administration of lorlatinib and thus, ease of treatment; however, pERC acknowledged that in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications, which potentially limits patient access. Additionally, pERC noted that the Provincial Advisory Group (PAG) is seeking guidance on sequencing of all oral targeted therapies (i.e., choice of first-line ALK inhibitors as well as other ALK targeted therapies), intravenous chemotherapies and immunotherapies for ALK-positive NSCLC.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the sponsor's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from two patient advocacy groups: Ontario Lung Association (OLA) and LCC
- input from nine registered clinicians: one joint submission on behalf of seven clinicians from LCC as well as one joint submission on behalf of two clinicians from Cancer Care Ontario Lung Drug Advisory Committee
- input from pCODR's PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- two patient advocacy groups: OLA and LCC
- nine registered clinicians: one joint submission on behalf of seven clinicians from LCC as well as one joint submission on behalf of two clinicians from Cancer Care Ontario's Lung Drug Advisory Committee
- the PAG
- the submitter: Pfizer Canada ULC

The pERC Initial Recommendation was to not recommend the reimbursement 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. Feedback on the pERC Initial Recommendation indicated that the sponsor, patient advocacy groups, and registered clinician groups disagreed with the Initial Recommendation. PAG agreed and supported an early conversion to Final Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of lorlatinib for the treatment of adult patients with 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.

Study included: non-randomized, phase II, ongoing, open-label, single-arm study (Trial 1001)

The pCODR systematic review included one non-randomized, phase II, ongoing, multicentre, open-label, single-arm study (Trial 1001). The aim of this study was to investigate the activity of single-drug lorlatinib in patients with ALK-positive, advanced NSCLC.

pERC noted that Trial 1001 enrolled 276 patients between September 15, 2015 and October 3, 2016 across 47 centres from 14 countries including Canada. Randomization was not performed; patients were treated with 100 mg of lorlatinib once daily. Patients were placed in one of the following cohorts:

- EXP 1 — treatment naive (n = 30)
- EXP 2 — prior crizotinib only (n = 27)
- EXP 3A — prior crizotinib plus chemotherapy (n = 32) or EXP 3B — one second generation ALK TKI ± chemotherapy (n = 28)
- EXP 4 — two prior ALK TKIs± chemotherapy (n = 65)
- EXP 5 — three prior ALK TKIs± chemotherapy (n = 46)
- ROS-1 positive patients were placed in the EXP 6 cohort — any line of treatment (n = 47).

Patient populations: EXP 3B to 5 considered relevant to reimbursement request

Key eligibility criteria included: adults (≥ 18 years) with histologically or cytologically confirmed diagnosis of metastatic NSCLC that carried either an ALK rearrangement or ROS-1 rearrangement and ECOG 0 to 2, among other criteria. pERC noted that three cohorts (n = 139): EXP 3B (one second generation ALK TKI ± chemotherapy [n = 28]), EXP 4 (two prior ALK TKIs ± chemotherapy [n = 65]), and EXP 5 (three prior ALK TKIs ± chemotherapy [n = 46]), were considered relevant to the reimbursement request.

Key efficacy results: Primary outcomes (ORR and intracranial ORR), uncertain surrogate for survival

The key efficacy outcomes deliberated on by pERC included ORR, intracranial ORR, PFS, EFS, and OS. pERC discussed the primary outcomes: ORR and intracranial ORR. At the data cut-off of March 15, 2017, the median duration of follow-up was 7.0 months (95% confidence interval [CI], 5.6 to 12.7) in EXP 3B and 7.2 months (95% CI, 6.9 to 7.2) in EXP 4-5, respectively. There were nine patients (33.3%, 95% CI, 16.5 to 54.0) and 43 patients (38.7%, 95% CI, 29.6 to 48.5) who had a confirmed ORR in EXP 3B and EXP4-5 respectively. One patient (3.7%) in EXP 3B and two patients (1.8%) in EXP 4-5 had a complete response (CR). Eight patients (29.6%) in EXP 3B and 41 patients (36.9%) in EXP 4-5 had a partial response (PR).

At the data cut-off of February 2, 2018, the median follow-up was 9.9 months (EXP 4-5). The ORR was slightly higher in EXP 3B, EXP 4, and EXP 5. pERC noted that the pooled ORR [EXP 3B-5] was 40.3%.

At the data cut-off of March 15, 2017 for intracranial ORRs, five patients (55.6%), (95% CI, 21.2 to 86.3) and 26 patients (53.1%), (95% CI, 38.3 to 67.5) had a confirmed ORR in EXP 3B and EXP 4 to 5 respectively. One patient (11.1%) in EXP 3B and 10 patients (20.4%) in EXP 4 to 5 had a CR. Four patients (44.4%) in EXP 3B and 16 patients (32.7%) in EXP 4 to 5 had a PR. At the data cut-off of February 2, 2018 for intracranial ORRs, the confirmed ORR was higher in EXP 3B and similar in EXP 4 to 5 compared with the results of the earlier data cut-off (March 15, 2017). pERC noted that the pooled intracranial ORR [EXP 3B-5] was 54.4%.

pERC noted that PFS, EFS, and OS were secondary outcomes. pERC discussed the median PFS was 5.5 months in EXP 3B and 6.9 months in EXP 4 to 5 as of the February 2, 2018 data cut-off date and the corresponding EFS at 12 months was 27.3% and 33.3% respectively, and at 18 months was 21.9% and 23.1% respectively. The pooled EFS (EXP 3B to 5) at 12 months and 18 months was 32.1% and 22.6%.

At the data cut-off of February 2, 2018, the median duration of follow-up for OS was approximately 20 months for EXP 3B-5. Among patients in EXP3B and EXP 4-5, the median OS reached 21.1 months (95% CI, 12.3 to not reached [NR]) and 19.2 months (95% CI: 15.4 to NR), respectively.

pERC noted the CGP's conclusions that 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. CGP acknowledged that their conclusion has some uncertainty, as it is based on one, single-arm, phase II trial, with an unplanned pre-specified statistical analysis (i.e., pooled analysis plan for EXP 3B-5 was not outlined a priori in the protocol, and the sample size of EXP 3B, EXP 4, and EXP 5 was not powered to detect statistical significance for the primary and secondary end points), using surrogate primary end points of ORR and intracranial ORR. CGP noted that the trial lacked a pre-specified determination of what would be considered a clinically significant response rate, and that there is a lack of robust data to conclude that a 40% response rate will result in a clinically meaningful benefit with traditional markers of patient benefit such as length of survival or QoL.

Patient-reported outcomes: Variability on the effect of lorlatinib on QoL, difficult to interpret

The EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires were administered at each cycle up to 24 cycles. Improvement in QoL was defined as a ≥10-point increase from baseline and worsening of QoL was defined as a ≥ 10-point decrease from baseline. Stable QoL was defined as a patient who neither improved nor worsened. pERC noted that at the data cut-off of March 15, 2017, there were 128 ALK-positive patients in the pooled EXP 3B-EXP 5 cohort out of 275 patients evaluable for patient-reported outcomes. pERC noted that 38.3% of patients reported improved global QoL, 38.3% of patients reported stable global QoL, and 23.4% of patients reported worsened global QoL. pERC found these QoL data were difficult to interpret given the non-comparative nature of the study and limitations noted by the Methods team.

Limitations: single-arm study, pooled analysis not outlined a priori, sample sizes not powered to detect difference, patient-reported outcomes were descriptive only

pERC discussed the key limitations highlighted by the Methods team: although this phase II trial was comprised of several cohorts (EXP 1 to 6), only EXP 3B to 5 was of interest for this review. A pooled analysis plan for EXP 3B to 5 was not outlined a priori in the protocol. In addition, the sample size of EXP 3B, EXP 4, and EXP 5 was not powered to detect statistical significance for the primary and secondary end points. Therefore, the interpretation of these pooled EXP3B-5 results is limited. The sponsor provided feedback on the pERC Initial Recommendation and disagreed with the interpretation that the results of Trial 1001 are only hypothesis generating. In their feedback, the sponsor stated that the EXP 3B-5 cohorts had the robustness to justify lorlatinib's conditional approval from Health Canada. In response to the sponsor's feedback, the Methods team confirmed that the trial publication stated that the sample size of each cohort was based on an estimation design with no specific hypothesis testing. The sponsor clarified at the checkpoint meeting that when the study first started, data were available only for the activity of other ALK TKIs after crizotinib, not for the other cohorts that the sponsor tested; thus, the study was based on a simple estimation design to evaluate the activity of lorlatinib in the different before-treatment settings. Therefore, the sample size of EXP 3B, EXP4 and EXP5 was not powered to detect statistical significance for the primary and secondary end points. Moreover, a single-arm clinical trial was conducted, thus, comparative effectiveness cannot be assessed. Methods for testing for multiplicity were not outlined in the protocol for primary and secondary end points. Results related to patient-reported outcomes were descriptive only. It is unclear if the characteristics of patients who did not complete the EORTC QLQ C30 at baseline and patients who did complete it might have been different. Lastly, approximately 20% of major protocol deviations were attributed to inclusion criteria which suggests a possible selection bias and implications on sample sizes of the cohorts.

In the absence of an RCT comparing lorlatinib with chemotherapy, the sponsor submitted an unanchored match-adjusted indirect comparison which compared lorlatinib to chemotherapy. As well, in the absence of an RCT comparing lorlatinib to best supportive care, the sponsor submitted a published meta-analysis which was used to inform the comparison of lorlatinib with best supportive care. The analyses were used to inform the cost-effectiveness analysis that compared lorlatinib with chemotherapy and to best supportive care. Although CGP highlighted that the unanchored match-adjusted indirect comparison had a reasonable framework, according to the Methods team, overall results should be interpreted with caution. Of note, no comparison to chemotherapy for the outcome of OS was conducted due to the lack of availability of data.

CGP considered the meta-analysis to have little external validity to ALK-positive lung cancer. The Methods team highlighted several limitations of the meta-analysis in the clinical guidance report; most notably as pointed out by the CGP, the meta-analysis included all NSCLC patients, whereas the population of interest in this pCODR review is ALK-positive patients. The Methods team also raised concerns about the reporting of the methodological quality of the included studies.

Safety: Biochemical adverse events, neurocognitive effects, but manageable

At the March 15, 2017 data cut-off, in the safety analysis set of 275 patients (cohort 1 to 6), patients received lorlatinib 100 mg orally once daily in 21-day cycles. Hypercholesterolemia was the most common treatment-related adverse event that occurred in 224 patients (81%) followed by hypertriglyceridemia among 166 patients (60%), edema in 119 patients (43%) and peripheral neuropathy among 82 patients (30%). The most commonly reported Grade 3 and Grade 4 treatment-related adverse event was hypercholesterolemia and hypertriglyceridemia, which occurred in 43 patients (16%) each. Serious treatment-related adverse events across all grades occurred in 19 (7%) of 275 patients. Cognitive effects were the most common serious treatment-related adverse event which occurred in two patients (0.7%). There were seven patients (3%) that discontinued therapy due to treatment-related adverse events. Reasons for permanent discontinuation from the study included affect lability, cognitive disorder, confusional state, hallucinations (auditory/visual), hydrocephalus, leukocytosis, pneumonitis, and tinnitus.

In the pooled EXP 3B-5 cohort (data cut-off February 2, 2018), any Grade 3 and Grade 4 adverse event was reported in 51 patients (36.7%) and nine patients (6.5%) respectively. Grade 3 and Grade 4 hypercholesterolemia occurred in 19 patients (13.7%) and one patient (0.7%) respectively. In addition, Grade 3 and Grade 4 hypertriglyceridemia was observed in 20 patients (14.4%) and five patients (3.6%) respectively.

Need and burden of illness: Continued need for effective treatment options with more manageable toxicity profiles

The standard first-line treatment for patients with ALK-positive advanced NSCLC is crizotinib or alectinib. For those who have disease progression, current treatment in the second-line include ALK inhibitors (alectinib or ceritinib), and chemotherapy with platinum-based doublet therapy. Third-line options include single-drug chemotherapies or immunotherapies. CGP also considered best supportive care as a treatment option for this patient population. pERC recognized that even though there are treatment options available for these patients, there is a continued need for effective treatment options with more manageable toxicity profiles.

Registered clinician input: LCC clinicians suggested that the positive results in the phase II trial prove lorlatinib's potential

Clinicians considered access to multiple lines of ALK directed therapy to be valuable for ALK-positive patients as there is an unmet need for these patients and clinicians felt that access to new therapies translated directly into improved OS outcomes. According to clinicians, the primary benefit of lorlatinib was that it acted as an additional line of therapy before chemotherapy for this indication. Clinicians acknowledged that lorlatinib was not a replacement for any current treatments. Clinicians stated that compared with lorlatinib, other treatment options (chemotherapy, immunotherapy) offered limited benefit and greater toxicity. Clinicians found the eligibility criteria for the phase II trial applicable to clinical practice. In treatment sequence, clinicians expressed that lorlatinib should follow use of a next generation ALK inhibitor. As well, clinicians did not find conclusive evidence to support the number of ALK inhibitors a patient should receive in their treatment course. Clinicians noted that companion testing is not required for lorlatinib.

Clinicians from LCC noted that past pCODR submissions and clinical experience have demonstrated remarkable consistency between phase II and phase III targeted therapy clinical trial results. Therefore, LCC clinicians suggested that the positive results in the phase II trial prove lorlatinib's potential. They cautioned that a delayed positive recommendation means unnecessary delays in patient access to the drug.

PATIENT-BASED VALUES

Values of patients with NSCLC: Treatment options, control disease, delay progression, prolong survival, manageable side effects, maintained QoL, ease of treatment, and avoidance of out-of-pocket costs

From a patient perspective, symptoms of lung cancer include: pain (very intense at times), a persistent cough, wheezing, coughing up blood, discomfort when swallowing, chest pain, hoarseness, loss of appetite and weight loss, shortness of breath, weakness and extreme fatigue and/or exhaustion. Respondents noted that the ability to work, travel, socialize, and participate in leisure and physical activities were affected as were relationships with family and friends, independence, emotional well-being, and their financial situation.

From a caregiver perspective, they experienced anxiety, worry, depression, and psychological distress. It was noted that with an oral form of treatment, and fewer and more manageable side effects, patients were independent, functional, and active; this allowed caregivers to continue working and be more productive.

Patients value having treatment options that control disease, delay progression, prolong survival, have manageable side effects, maintain QoL, offer ease of treatment, and avoid of out-of-pocket costs to patients.

Patient values on treatment: Respondents with experience with lorlatinib indicated manageable side effects

Patient and caregiver respondents with experience with lorlatinib indicated that side effects of lorlatinib were manageable. Half of these respondents reported neuropathy as well as cognitive and memory loss as a side effect experienced while on lorlatinib. Some patients required treatment to manage side effects, including counselling, and medication to manage depression and high cholesterol. Patient respondents also reported improved symptoms, stable disease, and increased ability to function with lorlatinib. Some

patients were able to return to work or resume regular physical activity and were able to spend more time with friends and family.

Outcomes that patients and their caregivers most value include: to stop or slow the progression of disease; reduce pain, fatigue, cough and shortness of breath; and improve appetite and energy. Patients emphasized a desire to have more energy and to be able to do more each day before the exhaustion sets in. Patients value QoL and want to experience improved independence and require less assistance from others. Lastly, patients would like there to be less or no cost burden associated with new treatments (i.e., avoid out-of-pocket costs).

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis

The EGP assessed the cost-effectiveness and cost-utility analysis comparing lorlatinib with pemetrexed-platinum chemotherapy (cisplatin or carboplatin). The sponsor also included an additional comparison of lorlatinib with best supportive care (defined as any concomitant medications, treatments or symptomatic therapy, excluding chemotherapy).

Basis of the economic model: Partitioned-survival model

The submitted model was a partitioned-survival model. Model effectiveness parameters were estimated from Trial 1001: EXP 3B to 5, a sponsor-conducted, unanchored, match-adjusted indirect comparison and a published meta-analysis. Drug costs were estimated from previous pCODR reviews and published Canadian studies. Utilities were estimated from Trial 1001 using EORTC QLQ-C30 and mapped to EQ-5D-3L. Resource utilization was estimated from published Canadian studies and expert opinions.

Drug Costs: Higher Cost Drug Compared with Chemotherapy

	Unit Cost $	Dosing	$ per 28-day Model Cycle
Lorlatinib	Cost per 25 mg tablet: $112.44 Cost per 100 mg tablet: $337.33	100 mg/day	$8,958.38
Chemotherapy			
Pemetrexed	Cost per 100 mg vial: $83.18	500 mg/m^2 q3w (871.32 mg for an average person)	$966.36
Cisplatin	Cost per 100 mg: $19.00	75 mg/m^2 q3w (130.70 mg for an average person)	$33.11
Carboplatin	Cost per 50 mg: $106.12	500 mg q3w	$981.49

q3w. = Each cycle is given once every three weeks.

pERC noted that the cost of lorlatinib was higher than the cost of chemotherapy. pERC discussed whether the costs of pemetrexed and carboplatin were truly reflective of generic prices and noted that a higher cost of pemetrexed and carboplatin could bias the cost-effectiveness in favour of lorlatinib.

Cost-effectiveness estimates: Not cost-effective

The EGP's best estimate of ΔC and ΔE for lorlatinib when compared with chemotherapy:

• The EGP best estimate would likely be: $237,125/quality-adjusted life-year (QALY). According to EGP, this estimate is the best estimate because it uses a more plausible assumption of OS advantage for lorlatinib compared with chemotherapy, conservative extrapolation for PFS and accounts for treatment cost beyond progression. However, the cost-effectiveness analysis is built on indirect treatment comparisons that have serious limitations and thus lead to substantial uncertainty in the comparative effect estimates.

• The incremental cost in the EGP best-case estimate was $172,479 (compared with $125,117 in the sponsor's base-case estimate). This higher incremental cost estimate was because of accounting for lorlatinib treatment continuation beyond progression.

• The incremental clinical effect in the EGP best-case estimate was 0.73 QALYs (compared with 0.94 QALYs in the sponsor's base-case estimate). This lower incremental QALY estimate in reanalysis was because of changing the assumption of OS benefit of lorlatinib compared with chemotherapy.

The EGP's best estimate of ΔC and ΔE for lorlatinib when compared with best supportive care:

• The EGP best estimate would likely be: $153,113/QALY. According to EGP, this estimate uses appropriate extrapolation for PFS and accounts for treatment cost beyond progression. However, this cost-effectiveness analysis is built on indirect evidence on OS estimates that has introduced substantial uncertainty in the comparative effect estimates.

• The incremental cost in the best-case estimate was $191,961 (compared with $142,709 in the sponsor's base-case estimate). This higher incremental cost estimate resulted from the accounting for lorlatinib treatment continued beyond progression.

• The incremental clinical effect in the best-case estimate was 1.25 QALYs (which is close to the 1.23 QALYs in the sponsor's base-case estimate).

According to the EGP, the overall structure of the economic model was appropriate. However, there is considerable uncertainty around the clinical benefit of lorlatinib in terms of OS and PFS in comparison with chemotherapy and best supportive care (BSC). No direct comparative evidence was available for survival estimates for comparators against lorlatinib. Trial 1001 conducted by the sponsor was a phase II single-arm trial; therefore, relative treatment effects were based on a match-adjusted indirect comparison for chemotherapy and based on a broad NSCLC population for BSC. Furthermore, no direct comparative evidence was available for utilities, and adverse events were not appropriately modelled in the economic evaluation. Varying the choice of the parametric model for PFS, assumptions regarding hazard ratio for OS and time on treatment had a significant impact on the economic results. Thus, the best-case EGP estimate represents more plausible estimates for cost-effectiveness analysis; however, given uncertainties in the economic analyses, the results should be interpreted with caution.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: in some jurisdictions oral medications are not funded in the same mechanism as intravenous cancer medications

The budget impact analysis (BIA) was conducted from a national public-payer perspective (excluding Quebec). According to the EGP, the overall approach of the BIA appeared to be reasonable and appropriate.

The factors that most influenced the BIA were the estimated number of patients with adenocarcinoma, the percentage of patients who are ALK-positive, the assumed proportion of eligible patients that would be prescribed lorlatinib if it was reimbursed, the cost of lorlatinib and its market share, and the cost of alternative treatments.

A key limitation of the BIA highlighted by the EGP was that the BIA did not include the costs of administering treatments; which is a conservative assumption given that the use of oral lorlatinib instead of an IV regimen will reduce the cost of administration. pERC noted that the EGP conducted additional sensitivity analyses and found that assuming a higher proportion of patients with NSCLC who had an adenocarcinoma increased the BIA estimate.

pERC considered the feasibility of implementing a positive recommendation for lorlatinib. pERC noted that there is reimbursement of ceritinib and alectinib in most jurisdictions and acknowledged that there are second-line and beyond treatment options for patients with ALK-positive NSCLC who have failed crizotinib and at least one other ALK inhibitor, or who have progressed on ceritinib or alectinib. In terms of the eligible population, pERC acknowledged that the reimbursement request did not include ALK-positive treatment-naive patients, ROS-1 positive patients with any previous treatment, and ALK-positive patients with disease progression following previous crizotinib only. With regard to the implementation factors, pERC discussed the oral administration of lorlatinib and thus, ease of treatment; however, pERC acknowledged that in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. Lastly, pERC noted that PAG is seeking guidance on sequencing of all oral targeted therapies (i.e., choice of first-line ALK inhibitors as well as other ALK targeted therapies), intravenous chemotherapies and immunotherapies for ALK-positive NSCLC.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by CADTH's pERC following the pERC Deliberative Framework. For the Initial Recommendation, pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Anil Abraham Joy who was excluded from voting due to a conflict of interest
- Daryl Bell who did not vote due to his role as a patient member alternate

Recommendations are made by CADTH's pERC following the pERC Deliberative Framework. For the final recommendation, pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Catherine Moltzan and Dr. Michael Crump who were not present for the meeting
- Dr. Maureen Trudeau who did not vote due to her role as the pERC chair
- Dr. Anil Abraham Joy who was excluded from voting due to a conflict of interest.

Avoidance of conflicts of interest

All members of the pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of lorlatinib for NSCLC, through their declarations, one member had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, this member was excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this Recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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