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 pCODR Expert Review Committee (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: Alectinib (Alecensaro)

Submitted Funding Request:
As monotherapy for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib and have central nervous system (CNS) metastases.

Submitted By: Hoffmann-La Roche Limited	**Manufactured By:** Hoffmann-La Roche Limited
NOC Date: September 29, 2016	**Submission Date:** October 3, 2016
Initial Recommendation: March 3, 2017	**Final Recommendation:** May 4, 2017

pERC RECOMMENDATION

pERC does not recommend reimbursement of alectinib (Alecensaro) as monotherapy for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib and have central nervous system (CNS) metastases.

The Committee made this recommendation as it was not confident of the net clinical benefit of alectinib because of limitations in the evidence from available clinical trials. While pERC was confident that alectinib produces a CNS tumour response, the Committee was unable to determine how alectinib compares with other treatments with respect to outcomes important to decision-making, including overall survival (OS), progression-free survival (PFS), and quality of life.

pERC noted that alectinib aligned with patient values as there is a need for more effective treatment options, other than chemotherapy and whole-brain radiation therapy (WBRT), that have tolerable side effects for patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib and have CNS metastases.

pERC concluded that, at the submitted price, alectinib was not cost-effective compared with chemotherapy (pemetrexed with or without cisplatin); however, there was considerable uncertainty in the cost-effectiveness estimates because of a lack of direct comparative effectiveness data in the submitted economic evaluation.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

No next steps were identified.

SUMMARY OF pERC DELIBERATIONS

In Canada, an estimated 28,400 new cases and 20,800 deaths occurred in 2016 from lung cancer, with a five-year survival rate of 15% to 18%. Treatment decisions for advanced or metastatic NSCLC are typically dependent on the presence or absence and type of driver mutation status of patients in the first-line setting. Approximately 4% of patients with NSCLC are expected to have the ALK mutation. Standard treatment for patients with ALK-mutation positive advanced NSCLC is crizotinib, which has recently been approved for funding in the front-line setting in Canada. 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 treated initially with crizotinib at some point in their disease course. The development of CNS metastases is associated with deterioration of quality of life and shortened survival. Developing CNS metastases may be the initial or only site of treatment failure in those receiving crizotinib, a finding potentially related to the poor CNS penetrance of this drug. Therefore, control of CNS disease is an important consideration in ALK-positive NSCLC. The current second-line treatment for patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib and have CNS metastases is chemotherapy accompanied with stereotactic radiation therapy (SRS) or WBRT. pERC noted that intolerance to crizotinib will be infrequent among this patient population. pERC also noted that chemotherapy is not favoured as a treatment option due to lack of evidence documenting effectiveness in patients with CNS metastases and the potential detrimental impacts on quality of life. Radiation therapy is also associated with poor quality of life and the potential risk of permanent cognitive damage. Therefore, pERC agreed with the input from registered clinicians that there is a significant need for alternative effective treatment options in this particular patient population.

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

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

pERC deliberated upon the results of two open-label, non-randomized, non-comparative studies evaluating alectinib in ALK-positive patients who progressed on or were intolerant to crizotinib with or without CNS metastases (NP28761 and NP28673). pERC was concerned about the strength of the evidence from the non-comparative trials because of the potential biases in non-comparative studies. Furthermore, the Committee noted that the primary analyses of overall objective response rates (ORRs) in both trials were not conducted in the intention-to-treat (ITT) population (i.e., all patients treated with at least one dose of alectinib), but rather in the response-evaluable (RE) population. Furthermore, efficacy data on the eligible population of ALK-positive NSCLC patients with measurable or non-measurable CNS metastases, a subgroup of patients in both trials, were based on unplanned exploratory analyses. pERC considered the fact that ORR, PFS, and OS were measured in both trials; however, given the trials' non-comparative designs, the ability to meaningfully interpret ORR, PFS, and OS is limited. pERC also considered that NP28761 evaluated patient-reported outcomes using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire and a lung cancer-specific questionnaire (QLQ-LC13). The Committee noted that patient compliance with completing questionnaires declined substantially over time. Although minimal clinically important differences were attained, suggesting improvement in symptoms and side effects, pERC agreed that the open-label design of the trial and the lack of a comparator group make interpreting the improvement in quality of life difficult. pERC also considered the safety of alectinib and noted that the majority of adverse events (AEs) experienced by patients were mild and minimal grade 3 to 4 AEs were reported. pERC noted that fatigue was a main AE reported among patients in both trials, and that fatigue is also a side effect experienced with brain radiation. Overall, the Committee concluded that toxicities were mild and side effects manageable.

pERC noted that there appears to be antitumour activity with alectinib and was confident that there was tumour response with alectinib; however, the magnitude of effect compared with available treatments is unknown, given the lack of comparative data on outcomes important to patients, such as OS, PFS, and quality of life. pERC has accepted evidence from non-comparative studies in previous submissions for reasons that are context (drug and disease)-specific; however, in this situation, pERC was not confident that the overall available evidence demonstrated a net overall clinical benefit of treatment with alectinib.

pERC noted that it was challenging to interpret the data and that limited conclusions could be drawn from these non-comparative trials. The Committee discussed the likelihood of conducting a higher-quality non-comparative trial to evaluate the efficacy of alectinib and whether it would be plausible to conduct a phase III randomized controlled trial (RCT) in this patient population. pERC noted that there are currently ongoing RCTs that are investigating targeted therapies in the broader pre-treated ALK-positive NSCLC patient population and that include a relatively large subgroup of patients with stable CNS metastases. The Committee noted that there is an ongoing randomized phase III trial comparing alectinib to docetaxel or pemetrexed in patients who have received two prior lines of systemic therapy including platinum-based chemotherapy and crizotinib. The estimated completion date of the trial is April 2019. Upon reconsideration of the pERC Initial Recommendation, pERC agreed that the evidence from available clinical trials was insufficient to conclude that there was a net clinical benefit with treatment with alectinib compared to other available treatments and thus was unable to recommend reimbursement of alectinib. pERC reiterated that ongoing randomized trials with alectinib may provide clarity on the effectiveness of alectinib compared with treatment options in this setting.

Upon reconsideration of the pERC Initial Recommendation, pERC extensively discussed feedback from the submitter, the patient advocacy group, and the registered clinicians regarding the clinical benefit of alectinib in patients with CNS metastases. pERC acknowledged that the observed antitumour activity in the two trials with alectinib was encouraging. However, pERC reiterated that the magnitude of effect compared with available treatments is unknown. pERC remained uncertain about whether alectinib improved outcomes important to decision-making, including OS, PFS, and quality of life.

The Committee deliberated upon input from one patient advocacy group concerning alectinib. It was noted that alectinib is an oral treatment, which would be easier for patients to take and would not require as much personal and caregiver time and resources as receiving treatment with chemotherapy and brain radiation. pERC noted that disease control, improvement in quality of life, and additional treatment options were important to patients. pERC agreed that alectinib offers another treatment option and has a favourable toxicity profile. pERC also acknowledged that patients expressed a significant need for alternative treatment options, as some patients prefer to avoid receiving treatment with chemotherapy and radiation therapy, because both have the potential for detrimental side effects and deterioration of quality of life. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from the patient advocacy group regarding the high unmet need in this particular patient population. The Committee considered patient feedback that alectinib is needed now and that patients cannot wait any longer. pERC acknowledged that there is a significant need for more effective treatment options for patients with NSCLC with progressive disease with CNS metastases. However, the Committee reiterated that the magnitude of effect with alectinib compared with other available treatments is unknown due to the limitations of the evidence from trials NP28761 and NP28673 including the non-comparative study design and unplanned exploratory analyses on the larger subgroup of patients with measurable or non-measurable CNS metastases. pERC also noted that another therapy for ALK-positive NSCLC, following progression on crizotinib, recently received a positive reimbursement recommendation from pERC. The Committee discussed the lack of comparative evidence on the efficacy and safety of alectinib against currently available standard treatment options, as well as the absence of long-term follow-up data to understand the impact of alectinib on outcomes important to patients. Overall, pERC concluded that alectinib aligned with patient values because it provides oral treatment options for patients with manageable toxicity.

Upon reconsideration of the pERC Initial Recommendation for alectinib, pERC discussed feedback from the patient advocacy group, which stated that two of the key elements presented in their input were not fully considered: time and quality of life filled with hope. The Committee appreciated the feedback from the patient advocacy group and understood that patients with ALK-positive NSCLC who have progressed on crizotinib and have CNS metastases are in significant need of more effective treatment options that allow them to live longer. pERC reiterated that it relies on the deliberative framework to guide decision-making. After considerable discussion, the Committee was not confident that the current evidence demonstrates that alectinib improves health-related quality of life or survival compared with other treatment options. Ultimately, pERC felt that they did not have sufficient evidence to confirm that alectinib addresses the key outcomes that patients said they value.

Also, upon reconsideration, pERC discussed feedback from the patient advocacy group that the pERC Initial Recommendation stands in stark contrast to the FDA and Health Canada approvals for alectinib on safety, strength of evidence, and the need for a randomized trial. pERC noted that the role of regulatory agencies, such as Health Canada, is limited to assessing the safety and activity of an agent. pERC also

stressed that its role as a health technology assessment body is to determine the net clinical benefit of an agent relative to comparators and with consideration of other factors, including cost-effectiveness, patient perspectives and clinical evidence, a decision that is greatly influenced by the robustness of the clinical evidence provided. pERC further noted that while the FDA gave regulatory approval for alectinib based on preliminary evidence of clinical activity in patients with metastatic ALK-positive NSCLC previously treated with crizotinib, the agency required confirmatory phase III trials to further establish the efficacy, safety, and long-term outcomes of alectinib. Furthermore, upon reconsideration, pERC discussed feedback from the submitter regarding alectinib being granted a pCODR priority review based on a preliminary review of evidence. pERC reiterated that a submission that meets priority review criteria must still undergo the full pCODR review process and that pERC's deliberation process for formulating recommendations is different from the priority review process; therefore, whether a submission receives a positive pERC reimbursement recommendation is independent of whether a submission is granted priority review.

pERC deliberated upon the cost-effectiveness of alectinib. Because of the considerable limitations in the available clinical information of alectinib from the non-randomized studies and the lack of direct comparative effectiveness estimates for PFS and OS, pERC concluded that it was difficult to draw meaningful conclusions on the cost-effectiveness of alectinib. pERC noted that the pCODR Economic Guidance Panel's (EGP's) best estimate of cost-effectiveness was a large range compared with the manufacturer's best estimate. The Committee agreed that the cost-effectiveness would likely be in the EGP's upper range of the best estimate. It also highlighted that the incremental cost-effectiveness ratio (ICER) was primarily driven by the cost of alectinib and that a substantial decrease in the cost of alectinib at the submitted price would be necessary to make alectinib cost-effective. The Committee agreed with the EGP's overall conclusion that given the lack of direct comparative estimates for PFS and OS, there is a high degree of uncertainty with respect to the estimates of extra clinical effect of alectinib and that this considerable uncertainty is not fully captured in the EGP's range of ICER estimates. Additional factors that most influence the incremental effectiveness include the time horizon, utility values, and the parametric models used to fit OS and PFS data. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the submitter that the choice of a three-year time horizon in the EGP's reanalysis estimates was inappropriate. Specifically, the submitter expressed concern that the choice was based on the pCODR Clinical Guidance Panel's (CGP's) anecdotal estimate of median survival and not on the estimate of maximum survival. pERC reconsidered and discussed the use of a 10-year time horizon in the submitter's base case and agreed with the CGP and EGP that, given the poor prognosis in this patient group and the unknown life expectancy of ALK-positive NSCLC patients with brain metastases receiving alectinib after progressing on crizotinib, it is reasonable to include a shorter time horizon (i.e., three or five years) in sensitivity analyses to explore uncertainty in the extrapolation of overall survival (OS). pERC acknowledged that the CGP are not aware of any studies that report a maximum OS of 10 years in ALK-positive patients with CNS metastases who have progressed on crizotinib, and pERC also considered that the 10-year time horizon used by the submitter was driven by extrapolation of results that are subject to high uncertainty. The Committee reiterated the EGP's response to the submitter's concern regarding the time horizon and agreed that, in the case that extrapolation is required to estimate long-term effect, clinical expert judgment can be used to justify the plausibility of extrapolation. Furthermore, upon reconsideration of the pERC Initial Recommendation, the Committee also considered the submitter's feedback that the EGP misrepresented extreme scenarios as plausible. The Committee noted that the submitted pharmacoeconomic model used OS and PFS data derived from two single-arm trials and one retrospective cohort study. pERC noted that selection bias and confounding due to the potential systematic differences between characteristics of participants in alectinib and standard chemotherapy groups is the key concern the EGP noted for the submitted pharmacoeconomic report. Without comparative survival data and appropriate statistical adjustment for imbalances in baseline characteristics between alectinib and standard chemotherapy groups, pERC agreed with the EGP that any combination of OS data from the non-comparative studies to inform the incremental effect of alectinib compared with chemotherapy is plausible. Overall, pERC concluded that considerable uncertainty in the ICER was largely as a result of the high uncertainty regarding the estimates of the comparative effectiveness. pERC also considered factors affecting the budget impact, including the number of eligible patients and variations in the costs of cisplatin, pemetrexed, and alectinib.

pERC also discussed the feasibility of implementing a funding recommendation for alectinib. pERC considered there to be a small number of patients with ALK-positive NSCLC with CNS metastases. pCODR's Provincial Advisory Group noted that crizotinib is currently funded in the first-line setting. The Provincial Advisory Group (PAG) noted that guidance on sequencing of available treatments following crizotinib would be needed. pERC agreed with the input from registered clinicians that alectinib would replace

chemotherapy and WBRT or SRS therapy in the second-line setting. However, pERC noted that there is considerable uncertainty regarding the net clinical benefit and cost-effectiveness of alectinib in patients with ALK-positive locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib and who have CNS metastases. pERC also noted (PAG's) concern about first-line indication creep, considering that patients presenting with CNS metastases upon diagnosis would request access to alectinib. The Committee noted that there is an ongoing phase III trial (ALEX trial) comparing alectinib to crizotinib as first-line treatment, but considered that trial to be out of scope of the current review. pERC concluded that an overview of all available therapies for NSCLC may be helpful at a future date to understand the comparative effectiveness. The Committee, however, noted that the current review is based on the evidence presented for alectinib and must be considered on its own merits.

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 manufacturer's economic model and budget impact analysis
- Guidance from pCODR clinical and economic guidance panels
- Input from one patient advocacy group (Lung Cancer Canada)
- Input from pCODR's Provincial Advisory Group (PAG)
- Input from registered clinicians.

Feedback on the pERC Initial Recommendation was also provided by:

- pCODR's Provincial Advisory Group
- One patient advocacy group (Lung Cancer Canada)
- Registered clinicians
- The submitter (Hoffman La Roche)

The pERC initial recommendation does not recommend reimbursement of alectinib (Alecensaro) as monotherapy for the treatment of patients with anaplastic lymphoma kinase (ALK)–positive locally advanced or metastatic non–small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib and have central nervous system (CNS) metastases.

Feedback on the pERC Initial Recommendation indicated that pCODR's Provincial Advisory Group agreed with the Initial Recommendation; the submitter, Lung Cancer Canada patient advocacy group and the Registered clinicians disagreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of alectinib (Alecensaro) as monotherapy for the treatment of patients with ALK–positive locally advanced or metastatic non–small cell lung cancer (NSCLC) who have progressed on or who are intolerant to crizotinib and have CNS metastases.

Studies included: Two non-comparative, open-label phase II studies

The pCODR systematic review included two open-label, non-randomized studies (NP28761 and NP28673) that evaluated the safety and efficacy of alectinib in patients with ALK-positive NSCLC who progressed on or were intolerant to treatment with crizotinib. Patients in NP28761 (n = 87) and NP28673 (n = 138) received treatment with alectinib administered at a dose of 600 mg orally twice daily in 21-day cycles and 28-day cycles, respectively. pERC noted that the lack of comparative designs made interpreting the efficacy and safety results difficult, especially when assessing outcomes such as response rate, progression-free survival (PFS), overall survival (OS), and quality of life (QoL).

The pCODR review also provided contextual information, in the form of a relevant ongoing trial. The randomized phase III trial compares alectinib to docetaxel or pemetrexed in patients who have received two prior lines of systemic therapy including platinum-based chemotherapy and crizotinib. The estimated completion date of the trial is April 2019.

Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from the submitter that all data from all available sources should have been used to inform estimates of effectiveness, including pooled quantitative analyses to reflect the totality of the available evidence, and provide best estimates of outcomes and their uncertainties, citing the *CADTH Guidelines for the Economic Evaluation of Health Technologies, 4th Edition*. pERC noted that these CADTH guidelines refer to processes for parameter estimations when estimating effectiveness and harms specifically for an economic evaluation synthesizing data from all available sources. pERC noted that the study selection criteria to be included in the pCODR systematic review was specifically clinical trials. The reports of the pooled analyses did not meet the inclusion criteria of the pCODR systematic review and therefore were excluded. Considering

these guidelines, pERC noted that the Methods Team and the CGP felt that it was inappropriate to pool the trial results, in agreement with the conclusions of the FDA Statistical Review, due to differences in regimens, tumour assessment, and baseline characteristics between trials NP28761 and NP28673. Furthermore, the CGP and Methods Team noted that no methodology has been reported for pooling the efficacy and safety data for patients with CNS disease from the phase II NP28761 and NP28673 trials, and they expressed concern that multiple post-hoc analyses were performed and the pooled analyses for patients with measurable and non-measurable CNS disease at baseline were considered exploratory efficacy end points. Therefore, for these reasons, the CGP and Methods Team considered that pooled exploratory analyses of the data from the two phase II trials would not be appropriate and that any results from such an analysis would need to be interpreted with caution.

Patient populations: 60% of patients had central nervous system metastases at baseline in both studies

Both trials enrolled adult patients diagnosed with locally advanced or metastatic NSCLC with disease progression on or intolerance to crizotinib. Both trials required ALK testing to be performed using the FDA-approved, fluorescence in situ hybridization (FISH) test. In addition, both trials allowed patients with confirmed diagnosis of stage IIIB to IV ALK-positive NSCLC with disease progression (per Response Evaluation Criteria in Solid Tumors [RECIST]) while receiving crizotinib. Previous treatment with chemotherapy for metastatic disease was permitted. Brain or leptomeningeal metastases were permitted, treated or untreated, as long as metastases were asymptomatic and stable. Of the 87 patients in NP28761 with ALK-positive NSCLC, 18% (n = 16) had measurable CNS metastases at baseline, and 60% (n = 52) had CNS metastases at baseline that were either measurable or non-measurable. Of the 138 patients in NP28673, 25% (n = 35) had measurable CNS metastases at baseline and 61% (n = 84) had measurable or non-measurable CNS metastases at baseline. Among patients with CNS metastases (measurable and non-measurable), 65% (NP28761) and 73% (NP28673) had received prior brain radiation.

Key efficacy results: Objective response rate, central nervous system objective response rate, magnitude of comparative benefit uncertain

The primary outcome for both trials was objective response rate (ORR) by independent review committee (IRC) using RECIST criteria. NP28673 had a co-primary end point of ORR in patients pre-treated with chemotherapy. Key secondary outcomes included PFS and OS, and CNS ORR in patients with measurable disease at baseline. Neither trial assessed the primary outcome using an intention-to-treat (ITT) analysis (i.e., including all patients treated with at least one dose of alectinib). Because a percentage of patients in each trial — 21% (n = 18) in trial NP28761 and 12% (n = 16) in trial NP28673 — were deemed not to have measurable disease upon IRC assessment, the primary and key secondary efficacy analyses were instead carried out in a response-evaluable (RE) population. However, pERC noted that time-to-event outcomes, including PFS and OS, were assessed in an ITT analysis.

At the most updated analyses, the median follow-up was 17 months in NP28761 and 21 months in NP28673. The ORR was 52% (95% confidence interval [CI], 40% to 65%) in NP28761 and 51% (95% CI, 42% to 60%) in NP28673 in the full trial populations.

At the most recent updated analyses, there were n =39 and n = 74 patients with measurable or non-measurable CNS metastases in trials NP28761 and NP28673, respectively. In trial NP28761, the ORR was 49% (95% CI, 32% to 65%), and in trial NP28673, the ORR was 49% (95% CI, 37% to 61%).

At the time of the primary analyses, time-to-event outcome data were immature. However, in both trials PFS and OS were assessed at the updated analyses in the full trial populations. In trial NP28761, median PFS was 8.2 months and median OS was 22.7 months. In trial NP28673, median PFS was 8.9 months and median OS was 26 months.

Median PFS and OS were 8.4 months and 22.7 months, respectively, among the 52 patients with CNS metastases in trial NP28761. In trial NP28673, the estimates were 7.4 months and 26 months, respectively, among 84 patients with CNS metastases.

In trial NP28761, 16 patients had measurable CNS metastases at baseline. The CNS ORR for this patient subgroup was 69% (95% CI, 41% to 89%) at primary analysis and 75% (48% to 93%) at the most recent update analysis. In trial NP28673, 35 patients had measurable CNS metastases at baseline. The CNS ORR for this patient subgroup was 56% (95% CI, 38% to 73%) at primary analysis, and 59% (41% to 75%) at the most updated analysis. In trial NP28761, the CNS ORR was 40% (95% CI, 27% to 55%) in 52 patients with

measurable or non-measurable CNS metastases. In trial NP28673, the CNS ORR was 46% (95% CI, 36% to 58%) in 84 patients. pERC noted the difference in the CNS ORR in the measurable CNS metastases group compared with the CNS ORR in the measurable and non-measurable CNS metastases group and noted that the latter group is similar to that expected in clinical practice.

Quality of life: Minimal clinically important differences in quality of life

Patient-reported QoL was evaluated only in the NP28761 trial and was measured using the European Organization for Research and Treatment of Cancer Core 30 Quality of Life Questionnaire (EORTC QLQ-C30) and the lung cancer-specific questionnaire (QLQ-LC13). The NP28761 trial publication reported very limited data on QoL outcomes. 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. Over the course of treatment, the mean changes from baseline in overall QoL status were similar between patients with and without CNS metastases. pERC noted the lack of comparative QoL data and that the lack of a comparator treatment made it challenging to interpret the QoL data. Upon reconsideration of the pERC Initial Recommendation, the Committee considered feedback from the submitter regarding quality of life data reporting that minimal clinically important differences were exceeded in patients who received alectinib. The Committee reiterated that, although clinically important differences were attained in trial NP28761 from baseline to week 6, the lack of a comparator group made it challenging to meaningfully interpret the QoL data.

Safety: Preliminary limited evidence suggests tolerable and manageable toxicity

pERC noted that the majority of adverse events (AEs) were low grade, with the most common AEs being grade 1 to 2 constipation, fatigue, peripheral edema, and myalgia. The incidence of grade 3 to 4 AEs was below 5% for all AEs in both trials, with the exception of elevations in blood creatine phosphokinase (8%), alanine aminotransferase (6%), and aspartate aminotransferase (5%) in trial NP28761. Serious AEs were reported in 15% of patients in trial NP28761 and 16% of patients and in trial NP28673. At the primary analysis, the number of patients discontinuing treatment due to AEs was 2% and 8%, respectively. A similar AE profile was noted for patients with and those without CNS metastases at baseline. Four deaths were reported in trial NP28761 at the last updated analysis, with one death judged to be related to alectinib. Eight deaths were reported in trial NP28673 at the last update analysis, with five deaths judged to be related to alectinib. pERC considered that alectinib appeared to have a manageable toxicity profile; however, the non-comparative design of both trials made it challenging to assess the AEs against a relevant comparator.

Limitations: No comparative data

pERC noted that the Methods Team and the CGP identified several limitations in the two studies using alectinib in ALK-positive NSCLC with CNS metastases. Both studies were non-comparative; thus, there is substantial uncertainty regarding the magnitude of benefit with alectinib compared with other therapies. In addition, these trials had open-label designs, which increases the potential for bias, especially when assessing outcomes such as response rate and PFS. Efficacy data on the requested reimbursement population of ALK-positive NSCLC patients with CNS metastases are limited in both trials, as small numbers of patients had measurable CNS disease at baseline and efficacy data on the larger subgroup of patients with measurable or non-measurable CNS metastases were based on unplanned exploratory analyses in both trials. pERC noted that key outcomes including ORR and CNS ORR should have been analyzed in the ITT population, rather than in the RE population. pERC also noted that while there are ongoing randomized trials that may address some of the limitations noted and provide more certainty on the effectiveness of alectinib, there are currently no RCTs that specifically evaluate alectinib in the requested reimbursement population; that is, patients with CNS metastases.

Registered clinician input: Need in patients who have progressed on or are intolerant to crizotinib and have CNS metastases

pERC noted input from registered clinicians indicating that alectinib provides another treatment option for ALK-positive patients who have progressed on or are intolerant to crizotinib and have CNS metastases. Registered clinicians identified that treatment with alectinib has the potential to relieve hospital resources with regard to chemotherapy and radiation services, as alectinib is an oral medication that can

be taken at home. Additionally, registered clinicians, based on their limited clinical experience, felt that alectinib appears to be efficacious and well tolerated. The clinicians providing feedback noted that the current therapeutic approach with either SRS or whole-brain radiation therapy (WBRT) carries significant limitations and risks to patients. The clinicians noted that SRS is viable only if there are limited metastases and that WBRT requires hospital resources and exposes patients to the risk of long-term memory loss and permanent cognitive effects. In addition, registered clinicians noted that WBRT may not be an effective treatment option. The clinicians providing input indicated that alectinib will be used in those who have progressed on, or are intolerant to, crizotinib and have CNS metastasis and, if funded, it will replace SRS and WBRT therapies and chemotherapy as a second line of treatment.

Need: Unmet need for patients with ALK-positive NSCLC with CNS metastases

Lung cancer is the second-most commonly diagnosed cancer in both men and women, and is the leading cause of cancer deaths in Canada. NSCLCs are the most common type of lung cancers, comprising 85% of lung cancers and approximately 4% of all NSCLC are ALK-positive. Certain clinical characteristics are more likely to be associated with ALK-positive NSCLC, including younger age at diagnosis, never-smoking status, and adenocarcinoma histology. Furthermore, these cancers tend to be sensitive to inhibitors of the ALK fusion protein. Finally, CNS metastases are 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 development of CNS metastases is associated with deterioration of QoL and shortened survival. pERC agreed with the CGP that there are no effective systemic therapies available and that there is a significant need for effective treatments for patients with NSCLC with progressive disease with CNS metastases. In reconsideration of the pERC Initial Recommendation, pERC noted feedback from the submitter regarding an overestimate of ALK-positive NSCLC patients in Canada. The submitter felt that the CGP's estimate of 650 patients with advanced ALK-positive NSCLC in Canada was an overestimate as it assumes that 100% of NSCLC patients are tested for the ALK rearrangement. pERC noted and agreed with the CGP's response that the estimated number of NSCLC cases is reasonable considering the prevalence of new ALK-positive cases and cases that may be diagnosed at an earlier stage which then progress to metastatic disease requiring testing. pERC also reiterated that ALK testing is considered standard practice in Canada.

PATIENT-BASED VALUES

Values of patients with ALK-positive NSCLC and CNS metastases: Significantly diminished prognosis and reduction in quality of life

From a patient's perspective, a diagnosis of lung cancer can be devastating and, particularly, stage IV lung cancer patients experience the highest burden of symptoms. Key symptoms associated with lung cancer include fatigue, loss of appetite, shortness of breath, cough, pain, and blood in sputum. It was noted that loss of appetite, cough, pain, and shortness of breath were found to be significant predictors of QoL. Patient input indicated that having brain metastases is a huge additional burden for lung cancer patients, as it significantly diminishes their prognosis. ALK-positive patients tend to be younger and have never smoked, compared with the general NSCLC population. The input from patients and their families indicated that a diagnosis of lung cancer is associated with a heavy burden of stigma, which is particularly connected to smoking. Finally, input from patients and caregivers noted that a diagnosis of lung cancer carries a significant economic toll on household finances.

pERC noted that patients with ALK-positive advanced NSCLC who have progressed on or are intolerant to crizotinib and who have CNS metastases desire treatments that improve their QoL, reduce symptoms of their disease, and provide an alternative option to chemotherapy and radiation. Respondents indicated that when one line of treatment fails to respond, the only options currently available are radiation (SRS or WBRT) or treatment with chemotherapy again. It was also noted that SRS can be used only if patients have limited lesions, and that most patients are eventually treated with WBRT, which carries significant risk of permanent cognitive damage, memory loss, seizures, and permanent damage to the brain. Respondents indicated that other treatments such as crizotinib seem to provide a great QoL while shrinking or controlling their lung cancer. However, respondents reported the need for another option when crizotinib fails or cannot be tolerated. Upon reconsideration of the pERC Initial Recommendation, pERC reiterated that there is a significant unmet need for patients with lung cancer and CNS metastases and acknowledged that patients expressed a strong desire for more effective treatment options.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from a patient advocacy group and registered clinicians. pERC expressed some concern that identical feedback was received from these two stakeholders and agreed that it is important to maintain and engage distinct patient and registered clinician voices in the pERC deliberative process.

Patient values on treatment: Disease control, relief of symptoms of lung cancer, and more tolerable side effects

One patient advocacy group, Lung Cancer Canada, provided input on alectinib from 22 patients and 19 caregivers who had experience with alectinib. Respondents who have experience with alectinib indicated that alectinib works and relieves the symptoms of their lung cancer. Those who received alectinib reported relief that the treatment was effective for their lungs, and for their brain tumours as well. Some patients who were treated with alectinib felt that treatment with alectinib was effective in controlling their CNS disease, while also allowing them to avoid the permanent cognitive damage from WBRT. It was noted that current treatments are effective only for a few months, but many patients reported passing the 12-month and even the two-year mark with treatment with alectinib. Patients indicated that alectinib allowed patients to experience milestones and that it gave patients the ability to believe in long-term benefits and to think long term. With respect to side effects of alectinib, respondents indicated that these did not inhibit life, as many of the side effects were considered tolerable. The most commonly reported side effects were fatigue, photosensitivity, constipation, weight gain or loss, and edema. The majority of respondents reported no side effects or low side effects from treatment with alectinib, and those who experienced moderate side effects expressed that it was worth it for extending their lives.

ECONOMIC EVALUATION

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

The cost-effectiveness analysis and cost-utility analysis submitted to pCODR by the manufacturer compared alectinib to pemetrexed with or without cisplatin for ALK-positive, locally advanced or metastatic NSCLC patients who have progressed on or are intolerant to crizotinib and have CNS metastases (measurable or non-measurable) at study start.

Basis of the economic model: Partitioned survival model, clinical and economic inputs

The partitioned survival model comprised three health states, including PFS or pre-progression state, progressed disease (PD), and death. The submitter's base-case analysis used a 10 year time horizon.

Efficacy data for alectinib were sourced from the combined population of the pivotal phase II NP28761 and the NP28673 trials. There were no clinical trial data for the chemotherapies currently used in clinical practice in Canada after treatment with crizotinib in an ALK-positive locally advanced or metastatic NSCLC population. Therefore, the clinical data for the comparator treatment in the model (pemetrexed with or without cisplatin) were obtained from a historical control group that was taken from a retrospective analysis of 37 patients who enrolled in the expansion cohort of the PROFILE 1001 study or the PROFILE 1005 study and had received systematic therapies following progression on crizotinib. The submitter claimed that participants included in this retrospective study were comparable with the patients who participated in the NP28761 and NP28673 trials with respect to age, sex, smoking status, and Eastern Cooperative Oncology Group (ECOG) performance status. The pCODR Economic Guidance Panel (EGP) noted, however, that the type of systemic therapies and the proportion of patients with CNS metastases were not reported in the retrospective study. Additionally, the retrospective study reported only OS data. A similar curve-fitting approach as alectinib was used to predict the OS data beyond the trial. There were no PFS data available, so the submitter estimated PFS data by multiplying the ratio of the median PFS and median OS observed in the alectinib group by the data reported in the retrospective study.

Utility values for alectinib were derived from converting the EORTC QLQ measured in the NP28761 trial to the EuroQol 5-Dimensions questionnaire, 3-Levels (EQ-5D-3L) and from a cross-sectional study assessing utility values of patients' experiences with NSCLC in Canada.

Resource utilization and health care costs were based on Canadian data sources and therapeutic area experts' input. Cost information was sourced from Ontario data sources, Roche Canada, and IMS Brogan DeltaPA.

pERC noted that the clinical effect estimates were not based on data from direct head-to-head trials, and while the clinical data used in the submitted model reflect currently available evidence, the estimates were based on non-comparative clinical data. The Committee agreed with the EGP that the major limitation of the model was related to the paucity of comparative effectiveness data.

Drug costs: High alectinib drug cost

The list price for alectinib is $42.20 per 150 mg. At the recommended dose of 600 mg twice daily, alectinib costs $318.79 per day, or $10,119.99 per package of 240 150 mg capsules.

Cost-effectiveness estimates: Considerable uncertainty regarding clinical effectiveness estimates

pERC deliberated upon the cost-effectiveness of alectinib compared with pemetrexed with or without cisplatin for ALK-positive, locally advanced or metastatic NSCLC patients who have progressed on or are intolerant to crizotinib and have CNS metastases. The submitter's best estimate of the incremental cost-effectiveness ratio (ICER) is $108,958 per quality-adjusted life-year (QALY).

pERC considered the EGP's reanalyses of the submitted model and noted that the EGP performed reanalyses by taking shorter time horizons of three and seven years, assuming 80% and 90% of alectinib dose intensity, varying the hazard ratio of PFS versus OS by 20%, changing the duration of alectinib and pemetrexed with or without cisplatin by 20%, assuming a decrease/increase of 25%, 50%, and 75% of unit cost of pemetrexed with or without cisplatin, replacing utility data for pre-progression and post-progression health states with data reported in the literature, and replacing a utility value for progression with CNS metastases with a value of 0.40 as reported by Lester-Coll et al. (2016). The EGP also reduced the unit cost of alectinib by 25%, 50%, and 75% of the submitted price. Upon reconsideration of the pERC Initial Recommendation, the Committee considered feedback from the submitter that the EGP cannot misrepresent extreme scenarios as plausible, most-likely base cases as evidence of large uncertainty to pERC. The submitter noted that the EGP used the lower 95 % CI of alectinib OS with the upper 95 % CI of chemotherapy OS and that the probability of the two 95% CI values or more extreme occurring together is 0.025^2=0.000625. The Committee noted that the EGP's best estimate of the ICER had changed in the Final Economic Guidance Report. The Committee noted that the EGP's best estimate of the ICER was based on the best case lower-bound scenarios and the worst case upper-bound scenarios. The EGP's best estimate of the ICER as reported in the Final Economic Guidance Report is between $67,993/QALY and $417,128/QALY.

pERC noted that the price of alectinib was the main driver of the incremental cost of alectinib and that the extra clinical effect of alectinib is most influenced by the time horizon, utility values associated with disease-free and PD health states, and parametric models used to fit OS and PFS data. pERC discussed the EGP's conclusions that, given the lack of direct comparative estimates for PFS and OS, there is considerable uncertainty in the clinical effect estimates in the model, and this uncertainty is not fully captured in the range of ICER estimates. pERC agreed with the EGP's conclusion that the uncertainty may not be reflected in the estimates of incremental effect captured in the model and the EGP's range of ICER estimates.

pERC discussed the lack of comparative safety and efficacy data for alectinib compared with pemetrexed with or without cisplatin. pERC noted that the submitted model based the clinical effect estimates for alectinib on two phase II single-arm trials, while the efficacy of pemetrexed with or without cisplatin was assumed to be equal to the efficacy of systemic therapies reported in a retrospective analysis of 37 ALK-positive NSCLC patients who discontinued crizotinib. This retrospective study did not report the type of systemic therapies used, the proportion of patients with CNS metastases at baseline, and specific time from last dose of crizotinib to first dose of the systemic therapy. Additionally, in the submitted pharmacoeconomic model, PFS and OS were extrapolated from short-term trial data over a 10-year time horizon. Upon reconsideration of the pERC initial recommendation, pERC considered feedback from the submitter that using a shorter time horizon of three years in the reanalysis estimates for this population treated with alectinib is incorrect, as the choice of a three-year time horizon was based on the CGP's estimate of median survival and not on the estimate of a patient's maximum survival. pERC noted and agreed with feedback from the CGP, that given the poor prognosis in this patient group and the unknown life expectancy of NSCLC ALK patients with CNS metastases after progressing on crizotinib, a shorter time horizon should be explored. Furthermore, pERC also noted that the CGP were unaware of studies that

report a maximum OS of 10 years in ALK-positive patients with CNS metastases who have progressed on crizotinib. The model estimated utilities for the progression-free (PF) health state for alectinib by mapping responses from the EORTC QLQ-C30 questionnaire reported in the NP28761 trial. However, the submitter reported only a mean utility value and did not provide sufficient details of the mapping method. The utility value reported was slightly higher than other utility data for NSCLC patients reported in the literature. Moreover, the submitter used equal utility values for patients with and without CNS metastases. pERC agreed with the CGP and EGP and noted that this assumption was inconsistent with existing evidence cited in the submitted pharmacoeconomic report that suggested patients with CNS metastases may have shorter life expectancy and poorer QoL than patients who do not develop CNS metastases. Because of the high uncertainty associated with the utility data, the EGP performed the reanalyses based on a range of different utility values reported in the literature. pERC also noted that the submitter assumed that the duration of treatment would be equal to PFS, which may under- or overestimate the costs of the treatments (including alectinib and standard chemotherapy) and the ICER. pERC agreed with the EGP that the unit costs of pemetrexed and cisplatin used in this study may be too high, given the availability of generic versions. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the submitter that the submitted pharmacoeconomic model used the only publicly available generic unit costs available from Quintiles IMS's Delta PA database. pERC noted that the EGP considered that the high unit cost of standard chemotherapy used by the submitter is acceptable, given the limited access to generic unit cost information, and acknowledged that the one-way sensitivity analysis of the unit cost of pemetrexed and cisplatin was performed to assess the impact of generic pricing of pemetrexed and cisplatin on the cost-effectiveness of alectinib. Overall, pERC agreed with the EGP's conclusion that the degree of uncertainty with respect to the cost-effectiveness of alectinib is too high, and that much of the uncertainty regarding the ICER is as a result of uncertainty in the incremental clinical effect of alectinib. pERC concluded that the ICER is likely at the upper end of the EGP's best estimate.

Upon reconsideration of the pERC Initial Recommendation, the Committee considered feedback from the submitter regarding the implausibility of the EGP's reanalyses by increasing the current unit cost of alectinib by 20%, 50%, and 75%. pERC noted that the EGP explained that the objective of its one-way sensitivity analyses was to assess the extent to which the cost-effectiveness of alectinib varies by changes in its unit cost. The results of these analyses showed that the incremental cost-effectiveness ratios of alectinib were highly sensitive to its unit costs. pERC noted that the EGP acknowledged the submitter's concern and further noted that the results of the one-way sensitivity analyses representing increases to the unit costs of alectinib by 20%, 50%, and 75% were removed from the Final Economic Guidance Report. pERC agreed that removing the one-way sensitivity analyses increasing the unit cost of alectinib was acceptable.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Small patient population with ALK-positive mutation and CNS metastases and the potential for first-line indication creep

pERC discussed the feasibility of implementing a funding recommendation for alectinib. pERC noted that the indication under review at Health Canada is broader and not restricted to patients with CNS metastasis as compared with the pCODR reimbursement request. Input from PAG noted that a small number of patients with ALK mutation have CNS metastases. PAG input also noted the concern for the possibility of indication creep of alectinib into first-line treatment, particularly for patients who already have CNS metastasis upon diagnosis and if intolerance to crizotinib is not defined. pERC agreed with PAG that guidance on sequencing of available treatments for this patient population following crizotinib would be needed. Moreover, pERC agreed with the CGP that there will be few patients who are intolerant to crizotinib. pERC also noted PAG's concern and input from registered clinicians regarding the place of therapy, sequencing, and priority of treatment with alectinib compared with other new therapies that are currently being reviewed by pCODR. pERC concluded that an overview of all available therapies for NSCLC may be beneficial at a future date to understand the comparative effectiveness of these therapies. However, the Committee noted that the current review is based on the evidence presented for alectinib and must be considered on its own merits.

pERC also acknowledged input from PAG that alectinib is administered orally, and this would be an enabler to implementation as chemotherapy units and chair time would not be required. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medication, which may limit accessibility of treatment for patients in these jurisdictions. Finally, pERC

noted that alectinib is available in one capsule strength, and dose adjustments are accomplished by adjusting the number of capsules per day. However, pERC noted PAG's concerns regarding the pill burden, given that the recommended dose is four capsules twice daily (eight capsules daily).

DRUG AND CONDITION INFORMATION

Drug Information	• Alectinib is an oral, small molecule, ATP-competitive, tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK) • 150 mg tablet reviewed by pCODR • Recommended dosage of 600 mg tablet twice daily (oral)
Cancer Treated	• ALK-positive locally advanced or metastatic non-small cell lung cancer (NSCLC)
Burden of Illness	• 4% of all NSCLC are ALK-positive. 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 treated with crizotinib. The development of brain metastases is associated with deterioration of quality of life and shortened survival
Current Standard Treatment	• Chemotherapy • Stereotactic radiation therapy and whole-brain radiation therapy (WBRT) • Best supportive care
Limitations of Current Therapy	• Absence of reliably effective therapeutic alternatives • Cytotoxic chemotherapy has a lack of evidence documenting effectiveness in CNS metastases and potential unfavourable impacts on quality of life • WBRT is associated with the risk of memory loss and permanent cognitive effects

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Paul Hoskins, Oncologist (Co-Chair)
Dr. Scott Berry, Oncologist
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy Thompson, Pharmacist
Valerie McDonald, Patient Member Alternate
Carole McMahon, Patient Member
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Dr. Marianne Taylor, Oncologist
Danica Wasney, Pharmacist

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

- Craig Earle, Allan Grill, and Danica Wasney, who were not present for the meeting
- Valerie McDonald, who did not vote due to her role as a patient member alternate.

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

- Matthew Cheung , Allan Grill, and Anil Abraham Joy who were not present for the meeting
- Valerie McDonald who did not vote due to her role as a patient member alternate.

Avoidance of conflicts of interest

All members of 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 alectinib for metastatic non-small cell lung cancer, through their declarations, six members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members 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, registered clinician, 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 pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

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.

Disclaimer

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report. This document is composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).