# pCODR EXPERT REVIEW COMMITTEE (pERC)
# INITIAL 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.

**Providing Feedback on This Initial Recommendation**
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with the *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

**Drug:**
Alectinib (Alecensaro)

**Submitted Reimbursement Request:**
As monotherapy for the treatment of patients with anaplastic lymphoma kinase-positive, locally advanced (not amenable to curative therapy), or metastatic non-small cell lung cancer who have progressed on or are intolerant to crizotinib until loss of clinical benefit

**Submitted by:**
Hoffmann-La Roche Limited

**Manufactured by:**
Hoffmann-La Roche Limited

**NOC Date:**
September 29, 2016

**Submission Date:**
August 18, 2017

**Initial Recommendation Issued:**
February 1, 2018

| Drug Costs | |
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| **Approximate per Patient Drug Costs, per Month (28 Days):**<br>Submitted list price of $42.17 per 150 mg capsule | **Alectinib Costs:**<br>• $337.36 per day<br>• $9,446.08 per 28-day course |

## pERC RECOMMENDATION

pERC recommends the reimbursement of alectinib for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced (not amenable to curative therapy), or metastatic non-small cell lung cancer (NSCLC) who have disease progression on or intolerance to crizotinib conditional on the cost-effectiveness being improved to an acceptable level. Reimbursement should be for patients with good performance status. Treatment should continue until disease progression or unacceptable toxicity.

The Committee made this recommendation because it was satisfied that there is a net clinical benefit of alectinib, based on the statistically significant and clinically meaningful improvement in progression-free survival (PFS) and no appreciable detriment in quality of life (QoL) compared with chemotherapy. However, pERC was uncertain as to how alectinib compares with ceritinib with regards to outcomes important to decision-making such as overall survival (OS), PFS, and QoL, due to a lack of robust direct or indirect comparative efficacy data.

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| | pERC acknowledged that alectinib has a favourable toxicity profile compared with chemotherapy. The Committee agreed that alectinib aligns with patient values of symptom control, disease control, and the need for an effective treatment option to delay progression and delay subsequent treatment with chemotherapy and radiation.<br><br>pERC concluded that, at the submitted price, alectinib may be cost-effective compared with chemotherapy. The Committee concluded that at the submitted price, alectinib is likely not cost-effective compared with ceritinib and would require a substantial price reduction to improve the cost-effectiveness to an acceptable level. pERC noted that there was considerable uncertainty in the cost-effectiveness estimates of alectinib compared with chemotherapy and ceritinib due to a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation. |
| **POTENTIAL NEXT STEPS FOR STAKEHOLDERS** | **Pricing Arrangements to Improve Cost-Effectiveness of Alectinib Compared With Ceritinib**<br>Given that pERC concluded that the overall efficacy of alectinib compared to ceritinib is uncertain based on the available evidence, jurisdictions may want to consider pricing arrangements or cost structures that would improve the cost-effectiveness of alectinib compared with ceritinib.<br><br>**Generalizability of Results Regarding Patients With Central Nervous System Metastases**<br>pERC noted that the majority of patients in the ALUR trial had stable central nervous system (CNS) metastases at baseline. Subgroup analysis in these patients demonstrated that the treatment effect observed in the overall trial population was maintained in patients with CNS metastases. pERC therefore agreed that the available evidence is sufficient to conclude that alectinib is effective in this population.<br><br>**Time-Limited Need for Patients who are Currently on or Have Recently Completed Treatment With Chemotherapy or an Immune Checkpoint Inhibitor**<br>At the time of implementing a reimbursement recommendation for alectinib, jurisdictions may want to consider addressing the short-term, time-limited need for alectinib for patients who have progressed on or are intolerant to crizotinib and are currently on or have recently completed treatment with chemotherapy, or patients who are currently on or have recently completed treatment with an immune checkpoint inhibitor.<br><br>**Optimal Sequencing of Alectinib and Other Available Therapies**<br>pERC noted that there is currently no clinical trial evidence to inform the optimal sequencing of alectinib and other available treatments for ALK-positive, locally advanced, or metastatic NSCLC. Although the ALUR trial included patients who had been treated with crizotinib and a platinum-based doublet chemotherapy, pERC agreed that treatment with alectinib is likely to be used as a second-line option, following progression on crizotinib, followed by platinum-based doublet chemotherapy as a third-line treatment and subsequently with single-agent chemotherapy or immune checkpoint inhibitors. However, the Committee acknowledged that there is no direct evidence investigating head-to-head efficacy and safety nor for the appropriate sequence for alectinib with other available therapies (e.g., ceritinib) for the treatment of ALK-positive NSCLC patients who have progressed on crizotinib. Upon implementation of reimbursement of alectinib, pERC |

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| | recognized that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of value.<br><br>**Note**: The Provincial Advisory Group (PAG) implementation questions have been addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1. |

# SUMMARY OF pERC DELIBERATIONS

An estimated 28,000 new cases of lung cancer were diagnosed in Canada in 2017, with a five-year survival rate of 15% to 18%. Treatment decisions for locally advanced or metastatic NSCLC are dependent on the presence or absence of the type of driver mutation status of patients in the first-line setting. Approximately 4% of NSCLC patients will have a specific genetic mutation or rearrangement of the ALK gene. Standard treatment for patients with ALK-positive advanced NSCLC is crizotinib, which is approved for reimbursement in the front-line setting in Canada. For patients who have disease progression or intolerance to crizotinib, current treatment in the second-line setting includes intravenous chemotherapy with platinum-based doublet therapy. Ceritinib has been recently recommended for reimbursement conditional on the cost-effectiveness of the treatment being improved; however, no jurisdictions are currently reimbursing this therapy. Third-line options include single-agent chemotherapies (e.g., docetaxel, pemetrexed) or immunotherapies. pERC noted that instances of intolerance to crizotinib will be few. Patients with CNS metastases in the context of stage IV NSCLC have a particularly poor prognosis. Therefore, pERC agreed that there is a continued need for more effective treatment options with more manageable toxicity profiles for patients with ALK-positive NSCLC who progress on or are intolerant to crizotinib.

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

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

pERC deliberated on the preliminary abstract results of one phase III randomized controlled trial, ALUR, which evaluated the safety and efficacy of alectinib compared with single-agent chemotherapy in patients with ALK-positive, locally advanced (not amenable to curative therapy), or metastatic NSCLC who have disease progression or intolerance to crizotinib. pERC noted that the ALUR trial demonstrated a statistically significant and clinically meaningful improvement in PFS in favour of alectinib. pERC also considered the fact that the majority of patients enrolled in the trial had stable CNS metastases at baseline, and that subgroup analyses demonstrated the treatment effect observed in the overall population was maintained in patients with CNS metastases. The Committee also discussed that there was a similar trend favouring alectinib for all CNS efficacy outcomes. The Committee noted that OS data were immature at the primary analysis, and considered the fact that frequent crossover in the trial may confound any OS benefit observed with longer follow-up.

pERC discussed the available QoL data from the ALUR trial. Although few significant minimally important differences were reported between the alectinib group and the chemotherapy group, pERC noted that treatment with alectinib was not associated with an appreciable deterioration in QoL compared with chemotherapy. pERC considered that the frequency of grade 3 or grade 4 adverse events (AEs) occurred less frequently in the alectinib group. The most common AEs associated with alectinib were constipation, anemia, asthenia, and dyspnea. pERC noted that alectinib has a more favourable toxicity profile compared with chemotherapy. Overall, based on the improvement in PFS, the maintenance of QoL, the favourable toxicity profile compared with chemotherapy, and the need for more effective treatment options, pERC concluded that there is a net clinical benefit of alectinib for patients with ALK-positive NSCLC who have disease progression on or intolerance to crizotinib.

pERC considered the comparison with chemotherapy in the ALUR trial to be reasonable in this setting, but also discussed the results of a network meta-analysis provided by the submitter that compared alectinib with relevant therapies including chemotherapy and ceritinib. pERC discussed the critical appraisal of the NMA and noted, in agreement with the pCODR Methods Team, there are a number of limitations (e.g., substantial heterogeneity between the included studies and the use of unpublished preliminary data), making the overall conclusions on the comparative efficacy limited. pERC also considered the opinion of the pCODR Clinical Guidance Panel and input from registered clinicians that alectinib appears to have better CNS activity and a more favourable toxicity profile compared with ceritinib. Based on the lack of a direct head-to-head comparison of alectinib and ceritinib and the limitations of the indirect evidence submitted to pCODR, pERC concluded that there is considerable uncertainty on how alectinib compares with ceritinib with regard to outcomes important to decision making such as OS, PFS and QoL.

pERC deliberated on input from one patient advocacy group, which indicated that patients value new effective treatment options that offer disease control, symptom control, tolerable side effects, improvements in QoL, and prolonged survival. The Committee discussed that toxicities associated with chemotherapy and radiation were particularly difficult for patients, who value less toxic, tolerable treatment alternatives. pERC considered that alectinib has a favourable toxicity profile compared with the long-term toxicities associated with intravenous chemotherapy and radiation. pERC discussed that treatment with alectinib allows patients to delay subsequent treatment with chemotherapy and radiation. The Committee also noted that alectinib would be an effective oral treatment option that would be easier for patients to take, as it may require less personal and caregiver time and fewer resources compared with chemotherapy. pERC considered that the majority of patients who had direct experience with alectinib reported tolerable and manageable side effects, and that some patients were able to return to work and resume caring for their family members after treatment with alectinib. Overall, pERC concluded that alectinib aligns with patient values because it offers patients an effective oral treatment option with tolerable side effects.

pERC deliberated on the cost-effectiveness of alectinib compared with chemotherapy and ceritinib based on the submitted economic evaluation and reanalysis estimates provided by the pCODR Economic Guidance Panel (EGP). pERC noted that the following factors had an impact on the incremental cost-effectiveness ratio (ICER): the drug-acquisition costs, the time horizon, the comparative OS estimates, and the statistical model chosen for PFS and time to off-treatment. The Committee noted that the factor that most influenced the incremental costs were the drug-acquisition costs, while the incremental effect was most influenced by the OS estimates and the time horizon. pERC discussed that the indirect evidence that was used to inform the comparative efficacy estimates of alectinib, chemotherapy, and ceritinib, as well as the extrapolation of short-term trial data, were the main sources of uncertainty in the economic analysis. The Committee agreed with the EGP and the Clinical Guidance Panel that a shorter time horizon was more clinically plausible in this particular patient population and that the use of indirect evidence creates considerable uncertainty around the cost-effectiveness estimates of alectinib compared with chemotherapy and ceritinib. Overall, pERC agreed with the EGP's best estimates of the ICER when alectinib was compared with chemotherapy and ceritinib. pERC concluded that the true ICER for alectinib compared with chemotherapy is likely near the lower end of the EGP's reanalysis estimate, thus alectinib is likely to be cost-effective compared with chemotherapy. pERC concluded that the true ICER for alectinib compared with ceritinib is likely near the upper end of the EGP's reanalysis estimate. Therefore, pERC concluded that alectinib, at the submitted price, is likely not cost-effective and would require a substantial price reduction to improve the cost-effectiveness to an acceptable level. Overall, pERC cautioned that there was considerable uncertainty in the cost-effectiveness estimates due to a lack of robust direct or indirect comparative effectiveness data in the submitted model.

pERC considered the feasibility of implementing a reimbursement recommendation for alectinib. Overall, pERC agreed with the EGP that the Ontario-specific budget-impact analysis was reasonable. pERC noted that the budget impact will vary across provinces depending on the coverage of oral anti-cancer therapies. The Committee discussed that ALK-positive patients tend to be younger, and that the budget impact may be overestimated or underestimated depending on whether oral anti-cancer medications are reimbursed. pERC noted that the factors that most influence the budget-impact analysis include the number of patients eligible for alectinib in the next three years, the assumed proportion of eligible patients that would be prescribed alectinib if it was reimbursed, and the cost of alectinib and other treatment alternatives.

The Committee noted input from PAG, which requested guidance and clarification on the implementation of alectinib. pERC discussed the definition of "until loss of clinical benefit" in the reimbursement request. The Committee noted that patients in the ALUR trial could continue treatment with alectinib after radiologic disease progression if the patient was benefiting from treatment. pERC discussed that there may be clinical situations for continuing treatment beyond radiologic-defined progression to maintain disease control and reduce disease burden for patients. Given this, pERC concluded that treatment with alectinib should be continued until clinically meaningful progression occurs, based on the judgment of the treating oncologist.

pERC also discussed PAG's concern for indication creep to first-line, particularly for patients with CNS metastases at baseline. pERC noted that the ALUR trial did not include patients who were treatment naive; therefore, treatment with alectinib in the first-line setting is out of scope for this review. pERC noted that a request for reimbursing alectinib in patients who are treatment naive would require a Health Canada–approved indication and a submission to pCODR.

The Committee noted PAG's request for a clear definition of intolerance to crizotinib as there may be cases in which patients may be deemed intolerant after one dose of crizotinib to be eligible for alectinib. pERC discussed that there would be very few patients who would be intolerant to crizotinib, and that in such cases, intolerance would be determined by the treating oncologist.

Finally, pERC discussed PAG's input on the preferred sequencing of ALK inhibitors. The Committee considered input from registered clinicians, who indicated that alectinib should be available to those who have failed prior crizotinib and possibly ceritinib. Clinician input indicated that patients would likely try crizotinib first-line, then either ceritinib or alectinib as second-line, and then the other second-generation ALK inhibitor that was not utilized as third-line. pERC noted that there is currently no clinical trial evidence to inform the optimal sequencing of alectinib and other available treatments for ALK-positive, locally advanced, or metastatic NSCLC. Although the ALUR trial included patients who had been treated with crizotinib and chemotherapy, pERC agreed that treatment with alectinib is likely to be used as a second-line option following progression on crizotinib, followed by platinum-based doublet chemotherapy as a third-line treatment and subsequently with single-agent chemotherapy or immune checkpoint inhibitors. However, the Committee acknowledged that there is no direct evidence investigating head-to-head efficacy and safety nor the appropriate sequence for alectinib with other available tyrosine kinase inhibitor therapies (e.g., ceritinib) for the treatment of ALK-positive NSCLC patients who have progressed on or are intolerant to crizotinib. Upon implementation of reimbursement of alectinib, pERC recognized that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of value.

# 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 review panels
- input from one patient group, Lung Cancer Canada (LCC)
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

## OVERALL CLINICAL BENEFIT

### pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of alectinib (Alecensaro) as monotherapy compared with standard therapies in patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced (not amenable to curative therapy), or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib until loss of clinical benefit.

### Studies included: One unpublished randomized controlled trial

The pCODR systematic review included one open-label, phase III randomized controlled trial: the ALUR trial. The ALUR trial is an ongoing, international (Europe and Asia) trial evaluating the efficacy and safety of alectinib compared with chemotherapy in patients with ALK-positive, locally advanced, or metastatic NSCLC who have progressed on or are intolerant to crizotinib. To date, the results of the ALUR trial have been published in abstract and poster form only. Patients (n = 107) were randomized to receive either alectinib (600 mg orally twice daily; n = 72) or chemotherapy (intravenously every three weeks; n = 35) consisting of pemetrexed (500 mg/m$^2$) or docetaxel (75 mg/m$^2$). Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) Performance Status (zero to one versus two) and central nervous system (CNS) metastases (yes or no); patients with CNS disease were further stratified based on previous radiation therapy (yes or no).

Patients in both treatment groups received the study drug until disease progression, unacceptable toxicity, and withdrawal of consent or death. Upon radiologic progression, patients in the alectinib group could continue to receive alectinib if still clinically benefiting from the drug; patients in the chemotherapy group were permitted to cross over to alectinib. Seven per cent of the patients treated with alectinib continued treatment beyond progression. The dose intensity for alectinib in the ALUR trial was 86%.

The pCODR review also provided contextual information on a critical appraisal of a network meta-analysis (NMA) and an indirect comparison (ITC) of alectinib versus other comparators, such as chemotherapy and ceritinib.

### Patient populations: Majority with central nervous system metastases

pERC noted that baseline characteristics were generally well-balanced between the treatment arms. The median age of patients was between 56 and 59 years, with a majority of patients being under the age of 65 years (79%), male (54%), Caucasian (84%), previous smokers (49%) or never smoked (48%), metastatic disease (96%), and an ECOG Performance Status of zero or one (90%). The majority of patients had CNS metastases at baseline (68%); among those patients, most had undergone previous radiation treatment for their CNS disease (59%).

### Key efficacy results: Significant improvement in progression-free survival; overall survival data immature; frequent crossover

pERC noted the primary analysis results with a median follow-up time of 6.5 months in the alectinib group versus 5.8 in the chemotherapy group. The primary outcome of the ALUR trial was progression-free survival (PFS) by investigator (INV). pERC noted that there was a statistically significant improvement in PFS by INV with treatment with alectinib compared with chemotherapy; median PFS by INV was 9.6 months with alectinib and 1.4 months with chemotherapy (hazard ratio [HR] = 0.15, 95% confidence interval [CI], 0.08 to 0.29; $P < 0.001$). A similar treatment effect was observed for PFS by independent review committee. pERC noted that the results of subgroup analyses were consistent with the primary analysis results across most patient subgroups examined, including patients with CNS metastases at baseline.

pERC noted that treatment with alectinib was favoured compared with chemotherapy for all CNS efficacy outcomes (CNS overall response rate and, CNS disease control rate). The CNS overall response rate among patients with measurable CNS metastases at baseline was 54% in the alectinib group versus 0% in the chemotherapy group ($P < 0.001$), demonstrating a significant treatment benefit in the CNS with alectinib compared with chemotherapy. Similar results were observed in the subgroup of patients with measurable and non-measurable CNS metastases at baseline. Considering all patients, the risk of CNS progression was significantly reduced in patients treated with alectinib compared with chemotherapy (median not estimable for alectinib versus 2.4 months with chemotherapy; HR = 0.14, 95% CI, 0.06 to 0.36; $P < 0.001$).

pERC noted that data on overall survival (OS) were deemed immature at primary analysis. At the time of the primary analysis, 24 (69%) patients receiving chemotherapy crossed over to receive treatment with alectinib.

### Limitations: No direct comparison between alectinib and ceritinib

The pCODR Review Team conducted literature search identified only one randomized control trial that assessed the efficacy and safety of alectinib versus chemotherapy in patients with advanced or metastatic ALK-positive NSCLC who progress on or are intolerant to crizotinib. As such, there is a lack of direct evidence comparing alectinib with other available therapies, including ceritinib. Given the absence of head-to-head trials, the submitter conducted an ITC and NMA comparing alectinib to ceritinib and chemotherapy. As a result, the pCODR Methods Team conducted a critical appraisal of the submitted ITC and NMA that provided evidence for the efficacy of alectinib versus active therapies in patients with ALK-positive NSCLC who progress on or are intolerant to crizotinib.

pERC noted the results of the submitted ITC and NMA. The results of the NMA indicated that treatment with alectinib significantly improved PFS by investigator compared with ceritinib (HR=0.38, 95% credible intervals [CrI], 0.19 to 0.76), but no difference in PFS by independent review committee was detected (HR=0.65, 95% CrI, 0.32 to 1.31). Alectinib was associated with significantly fewer adverse events (AEs) of grade 3 or higher as well as dose reductions when compared with ceritinib. The quality assessment judged the overall relevance of the ITC/NMA to be sufficient, but concerns were noted related to internal validity. pERC noted the main limitations of the NMA included heterogeneity across the included studies, which was not investigated in analyses due to constraints in the structure of the evidence network (e.g., single trial connections), and the use of preliminary or unpublished data. It was concluded that the comparative efficacy estimates obtained for alectinib versus ceritinib are likely biased due to uncontrolled heterogeneity; however, the direction and magnitude of the bias is unclear, and therefore, the estimates obtained may overestimate or underestimate the true treatment effect associated with alectinib.

pERC noted that the OS data in the ALUR trial was immature and unadjusted for crossover. Therefore, the submitter was unable to provide an estimate of the comparative efficacy. As a result, data from two single-arm, phase II alectinib clinical trials (NP28673 and NP28761) and real-world patient data from an electronic health record database of patients treated with ceritinib were retrospectively analyzed to indirectly compare OS in the target population and derive an estimate of treatment effect. The analysis demonstrated that alectinib was associated with a significantly reduced risk of death compared with ceritinib (HR = 0.65, 95% CI, 0.48 to 0.88; $P = 0.006$). Median OS for the weighted treatment groups was 24.3 months (95% CI, 21 to not reached) in the alectinib group and 15.6 months (95% CI, 16 to 19) for the ceritinib group. Overall, the ITC used methods that align with best practice; however, pERC noted important limitations in the analysis, including issues related to relevancy (a substantial proportion of patients in the ceritinib real-world data treatment group did not experience crizotinib failure in the first-line setting) and internal validity (important key prognostic baseline variables were left out of the model used to balance treatment groups). Overall, the reported OS estimate is likely confounded because the effects of all important prognostic baseline variables were not controlled for simultaneously in the analysis.

### Patient-reported outcomes: Limited reporting on quality of life

Patient–reported health-related quality of life (QoL) was assessed using the European Organisation for Research and Treatment of Cancer's Quality of Life Questionnaire (QLQ)–Core 30, QLQ–Lung Cancer Module, and three items from the QLQ–Brain Cancer Module. Compliance in completed QoL questionnaires was generally high in the alectinib group but declined substantially over time in the chemotherapy group. pERC noted that the majority of QoL scores numerically favoured treatment with alectinib; however, few significant differences (in terms of the minimal clinically important difference of 10% or greater) were observed between the treatment groups. pERC noted that, overall, alectinib was not associated with an appreciable detrimental effect on QoL compared with chemotherapy.

### Safety: Manageable toxicities with alectinib compared with chemotherapy

Overall, AEs of any grade and AEs of grade 3 or higher occurred less frequently in patients treated with alectinib compared with chemotherapy (AEs any grade: 77% versus 85%; AEs grade ≥ 3: 27% versus 41%). The most common all-grade AEs associated with alectinib were constipation (19%), anemia (14%), asthenia (10%), and dyspnea (9%). The incidence of serious AEs was higher in patients treated with alectinib compared with chemotherapy (19% versus 15%); of those patients in the alectinib group, 6% of serious AEs (n = 4) occurred in more than one patient and included pneumonia (n = 2) and acute kidney failure (n = 2, one of which was deemed related to the study drug). pERC noted that treatment with alectinib led to a higher frequency of treatment interruption compared with chemotherapy (19% versus 9%); however, the chemotherapy group had a greater frequency of dose reductions (12% versus 4%) and treatment discontinuation (9% versus 6%). During the treatment period, six patients discontinued study treatment due to death; one patient who received docetaxel died from pneumonia deemed unrelated to study treatment, and the remaining five patients died due to disease progression that was also unrelated to study treatment. Overall, pERC noted that alectinib has a favourable toxicity profile compared with chemotherapy.

### Registered clinician input: Unmet need to delay central nervous system progression, improve progression-free survival

Clinicians providing input noted that compared with crizotinib and ceritinib, alectinib provides improvement in PFS, overall response rate, duration of response, and toxicity profile in patients with ALK-positive NSCLC, including those with brain metastases. pERC noted that clinician input suggested that alectinib may be used for ALK-positive treatment-naive NSCLC, patients who have progressed on crizotinib, or those who failed both crizotinib and ceritinib, where multiple second-generation ALK inhibitors would provide the maximum number of treatment lines for patients who acquire treatment resistance. However, pERC noted that the use of alectinib in the treatment-naive setting is out of scope.

pERC noted that clinician input indicated that patients with ALK-positive NSCLC commonly present with brain metastases and there is long-term CNS toxicities from whole-brain radiation that has a significant negative impact on QoL and function. Clinicians indicated that alectinib reduces the incidence of brain metastases and was associated with improved response, which could potentially improve QoL and function. Of note, clinician input suggested that brain radiation could be delayed until CNS progression on alectinib.

### Need: Effective treatment options that improve survival

Lung cancer is the second-most commonly diagnosed cancer in both men and women, and is the leading cause of cancer deaths in Canada. NSCLC is the most common type of lung cancer, comprising 85% of lung cancers. Approximately 4% of all cases of 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. The majority of patients with NSCLC will present with or develop advanced or metastatic disease. For these patients, treatment intent is to palliate symptoms and prolong survival. Crizotinib is the current accepted first-line therapy for metastatic, ALK-positive NSCLC in Canada. However, progression on crizotinib occurs in the majority of patients usually within 12 months. The CNS appears to be a common site of progression on crizotinib, likely related to the low penetration of crizotinib into the CNS. For patients with disease progression or intolerance to crizotinib, treatment options are limited to platinum-based doublet chemotherapy, single-agent chemotherapy, or ceritinib (a second-generation ALK tyrosine kinase inhibitor). Although ceritinib is available through a special access program, it is not currently publically reimbursed in Canada. pERC agreed with the pCODR Clinical Guidance Panel (CGP) that there are limited therapies available, and that there is a significant need for effective treatments when patients progress on or are intolerant to crizotinib.

## PATIENT-BASED VALUES

### Experiences of patients with NSCLC: High symptom burden, current therapies have high toxicity

pERC noted patient input from LCC which indicated that a diagnosis of NSCLC comes with high symptom burden, including fatigue, loss of appetite, cough, pain, and shortness of breath. LCC reported that standard treatment for ALK-positive NSCLC patients, such as chemotherapy and whole-brain radiation, is associated with high toxicity, significant side effects, and permanent cognitive damage. Patient input reported that other therapies, such as crizotinib and ceritinib, were considered effective and tolerable. However, more effective treatment options are needed following progression.

### Patient values regarding treatment: Disease control, manageable symptoms, and tolerable side effects

pERC noted that patient input indicated that patients value new effective treatment options that offer disease control, symptom control, tolerable side effects, improvements in QoL and prolonged survival. The Committee noted that toxicities associated with chemotherapy and radiation were particularly difficult for patients, who value less toxic, more tolerable treatment alternatives. pERC noted that alectinib has a favourable toxicity profile compared with the long-term significant toxicities associated with chemotherapy and brain radiation. Patient input indicated that patients on alectinib were able to delay and avoid treatment with chemotherapy and radiation. Specifically, patient input noted that treatment with alectinib allows patients with brain metastases to delay or avoid the permanent cognitive damage from who brain radiation. pERC also noted that alectinib would be an effective oral treatment option that would be easier for patients to take, as it may require less personal and caregiver time and fewer resources compared with treatment with intravenous chemotherapy and radiation. pERC also discussed that the majority of patients who had direct experience with alectinib reported tolerable and manageable side effects, and that some patients were able to return back to work and resume caring for their family members with treatment with alectinib. Overall, pERC concluded that alectinib aligns with patient values because it offers patients an effective oral treatment option with tolerable side effects.

## ECONOMIC EVALUATION

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

The pCODR Economic Guidance Panel (EGP) assessed the submitter's cost-effectiveness and cost-utility analyses of alectinib compared with chemotherapy and ceritinib for patients with ALK-positive advanced or metastatic NSCLC who have previously been treated with crizotinib.

### Basis of the economic model: Partitioned survival model comprising three health states

The pharmacoeconomic model comprised three health states: progression free, progressed disease, and dead. PFS and OS determined the proportion of patients that are in each of the health states in every cycle.

Costs considered in the analysis included drug costs, drug administration costs, costs of supportive care, AE costs and the cost of treatment of CNS metastases.

Key data sources:

ALUR trial
- PFS for alectinib and chemotherapy
- time on treatment for alectinib and chemotherapy
- utility values for alectinib and chemotherapy (pre-progression)
- AEs for alectinib and chemotherapy

NP28761 and NP28673 (two single-arm, phase II trials investigating alectinib treatment in patients who were ALK-positive and previously on crizotinib)
- OS for alectinib

A cohort study by Ou et al. that investigated the impact of continuing crizotinib therapy after progressed disease in patients with advanced ALK-positive NSCLC
- OS for chemotherapy

ASCEND-5 trial (a phase III randomized controlled trial that compared ceritinib with chemotherapy in patients who were ALK-positive and previously on chemotherapy and crizotinib)
- PFS for ceritinib (NMA with ASCEND-5 and ALUR)
- utility values for ceritinib (pre-progression)
- AE rates for ceritinib

Flatiron Health electronic records database
- OS for ceritinib (propensity score–adjusted analysis, combining ceritinib data from database with alectinib data from phase II studies)

Labbe et al.

- post-progression utility values for all treatments

### Drug costs: High cost of alectinib

The list price of alectinib is $42.17 per 150 mg capsule. At the recommended dose of 600 mg twice daily, alectinib costs $337.36 per day and $9,446.08 per 28 days.

The costs of chemotherapy, assuming an average body weight of 80 kg, are as follows:

- Pemetrexed costs $0.62 per milligram. The recommended dose is 500 mg/$m^2$ every three weeks. The cost per three-week cycle is $558.00. The cost per day is $26.57, and the cost per 28 days is $744.00.
- Docetaxel costs $3.43 per mg. The recommended dose is 75 mg/$m^2$ every three weeks. The cost per three-week cycle is $463.00. The cost per day is $22.05, and the cost per 28 days is $617.00.

The list price of ceritinib is $52.00 per 150 mg capsule. At the recommended dose of 750 mg twice daily, ceritinib costs $260.00 per day and $7,280.00 per 28 days.

### Cost-effectiveness estimates: Alectinib is likely cost-effective compared with chemotherapy; Alectinib is likely not cost-effective compared with ceritinib at the submitted price

pERC noted that the pCODR EGP's best estimate for the comparison of alectinib and chemotherapy ranged from $87,357 to $159,544 per quality-adjusted life-year (QALY) and was different from the submitter's estimate ($84,444 per QALY). The pCODR EGP's best estimate for the comparison of alectinib and ceritinib ranged from $36,935 to $224,235 per QALY and was different from the submitter's estimate ($67,903 per QALY).

pERC noted that the OS data from the ALUR trial were immature and there was frequent crossover. Thus, indirect comparative OS estimates were obtained from various sources: phase II studies for alectinib, a cohort study (Ou et al.) for chemotherapy, and the Flatiron Health electronic records database for ceritinib. In addition, pERC noted that patients in the trial continued treatment beyond radiologic progression as long as the patient was benefiting. The Committee noted that the model accounted for the cost of treatment with alectinib beyond radiologic progression (until loss of clinical benefit) by modelling the time to off-treatment (TTOT) data observed in the ALUR trial.

pERC noted that the EGP identified a number of limitations with the submitted model, including but not limited to:

- the use of a time horizon of 10 years with limited trial follow-up
- the use of indirect comparative evidence to estimate and project OS of alectinib and its comparators (chemotherapy and ceritinib)
- the statistical model chosen for PFS and TTOT
- the use of different drug-acquisition costs for the comparators.

The EGP conducted reanalyses to adjust for these limitations in the submitted model, including:

- shortening the time horizon to five years, as advised by CGP, to be more clinically plausible for this patient population
- using the best fit statistical model (the exponential model) to estimate PFS and TTOT
- exploring the relative OS for chemotherapy versus alectinib, and for ceritinib versus alectinib, and undertaking two extreme scenarios
- changing drug-acquisition costs to pCODR-sourced costs from IMS Brogan.

Furthermore, pERC noted that subsequent treatment following progression after chemotherapy was not included in the model, which may underestimate the total costs for the chemotherapy arm. pERC noted that drug-acquisition costs most influenced the incremental cost. The factors that most influenced the incremental effectiveness included the OS estimates and the time horizon. pERC considered that, given the lack of direct comparative estimates for OS, there is a high degree of uncertainty in the indirect clinical effect estimates of alectinib compared with chemotherapy and compared with ceritinib and thus the incremental cost effectiveness estimates derived from these endpoints. The Committee agreed with the EGP and the CGP that a shorter time horizon was more clinically plausible in this particular patient population, and that the use of indirect evidence creates considerable uncertainty around the cost-effectiveness estimates of alectinib and its comparators. Overall, pERC agreed with the EGP's best estimates of the ICER when alectinib was compared with chemotherapy and ceritinib.

pERC concluded that the true ICER for alectinib compared with chemotherapy is likely near the lower end of the EGP's reanalysis estimate, thus alectinib compared with chemotherapy is likely cost-effective. pERC concluded that the true ICER for alectinib compared with ceritinib is likely near the upper end of the EGP's reanalysis estimate. pERC also noted that the best estimate range provided by the EGP were wide, suggesting high uncertainty in the estimates. pERC concluded that alectinib, at the submitted price, is likely not cost-effective compared with ceritinib, and would require a substantial price reduction. Overall, pERC cautioned that there was considerable uncertainty in the cost-effectiveness estimates for alectinib and its comparators due to a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation.

## ADOPTION FEASIBILITY

### Considerations for implementation and budget impact: Small population with ALK-positive mutation, potential for first-line indication creep

Input from PAG highlighted various considerations around implementing alectinib. The Committee noted that upon implementing a reimbursement recommendation for alectinib, jurisdictions may want to consider addressing the short-term, time-limited need for alectinib for patients who are currently on or have recently completed treatment with chemotherapy, or patients who are currently on or have recently completed treatment with an immune checkpoint inhibitor. In these cases, pERC agreed that it would be reasonable to offer alectinib to these patients.

Overall, pERC agreed with the EGP that the Ontario-specific budget-impact analysis was reasonable. pERC noted that the budget impact will vary across provinces depending on the coverage of oral cancer therapies. The Committee discussed that only 4% of cases of NSCLC are ALK-positive. These patients tend to be younger in age, and the budget-impact analysis may be overestimated or underestimated depending on whether oral anti-cancer medications are reimbursed. pERC noted that the factors that most influence the budget impact include the number of patients that would receive alectinib or the comparators, the market share of alectinib, and the acquisition costs of medications.

The Committee noted input from the pCODR Provincial Advisory Group (PAG), which requested guidance and clarification on the implementation of alectinib. pERC discussed the definition of "until loss of clinical benefit" included in the reimbursement request. The Committee noted that patients in the ALUR trial could continue treatment with alectinib after radiologic disease progression if the patient was benefiting from treatment. pERC noted that there may be clinical situations for continuing treatment beyond radiologic-defined progression to maintain disease control. Given this, pERC concluded that treatment with alectinib should be continued until clinically meaningful progression occurs, based on the judgment of the treating oncologist. pERC also noted PAG's concern about indication creep to first-line, particularly for patients with CNS metastases at baseline. pERC noted that the ALUR trial did not include patients who were treatment naive; therefore, treatment with alectinib as first-line is out of scope at this time in the review. pERC noted that a request for reimbursing alectinib in patients who are treatment naive would require a Health Canada–approved indication and a submission to pCODR for the review of alectinib in treatment-naive patients.

The Committee noted PAG's request for a clear definition of intolerance to crizotinib as patients may be deemed intolerant after one dose of crizotinib in order to establish eligibility for alectinib. pERC noted that there would be very few patients who would be intolerant to crizotinib, and that intolerance would be determined by the patient and the treating oncologist.

pERC noted that there is currently no clinical trial evidence to inform the optimal sequencing of alectinib and other available treatments for ALK-positive, locally advanced, or metastatic NSCLC. Clinician input indicated that patients would likely try crizotinib first-line, then either ceritinib or alectinib as second-line, and then the other second-generation ALK inhibitor that was not utilized as third-line. pERC noted that there is currently no clinical trial evidence to inform the optimal sequencing of alectinib and other available treatments for ALK-positive, locally advanced, or metastatic NSCLC. Although the ALUR trial included patients who had been treated with crizotinib and platinum-based doublet chemotherapy, pERC agreed that treatment with alectinib is likely to be used as a second-line option, following progression on crizotinib, followed by platinum-based doublet chemotherapy as a third-line treatment, and subsequently with immune checkpoint inhibitors. However, the Committee acknowledged that there is no direct evidence investigating head-to-head efficacy and safety nor for the appropriate sequence for alectinib with other available therapies (e.g., ceritinib) for the treatment of ALK-

positive NSCLC patients who have progressed on crizotinib. Upon implementation of reimbursement of alectinib, pERC recognized that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of value.

# DRUG AND CONDITION INFORMATION

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| **Drug Information** | • Alectinib is an oral, small molecule, ATP-competitive, tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK)<br>• 150 mg capsule<br>• Recommended dosage of 600mg capsule twice daily (oral) |
| **Cancer Treated** | • ALK-positive, locally advanced, or metastatic non-small cell lung cancer |
| **Burden of Illness** | • Four per cent of all non-small cell lung cancers are ALK-positive.<br>• Central nervous system 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.<br>• The development of brain metastases is associated with deteriorated quality of life and shortened survival. |
| **Current Standard Treatment** | • Platinum-based doublet chemotherapy<br>• Pemetrexed<br>• Docetaxel<br>• Ceritinib |
| **Limitations of Current Therapy** | • Response rates to chemotherapy are approximately 20%, and responses generally last only a few months.<br>• Disease progression typically occurs within three to four months, at which point patients require alternative treatment options. |

# 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. Catherine Moltzan, Oncologist (Vice-Chair)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Craig Earle, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

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

- Dr. Craig Earle, Dr. Winson Cheung, and Dr. Kelvin Chan, who were not present for the meeting
- Dr. Anil Abraham Joy, who did not vote due to a conflict of interest
- Cameron Lane, who did not vote due to his 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 (Alecensaro) for non–small cell lung cancer, through their declarations, one member declared a real, potential, or perceived conflict. Based on the application of the *pCODR Conflict of Interest Guidelines*, one member was excluded from voting.

### Information sources used

To inform its deliberations, pERC was provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which included input from a patient advocacy group, a registered clinician, and the pCODR Provincial Advisory Group, as well as original patient advocacy group input submissions. pCODR guidance reports are developed following the pCODR review process and 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

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## APPENDIX 1: pERC RESPONSES TO PAG IMPLEMENTATION QUESTIONS

| PAG Implementation Questions | pERC Recommendation |
|---|---|
| • PAG is seeking information on how alectinib compares with ceritinib in terms of benefits and safety, especially in the subgroup of patients with CNS metastases, recognizing there is no direct comparison between alectinib and ceritinib. | • pERC was uncertain of how alectinib compares with ceritinib with regards to outcomes important to decision-making such as overall survival, progression-free survival, and quality of life due to a lack of robust direct or indirect comparative efficacy data. pERC concluded that alectinib is likely not cost-effective compared with ceritinib. However, there was considerable uncertainty in the cost-effectiveness estimates due to a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation.<br>• Input and opinions from the pCODR Clinical Guidance Panel and registered clinicians indicated that alectinib has better CNS activity and a more favourable toxicity profile compared with ceritinib. |
| • PAG is seeking clarity on treatment duration and treatment discontinuation criteria.<br>• PAG is seeking guidance on the definition of "until loss of clinical benefit." | • Treatment with alectinib should continue until disease progression or unacceptable toxicity. However, in the ALUR trial, patients could continue treatment beyond radiologic disease progression if clinically benefiting.<br>• There may be clinical situations for continuing treatment beyond radiologic-defined progression to maintain disease control and reduce disease burden for patients. pERC concluded that treatment with alectinib should continue until clinically meaningful progression occurs, based on the judgment of the treating oncologist.<br>• The duration of treatment of alectinib in the pharmacoeconomic model is based on statistical modelling of the time to off-treatment data observed in the ALUR trial. |
| • PAG noted that if intolerance to crizotinib is not defined, there would be a lower threshold of tolerance to crizotinib and patients may be deemed intolerant after one dose. | • There will be very few patients who would be intolerant to crizotinib. Intolerance would be determined by the patient and the treating oncologist. |
| • PAG is seeking advice on the preferred sequencing of ALK inhibitors by clinicians (to determine uptake and budget impact).<br>• PAG is seeking guidance on sequencing of ALK inhibitors, chemotherapy, and immunotherapy for ALK-positive NSCLC. | • Optimal sequencing of alectinib and other therapies is unknown.<br>• Although the ALUR trial included patients who had been treated with crizotinib and a platinum-based doublet chemotherapy, pERC agreed that treatment with alectinib is likely to be used as a second-line option following progression on crizotinib, followed by platinum-based doublet chemotherapy as a third-line treatment and subsequently with immune checkpoint inhibitors. However, the Committee acknowledged that there is no direct evidence investigating head-to-head efficacy and safety nor for the appropriate sequence for alectinib with other available therapies (e.g., ceritinib) for the treatment of ALK-positive NSCLC patients who have progressed on crizotinib.<br>• Clinician input indicated that patients would likely try crizotinib first-line, then either ceritinib or alectinib as second-line, and then the other second-generation ALK inhibitor that was not utilized as third-line. pERC noted that there is currently no clinical trial evidence to inform the optimal sequencing of alectinib and other available treatments for ALK-positive, locally advanced, or metastatic NSCLC. |
| • PAG is concerned about indication creep into first-line. | • The ALUR trial did not include patients who were treatment naive; therefore, treatment with alectinib as first-line is out of scope for this review. pERC noted that a request for reimbursing alectinib in patients who are treatment naive would require a Health Canada–approved indication and a submission to pCODR. |