pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

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

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

Drug: Alectinib (Alecensaro)	
Submitted Reimbursement Request: For the treatment of patients with anaplastic lymphoma kinase-positive, locally advanced or metastatic non-small cell lung cancer	
Submitted By: Hoffmann-La Roche Limited	**Manufactured By:** Hoffmann-La Roche Limited
NOC Date: June 11, 2018	**Submission Date:** January 15, 2018
Initial Recommendation: July 6, 2018	**Final Recommendation:** July 25, 2018

Approximate per Patient Drug Costs, per Month (28 Days)	Alectinib costs $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.

pERC RECOMMENDATION

pERC recommends the reimbursement of alectinib for the first line treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) only if the following condition is met:

- Cost-effectiveness is improved to an acceptable level.

If the aforementioned condition cannot be met, pERC does not recommend reimbursement of alectinib. Eligible patients should have a good performance status and treatment should be continued until disease progression or unacceptable toxicity.

pERC 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), a manageable toxicity profile, and no appreciable detriment in quality of life (QoL) compared with crizotinib.

The Committee agreed that alectinib aligns with patient values of symptom control and disease control in patients with central nervous system (CNS) metastases. Alectinib also addresses the need for an effective oral treatment option to delay progression with manageable side effects and offering a delay in the start of subsequent treatment with chemotherapy and whole-brain radiation.

pERC concluded that, at the submitted price, alectinib is not cost-effective compared with crizotinib.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness of Alectinib Compared with Crizotinib
Given that pERC concluded that there is a net clinical benefit with alectinib in patients with ALK-positive, locally advanced or metastatic NSCLC, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of alectinib compared with crizotinib.

Generalizability of Results Regarding Patients with Central Nervous System Metastases
pERC noted that a large percentage of patients in the Global-ALEX trial had stable 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.

Time-Limited Need for Patients Currently on Chemotherapy and Awaiting ALK Test Results
pERC agreed that patients who have started on chemotherapy while awaiting test results for ALK mutation status should be able to switch to alectinib once their results are confirmed. pERC agreed that patients should be treated with the most effective agent available and switching from chemotherapy to alectinib once ALK mutation status is confirmed is reasonable. Based on input from the pCODR Clinical Guidance Panel (CGP), the number of patients that would be switched from chemotherapy to alectinib are expected to be few.

Optimal Sequencing of Alectinib and Other Available Therapies
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. pERC also noted that patients progressing on alectinib are unlikely to be treated with another targeted agent and may instead be offered chemotherapy followed by immunotherapy or be enrolled in a clinical trial.

Please note: Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 11.

SUMMARY OF pERC DELIBERATIONS

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

An estimated 28,600 new cases of lung cancer were diagnosed in Canada in 2017. Approximately 3% to 5% of patients with NSCLC will have a specific genetic mutation or rearrangement of the ALK gene. The estimated number of new patients with ALK-positive advanced lung cancer annually is estimated to be approximately 600 to 800. There are no clear risk factors for the development of ALK-positive NSCLC, and as such, it is a cancer that currently cannot be prevented through risk reduction or screening strategies. Patients with ALK-positive NSCLC are more likely to be younger at diagnosis, have never smoked, and have adenocarcinoma histology. At the time of diagnosis, approximately 25% to 30% of patients with ALK-positive disease have CNS metastases, and for patients alive at three years, the cumulative incidence of CNS metastases is 60% to 70%. Standard treatment for patients with ALK-positive advanced NSCLC is crizotinib, which is approved for reimbursement in the front-line setting in Canada. The penetration of crizotinib into the CNS is low, however. If CNS is the only site of progression, and the disease outside of the CNS is controlled with crizotinib, then local therapy with radiation is often used to treat the site(s) of progression and crizotinib is continued. This temporarily halts progression in the CNS, but inevitably the CNS disease progresses. 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, especially in patients who develop CNS metastases.

pERC deliberated on the results of two phase III randomized controlled trials, Global-ALEX and J-ALEX, which evaluated the safety and efficacy of alectinib compared with crizotinib in patients with ALK-positive, locally advanced (not amenable to curative therapy) or metastatic NSCLC. pERC's discussions were however informed mainly by the Global-ALEX trial. pERC noted that the Global-ALEX trial demonstrated a statistically significant and clinically meaningful improvement in PFS in favour of alectinib. Based on a recent update to the primary analysis, the median PFS was more than tripled in favour of alectinib compared with crizotinib. The benefit was maintained in most subgroups, including in patients with CNS metastases at baseline who comprised just under half of the trial population. The Committee noted that overall survival (OS) data were immature at the primary analysis, and considered the fact that subsequent access to alectinib off the trial may confound any OS benefit observed with longer follow-up.

pERC discussed the available QoL data from the Global-ALEX trial. Although few significant minimally important differences were reported between the alectinib group and the crizotinib group, pERC noted that treatment with alectinib was not associated with an appreciable deterioration in QoL compared with crizotinib. Also, in terms of safety, pERC considered that grade 3 or grade 4 adverse events occurred less frequently in the alectinib group. Although patients on average stayed on alectinib longer than crizotinib, the toxicity profile of alectinib appeared to be better than crizotinib. Although no grade 3 or higher photosensitivity was reported in the trial, the frequency of all grades photosensitivity was higher in the alectinib group (5% versus 0%). Overall, based on the dramatic improvement in PFS; the maintenance of QoL; the favourable toxicity profile compared with crizotinib; and the need for more effective treatment options, particularly in patients with CNS metastases; pERC concluded that there is a net clinical benefit of alectinib for patients with ALK-positive NSCLC.

pERC discussed the generalizability of the trial results and discussed the following considerations. Although the Global-ALEX and J-ALEX trials used different doses of alectinib, pERC agreed that the 600 mg dose, in accordance with the Global-ALEX and Health Canada-approved dose, should be used in the Canadian setting. pERC also noted that few patients with an Eastern Cooperative Oncology Group performance status of two were recruited on the trial. pERC, however, agreed that the decision to treat patients with poorer performance status should be at the discretion of the treating oncologist.

pERC deliberated on input from one patient advocacy group, which indicated that patients value new oral treatment options that offer improvements in PFS, offer improvements in QoL, provide a quick response,

reduce their tumour size, reduce or manage symptoms, and delay the need for whole CNS radiation in patients with CNS metastases. Patients also indicated that their tolerability of a therapy is important. pERC considered that alectinib maintained patients' QoL and has a favourable toxicity profile compared with crizotinib, despite the longer duration of treatment. In patients with CNS metastases, pERC discussed how treatment with alectinib allows patients to delay subsequent treatment with whole brain radiation. The Committee also noted that alectinib would be an effective oral treatment option. pERC considered that the majority of patients who had direct experience with alectinib reported tolerable and manageable side effects, and that it was effective in treating their CNS metastases. Some patients, however, experienced side effects such as severe photosensitivity. Overall, pERC concluded that alectinib aligns with patient values. While pERC acknowledged the patient group's input supporting the use of alectinib, they also noted that the patient group expressed a need for further education for patients using alectinib and concern regarding the high cost of alectinib and the impact on the health system.

pERC deliberated on the cost-effectiveness of alectinib compared with crizotinib based on the submitted economic evaluation and reanalysis estimates provided by the pCODR Economic Guidance Panel. pERC noted that the factor that most influenced the incremental costs was the drug-acquisition costs, while the incremental effect was most influenced by the method for extrapolating OS and the time horizon. pERC noted that the submitter's use of a 30-year time horizon was not reflective of the clinical course of the disease in this patient population under review and considered a number of factors in determining the anticipated long-term benefit with alectinib. pERC established that the Global-ALEX trial has not reported mature OS data and the estimates are likely to be confounded due to subsequent treatments patients may receive with alectinib receive. pERC also considered the CGP's opinion that recent advances in the treatment of ALK-positive NSCLC have improved the overall prognosis of patients. Furthermore, although the median PFS was not reported in the primary analysis, based on a recent updated analysis, median PFS was reported to be 34.8 months in the alectinib group. Based on this, pERC noted that shortening the time horizon to 10 years is reasonable compared with the significantly lower time horizon used in previous CADTH-pCODR reviews in the same indication (use of a 4 year time horizon by the EGP for the review of crizotinib in a similar indication). pERC also noted that, when the best fitting parametric curve is chosen to extrapolate the OS data, the incremental cost-effectiveness ratio is increased. Therefore, pERC concluded that alectinib, at the submitted price, is not cost-effective and would require a substantial price reduction to improve the cost-effectiveness to an acceptable level.

pERC considered the feasibility of implementing a reimbursement recommendation for alectinib. pERC noted that the factors that influenced the budget impact analysis include the number of patients eligible for alectinib and the assumed proportion of eligible patients who would be reimbursed under provincial drug plans. pERC also noted that the number of patients eligible for treatment is likely underestimated, particularly in year two and beyond, as the prevalent population will accumulate yearly.

The Committee noted input from the Provincial Advisory Group, which requested guidance and clarification on the implementation of alectinib. pERC noted that there will be few patients who would have started on chemotherapy while awaiting test results for ALK mutation status and agreed that patients should be able to switch to alectinib once their results are confirmed. Input from the CGP indicated that alectinib is not active in ROS1 mutations. pERC therefore agreed that patients with ROS1 mutation should not be eligible for treatment with alectinib. 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. Input from the CGP indicated that, following progression on alectinib, patients are likely to receive chemotherapy followed by (subsequent to disease progression) treatment with immunotherapy. Clinicians may also opt to enroll patients in a clinical trial following progression on alectinib. Based on the CGP and input from registered clinicians, pERC agreed that it is unlikely patients will receive a targeted agent following alectinib in the first-line setting and that sequencing of agents in this setting is an evolving field. pERC further agreed that it would be reasonable for patients with oligometastases to continue treatment with alectinib as the site of progression can be treated with localized treatment.

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 the pCODR clinical and economic review panels
- Input from one patient advocacy group, Lung Cancer Canada (LCC)
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- One clinician group, [Cancer Care Ontario Lung DAC]
- The PAG
- The submitter [Hoffmann-La Roche Limited]

The pERC Initial Recommendation was to not recommend reimbursement of alectinib for the first line treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non–small cell lung cancer (NSCLC). Feedback on the pERC Initial Recommendation indicated that the manufacturer, PAG and registered clinician group agreed with the Initial Recommendation.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC 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 treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non–small cell lung cancer (NSCLC).

Studies included: Two randomized phase III trials

The pCODR systematic review included two ongoing, open-label, randomized phase III trials, Global-ALEX (N = 303) and J-ALEX (N = 207), evaluating the efficacy and safety of alectinib compared with crizotinib for the first-line treatment of patients with ALK-positive, locally advanced or metastatic NSCLC. In the Global-ALEX trial, patients were allocated 152 patients to the alectinib group and 151 patients to the crizotinib group.

Patient populations: Previously untreated, central nervous system metastases, treatment beyond progression allowed

Key eligibility criteria for both studies included histologically or cytologically confirmed advanced, recurrent (stage IIIB, not amenable to curative treatment), or metastatic (stage IV) NSCLC; ALK positivity confirmed by a validated immunohistochemistry or fluorescence in situ hybridization test; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; asymptomatic central nervous system (CNS) metastases (if CNS metastases present) and adequate organ function. There were key differences between the Global-ALEX and J-ALEX trials. The Global-ALEX trial included patients from international sites (including 18 Canadian patients), previously untreated patients. Alectinib was administered at 600 mg orally twice daily (the approved dose in all countries except Japan), and crossover (after disease progression and discontinuation of assigned treatment) was not permitted, though patients may have received alectinib post-progression outside of the trial if the agent was already approved or available in their country of residence. The J-ALEX trial included only Japanese patients, included previously treated patients. Alectinib was administered at 300 mg orally twice daily, and crossover (upon disease progression and discontinuation of assigned treatment) was permitted. In both trials crizotinib was administered at the same dose and schedule: 250 mg orally twice daily. Patients in both trials were also permitted to receive alectinib post-progression if they were considered to be still benefiting clinically from the agent.

In the Global-ALEX trial, 152 and 151 patients were assigned to alectinib and crizotinib, respectively. Baseline characteristics and demographics were well balanced between the treatment groups. Median age was between 54 years and 58 years, and the majority of patients were female (56%), of Caucasian (50%) or Asian race (46%), non-smokers (63%), and had an ECOG performance status of 0 or 1 (93%). Almost all patients had metastatic disease (97%) and CNS metastases were present in 40% of patients at baseline; of those patients, approximately 16% had received some form of radiation therapy to treat their CNS disease.

In the J-ALEX trial, 103 and 104 patients were assigned to alectinib and crizotinib, respectively. Baseline characteristics were generally balanced between the treatment groups, with the exception of the distribution of CNS metastases at baseline, which were higher in the crizotinib treatment group (28% versus14%). Compared with the Global-ALEX trial, patients in J-ALEX were slightly older (median age between 60 years and 61 years), all Japanese (100%), 36% were second-line and 64% (n = 133) were first-line; and 21% had CNS metastases at baseline.

Key efficacy results: Statistically significant improvement in progression-free survival, benefit in patients with central nervous system metastases

The key efficacy outcome deliberated on by pERC included the investigator-assessed (INV) progression-free survival (PFS) for the Global-ALEX trial. Median INV PFS was not reached (95% CI, 17.7 to not estimable) in the alectinib group and was 11.1 months in the crizotinib group (95% CI, 9.1 to 13.1), demonstrating a statistically significant 53% reduction in disease progression or death with alectinib (hazard ratio [HR] = 0.47; 95% CI, 0.34 to 0.65; $P < 0.001$). An unplanned 10 month updated analysis reported median INV PFS was 34.8 months versus 10.9 months in the alectinib versus crizotinib groups, respectively; demonstrating a 57% reduction in the risk of progression or death in favour of the alectinib group (HR = 0.43; 95% CI, 0.32 to 0.58). The magnitude of the PFS benefit observed with alectinib in the intention-to-treat population was consistent in most pre-specified patient subgroups.

Key secondary outcomes in the Global-ALEX trial included overall survival (OS), CNS outcomes, health-related quality of life (QoL), and safety. No statistically significant differences between the treatment groups were demonstrated for OS at the primary analysis date and the unplanned updated analysis since median overall survival has not been reached. Time-to-CNS progression was significantly longer in the alectinib treatment group (median estimates not reported; HR = 0.16; 95% CI, 0.10 to 0.28; $P < 0.001$), regardless of CNS metastases status at baseline.

pERC deliberated on the results of two phase III randomized controlled trials; however, the committee's conclusions were informed mainly by the Global-ALEX trial. pERC agreed that the Global-ALEX trial demonstrated a statistically significant and clinically meaningful improvement in PFS in favour of alectinib. pERC further noted that the benefit in patients with CNS metastases was clinically meaningful. The Committee agreed that OS data, although immature at the primary analysis, are likely to be confounded due to subsequent access to alectinib off trial. pERC discussed the generalizability of the trial results and discussed the following considerations. Although the Global-ALEX and J-ALEX trials used different doses of alectinib, pERC agreed that the 600 mg dose, in accordance with the global clinical trial, should be used in the Canadian setting. pERC also noted that few patients with an ECOG performance status of two were recruited to the trial. However, pERC agreed that the decision of how to treat patients with poorer performance statuses should be at the discretion of the treating oncologist.

Patient-reported outcomes: No appreciable decline in quality of life

Health-related QoL was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core-30 and Quality of Life Questionnaire–Lung Cancer-13. The primary objectives of the QoL analysis were to compare time to deterioration (TTD) in patient-reported symptoms (cough, dyspnea, chest pain, arm and shoulder pain, fatigue), global health and QoL, and cognitive function scores; and secondly, to compare overall global health and QoL, patient functioning, and side effects of treatment. TTD was defined as the time from randomization until the first confirmed clinically meaningful deterioration in lung cancer symptoms, global health and QoL, and cognitive function. Clinically meaningful change was defined as greater than and equal to 10-point change from baseline score held for at least two consecutive assessments, or an initial greater than and equal to 10-point change above baseline followed by death within five weeks of last assessment.

There were no differences in TTD of patient-reported global health status and QoL or lung cancer symptom scales between treatment groups, with the exception of dyspnea (multi-item scale). TTD in dyspnea favoured crizotinib relative to alectinib, with a median TTD of 22.8 months in the alectinib group and median was not reached in the crizotinib group. Between-group difference met the minimally important difference and was in favour of alectinib treatment for diarrhea, constipation, peripheral neuropathy, nausea and vomiting, appetite loss, and dysphagia. Clinically meaningful improvements were observed in both treatment groups for patient-reported cough, chest pain, pain in other parts, fatigue, and dyspnea (single-item scale). For the subgroup of patients with CNS metastases at baseline, a lower proportion of patients in the alectinib group reported clinically meaningful worsening in QoL compared with crizotinib, starting at week 12 and persisting for most assessments through week 84. Fewer patients receiving alectinib reported clinically meaningful worsening in cognitive functioning compared with crizotinib, starting at week 4 (8% versus 27%) and continuing through week 84 (10% versus 33%). A similar pattern was also observed for fatigue, physical function, and social function scores.

pERC discussed the available QoL data from the Global-ALEX trial. Although few significant minimally important differences were reported between the alectinib group and crizotinib group, pERC noted that treatment with alectinib was not associated with an appreciable deterioration in QoL compared with crizotinib.

Safety: Manageable toxicity profile despite longer duration of treatment

In the Global-ALEX trial the frequency of grade 3 or greater adverse events (AE) was higher in patients treated with crizotinib (50% versus 41% with alectinib); and laboratory abnormalities (i.e., increases in alanine aminotransferase, aspartate aminotransferase and blood bilirubin, and anemia) were the main cause of grade 3 to grade 5 AEs in both treatment groups. Although no grade 3 or higher photosensitivity was reported in the trial, the frequency of all grades photosensitivity was higher in the alectinib group (5% versus 0). The incidence and types of serious adverse events were similar in the two treatment groups (28% with alectinib and 29% with crizotinib). AEs leading to dose reduction (16% versus 21%), interruption (19% versus 25%), and treatment discontinuation (11% versus 13%) occurred in similar proportions of patients in the alectinib group and crizotinib group, respectively. There were five fatal AEs (3%) that occurred in the alectinib group, all deemed unrelated to the study treatment. In the crizotinib group, seven (5%) fatal AEs occurred with two deaths (pneumonitis and cardiac arrest) being considered treatment-related by the investigator. In the J-ALEX trial, the frequency of grade 3 to grade 4 AEs (52% versus 26%) and serious adverse events (26% versus 15%) were higher in the crizotinib group. Treatment interruptions (74% versus 29%) and discontinuations (20% versus 9%) were also higher in patients treated with crizotinib. No fatal AEs were reported in the trial.

pERC considered that grade 3 or grade 4 AEs occurred less frequently in the alectinib group. Although the median PFS with alectinib was more than three times that of crizotinib, it is notable that the toxicity profile of alectinib appeared to be better than crizotinib. Overall pERC agreed that the toxicity profile of alectinib was manageable.

Need and burden of illness: Need in patients with central nervous system metastases

An estimated 28,600 new cases of lung cancer were diagnosed in Canada in 2017. If one assumes that 85% are NSCLC, 70% of which present with advanced or metastatic disease, and 3% to 5% of those are ALK-positive, the estimate of the number of advanced ALK-positive NSCLC cases in Canada in 2017 was approximately 600 to 800. Input from registered clinicians put this figure to between 300 to 1,000 patients per year. Determination of ALK positivity in Canada is standard. There are no clear risk factors for the development of ALK-positive NSCLC; as such, it is a cancer that currently cannot be prevented through risk reduction or screening strategies. Patients with ALK-positive NSCLC are more likely to be a younger age at diagnosis, have never-smoking status, and adenocarcinoma histology. The CNS appears to be a common site of metastases and site of progression. At the time of diagnosis, approximately 25% to 30% of patients with ALK-positive disease have CNS metastases, and for patients alive at three years, the cumulative incidence of CNS metastases is 60% to 70%. Standard treatment for patients with ALK-positive advanced NSCLC is crizotinib, which is approved for reimbursement in the front-line setting in Canada. The penetration of crizotinib into the CNS is low, however. If CNS is the only site of progression, and the disease outside the CNS is controlled with crizotinib, then local therapy with radiation is often used to treat the site(s) of progression and crizotinib is continued. This temporarily halts progression in the CNS, but it inevitably grows again in this area. 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, especially in patients who develop CNS metastases.

Registered clinician input: Alectinib superior to crizotinib, unclear sequencing post alectinib

Clinicians providing input noted that alectinib demonstrated a clinically and statistically significant improvement in median PFS, overall response rate, time-to-CNS metastases, and median duration of response. Input indicated that the OS results may have been confounded due to subsequent access to alectinib off trial. In patients with a history of CNS metastases, registered clinicians indicated that alectinib demonstrated superiority over crizotinib. Registered clinicians noted that the use of whole brain radiation can be delayed with the use of alectinib. Based on clinical practice, registered clinicians also indicated that both alectinib and crizotinib are well tolerated, although some slight differences are present.

Registered clinicians discussed sequencing of agents and noted that alectinib would likely be the preferred first-line option as the general oncology principle is to give the best agent first. It is, however, unclear what role crizotinib would have as a treatment subsequent to alectinib. Furthermore, it was indicated that sequencing of ALK inhibitors is an evolving field with multiple emerging agents and a move toward clarifying resistance mechanisms that can define the optimal agent, though this practice is still a research area.

PATIENT-BASED VALUES

Values of patients with ALK- positive NSCLC: Treatment options, improved quality of life , improved survival, reduced side effects

pERC noted input from Lung Cancer Canada (LCC) indicating that patients with ALK- positive NSCLC tend to be young, non-smokers, and have a relatively low five-year survival rate compared with the general population of NSCLC patients. LCC indicated that patients experience symptoms that are consistent with lung cancer patients in general. LCC noted that targeted oral therapies may decrease the burden of lung cancer by maintaining QoL, delaying or avoiding less tolerable treatments, reducing fear and side effects, and allowing patients to maintain a normal lifestyle that is not common with other forms of treatment. Crizotinib was described as being an effective, highly active, valuable oral treatment option that allows patients to be active and high functioning. Patients, however, expressed feeling anxiety and frustration about their access to available treatments.

Patient values on treatment: Improved progression-free survival, quality of life, reduced side effects, delay whole brain radiation

pERC noted that patients value new oral treatment options that offer improvements in progression-free survival, improvements in QoL, provide a quick response, reduce their tumour size, reduce or manage symptoms, and delay the need for whole brain radiation in patients with CNS metastases. Patients also indicated that tolerability of the new option is important. Patients with direct experience using alectinib indicated that they found alectinib to be very effective, reducing tumour size up to 75%, and in some cases resulting in complete elimination of the tumour. Patients also reported living, in some cases, beyond the 12-month, 18-month, and two-year marks. Patients reported relief from the symptoms of lung cancer. The majority of patients reported either no or low side effects from alectinib. Commonly reported side effects included fatigue, photosensitivity, constipation, weight gain, edema, or even no side effects. Patients noted that the ability to return to work or raise their families were advantages of alectinib therapy. pERC considered that the majority of patients who had direct experience with alectinib reported tolerable and manageable side effects, and that it was effective in treating their CNS metastases. Some patients, however, experienced side effects such as severe photosensitivity. Caregivers reported positive impact on their QoL given the effectiveness of alectinib in reducing the disease burden of their loved one.

LCC indicated that having multiple treatment options may possibly improve their patient outcomes as treating oncologists will be able to pick the best option for the patient. pERC noted that alectinib is likely to be the preferred option in this setting as the efficacy outcomes were superior to crizotinib. This was supported by the pCODR Clinical Guidance Panel (CGP) and registered clinician input. Although the median PFS is dramatically improved with alectinib, pERC noted less certainty on the treatment options that will be available to patients subsequent to alectinib. While the rate of side effects is low with the use of these new innovative, targeted therapies, LCC noted that the impact of infrequently occurring side effects such as photosensitivity could be significant.

pERC considered that alectinib maintained patient's QoL and has a favourable toxicity profile compared with crizotinib, despite the longer duration of treatment. In patients with CNS metastases, pERC noted that treatment with alectinib allows patients to delay subsequent treatment with whole brain radiation. Overall, pERC concluded that alectinib aligns with patient values.

ECONOMIC EVALUATION

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

The pCODR Economic Guidance Panel assessed cost-effectiveness and cost-utility analyses comparing alectinib (Alecensaro) to crizotinib for the treatment of patients with previously untreated ALK-positive, advanced or metastatic NSCLC.

Basis of the economic model: Clinical and cost inputs

Costs included were drug-acquisition cost, supportive care costs, subsequent therapies cost, AEs cost, CNS metastases costs, CNS monitoring costs, and terminal care costs.

Key clinical effect estimates considered in the analysis include OS, PFS, duration of treatment, CNS PFS, utilities, disutilities, and CNS metastases progression disutilities. pERC noted that although OS data in the Global-ALEX trial was not mature and is likely to be confounded with future follow-up, altering the method of extrapolating the long-term OS benefit had a significant impact on the incremental cost-effective ratio (ICER).

Drug costs: High drug cost

Alectinib costs $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.

Crizotinib costs $130.00 per 250 mg tablet. At the recommended dose of 250 mg twice daily, crizotinib costs $260.00 per day and $7280.00 per 28 days.

Cost-effectiveness estimates: Sensitive to the time horizon and long-term overall survival extrapolation

pERC deliberated on the cost-effectiveness of alectinib compared with crizotinib based on the submitted economic evaluation and reanalysis estimates provided by the pCODR Economic Guidance Panel. pERC noted that the factor that most influenced the incremental costs was the drug-acquisition costs, while the incremental effect was most influenced by the method for extrapolating OS and the time horizon. pERC noted that the submitter's use of a 30-year time horizon was not reflective of the clinical course of the patient population under review and considered a number of factors in determining the anticipated long-term benefit with alectinib. pERC stated that the Global-ALEX trial has not reported mature OS data and the estimates are likely to be confounded due to subsequent treatments patients may receive with alectinib. pERC also considered discussion from the CGP that indicated that recent advances in the treatment of ALK-positive NSCLC have improved the overall outlook of patient prognosis. Furthermore, although the median PFS was not reported in the primary analysis, in a recent updated analysis, median PFS was reported to be 34.8 months in the alectinib group. Based on this, pERC noted that shortening the time horizon to 10 years is reasonable compared with the significantly lower time horizon used in previous CADTH–pCODR reviews for the same indication (use of a 4 year time horizon by the EGP for the review of crizotinib in a similar indication).

pERC also noted that the curve used to extrapolate long-term OS was not the best fitting for the available data. When the best fitting parametric curve is chosen to extrapolate the OS data, the ICER is increased significantly. In the base-case results, utility estimates were the same between treatment groups. Given that patients progressing on alectinib will likely go onto chemotherapy compared with patients progressing on crizotinib who still have targeted agents as options, the pCODR Economic Guidance Panel lowered the utility estimate in the alectinib group in the post-progression state. Although this had a smaller impact on the ICER, when all inputs were combined, the ICER was more than doubled compared with the base-case results. Therefore, pERC concluded that alectinib, at the submitted price, is not cost-effective and would require a substantial price reduction to improve the cost-effectiveness to an acceptable level.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Unknown sequencing, underestimated budget impact analysis

pERC considered the feasibility of implementing a reimbursement recommendation for alectinib. pERC noted that the factors that influenced the budget impact analysis include the number of patients eligible for alectinib and the assumed proportion of eligible patients who would be reimbursed under provincial drug plans. Based on the reported median PFS, patients remained on treatment for nearly three years; pERC therefore noted that the number of patients eligible for treatment is likely underestimated especially starting in year two as the prevalent population will grow. pERC noted that the Ontario-specific budget impact analysis was likely underestimated.

The Committee noted input from pCODR's Provincial Advisory Group, which requested guidance and clarification on the implementation of alectinib. pERC agreed that patients who have started on chemotherapy while awaiting test results for ALK mutation status should be able to switch to alectinib once their results are confirmed. pERC noted input from the CGP that indicated that such instances would be few. pERC noted input from the CGP indicating that alectinib is not active in ROS1 mutations and agreed that patients with ROS1 mutation should not qualify for treatment with alectinib. pERC further agreed that it would be reasonable for patients with oligometastases to continue treatment with alectinib as the site of progression can be treated with localized treatment. pERC noted that a large percentage of patients in the Global-ALEX trial had stable 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.

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. Input from the CGP indicated that patients are likely to move onto chemotherapy post alectinib, followed by immunotherapy. Clinicians may also opt to enroll patients in a clinical trial following progression on alectinib. Based on the CGP and input from registered clinicians, pERC agreed that it is unlikely patients will receive a targeted agent following alectinib in the first-line setting, as the sequencing of agents in this setting is an evolving field.

DRUG AND CONDITION INFORMATION

Drug Information	• Oral, small molecule, adenosine triphosphate-competitive, tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK) • 150 mg capsule • Recommended dosage of 600 mg capsule twice daily (oral)
Cancer Treated	• ALK-positive, locally advanced or metastatic non-small cell lung cancer
Burden of Illness	• Three to five per cent of all non-small cell lung cancers 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 60% to 70% of patients treated in later stages • The development of CNS metastases is associated with deteriorating quality of life and shortened survival
Current Standard Treatment	• Crizotinib
Limitations of Current Therapy	• Low penetration of the CNS • Eventual progression

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
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Christopher Longo, Economist
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. Anil Abraham Joy, Dr. Kelvin Chan, and Dr. Avram Denburg, who were not present for the meeting
- Cameron Lane, who did not vote due to his role as a patient member alternate.

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

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, 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 and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

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

Use of this Recommendation

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

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG is seeking guidance on whether patients who have started on chemotherapy while waiting for test results could be switched to alectinib either prior to disease progression or after progression on chemotherapy, if the decision was to complete chemotherapy treatments.	• pERC agreed that patients who have started on chemotherapy while awaiting test results for ALK mutation status should be able to switch to alectinib once their results are confirmed. pERC noted input from the CGP that indicated that such instances would be few.
• PAG noted that ROS1 mutations are treated similarly to ALK mutations and is seeking information on the use of alectinib in this subgroup of patients, recognizing this may be out of scope of this review.	• pERC noted input from the CGP indicating that alectinib is not active in ROS1 mutations. pERC therefore agreed that patients with ROS1 mutations should not qualify for treatment with alectinib.
• PAG noted that the trial in Japan (J-ALEX) used a dose of 300 mg twice daily, which is half the dose approved by Health Canada for second-line treatment. PAG is seeking information on the use of the lower dose in the Canadian population.	• pERC agreed with the CGP that the J-ALEX trial involved patients of a specific ethnicity, with specific genetic and ethno cultural differences that make the generalizability to the Canadian population tenuous. Therefore, the standard dose in the Canadian setting should be 600 mg taken orally twice daily.
• PAG is seeking guidance from CGP and pERC on whether continuing alectinib in patients with oligometastatic progression would be acceptable, particularly for patients who develop CNS metastasis.	• pERC further agreed that it would be reasonable for patients with oligometastases to continue treatment with alectinib as the site of progression can be treated with localized treatment.
• PAG is seeking guidance on the sequencing of all available therapies (crizotinib, ceritinib, platinum chemotherapy, pemetrexed, docetaxel, and nivolumab [or pembrolizumab if PD-L1 positive) and whether there is information from the Global-ALEX trial on what treatments were used post-progression, as use of downstream therapies affects the economic evaluation of alectinib and funding criteria of other treatments. • PAG is seeking data on the clinical benefits of using crizotinib after alectinib, as there may be pressure to fund this sequence. • Ceritinib for treatment of ALK-positive NSCLC after crizotinib was reviewed recently by pERC. Thus, PAG is also seeking information and cost-effectiveness on the use of ceritinib after alectinib and whether the sequence of alectinib to ceritinib is better, or equivalent, to the sequence of crizotinib to ceritinib.	• 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. Input from the CGP indicated that patients are likely to move to chemotherapy post alectinib followed by immunotherapy. Clinicians may also opt to get patients onto a clinical trial following progression on alectinib. • Based on the CGP and input from registered clinicians, pERC agreed that it is unlikely patients will receive a targeted agent following alectinib in the first-line setting. pERC also noted that the sequencing of agents in this setting is an evolving field.

ALK = anaplastic lymphoma kinase; CGP = CADTH pCODR Clinical Guidance Panel; CNS = central nervous system; NSCLC = non-small cell lung cancer; PAG = pCODR Provincial Advisory Group; PD-L1 = programmed death-ligand 1; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee.