CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Alectinib (Alecensaro) for Non-Small Cell Lung Cancer

July 25, 2018

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List of Abbreviations

ALK	Anaplastic lymphoma kinase
AEs	Adverse events
CGP	Clinical Guidance panel
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EMA	European Medicines Agency
EUnetHTA	European Network for Health Technology Assessment
FISH	Fluorescence in situ hybridization
GI	Gastrointestinal
HR	Hazard ratio
IHC	Immunohistochemistry
INV	Investigator assessment
IRC	Independent review committee
ITT	Intent-to-treat
MCID	Minimal clinically important difference
MEDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
pCODR	pan-Canadian Oncology Drug Review
pERC	pCODR Expert Review Committee
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
QLQ-C30	Quality of Life Questionnaire Core-30
QLQ-LC13	Quality of Life Questionnaire Lung Cancer Module-13
QOL	Quality of life
RCTs	Randomized controlled trials
RECIST	Response Evaluation Criteria for Solid Tumours
SAEs	Serious adverse events
SAP	Statistical analysis plan
SD	Standard deviation
TTD	Time-to-deterioration

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding alectinib (Alecensaro) for NSCLC. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding alectinib (Alecensaro) for NSCLC conducted by the Lung Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on alectinib (Alecensaro) for NSCLC, a summary of submitted Provincial Advisory Group Input on alectinib (Alecensaro) for NSCLC, and a summary of submitted Registered Clinician Input on alectinib (Alecensaro) for NSCLC, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of alectinib (Alecensaro) as monotherapy for treatment of patients with ALK-positive, locally advanced or metastatic NSCLC.

The Health Canada regulatory approval was for the first-line treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC). Alectinib is an oral, small molecule, ATP-competitive, tyrosine kinase inhibitor of ALK. The recommended dose of alectinib is 600 mg (four 150 mg capsules) given orally, twice daily with food (total daily dose of 1200 mg). Patients continue to receive treatment until disease progression or unacceptable toxicity.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Two ongoing, open label, randomized phase 3 trials, Global ALEX[1] and J-ALEX,[2] were identified that met the selection criteria of the pCODR systematic review. Both trials evaluated the efficacy and safety of alectinib as first-line treatment in patients with ALK-positive, locally advanced or metastatic NSCLC, and were funded by Hoffman La Roche Ltd.

The trials used similar eligibility criteria to enroll patients, which included the following:

- histologically or cytologically confirmed advanced or recurrent (stage IIIB not amenable to curative treatment) or metastatic (stage IV) NSCLC
- ALK-positivity confirmed by a validated IHC or FISH test
- measurable disease by RECIST version 1.1
- ECOG performance status of 0-2
- asymptomatic CNS metastases (if CNS metastases present)
- adequate organ function

In both trials alectinib was compared to crizotinib, which was administered at the same dose and schedule in each trial, and trial outcomes were also similar. However, there were a number of features that distinguished the trials; these differences are summarized below:

- Global ALEX[1]
    - included international patients (from 98 centres in 29 countries including Canada, enrolled between August 2014 and January 2016) who were previously untreated
    - administered alectinib at a dose of 600 mg (4 capsules twice daily), which is the approved dose in all countries outside of Japan
    - randomization was stratified by ECOG performance status, race and presence/absence of CNS metastases at baseline
    - the primary outcome was PFS by INV
    - treatment crossover (upon disease progression and discontinuation of assigned treatment) was not permitted
- J-ALEX[2]
    - included Japanese patients (from 41 centres in Japan, enrolled between November 2013 and August 2015) who were previously untreated or had received one prior regimen of chemotherapy (second-line patients)
    - administered alectinib at a dose of 300 mg (8 capsules twice daily), which is the approved dose in Japan
    - randomization was stratified by ECOG performance status, treatment line, and disease stage
    - the primary outcome was PFS by IRC
    - treatment crossover (upon disease progression and discontinuation of assigned treatment) was permitted

For the J-ALEX trial,[2] the pCODR review focused on the efficacy results that have been reported for the subgroup of patients treated in the first-line setting (treatment naïve target population); and therefore, are limited to a subgroup analysis of these patients for the primary outcome of trial. The pCODR Methods Team put in a request to the Submitter to provide additional efficacy and safety outcome data for this patient subgroup, however, they indicated data were not available. For safety, the results of all patients in the J-ALEX trial were summarized to enable a comparison of AEs at the two different doses of alectinib.

Global ALEX Trial[1]

The primary outcome of the Global ALEX trial was PFS by INV in the ITT population. The secondary outcomes of interest included ORR, DOR, PFS by IRC, OS, CNS outcomes, which included time-to-CNS progression, CNS ORR, CNS DOR, and CNS progression rates at selected time points, health-related QOL and safety.[3]

A total of 303 patients were randomized to either alectinib or crizotinib treatment groups using a centralized and stratified block randomization method. As previously noted, treatment crossover after disease progression was not permitted in the trial; however, patients assigned to crizotinib may have received alectinib post-progression outside of the trial if drug was already approved or available in their country of residence. Both treatment groups received study drug until disease progression, unacceptable toxicity, or withdrawal of consent or death. Patients were also permitted to receive alectinib post-progression if they were considered to be still benefiting clinically from the drug.[4] Patients with isolated, asymptomatic CNS progression were permitted to receive local therapy at

the investigators' discretion, followed by continued study treatment until systemic and/or symptomatic CNS progression.

The trial allocated 152 patients to the alectinib group and 151 patients to the crizotinib group. Most patients were treated at trial sites in Asia (50%), Europe (26%), and North America (16%). The trial included 18 (6%) Canadian patients.[4] Overall, the distributions of baseline characteristics between the treatment groups were well-balanced. The median age of patients was between 54 and 58 years old, with the majority of patients under the age of 65 (77%).[5] The majority of patients were female (56%), of Caucasian (50%) or Asian race (46%),[5] non-smokers (63%), and had an ECOG 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.

All efficacy analyses, including all secondary outcomes, were performed in the ITT population. Patient–reported health-related QOL was assessed using the EORTC QLQ-C30 and QLQ- LC13.[3] At the primary analysis data cut-off date (February 9, 2017), median duration of follow-up was 18.6 months (range, 0.5-29.0) in the alectinib group and 17.6 months (0.3-27.0) in the crizotinib group. Highlights of the key outcomes of the Global ALEX trial are presented in Table 1, and are summarized below:

Systemic Efficacy

- The trial met its primary endpoint for efficacy; median PFS by INV was not reached (95% CI, 17.7-not estimable) in the alectinib group and was 11.1 months in the crizotinib group (95% CI, 9.1-13.1), demonstrating a statistically significant reduction in disease progression or death with alectinib (HR=0.47, 95% CI, 0.34-0.65; p<0.001). A similar treatment benefit, albeit of slightly lower magnitude, was observed for PFS by IRC.
- The magnitude of PFS benefit observed with alectinib in the ITT population was consistent in all pre-specified patient subgroups with the exception of active smokers (n=17) and patients with an ECOG of 2 (n=20) at baseline. The results of these two latter subgroups should be interpreted with caution, however, in light of the small sample sizes, which can lead to unreliable estimates.
- No statistically significant differences between the treatment groups were demonstrated for the outcomes of ORR and OS.
- Time-to-CNS progression was significantly longer in the alectinib treatment group (median estimates not reported; HR=0.16, 95% CI, 0.10-0.28; p<0.001), regardless of CNS metastasis status at baseline.

CNS Efficacy

- In patients with measurable/non-measurable CNS metastases at baseline, the CNS ORR in the alectinib group was 59% (n=38/64; 95% CI, 46-71) compared to 26% (n=15/58; 95% CI, 15-39) in the crizotinib group; and a CR was obtained in 29 (45%) patients and 5 (9%) patients, respectively. The difference in CNS ORR between the treatment groups was statistically significant (OR=4.05, 95% CI, 1.89-8.70; p=0.0002).[5] In this patient subgroup, time-to-CNS progression also demonstrated statistically significant improvements in favour of alectinib versus crizotinib.
- In the smaller group of patients with measurable CNS metastases at baseline, results were similar but of lower magnitude (Table 1).

Quality of Life

- No differences between the treatment groups were demonstrated in TTD of patient-reported global health status/QOL[6] or lung cancer symptom scales (composite or individual symptom scales including cough, dyspnea, chest pain, arm/shoulder pain, fatigue) with the exception of dyspnea (multi-item scale); the TTD in dyspnea favoured crizotinib relative to alectinib, with a median TTD of 22.8 months in the alectinib group and median not reached in the crizotinib group (HR=1.76, 95% CI, 1.05-2.92; p=0.0285).[7,8]
- There was also no difference between the groups in TTD in cognitive functioning.[6]
- In terms of side effects of treatment, alectinib demonstrated greater tolerability (that is, the difference between groups met the MCID of ≥10) versus crizotinib for the following treatment-related symptoms: diarrhea, constipation, peripheral neuropathy, nausea/vomiting, appetite loss, and dysphagia.[5] Both treatment groups demonstrated clinically meaningful improvements (≥10-point decrease) in other lung cancer symptoms, including patient-reported cough, chest pain, pain in other parts, fatigue, and dyspnoea (single-item scale).[6]
- For the subgroup of patients with CNS metastases at baseline, a lower proportion (≥10% difference) of patients in the alectinib group reported clinically meaningful worsening in QOL compared with crizotinib, starting at week 12 (4% in the alectinib group versus 16% in the crizotinib group) and persisting for most assessments through week 84 (0% alectinib versus 17% crizotinib).[5] Fewer patients receiving alectinib reported clinically meaningful worsening in cognitive functioning compared with crizotinib, starting at week 4 (8% vs. 27%) and continuing through week 84 (10% vs. 33%).[5] A similar pattern was also observed for fatigue, physical function and social function scores.[5]

Harms

Duration of treatment was significantly longer in the alectinib treatment group at 17.9 months (range, 0-29) compared to 10.7 months (range, 0-27) in the crizotinib group. Overall, AEs of any grade occurred in equal frequency in the two groups (97% in each group). There were five AEs that occurred in greater frequency in alectinib-treated patients compared to crizotinib-treated patients, which included anemia (20% versus 5%), myalgia (16% versus 2%), blood bilirubin increase (15% versus 1%), weight increase (10% versus 0%), musculoskeletal pain (7% versus 2%) and photosensitivity reaction (5% versus 0%). Comparatively, crizotinib was associated with a higher frequency of GI disorders and liver enzyme abnormalities.

The frequency of grade 3 or greater AEs was higher in patients treated with crizotinib (50% versus 41% with alectinib); and laboratory abnormalities (i.e., increases in ALT, AST and blood bilirubin, and anemia) were the main cause of grade 3-5 AEs in both treatment groups. The incidence of SAEs was similar in the two treatment groups (Table 1), and fatal AEs occurred more in patients treated with crizotinib (n=7, 5%; two treatment-related deaths) compared to the alectinib group (n=5, 3%; all deaths unrelated to study treatment). Adverse events leading to dose reduction, interruption, and treatment discontinuation were slightly lower in patients treated with alectinib compared to patients treated in the crizotinib group (Table 1).

Table 1: Highlights of key outcomes of the Global ALEX trial.

Outcomes	Global ALEX Trial[1]	
	Alectinib 600 mg (n=152)	Crizotinib (n=151)
Median follow-up in months	18.6 (0.5-29)	17.6 (0.3-27)
Median duration of treatment in months	17.9 (0-29)	10.7 (0-27)
Primary Outcome		
PFS by INV, median	Not reached (17.7-NE)	11.1 (9.1-13.1)
HR (95% CI); p-value[a]	0.47 (0.34-0.65); p<0.001	
Key Secondary Outcomes - Systemic Efficacy		
PFS by IRC, median	25.7 (19.9-NE)	10.4 (7.7-14.6)
HR (95% CI); p-value[a]	0.50 (0.36-0.70); p<0.001	
ORR by INV	82.9 (76.0-88.5)	75.5 (67.8-82.1)
CR	6 (4)	2 (1)
PR	120 (79)	112 (74)
OR (95% CI); p-value[b]	1.62 (0.92-2.84); p=0.0936[5]	
Time-to-CNS progression,[c] median	NR	NR
HR (95% CI); p-value	0.16 (0.10-0.28); p<0.001	
OS, median	NE	NE
No. events	35 (23)	40 (26)
HR (95% CI); p-value[a]	0.76 (0.48-1.20); p=0.24	
Key Secondary Outcomes - CNS Efficacy		
Patients with measurable CNS metastases at baseline		
n for subgroup	n=21	n=22
CNS ORR by IRC, n	17	11
% (95% CI)	81.0 (58.0-95.0)	50.0 (28.0-72.0)
CNS CR, n (%)	8 (38)	1 (5)
OR (95% CI); p-value[b]	4.34 (1.10-8.7217.17); p=0.0306[5]	
Patients with measurable/non-measurable CNS metastases at baseline		
n for subgroup	n=64	n=58
CNS ORR by IRC, n	38	15
% (95% CI)	59.0 (46-71)	26.0 (15-39)
CNS CR, n (%)	29 (45)	5 (9)
OR (95% CI); p-value[b]	4.05 (1.89-8.7); p=0.0002	
Time-to-CNS progression, median	NR	NR
HR (95% CI); p-value[a]	0.18 (0.09-0.36); p<0.0001[9]	
Harms Outcomes, n (%)		
n evaluated for safety	n=152	n=151
Grade ≥3 AEs	63 (41)	76 (50)
AEs (any grade)	147 (97)	146 (97)
SAE	43 (28)	44 (29)
Fatal AE	5 (3)	7 (5)
AEs leading to treatment discontinuation	17 (11)	19 (13)
AEs leading to dose reduction	24 (16)	31 (21)
AEs leading to dose interruption	29 (19)	38 (25)

Abbreviations: AEs - adverse events, CI - confidence interval, CNS - central nervous system; CR - complete response; HR - hazard ratio, INV - investigator; IRC - independent review committee; NE - not estimable; NR - not reported; OR - odds ratio; ORR - overall response rate as per RECIST version 1.1; OS - overall survival; PFS - progression-free survival per RECIST version 1.1; SAEs - serious adverse events.

Notes:
[a] - An HR <1.00 favours alectinib; treatment groups were compared using a stratified log-rank test at a two-sided α=0.05.
[b] - An OR >1.00 favours alectinib; treatment groups were compared using a stratified Mantel-Haenszel

test at a two-sided α=0.05.
[c] - Time-to-CNS progression was defined as the time from randomization to first radiographic evidence of CNS progression by IRC, where CNS progression was defined as progression due to newly developed CNS lesions and/or progression of pre-existing baseline CNS lesions (per RECIST version 1.1). The analysis was adjusted for the competing risks (from non-CNS progression and death) between treatment groups.

Updated efficacy data from the Global Alex trial, which are based on an additional 10 months of follow-up, have been published in abstract form (December 1, 2017 data cut-off date).[10] The median follow-up in the alectinib and crizotinib groups was 27.8 and 22.8 months, respectively. At this updated (unplanned) analysis, 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, 0.32-0.58). The magnitude of PFS benefit observed with alectinib in the ITT population was consistent in patients with (HR=0.35; 95% CI, 0.22-0.56) and without (HR=0.47;95% CI, 0.32-0.71) baseline CNS metastasis.[10] Overall survival data remained immature with 28.3% and 31.8% of events having occurred in the alectinib and crizotinib groups, respectively (HR=0.76; 95% CI, 0.50-1.15). The percentage of patients with AEs leading to dose reduction, interruption, and treatment discontinuation, and fatal AEs were similar to the primary analysis.

J-ALEX[2]

A total of 207 patients were randomized in the J-ALEX trial, with 103 and 104 patients allocated to alectinib and crizotinib, respectively; these patients comprised the ITT patient population. All patients received randomized treatment until disease progression, unacceptable toxicity, or withdrawal of consent or death. Similar to the Global ALEX trial, patients could continue treatment with alectinib beyond disease progression (based on physician discretion) if they were still benefiting clinically from the drug.

The baseline characteristics of randomized patients 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% vs.14%). Compared to the patient population in the Global ALEX trial, patients in J-ALEX were slightly older (median age between 60 and 61 years old) and were all Japanese (100%). Approximately 24% of patients were staged with post-operative recurrence, 36% were treated with alectinib after one previous line of chemotherapy (second-line), and 64% (n=133) of patients were treated in the first-line setting. Compared to the Global ALEX trial, a lower proportion of patients had CNS metastases at baseline (21% versus 40%).

Systemic Efficacy

At the primary analysis data cut-off date (December 3, 2015), median duration of follow-up was 12 months (range, 6.5-15.7) in the alectinib group and 12.2 months (range, 8.4-17-4) in the crizotinib group. At that time, the trial met its primary endpoint, demonstrating both non-inferiority and superiority of alectinib compared to crizotinib. In the subgroup of patients treated in the first-line setting (n=133), median PFS by IRC was not estimable in the alectinib group (95% CI, 17.5-not estimable) and 10.2 months (95% CI, 8.3-13.9) in the crizotinib group (HR=0.31; 95% CI, 0.17-0.57).

Harms

Duration of treatment was similar between the two treatment groups (13 months in the alectinib group versus 12 months in the crizotinib group). Compared to the Global ALEX trial, patients in the J-ALEX trial had a shorter duration of treatment exposure to alectinib (an approximately five month difference). Similar to the Global ALEX trial, almost all patients in J-ALEX experienced an AE (any grade, 97% with alectinib versus 100% with

crizotinib). The most common AEs (any grade) in the alectinib group were constipation (35%), nasopharyngitis (20%), dysgeusia (18%), blood creatine phosphokinase increase (17%), upper respiratory tract infection (17%), myalgia (16%), rash (13%), blood bilirubin increase (12%), and stomatitis (12%). There were three AEs that occurred in greater frequency in alectinib-treated patients (versus crizotinib), which included blood bilirubin increase (12% versus 1%), myalgia (16% versus 3%), and anemia (6% versus 1%). The frequency of grade 3-4 AEs (52% versus 26%) and SAEs (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.

Critical Appraisal and Limitations

The systematic review performed identified two RCTs that met the selection criteria for inclusion: the Global ALEX trial,[1] which is the basis of the Submitter's pCODR submission and funding request, and the J-ALEX trial.[2] As previously mentioned, the J-ALEX trial evaluated alectinib at a lower dose (300 mg), which is the approved dose in Japan, but not in Canada and all other countries where alectinib is available. For that reason, as well as the unavailability of data for a majority of outcomes in the target population of patients treated in the first-line setting, the critical appraisal of evidence focused on the Global ALEX trial.[1]

When considering the totality of evidence from the trials, it's important to highlight that evidence on the efficacy of alectinib in treatment naïve patients from the J-ALEX trial is based on a subgroup analysis that included 133 patients for one outcome (PFS). At least nine different subgroup analyses were performed in the J-ALEX trial but none of the subgroups were pre-specified in the protocol. Consequently, the subgroup analysis results from the trial should be considered exploratory (refer to the discussion on subgroup analyses below, which outlines limitations also applicable to the J-ALEX trial).

Overall, the Global ALEX trial was well conducted owing to specific design features (e.g., appropriate randomization and allocation concealment procedures, ITT analysis, and minimal losses to follow-up), however, the following limitations were noted:

- The open-label design of the trial makes it prone to different biases (patient selection and performance bias), which can affect internal validity. The investigators, trial personnel, patients, as well as data analysts were all aware of study drug assignment, which can potentially bias outcome assessment in favour of alectinib if assessors (investigators, patients, and data analysts) believe the study drug is likely to provide benefit. An attempt was made in the trial to mitigate bias by using an IRC to assess outcomes using standardized criteria (RECIST) and identical assessment schedules in the treatment groups, as well as conducting pre-specified sensitivity analyses to measure the robustness of the primary outcome analysis results. However, for subjective outcomes like health-related QOL and AEs, there is a greater risk of detection bias because patients and investigators would be aware of the specific treatment being administered.
- Although the subgroup analyses performed in the trial were pre-specified and demonstrated a consistent treatment benefit in most of the subgroups examined, caution is warranted in interpreting these results. Testing a large number of subgroups (including additional subgroups analyses performed post-hoc) can increase the chances of detecting false positive results. A proper subgroup analysis includes a statistical test for interaction to assess whether the treatment effect differs among subgroups, opposed to individual tests within each subgroup. Since the trial protocol indicated no adjustments were made for multiple testing and no tests for interaction were performed, the subgroup analysis results should be considered exploratory and interpreted within this context.
- Although the protocol specified treatment crossover was not permitted in the trial, the endpoint of OS is confounded by patients who received subsequent therapies post-progression. Subsequent therapies included receipt of alectinib in patients assigned to crizotinib and who lived in participating countries where alectinib received approval in the second-line setting after crizotinib during the course of the trial. Further, it should be highlighted that OS was not formally tested in the trial (based on the testing hierarchy of ORR not being statistically significant) nor sufficiently powered to test for differences in OS between the two treatment groups.

- The assessment of health-related QOL had limitations that raise uncertainty about the validity of the QOL findings, more specifically:
    - Patient compliance in completing questionnaire assessments was sub-optimal in both treatment groups, which resulted in missing data. This may bias findings since there may be systematic differences in the characteristics of patients who complete and don't complete questionnaires. This, combined with the much longer treatment exposure of patients treated with alectinib compared to crizotinib, reduces the reviewer's ability to accurately assess and compare QOL between the treatment groups.
    - The published and unpublished data on QOL available to pCODR was limited by incomplete and selective reporting of outcomes and therefore as presented may not reflect the true QOL experience of patients in the trial.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, lung cancer severely limits the time patients have to experience their lives. While crizotinib is another therapy currently available for patients with NSCLC who are ALK-positive, alectinib provides patients the opportunity of choice in their treatments, and ensures that another option will be made available to them should intolerance to crizotinib occur. As stated by LCC, alectinib may halt or slow the progression of brain metastasis, and has given patients the ability to spend longer and more quality time with their loved ones and doing the things they want (for example, going to work, or raising a family). A number of quotes were provided by LCC indicating patient's excitement about the reduced side effects of alectinib and the sudden increase in quality of life. Within the sample of 73 respondents, 59 provided information regarding side effects 40 of the 59 respondents reported low or no side effects. Commonly reported side effects of alectinib included fatigue, photosensitivity, constipation, weight gain, edema or no side effects. Photosensitivity was mentioned by 10 respondents with severity ranging from mild to severe. Many patients reporting side effects stated that they would still recommend alectinib to others, as it extended their lives or gave them more time to wait for different treatments. LCC posits that alectinib allows patients and caregivers to return to their normal lives, and provides versatility in treatment options.

Please see Section 3 below for more details.

Provincial Advisory Group (PAG) Input

Clinical factors:

- Sequencing of other targeted therapies and chemotherapies with alectinib

Economic factors:

- Cost effectiveness of sequencing other targeted therapies and chemotherapies after progression on alectinib

Please see Section 4 below for more details.

Registered Clinician Input

In summary, the clinicians providing input feel that alectinib is clinically superior first line treatment for all ALK+ patients when compared to crizotinib, particularly in the subgroup of patients with CNS metastasis. They identified that the key benefits of alectinib are clear demonstrations that the lung cancer can be initially controlled for more than twice as long as with crizotinib, demonstrated clinically meaningful improvements in progression free survival and response rate compared to current standard first line treatment, and has slightly less toxicities. More importantly, alectinib significantly protects patients from the risk of developing brain metastases, which a particular problem in ALK positive lung cancer. The clinicians providing input feel that alectinib, if recommended for public reimbursement, would replace crizotinib in the first-line treatment of ALK positive NSCLC. Please see below for details from the clinician inputs.

Please see Section 5 below for more details.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for Alectinib.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the phase 3 Global ALEX trial[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="3">Population</td><td>ECOG Performance Status</td><td>The trial limited eligibility to ECOG PS 0-2.

The proportions of patients by ECOG performance status were as follows:

<table><tr><td colspan="3">ECOG PS, n (%)</td></tr><tr><td></td><td>Alectinib</td><td>Crizotinib</td></tr><tr><td>0 or 1</td><td>142 (93)</td><td>141 (93)</td></tr><tr><td>2</td><td>10 (7)</td><td>10 (7)</td></tr></table></td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The majority of patients enrolled in the trial had an ECOG PS of 0-1. Data on the efficacy and safety of alectinib in patients with an ECOG PS >1 is limited, but includes a small phase 2 study of 18 patients of performance status 2-4. Although there was a low proportion of patients with ECOG PS 2 in the randomized trials, the CGP agree that the use of alectinib in patients with ECOG PS ≥2 may be appropriate and should be left to the discretion of the treating oncologist.</td></tr>
<tr><td>Asymptomatic CNS Metastases</td><td><table><tr><td colspan="3">CNS metastases at baseline, n (%)</td></tr><tr><td></td><td>Alectinib</td><td>Crizotinib</td></tr><tr><td>No</td><td>64 (42)</td><td>58 (38)</td></tr><tr><td>Yes</td><td>88 (58)</td><td>93 (62)</td></tr><tr><td colspan="3">Treatment for CNS metastases at baseline:</td></tr><tr><td>Any</td><td>27 (18)</td><td>22 (15)</td></tr><tr><td>Surgery</td><td>1 (4)</td><td>1 (5)</td></tr><tr><td>Radiosurgery</td><td>5 (19)</td><td>4 (18)</td></tr><tr><td>Whole-brain radiotherapy</td><td>17 (63)</td><td>16 (73)</td></tr><tr><td>Other</td><td>4 (15)</td><td>1 (5)</td></tr></table></td><td>Are the results of the trials generalizable to patients with CNS metastases?</td><td>The benefits of alectinib in this population are generalizable to patients with and without brain metastases, whether symptomatic or asymptomatic at baseline.</td></tr>
<tr><td>Organ dysfunction</td><td>The trial limited eligibility to patients with adequate hepatic, renal and bone marrow function. Patients with liver disease were excluded from the trial.</td><td>Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population?</td><td>The use of alectinib should be limited to patients with adequate hepatic function as determined by the treating oncologist. Use in patients with bone marrow dysfunction or renal dysfunction should be done cautiously, but the benefits of alectinib may outweigh the risks in some cases. There are few situations where one would anticipate crizotinib to be the preferred option.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the phase 3 Global ALEX trial[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Ethnicity or Demographics</td><td>ALEX was a global trial that enrolled patients from 98 centres in 29 countries including Canada (n=18),[11] and:

Australia (n=16), Bosnia and Herzegovina (n=1), Brazil (n=1), Chile (n=1), China (n=10), Costa Rica (n=3), Egypt (n=1), France (n=8), Guatemala (n=1), Hong Kong (n=19), Israel (n=4), Italy (n=23), Republic of Korea (n=48), Mexico (n=3), New Zealand (n=4), Poland (n=13), Portugal (n=7), Russian Federation, (n=17) Serbia (n=3), Singapore (n=14), Spain (n=8), Switzerland (n=9), Taiwan (n=14), Thailand (n=19), Turkey (n=7), Ukraine (n=4), United Kingdom (n=3), and the United States (n=24).[12,13]

Race subgroups assessed in the trial:
<table><tr><td colspan="3">Race, %</td></tr><tr><td></td><td>Alectinib</td><td>Crizotinib</td></tr><tr><td>Asian</td><td>69 (45)</td><td>69 (46)</td></tr><tr><td>Non-Asian</td><td>83 (55)</td><td>82 (54)</td></tr></table>
<table><tr><td colspan="2">PFS by INV results for race subgroups:</td></tr><tr><td></td><td>HR (95% CI)</td></tr><tr><td>Asian</td><td>0.46 (0.28-0.75)</td></tr><tr><td>Non-Asian</td><td>0.49 (0.32-0.75)</td></tr></table></td><td>If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting?</td><td>The CGP agrees that the ethnicity of the study population would be comparable to the Canadian population and therefore the results of the trial would be generalizable to the Canadian population.</td></tr>
<tr><td></td><td>Dose of intervention</td><td>The ALEX Global trial evaluated alectinib at a dose of 600mg (4 capsules) orally twice daily.

The J-ALEX trial evaluated alectinib (versus crizotinib at the same dose and schedule) at a dose of 300mg (8 capsules) orally twice daily.</td><td>Are the results of the trial generalizable to a different dose or administration schedule?</td><td>The CGP agrees that the results at this time are not generalizable to the dose used in the J-ALEX trial. The J-ALEX trial was a specific ethnicity, with specific genetic and ethnocultural differences that make the generalizability to the Canadian Population tenuous. The standard dose (until proved otherwise) should be 600 mg PO BID without food.</td></tr>
<tr><td>Setting</td><td>Countries participating in the trial</td><td>Refer to “Ethnicity/demographics above.</td><td>If the trial was conducted in other countries, is there any known difference in the practice pattern between those countries and Canada? Differences in the patterns of care might impact the clinical outcomes or the resources used to</td><td>Overall, most patients were from Europe and Asia where practice patterns would be similar to Canada. The CGP agree that the locations where the trials were conducted would be comparable to the Canadian population and therefore the results of the trial would be generalizable to the broader</td></tr>
</table>

Domain	Factor	Evidence from the phase 3 Global ALEX trial[1]	Generalizability Question	CGP Assessment of Generalizability
			achieve the outcomes.	Canadian population.
	Location of the participating centres	Participating centres included academic and community-based treatment centres.	If the trial was conducted only in academic centres are the results applicable in the community setting?	The CGP agree that the locations of participating centres would be comparable to Canadian treatment centres and therefore the results of the trial would be generalizable to the broader Canadian population.
	Supportive medications, procedures, or care	The type and frequency of concomitant medication use and procedures were generally comparable between the treatment groups. The most commonly used medications were steroids, analgesics (slightly higher in the alectinib group), supplements, antiemetics, laxatives and stool softeners.[4] Approximately one third of patients in each group had concomitant surgery; the majority of these procedures were performed to evaluate CNS metastases. In the subgroup of patients with CNS metastases, [redacted].' *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.)*	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	Overall, alectinib was well tolerated by patients. The majority of AEs were low grade with low toxicity. The CGP agree that given the modest side effects of alectinib, the support medications, procedures and care given in the ALEX trial are generalizable to the majority of Canadian treatment centres. The management of CNS metastases in particular with surgery and radiation appears similar to what one would expect in Canada.

Abbreviations: AEs - adverse events; CGP - clinical guidance panel; CNS - central nervous system; ECOG - Eastern Cooperative Oncology Group; PFS INV - progression-free survival by investigator assessment; PS - performance status.

1.2.4 Interpretation

Burden of Illness

Although no national data are available for Canadian patients, the French Cooperative Thoracic Intergroup (IFCT) reported a 5% ALK positivity in 8,134 patients assessed in a one year period.[14] Given that lung cancer rates and smoking rates are similar between Canada and France, a 3%-5% incidence is a reasonable assumption for Canada. Roughly 20 000 patients per year die of lung cancer in Canada and the majority with advanced disease. Based on these figures, the estimated number of new Anaplastic Lymphoma Kinase (ALK) positive advanced lung cancer patients annually would be ~600-800. ALK positive lung cancer, in contrast to the majority of lung cancer in Canada, is a disease that develops in people independent of tobacco exposure and in younger patients. Unfortunately, as a disease without any known risk factors for the development, there are no methods of prevention or early detection. Tobacco control efforts and early lung cancer screening programs are not expected to alter the burden of ALK positive advanced lung cancer. The central nervous system (CNS) appears to be a common site of metastases and site of progression. At the time of diagnosis, approximately 25-30% of patients with ALK positive disease have CNS metastases, and for patients alive at 3 years, the cumulative incidence of CNS metastases is 60-70%.

Current Practice Patterns in Canada and Clinical Need

Determination of ALK positivity by immunohistochemistry or other methods is standard practice for advanced, non-squamous, non-small cell lung cancer (NSCLC). Crizotinib, an oral small molecule inhibitor of ALK, MET and ROS1 kinase, is the currently accepted first-line therapy for metastatic ALK-positive NSCLC in Canada, is recommended as such in various practice guidelines, and is funded for this indication. The benefit of Crizotinib over standard chemotherapy in these patients was shown in the Profile 1014 trial and led to the widespread use where funding was available.

In terms of management while on Crizotinib, this has not been well described. Although it is known that CNS metastases are common in these patients, there is significant variability in whether screening or surveillance for metastases should occur. Opinions range from no surveillance in an asymptomatic patient (i.e. wait to screen the CNS until symptoms develop or therapies change), to surveillance MRI scans at regular intervals (as frequent as every 6 months). The practice pattern of CNS surveillance in ALK positive lung cancer in Canada has not been well described.

Despite crizotinib's success, it was a drug designed to target a separate pathway (MET), and was developed without the known predilection of ALK positive disease for the CNS. Progression on crizotinib inevitably occurs in the majority of patients - often within 12 months. The CNS is the most common site of progression on crizotinib, likely related to the low penetration of crizotinib into the CNS coupled with the high incidence of ALK positive NSCLC CNS spread.

For patients with CNS progression alone, physicians may have treated with local modality therapies (such as stereotactic radiosurgery), and continued with crizotinib, while others may switch to a second line ALK inhibitor such as alectinib or ceritinib if available. For patients with CNS progression and extra-CNS progression, patients may have received a second line ALK inhibitor, continue on crizotinib with local treatment to resistant areas in some cases, or a switch to a platinum-based doublet chemotherapy, or single agent chemotherapy. For patients with symptomatic progression in the CNS and rapid deterioration, profound loss of function, or drug toxicity, best supportive care alone may be used. After one or more lines of ALK inhibitor therapy, after platinum doublet therapy

maintenance pemetrexed, and often after multiple radiation treatments, patients may receive immunotherapy with a PD-L1 or PD-1 inhibitor, although very few ALK positive patients were included in the checkpoint inhibitor clinical trials, and they are generally thought to be less effective in non-smoking patients with driver mutations – such as this group.

Given the recognition of the unique patterns of spread of ALK-positive disease, and the potential consequences of CNS spread – both in terms of the disease itself and radiation therapy, a clinical need for a therapy that controlled disease for longer than crizotinib – particularly in the CNS was identified. Alectinib is a second generation ALK TKI that has significant activity in crizotinib resistant NSCLC and is not a substrate for p-glycoprotein, leading to significantly higher CNS penetration and clinical activity. The Global - ALEX and J-Alex trials were randomized phase 3 trials of alectinib versus crizotinib as first targeted therapy in advanced ALK positive patients.

Efficacy

The primary end-points of both the Global- ALEX and J-ALEX trial were progression-free survival (PFS) as assessed by the investigator. Important secondary end points included PFS by an independent review committee (IRC), systemic and CNS objective response and disease control. The trials had some differences – the major differences in design were the dose of alectinib used (300mg PO BID in the J-ALEX) and 600 mg PO BID in the Global-ALEX; and the inclusion of patients pretreated with chemotherapy (36%) in the J-ALEX study, and the possibility of cross-over on progression in the J-ALEX Study. These differences likely led to the higher percentage of patients in the J-ALEX study having CNS disease at baseline, as patients further in their disease course are more likely to have brain metastases.

The results of the ALEX and J-ALEX trials include a significant reduction in the combined risk of progression or death, with hazard ratios of 0.47 and 0.31, respectively. For G-ALEX, the likelihood of progression at 12 months was 68% versus 49%. The median PFS as determined by independent central review was significantly better with alectinib (25.7 months) versus crizotinib (10.4 months) at publication time, and recently updated to 10.9 months for crizotinib to 34.8 months for alectinib (updated June 1, 2018 at ASCO). CNS progression was significantly delayed (HR=0.16, $p< 0.001$) with alectinib in comparison to crizotinib, with a 12 month CNS progression of 9.4% for alectinib and 41% for crizotinib. For patients with CNS disease at baseline, the 12 month CNS progression rate was 16% versus 58%.

For QOL results, both crizotinib and alectinib were associated with a clinically meaningful improvement in lung cancer symptoms. For patients with CNS metastases at baseline, 16% of patients on crizotinib had clinically meaningful QOL worsening at 12 weeks in comparison to 4% in the alectinib group. In addition, a clinically meaningful worsening in cognitive function in these patients occurred more frequently with crizotinib than with alectinib, with a difference that appeared sustained (8% worsening at week 4 in alectinib arm versus 27% worsening in crizotinib arm).

Both the crizotinib and alectinib treatment groups had low numbers of patients with confirmed deterioration in HRQOL, with 13.2 % or less in both groups. For all comers (CNS and no CNS events) there was no significant difference in time to deterioration in cognitive function, with a median of 20 months in the crizotinib group and not reached in the alectinib group.

Harms Safety and Tolerability
In terms of important patient related outcomes, alectinib appears to be associated with both increased tolerability from a medication perspective and improved quality of life from a disease perspective.

Only 11% of alectinib patients and 13% of crizotinib patients discontinued treatment due to an adverse event. However, given that alectinib patients had a duration of treatment of 18 months in comparison to 10.7 months for crizotinib (i.e. crizotinib patients had significantly shorter time to discontinue treatment).

The frequency of grade 3 or greater AEs were higher in patients treated with crizotinib (50%) compared to patients treated with alectinib (41%); those occurring most often with alectinib were laboratory abnormalities including increases in ALT, AST or blood bilirubin, and anemia, which each occurred in ≤ 5% of patients.

The incidence of serious AEs (SAEs) was similar in the two treatment groups: 28% with alectinib and 29% with crizotinib. The types of SAEs were also similar, and included pneumonia, lung infection, pneumonitis, pulmonary embolism, pyrexia, ALT increased, and acute kidney injury, which each occurring in ≤ 5% of patients in both treatment groups. Diarrhea, constipation, dysphagia, and anorexia – GI toxicity - are important for patient QOL, and these were lower with alectinib. Musculoskeletal side effects – also important for QOL - were at a higher frequency with alectinib as were weight gain and photosensitivity. Laboratory abnormality adverse events (not patient symptom related) included an increased frequency of bilirubin elevations in the alectinib arm and a decreased frequency of ALT/AST elevation. Anemia occurred at a higher frequency with alectinib – although the majority was Grade 1 and 2.

1.3 Conclusions

The CGP concluded that there is a net clinical benefit to alectinib in the treatment of ALK-positive NSCLC patients as first line targeted therapy – either in the true first line setting prior to any chemotherapy, or in the first targeted setting for patients for whom ALK positivity is not determined until after chemotherapy has begun. The evidence for this comes from two randomized studies – the randomized phase 3 J-ALEX trial[1] and the ALEX trial.

The CGP considered the following:

- The benefits of alectinib in this population are particularly evident and measurable in patients with CNS metastases at baseline, but appear regardless of the presence of CNS metastases. Alectinib should be seen as a clinically significant advance in the first line treatment of ALK positive patients regardless of CNS metastases status and be considered as a standard option for patients in this setting.
- OS data in the ALEX and J-ALEX trials were immature at the time of data analysis. With sufficient follow-up, OS could be evaluated but any benefit may be confounded by either on study cross-over or subsequent treatments outside of study.
- The difference in PFS was early and profound. Crizotinib performed as expected, and in concordance with previous trials (PROFILE 1014). Alectinib was associated with earlier and more prolonged quality of life benefit.
- Without mature OS data from the ALEX study, some clinicians may consider it premature to conclude replacing crizotinib with alectinib in the first line setting, and crizotinib should remain a valid therapeutic option. However, it would be anticipated that the

majority of clinicians would favour using alectinib and prefer to give the more efficacious and better tolerated treatment as first line therapy.

- The trial(s) employed a very frequent monitoring schedule for CNS metastases, incorporating MRI scanning every two months. This deviation from what is normal practice in much of the country and has implications for the translation of this therapy to the non-clinical trial population. Given the low rate of CNS progression with alectinib, and the lack of alternative systemic therapy options, clinical practice may include MRI scanning for asymptomatic patients at much less frequent intervals (if at all) than if crizotinib were used first line. However, if alectinib were not funded first line (but available second line), physicians would be incentivized to adopt frequent monitoring for CNS progression on crizotinib in order to switch to alectinib as second line therapy earlier.
- A potential clinical concern with the use of alectinib as first line therapy is determining what the optimal second line therapy is upon progression. First line crizotinib patients for whom crizotinib fails may be able to subsequently use alectinib and have a potentially efficacious treatment. First line alectinib patients will fail treatment with alectinib much later, but there are to date no known subsequent efficacious targeted therapies. Although this is a potential clinical concern, it is unlikely physicians would choose to use a less effective therapy up front, and crizotinib would be expected to be used first line in less than 10% of patients if alectinib were available.
- Although high grade adverse event rates were similar, the patients on alectinib were exposed to drug significantly longer.
- While PFS has not been validated as a surrogate endpoint for either quality of life or overall survival benefit in non-small cell lung cancer, it appears from the patient and physician input that the fear of cancer progression – particularly in the CNS – is a relevant clinical issue in these patients. Reducing CNS metastases and preventing growth is a very important goal, particularly of this magnitude, and is likely to lead to a lengthened life with improved quality. CNS metastases may be associated with significant morbidity and are of an unpredictable nature, making their prevention and control an important clinical goal.
- The CGP agreed that alectinib does not have proven activity in ROS 1 mutations at this time, and this indication is only to replace crizotinib as first line therapy for ALK positive patients. While crizotinib targets multiple different mutations (ALK, ROS, cMET), alectinib does not target these other mutations, but is specific for ALK.
- The CGP agrees that the results at this time are not generalizable to the dose used in the J-ALEX trial. The J-ALEX trial was a specific ethnicity, with specific genetic and ethnocultural differences that make the generalizability to the Canadian Population tenuous. The standard dose (until proved otherwise) should be 600 mg taken orally twice daily without food.
- The CGP agrees that there will be some patients who may continue on alectinib after oligoprogression of a single site of disease (CNS or non-CNS). However, as criteria for progression on clinical trials include a sum of multiple lesions, it is quite possible that the phenomenom of oligoprogression would not have been captured as a progression event using RECIST 1.1. criteria regardless, so the estimates of duration of therapy are likely accurate from the clinical trial.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lung Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

In Canada, 2 out of every 5 people are expected to develop cancer in their lifetime. Furthermore, 1 out of 4 Canadians are expected to die of cancer. Lung cancer is the second-most commonly diagnosed cancer in both men and women, and is the leading cause of cancer deaths in Canada. Non-small cell lung cancers (NSCLC) are the most common type of lung cancers, comprising 85% of lung cancers. In 2017, it is estimated that there will be 28,600 new cases of lung cancer diagnosed and 21,100 deaths associated with lung cancer, with incidence and mortality rates of 69.9/100,000 and 51.4/100,000 respectively.[15] NSCLC represents approximately 85 % of all cases of lung cancer and for the purposes of therapeutic decision, are categorized by histologic appearance as either squamous or non-squamous NSCLC. The majority of patients with NSCLC will present with or develop advanced/metastatic disease. For these patients, treatment intent is to palliate symptoms and prolong survival. In patients with non-squamous NSCLC, the first step in determining treatment options is assessment of molecular markers, including chromosomal rearrangement of the Anaplastic Lymphoma Kinase (ALK) gene on chromosome 2 (ALK positive NSCLC). In these cases, the product of an ALK fusion gene acts as an oncogenic driver. No clear risk factors for the development of ALK positive NSCLC exist. As such, it is a cancer that currently cannot be prevented through risk reduction or screening strategies. Certain clinical characteristics amongst lung cancer patients are more likely to be associated with ALK positive NSCLC, including younger age at diagnosis, never smoking status and adenocarcinoma histology.[16] Although no national data is available for Canadian patients, The French Cooperative Thoracic Intergroup (IFCT) report a 5% ALK positivity in 8134 patients assessed in the 1 year period between April 2012-April 2013.[14] Central nervous system (CNS) metastases are quite common in ALK positive lung cancers, presenting in up to 30 % of patients at diagnosis, and developing in more than 50 % of patients initially treated with crizotinib at some point in their disease course.[17]

2.2 Accepted Clinical Practice

Crizotinib, an oral small molecule inhibitor of ALK, MET and ROS1 kinase, is the available and funded first-line therapy for metastatic ALK-positive NSCLC in Canada. This is based on an open label phase III study that confirmed superior objective response rates [74% vs. 45%, (P<0.001)] and progression-free survival (PFS) [median 10.9 months vs. 7.0 months; hazard ratio for progression or death with crizotinib, 0.45; 95% confidence interval [CI], 0.35 to 0.60; P<0.001)] favouring crizotinib when compared to first-line platinum doublet chemotherapy; overall survival was not different between the two arms, likely due to the high rate of cross-over to crizotinib in the chemotherapy arm.[18] Crizotinib is continued in the absence of disease progression or unacceptable toxicity, and may be continued past radiologic progression particularly if progression occurs only in limited sites of disease and is controlled with other modalities, or if the patient is continuing to derive clinical benefit in the prevention of symptoms and maintenance of quality of life. In the PROFILE 1014 trial, 73% of patients were treated beyond radiologic progression with crizotinib, for a median of 3.1 months. However, patient impactful disease progression on crizotinib inevitably occurs in the majority of patients usually within 12 months. This may be due to development of ALK resistance mutations, gain in copy number, or alternative signaling pathways.[19] Most commonly, disease progresses in the Central Nervous System (CNS), as

not only is the penetration of crizotinib low into the CNS, but ALK positive disease has a predilection for CNS spread. If CNS is the only site of progression, and 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.

The second generation ALK inhibitor ceritinib has demonstrated ability to overcome resistance to crizotinib and is shown to provide durable responses and meaningful benefit in terms of progression free survival in both crizotinib resistant and crizotinib naive patients.[20] In the randomized phase III trial ASCEND-5, ceritinib was superior to single agent pemetrexed or docetaxel in ALK positive patients who had been previously treated with crizotinib and platinum doublet chemotherapy.[21] Although, ceritinib is available through a special access program, it is not currently publically funded in Canada.

Alectenib is another ALK inhibitor, which has demonstrated both an improvement in the second line setting in terms of disease control outside of the CNS, but also an ability to control intracranial disease due to its pharmacokinetic profile. For patients with ALK positive advanced NSCLC progressing on crizotinib intra or extracranially, alectinib therapy can be used where funded/available. In addition, platinum doublet chemotherapy, particularly platinum combined with pemetrexed is an additional option for treatment. Platinum pemetrexed chemotherapy appears to have activity in ALK positive NSCLC that is similar to that seen in advanced NSCLC without ALK rearrangements.[22]

The activity of check-point inhibitors (immunotherapy) is largely unknown as very few ALK positive patients were included in the check-point inhibitor clinical trials. In first line immunotherapy clinical trials, ALK, ROS, and EGFR positive patients were specifically excluded. Although there were some of these patients in second line trials, the durable clinical benefit rate for immunotherapy is quite low in low mutation burden tumours. Oncogenic dominant driver mutation cancers – such as ALK positive lung cancers – fit this group of poor responders to immunotherapy. The paradigm for the management of patients with dominant treatable oncogenic mutations is to treat with all active TKI's first before considering chemotherapy, with immunotherapy most often reserved for progression after chemotherapy options are exhausted.

Alectinib is seeking reimbursement approval for the treatment of those patients with ALK-positive NSCLC who have not previously received crizotinib. As ALK positive NSCLC has such a high predilection for CNS spread, the activity of Alectinib in preventing or treating progression – largely caused by intracranial metastases appears to offer a significant advantage over crizotinib as first line therapy

2.3 Evidence-Based Considerations for a Funding Population

The Canadian Cancer Society estimates that in 2017, there were 28,600 new cases of lung cancer in Canada.[15] If one assumes that 85 % are NSCLC, 70 % of which present with advanced / metastatic disease, and 4 % of those are ALK-positive, the estimate of the number of advanced ALK-positive NSCLC in Canada in 2017 was approximately 680. Determination of ALK positivity in Canada is standard. It uses an immunohistochemistry test to screen advanced non-squamous NSCLC, with confirmation in equivocal cases by fluorescent in-situ hybridization.[23]

Alectinib has clinically meaningful activity in those patients whose disease has progressed on crizotinib. Two phase II trials of alectinib at a dose of 600 mg taken orally twice daily have been conducted in patients previously treated with crizotinib. In study NP28716 (n=87 patients) which was conducted in centers in Canada and the US, objective response was seen in 52% of patients,

with a median duration of response of 13.5 months.[24] Brain metastases were present in 60% of patients at baseline. The CNS response was seen in 75% of patients with measureable brain metastases with median duration of CNS response of 11 months. In study NP28673 (n=138) the objective response rate was 50% with median PFS 8.9 months.[25] In the 60% of patients with CNS metastases at baseline, the CNS response rate was 57% with CNS disease control rate of 83%. In both phase II trials alectinib was well tolerated with majority of adverse events being Grade 1 or 2. pCODR previously reviewed alectinib in a narrower population for patients with ALK positive NSCLC with CNS metastases in February 2017. pERC did not recommend reimbursement of alectinib as the Committee was not confident of the net clinical benefit of alectinib because of limitations in the evidence from available clinical trials studies NP28716 and NP28673. While pERC was confident that alectinib produces a CNS tumour response, the Committee was unable to determine how alectinib compares with other treatments with respect to outcomes important to decision-making, including OS, PFS and quality of life.[26]

The phase II trials served as the basis for the ALUR trial, a randomized phase III trial of alectinib versus chemotherapy in patients previously treated with platinum-doublet chemotherapy and failed on crizotinib. The ALUR trial addresses the evidence gap cited in the initial pCODR review mentioned above. The preliminary results of the ALUR trial were presented at ESMO 2017.[27] Eligible patients (n=107) were randomized 2:1 to receive alectinib at 600 mg BID or single agent chemotherapy (pemetrexed or docetaxel). At baseline, brain metastases were present in 65% of the alectinib patients and 74% of the chemotherapy patients. The median PFS as determined by investigator was significantly better with alectinib (9.6m) versus chemotherapy (1.4 m) (HR=0.15) as was the response rate (37.5 % versus 2.9%). Response in CNS was seen in 54% with alectinib versus 0% of chemotherapy patients. Alectinib was well tolerated with less grade 3-5 AE's (27%) versus chemotherapy (41%).

These trials have demonstrated that alectinib is an active drug in ALK positive NSCLC after progression on crizotinib and is superior to the alternative of single agent chemotherapy. In the ALUR trial all patients had received platinum doublet chemotherapy in addition to crizotinib, and in both phase II trials the majority of patients also received platinum chemotherapy (75%-80%). In NP28673, the chemotherapy naïve patients had a higher ORR (69%) and PFS (13 m) than the ITT population. It is difficult to draw firm conclusions from this because of the small numbers of chemo-naïve patients. It is reasonable to conclude that switch to alectinib after crizotinib is at least as effective as in patients who also received prior chemotherapy.

The ALEX Global and J-ALEX trials were designed to run worldwide and in Japan respectively, to examine the question as to whether beginning with alectinib would result in improved patient outcomes in comparison to beginning treatment with crizotinib. Due to the both the ability to overcome crizotinib resistance from a pharmacokinetic point of view – with increased CNS bioavailability, and from a pharmacodynamic point of view – with activity in crizotinib resistant cells, the drug was trialled in first line. Both of these studies showed significant improvements with alectinib in terms of PFS and intracranial progression. In J-ALEX, the median PFS increased from 10.2 months to 25.9 months, while the ALEX Global study reported an increase in median PFS from 11.1 months to not yet reached. In the ALEX Global trial, 41.4% of patients in the crizotinib arm had intracranial progression by 12 months, while 9.4% of patients in the alectinib group had intracranial progression by 12 months. Overall survival data are not mature at this time.

The potential number of patients in Canada for whom alectinib would be considered as first line therapy would include virtually all patients with a known ALK positive advanced/recurrent NSCLC, although some clinicians may prefer to use crizotinib as first line therapy so that they have a second line therapy they may also be able to use (alectinib). Patients with alectinib treatment as first line therapy will have disease control with first line therapy for a median of

over one year longer patients receiving crizotinib, so will be forced to face the question of what to do as second line therapy at a significantly later date. Although it is clear that not all patients with advanced NSCLC have molecular testing done, either because of lack of accessible/adequate tissue samples or because they are too ill for systemic therapy (poor performance status or co-morbidities), it is anticipated that the number of these patients will be small.

2.4 Other Patient Populations in Whom the Drug May Be Used

The funding indication being sought is in patients with ALK-positive advanced NSCLC as first line therapy. The use of alectinib in patients with a poor performance status (3,4) appears to be feasible and effective based on phase II data. It is unlikely that randomized trials will ever be completed in this difficult to treat and rare population, and the encouraging results from phase II studies show the use of alectinib in this patient population is feasible and effective.

For other patients for whom crizotinib has shown efficacy – such as ROS positive and MET exon 14 mutation positive patients, it is not expected that alectinib will be substituted for crizotinib in those populations unless clinical trials report otherwise.

In the rare patient who receives palliative chemotherapy before ascertaining ALK status, it is anticipated that alectinib would be used as the first targeted therapy in these patients.

In extremely rare situations with stage IIIB/C ALK positive NSCLC for whom radical treatment is not feasible up front, alectinib may be used followed by consolidative curative type therapies (surgery/radiation) if no distant metastases are found and the patient has had a dramatic response. In cases such as these, or in cases with oligometastatic ALK positive disease for whom radical treatments to all sites of disease are treated, there will be uncertainty regarding the use of alectinib following radical treatment to all sites of disease. These situations will be extremely rare.

The CGP feels it would be reasonable to offer alectinib to patients with known ALK positive advanced lung cancer, previously untreated with targeted therapy. It is also reasonable to use alectinib for patients with poor performance status. In cases of stage IVA and IIIB/C disease not amenable to radical therapy upfront, it would also be reasonable to include first line alectinib as part of the patients treatment plan.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Patient input regarding alectinib (Alecensaro) for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) was provided by Lung Cancer Canada (LCC). LCC obtained information from patients with experience with alectinib when it was used as:

- second-line therapy in patients with ALK-positive NSCLC with central nervous system (CNS) metastases (for a previous pCODR submission in October 2016);
- second-line therapy in patients with ALK-positive NSCLC with and without CNS metastases (for a previous pCODR submission in August 2017); and
- first-line therapy in patients with and without CNS metastases (for the current submission in January 2018).

For the October 2016 submission, information regarding patient and caregiver experiences with alectinib were obtained by LLC through an environmental scan of online forums, and subsequent one-to-one follow-up telephone interviews to further understand the alectinib experience (three interviews). In total, input from 41 respondents, which included 22 patients and 19 caregivers all with alectinib experience, was contained in the submission and is included here. Attempts were made to locate the individuals from the forums who were included here but none continued to post and therefore updated information was not obtained for this submission.

For the August 2017 submission, patient and caregiver experiences were obtained through another environmental scan consisting of online forums and questionnaires; there were five patients and eight caregivers who provided input. An additional 11 patients and two caregivers provided further information through one-on-one interviews. Of the 11 patients interviewed, three were actually re-interviewed; two patients were interviewed for the October 2016 submission for alectinib, and one was interviewed for a previous submission on ceritinib. Each of these patients was counted once in the total of 26 respondents, which included 16 patients and 10 caregivers. Two of the interviewed patients used alectinib as a first-line therapy.

For the current submission (first-line therapy), information was obtained through telephone interviews that were conducted in January 2018 with seven patients and one caregiver. Of the eight respondents, there were four males and four females between the ages of 44 and 61 years; four had experience with alectinib as a first-line therapy, three had experience with alectinib as a second-line therapy, and one had experience with alectinib as a third-line therapy. None of the interviewed respondents were previously interviewed for the other two pCODR submissions. Patients were asked verbal, open-ended questions in a semi-structured interview format.

Considering all three pCODR submissions, input on alectinib was obtained from a total of 73 respondents, which included 43 patients and 30 caregivers; of these, six patients clearly identified as having used alectinib as first-line therapy. A summary of the sources of patient and caregiver input can be found in Table 1.

Table 1: Summary of patient and caregiver data sources

Submission date	Data source	Patient no.	Caregiver no.
October 2016	Phone*	3	1
	Forum	22	19
	Questionnaire	0	0
August 2017	Phone	11	2
	Forum	5	7
	Questionnaire	0	1
January 2018	Phone	7	1
	Forum	0	0
	Questionnaire	0	0

*follow-up interviews

From a patient's perspective, lung cancer severely limits the time patients have to experience their lives. While crizotinib is another therapy currently available for patients with NSCLC who are ALK-positive, alectinib provides patients the opportunity of choice in their treatments, and ensures that another option will be made available to them should intolerance to crizotinib occur. As stated by LCC, alectinib may halt or slow the progression of brain metastasis, and has given patients the ability to spend longer and more quality time with their loved ones and doing the things they want (for example, going to work, or raising a family). A number of quotes were provided by LCC indicating patient's excitement about the reduced side effects of alectinib and the sudden increase in quality of life. Within the sample of 73 respondents, 59 provided information regarding side effects 40 of the 59 respondents reported low or no side effects. Commonly reported side effects of alectinib included fatigue, photosensitivity, constipation, weight gain, edema or no side effects. Photosensitivity was mentioned by 10 respondents with severity ranging from mild to severe. Many patients reporting side effects stated that they would still recommend alectinib to others, as it extended their lives or gave them more time to wait for different treatments. LCC posits that alectinib allows patients and caregivers to return to their normal lives, and provides versatility in treatment options.

A recurring theme in the input provided by LCC was patient frustration in regards to access to alectinib. Patients found it bothersome to have to be the ones to advocate for alectinib treatment, and that the process of waiting for treatment can be long and detrimental with patients in fear of progression as they wait. Due to this, some patients reported paying out-of-pocket between $12,000 to over $36,000 CAD for alectinib. LCC noted that one caregiver who paid for his wife's treatment reported seeing an improvement, which brought hope, but his wife passed away before alectinib could really have a strong impact. LCC stated stakeholders, including manufacturers, should work together to find a solution regarding the high cost of the drug.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with NSCLC

LCC did not provide information on the specific symptoms patients in the sample experienced with their cancer, however, they indicated patients who are ALK-positive experience symptoms that are generally consistent with the lung cancer patient population.

3.1.2 Patients' Experiences with Current Therapy for NSCLC

LCC highlighted that patients with NSCLC who are ALK-positive are a unique population, as they tend to be young, non-smokers, and have a relatively low five-year survival rate (17%) compared to the general population of NSCLC patients. Of the interviewed patients, eight were under 50 years of age including two who were in their twenties. In the first-line setting patients are only provided with the option of crizotinib as an available targeted therapy. LCC highlighted the burden associated with non-targeted treatments for NSCLC patients who are ALK-positive, and that targeted oral take-home therapies may decrease the burden of lung cancer by maintaining quality of life, 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 treatments.

Critozinib is currently the only publicly funded targeted treatment for ALK-positive NSCLC patients in the first-line setting. LCC summarized crizotinib as being effective, a highly active, valuable oral treatment option that allows patients to be active and high functioning. "In six weeks, my tumour was half the size it was and in 12 weeks it was quarter of the size. I was symptom free and off oxygen. I was back to being myself. I looked so good I was apologizing for looking so good!"

3.1.3 Impact of NSCLC and Current Therapy on Caregivers

LCC included several points in their submission regarding the benefits of alectinib therapy. These points are summarized below.

LCC reported that many patients 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 mark. The following quotes from patients and caregivers were provided by LCC:

- *"There was significant reduction in tumour size and metastasis with no side effects. I feel like I got the golden ticket!"*
- *"Three and a half months on alectinib (and) my son's scans show… shrinkage in the lung tumour as well. Miraculous! Just can't put words to what I'm feeling."*
- *"No evidence of disease after the first two months on alectinib!"*
- *"I'm hoping to ride alectinib for a while."*
- *"There is light!"*
- *"I am at 18 months on alectinib with only one lymph node showing disease. The doctor says I'm boring. This (is a) wonderful drug."*

Patients reported relief from the symptoms of lung cancer. One caregiver mentioned that within 16 days of starting alectinib treatment his wife's pain decreased from an eight out of ten to zero. The following quotes were provided by LCC:

- *"My right lung was completely shot… shut down, almost completely encrusted in tumour tissue… many quarter size or bigger and too many to count. (They) were growing into my bones and causing lots of pain. I could not breathe without oxygen. I was so weak I could barely get out of bed. 16 weeks later, my CT scans were summarized as: 'No CT evidence of residual or recurrent disease.' A complete response!"*
- *"No more pain or cough. I'm a little tired but it has allowed me to do pretty well anything."*

Information regarding side effects was available from 43 patients and 30 caregivers. Forty respondents reported either no or low side effects from alectinib (Table 2). Three patients reported that after dose reductions, their side effects were eliminated or became more manageable. Some commonly reported side effects included fatigue, photosensitivity, constipation, weight gain, edema or even no side effects. Specifically, photosensitivity was mentioned by 10 respondents, with severity ranging from mild to severe. One patient mentioned that photosensitivity was not even a known side effect of alectinib by their own doctor. The following are quotes from patients in regards to photosensitivity:

- *"I wear a hat every time I go outside"*
- *"I can get a sunburn in my car, my cuticles will burn, my eyelids. Sunscreen isn't enough because there is always one spot I miss. I have to cover up completely with UV clothing"*

Table 2: Severity of side effects	
Severity	No.
None	14
Low	26
Moderate	10
High/intolerable	9
Total	59

Overall, patients considered alectinib to be *"worth it"* for extending their lives or giving them time to wait for newer treatments. A patient on first-line alectinib said, *"Because of alectinib, there is no nothing that I cannot do. Isn't that the point?"*

As mentioned previously, caregivers felt that alectinib allowed them to return to their normal lives and maintain a work life. LCC reported that patients with lung cancer also felt the ability to return to work or raise their family were advantages of alectinib therapy. Twelve interviewed patients, including six interviewed for this submission, were well enough to return to work. The ability for patients to resume their responsibilities was important for restoring feelings of normalcy. One business owner said she felt *"back to normal schedule"* while on alectinib, *"running the business I've owned for 18 years. I love alectinib, I can treat (lung cancer) like a chronic condition."* Another patient diagnosed while pregnant said, *"The normal me is back. Alectinib has allowed me to stay at home with my son and enjoy my maternity leave."* Patients also reported being able to plan for the future and achieve long-term goals, such as planning trips with their kids, organizing their own wedding, or have lasting impressions on their grandchildren.

Versatility in treatment options may provide patients with needed choice in regards to their treatment options, possibly improving their outcomes. LCC highlighted that multiple ALK inhibitors will allow doctors to provide the treatment they believe may be best for their patient, while also providing them with a back-up in case of intolerance. Gathering of real world data may shed further light about which ALK inhibitor doctors should prescribe in future situations. Further, LCC also stated that the incorporation of another take-home therapy, such as alectinib, may reduce burden on patients, caregivers and hospital resources and staff by reducing travel time spent by patients to go to hospitals, and delay hospital-based therapies, which further drain hospital resources, for longer.

Patients reported feeling anxiety and frustration about their access to available treatments. LCC posits that patients with lung cancer may face greater anxiety about waiting for treatments compared to patient with other types of cancers, due to their lack of time; patients with brain metastases may have even less time than lung cancer patients without brain metastasis. It was noted by LCC that patients try to remain educated about available treatments and are aware of those that have received approval, but express frustration that they, *"have to do the work*" by advocating for treatments for themselves. While waiting six months completing forms and paperwork to be approved for treatment, one patient had begun to show progression. Another patient stated, *"We get the wonderful hope (of a new treatment) and then it's dashed. A hell of a ride to be on, it is f*** up! We need options faster".* One mother said that alectinib saved his son *"by the skin of his teeth"* and that her son was able to enjoy three years on alectinib; *"Alectinib saved my son's life. He would have died without it at the age of 22."* Patients felt that having access to alectinib, which was described as a, *"miracle drug"* is what is most important, and that they were as "lucky" as they could be to have had it considering their situation. The following are quotes from two separate patients: *"I am able to* live*. I have a very good quality of life with few side effects and was able to avoid the whole brain radiation. This*

drug is realty amazing." "Alectinib helped me a lot, I like it. Other patients should get this as soon as possible. The government should accept this drug."

Due to delays in getting access to alectinib, three patients reported having to pay out-of-pocket. LCC raised the issue of putting, *"a dollar value on life or death."* One caregiver reported paying approximately $13,000 CAD due to the barriers his wife faced trying to access alectinib. This caregiver stated that while alectinib was initially effective, his wife eventually passed away, *"she had no side effects and it was beginning to work, we were optimistic. We just ran out of time."* Another patient payed $12,000 CAD out-of-pocket while waiting for insurance forms to be reviewed, *"It made me very anxious over the cost. These were forms that were going to need filling out every month, not just once. This drug needs to have its price lowered or covered (by a public plan)."* A third patient, who mentioned no ALK testing was available back in 2012 and that Health Canada had not yet approved her treatment, paid over $36,000 for alectinib after consulting and treatment costs, even going so far as to seek treatment in the US. *"I'm not sure what will happen to those who can't afford it or have no insurance. I'm lucky."* LCC made a point to mention that new therapies should not be limited to those who can afford it, or to those with the correct type of insurance. LCC made a statement recognizing the burden high costs that new cancer drugs will place on a publicly funded health care system, and can call upon stakeholders, including manufacturers and payers, to be aware of this burden and explore innovating pricing models to reduce this burden.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for alectinib

While LCC provides a positive outlook on the addition of alectinib therapy for ALK-positive NSCLC patients, they also make a few points regarding the implementation of alectinib. Mainly, LCC raises the importance of physicians accurately communicating the effectiveness and side effects of alectinib to patients, and procedures on how to appropriately take alectinib for patients. LCC acknowledges that ALK inhibitors may not present patients with a permanent cure, and that open and ongoing communication between physicians and patients will establish clear understanding of treatment expectations and changes to patient's conditions, as well as clear understanding of side effects. Patients reported to LCC that the directions for taking alectinib were not always clear. For example, patients had to learn through trial and error, or word of mouth that taking alectinib with fatty foods in particular can help with swallowing and protect against an upset stomach.

3.2.2 Impact of Alectinib on Caregivers

Caregivers reported that the use of alectinib therapy by their loved ones has allowed them to continue to plan for the future and celebrate important life milestones with their loved ones, such as weddings and anniversaries, continue to maintain their job and financial situation, and resume living normally. The following quotes from caregivers were provided by LCC:

- *"Options are vital. They allow you as a family to stay hopeful and (experience) one of two more birthdays. It breaks my heart to think of anyone who can't access alectinib"*
- *"My (24 year old) son is still doing brilliantly on alectinib with no brain cancer and the lung tumour unchanged for 18 months. He studies full time, works part time, is still super fit and he has a lovely girlfriend and I would like to say so normal. He is so grateful for his life he loves every moment of it!"*

- *"We are looking down the line (and) there is lots of hope"*
- *"Alectinib also worked on clearing the disease in the body as well. My husband's brain was totally clear of disease, all 7 tumours were gone. Without access to alectinib, my husband most likely may not even be alive today. Targeted therapies like alectinib allow patients and caregivers to still have a normal quality of life experience. This is HUGE!"*

  "I wake up knowing the person on the pillow next to mine is ok"

3.3 Related Information about Alectinib

Within the LCC sample, four respondents who were interviewed for previous submissions and six interviewed for the current submission did not receive any traditional therapy. One patient received a single dose of chemotherapy, and then was placed on alectinib after confirmation of ALK-positive status. While crizotinib is viewed positively, LCC highlights several reasons why additional therapies, mainly alectinib, are important:

1) Variability of treatment responses

The responses of patients to treatments is not always certain, and may range from extremely good to very poor. Within the LCC patient sample, three patients interviewed for this submission said they had a fast, effective response to first-line alectinib. One patient reported that she had no evidence of disease "NED", while another reported having progressed after three months on alectinib. The following quotes were provided by LCC from patient respondents using alectinib:

- *"Significant reduction to my tumours and metastasis"*
- *"50% reduction (to tumours) right away and now, almost gone"*
- *"I was sad that alectinib didn't work (for long), I was in perfectly good shape with no side effects. (Alectinib) worked on the metastasis in my brain and liver but there was progression in my lung"*

2) Tolerability of crizotinib

Having multiple effective treatment options can ensure that patients will have an available therapy if intolerance to a first-line therapy occurs, especially since intolerance cannot always be predicted. While, in general, crizotinib is regarded as tolerable, some patients may find it to be intolerable. LCC reported that eight interviewed respondents had low tolerance to crizotinib due to side effects, affecting patients' quality of life, and physical functioning, including being unable to get out of bed due to nausea, liver dysfunction, rash, and everyday sickness. LCC also reported variable tolerability to alectinib, as one patient said their *"numbers started going down rapidly. It was effective, fast"* after taking alectinib, while a caregiver stated that her husband's *"CPK level were extremely high, his oncologist wants him to stop alectinib today".*

3) Protection from brain metastasis

Spread of disease can cause fear among patients and caregivers, and LCC stated that, unfortunately, there is no available data that show protection from brain metastasis by crizotinib. LCC mentioned that most of the interviewed respondents for second-line alectinib reported having switched to alectinib specifically because of metastasis to other body parts. An alternative first-line treatment with the ability to prevent or slow the spread of metastasis to the brain may eliminate or delay the need for whole brain radiation.

4) Progression-free survival and living

A patient stated, *"Eventually my cancer will find some way out".* While it is accepted among patients that their lung cancer will eventually progress, LCC highlights a need for living with greater quality of life, and the fear patients face living with an unstable disease; LCC posits that an alternative therapy that results in greater progression-free survival will provide greater options to treat the condition at the start of the treatment. Another patient stated, *"Options chance from wondering, to planning to meet my grandchildren. It's a bridge, a lifeline. (Options) provide time to go from bridge to bridge."*

3.4 Additional Information

LCC stated that the approval of both crizotinib and alectinib have extended patients' abilities to live well and longer, giving patients the quality of life to live achieve their goals, take care of their families and continue their careers. LCC encourages pCODR to make a positive recommendation for alectinib in first-line setting. However, it was also mentioned that cost should be addressed by all relevant stakeholders. A caregiver stated, *"I'm disappointed that it costs so much. I understand that money spent to produce and market these drugs is high, but the cost is insane."* LCC extends this as an opportunity to state they are willing to help work with HTA bodies to discuss funding models.

Furthermore, LCC acknowledges that further research through clinical trials may bring light to the effectiveness of alectinib, and how it can serve patients as a therapy. They posed the following questions as a guide for how further evidence can help guide questions regarding the effectiveness of alectinib, and how the answers, obtained through clinical trials, can help guide funding choices:

- Is it truly effective?
- Does it work better for specific subsets of patients?
- What is the best treatment algorithm that should be followed?

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from eight of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Sequencing of other targeted therapies and chemotherapies with alectinib

Economic factors:

- Cost effectiveness of sequencing other targeted therapies and chemotherapies after progression on alectinib

Please see below for more details.

4.1 Currently Funded Treatments

Crizotinib is the current standard of care and is funded in all provinces for first-line treatment of ALK+ NSCLC, except in PEI. Thus, the comparator in the ALEX trial is applicable to Canadian practice.

4.2 Eligible Patient Population

Alectinib provides a treatment option to crizotinib for patients with ALK mutation positive NSCLC as first line ALK inhibitor therapy over crizotinib which was the previous standard of care vs chemotherapy, or an option for patients who cannot tolerate first line crizotinib rather than switching to chemotherapy.

PAG noted that pERC did not recommend reimbursement of alectinib in the second line treatment of ALK mutation +ve NSCLC after crizotinib failure in patients with brain metastasis. At the time of this PAG input, a submission for alectinib in second line treatment is being reviewed by pCODR/pERC (in patients with or without brain metastases). PAG identified that crizotinib may also be used as second line treatment after chemotherapy, not as a standard of care, but in situations where molecular test results are not immediately available or when there was initially insufficient tissue to determine ALK status. In these situations, chemotherapy would be given first, then crizotinib if ALK +ve results later became available. 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.

PAG noted that ROS-1 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.

4.3 Implementation Factors

The recommended dose is 600mg taken twice daily, which is eight tablets per day. As there is only one tablet strength, dose adjustments are made by adjusting the number of tablets. PAG is seeking information on the dose intensity from the ALEX trial as this would be helpful to incorporate into the economic analysis, as crizotinib tablets are 'flat-priced'.

PAG noted that the trial in Japan (J-ALEX trial) used a dose of 300mg 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.

Treatment with alectinib is continued until disease progression. Some patients develop "oligometastatic" disease (isolated metastasis). Some experts recommend local treatment (e.g., surgery, stereotactic RT) for oligometastatic disease and continuation of alectinib (or other ALK inhibitors), if the rest of the systemic disease is controlled. 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.

4.4 Sequencing and Priority of Treatments

As there are now multiple treatments available for ALK+ve NSCLC, PAG is seeking guidance on the sequencing of all available therapies and whether there is information from the 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. What is the data on using crizotinib, ceritinib, platinum chemotherapy, pemetrexed, docetaxel and nivolumab (or pembrolizumab if PD-L1 +ve) after progression on first line alectinib?

PAG is seeking data on the clinical benefits of using crizotinib after alectinib, as there may be pressure to fund this sequence. If recommended and funded, alectinib would be available second line after crizotinib first line. PAG is seeking data to inform the clinical benefits and cost effectiveness of treating with alectinib then crizotinib compared to treating with crizotinib then alectinib.

In addition, ceritinib for treatment ALK+ve 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.

4.5 Companion Diagnostic Testing

ALK mutation testing is already being conducted at diagnosis to determine appropriate treatment. However, PAG indicated when there is a delay in obtaining the test results, patients may be started on intravenous chemotherapy in the interim. PAG is seeking guidance on the appropriateness of switching from chemotherapy to alectinib, prior to or after progression, if subsequent availability of test results demonstrate ALK+ve disease.

4.6 Factors Related to Manufacturer

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were received from two groups: Cancer Care Ontario Lung Drug Advisory Group and Lung Cancer Canada Medical Advisory Group.

In summary, the clinicians providing input feel that alectinib is clinically superior first line treatment for all ALK+ patients when compared to crizotinib, particularly in the subgroup of patients with CNS metastasis. They identified that the key benefits of alectinib are clear demonstrations that the lung cancer can be initially controlled for more than twice as long as with crizotinib, demonstrated clinically meaningful improvements in progression free survival and response rate compared to current standard first line treatment, and has slightly less toxicities. More importantly, alectinib significantly protects patients from the risk of developing brain metastases, which a particular problem in ALK positive lung cancer. The clinicians providing input feel that alectinib, if recommended for public reimbursement, would replace crizotinib in the first-line treatment of ALK positive NSCLC. Please see below for details from the clinician inputs.
Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for NSCLC

Crizotinib has been established as the standard first-line therapy in ALK+ advanced or metastatic NSCLC since the publication of the PROFILE 1014 study comparing crizotinib with platinum/pemetrexed. Crizotinib is now widely publicly available and funded in Canada.

5.2 Eligible Patient Population

The clinicians providing input noted that the ALK translocation is present in 3-5% of all advanced non-squamous non-small cell lung cancer. There are estimated to be about 300 to 1000 cases per year in Canada.

5.3 Identify Key Benefits and Harms with alectinib

The ALEX trial was a global phase III study comparing alectinib with crizotinib in treatment-naïve ALK+ advanced or metastatic NSCLC. In the overall population, one group of clinicians providing input noted that alectinib demonstrated a clinically and statistically improvement in

1. Median progression-free survival (mPFS) by investigator was more than doubled at 25.7 months in the alectinib arm, compared to 10.4 months for those receiving crizotinib ($p<0.001$).
2. Overall response rate (ORR): 82.9% for alectinib-treated patients and 75.5% for crizotinib-treated patients.
3. Time to development of brain metastases. The 12-month cumulative risk for brain metastases was 9.4% for alectinib and 41.4% for crizotinib. The risk of development of new CNS disease seemed to plateau at 18 months for alectinib-treated patients while the risk continued to increase for those treated with crizotinib.
4. Median duration of response of 17.9 month versus 10.7 month.

As the trial is still immature for survival, the median overall survival (mOS) has not been reached for both arms. The 12-month OS rate was 84.3% in the alectinib-arm and 82.5% in the crizotinib-arm (HR=0.76 CI: 0.48-.120, $p>0.05$). The clinicians providing input noted

that crossover occurred in this trial and may be a significant contributing factor to the similar OS rates in both trial arms.

The incidences of grade 3-5 toxicity were similar for the both arms (41% for alectinib arm and 50% crizotinib arm).

One group of clinicians providing input noted that the patients with a history of brain metastases at the time of enrolment, alectinib demonstrated superiority to crizotinib, by demonstrating higher rates of response and more durable responses:

1. Response rate for measurable brain lesions 81% versus 50% and for both measurable and non-measurable lesion 59% versus 29%.
2. Median duration of response for measurable brain lesions at 17.3 month versus 5.5 month and for both measurable and non-measurable lesions was not reached versus 3.7 month.

The clinicians providing input noted that in clinical practice, both alectinib and crizotinib are well tolerated, as evidence by high median dose intensity for the two drugs (95.6% for alectinib-treated patients as compared to 92.4% for the crizotinib-treated patients). However, there are some slight differences in toxicity profiles that are manageable:

- Alectinib-treated patients experienced at least 5% higher in the incidences for anemia, myalgia, increase in bilirubin, weight gain, musculoskeletal pain and photosensitivity.
- Crizotinib-treated patients experienced at least 5% higher in the incidences for nausea, diarrhea and vomiting.

The clinicians providing input noted that overall, alectinib has clinically meaningful improvements in progression free survival and response rate compared to crizotinib, with slightly less toxicity and is particularly beneficial for brain metastasis.

5.4 Advantages of Alectinib Over Current Treatments

The clinicians providing input feel that alectinib is clinically superior first line treatment for all ALK+ patients when compared to crizotinib, as shown by HR of 0.47 for combined endpoint of disease progression or death and HR of 0.16 for CNS progression versus crizotinib.

Based on the ALEX trial, and the corresponding J-ALEX trial performed in Japan with similar results, one group of clinicians identified that alectinib not only demonstrated a clinically significant improvement in response rate and progression free survival (more than doubled!) but also a major and important benefit in preventing or controlling brain metastases. Furthermore, there was a modestly better toxicity profile when compared to crizotinib.

Given the understanding that ALK+ NSCLC patients commonly present with brain metastases, and the long-term CNS toxicity from whole brain radiation can have a significant impairment of function and quality of life, alectinib is neuroprotective, reducing the incidence of brain metastases in patients who are clear from this site of disease at the start of therapy. For those with brain metastases, the higher response rate can also reduce the need for radiotherapy and its side effects, and thus potentially protecting function and quality of life. The clinicians providing input noted that the use of brain radiation can be delayed until CNS progression on alectinib.

Therefore alectinib clearly provides a clinically important benefit for all ALK+ treatment naïve NSCLC patients including those with brain metastases, which is an improvement on crizotinib in all domains.

5.5 Sequencing and Priority of Treatments with Alectinib

One group of clinicians noted that alectinib would replace crizotinib as first line treatment for ALK+ advanced NSCLC, if recommended for public reimbursement. They indicated that it is not clear if there would be any role for crizotinib second line after alectinib.

The second group of clinicians noted that sequencing of ALK inhibitors is an evolving field with multiple emerging drugs and a move towards clarifying resistance mechanisms that can define the optimal drug but this practice is still a research area. Further ALK mutations and resistance mechanisms are multiple and varied (in contrast, for example, to the EGFR mutation lung cancer population). Therefore the optimal sequence will be the subject of debate for some time to come.

However a general oncology principle is to give your best drug first. With the approximate doubling of PFS, and the CNS response and neuroprotective aspect of alectinib, plus tolerability, alectinib should be a clear first line option for patients and physicians, and indeed that has been accepted by published guidelines (such as NCCN). The clinicians providing input support a recommendation for public reimbursement of alectinib for treatment naive ALK positive NSCLC patients. The clinicians providing input feel that with negotiation, this recommendation may be cost neutral as alectinib in the first line setting would replace the use of crizotinib.

5.6 Companion Diagnostic Testing

The clinicians providing input do not anticipate any changes in testing practice with the approval of alectinib. ALK IHC has been adopted as a routine companion diagnostic test for all patients with advanced or metastatic, non-squamous NSCLC. The clinicians providing input noted that although the ALEX trial employed the Ventana ALK IHC, the C-ALK study by Cutz et al (JTO 2014) has demonstrated excellent concordance (correlation coefficient of 0.94) of ALK IHC by 5A4, ALK1 and D5F3.

5.7 Additional Information

None provided.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of alectinib (Alecensaro) as monotherapy for the first-line treatment of patients with ALK-positive, locally advanced or metastatic NSCLC.

Note: Supplemental Questions relevant to the pCODR review and to the Provincial Advisory Group were not identified while developing the review protocol.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups, are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 3. Study Selection Criteria.

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes

Published or unpublished RCTs	• Previously untreated patients with ALK-positive, advanced or metastatic NSCLC.
	
	Patient subgroups of interest:
	• With or without CNS metastases
		• Alectinib monotherapy	• Crizotinib	Primary:
				• **PFS**
				• **OS**
				• **QOL**
				• **CNS efficacy**
				  ○ CNS ORR
				  ○ CNS DOR
				  ○ Time-to-CNS progression
				• **Safety**
				
				Secondary:
				• ORR
				• DOR

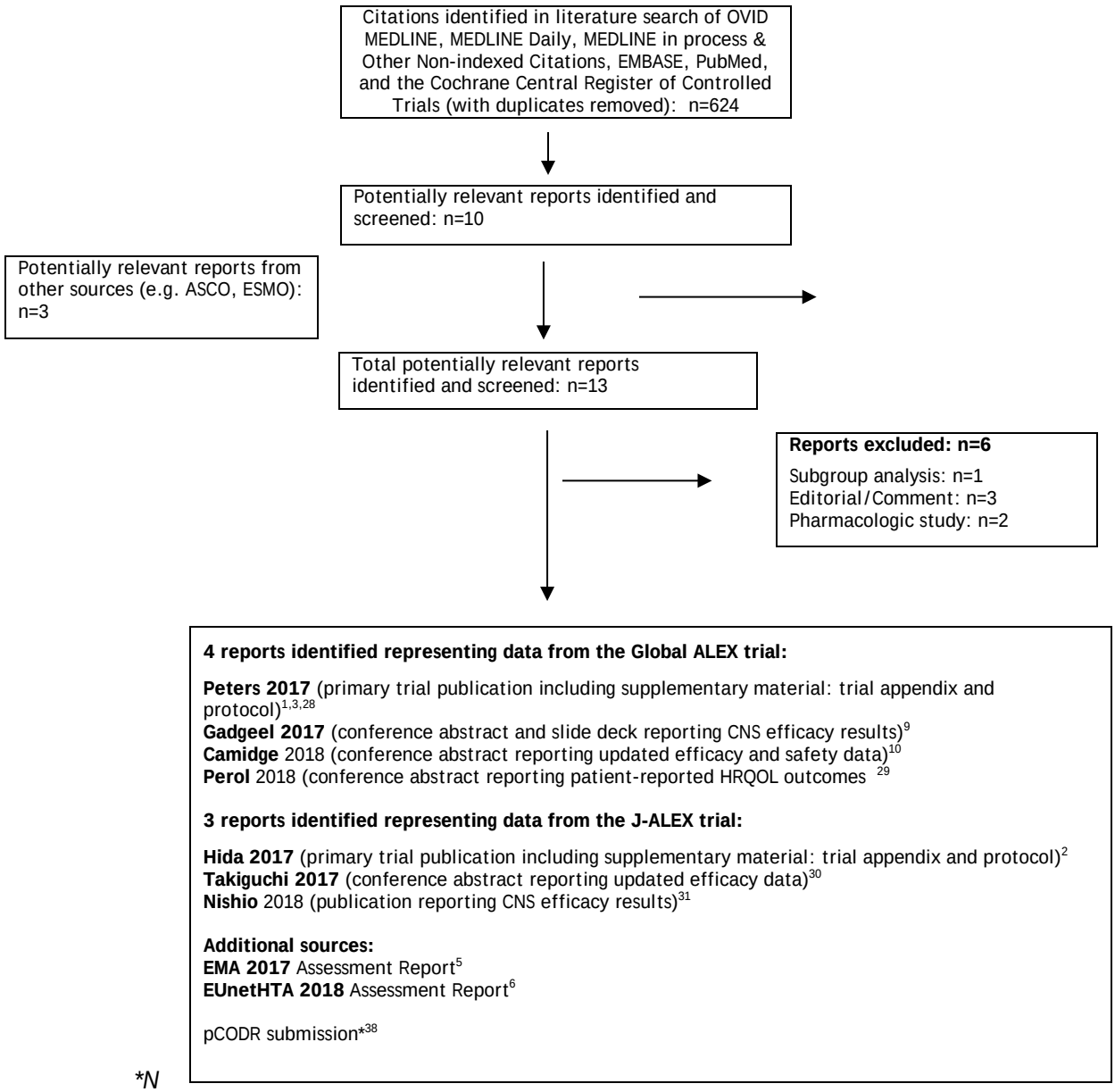
Abbreviations: ALK - anaplastic lymphoma kinase; **CNS** - central nervous system; **DOR** - duration of response; **NSCLC** - non-small cell lung cancer; **ORR** - objective response rate; **OS** - overall survival; **PFS** - progression-free survival; **QOL** - quality of life; **RCTs** - randomized controlled trials.				
Notes: * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions). **Dose escalation trials were excluded but mixed design clinical trials (i.e., trials with a dose escalation phase followed by an efficacy-determining phase in which the intervention is administered at the same dose and schedule to all patients) were included if data were reported separately for the two phases of the trial.				

6.3 Results

6.3.1 Literature Search Results

Of the 624 potentially relevant reports identified, seven reports were included in the pCODR systematic review[1-3,9,10,28-31] and six[32-37] were excluded. Studies were excluded because they were either a subgroup analysis not of interest to the review, editorial or commentary in nature, or were the wrong study design.

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of Studies



Note: Additional data related to the Global ALEX and J-ALEX trials were also obtained through requests to the Submitter by pCODR.[4,7,13]

6.3.2 Summary of Included Studies

Two randomized phase 3 trials, Global ALEX[1] and J-ALEX[2], were identified that met the selection criteria of the systematic review. Both trials evaluated the efficacy and safety of alectinib compared to crizotinib as first-line treatment in patients with ALK-positive, locally advanced or metastatic NSCLC. Key characteristics of the two trials are summarized in Table 4.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of trial characteristics of the included Global ALEX and J-ALEX trials.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Global ALEX[1] (NCT02075840; BO28984) Phase 3, open-label, randomized trial, 1:1 ratio N randomized=303; N treated=303 98 centres in 29 countries including Canada (18 patients)[38] Patient Enrolment Dates: August 18, 2014 to January 20, 2016 Data cut-off date: February 9, 2017 Updated efficacy analysis data cut-off date: December 1, 2017[10] Final Analysis Date: NR Funded by Hoffman-La Roche Ltd.	Key Inclusion Criteria: • ≥18 years • Histologically or cytologically confirmed advanced or recurrent (stage IIIB not amenable to multimodality treatment) or metastatic (stage IV)[3] NSCLC and ALK-positive by VENTANA ALK IHC or FISH test • Sufficient tumour tissue to perform IHC and FISH test[3] • Measurable disease (RECIST version 1.1) at baseline • No previous treatment for advanced/recurrent/metastatic disease • ECOG PS 0-2 • Adequate hepatic, renal and bone marrow function • Life expectancy of at least 12 weeks[3] • Prior CNS or leptomeningeal metastases allowed if asymptomatic; and previous CNS radiotherapy was allowed if completed at least 14 days before enrollment Key Exclusion Criteria:[3] • Previous malignancy within previous 3 years[a] • Any GI disorder affecting absorption of oral medications • Liver disease[b] • History of organ transplant • No pregnancy	Alectinib 600mg (4 capsules) orally twice daily *versus* Crizotinib 250mg (1 capsule) orally twice daily Until PD,[c] unacceptable toxicity, withdrawal of consent or death	Primary: • PFS by INV Secondary: • PFS by IRC • Time-to-CNS progression by IRC • ORR by INV (systemic) • DOR by INV • OS • CNS ORR by IRC[d] • CNS DOR by IRC[e] • QOL (EORTC QLQ-C30 and LC-13, TTD)[3] • Safety
J-ALEX[2] (JapicCTI-132316) Phase 3, open-label, randomized trial, 1:1 ratio N randomized=207; N treated=207 41 centres in Japan Patient Enrolment Dates: November 18,	Key Inclusion Criteria:[39] • ≥20 years • Histologically or cytologically confirmed stage IIIB (not amenable to curative radiotherapy), stage IV, or postoperative recurrent NSCLC[f] and ALK-positive by IHC and FISH test, or RT-PCR using tissue or cell samples. • ECOG PS 0-2 • At least one measurable lesion (RECIST version 1.1) • Chemotherapy naïve or received one regimen of chemotherapy for NSCLC[g]	Alectinib 300mg (8 capsules) orally twice daily *versus* Crizotinib 250mg (1 capsule) orally twice daily Until PD,[j] unacceptable toxicity,	Primary: • PFS by IRC Secondary: • PFS by INV • OS • ORR by IRC (systemic) • DOR by IRC • Time-to-response by IRC • Time-to-CNS progression

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
2013 to August 4, 2015 Data cut-off date: December 3, 2015 Final Analysis Date: NR Funded by Chugai Pharmaceutical Co. Ltd.	• Adequate major organ function within 14 days of enrollment <u>Key Exclusion Criteria:</u> • Previous treatment with an ALK inhibitor • Prior therapy or treatment for which the specified time periods have not elapsed from date of completion to time of enrollment • Meningeal metastases or brain metastases that were symptomatic or required treatment[h] • Concurrent or prior radiographically evident interstitial lung disease • Clinically significant heart disease[i] • Uncontrolled diabetes • GI disorders affecting absorption of oral medications • Previous malignancy within previous 5 years [a] • No pregnancy	withdrawal of consent or death	• QOL • Safety
Abbreviations: ALK - anaplastic lymphoma kinase; **IRC** -independent central review; **CNS** - central nervous system; **DOR** - duration of response; **ECOG** - Eastern Cooperative Oncology Group; **EORTC** - European Organization for Research and Treatment of Cancer; **FISH** - fluorescence in situ hybridization; **GI** - gastrointestinal; **IHC** - immunohistochemistry; **INV** - investigator assessment; **NR** - not reported; **NSCLC** - non-small cell lung cancer; **ORR** - objective response rate; **OS** - overall survival; **PD** - progressive disease; **PFS** - progression-free survival; **PS** - performance status; **QLQ-C30** - Quality of Life Questionnaire Core-30; **QLQ-LC13** - Quality of Life Questionnaire Lung Cancer-13; **RECIST** - Response Evaluation Criteria for Solid Tumours; **TTD** - time-to-deterioration in Lung Cancer Symptoms using EORTC QLQ-C30 and/or QLQ-LC-13.			
Notes: [a] - With the exception of curatively treated basal cell carcinoma of the skin, early gastrointestinal cancer by endoscopic resection or in situ carcinoma of the cervix. [b] - Includes ALT or AST >3 x ULN (≥5 x ULN for patients with concurrent liver metastases) confirmed on two consecutive measurements; or impaired excretory function, synthetic function or other conditions of decompensated liver disease such as coagulopathy, hepatic encephalopathy, hypoalbuminemia, ascites, and bleeding from esophageal varices; or acute viral or active autoimmune, alcoholic, or other types of hepatitis.[3] [c] - Crossover between treatment groups was not permitted in the trial. [d] - In patients with CNS metastases who have measurable disease in the CNS at baseline. [e] - In patients who have a CNS objective response, and a CNS partial response at 6, 12, 18, and 24 months.[3] [f] - Disease stages as defined in General Rules for Clinical and Pathological Records of Lung Cancer, 7th Edition.[39] [g] - Continuous maintenance is included in the initial therapy; neoadjuvant or post-operative adjuvant chemotherapy only counted as one regimen if the cancer recurs within six months after finishing therapy.[39] [h] - If palliative treatment with agents such as steroids has been administered after treatment with of metastatic brain lesions, less than two weeks must have elapsed since last dose at enrollment. [i] - Includes concurrent congestive heart failure, uncontrolled hypertension, unstable angina, arrhythmia requiring drug therapy, marked prolongation of QTc interval or previous history of myocardial infarction within six months before enrollment. [j] - Treatment was until progression unless continuation of treatment was considered clinically meaningful for the patient. Crossover after study withdrawal was permitted in both treatment groups.			

a) Trials

The Global ALEX[1] and J-ALEX trials[2] are both ongoing, open-label, multi-centred, active-controlled randomized phase 3 trials.

The Global ALEX trial is an international trial that recruited patients from 98 centres in 29 countries including Canada, and participating sites included both academic and community centres.[4] Patient enrolment took place between August 2014 and January 2016. The trial was funded by Hoffman La Roche Ltd.

The J-ALEX trial preceded the Global ALEX trial and restricted patient enrolment to 41 centres in Japan, which occurred between November 2013 and August 2015. The trial was funded by Chugai Pharmaceuticals Ltd., which is a subsidiary of Hoffman La Roche Ltd.

In both trials the trial Sponsor was involved in all aspects of trial conduct, including design, data collection, analysis and interpretation, and preparation of the trial publication.

The trials used similar eligibility criteria to enroll patients, which included the following (refer to Table 4 for a more comprehensive list):

- histologically or cytologically confirmed advanced or recurrent (stage IIIB not amenable to curative treatment) or metastatic (stage IV) NSCLC
- ALK-positivity confirmed by a validated IHC or FISH test
- measurable disease by RECIST version 1.1
- ECOG performance status of 0-2
- asymptomatic CNS metastases (if CNS metastases present)
- adequate organ function

In both trials alectinib was compared to crizotinib, which was administered at the same dose and schedule in each trial. The outcomes assessed were also similar (Table 4). However, there were a number of features that distinguished the trials; these important differences are summarized below:

- Global ALEX[1]
    - included international patients who were previously untreated
    - administered alectinib at a dose of 600mg (4 capsules twice daily)
    - randomization was stratified by ECOG performance status, race and presence/absence of CNS metastases at baseline
    - the primary outcome was PFS by INV
    - treatment crossover (upon disease progression and discontinuation of assigned treatment) was not permitted

- J-ALEX[2]
    - included Japanese patients who were previously untreated or had received one prior regimen of chemotherapy (second-line patients)
    - administered alectinib at a dose of 300mg (8 capsules twice daily)
    - randomization was stratified by ECOG performance status, treatment line, and disease stage
    - the primary outcome was PFS by IRC
    - treatment crossover (upon disease progression and discontinuation of assigned treatment) was permitted

For ALK-positive NSCLC, alectinib at 600mg (orally twice daily) is the approved dose in all countries outside of Japan. Therefore, the pCODR funding request (and Health Canada indication) is for the 600mg dose, based on evidence from the submitted Global ALEX trial. While both the Global ALEX and J-ALEX trials were reviewed for the pCODR clinical evaluation of alectinib as first-line treatment for

patients with ALK-positive NSCLC, reporting of the evidence is primarily focused on the Global ALEX trial.

Outcomes and Assessment

Global ALEX[1]

The primary outcome of the Global ALEX trial was PFS by INV in the ITT population. The secondary outcomes of interest included ORR, DOR, PFS by IRC, OS, CNS outcomes, which included time-to-CNS progression, CNS ORR, CNS DOR, and CNS progression rates at selected time points (6, 12, 18, and 24 months), health-related QOL and safety.[3]

For the assessment of disease status, all patients underwent tumour imaging at baseline, which included scans of the brain, and every eight weeks until disease progression. Patients who discontinued treatment prior to disease progression for any reason (i.e., due to AEs, withdrawal of consent) were followed until progression or death independent of whether they received subsequent anti-cancer therapy, and were further followed until death, withdrawal of consent, or lost to follow-up.[28] All tumour assessments were performed according to RECIST version 1.1, and all systemic and CNS imaging data were reviewed by IRC. For the assessment of safety, AEs were graded and classified according to NCI Common Terminology for AEs (version 4) and MeDRA, respectively.

J-ALEX[2]

The primary outcome of the J-ALEX trial was PFS by IRC in the ITT population. The secondary outcomes of interest included PFS by INV, OS, ORR, DOR, time-to-response, time-to-CNS progression in patients with and without CNS metastases at baseline, health-related QOL, and safety.

Tumour assessments were performed every four weeks until week 12, every eight weeks from week 12 to week 76, and every 12 weeks until progressive disease or death according to RECIST version 1.1. For the analysis of safety, AEs were graded and classified according to NCI Common Terminology for AEs (version 4) and MeDRA, respectively.

Randomization, Sample Size and Statistical Analyses

Information on randomization procedures, required sample size, statistical assumptions, and other indicators of trial quality are detailed in Table 5.

Global ALEX[1]

Patients were randomized in a 1:1 ratio to alectinib or crizotinib treatment groups using a centralized and stratified block randomization method. Patients were stratified according to ECOG performance status (0 or 1 vs. 2), race (Asian vs. non-Asian), and CNS metastases at baseline (yes/no). Treatment crossover after disease progression was not permitted in the trial; however, patients assigned to crizotinib may have received alectinib post-progression outside of the trial if alectinib was already approved or available in their country of residence.

During the course of the trial, the protocol was amended four times.[5] One notable amendment (amendment 2) related to updated efficacy data on crizotinib from the PROFILE 1014 trial, which was used to inform trial sample size. The updated crizotinib data lead to a reassessment of the assumptions (expected median PFS) used in the crizotinib treatment group. It was indicated that the updated data did not impact the superiority hypothesis and targeted HR of the trial (refer to Table 5).[5]

The SAP of the trial specified that the primary efficacy analysis of the primary outcome (PFS by INV) take place after 170 PFS event were observed. No interim analysis for efficacy or futility was planned.[3] Two analyses of OS were pre-specified; one to occur at the time of the primary analysis of PFS, and the second to take place once approximately 50% of deaths (143 patients) have occurred. Based on the expected median OS in each treatment group (24 months for crizotinib and 30 months for alectinib) and the trial sample size, it was noted that the Global ALEX trial was not powered to detect a statistically significant difference in OS between the treatment groups.[3]

All efficacy analyses, including all secondary outcomes, were performed in the ITT population according to treatment and stratification assignment at randomization. Hierarchical testing procedures were used to account for multiple comparisons and control the risk of type 1 error, such that secondary outcomes were only tested if the primary efficacy analysis of PFS was statistically significant. Further, secondary outcomes were to be tested in a pre-specified sequential order and only formally tested if the preceding outcome demonstrated a statistically significant difference between treatment groups. All HR and 95% CI were estimated using a stratified Cox proportional hazard regression model. Multiple subgroup analyses were pre-specified to explore the internal consistency of the treatment effect based on baseline characteristics, however, they were uncontrolled for type 1 error arising from multiple comparisons.[3]

The assessment of time-to-CNS progression, which included all patients regardless of CNS metastasis status at baseline, was analyzed using a stratified two-sided log rank test based on cause-specific hazard functions[28] in order to account for competing risks between the treatment groups; the treatment groups were compared with respect to the probability of CNS progression, non-CNS progression, and death.

Patient–reported health-related QOL was considered a secondary endpoint of the trial, and was assessed using the EORTC QLQ-C30 and QLQ- LC13.[3] The QLQ-C30 measures overall QOL and different aspects of patient functioning including lung cancer symptoms, symptoms associated with treatment, and the disease and

treatment's impact on QOL. It comprises five function scales (physical, emotional, cognitive, social and role), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and QOL scale. The QLQ-LC13 is specific to lung cancer, and assesses lung cancer symptoms (coughing, hemoptysis, dyspnea, and pain) and side effects from treatment (hair loss, neuropathy, sore mouth and dysphagia). All scales range from 0 to 100, with higher scores representing a higher response level (i.e., a high score on a function score represents a high level of functioning versus a high score on a symptom scale represents a high level of symptomatology). A mean change from baseline of 10% or greater is considered the MCID.[3]

The primary objectives of the QOL analysis were to compare TTD in patient-reported symptoms (cough, dyspnea, chest pain, arm/shoulder pain, fatigue), global health/QOL and cognitive function scores; and secondly, to compare overall global health/QOL, patient functioning, and side effects of treatment.[3] TTD was defined as the time from randomization until the first confirmed clinically meaningful deterioration in:

- Lung cancer symptoms – defined as ≥10-point increase from baseline score held for at least 2 consecutive assessments, or an initial ≥10-point increase above baseline followed by death within five weeks of last assessment.[3]
- Global health/QOL and cognitive function - defined as ≥10-point decrease from baseline score held for at least 2 consecutive assessments, or an initial ≥10-point decrease from baseline followed by death within five weeks of last assessment.[3]

Patients completed questionnaires according to the following schedule: every four weeks until disease progression, at post-treatment visit, and at subsequent survival follow-up visits every eight weeks for six months.[3] Only patients with a baseline assessment and at least one post-baseline assessment were included in analyses. TTD was evaluated as a time-to-event outcome using Kaplan Meier methods; and differences in TTD between groups were assessed using a stratified log-rank test and a stratified Cox model (to generate HR and 95% CI). QLQ-C30 and LC13 scores and changes from baseline were analyzed descriptively using summary statistics (mean, SD, median, range) of linear transformed scores (0-100) for all items and subscales at all evaluation time points. The number and proportion of patients who improved or worsened (based on ≥10-point decrease or increase from baseline, respectively), or remained stable were also summarized by treatment group for all scales at all evaluation time points. No imputations for missing data were made for any of the QOL analyses.[3]

The safety analysis included all patients who received at least one dose of study medication.

J-ALEX[2]

Patients were randomized in a 1:1 ratio to alectinib and crizotinib treatment groups using a centralized and stratified block randomization method (Table 5). Patients were stratified according to ECOG performance status (0 or 1 vs. 2), treatment line (first vs. second), and disease stage (IIIB or IV vs. post-operative recurrence). Treatment crossover was permitted for patients in both treatment groups after disease progression and study withdrawal.

All efficacy analyses were carried out in the ITT population, which comprised of all randomized patients. The trial protocol was amended (after the AF-001JP study demonstrated results in favour of alectinib) to perform the first interim analysis of

the primary outcome earlier, after 33% PFS events (n=55/164) had occurred, and the second was planned for 75% PFS events (n=123). An O'Brien and Fleming-type alpha spending function was employed to control for multiple analyses. Details of the primary efficacy analysis (PFS) are provided in Table 5. The trial protocol did not pre-specify any subgroup analyses.

Table 5: Select quality features of the Global ALEX and J-ALEX trials.

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
Global ALEX[1]	Alectinib 600mg *versus* Crizotinib	PFS by INV	286 patients (170 PFS events) required to provide 80% power to detect an improvement in median PFS from 10.9 months with crizotinib to 16.8 months with alectinib (HR=0.65) based on a stratified long-rank test at a two-sided significance level of α=0.05.	303	Central via interactive voice or web-based response system; and blocked stratified by ECOG PS (0 or 1 vs. 2), race (Asian/non-Asian), and CNS metastases at baseline (yes/no).	Yes	Open label; outcome assessment by IRC; data analysts were not blinded.[4]	Yes	No	No	Yes
J-ALEX[2]	Alectinib 300mg *versus* Crizotinib	PFS by IRC	200 patients (164 PFS events) required to provide 80% power for superiority hypothesis (improvement in median PFS from 9 months with crizotinib to 14 months with alectinib, HR=0.64), and 97.8% power for non-inferiority hypothesis (non-inferiority margin of 1.2) based on a stratified log rank test at a two-sided significance level of α=0.05.[a]	207	Central via interactive web response system; and blocked stratified by ECOG PS (0 or 1 vs. 2), treatment line (first vs. second), and disease stage (IIIB or IV vs. post-operative recurrence).	Yes	Open label; outcome assessment by IRC; data analysts were not blinded.	Yes	No	No	Yes

Abbreviations: CNS - central nervous system; ECOG - Eastern Cooperative Oncology Group; HR - hazard ratio; INV - investigator assessment; IRC - independent review committee; ITT - intent-to-treat; PFS - progression-free survival; PS - performance status.

Notes:
[a] - The trial had two clinical hypotheses for the analysis of PFS that included a non-inferiority hypothesis, where non-inferiority would be demonstrated if the non-inferiority margin on the HR (upper bound of confidence interval) was lower than 1.2; and a superiority hypothesis (described in table). A hierarchical testing procedure was used to control for type 1 error arising from multiple testing, such that the non-inferiority hypothesis was tested first, and if statistically significant, the test for superiority was also performed. If the superiority test of PFS was statistically significant, OS was then tested.

b) Populations

Global ALEX[1]

A total of 303 patients were randomized in the Global ALEX trial, with 152 allocated to alectinib and 151 allocated to crizotinib. Most randomized patients were treated at trial sites in Asia (50%), Europe (26%), and North America (16%). The trial included 18 (6%) Canadian patients.[4] The baseline characteristics of patients are summarized in Table 6. Overall, the distributions of baseline characteristics between the treatment groups were well-balanced. The median age of patients was between 54 and 58 years old, with the majority of patients under the age of 65 (77%).[5] The majority of patients were female (56%), of Caucasian (50%)[5] or Asian race (46%), non-smokers (63%), and had an ECOG status of 0 or 1 (93%). Almost all patients had metastatic disease (97%) and adenocarcinoma histological type (92%). Central nervous system 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.

J-ALEX[2]

A total of 207 patients were randomized in the J-ALEX trial, with 103 and 104 patients randomized to alectinib and crizotinib, respectively. The baseline characteristics of randomized patients (Table 6) 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% vs.14%).

Compared to the patient population in the Global ALEX trial, patients in the J-ALEX trial were slightly older (median age between 60 and 61 years old) and were all Japanese (100%). Approximately 24% of patients were staged with post-operative recurrence, and 36% were treated with alectinib after one previous line of chemotherapy (second-line). Approximately 64% (n=133) of patients were treated in the first-line setting. Compared to the Global ALEX trial, a lower proportion of patients had CNS metastases at baseline (21% versus 40%). The specific treatment(s) received by patients to treat CNS metastases were not reported; however, it was noted that 11% of patients had received radiotherapy.

c) Interventions

Global ALEX[1]

After randomization, patients were treated with alectinib at a dose of 600 mg (4 capsules) twice daily or crizotinib at a dose of 250mg (1 capsule) twice daily. Both treatment groups received study drug until disease progression, unacceptable toxicity, or withdrawal of consent or death. Patients with isolated, asymptomatic CNS progression were permitted to receive local therapy at the investigators' discretion, followed by continued study treatment until systemic and/or symptomatic CNS progression. Further, it was confirmed by the Submitter that patients were also permitted to receive alectinib post-progression if they were considered to be still benefiting clinically from the drug.[4] The trial protocol did not mandate local therapy prior to initiating post-progression treatment.[4]

Dose reductions were permitted in both treatment groups, with guidelines for dose reduction and discontinuation of study medication for specific AEs.[3] The median time on treatment was 17.9 months (range, 0-29) in the alectinib group and 10.7 months (range, 0-27) in the crizotinib group; mean dose intensity (±SD) was 95.6% (±10.3) and 92.4% (±14.1), respectively.

Concomitant medications were used by most patients in the trial. The type and frequency of medication use was generally comparable between the treatment groups. The most commonly used medications were steroids, analgesics (slightly higher in the alectinib group), supplements, antiemetics, laxatives and stool softeners.[4] The percentages of patients by treatment group who had at least one concomitant surgery for NSCLC was also comparable; just over one third of patients in each group had concomitant surgery and the majority of these were performed to evaluate CNS metastases. In the subgroup of patients with CNS metastases, [redacted].[7] (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed*.)

J-ALEX[2]

Patients in the J-ALEX trial were randomized to treatment with either alectinib at a dose of 300 mg (eight capsules) twice daily or crizotinib at a dose of 250 mg (1 capsule) twice daily. All patients received randomized treatment until disease progression, unacceptable toxicity, or withdrawal of consent or death. The 300 mg dose of alectinib is the approved dose in Japan based on results of the AF-001JP study.[40] The trial permitted dose reductions in both treatment groups with guidelines for dose reduction, treatment suspension and discontinuation for specific AEs.[3] Patients could continue with alectinib beyond disease progression (based on physician discretion) if they were still benefiting clinically from treatment. The median time on treatment was similar in the two treatment groups; 13 months (range, 4-24) in patients randomized to alectinib and 12 months (range, 2-13) in patients randomized to crizotinib.[5] The mean dose intensity of treatment was not reported for either treatment group. Treatment crossover was permitted in both treatment groups after disease progression. The concomitant medications used by patients during the trial were not specified.

Table 6: Baseline patient characteristics of the Global ALEX and J-ALEX trials.

Trial	Global ALEX[1]		J-ALEX[2]	
Treatment Groups	Alectinib 600mg (n=152)	Crizotinib (n=151)	Alectinib 300mg (n=103)	Crizotinib (n=104)
Baseline Characteristics				
Age, in years				
Median	58	54	61	60
Range	25-88	18-91	27-85	25-84
Sex, n (%)				
Male	68 (45)	64 (42)	41 (40)	41 (39)
Female	84 (55)	87 (58)	62 (60)	63 (61)
Race[a]				
Asian	69 (45)	69 (46)	103 (100)	104 (100)
Non-Asian	83 (55)	82 (54)	0	0
ECOG PS				
0 or 1	142 (93)	141 (93)	101 (98)	102 (98)
2	10 (7)	10 (7)	2 (2)	2 (2)
Smoking status, n (%)				
Active smoker	12 (8)	5 (3)	2 (2)	3 (3)
Former smoker	48 (32)	48 (32)	45 (44)	40 (38)
Non-smoker	92 (61)	98 (65)	56 (54)	61 (59)
Disease stage, n (%)				
IIIB	4 (3)	6 (4)	3 (3)	3 (3)
IV	148 (97)	145 (96)	76 (74)	75 (72)
Post-operative recurrence	NR	NR	24 (23)	26 (25)
Treatment line				
First	152 (100)	151 (100)	66 (64)	67 (64)
Second	0	0	37 (36)	37 (36)
Histologic type, n (%)				
Adenocarcinoma	137 (90)	142 (94)	100 (97)	103 (99)
Squamous cell carcinoma	5 (3)	2 (1)	2 (2)	0
Other	10 (7)	7 (5)	1 (1)	1 (1)
CNS metastases by IRC, n (%)				
Yes	64 (42)	58 (38)	14 (14)	29 (28)
No	88 (58)	93 (62)	89 (86)	75 (72)
Treatment for CNS metastases, n (%)				
Any	27 (18)	22 (15)	NR	NR
Brain surgery	1 (4)	1 (5)	NR	NR
Radiosurgery	5 (19)	4 (18)	NR	NR
Whole-brain radiotherapy	17 (63)	16 (73)	6	16
Other	4 (15)[b]	1 (5)[b]	NR	NR
Previous brain radiation, n (%)				
Yes	26 (17)	21 (14)	NR	NR
No	126 (83)	130 (86)	NR	NR

Abbreviations: CNS - central nervous system; **ECOG** - Eastern Cooperative Oncology Group; **IRC** - independent review committee; **NR** - not reported; **PS** - performance status.

Notes:

[a] - In the Global ALEX trial, race was reported by investigator.

[b] - Three patients in the alectinib group and one patient in the crizotinib group underwent brain surgery combined with radiotherapy. An additional patient in the alectinib group underwent both radiosurgery and whole-brain radiotherapy.

d) Patient Disposition

The disposition of patients in the Global ALEX and J-ALEX trials is summarized in Table 7.

Global ALEX[1]

Of the 1298 patients screened, 303 were randomized and comprise the ITT patient population. At the primary analysis data cut-off date (February 9, 2017), median duration of follow-up was 18.6 months (range, 0.5-29.0) in the alectinib group and 17.6 months (0.3-27.0) in the crizotinib group. At that time, more patients in the crizotinib group had discontinued study treatment: 70% versus 45% of patients in the alectinib group. Progressive disease was the primary reason for treatment discontinuation in both groups, which occurred in greater frequency in patients treated with crizotinib (40% versus 27% in the alectinib group). The percentage of patients who discontinued the trial was also higher in the crizotinib group; 46% compared to 35%. In both treatment groups the most common reason for trial discontinuation was death (27% in the crizotinib group versus 23% in the alectinib group).

Of the 54 and 90 patients with disease progression at the data cut-off date in the alectinib and crizotinib groups, respectively, 67% of patients (36/54) and 61% of patients (55/90) received subsequent treatment post-progression.[4] TKIs were the most common type of subsequent treatment in both treatment groups (Table 7). Of note, there were 11 patients (7%) in the alectinib group and 36 patients (24%) in the crizotinib group who continued to receive assigned treatment post-progression; of those patients,[4] 5 and 30 patients, respectively, had isolated asymptomatic CNS progression[43]. Considering the 11 patients treated with alectinib post-progression, eight had discontinued trial treatment due to disease progression at the primary data cut-off date.[13]

The number of major trial protocol deviations that took place during the trial were evenly distributed between the treatment groups (34% in both groups), and therefore, likely did not have an impact on the efficacy results of the trial.[5] The most frequent type of deviations occurring in both treatment groups were procedural in nature (e.g. omission of disease assessments, failure to perform tumour assessments per protocol, non-required tests, dose not modified for toxicity according to protocol) and occurred in 22% and 23% of patients in the alectinib and crizotinib groups, respectively.[5]

J-ALEX[2]

Of the 622 patients screened, 207 were randomized and comprise the ITT patient population. At the primary analysis data cut-off date (December 3, 2015), median duration of follow-up was 12 months (range, 6.5-15.7) in the alectinib group and 12.2 months (range, 8.4-17-4) in the crizotinib group. There were 23% and 59% of patients in the alectinib and crizotinib treatment groups, respectively, who had discontinued randomized treatment at the time of the primary analysis. The majority of treatment discontinuations were due to progressive disease, which were higher in the crizotinib treatment group (31% versus 14%). The proportion of patients who received assigned treatment post-progression, as well as other subsequent anti-cancer treatments were not reported. The frequency of protocol deviations that occurred during the trial was also not reported.

Table 7: Patient disposition in the Global ALEX and J-ALEX trials.

Trial	Global ALEX[1]		J-ALEX[2]	
Treatment Groups	Alectinib 600 mg	Crizotinib	Alectinib 300 mg	Crizotinib
Analysis Date:	February 9, 2017		December 3, 2015	
Disposition, n (%)				
Screened	1298		622	
Randomized total	303		207	
Randomized per group	152 (100)	151 (100)	103 (100)	104 (100)
Treated	152 (100)	151 (100)	103 (100)	104 (100)
Included in primary efficacy analysis	152 (100)	151 (100)	103 (100)	104 (100)
Included in safety analysis	152 (100)	151 (100)	103 (100)	104 (100)
Discontinuing treatment	68 (45)	105 (70)	24 (23)	61 (59)
Progressive disease	41 (27)	60 (40)	14 (14)	32 (31)
Death	2 (1)	6 (4)	NR	NR
Withdrawal by patient	3 (2)	11 (7)	0	4 (4)
Symptomatic deterioration	2 (1)	5 (3)	NR	NR
Physician decision	0	2 (1)	NR	NR
Other	3 (2)	2 (1)	1 (1)	4 (4)
Adverse event	17 (11)	19 (13)	9 (9)	21 (20)
Patient status at data-cut-off				
Continuing trial treatment	84 (55)	46 (30)	79 (77)	43 (41)
No longer in trial	53 (35)	69 (46)	NR	NR
Death	35 (23)	40 (26)		
Lost to follow-up/declined to participate	17 (11)	27 (18)		
Adverse events	0	2 (1)		
Other	1 (<1)	0		
Being followed for survival (after treatment discontinuation)	15 (10)	36 (24)		
Any therapy post-progression,[a,4]	36 (67)	55 (61)	NR	NR
Received alectinib post-progression	11 (20)	8 (9)	NR	NR
Any TKI	25 (46)	51 (57)		
Crizotinib	7 (13)	36(40)		
Ceritinib	2 (4)	12 (13)		
Lorlatinib	5 (9)	2 (2)		
Brigatinib	1 (2)	4 (4)		
Other	0	3 (3)		
Carboplatin or cisplatin	17 (32)	4 (4)		
Pemetrexed or gemcitabine	16 (30)	4 (4)		
Major Protocol Deviations[5]	51 (34)	52 (34)	NR	NR
Inclusion criteria	3 (2)	2 (1)		
Medication	5 (3)	5 (3)		
Procedural	34 (22)	34 (23)		

Notes:
[a] - Percentages are based on denominator that includes patients who had disease progression at the data cut-off date (n=54 in the alectinib group, and n=90 in the crizotinib group). It was noted by the pCODR review team that the number of disease progressions at the data cut-off date (per treatment group) do not equate to sum of the number of patients in each treatment group discontinuing treatment due to progressive disease, and the number of patients receiving assigned treatment post-progression.

e) Limitations/Sources of Bias

The systematic review performed identified two RCTs that met the selection criteria for inclusion: the Global ALEX trial,[1] which is the basis of the Submitter's pCODR submission and funding request, and the J-ALEX trial.[2] As previously mentioned, the J-ALEX trial evaluated alectinib at a lower dose (300 mg), which is the approved dose in Japan, but not in Canada and all other countries where alectinib is available. For that reason, as well as the unavailability of data for a majority of outcomes in the target population of patients treated in the first-line setting, the critical appraisal that follows below is focused on the Global ALEX trial.

When considering the totality of evidence from the randomized trials, it's important to highlight that evidence on the efficacy of alectinib in treatment naïve patients from the J-ALEX trial is based on a subgroup analysis that included 133 patients for one outcome (PFS). At least nine different subgroups analyses were performed in the J-ALEX trial but none of the subgroups were pre-specified in the trial protocol.[39] Consequently, the subgroup analysis results from the trial should be considered exploratory (refer to the discussion on subgroup analyses below, which outlines limitations also applicable to the J-ALEX trial). An exploratory analysis examining CNS progression in the J-ALEX trial was published in June 2018; however, data from this publication were not included in this report since results were not reported separately for the treatment naïve patient subgroup.[31]

Table 5 provides a summary of key quality-related features of both trials.

Overall, the Global ALEX trial[1] was well conducted owing to specific design features, including the use of appropriate randomization and allocation concealment procedures, clear explanation of sample size considerations, transparent disposition of patients through the trial with minimal losses to follow-up, the use of an IRC for assessment of the primary outcome, and performing all efficacy analyses by assigned treatment. However, the following limitations were noted:

- The open-label design of the trial makes it prone to different biases (patient selection and performance bias), which can affect internal validity. The investigators, trial personnel, patients, as well as data analysts were all aware of study drug assignment, which can potentially bias outcome assessment in favour of alectinib if assessors (investigators, patients, and data analysts) believe the study drug is likely to provide benefit. A double-blind design was not used in the trial because it would necessitate what was considered a significant pill burden to patients (in terms of number and size), which could increase the risk of non-compliance, as well as introduce more complex dose reductions that have the potential to increase the risk of dosing errors.[3] An attempt was made in the trial to mitigate bias by using an IRC to assess outcomes using standardized criteria (RECIST) and identical assessment schedules in the treatment groups, as well as conducting pre-specified sensitivity analyses to measure the robustness of the primary outcome analysis results. However, for subjective outcomes like health-related QOL and AEs, there is a greater risk of detection bias because patients and investigators would be aware of the specific treatment being administered.
- Although the subgroup analyses performed in the trial were pre-specified and demonstrated a consistent treatment benefit in most of the subgroups examined, caution is warranted in interpreting these results. Testing a

large number of subgroups (including additional subgroups analyses performed post-hoc) can increase the chance of detecting false positive results. A proper subgroup analysis includes a statistical test for interaction to assess whether the treatment effect differs among subgroups, opposed to individual tests within each subgroup.[41] Since the trial protocol indicated no adjustments were made for multiple testing and no tests for interaction were performed,[3] the subgroup analysis results should be considered exploratory and interpreted within this context.

- Although the protocol specified treatment crossover was not permitted in the trial, the endpoint of OS is confounded by patients who received subsequent therapies post-progression. Subsequent therapies included receipt of alectinib in patients assigned to crizotinib and who lived in participating countries where alectinib received approval in the second-line setting after crizotinib during the course of the trial. Further, it should be highlighted that OS was not formally tested in the trial (based on the testing hierarchy of ORR not being statistically significant) nor sufficiently powered to test for differences in OS between the two treatment groups.
- The assessment of health-related QOL had limitations that raise uncertainty about the validity of the QOL findings, specifically:
    - Patient compliance in completing questionnaire assessments was sub-optimal in both treatment groups, which resulted in missing data. This may bias the findings since there may be systematic differences in the characteristics of patients who complete and don't complete questionnaires. This, combined with the much longer treatment exposure of patients treated with alectinib compared to crizotinib, reduces the reviewer's ability to accurately assess and compare QOL between the treatment groups.
    - The published and unpublished data on QOL available to pCODR was limited by incomplete and selective reporting of outcomes.

  Given these limitations, it is likely that the QOL data as presented do not fully capture the QOL experience of all patients in the trial and therefore should be interpreted with caution.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The efficacy outcomes of the Global ALEX trial are summarized in Table 8. For the J-ALEX trial, this report focused on the efficacy results for the subgroup of patients treated in the first-line setting (treatment naïve target population); and therefore, are limited to a subgroup analysis of these patients for the outcome of PFS (primary outcome). The pCODR Methods Team requested additional efficacy and safety outcome data for this patient subgroup; however, the Submitter indicated data were not available. For safety, the results of all patients in the J-ALEX trial were summarized to enable a comparison of AEs at the two different doses of alectinib.

Systemic Efficacy Outcomes

Progression-free survival

Global ALEX[1]

Progression-free survival by INV was defined as the time from randomization to documentation of disease progression (RECIST) or death, whichever occurred first.[3]

At the primary data cut-off date (February 9, 2017), the Global ALEX trial met its primary endpoint; 41% (n=62/152) and 68% (n=102/151) of PFS events had occurred in the alectinib and crizotinib treatment groups, respectively. The median PFS by INV was not reached (95% CI, 17.7-not estimable) in the alectinib group and 11.1 months in the crizotinib group (95% CI, 9.1-13.1), demonstrating a statistically significant reduction in disease progression or death with alectinib (HR=0.47, 95% CI, 0.34-0.65; p<0.001; Figure 2A). The Kaplan-Meier PFS curves show a pronounced and persistent separation between the two treatment groups starting at approximately six months of follow-up. A similar treatment benefit, albeit of slightly lower magnitude, was observed for PFS by IRC (Table 8).

From a comparison of PFS event rates in each group by method of assessment, it appears the discordance observed can be attributed to a slightly higher proportion of PD in the crizotinib group by investigator assessment that was not confirmed by IRC (Table 8). This degree of discordance, however, unlikely biased the efficacy results; this is supported by the IRC analysis, which produced similar results to the primary analysis.

The magnitude of PFS benefit observed with alectinib in the ITT population was consistent in all pre-specified patient subgroups with the exception of active smokers (n=17) and patients with an ECOG of 2 (n=20) at baseline. The results of these two latter subgroups should be interpreted with caution, however, in light of the small sample sizes, which can lead to unreliable estimates. The estimated HRs (versus crizotinib) for the other patient subgroups ranged between 0.33 and 0.61 (Figure 2B). Of interest to note, the treatment benefit was observed in patients with and without CNS metastases, and regardless of prior radiotherapy to treat CNS disease.[9]

Results of several sensitivity analyses, which were performed to assess the robustness of the primary analysis findings to different censoring rules (i.e., missing tumour assessments, losses to follow-up, stratification factors applied at randomization), were also consistent with the primary analysis results.[5]

Updated efficacy data, which are based on an additional 10 months of follow-up, have been published in abstract form (December 1, 2017 data cut-off date).[10] The

median follow-up in the alectinib and crizotinib groups was 27.8 and 22.8 months, respectively. At this updated (unplanned) analysis, 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, 0.32–0.58). The magnitude of PFS benefit observed with alectinib in the ITT population was consistent in patients with (HR=0.35; 95% CI, 0.22–0.56) and without (HR=0.47;95% CI, 0.32–0.71) baseline CNS metastasis.[10]

J-ALEX[2]

Progression-free survival by IRC was defined as the time from randomization to imaging confirmed PD (RECIST) or death, whichever occurred first.

The J-ALEX trial met its primary endpoint at the second, planned interim analysis of PFS (data cut-off date December 3, 2015), demonstrating both non-inferiority and superiority of alectinib compared to crizotinib. In the subgroup of patients treated in the first-line setting (n=133), median PFS by IRC was not estimable in the alectinib group (95% CI, 17.5-not estimable) and 10.2 months (95% CI, 8.3-13.9) in the crizotinib group (HR=0.31; 95% CI, 0.17-0.57).

Updated efficacy data, which are based on an additional 10 months of follow-up, have been published in abstract form;[30] however, results are reported for the ITT population and not the first-line patient subgroup.

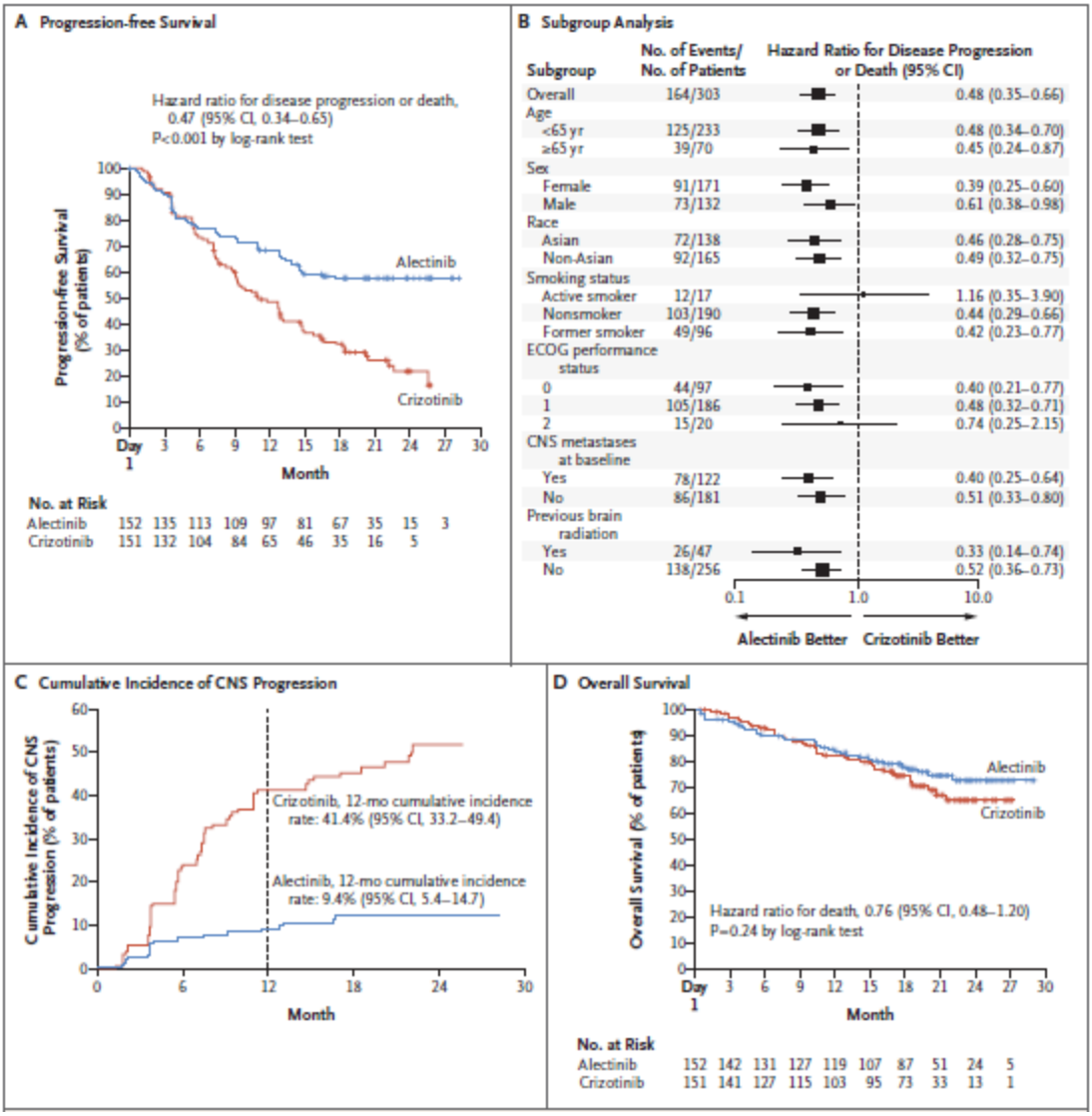


Figure 2. Efficacy outcomes in the Global ALEX trial: (A) PFS by INV for ITT; (B) PFS by INV for pre-specified subgroups; (C) Cumulative incidence of CNS progression; (D) OS.[1]

From The New England Journal of Medicine, Peters et al, Alectinib versus crizotinib in untreated ALK-positive non-small cell lung cancer, Volume 377, Page 834. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Time-to-CNS Progression

Time-to-CNS progression was defined as the time from randomization until first radiographic evidence of CNS progression by IRC, where CNS progression was progression due to newly developed CNS lesions and/or progression of pre-existing baseline CNS lesions. This outcome was adjusted for the competing risks of non-CNS progression and death.

At the primary data cut-off date, there were 18 (12%) and 68 (45%) patients who had a CNS progression event in the alectinib and crizotinib treatment groups, respectively. Time-to-CNS progression was significantly longer in the alectinib treatment group (median estimates not reported; HR=0.16, 95% CI, 0.10-0.28; p<0.001). The cumulative incidence of CNS progression was lower over time in the alectinib group compared to the crizotinib group (Figure 2C); the 12-month incidence rates were 9.4% (95% CI, 5.4-14.7) versus 41.4% (95% CI, 33.2-49.4), respectively. A similar treatment benefit was observed for patients with and without prior radiotherapy for CNS metastases.[9]

Objective Response and Duration of Response

ORR was defined as the percentage of patients with a CR or PR according to RECIST version 1.1; and DOR was defined as the time from when CR or PR was first met to the occurrence of progression or death.

The ORR by INV was 82.9% (95% CI, 76.0-88.5) in the alectinib group and 75.5% (95% CI, 67.8-82.1) in the crizotinib group. In both treatment groups the ORR was primarily comprised of partial responses (Table 8). The difference in ORR between the groups (7.4%, 95% CI -1.71-16.5) was not statistically significant (p=0.0936). Duration of response was significantly longer in the alectinib group; median DOR was not estimable in the alectinib group and 11.1 (95 % CI, 7.9-13.0) months in the crizotinib group (HR=0.36; 95% CI, 0.24-0.53; p<0.0001).[5]

At the updated December 1, 2017 data cut-off date, ORR was similar to the results reported in the primary trial publication (82.9% versus 75.5% in the alectinib and crizotinib groups, respectively). Median DOR was 33.3 months versus 11.1 months in the alectinib and crizotinib groups, respectively (HR=0.33; 95% CI, 0.23–0.48).[10]

Overall Survival

At the primary data cut-off date, a total of 75 patients had died: 35 (23%) in the alectinib group and 40 (27%) in the crizotinib group. Median OS was not reached in either treatment group (HR=0.76, 95% CI, 0.48-1.20; Figure 2D).

At the December 1, 2017 update, OS data were still immature with 28.3% and 31.8% of events having occurred in the alectinib and crizotinib groups, respectively (HR=0.76; 95% CI, 0.50–1.15).[10]

CNS Efficacy Outcomes

There were 64 (42%) patients in the alectinib group and 58 (38%) patients in the crizotinib group who had CNS metastases (measurable or non-measurable) at baseline; the subgroup of patients with measurable CNS lesions included 21 (14%) patients and 22 (15%) patients, respectively. All CNS efficacy outcomes were assessed by IRC and were assessed using the same outcome definitions as the ITT population.

CNS Response and CNS Duration of Response

Among patients with measurable CNS metastases, the CNS ORR was 81% (n=17/21; 95% CI, 58-95) in the alectinib group compared to 50% (n=11/22; 95% CI, 28-72) in the crizotinib group, where a CR in the CNS was obtained in eight (38%) patients and 1 (5%) patient, respectively (Table 8). The difference in CNS ORR between the treatment groups was statistically significant (OR=4.25, 95% CI, 1.08-16.77; p=0.03). The duration of CNS response was estimated at 17.3 months (95% CI, 14.8-not estimable) with alectinib versus 5.5 months (95% CI, 2.1-17.3) with crizotinib but did not reach statistical significance (HR=0.42, 95% CI, 0.15-1.24; p=0.11).[5]

In patients with measurable/non-measurable CNS metastases, the CNS ORR in the alectinib group was 59% (n=38/64; 95% CI, 46-71) compared to 26% (n=15/58; 95% CI, 15-39) in the crizotinib group; and a CR was obtained in 29 (45%) patients and 5 (9%) patients, respectively. The difference in CNS ORR between the treatment groups was statistically significant (OR=4.05, 95% CI, 1.89-8.70; p=0.0002).[5] The CNS DOR was not estimable in the alectinib group and 3.7 months (95% CI, 3.2-6.8) in the crizotinib group (HR=0.23, 95% CI, 0.10-0.53; p=0.0002).[5] In this patient subgroup, PFS by INV and time-to-CNS progression outcomes also demonstrated statistically significant improvements in favour of alectinib versus crizotinib (Table 8).

At the December 1, 2017 update, the magnitude of PFS benefit observed in patients with CNS metastasis at baseline was consistent with the updated ITT analysis (HR 0.35, 95% CI 0.22–0.56).[10]

Table 8: Efficacy outcomes in the Global ALEX and J-ALEX trials in treatment naïve (first-line) patients with advanced or metastatic ALK-positive NSCLC.

Trials	Global ALEX		J-ALEX	
Treatment Groups	Alectinib 600 mg (n=152)	Crizotinib (n=151)	Alectinib 300 mg (n=103)	Crizotinib (n=104)
Systemic Efficacy Outcomes				
Median follow-up time in months (range)	18.6 (0.5-29)	17.6 (0.3-27)	12.0 (6.5-15.7)	12.2 (8.4-17.4)
Median duration of treatment in months (range)	17.9 (0-29)	10.7 (0-27)	13.0 (4-24)[5]	12.0 (2-23)[5]
PFS[a] by INV	Primary Outcome		Secondary Outcome	
			n=66	n=67
Events, n (%)	62 (41)	102 (68)	NR	NR
Median in months (95% CI)	Not reached (17.7-NE)	11.1 (9.1-13.1)	NE (17.5-NE)	10.2 (8.3-13.9)
HR (95% CI); p-value[b]	0.47 (0.34-0.65); p<0.001		0.31 (0.17-0.57)	
12-month event-free rate, % (95% CI)	68.4 (61.0-75.9)	48.7 (40.4-56.9)		
December 1, 2017 data cut-off[10]			NR	
Median in months (95% CI)	34.8 (NA)	10.9 (NA)		
HR (95% CI)	HR 0.43, 95% CI 0.32-0.58			
PFS[a] by IRC				
Events, n (%)	63 (41)	92 (61)	NR	
Median in months (95% CI)	25.7 (19.9-NE)	10.4 (7.7-14.6)		
HR (95% CI); p-value[b]	0.50 (0.36-0.70); p<0.001			
12-month event-free rate, % (95% CI)	67.0 (59.0-74.0)[5]	46.0 (38.0-55.0)[5]		
Time-to-CNS progression by IRC[g]				
Events, n (%)	18 (12)	68 (45)	NR	
Median in months (95% CI)	NR	NR		
HR (95% CI); p-value[b]	0.16 (0.10-0.28); p<0.001			
12-month CNS progression rate % (95% CI)[c]	9.4 (5.4-14.7)	41.4 (33.2-49.4)		
ORR[d] by INV				
n	126	114	NR	
% (95% CI)	82.9 (76.0-88.5)	75.5 (67.8-82.1)		
CR, n (%)	6 (4)	2 (1)		
PR, n (%)	120 (79)	112 (74)		
SD, n (%)	9 (6)	24 (16)		
Difference in ORR (95% CI)	7.4 (-1.71-16.5)			
OR (95% CI); p-value[e]	1.62 (0.92-2.84); p=0.0936[5]			
December 1, 2017 data cut-off[10]				
n	NR	NR		
% (95% CI)	82.9% (75.95-88.5)	75.5% (67.8-82.1)		
DOR[f] by INV				
Median in months (95% CI)	NE (NE)	11.1 (7.9-13.0)	NR	
HR (95% CI); p-value[b]	0.36 (0.24-0.53); p<0.0001[5]			
December 1, 2017 data cut-off[10]				
Median in months (95% CI)	33.3 (31.1-NE)	11.1 (7.5-13.0)		
HR (95% CI)	0.33 (0.23-0.48)			
OS				
Events, n (%)	35 (23)	40 (26)	NR	
Median in months (95% CI)	NE	NE		
HR (95% CI); p-value[b]	0.76 (0.48-1.20); p=0.24			
December 1, 2017 data cut-off[10]				
Events, n (%)	NR (28.3)	NR (31.8)	NR	
Median in months (95% CI)	NR	NR		
HR (95% CI)	0.76 (0.50-1.15)			
CNS Efficacy				
Patients with measurable CNS metastases at baseline				
n for subgroup	21	22	NR	

Trials	Global ALEX		J-ALEX	
Treatment Groups	Alectinib 600 mg (n=152)	Crizotinib (n=151)	Alectinib 300 mg (n=103)	Crizotinib (n=104)
Systemic Efficacy Outcomes				
CNS ORR by IRC, n	17	11		
% (95% CI)	81.0 (58.0-95.0)	50.0 (28.0-72.0)		
CNS CR, n (%)	8 (38)	1 (5)		
Difference in CNS ORR (95% CI)	31 (4.2-57.8)			
OR (95% CI); p-value[d]	4.34 (1.10-17.17); p=0.0306[5]			
CNS DOR[f] by IRC, median (95% CI)	17.3 (14.8-NE)	5.5 (2.1-17.3)		
Patients with measurable/non-measurable CNS metastases at baseline				
n for subgroup	64	58	NR	
CNS ORR by IRC, n	38	15		
% (95% CI)	59.0 (46-71)	26.0 (15-39)		
CNS CR, n (%)	29 (45)	5 (9)		
Difference in CNS ORR (95% CI)	33.5 (17-50)			
OR (95% CI); p-value[e]	4.05 (1.89-8.7); p=0.0002[5]			
CNS DOR[f] by IRC, median (95% CI)	NE (17.3-NE)	3.7 (3.2-6.8)		
PFS[a] by INV				
Median in months (95% CI)	NE (9.2-NE)[9]	7.4 (6.6-9.6)[9]		
HR (95% CI); p-value[b]	0.40 (0.25-0.64)[9]			
December 1, 2017 data cut-off[10]				
Median in months (95% CI)	27.7 (NR)	7.4 (NR)		
HR (95% CI)	0.35 (0.22-0.56)			
Time-to-CNS progression by IRC[g]				
Median in months (95% CI)	NR	NR		
HR (95% CI); p-value[b]	0.18 (0.09-0.36); p<0.0001[9]			
12-month CNS progression rate % (95% CI)[c]	16.0 (8.2-26.2)[9]	58.3 (43.4-70.5)[9]		

Abbreviations: IRC -independent central review; CI - confidence interval; CNS - central nervous system; CR - complete response; HR - hazard ratio; INV - investigator assessment; NE - not estimable; NR - not reported; OR - odds ratio; ORR - overall response rate; OS - overall survival; PFS - progression-free survival; PR - partial response; SD - stable disease.

Notes:
[a] - PFS defined as the time from randomization to documented disease progression (per RECIST version 1.1) or death, whichever occurred first.[3]
[b] - HR <1.00 favour alectinib; treatment groups were compared using a stratified log-rank test at a two-sided α=0.05.
[c] - Rate is based on cumulative incidence at 12 months.
[d] - ORR defined as the percentage of patients who obtained a CR or PR, as per RECIST version 1.1.[3]
[e] - OR >1.00 favour alectinib; treatment groups were compared using a stratified Mantel-Haenszel test at a two-sided α=0.05.
[f] - DOR defined as the time from when the criteria for CR or PR were first met to the occurrence of a PFS event.[3]
[g] - Time-to-CNS progression was defined as the time from randomization to first radiographic evidence of CNS progression by IRC, where CNS progression was defined as progression due to newly developed CNS lesions and/or progression of pre-existing baseline CNS lesions (per RECIST version 1.1).[3] The analysis was adjusted for the competing risks (from non-CNS progression and death) between treatment groups.

Quality of Life

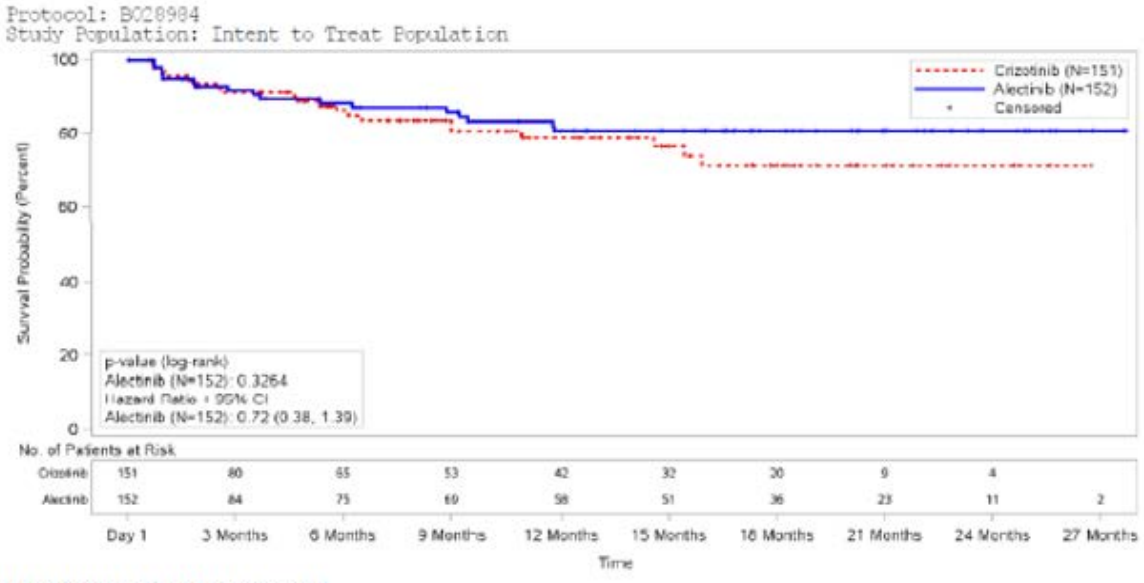
At the time of writing this report, one conference abstract has been published that reports QOL data from the Global ALEX trial.[29] Additional QOL data published in publically available documents including reports by EMA[5] and EUnetHTA[6] were used to supplement the QOL data reported here. The data contained here were also supplemented with unpublished data provided by the Submitter, where deemed necessary, for clarity of reporting.

Baseline compliance for completing QOL questionnaires was moderate in both treatment groups, with approximately 65% of patients (n=100 in the alectinib group versus n=97 in the crizotinib group) completing baseline assessments.[29] It was

reported that compliance rates were impacted by suboptimal initial site training with the electronic device used for patient reporting.[5] Among patients who had baseline data (evaluable patient population), moderate-to-high compliance rates (≥60%) were observed throughout the trial in the alectinib treatment group, except for Weeks 112 and 116.[5] Conversely, compliance rates in the crizotinib arm dropped to ≤60% from Week 68 onwards, except for Weeks 120 through 128, when one patient remained on treatment.[5] Patient-reported QOL data were only interpreted when at least 20% of the evaluable population remained at an assessment time point, which corresponded to week 84 in the crizotinib group and week 96 in the alectinib group; after these time points, the low number of patients limited interpretation of the results.[7] The TTD analyses were performed in the ITT population, while the other PRO endpoints were conducted in the evaluable patient population.[5] Patients in both treatment groups reported minimal to moderate lung cancer symptom burden at baseline.[7]

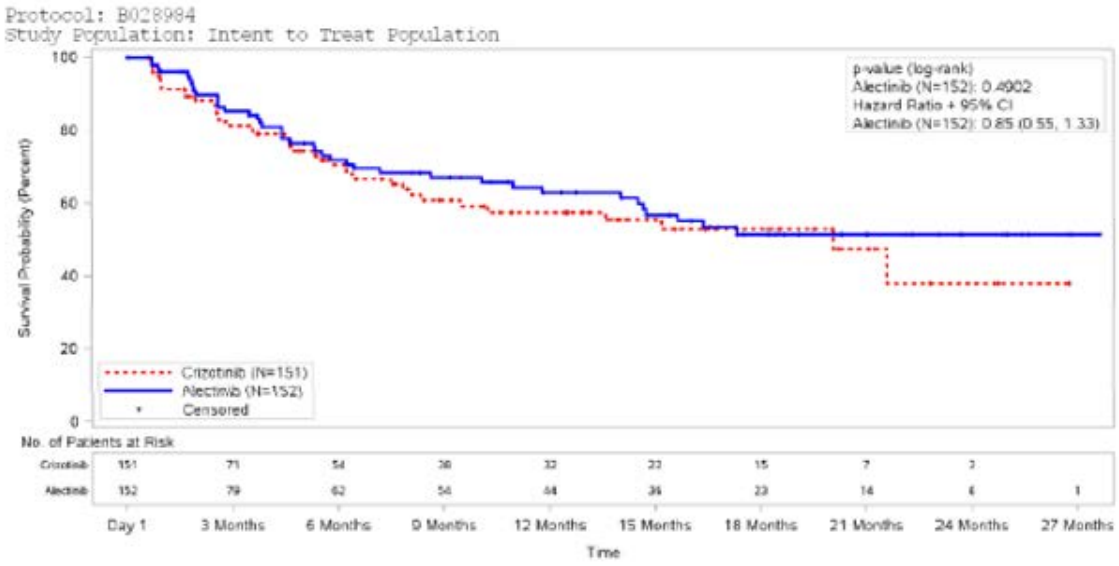
Time-to-Deterioration Analysis

Over the course of the trial, no difference between the treatment groups was demonstrated in TTD of patient-reported global health status/QOL (HR=0.72, 95% CI, 0.38, 1.39; p=0.3264; Figure 3).[6] The proportion of patients with confirmed deterioration events was less than 13.2% in both treatment groups.[6] For the analysis of TTD of patient-reported lung cancer symptoms (cough, dyspnea, chest pain, arm/shoulder pain, fatigue), no differences between the treatment groups were observed for the composite symptom score (comprised of cough, pain in chest, and dyspnea; HR=1.10; 95% CI, 0.72-1.68)[29] or any of the individual symptom scores, with the exception of dyspnea; the TTD in dyspnea (multi-item scale) favoured crizotinib relative to alectinib, with a median TTD of 22.8 months in the alectinib group and median not reached in the crizotinib group (HR=1.76, 95% CI, 1.05-2.92; p=0.0285).[7,8] There was also no difference in TTD in cognitive functioning between the groups; the median TTD in cognitive functioning was not reached in the alectinib group and was 20 months in the crizotinib group (HR=0.85, 95% CI, 0.55, 1.33; p=0.4902; Figure 4).[6]



Abbreviation: CI=confidence interval.

Figure 3: Time-to-deterioration in the EORTC QLQ-C30 global health score in the Global ALEX trial (ITT population).[6,42]



Abbreviation: CI=confidence interval.

Figure 4: Time-to-deterioration in the EORTC QLQ-C30 cognitive functioning score in the Global ALEX trial (ITT population).[6,42]

Health-related QOL, Treatment Side Effects, and Functional Status

At baseline, it was reported that patients had moderate to high scores on assessments of functional status and QOL, with no notable differences observed between treatment groups.[7] On average, patients in the alectinib treatment group (versus crizotinib) reported clinically meaningful improvements in QOL earlier (week 8 vs. week 12), and for a longer duration of time (until week 88 vs. week 68),[29] than patients in the crizotinib treatment group (Figure 5).[6]

The patient-reported QOL data showed greater tolerability (that is, the difference between groups met the MCID of ≥10) with alectinib (versus crizotinib) for the following treatment-related symptoms: diarrhea, constipation, peripheral neuropathy, nausea/vomiting, appetite loss, and dysphagia.[5] Both treatment groups demonstrated clinically meaningful improvements (≥10-point decrease) in multiple lung cancer symptoms, including patient-reported cough, chest pain, pain in other parts, fatigue, and dyspnoea (single-item scale).[6] Patients also reported clinically meaningful improvements in baseline lung cancer symptoms for a longer duration in favour of the alectinib group compared to crizotinib (week 8 versus week 12), and for a longer duration of time (cough, week 96 versus week 84; chest pain, week 96 versus week 80; fatigue, week 96 versus 68; pain in other parts, week 96 versus 68, respectively.[29]

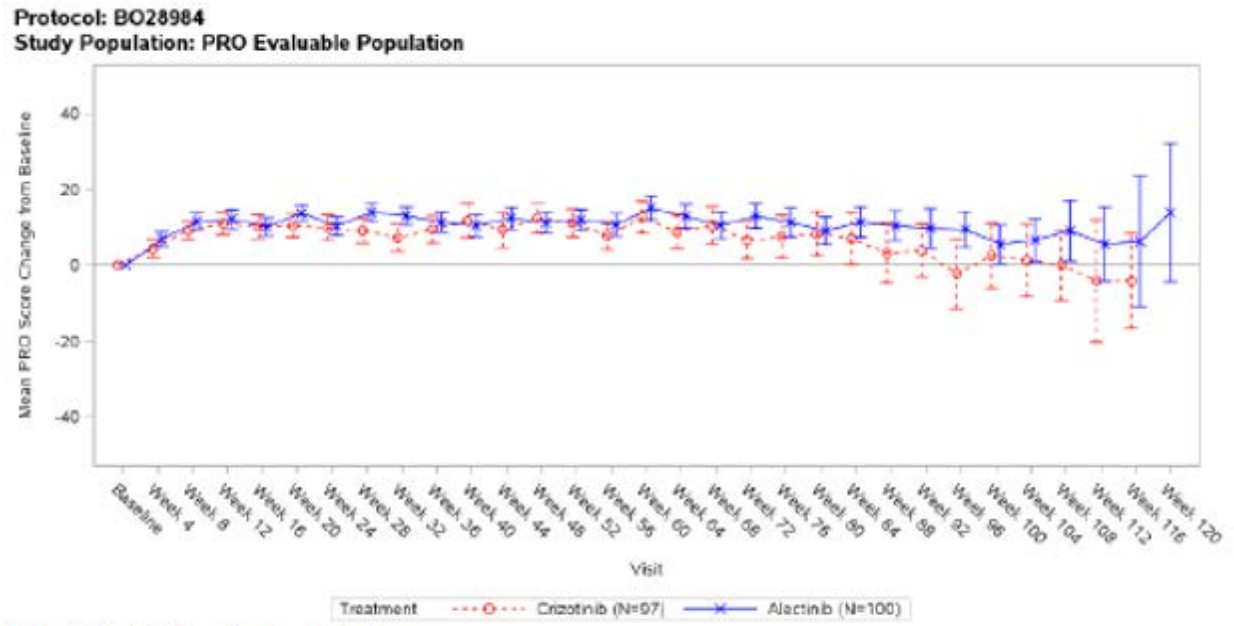


Figure 5: Mean change from baseline in the EORTC QLQ-30 global health score in the Global ALEX trial (evaluable patient population).[6,42]

For the subgroup of patients with CNS metastases at baseline, a lower proportion (≥10% difference) of patients in the alectinib group reported clinically meaningful worsening in QOL compared with crizotinib, starting at week 12 (4% in the alectinib group versus 16% in the crizotinib group) and persisting for most assessments through week 84 (0% alectinib versus 17% crizotinib).[5] Although no differences between treatment groups were seen in cognitive functioning in the evaluable patient population, a benefit with alectinib was reported within the subgroup of patients with CNS metastases at baseline; fewer patients receiving alectinib reported clinically meaningful worsening in cognitive functioning compared with crizotinib, starting at week 4 (8% vs. 27%) and continuing through week 84 (10% vs. 33%).[5] A similar pattern was also observed for fatigue, physical function and social function scores.[5]

Harms Outcomes

Adverse Events

Global ALEX[1]

Duration of treatment was significantly longer in the alectinib treatment group at 17.9 months (range, 0-29) compared to 10.7 months (range, 0-27) in the crizotinib group; while mean dose intensity was comparable between the groups at 96% and 92%, respectively. Compared to the alectinib group, a lower proportion of patients in the crizotinib group completed more than 12 months (45% versus 66%) and more than 18 months (27% versus 49%) of study treatment.[6] The incidence of all-cause AEs occurring in the Global ALEX trial (that differed by ≥5% or more) at the time of primary analysis are summarized in Table 9.

Overall, AEs of any grade occurred in equal frequency in the two treatment groups (97% in each group). The most common all grade AEs associated with alectinib were constipation (34%), anemia (20%), fatigue (19%), peripheral edema (17%), myalgia (16%), blood bilirubin increased (15%), ALT increased (15%), AST increased (14%), nausea (14%), rash (11%), and arthralgia (11%). There were five AEs that occurred in greater frequency in alectinib-treated patients compared to crizotinib-treated patients, which included anemia (20% versus 5%), myalgia (16% versus 2%), blood bilirubin increase (15% versus 1%), weight increase (10% versus 0%), musculoskeletal pain (7% versus 2%) and photosensitivity reaction (5% versus 0%). Comparatively, crizotinib was associated with a higher frequency of GI disorders and liver enzyme abnormalities.

The frequency of grade 3 or greater AEs was higher in patients treated with crizotinib (50% versus 41% with alectinib) and laboratory abnormalities were the main cause of grade 3-5 AEs in both treatment groups. The laboratory abnormalities occurring most often with alectinib were increases in ALT, AST and blood bilirubin, and anemia, which each occurred in ≤ 5% of patients.

The incidence of SAEs was similar in the two treatment groups: 28% with alectinib and 29% with crizotinib. The types of SAEs were also similar, and included pneumonia, lung infection, pneumonitis, pulmonary embolism, pyrexia, ALT increase, and acute kidney injury, which each occurred in ≤ 5% of patients in both treatment groups (Table 9).

Adverse events leading to dose reduction, interruption, and treatment discontinuation were slightly lower in patients treated with alectinib, occurring in 16%, 19%, and 11% of patients, compared to 21%, 25%, and 13% of patients treated in the crizotinib group.

During the Global ALEX trial there were five fatal AEs (3%) that occurred in the alectinib group and seven (5%) that occurred in the crizotinib group. The five deaths in the alectinib group were all deemed unrelated to study treatment and included acute kidney injury, blood creatinine increased, death (not specified), cardiac arrest, and lung infection.[5] In the crizotinib group, two deaths were considered treatment-related by investigator, which included pneumonitis and cardiac arrest; the other causes of death included sudden death, cerebral hemorrhage, necrotising fascitis, respiratory failure and dyspnea.[5]

Some safety data were reported in the updated analysis (conference abstract with a December 1, 2017 data cut-off, which provided 10 months of additional follow-up).[10] Adverse events leading to dose reduction, interruption, and treatment discontinuation were similar to the primary analysis, and slightly lower in patients treated with alectinib, occurring in 16.4%, 22.4%, and 13.2% of patients, compared to 20.5%, 25.2%, and 13.2% of patients treated in the crizotinib group. Fatal adverse events occurred in 4% of patients in the alectinib group (none were attributed to treatment) and 5% of patients in the crizotinib group (2 treatment-related).[10]

J-ALEX[2]

The AEs reported in Table 9 include AEs occurring in the safety population, which comprised of patients treated with alectinib or crizotinib in the first- and second-line setting. Duration of treatment was similar between the two treatment groups (13 months in the alectinib group versus 12 months in the crizotinib group).[5] Compared to the Global ALEX trial, patients in the J-ALEX trial had a shorter

duration of treatment exposure to alectinib (an approximately five month difference).

Similar to the Global ALEX trial, almost all patients in the J-ALEX trial experienced an AE (any grade, 97% with alectinib versus 100% with crizotinib). The most common AEs (any grade) in the alectinib group were constipation (35%), nasopharyngitis (20%), dysgeusia (18%), blood creatine phosphokinase increase (17%), upper respiratory tract infection (17%), myalgia (16%), rash (13%), blood bilirubin increase (12%), and stomatitis (12%). There were three AEs that occurred in greater frequency in alectinib-treated patients (versus crizotinib), which included blood bilirubin increase (12% versus 1%), myalgia (16% versus 3%), and anemia (6% versus 1%). The frequency of grade 3-4 AEs (52% versus 26%) and SAEs (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; the main reasons for treatment discontinuation included grade 1-3 interstitial lung disease (8% in both treatment groups), grade 3-4 abnormal hepatic function (5% in the crizotinib group versus 0), and elevated ALT (4% in crizotinib group versus 0). No fatal AEs were reported in the trial.

Table 9: Safety outcomes and adverse events in the Global ALEX and J-ALEX trials.

Events, n (%)	Global ALEX[1]				J-ALEX[c,2]			
	Alectinib 600 mg (n=152)		Crizotinib (n=151)		Alectinib 300 mg (n=103)		Crizotinib (n=104)	
Median time on treatment in months	17.9		10.7		13.0[5]		12.0[5]	
Dose intensity (±SD)	95.6 (±10.3)		92.4 (±14.1)		NR		NR	
Grade	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
Any AE	147 (97)	63 (41)	146 (97)	76 (50)	100 (97)	27 (26)	104 (100)	54 (52)
AE leading to treatment discontinuation	17 (11)		19 (13)		9 (9)		21 (20)	
AE leading to dose reduction	24 (16)		31 (21)		NR		NR	
AE leading to dose interruption	29 (19)		38 (25)		30 (29)		77 (74)	
AE that differed by ≥5% in frequency between treatment groups:								
Nausea	21 (14)	1 (1)	72 (48)	5 (3)	11 (11)	0	77 (74)	2 (2)
Diarrhea	18 (12)	0	68 (45)	3 (2)	9 (9)	0	76 (73)	2 (2)
Constipation	-	-	-	-	36 (35)	1 (1)	46 (44)	1 (1)
Vomiting	11 (7)	0	58 (38)	5 (3)	6 (6)	0	60 (58)	2 (2)
Upper abdominal pain	NR	NR	NR	NR	2 (2)	0	7 (7)	0
ALT Increased	23 (15)	7 (5)	45 (30)	22 (15)	9 (9)	1 (1)	33 (32)	13 (13)
AST Increased	21 (14)	8 (5)	37 (25)	16 (11)	11 (11)	1 (1)	32 (31)	5 (5)
Neutrophil count decrease	NR	NR	NR	NR	3 (3)	2 (2)	19 (18)	14 (14)
Blood bilirubin increased	23 (15)	3 (2)	2 (1)	0	12 (12)	0	1 (1)	0
Weight increased	15 (10)	1 (1)	0	0	NR	NR	NR	NR
Glutamyltransferase increased	1 (1)	1 (1)	10 (7)	2 (1)	NR	NR	NR	NR
Peripheral edema	26 (17)	0	42 (28)	1 (1)	9 (9)	0	19 (18)	1 (1)
Pyrexia	NR	NR	NR	NR	10 (10)	1 (1)	21 (20)	0
Malaise	NR	NR	NR	NR	10 (10)	0	19 (18)	0
Dizziness	12 (8)	0	21 (14)	0	2 (2)	0	7 (7)	0
Dysgeusia	4 (3)	0	29 (19)	0	19 (18)	0	54 (52)	0
Visual impairment	2 (1)	0	18 (12)	0	1 (1)	0	57 (55)	0
Vision blurred	3 (2)	0	11 (7)	0	NR	NR	NR	NR
Photopsia	0	0	9 (6)	0	0	0	14 (14)	0
Myalgia	24 (16)	0	3 (2)	0	16 (16)	0	3 (3)	0
Musculoskeletal pain	11 (7)	0	3 (2)	0	7 (7)	6 (6)	0	0
Anemia	30 (20)	7 (5)	7 (5)	1 (1)	6 (6)	1 (1)	1 (1)	0
Alopecia	1 (1)	0	11 (7)	0	NR	NR	NR	NR
Decreased appetite	NR	NR	NR	NR	1 (1)	1 (1)	21 (20)	1 (1)
Photosensitivity reaction	8 (5)	1 (1)	0	0	NR	NR	NR	NR
Sinus brachycardia	NR	NR	NR	NR	1 (1)	0	6 (6)	0
EGC QT prolonged	NR	-	NR	-	3 (3)	2 (2)	15 (14)	7 (7)
Hepatic function abnormal	NR	NR	NR	NR	2 (2)	0	8 (8)	6 (6)
Insomnia	NR	NR	NR	NR	3 (3)	0	8 (8)	0
Serious AE occurring in >2% of patients in each treatment group:[28]								
Any	43 (28)		44 (29)		15 (15)		27 (26)	
Pneumonia	5 (3)		4 (3)		NR		NR	
Lung infection	3 (2)		0					
Pneumonitis	2 (1)		4 (3)					
Pulmonary embolism	2 (1)		3 (2)					
Pyrexia	1 (1)		3 (2)					
ALT increased	1 (1)		4 (3)					
Acute kidney injury	4 (3)		0					

Events, n (%)	Global ALEX[1]		J-ALEX[c,2]	
	Alectinib 600 mg (n=152)	Crizotinib (n=151)	Alectinib 300 mg (n=103)	Crizotinib (n=104)
Median time on treatment in months	17.9	10.7	13.0[5]	12.0[5]
Dose intensity (±SD)	95.6 (±10.3)	92.4 (±14.1)	NR	NR
Nausea	0	3 (2)		
Fatal AE	5 (3)[a]	7 (5)[b]	0	0

Abbreviations: AE - adverse event (s); ALT - alanine aminotransferase; AST - aspartate aminotransferase; NR - not reported; SD - standard deviation; "-" indicates AE occurred, but difference between groups was not ≥5%.

Notes:
[a] - The five deaths were attributed to acute kidney failure, blood creatine increased, death (not specified), cardiac arrest and lung infection.[5]
[b] - Two deaths were reported by investigators as being related to study treatment (pneumonitis, cardiac arrest); the other five deaths were attributed to sudden death, cerebral hemorrhage, necrotising fascitis, respiratory failure, and dyspnea.[5]
[c] - Safety population includes patients treated in the first- and second-line setting.

6.4 Ongoing Trials

One ongoing randomized phase 3 trial was identified that met the selection criteria of the review. Trial NCT02838420 is evaluating the efficacy and safety of alectinib at the 600 mg dose compared to crizotinib in Asian participants with treatment naïve ALK-positive advanced or metastatic NSCLC.[12] Details of the trial are summarized in Table 10.

Table 10: Ongoing trial of alectinib in ALK-positive, advanced or metastatic NSCLC.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NCT02838420[12] Phase 3, open label, randomized trial; 2:1 ratio n=187 Multicentre; patient enrolment in China, Republic of Korea and Thailand Status: active, not recruiting Patient enrolment start date: August 3, 2016 Primary analysis data cut-off: April 1, 2018 Study completion date: December 6, 2019 Funded by Hoffman La Roche Ltd.	<u>Key Inclusion Criteria:</u> • Histologically or cytologically confirmed diagnosis of advanced or recurrent (stage IIIB not amenable for multimodality treatment) or metastatic (stage IV) NSCLC • ALK-positive by IHC test (sufficient tumour tissue available to perform ALK IHC testing required) • Measurable disease by RECIST v. 1.1 • Previous brain or leptomeningeal metastases permitted if asymptomatic • ECOG PS of 0-2 • No previous systemic treatment for advanced/recurrent NSCLC • Adequate hematologic and renal function • Life expectancy of at least 12 weeks <u>Key Exclusion Criteria:</u> • A malignancy within the previous 3 years (other than curatively treated basal cell carcinoma of the skin, early GI cancer by endoscopic resection, in situ carcinoma of the cervix, or any cured cancer that is considered to have to no impact in PFS or OS for current NSCLC) • Any GI disorder that may affect absorption or oral medications • Liver disease • NCIC terminology criteria for AEs version 4.0 grade 3 or higher toxicities due to any previous therapy (excluding alopecia) which have not improved and considered to interfere with current study medication • History of organ transplant • Coadministration of anti-cancer therapies other than those administered in study	Alectinib 600 mg orally twice daily until disease progression, unacceptable toxicity, withdrawal of consent or death *versus* Crizotinib 250 mg orally twice daily until disease progression, unacceptable toxicity, withdrawal of consent or death	<u>Primary:</u> • PFS by INV <u>Secondary:</u> • PFS by IRC • ORR by INV • Time-to-CNS progression by IRC • DOR • OS • QOL • Safety
Abbreviations: ALK - anaplastic lymphoma kinase; CNS - central nervous system; DOR - duration of response; ECOG - Eastern Cooperative Oncology Group; GI -gastrointestinal; IHC - immunohistochemistry; INV - investigator assessment; IRC - independent review committee; NSCLC - non-small cell lung cancer; ORR - objective response rate; OS -overall survival; PFS -progression-free survival; RECIST - Response Evaluation Criteria for Solid Tumours -QOL - health-related quality of life.			

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were identified during development of the review protocol as relevant to the pCODR review of alectinib as monotherapy for the first-line treatment of patients with ALK-positive, locally advanced or metastatic NSCLC.

8 COMPARISON WITH OTHER LITERATURE

No comparisons with other literature were included in this pCODR review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lung Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available Alectinib (Alecensaro) for Non-Small Cell Lung Cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Lung Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials December 2017, Embase 1974 to 2018 January 25, Ovid MEDLINE(R) ALL 1946 to January 25, 2018

#	Searches	Results
1	(alectinib* or alecensa* or RO 5424802 or RO5424802 or AF 802 or AF802 or CH 5424802 or CH5424802 or RG 7853 or RG7853 or 1256580-46-7 or 1256589-74-8 or 1416163-60-4 or LIJ4CT1Z3Y or P9YY73LO6J).ti,ab,ot,kf,kw,hw,rn,nm.	1153
2	1 use cctr	46
3	1 use medall	260
4	*Alectinib/	266
5	(alectinib* or alecensa* or RO 5424802 or RO5424802 or AF 802 or AF802 or CH 5424802 or CH5424802 or RG 7853 or RG7853).ti,ab,kw,dq.	844
6	4 or 5	850
7	6 use oemezd	556
8	2 or 3 or 7	862
9	8 and conference abstract.pt.	220
10	limit 9 to english language	220
11	limit 10 to yr="2013 -Current"	212
12	8 not 9	642
13	remove duplicates from 12	386
14	limit 13 to english language	362
15	11 or 14	574

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

#	Query	Items found
#5	Search #4 AND publisher[sb] Filters: English	10
#4	Search #3 AND publisher[sb]	10
#3	Search #1 OR #2	257

#2	Search alectinib*[tiab] OR alecensa*[tiab] OR RO 5424802[tiab] OR RO5424802[tiab] OR AF 802[tiab] OR AF802[tiab] OR CH 5424802[tiab] OR CH5424802[tiab] OR RG 7853[tiab] OR RG7853[tiab] OR 1256580-46-7[rn] OR 1256589-74-8[rn] OR 1416163-60-4[rn] OR LIJ4CT1Z3Y[rn] OR P9YY73LO6J[rn]	249
#1	Search CH5424802 [Supplementary Concept]	94

3. Cochrane Central Register of Controlled Trials (Central)
   Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

U.S. NIH ClinicalTrials. gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Alecensa/alectinib, NSCLC

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Alecensa/alectinib

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Onoclogy (ESMO)
http://www.esmo.org/

Search: Alecensa/alectinib, NSCLC – last 5 years

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2018 Jan 25) with in-process records & daily updates via Ovid; Embase (1974-2018 Jan 25) via Ovid; The Cochrane Central Register of Controlled Trials (Dec 2017) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were alectinib, Alecensa and Alecensaro.

No filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of June 7, 2018.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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