pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Alectinib (Alecensaro) for Non-Small Cell Lung Cancer

March 29, 2018

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

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TABLE OF CONTENTS

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 ALK positive non-small cell lung cancer (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 ALK positive 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 of Clinical Information provided by the CGP, a summary of submitted patient advocacy group input on alectinib (Alecensaro) for ALK positive NSCLC, a summary of submitted Provincial Advisory Group Input on alectinib (Alecensaro) for ALK positive NSCLC, and a summary of submitted registered clinician input on alectinib (Alecensaro) for ALK positive 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 the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib until loss of clinical benefit.

The Health Canada approved indication for market authorization has been granted with conditions (pending the results of studies to verify its clinical benefit) is for patients with ALK-positive, locally advanced (not amenable to curative therapy) or metastatic NSCLC who have progressed on or are intolerant to crizotinib. 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

One randomized controlled trial, ALUR,[1] was identified that met the selection criteria of this review. ALUR is an ongoing, open-label, international (Europe and Asia) phase 3 trial evaluating the efficacy and safety of alectinib compared to chemotherapy in patients with ALK-positive, locally advanced or metastatic NSCLC, who progressed on or were intolerant to crizotinib. To date, the results of ALUR have been published in abstract and poster form only.

Patients included in the trial met the following criteria:

i. advanced (stage IIIB not amenable for multimodality treatment) or metastatic (stage IV) ALK-positive NSCLC, determined by a validated IHC or FISH test;

ii. two previous systemic lines of therapy consisting of one platinum-based chemotherapy regimen and one line of crizotinib; and
iii. ECOG performance status of 0-2.

Patients were centrally randomized to receive either alectinib (600mg orally twice daily) or chemotherapy (intravenously every three weeks) consisting of pemetrexed (500 mg/m^2) or docetaxel (75mg/m^2). Randomization was stratified by performance status (0-1 versus 2) and CNS metastases (yes/no); and patients with CNS disease were further stratified based on previous radiation therapy (yes/no).

The primary efficacy outcome of the trial was PFS by investigator assessment (PFS by INV) in the intent-to-treat (ITT) population. The key secondary outcome was CNS objective response rate (CNS ORR) in patients with measurable CNS metastases at baseline assessed by independent review committee (IRC). The additional secondary outcomes of the trial are detailed in Table 1.

Patients in both treatment groups received study drug until disease progression, unacceptable toxicity, withdrawal of consent or death. Upon progression, patients in the alectinib group could continue to receive alectinib if still clinically benefitting from the drug; and patients in the chemotherapy group were permitted to cross over to alectinib. The median time on treatment was 20 weeks and six weeks for patients in the alectinib and chemotherapy groups, respectively.

There were 107 patients randomized in ALUR; 72 allocated to alectinib and 35 allocated to chemotherapy. The distributions of baseline characteristics were generally balanced between treatment groups. The median age of patients was between 56 and 59 years, with a majority of patients under the age of 65 (79%), male (54%), Caucasian (84%), previous smokers (49%) or never smoked (48%), metastatic disease (96%), and an ECOG status of 0 or 1 (90%). Most patients had CNS metastases at baseline (68%) and among those patients, a majority had undergone previous radiation to treat their CNS disease (59%).

At primary analysis (January 26, 2017) the median follow-up time was 6.5 months in the alectinib group and 5.8 months in the chemotherapy group. At this time, 36% of patients in the alectinib group and 83% of patients in the chemotherapy group had discontinued treatment, with progressive disease (PD) as the primary cause of discontinuation in both treatment groups (28% versus 66%, respectively).[2] In the alectinib group, 61% of patients were continuing assigned treatment and five patients (7%) received alectinib post-progression.[2] In the chemotherapy group, 14% of patients were continuing assigned treatment and 24 patients (69%) had crossed over to receive alectinib post-progression. [2]

Limitations

The quality of the ALUR trial was challenging to appraise in the absence of a peer-reviewed trial publication. Additional limitations may come to light upon longer follow-up and full publication of the trial. Based on presently available data, the trial was well conducted owing to specific design features (appropriate randomization, clear explanation of sample size considerations, use of an IRC for the primary outcome and blinded data analysts, 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, such as patient selection and performance bias, which can affect internal validity; however, an attempt was made to mitigate such bias by using an IRC to assess outcomes using standardized criteria and blinding data analysts to treatment assignment. Conversely, for the assessment of subjective outcomes, like health-

related quality of life (QOL) and adverse events (AEs), there is greater risk of detection bias because patients and investigators would be aware of the specific treatment being administered.

- While the subgroup analyses conducted in the trial were pre-specified, the trial was only powered to detect differences between treatment groups for the primary outcome. Heirarchical testing was used to control the risk of type 1 error for the subgroup analysis of patients with CNS metastases at baseline, however, for the remainder of secondary and subgroup analyses, of which there were many, adjustments for multiplicity (that is, adjustment of the statistical confidence level to account for the number of comparisons being tested) were not made. Therefore, given the likelihood of obtaining a positive result increases with increasing number of comparisons, the subgroup analysis results should be interpreted with caution.
- The assessment of health-related QOL has a number of limitations (poor patient compliance in completing questionnaires in the chemotherapy treatment group, much longer treatment exposure of patients in the alectinib group compared to the chemotherapy group resulting in shorter follow-up for patients treated with chemotherapy) that raise uncertainty about the validity of the QOL findings obtained, and precludes an accurate assessment and comparison of QOL between the treatment groups. Further, both the published and unpublished data made available to pCODR were limited by incomplete and selective reporting. Given these factors, it is likely that the health-related QOL results do not fully capture the QOL experience of all patients in the trial and therefore should be interpreted with caution.

Efficacy

A summary of key outcomes of the ALUR trial are summarized in Table 1. The primary efficacy results were based on the 107 patients who comprised the ITT population. Some secondary efficacy outcomes were based on the subgroup of patients who had measurable/non-measurable CNS metastases at baseline (n=76, C-ITT) and the subgroup of patients who had measurable CNS metastases at baseline (n=40, mC-ITT). The efficacy analyses conducted in these two subgroups were prospectively planned.

At primary analysis, a statistically significant improvement in PFS by INV, of approximately eight months, was demonstrated in the alectinib treatment group compared to chemotherapy; median PFS by INV was 9.6 months with alectinib and 1.4 months with chemotherapy (HR=0.15, 95% CI, 0.08-0.29; p<0.001). A similar treatment benefit, albeit of slightly lower magnitude, was observed for PFS by IRC. The results of subgroup analyses were consistent with the primary analysis results across most patient subgroups examined; however, for some groups low event rates and small sample sizes made treatment effect estimates unreliable or not estimable. Data on OS were deemed immature at primary analysis.

Alectinib was superior to chemotherapy for all tumour response outcomes [objective response rate (ORR), duration of response (DOR), and disease control rate (DCR)]. The ORR by INV was 38% in patients treated with alectinib compared to 3% in chemotherapy-treated patients (3%). The ORRs in both treatment groups comprised of all partial responses. Duration of response was longer in patients treated with alectinib compared to chemotherapy (median DOR in months, 9.3 versus 2.7). These estimates are based on 27 partial responses and one partial response observed in the alectinib and chemotherapy groups, respectively. The DCR for alectinib and chemotherapy were 81% and 29%, respectively.

Alectinib was superior to chemotherapy for all CNS efficacy outcomes (CNS ORR, CNS DCR). The CNS ORR among patients with measurable CNS metastases at baseline (mC-ITT) was 54% in the alectinib group versus 0% in the chemotherapy group (p<0.001), demonstrating a significant treatment benefit in the CNS with alectinib compared to chemotherapy. There were one complete and 12 partial CNS responses in patients treated with alectinib. Duration of response was not estimable in either patient subgroup. The CNS DCR by IRC also favoured alectinib (79% versus 31%). Similar results were observed in the subgroup of patients with measurable and non-measurable CNS metastases at baseline (C-ITT) but of lower magnitude.

Considering all patients (ITT), the risk of CNS progression was significantly reduced in patients treated with alectinib compared with chemotherapy (median not estimable for alectinib versus 2.4 months with chemotherapy;[2] HR=0.14, 95% CI, 0.06-0.36, p<0.001). Similar results were observed in patients with CNS metastases (C-ITT) at baseline.

Patient–reported health-related QOL was assessed using the EORTC Quality of Life Questionnaire (QLQ)-C30, the QLQ-Lung Cancer Module (LC-13) and three items from the QLQ-Brain Cancer Module (BN20).[3] Compliance in completed QOL questionnaires was generally high in the alectinib group but declined substantially over time in the chemotherapy group. In general, the majority of QOL scores numerically favoured treatment with alectinib, however, few significant differences [in terms of the minimal clinically important difference (MCID) of 10% or greater] were observed between the treatment groups, and include:

- For the EORTC-QLQ-C30 function scales, differences in the mean change from baseline in cognitive function, which favoured alectinib, met the MCID threshold (least squares mean difference=10.0, 95% CI, 2.2-17.7). For symptom scales, constipation was the only scale where differences in the mean change from baseline, which favoured chemotherapy, reached the MCID (least squares mean difference=17.1, 95% CI, 3.3-30.9).
- For the EORTIC QLQ-LC symptom scales, differences in the mean change from baseline in alopecia, which was worse with chemotherapy, was the only scale that met the MCID (least squares mean difference -20.8, 95% CI, -33.6—8.0).
- Time-to-deterioration (TTD) of lung symptoms was assessed for all single- and composite scales; only TTD in patient-reported fatigue and arm/shoulder pain were significantly delayed with alectinib compared to chemotherapy (TTD in arm/shoulder pain: median TTD 8.1 versus 1.9 months; TTD in fatigue: 2.7 versus 1.4 months).
- The BN20 showed patients treated with alectinib reported improvements in coordination (18% versus 4%) and communication (18% versus 8%).

Harms

Overall, AEs of any grade and AEs of grade 3 or higher occurred less frequently in patients treated with alectinib compared to chemotherapy (any grade: 77% versus 85%; grade ≥3: 27% versus 41%). The most common all grade AEs associated with alectinib were constipation (19%), anemia (14%), asthenia (10%), and dyspnea (9%). Three AEs occurred more frequently in alectinib-treated patients and included constipation (19% versus 12%), dyspnea (9% versus 0%), and blood bilirubin increased (6% versus 0%). The incidence of serious AEs (SAEs) was higher in patients treated with alectinib compared to chemotherapy (19% versus 15%); of those patients in the alectinib group, 6% of SAEs (n=4) occurred in more than one patient and included pneumonia (n=2) and acute kidney failure (n=2, one of which was deemed related to study drug).[2] Treatment with alectinib led to a higher

frequency of treatment interruption compared to chemotherapy (19% versus 9%); however, the chemotherapy group had a greater frequency of dose reductions (12% versus 4%) and treatment discontinuation (9% versus 6%). During the treatment period six patients discontinued study treatment due to death; one patient who received docetaxel died from pneumonia deemed unrelated to study treatment, while the remainder in either group died due to disease progression that was also unrelated to study treatment.[2]

Table 1: Highlights of Key Efficacy Outcomes in the ALUR trial.[1,2,4]

Efficacy Outcomes	Alectinib	Chemotherapy
Systemic Efficacy (ITT, n=107)[1,2]		
n	72	35
PFS[a] by INV (primary outcome)		
Events, n (%)	24 (33)	28 (80)
Median in months (95% CI)	9.6 (6.9-12.2)	1.4 (1.3-1.6)
HR[b] (95% CI); p-value	0.15 (0.08-0.29); p<0.001	
PFS[a] by IRC		
Events, n (%)	28 (39)	21 (60)
Median in months (95% CI)	7.1 (6.3-10.8)	1.6 (1.3-4.1)
HR[b] (95% CI); p-value	0.32 (0.17-0.59); p<0.001	
ORR[c] by INV, % (95% CI)	38 (26-50)	3 (0-15)
ORR[c] by IRC, % (95% CI)	36 (25-48)	11 (3-27)
DCR[d] by INV, % (95% CI)	81 (70-89)	29 (15-46)
DCR[d] by IRC, % (95% CI)	76 (0.65-0.86)[2]	49 (0.31-0.66)[2]
OS	NE	NE
CNS Efficacy in Patients with Measurable CNS Metastases (mC-ITT, n=40)[1,4]		
n	n=24	n=16
CNS ORR[e] by IRC (key secondary outcome)		
% (95% CI)	54 (33-74)	0 (0-21)
p-value[f]	p<0.001	
CNS DCR[g] by IRC, % (95% CI)	79 (58-93)	31 (11-59)
p-value[f]	p<0.001	
CNS Efficacy in Patients with Measurable/Non-measurable CNS Metastases (C-ITT, n=76)[4]		
n	50	26
CNS ORR[e] by IRC		
% (95% CI)	36 (23-51)	0 (0-13)
p-value[f]	p<0.001	
CNS DCR[e] by IRC, % (95% CI)	80 (66-90)	27 (12-48)
p-value[f]	p<0.001	
Time-to-CNS progression[g,2,4]		
All patients, n	72[2]	35[2]
Median (95% CI)	NE (8.1-NE)[2]	2.4 (1.4-NE)[2]
HR (95% CI); p-value	0.14 (0.06-0.36); p<0.001	
Patients with CNS metastases at baseline, n	50[2]	26[2]
Median (95% CI)	NE (6.8-NE)	1.6 (1.3-9.9)
HR (95% CI)	0.16 (0.06-0.43)	

Abbreviations: CI – confidence interval; **C-ITT** – analysis population comprised of patients with CNS metastases at baseline; **CNS** – central nervous system; **DCR** – disease control rate; **HR** – hazard ratio; **INV** – investigator assessment; **IRC** – independent review committee; **mC-ITT** – analysis population comprised of patients with measurable CNS metastases at baseline; **NE** – not estimable; **NR** – not reported; **ORR** – objective response rate; **OS** – overall survival; **PFS** – progression-free survival.

Notes:

[a] – PFS defined as the time from randomization to the first documented disease progression (as determined by RECIST version 1.1) or death, whichever occurred first.

[b] - Hazard ratios derived from stratified Cox model using treatment as a covariate (HR <1.00 favour alectinib); the treatment groups were compared using a log-rank test at a two-sided α=0.05.

[c] – ORR defined as the percentage of patients who obtained a CR or PR, as determined by RECIST v1.1.

[d] - DCR defined as percentage of patients who attained a CR, PR or SD of at least five weeks as determined by RECIST version 1.1.
[e] – Outcome is defined the same way as in the ITT population but applied to lesions in the CNS only. Patients with non-measurable disease can only achieve a CR and SD, and not a PR.
[f] – The difference between treatment groups was compared using a Chi-square test at a one-sided α=0.05.[2]
[g] –Defined as the time from randomization to the first documented disease progression in the CNS.

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

One patient advocacy group, Lung Cancer Canada (LCC), provided input on alectinib (Alecensaro) for the treatment of patients with ALK positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. From a patient's perspective, receiving a diagnosis of lung cancer can be devastating and specifically stage IV lung cancer patients experience the highest burden of symptoms. LCC highlighted that crizotinib and ceritinib were reported to be highly effective, tolerable (for some patients), and allow patients to have a very high quality of life. While treatments such as crizotinib or ceritinib seem to provide a good quality of life, and shrink or control their lung cancer; respondents reported needing another option when ALK inhibitors fail or cannot be tolerated.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine of the provinces (Ministries of Health and/or cancer agencies) and the federal drug plan participating in pCODR. PAG identified the following as factors that could be impact implementation of alectinib in the treatment of non-small cell lung cancer (NSCLC):

Clinical factors:
- Indication creep into first-line treatment, particularly for patients who already have CNS metastasis upon diagnosis
- Clarity on "treatment until loss of clinical benefit"

Economic factors:
- Unknown treatment duration
- Additional costs to manage and treat adverse events

Registered Clinician Input

Two clinician inputs were provided on alectinib for locally advanced or metastatic NSCLC. According to the input received, compared to crizotinib and ceritinib, alectinib provides improvement in progression-free survival, overall response rate, duration of response, and toxicity profile; this includes patients with brain metastases. Clinician input suggested that alectinib may be used for ALK+ treatment naïve NSCLC (however this is out of scope for this review), patients who have progressed on crizotinib, or those who failed both crizotinib and ceritinib; where multiple second generation ALK inhibitors would provide the maximum number of treatment lines for patients who acquire treatment resistance. Overall, clinician input noted that the sequential use of multiple ALK inhibitors improves outcomes and should be available for this patient population.

Summary of Supplemental Questions

- **Critical appraisal of the Manufacturer's submitted indirect treatment comparison and network meta-analysis comparing alectinib to ceritinib in patients with ALK-positive metastatic NSCLC who have progressed on crizotinib.**

A manufacturer-submitted indirect treatment comparison (ITC) and network meta-analysis (NMA),[2,5] which compared alectinib to ceritinib and chemotherapy as treatment for patients with advanced or metastatic NSCLC who progressed on were intolerant to crizotinib, was summarized and critically appraised using the ISPOR Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire. The ITC and NMA found that alectinib significantly improved PFS by INV compared to ceritinib, but no difference in PFS by IRC was detected. Alectinib significantly improved PFS by INV and IRC compared to chemotherapy. No differences in OS were demonstrated between the treatment groups, however, OS data were considered immature and unadjusted for treatment crossover. There were no differences between alectinib and ceritinib for response outcomes including ORR and DCR (by INV and IRC); however, each ALK inhibitor showed significantly better response outcomes compared to chemotherapy. Alectinib was associated with significantly fewer grade ≥3 AEs and dose reductions when compared to ceritinib; and no differences in safety outcomes were observed when alectinib was compared to chemotherapy. Conversely, ceritinib was associated with significantly more grade ≥3 AEs, treatment interruptions, and dose reductions compared to chemotherapy. Health-related QOL data were available but not amenable to meta-analysis. The quality assessment judged the overall relevance of the ITC and NMA to be sufficient, but concerns were noted related to credibility (internal validity). The main limitations of the ITC and NMA included heterogeneity across the included studies that was not investigated in analyses due to constraints in the structure of the evidence network (single trial connections) and the use of preliminary and/or unpublished data. It was concluded that the comparative efficacy estimates obtained (alectinib versus ceritinib) are likely biased due to uncontrolled heterogeneity; however, the direction and magnitude of the bias is unclear, and therefore, the estimates may over or under estimate the true treatment effect associated with alectinib.

See section 7.1 for more information.

- **Critical appraisal of the Manufacturer's submitted indirect treatment comparison of alectinib phase 2 data versus ceritinib real world data.**

The Manufacturer's submitted ITC and NMA described in section 7.1 was unable to provide an estimate of the comparative efficacy of alectinib versus ceritinib for OS due to immaturity of trial data. Therefore, data from two single-arm, phase 2 alectinib clinical trials[6,7] (refer to section 8 for a brief summary of trials NP28673 and NP28761) and real world data (RWD) from an electronic health record (EHR) database for ceritinib patients were retrospectively analyzed to indirectly compare OS in the target population and derive an estimate of treatment effect.[2,5] The quality of the analysis was assessed according to best practice principles, set out by Austin and Stuart (2015),[8] when using inverse probability of treatment weighting (IPTW) using propensity scores to estimate causal treatment effects from observational data. Overall, the ITC used methods that align with best practice; however, important limitations in the analysis were noted, including issues related to relevancy (a substantial proportion of patients in the ceritinib RWD treatment group did not experience crizotinib failure *in the first-line setting*)[5] and internal validity (important key prognostic baseline variables were left out of the model used to balance treatment groups for the primary analysis). Therefore, the reported OS estimate may be

confounded since the effects of all important prognostic baseline variables were not controlled for simultaneously in the primary analysis.

See section 7.2 for more information on the ITC and for the pCODR Review Team's response to Submitter feedback on the Initial Recommendation of alectinib and the critical appraisal of the ITC.

Comparison with Other Literature

See Section 8 for further details on the comparison with other literature section.

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 in patients with ALK-positive, advanced/metastatic NSCLC who have progressed on or are intolerant to crizotinib.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the phase 3 ALUR trial[1,2,9]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>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>Chemotherapy</td></tr>
<tr><td>0</td><td>29 (40)</td><td>11 (31)</td></tr>
<tr><td>1</td><td>37 (51)</td><td>19 (54)</td></tr>
<tr><td>2</td><td>6 (8)</td><td>5 (14)</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 was limited. Although there was a low proportion of patients with ECOG PS 2, 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>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the phase 3 ALUR trial[1,2,9]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>CNS Metastases</td><td>CNS metastases at baseline, n (%)<table><tr><td></td><td>Alectinib</td><td>Chemotherapy</td></tr><tr><td>No</td><td>25 (35)</td><td>9 (26)</td></tr><tr><td>Yes</td><td>47 (65)</td><td>26 (74)</td></tr><tr><td>CNS mets treated</td><td>28 (60)</td><td>15 (58)</td></tr></table></td><td>Are the results of the trials generalizable to patients with CNS metastases who have progressed on crizotinib?</td><td>The benefits of alectinib in this population are particularly evident in patients with CNS metastases. This includes those with CNS metastasis at initial presentation, those who developed CNS disease on first-line crizotinib or other systemic therapies.</td></tr>
<tr><td></td><td>Age</td><td>ALUR enrolled patients aged 18 years or older. The median age of patients was approximately 57 years old.

The proportions of patients by age group were as follows:

Age category (years), n (%):<table><tr><td>Age category, years, (%)</td><td></td><td></td></tr><tr><td></td><td>Alectinib</td><td>Chemotherapy</td></tr><tr><td>18 - 64</td><td>60 (83)</td><td>25 (71)</td></tr><tr><td>≥65</td><td>12 (17)</td><td>10 (29)</td></tr></table></td><td>Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?</td><td>ALK-positive NSCLC patients tend to be younger at the age of diagnosis. The CGP noted that the trial enrolled patients aged 18 years or older. The CGP recognizes that the proportion of patients ≥65 years in the trial was small. However, the CGP agree that the use of alectinib may be appropriate among patients ≥65 and treatment with alectinib should be left to the discretion of the treating oncologist.</td></tr>
<tr><td></td><td>Organ dysfunction</td><td>The trial limited eligibility to patients with adequate hematologic and renal function. Patients with liver dysfunction 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 hematologic and renal function as determined by the treating oncologist.</td></tr>
<tr><td></td><td>Ethnicity or Demographics</td><td>ALUR was a global trial that enrolled patients from 15 countries: Belgium, Bulgaria, China, France, Germany, Hungary, Italy, Norway, Poland,</td><td>If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a</td><td>The CGP agrees that the ethnicity of the study population would be comparable to the Canadian population and therefore the results</td></tr>
</table>

Domain	Factor	Evidence from the phase 3 ALUR trial[1,2,9]	Generalizability Question	CGP Assessment of Generalizability
		Portugal, Russia, Slovakia, Korea, Spain, and Turkey.[9]	different result in a Canadian setting?	of the trial would be generalizable to the Canadian population.
	Biomarkers	ALUR enrolled patients who had ALK-positive NSCLC ascertained by a validated FISH or IHC test.	Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)?	Determination of ALK positivity in Canada is standard. It uses an IHC test to screen advanced non-squamous NSCLC.
Intervention	Treatment intent	What was the intent of the treatment in the trial?	Are the results of the treatment generalizable to an alternative treatment intent?	The intent of treatment is palliative.
	Line of therapy	ALUR evaluated alectinib in patients with advanced or metastatic ALK-positive NSCLC who progressed on two previous lines of therapy, which must have included one line of platinum-based chemotherapy and one line of crizotinib.	Are the results generalizable to patients that received crizotinib first-line and subsequently treated with chemotherapy or immunotherapy? Are the results of the trial generalizable to patients who are intolerant to crizotinib? PAG also noted that if intolerance to crizotinib is not defined, there would be a lower threshold of tolerance to crizotinib and patients may be deemed intolerant after one dose.	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%). The CGP agree that it is reasonable to conclude that a switch to alectinib after crizotinib is at least as effective as in patients who also received prior chemotherapy. The activity of checkpoint inhibitors (immunotherapy) is largely unknown as very few ALK positive patients have been included in the checkpoint inhibitor clinical trials. In addition, the evolving paradigm for the management of patients with driver mutations is to treat with all active TKI's first before considering chemotherapy, with immunotherapy most often reserved for progression after platinum doublet. The ALUR trial did not report the number of patients who were intolerant to crizotinib. The CGP agree that there would be very few patients who would be intolerant to crizotinib. However, in such instances, the CGP agreed that alectinib may be a reasonable treatment alternative. The CGP felt that the definition of intolerant is side

Domain	Factor	Evidence from the phase 3 ALUR trial[1,2,9]	Generalizability Question	CGP Assessment of Generalizability
				effects despite optimal medical management, as determined by the treating oncologist. The CGP also felt that it is very unlikely that crizotinib would be discontinued after one dose.
Setting	Countries participating in the trial	Refer to "Ethnicity/demographics above.	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 achieve the outcomes.	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 Canadian population.
	Location of the participating centre	Participating centres included academic and/or community-based treatment centres.[2]	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	Concomitant medications were used by 76% (n=53) of patients receiving alectinib and 97% (n=33) of patients receiving chemotherapy. The most common medications were steroids (34% vs. 65%, respectively), analgesics (34% vs. 47%), proton pump inhibitors (31% vs. 38%), opioid analgesics (21% vs. 24%), and anticoagulants (17% vs. 29%).[2]	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 ALUR trial are generalizable to the majority of Canadian treatment centres.

1.2.4 Interpretation

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.[10] Determination of ALK positivity by immunohistochemistry or other methods in Canada 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 current 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. However, progression on crizotinib inevitably occurs in the majority of patients usually within 12 months. The CNS appears to be a common site of progression on crizotinib, likely related to the low penetration of crizotinib into the CNS. For patients with disease progression or intolerance to crizotinib, treatment options are limited to platinum-based doublet, single agent chemotherapy, or ceritinib, a second generation ALK tyrosine kinase inhibitor (TKI). The activity of checkpoint inhibitors (immunotherapy) is largely unknown as very few ALK positive patients were included in the checkpoint inhibitor clinical trials. In addition, the evolving paradigm for the management of patients with actionable (driver) mutations is to treat with all active TKIs first before considering chemotherapy or immunotherapy.

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 ALUR trial was a randomized phase 3 trial of alectinib versus chemotherapy in patients previously treated with platinum-doublet chemotherapy and crizotinib.[1] The trial enrolled patients with ECOG performance status of 0-2 who had progressed on or were intolerant (not defined) of, crizotinib and had also received platinum doublet chemotherapy. As the CNS is a common site of progression in ALK-positive patients, patients with CNS metastases were eligible. More than 60% of 107 enrolled patients had CNS metastases at baseline, and 59% had received prior CNS radiation. Patients were randomized 2:1 to receive alectinib at 600 mg orally twice daily or standard chemotherapy with docetaxel or pemetrexed, depending on prior treatment. Patients randomized to alectinib could continue past progression if the investigator felt they were deriving clinical benefit. Patients randomized to chemotherapy were permitted to cross-over to receive alectinib upon disease progression.

The primary end-point of the ALUR trial was 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 trial was well designed and conducted but interpretation is limited as it has only been presented in abstract form and not in a peer reviewed publication.

The preliminary results of the ALUR trial were presented at ESMO 2017.[1] The ALUR trial met its primary end-point of improved PFS by investigator. The median PFS as determined by investigator was significantly better with alectinib (9.6 months) versus chemotherapy (1.4 months) (HR=0.15, p< 0.001) as was the response rate (37.5 % versus 2.9%). Both the PFS advantage and the higher ORR were confirmed by the IRC (PFS 7.1 months versus 1.6 months, HR 0.32, p < 0.001, ORR 36.1 25-48). Response in the CNS was seen in 54% of patients treated with alectinib versus 0% of patients treated with chemotherapy. Time-to-CNS progression was significantly better in the alectinib arm, for patients with and without CNS metastases at baseline. In the ALUR trial, 69% of patients in the chemotherapy arm crossed-over to receive alectinib post-progression.

Alectinib was well tolerated with fewer grade 3-5 AEs (27%) compared with chemotherapy (41%). Although patient reported outcomes (PRO) were assessed in the ALUR, these data have only been presented as a poster presentation. The majority of quality of life scores numerically favoured treatment with alectinib, however, few significant differences (in terms of the minimal clinically important difference of 10% or greater) were observed between the treatment groups.

The main limitations of the ALUR trial are its short follow-up and the fact that it has not yet been published in a peer review journal. The primary outcome of PFS was superior for alectinib compared to chemotherapy and similar to that seen in two phase 2 trials (8.1 months and 8.9 months).[6,7] The poor performance of the standard chemotherapy arm reflects the third-line nature of the trial and the patient population that includes 60% with brain metastases at baseline. The six week PFS in the chemotherapy arm corresponds to the time of the first response assessment. The PFS in the chemotherapy arm is similar to that seen in the ASCEND-5 trial of ceritinib versus chemotherapy in a similar patient population.[11]

Patients in the ALUR trial could continue on alectinib past radiologic progression per RECIST v1.1 if patients were deemed to continue to derive clinical benefit. Treatment beyond radiologic progression has become the standard practice for patients with molecular drivers treated with TKIs as long as a patient is asymptomatic. Many of these patients progress in one or a few sites that can be managed with local therapy such as radiation, or have asymptomatic progression not requiring intervention. In the ALUR trial, 5 patients (7%) treated with alectinib continued on alectinib past progression.

1.3 Conclusions

The CGP concluded that there is a net clinical benefit to alectinib in the treatment of ALK-positive NSCLC patients progressing after or who are intolerant to crizotinib. The evidence for this comes from the randomized phase 3 ALUR trial[1] and is supported by 2 phase 2 non-randomized trials showing similar outcomes.[6] The CGP considered the following:

- The benefits of alectinib in this population are particularly evident in patients with CNS metastases. Alectinib is also better tolerated than chemotherapy.

- OS data in the ALUR trial was immature at the time of data analysis. With sufficient follow-up, OS could be evaluated but any benefit will likely be confounded by crossover given that 69% of patients in the chemotherapy arm crossed-over to receive alectinib post- progression in the trial.

- Although ceritinib, another second generation ALK TKI, has shown similar benefits compared to chemotherapy in the ASCEND 5 trial, there is no direct comparison between ceritinib and alectinib in this population. An indirect treatment comparison and network meta-analysis provided by the manufacturer suggested that alectinib was better than ceritinib for PFS, but this analysis is likely biased by uncontrolled heterogeneity in patients in these trials.[2] Due to immaturity of OS trial data, data from two single-arm, phase 2 alectinib clinical trials and real world patient data from an electronic health record database were retrospectively analysed to indirectly compare OS and derive an estimate of treatment effect.[2,5] The hazard ratio was obtained from a propensity-score adjusted analysis. The analysis suggested that alectinib was associated with prolonged OS compared to ceritinib. However, the reported estimate may be confounded since the effects of all important prognostic baseline variables were not controlled for simultaneously in the primary analysis. Overall, several limitations were identified in these indirect comparisons and should be interpreted with caution. It is the opinion of the members of the CGP that alectinib appears to have better CNS activity and appears to be better tolerated than ceritinib.

- The results of this trial are likely to be relevant for the management of ALK-positive NSCLC for a limited time. In a recent RCT, alectinib has demonstrated statistically significant efficacy compared to crizotinib as a first-line therapy in ALK-positive NSCLC.[12] However, even if alectinib eventually becomes a reimbursed treatment option for first-line therapy, there remain significant numbers of patients who have received first-line crizotinib and subsequently progressed for who alectinib after crizotinib represents a significant advance.

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, two out of every five people are expected to develop cancer in their lifetime. Furthermore, one out of four 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.[13] Non-small cell lung cancers (NSCLC) are the most common type of lung cancers, comprising 85% of lung cancers. In 2015, it is estimated that there will be 26,600 new cases of lung cancer diagnosed and 20,900 deaths associated with lung cancer, with incidence and mortality rates of 51.9/100,000 and 40.2/100,000 respectively.[13] 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 the fusion ALK gene acts as an oncogenic driver. Certain clinical characteristics are more likely to be associated with ALK-positive NSCLC, including younger age at diagnosis, never smoking status and adenocarcinoma histology.[14] Although no national data are available for Canadian patients, The French Cooperative Thoracic Intergroup (IFCT) report a 5% ALK positivity in 8134 patients assessed in the one year period between April 2012 - April 2013.[10] 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.[15]

2.2 Accepted Clinical Practice

Crizotinib, an oral small molecule inhibitor of ALK, MET and ROS1 kinase, is the current 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. This is based on an open-label phase 3 study that confirmed superior objective response rates [74% vs. 45%, (P<0.001)] and progression-free survival (PFS) [median PFS 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 treatment groups, likely due to the high rate of crossover to crizotinib in the chemotherapy arm.[16] Crizotinib is continued in the absence of disease progression or unacceptable toxicity, and is often continued past radiologic progression if a patient is not symptomatic, in large part because the alternative has been cytotoxic chemotherapy. In the PROFILE 1014 trial, 73% of patients were treated beyond progression with crizotinib, for a median of 3.1 months. However, 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.[17] In addition, the CNS appears to be a common site of progression on crizotinib, likely related to the low penetration of crizotinib into the CNS. If CNS is the only site of progression, local therapy with radiation is often used to treat the site(s) of progression and crizotinib is continued.

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 PFS in both crizotinib resistant and crizotinib naive patients.[18] In the randomized phase 3 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.[11] Although ceritinib is available through a special access program, it is not currently publically funded in Canada.

For patients with ALK-positive advanced NSCLC progressing on crizotinib, 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.[19]

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 addition, the evolving paradigm for the management of patients with actionable (driver) mutations is to treat with all active TKI's first before considering chemotherapy, with immunotherapy most often reserved for progression after platinum doublet.

Alectinib is seeking reimbursement approval for the treatment of those patients with ALK-positive NSCLC who have previously received crizotinib and subsequently had progressive disease, or who were intolerant of crizotinib until loss of clinical benefit. Alectinib is active in crizotinib resistant patients and is not a substrate for p-glycoprotein, leading to higher CNS activity.

2.3 Evidence-Based Considerations for a Funding Population

The Canadian Cancer Society estimates that in 2015, there were 26600 new cases of lung cancer in Canada.[13] 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 2015 was approximately 650. 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.[20] Testing would have been done in the population under consideration in order for them to have received crizotinib as initial ALK-directed therapy.

Alectinib has clinically meaningful activity in those patients whose disease has progressed on crizotinib. Two phase 2 trials of alectinib at a dose of 600 mg po BID have been conducted in patients previously treated with crizotinib. In study NP28716 (n=87 patients),[7] 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. 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)[6] the objective response rate was 50% with median PFS 8.9 months. 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 2 trials alectinib was well tolerated with the 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.[21] 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.[22] 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.[21]

The phase 2 trials served as the basis for the ALUR trial, a randomized phase 3 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.[1] 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 (9.6 months) versus chemotherapy (1.4 months) (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 AEs (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 2 trials the majority of patients also received platinum chemotherapy (75%-80%). In NP28673,[6] the chemotherapy naïve patients had a higher ORR (69%) and PFS (13 months) than the ITT population. It is difficult, however, to draw firm conclusions from these data because of the small numbers of chemo-naïve patients. It is reasonable to conclude that a switch to alectinib after crizotinib is at least as effective as in patients who also received prior chemotherapy.

It is difficult to estimate the potential number of patients in Canada for whom alectinib after progression on crizotinib would be the recommended treatment. While it may be simple enough to use crude incidence rates for advanced NSCLC and the expected percentage of ALK-positive patients to arrive at an estimate, these crude calculations likely over-estimate the number of eligible patients. 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) or because of death on treatment. It is also clear that not all patients receiving crizotinib will receive subsequent therapy, due to decline in performance status or unresolved toxicities. The availability of alectinib for patients progressing on crizotinib may decrease the number of patients treated beyond progression with crizotinib. Considering the efficacy and tolerability of alectinib compared to chemotherapy, an immediate switch at time of progression may be appealing to oncologists and patients.

2.4 Other Patient Populations in Whom the Drug May Be Used

The funding indication being sought is in patients with ALK-positive NSCLC intolerant to crizotinib or with progression following crizotinib until loss of clinical benefit. It is likely that the number of patients who will receive alectinib (or other second generation ALK inhibitor) after crizotinib failure will decrease over time given the results of the ALEX trial of first line alectinib versus crizotinib.[12] This randomized phase 3 trial showed first-line alectinib to be superior in terms of PFS by IRC assessment (25.7 months versus 10.4 months). Alectinib was also superior in controlling CNS disease and appeared to be better tolerated.

Although there is little data regarding the activity of alectinib in patients previously treated with both crizotinib and ceritinib, given the higher toxicity of ceritinib and the higher CNS penetration of alectinib, the CGP feels it would be reasonable to offer alectinib to patients intolerant of or progressing after both crizotinib and ceritinib.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Lung Cancer Canada (LCC), provided input on alectinib (Alecensaro) for the treatment of patients with anaplastic lymphoma kinase (ALK) positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib, and their input is summarized below.

LCC gathered information from: 1) summary from previous submission to the pCODR program for alectinib, 2) environmental scans of online forums, 3) one-on-one interviews with patients and caregivers, and 4) an updated literature review.

With regards to the previous alectinib submission to pCODR of experience with alectinib gathered in October 2016, LCC conducted an environmental scan of online forums to gather patient and caregiver experiences with alectinib. The opinions and perspectives of 22 patients and 19 caregivers, all with alectinib experience, were included in this submission; this included one-on-one interviews with three patients and one caregiver. Then in August 2017 to support the current alectinib submission, LCC conducted another environmental scan of online forums and questionnaires to gather patient and caregiver experiences with alectinib. The opinions and perspectives of 16 patients (two interviewed in the previous submission) and 10 caregivers, all with alectinib experience, were included in this submission. The opinions and perspectives of 36 patients and 29 caregivers, all with alectinib experience, have been included in this submission (total of 65).

From a patient's perspective, receiving a diagnosis of lung cancer can be devastating and specifically stage IV lung cancer patients experience the highest burden of symptoms. LCC highlighted that crizotinib and ceritinib were reported to be highly effective, tolerable (for some patients), and allow patients to have a very high quality of life. Because brain metastases are a huge concern for lung cancer patients, LCC asserted that having brain metastases is a huge additional burden for lung cancer patients as it significantly diminishes their prognosis. LCC highlighted that when one line of treatment either begins to show progression or fails to respond, patients switch to another ALK inhibitor. While treatments such as crizotinib or ceritinib seem to provide a good quality of life, and shrink or control their lung cancer; respondents reported needing another option when ALK inhibitors fails or cannot be tolerated. Respondents who have experience with alectinib reported that they went from feeling very sick before treatment or in between treatments to feeling much better within days of starting on alectinib. The most commonly reported side effects with using alectinib were: fatigue, photosensitivity, constipation, weight gain/loss and edema. While on alectinib, some respondents have reported passing the 12 month, 18 month and even 2 year mark. LCC noted that targeted, oral, take home therapies offer a real chance to lessen the burden of lung cancer.

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with NSCLC

LCC reported that about 3–5% of NSCLC patients have the ALK positive mutation. Compared to the general NSCLC population, ALK+ patients tend to be younger and never smoked. Of those interviewed, six were under 50 years and there were two in their 20's.

LCC indicated that stage IV lung cancer patients experience the highest burden of symptoms. Lung cancer symptoms may include: fatigue, loss of appetite, shortness of breath, cough, pain, and blood in sputum. It was noted that loss of appetite, cough, pain, and shortness of breath were found to be significant quality of life predictors. In a survey of Canadian patients with advanced lung cancer, LCC reported that two-thirds of patients feel their symptoms interfere with daily activities; anxiety or worry is common, and stated as "frequent" or "constant". In one study, it was found that the rates of depression in advanced lung cancer patients varied from 16-50%. In one Canadian study, LCC noted that financial hardship was experienced by 41% of respondents and 69% of respondents believed their illness imposed a significant hardship on those close to them.

LCC submits that targeted, oral, take home therapies offer a real chance to lessen the burden of lung cancer. As such, the addition of treatment options such as alectinib may offer an opportunity to increase the quality of life, reduce fear, side effects and time spent away from more enjoyable aspects of life than combatting a disease.

3.1.2 Patients' Experiences with Current Therapy for NSCLC

Chemotherapy patients report that they frequently need to take time off of work for their treatments. These patients are not allowed to drive themselves during treatment, and therefore, it is a burden on caregivers who must take time off work themselves. There is also a trickle-down effect, as younger patients with families could have child care, family time and general quality of life affected by their cancer.

LCC noted that currently the only publically funded treatment for ALK positive NSCLC is crizotinib, ceritinib has been approved post-crizotinib failure but has not yet been publically funded. Patient testimonies to LCC's pCODR submission for first-line crizotinib highlighted that this treatment extends life and allows patients to have a very high quality of life, which is not common with patients with lung cancer. In LCC's pCODR submission for ceritinib, ceritinib was also reported to be highly effective and tolerable.

LCC highlighted that some patients found current therapies to be tolerable and some found them to be intolerable. Many patients interviewed found both crizotinib and ceritinib to be intolerable due to the side effects. One caregiver stated "*My friend moved to Zykadia but had horrible side effects. She went from Xalkori to alectinib due to brain metastases. She tolerated it (alectinib) much better.*" One patient replied that crizotinib gave them bad headaches that would not go away. According to LCC, when intolerance is an issues, another treatment choice needs to be available.

Progression on crizotinib and ceritinib were a concern, especially for patients with brain metastases. Many of those interviewed mentioned that their treatment was switched to alectinib because brain metastases (and to a lesser degree, bone metastases and liver enzymes) were found. According to LCC, patients experience a great deal of fear when told their disease has spread to their brain.

LCC noted that additional treatment options for patients with ALK+ NSCLC is not a luxury but is a necessity. One patient stated "*Options change from wondering, to planning to meet my grandchildren. It's a bridge, a lifeline. They provide time to go from bridge to bridge.*" Patients are able to live longer and live well by switching to another ALK inhibitor upon progression. LCC noted that seven of the patients interviewed were on their third ALK inhibitor.

3.1.3 Impact of NSCLC and Current Therapy on Caregivers

LCC noted that the caregivers of patients living with lung cancer experience many of the same negative impacts on their lives as the patients themselves. The following themes and quotes are highlighted below:

1) Take home medication relieves the burden on caregivers
Caregivers and patients do not want to spend their time in hospital to receive treatment. The ability to access take home oral pills is not only convenient and easy, it also relieves the entire system from a heavier burden. There are less patients in beds in hospital, less families disrupted by travel to clinic and caregivers are able to take less time off work.

2) Young families can plan weddings, graduations and milestones
One respondent highlighted that options are vital and stated that "*They allow you as a family to stay hopeful and (experience) one or two more birthdays. It breaks my heart to think of anyone who can't access alectinib.*" Another caregiver reported "*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!*" One caregiver mentioned that his wife is doing so well that they recently decided on her wedding dress for their wedding in the spring of 2018 in the Dominican Republic, "*We are looking down the line for the 3rd, 4th and 5th lines (of treatment). There is lots of hope*."

Overall, LCC noted that this is not the type of long-term planning that is typical of a lung cancer patient with limited options.

3) Return to new normal – work and other life moments
One caregiver reported "*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 would have had to do traditional methods of whole brain radiation and standard IV chemotherapies that are very difficult on the patient/caregiver. He 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!*"

According to the 2015 Faces of Lung Cancer Report, 59% of caregivers reduced the number of hours they worked and a further 8% quit their jobs. There was a negative impact on household financial situation reported by 50% of caregivers. All three caregivers interviewed in this current submission indicated that they were able to continue work or return to work because their loved ones were doing so well on alectinib.

4) Caregivers really feel time and life is possible
LCC noted that alectinib is allowing patients to live longer and spend more time with loved ones, at home, travelling, working, and enjoying day-to-day activities. They noted that when treatment stops, so does the likelihood of extending life. The ability to move from one ALK inhibitor to another and then the next increases that time. One caregiver stated "*One can basically live a long time with ALK+ lung cancer as a chronic illness*." Caregivers are able to

take small life moments for granted again. A caregiver whose wife started on crizotinib then moved onto ceritinib and is now on alectinib, stated "*I wake up knowing the person on the pillow next to mine is ok.*"

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Alectinib

With regards to the previous alectinib submission to pCODR of experience with alectinib gathered in October 2016, LCC conducted an environmental scan of online forums to gather patient and caregiver experiences with alectinib. The opinions and perspectives of 22 patients and 19 caregivers, all with alectinib experience, were included in this submission. To further probe and understand their alectinib experience, LCC conducted one-on-one interviews with three patients and one caregiver. Then in August 2017 to support the current alectinib submission, LCC conducted another environmental scan of online forums and questionnaires to gather patient and caregiver experiences with alectinib. The opinions and perspectives of 16 patients (two interviewed in the previous submission) and 10 caregivers, all with alectinib experience, were included in this submission. In total the opinions and perspectives of 37 patients and 28 caregivers, all with alectinib experience, have been included in this submission.

1) Alectinib reduced the size of tumours

The most commonly reported result of alectinib was that it was effective and often worked very quickly. Patients were seeing reductions in their tumours of 50%, 75% and in some cases completely eliminated. Some of the respondents reported the following: "*No evidence of disease after the first two months on alectinib*!" "*I'm hoping to ride alectinib for a while*." "*Three and a half months on alectinib (and) my son's scans show just one remaining brain met and shrinkage in the lung tumour as well. Miraculous! Just can't put words to what I'm feeling.*"

LCC reported that durability is also a welcome hallmark of this treatment. It was noted that many respondents have reported passing the 12 month, 18 month and even 2 year mark. One respondent indicated "*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*."

2) Alectinib relieves the symptoms of lung cancer

Many respondents revealed that they went from feeling very sick before treatment or in between treatments to feeling much better within days of starting on alectinib. One respondent reported, "*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!*" One patient respondent, a grandmother of four, noted that her cancer gave her tremendous pain and bad cough. On alectinib she had "no more pain or cough. I'm a little tired but it has allowed me to do pretty well anything no more pain or cough." She was about to resume her favorite activity of baking "yummy buns" as her grandson calls them.

3) Alectinib allows patients to delay or avoid the permanent cognitive damage from Whole Brain Radiation by treating their brain metastases

According to LCC, one of the most terrifying prospects of lung cancer is the potential for it to spread to the brain. Patients are acutely aware of how much more dangerous the disease is when the brain is affected. One patient stated "*It feels like a death sentence.*"

Current treatment for brain metastases is whole brain radiation. This treatment carries significant side effects and has the potential for permanent cognitive damage. For one women, radiation treatments left her very sick, she experienced lots of fatigue, and it "*destroyed hair*". When this respondent progressed on chemotherapy, she was told that whole brain radiation would result in cognitive damage. She stated that "*I have two little kids, this was not an option. I was preparing for the end.*" She was then tested ALK+ and "*it was a game changer. Within three months there was nothing left in my body or my brain.*"

LCC highlighted that the clinical data with alectinib shows that it is effective in treating brain metastases. Five patients and caregivers interviewed stated that they were able to avoid radiation because they were on alectinib.

4) The side effects of alectinib were manageable and did not inhibit life

Of the 37 patients and 28 caregivers that provided input for this and the previous submission, 25 reported no (11), or low (24) side effects from treatment with alectinib. Only 16 reported moderate (7) or high/intolerable (9) side effects. The most commonly reported side effects were: fatigue, photosensitivity, constipation, weight gain, edema, and none. For three patients, dose reduction eliminated their side effects or brought the side effects to a manageable level. According to LCC, this meant alectinib was tolerable for 55 out of 64 patients (including those that were reported indirectly via their caregivers).

Photosensitivity was a side effect mentioned by 8 individuals, with the severity ranging from mild "I wear a hat every time I go outside" to severe "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." According to LCC, as alectinib gains widespread adoption, education may be needed from the manufacturer with respect to the range and potential severity of this particular side effect. One patient's doctor did not realize that photosensitivity was an issue with this treatment.

LCC noted that those who experienced moderate side effects expressed that it was "*worth it*", not only for extending their lives but by being another option to "*buy time*" until another treatment is found. LCC highlighted that when a treatment affords a higher quality of life, extends life, and provides hope for the future, it can be considered a "*wonderful drug*". One patient stated "*Because of alectinib, there is nothing that I cannot do. Isn't that the point?*"

5) The option to return to work or stay home to care for family is real

LCC considered that the ability to work or return to work following an illness is a strong barometer of how well that individual is performing on their treatment. LCC noted that for lung cancer, this is a new and unique topic that until now, was not possible for many patients. There is great psychological benefit for patients and caregivers to return to their daily routine and feel "*normal*". For individuals who choose not to return to work, it is important that this was their choice and not forced upon them due to symptoms and/or side effects. Six patients interviewed felt well enough to return to work. Three individuals interviewed had very young children at home and though they did not return to work, they chose to stay at home because they felt well enough to care for their little ones (in two cases these were infants). One patient, a 26 year old who was diagnosed when she was seven months pregnant stated that "*the normal me is back. Alectinib has allowed me to stay at home with my son and enjoy my maternity leave.*" Alectinib was key as she had been intolerant to her previous treatment and was so nauseous that getting out of bed was challenging.

According to LCC, many ALK+ patients are younger than the typical patient with lung cancer and have many years of productivity ahead of them. Treatment options that allow these

individuals to return to work and contribute to society or stay at home to raise a family, need to be recognized as valuable.

6) Patients were able to achieve ambitious career and life goals and have longer term plans

According to LLC, for perhaps the first time, patients are able to dream and achieve their dreams. All respondents spoke about life moments they were able to experience while on ALK inhibitors and alectinib. One patient reported driving to work, she had a bright promising career as a lawyer when she was diagnosed with lung cancer. ALK inhibitors have allowed her to return to work; while on alectinib, she made partner in her firm. Another patient brought a wedding dress last week and was planning for a wedding date nine months away. Others have hopes their grandchildren will remember them.

7) Lung cancer patients have no time to wait – "[as I wait] the suffering has been through the stratosphere." – S, patient

LCC noted that patients know there is treatment available to them and by making them wait, we are taking away their hope. Patients who are unable to wait for access to their treatment often express frustration and confusion. Patients are understandably anxious as they do not have much time as those with other forms of cancer and those with brain metastases have even less time. According to LCC, patients do their research and are aware of treatments that have been approved but remain unavailable to them or require waiting for the results of a test. LCC highlighted that it is even more frustrating when patients "*have to do the work*" and advocate for the treatment or travel to another city to receive it. Two patients interviewed had to endure "*abnormal delays*", however, upon receiving alectinib they expressed "*meant everything; I'm very grateful the trial was available, it breaks my heart that others can't get (alectinib).*"

Delays in approval can be the difference between life and death. The youngest patient started alectinib on his 22nd birthday, "*by the skin of his teeth*' as his mother responded. She stated "*Alectinib saved my son's life. He would have died without it at the age of 22.*" According to LCC, this young man enjoyed three full years on alectinib. LCC noted that approvals and public reimbursement for breakthrough treatments need to happen as quickly as possible in order to ensure treatment gets to the people who need them the most.

8) Options give people life – Life is now possible for lung cancer patients

LCC noted that in a life or death situation, such as is the case with lung cancer, options are wanted; however, this must be balanced by what is reasonable in terms of burden to the health system. Alectinib is already an approved medication that has met Health Canada's standards for safety and efficacy. According to LCC, having another choice, another chance at life cannot be restricted.

9) Access is imperative

LCC states that patients who have access to alectinib consider themselves "*lucky*", as lucky as you can be when you have cancer. These patients are the few who have targets for their disease and also have received what they consider to be a "*miracle drug*" as one patient noted. Some respondents reported the following "*I am able to live. I have a very good quality of life with few side effects and was able to avoid whole brain radiation. This drug is really amazing.*" and "*Alectinib helped me a lot, I like it. Other patients should get this as soon as possible. The government should accept this drug.*"

10) Hospital based therapy

According to LCC, another important factor to consider is that the addition of a targeted, take-home, oral therapy allows patients to delay hospital-based therapy, whether that is IV chemotherapy or immunotherapy. Hospital-based treatments are a burden on patients, their caregivers, loved ones, as well as the health system in general. LCC noted that more patients requiring IV infusions means a further drain of resources and staff.

11) The price of lung cancer drug costs should not be a barrier to access

When you have cancer, perspective can be everything. One patient reported that before her recommended treatment was approved by Health Canada, she had to "*do the work*" in order to get tested for ALK and even purchase the test and the treatment in the US. After consulting and test fees, she had paid approximately $10,000 CAD out-of-pocket. Even after she was able to get a script, the cost was approximately $18,000/month CAD. In total, she has paid more than $36,000 CAD for alectinib. "*I'm not sure what will happen to those who can't afford it or have no insurance. I'm lucky.*" Access to ground-breaking life extending therapies should not be accessible only to those individuals who are lucky enough to be able to afford it or have the correct type of insurance. Lung cancer does not discriminate. Neither should funding access.

One mother of three children who were 6, 10, and 12 at the time of her diagnosis asked "*How do you put a dollar value on life or death?*" She has done well on alectinib and says "*I've gotten to experience the key years and be present with my kids with a good quality of life and a lot of energy. It (alectinib) is a really good gift.*" Her family most recently enjoyed a trip to Nova Scotia due to how well she felt on alectinib.

LCC recognized that the high price of new cancer drugs places a burden on any publicly funded healthcare system. LCC calls upon the pharmaceutical industry as a whole to be cognizant of this burden and the pharmaceutical industry and provincial healthcare systems to explore innovative pricing models to reduce this burden.

3.3 Additional Information

Lung Cancer Canada indicated that crizotinib, ceritinib, and alectinib have been approved by Health Canada for ALK+ NSCLC. Targeted therapies have made hope real in ways that could not have been predicted. LCC noted that no one could have predicted that three patients who were interviewed three years ago for previous submissions would still be alive and able to participate in the current submission. Furthermore, no one could have predicted that seven of the patients interviewed are now using alectinib as a third ALK inhibitor.

LCC noted it is imperative that the pCODR recommendation does not restrict funding to either alectinib or ceritinib, that another ALK inhibitor is needed as an option; this is important as they are available and approved by Health Canada. Although trials have not specifically been done on a third-line ALK inhibitor, LCC acknowledged given the 3-5% prevalence rate and 17% 5-year survival rate, no one could have predicted that these treatments would have such life-extending results.

LCC recognizes that funding and overall burden on the public health system is a concern. LCC submits that all stakeholders including the manufacturer must work together to find solutions. As one caregiver states, "*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.*" Therefore, cost is an issue that must be globally addressed.

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. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from the nine of the nine provinces (Ministries of Health and/or cancer agencies) and the federal drug plan participating in pCODR. PAG identified the following as factors that could be impact implementation of alectinib in the treatment of non-small cell lung cancer (NSCLC):

Clinical factors:
- Indication creep into first-line treatment, particularly for patients who already have CNS metastasis upon diagnosis
- Clarity on "treatment until loss of clinical benefit"

Economic factors:
- Unknown treatment duration
- Additional costs to manage and treat adverse events

Please see below for more details.

4.1 Factors Related to Comparators

Currently, the standard second-line therapy for patients with ALK-positive NSCLC who have failed crizotinib would be chemotherapy (docetaxel, platinum doublet or pemetrexed) or immunotherapy (nivolumab or pembrolizumab). PAG noted that the comparators in the ALUR trial are single agent pemetrexed and single agent docetaxel. At the time of the PAG input, ceritinib is not yet funded. However, if and when ceritinib is funded, PAG is seeking information on the benefits and safety of alectinib compared to ceritinib, especially in the subgroup of patients with CNS metastasis.

4.2 Factors Related to Patient Population

Although NSCLC is a common cancer, alectinib would only be indicated for patients with ALK positive NSCLC and who have progressed on or are intolerant to crizotinib, which would be a small number of patients. PAG noted that an oral ALK inhibitor with CNS activity would fill a gap in therapy for patients who have CNS metastasis and failed crizotinib therapy.

PAG identified there may be indication creep to first-line treatment given the recent publication of the ALEX trial comparing alectinib to crizotinib in first-line. PAG also noted that if intolerance to crizotinib is not defined, there would be a lower threshold of tolerance to crizotinib and patients may be deemed intolerant after a one dose. If alectinib is demonstrating better benefits than crizotinib, alectinib would essentially replace crizotinib as first-line treatment. PAG is seeking information on the best sequencing of oral ALK targeted therapies.

PAG is seeking guidance on sequencing of all oral targeted therapies, intravenous chemotherapies and immunotherapies for ALK positive NSCLC.

4.3 Factors Related to Dosing

Alectinib is available as one capsule strength and dose adjustment is accomplished by adjusting the number of capsules to take. This is an enabler to implementation. However, there are concerns of pill burden given that the dose is four capsules twice daily (eight capsules daily).

PAG is seeking clarity on treatment "until loss of clinical benefit", treatment duration and treatment discontinuation.

4.4 Factors Related to Implementation Costs

As alectinib is administered orally, PAG noted that chemotherapy units and chair time would not be required. This is an enabler to implementation.

4.5 Factors Related to Health System

PAG noted that alectinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration as an enabler to implementation.

4.6 Factors Related to Manufacturer

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were provided on alectinib for locally advanced or metastatic non-small cell lung cancer (NSCLC). Input was provided as a joint submission from one thoracic surgeon on behalf of the Lung Drug Advisory Committee at Cancer Care Ontario and seven oncologists from the Lung Cancer Canada Medical Advisory Committee. Their input is summarized below.

The clinicians providing input noted that anaplastic lymphoma kinase positive (ALK+) NSCLC represents approximately 1-5% of all NSCLC and that it will not be a large patient population. According to the input received, compared to crizotinib and ceritinib, alectinib provides improvement in progression-free survival, overall response rate, duration of response, and toxicity profile; this includes patients with brain metastases. Clinician input suggested that alectinib may be used for ALK+ treatment naïve NSCLC, patients who have progressed on crizotinib, or those who failed both crizotinib and ceritinib; where multiple second generation ALK inhibitors would provide the maximum number of treatment lines for patients who acquire treatment resistance. Patients would likely use crizotinib in the first line, then either ceritinib or alectinib as second-line, and then the other ALK inhibitor that was not utilized as third-line. ALK immunohistochemistry (IHC) is routinely completed, however, it was noted that ideally a re-biopsy should be conducted after each failure of drug to test for mutations associated with acquired ALK inhibitor resistance. Overall, clinician input noted that the sequential use of multiple ALK inhibitors improves outcomes and should be available for this patient population.

Please see below for details from the clinician inputs.

5.1 Current Treatment(s) for this Type of Cancer

Crizotinib and ceritinib were identified as current treatments for locally advanced or metastatic NSCLC. Clinician input noted that crizotinib has been established as the standard first-line treatment for patients with ALK+ advanced or metastatic NSCLC based on PROFILE 1014, which compared crizotinib with pemetrexed plus platinum chemotherapy.

5.2 Eligible Patient Population

The clinicians providing input indicated that ALK+ NSCLC represents approximately 1-5% of all NSCLC and that this will not be a large patient population.

5.3 Identify Key Benefits and Harms with Alectinib

Referring to the results of the ALEX randomized trial (comparing 1st line crizotinib to 1st line alectinib), clinician input reported that alectinib compared to crizotinib demonstrated a clinically and statistically significant improvement in progression-free survival, overall response rate, time to development of brain metastases, and median duration of response. Clinicians providing input noted that overall survival data were still immature and median overall survival had not been reached in either treatment group. For patients with a history of brain metastases, alectinib was superior to crizotinib with respect to response rate and median duration of response for both measurable and non-measurable brain lesions. While the toxicity profile of alectinib and crizotinib varied, the incidence of grade 3-5 toxicity were similar. It is important to note that results of the ALEX trial are beyond the scope of the reimbursement request for this review.

Compared with ceritinib, clinician input noted that alectinib following crizotinib will be able to better prevent or treat brain metastases. Alectinib was found to be a bit more tolerable as ceritinib appears to cause more frequent transaminitis, QT prolongation, hyperglycaemia, increased

amylase/lipase, and diarrhea. However, alectinib was associated with more frequent increases in creatinine.

5.4 Advantages of Alectinib Over Current Treatments

Clinician input indicated that patients with ALK+ NSCLC commonly present with brain metastases and there are long-term CNS toxicity from whole brain radiation that has significant negative impact on quality of life and function. They noted that alectinib reduces the incidence of brain metastases and was associated with improved response which could potentially improve quality of life and function. Of note, clinician input suggested that brain radiation could be delayed until CNS progression on alectinib.

Clinician input indicated that alectinib provides clinically important benefit for all patients with ALK+ treatment naïve NSCLC, including those with brain metastases who do not derive as much benefit from crizotinib. Based on clinical trials, clinician input also indicated that alectinib should be available for patients with ALK+ NSCLC who have progressed on crizotinib as well as those who have failed both crizotinib and ceritinib. Clinician input noted that the mechanism of acquired ALK resistance differs among the second generation ALK inhibitors (crizotinib, ceritinib, and alectinib) and that both ceritinib and alectinib are needed to provide the maximum number of treatment lines to patients who acquire resistance after treatment.

5.5 Sequencing and Priority of Treatments with Alectinib

Clinician input indicated that currently crizotinib is reimbursed in the first-line and ceritinib has a pCODR recommendation conditional on improving the cost-effectiveness for second-line. Based on the ALEX trial, alectinib should be adopted as first-line treatment for newly diagnosed ALK+ advanced or metastatic NSCLC. Other clinical trials have suggested alectinib could be effective in second and subsequent lines of therapies; clinicians providing input indicated that alectinib should be available for those who have failed prior crizotinib and possibly ceritinib. Overall, patients would likely try crizotinib first, then either ceritinib or alectinib as second-line, and then the other second generation ALK inhibitor that was not utilized as third-line.

Clinicians providing input noted that options based on how patients tolerate their first ALK inhibitor are needed. Physicians may choose alectinib for patients with brain metastases, abnormal liver function tests or GI intolerance issues with crizotinib.

5.6 Companion Diagnostic Testing

ALK IHC is a routine companion diagnostic test for all patients with advanced or metastatic, non-squamous NSCLC. Clinician input noted that although the ALEX trial employed the Ventana ALK IHC, the C-ALK study demonstrated excellent concordance of ALK IHC by 5A4, ALK1 and D5F3. Ideally, a re-biopsy after each failure of drug to test for mutations associated with acquired ALK inhibitor resistance should be conducted; however, such tests are not funded or available yet.

5.7 Additional Information

Clinician input also noted that alectinib provides better benefit for patients with CNS disease while ceritinib may provide better benefit for patients with non-CNS disease. However, both of these ALK inhibitors have better disease control than chemotherapy and thus should be made available for patients who have progressed following a prior ALK inhibitor. Clinician input indicated that there is evidence that patients who receive multiple ALK inhibitors compared with chemotherapy and no ALK inhibitors have improved progression-free survival. However, an observed overall survival benefit from trials is immature and may have issues due to cross-over.

They also noted that with these treatments, this is the first time the population of lung cancer patients (ALK and EGFR) can have sequential, tolerable oral therapy without the need of utilizing chemotherapy.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of alectinib (alecensaro) as monotherapy for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- Critical appraisal of an indirect treatment comparison (ITC) and network meta-analysis (NMA) comparing alectinib to ceritinib in patients with ALK-positive metastatic NSCLC who have progressed on crizotinib.
- Critical appraisal of the Manufacturer's submitted ITC of alectinib phase 2 data versus ceritinib real world data (RWD).

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. Selection Criteria.

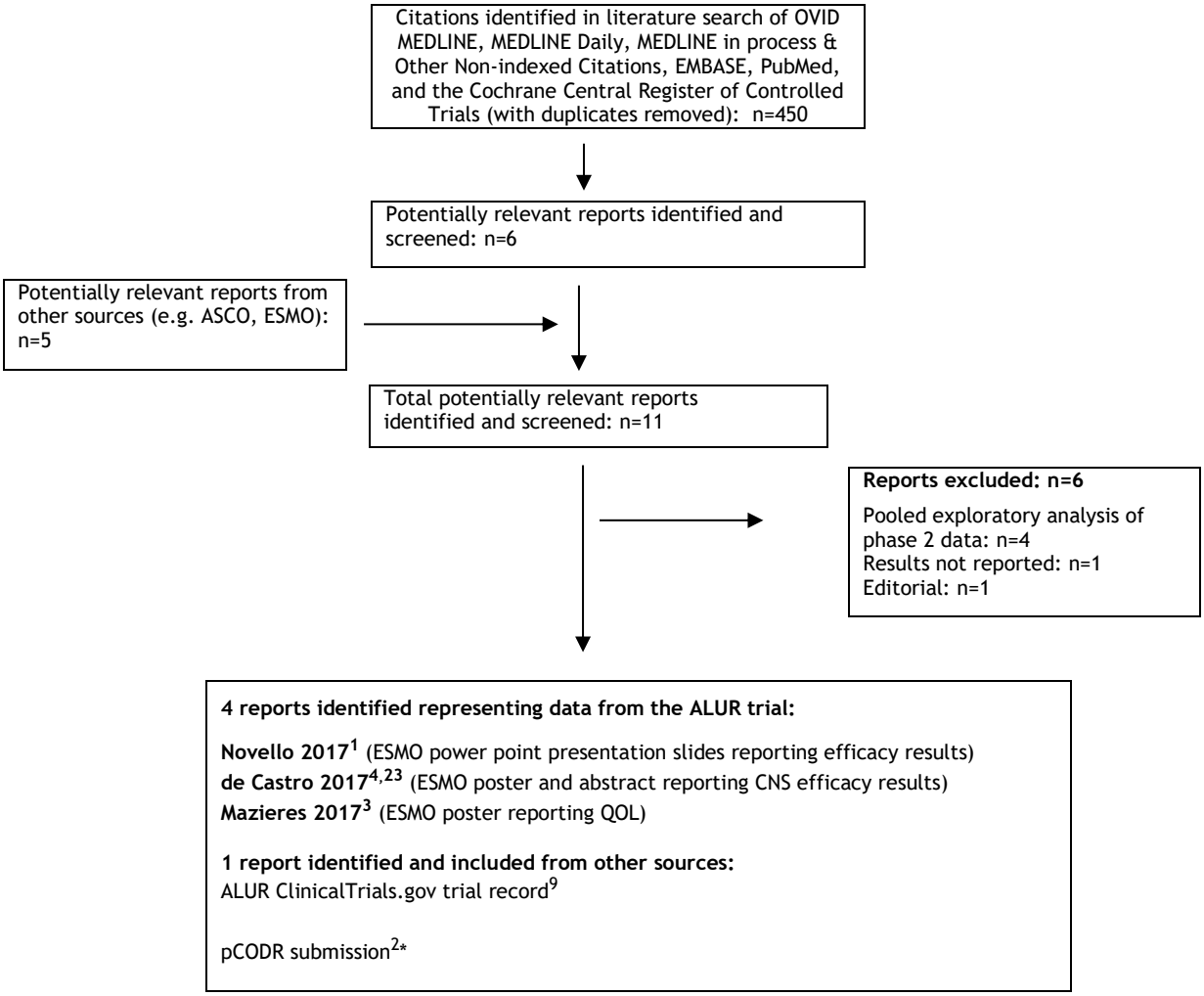
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs	Previously treated patients with ALK+, advanced or metastatic NSCLC resistant or intolerant to crizotinib Patient subgroups of interest: • With or without CNS metastases on crizotinib • Received crizotinib first-line and subsequently treated with chemotherapy or immunotherapy • ECOG ≥2	Alectinib monotherapy	• Platinum chemotherapy and pemetrexed • Ceritinib • BSC	Primary: • PFS • OS • QOL • Safety Secondary: • ORR • DOR • CNS ORR • Disease control • Time-to-CNS progression
Abbreviations: ALK+ – anaplastic lymphoma kinase positive; **BSC** – best supportive care; **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 11 potentially relevant reports identified, five reports were included in the pCODR systematic review[1,3,4,9,23] and six reports were excluded.[24-29] Studies were excluded because they reported on phase 2 data,[24-27] did not report efficacy or safety results,[28] or were editorial in nature.[29]

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



**Note: Additional data related to ALUR were also obtained through requests to the Submitter by pCODR.*

6.3.2 Summary of Included Studies

One randomized phase 3 trial, ALUR,[1] was identified that met the selection criteria of this review. ALUR evaluated the efficacy and safety of alectinib compared to chemotherapy in patients with ALK-positive, locally advanced or metastatic NSCLC, who progressed on or were intolerant to crizotinib. Key characteristics and quality features of the ALUR trial are summarized in Tables 4 and 5, respectively.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of trial characteristics of the included ALUR trial.[1,2,9]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
ALUR (NCT0260432)[1] Phase 3, open-label, randomized trial, 2:1 ratio N=randomized 107; n=104 treated 54 centres in 15 countries (not including Canada) Patient Enrolment Dates: November 2015 to January 2017[2] Data cut-off date: January 26, 2017 (primary outcome) Final Analysis Date: April 3, 2019[9] Funded by Hoffman-La Roche Ltd.	<u>Key Inclusion Criteria:</u> • ≥18 years • Histologically or cytologically confirmed advanced (stage IIIB) or metastatic (stage IV) NSCLC and ALK-positive by validated FISH or IHC test • Measurable disease (RECIST version 1.1) at baseline • One prior line of platinum-based chemotherapy • Crizotinib failure • Prior CNS or leptomeningeal metastases allowed if asymptomatic[c] • ECOG PS 0-2 • Adequate renal and hematologic function • Life expectancy of at least 12 weeks <u>Key Exclusion Criteria:[2]</u> • Previous treatment with any ALK inhibitor other than crizotinib • Previous malignancy within previous 3 years[d] • Any GI disorder affecting absorption of oral medications	Alectinib 600mg orally twice daily *versus* Pemetrexed 500mg/m^2 iv every three weeks, or Docetaxel 75 mg/m^2 iv every three weeks Until PD,[a] unacceptable toxicity, withdrawal of consent or death	<u>Primary:</u> • PFS by INV <u>Secondary:[9]</u> • CNS ORR by IRC[b] • PFS by IRC • ORR (systemic) • DCR, DOR • CNS DCR, CNS DOR • Time-to-CNS progression • OS <u>Tertiary:</u> • Safety • QOL (EORTC QLQ-C30 and LC13, EuroQOL-5D-5L, TTD)
Abbreviations: ALK – anaplastic lymphoma kinase; **CNS** - central nervous system; **DCR** – disease control rate; **DOR** – duration of response; **ECOG** – Eastern Cooperative Oncology Group; **EuroQOL-5D-5L** – European Quality of Life 5 Dimension 5 Level Questionnaire; **EORTC** – European Organization for Research and Treatment of Cancer; **FISH** – fluorescence in situ hybridization; **GI** – gastrointestinal; **IHC** – immunohistochemistry; **INV** - investigator assessment; **IRC** – independent review committee; **iv** – intravenously; **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] – Crossover from chemotherapy to alectinib was permitted for patients with PD.

[b] - In patients with measurable CNS disease at baseline as assessed by IRC.

[c] –Asymptomatic CNS lesions may have been treated by investigator as per local practice guidelines. In this case, prior treatment (radiotherapy or surgery) was to be completed 14 days prior to study enrollment and patients had to be clinically stable. Patients with symptomatic CNS metastases for whom radiotherapy was not an option were permitted on study.

[d] – 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.

Table 5: Select quality characteristics of the included ALUR trial.[1,2]

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
ALUR[1]	Alectinib vs. Pemetrexed or docetaxel	PFS by INV	*Original:* 120 patients required to provide 80% power to detect an improvement in median PFS from 3 to 6 months (HR=0.50; 74 events) using a two-sided significance level of α=0.05 *Revised:*[a] 90 patients required to provide 80% power to detect an improvement in median PFS from 3 to 7 months (HR=0.43; 50 events) using a two-sided significance level of α=0.05	107	Central via interactive voice or web-based response system;[2] and blocked[2] stratified by ECOG PS and CNS metastases at baseline (yes/no), and history of radiotherapy to the brain for CNS metastases at baseline (yes/no)	Yes	Open label; outcome assessment by IRC; data analysis was blinded[2]	Yes	No	No	Yes

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

Notes:

[a] – The required sample size of the trial was originally based on clinical data showing a median PFS of 6 months for the alectinib treatment group. After two phase 2 trials of alectinib in the crizotinib failure setting (NP28761 and NP28673) showed a consistent median PFS outcome of 8.2 to 8.9 months, the median PFS assumption used for the required sample size was changed to 7 months, as this was considered a more realistic but conservative assumption. If superiority of the primary endpoint was achieved, subsequent hierarchical testing of the key secondary endpoint of the trial (i.e., CNS ORR with measurable CNS metastases at baseline) was performed (70% power at one-sided alpha).

a) Trials

ALUR[1] is an ongoing, open-label, randomized phase 3 trial conducted in 54 sites in 15 countries across Europe and East Asia. Participating sites included both academic and community centres.[2] Patient enrolment took place between November 2015 and January 2017.[2] The trial was funded by Hoffman La Roche Ltd.

To be eligible for the trial, patients were required to have met the following criteria (refer to Table 4 for a complete list):

iv. advanced (stage IIIB not amenable for multimodality treatment) or metastatic (stage IV) ALK-positive NSCLC, determined by a validated IHC or FISH test,
v. two previous systemic lines of therapy consisting of one platinum-based chemotherapy regimen and one line of crizotinib, and
vi. an ECOG performance status of 0-2.

Patients with CNS or leptomeningeal metastases were permitted on the trial if they were asymptomatic or symptomatic and unable to receive radiation. Asymptomatic metastases could be treated at the discretion of the local treating investigator but radiation treatment was to be completed at least 14 days prior to trial enrollment. The key exclusion criteria are listed in Table 4.

Eligible patients were randomized 2:1 to receive either alectinib or chemotherapy consisting of pemetrexed or docetaxel. Blocked randomization was performed centrally and was stratified by ECOG performance status (0-1 versus 2) and CNS metastases (yes/no). Patients with CNS metastases were further stratified based on previous radiation therapy (yes/no). A recruitment cap of 50% was employed to ensure balance of CNS metastases in the treatment groups.[2]

The primary efficacy outcome of the trial was PFS by investigator assessment (PFS by INV) in the intent-to-treat (ITT) population. Key secondary outcomes included the following:

- CNS objective response rate (CNS ORR) in patients with measurable CNS metastases at baseline, as assessed by independent review committee (IRC)
- PFS by IRC, and PFS in patients with CNS metastases at baseline
- Systemic objective response rate (ORR), duration of response (DOR), and disease control rate (DCR)
- Time-to-CNS progression by baseline CNS disease status
- CNS DOR and CNS DCR in patients with CNS metastases at baseline
- Overall survival (OS)
- Health-related quality of life (QOL) as measured by the EORTC Quality of Life Questionnaire (QLQ)-C30 and the QLQ-Lung Cancer (LC)13
- Safety

During the trial, the protocol was amended to reduce the sample size from a required 120 patients to 90 patients based on phase 2 data (NP28761 and NP28673)[6,7] demonstrating a median PFS with alectinib ranging between 8.2 and 8.9 months. Therefore, the expected median PFS of alectinib used for sample size estimation in the ALUR trial was increased from 6 to 7 months. This change meant that fewer patients/events were required during the 12-month accrual period to achieve the same objective of superiority of alectinib over chemotherapy. The statistical assumptions of the trial are detailed in Table 5.

Populations

There were 107 patients randomized in ALUR, with 72 allocated to alectinib and 35 allocated to chemotherapy. The baseline characteristics of patients are summarized in Table 6. The median age of patients was between 56 and 59 years, with a majority of patients under the age of 65 (79%). The majority of patients were male (54%), Caucasian (84%), previous smokers (49%) or had never smoked (48%), had metastatic disease (96%), and an ECOG status of 0 or 1 (90%). Most patients had CNS metastases at baseline (68%) and among these patients, a majority had undergone previous radiation to treat their CNS disease (59%). The distributions of baseline characteristics appeared balanced between treatment groups for the majority of characteristics, however, for a few characteristics, including age, ECOG performance status and presence of CNS metastases, the distributions appeared to favour the alectinib group (i.e., more patients who were younger, an ECOG status of 0/1; and fewer patients with CNS metastases). The Submitter attributed the the slight imbalances to the 2:1 randomization scheme and mis-stratification, where 1 or 2 patients in the chemotherapy group made the percentage differences between the two treatment groups appear higher. After adjusting for the imbalances in ECOG status and CNS metastases in a sensitivity analysis of the primary outcome, the primary results appeared unchanged.[2]

Information on the type and number of previous anti-cancer therapies received by patients was not provided. The median time on treatment with crizotinib was approximately one year for patients in both treatment groups, with the last dose received within approximately two and four weeks in the alectinib and chemotherapy groups, respectively.[2]

Interventions

After randomization patients were treated with alectinib at a dose of 600mg orally twice daily, or chemotherapy, either pemetrexed at a dose of 500 mg/m^2 or docetaxel at a dose of 75/m^2, intravenously every three weeks. Both treatment groups received study drug until disease progression, unacceptable toxicity, withdrawal of consent or death. Upon radiological evidence of progression, patients in the alectinib group could continue to receive alectinib if still clinically benefitting from the drug; and patients in the chemotherapy group were permitted to cross over to alectinib. For patients who opted not to continue on or crossover to alectinib, subsequent treatment was at the discretion of the treating investigator according to local practice. The trial protocol[2] allowed for dose reductions of alectinib by no more than two dose levels (i.e., 150mg per intake) for adverse events (AEs), with specific guidelines for dose reduction for specific AEs. Alectinib was permanently discontinued if patients were unable to tolerate the 300mg twice daily dose reduction, or if dose interruption exceeded 21 days. The median time on treatment was 20 weeks for patients in the alectinib group and six weeks in the chemotherapy group. Concomitant medications were used by 76% (n=53) of patients receiving alectinib and 97% (n=33) of patients receiving chemotherapy; the most common medications were steroids (34% vs. 65%, respectively), analgesics (34% vs. 47%), proton pump inhibitors (31% vs. 38%), opioid analgesics (21% vs. 24%), and anticoagulants (17% vs. 29%).[2]

Patient Disposition

The disposition of patients in the ALUR trial is summarized in Table 7. Of the 136 patients screened, 107 patients were randomized and currently comprise the ITT

patient population. At the time of the primary analysis (January 26, 2017) screening and enrollment of patients were continuing as the required number of patients (n=120) had not been reached.[i] Therefore, future data analyses will include a greater number of patients in the ITT population.

The primary data analysis occurred after a median follow-up time of 6.5 months and 5.8 months in the alectinib and chemotherapy groups, respectively.[1] At this time, 36% of patients in the alectinib group and 83% of patients in the chemotherapy group had discontinued treatment, with progressive disease (PD) as the primary cause of discontinuation in both treatment groups (28% versus 66%, respectively).[2] In the alectinib group, 61% of patients were continuing assigned treatment and five patients (7%) received alectinib post-progression. In the chemotherapy group, 14% of patients were continuing assigned treatment and 24 patients (69%) had crossed over to receive alectinib post-progression.[2] Of the patients receiving alectinib post-progression, one patient (n=1/5) in the alectinib group discontinued treatment due to loss of clinical benefit; in the chemotherapy group (n=6/24), four patients discontinued treatment due to PD (n=4), two patients due to AEs (n=1) and death (n=1).[2]

Information on the protocol deviations that occurred during the trial was not provided in the pCODR submission. A request was made to the Submitter for this information and they indicated that the incidence of major protocol deviations was higher for the alectinib group at 26% compared to 20% in the chemotherapy group.[2] The most frequent deviations in both treatment groups were related to procedures (21% in alectinib group vs. 11% in chemotherapy group). Considering the type and frequency of these deviations, they likely did not impact the efficacy results of the trial.[2]

Limitations/Sources of Bias

Refer to Table 5 for a summary of key quality-related features of the ALUR trial.

The quality of the ALUR trial was challenging to appraise in the absence of a peer-reviewed trial publication. The appraisal that follows was based on preliminary data (abstracts and posters) presented at international symposia, as well as data provided by the Submitter. Additional limitations may come to light upon longer follow-up (median follow-up was 6.5 months and 5.8 months in the alectinib and chemotherapy groups, respectively) and full publication of the trial.

Based on available data, the trial was well conducted owing to specific design features, including the use of appropriate randomization procedures, clear explanation of sample size considerations, which accounted for an important patient subgroup (i.e., patients with CNS metastases at baseline), transparent disposition of patients through the trial, the use of an IRC for assessment of the primary outcome and blinded data analysts, 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 (such as, patient selection and performance bias), which can affect internal validity. The investigators, trial personnel, and patients were aware of the study drug administered, which can potentially bias outcome assessment in

[i] At the time of data cut-off (January 26, 2017) the protocol had not yet been amended (protocol version 4.0) to reduce the sample size from 120 to 90 patients; therefore, there were 4 subjects that met the eligibility criteria who had not yet been randomized. These patients will be included in a future data cut-off.[2]

favour of alectinib if assessors (investigators or patients) believe the study drug is likely to provide benefit. A double-blind design was not possible due to differences in the administration of interventions (i.e., oral versus intravenous) and chemotherapy assignments (i.e., pemetrexed versus docetaxel). An attempt was made in the trial to mitigate bias by using an IRC to assess outcomes using standardized criteria and blinding data analysts to treatment assignment. However, for the assessment of 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.

- While the subgroup analyses conducted in the trial were pre-specified, the trial was only powered to detect differences between treatment groups for the primary outcome. Heirarchical testing was used to control the risk of type 1 error for the subgroup analysis of patients with CNS metastases at baseline, however, for the remainder of secondary and sub-group analyses, of which there were many, adjustments for multiplicity (that is, adjustment of the statistical confidence level to account for the number of comparisons being tested) were not made. Therefore, given the likelihood of obtaining a positive result increases with increasing number of comparisons, the subgroup analysis results should be interpreted with caution.
- The assessment of health-related QOL had a number of limitations that question the validity of the QOL findings, including:
    - Patient compliance in completing questionnaire assessments was poor in the chemotherapy treatment group; this, combined with the much longer treatment exposure of patients in the alectinib group compared to chemotherapy resulting in shorter follow-up of patients treated with chemotherapy, precludes an accurate assessment and comparison of QOL between the treatment groups.
    - Both the published and unpublished data made available to pCODR was limited by incomplete and selective reporting.

      Given these factors, it is likely that the health-related QOL results provided to pCODR 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 primary efficacy analysis results (dated January 26, 2017) were based on the 107 patients who comprised the ITT population. Some secondary efficacy outcomes were based on the subgroup of patients who had measurable/non-measurable CNS metastases at baseline (n=76, C-ITT); and the subgroup of patients who had measurable CNS metastases at baseline (n=40, mC-ITT). The efficacy analyses conducted in these subgroups were prospectively planned. It was reported that the distribution of baseline characteristics within the C-ITT patient subgroup were similar to the ITT population.[4] Additional subgroup analyses were also prospectively performed to assess the treatment effect in selected patient and demographic-defined groups (e.g., age, sex, race, performance status, and prior radiotherapy).

The primary analysis was planned to be conducted when 50 patients had experienced a PFS by INV event, with no planned interim analysis of the data. At the primary analysis, 52 events occurred.[1] PFS for each treatment group was estimated using the methods of Kaplan-Meier and tested with a stratified log-rank

test; a PFS hazard ratio (HR) and 95% confidence interval (CI) was obtained using a stratified Cox regression model. If superiority of alectinib was demonstrated for the primary outcome, hierarchical testing was performed for the analysis of the key secondary outcome (CNS ORR in the mC-ITT population by IRC). The analyses of all secondary outcomes were not adjusted for multiple comparisons testing. The final efficacy analyses are planned for when all patients in the trial have been followed for at least 24 months or when 50% of patients have died, whichever occurs first.[2]

Patient–reported health-related QOL was considered a secondary endpoint of the trial, and was assessed using the EORTC Quality of Life Questionnaire (QLQ)-C30 and the QLQ-Lung Cancer Module (LC-13). Three items from the QLQ-Brain Cancer Module (BN20), considered exploratory analyses, were also included that provide a measure of morbidity related to CNS symptoms. Both instruments are validated and commonly used in oncology. The QOL data from the ALUR trial has only been published in abstract/poster form;[3] therefore, the Submitter provided additional QOL data for this report.

The QLQ-C30 measures overall QOL and different aspects of patient functioning. 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). The items from BN20 included questions related to headaches, coordination and balance, and communication. 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).[2] A mean change from baseline of 10% or greater is considered the minimal clinically important difference (MCID). For the various scales, mean changes from baseline were compared between treatment groups over the course of the first treatment period using a linear mixed model. Time-to-deterioration was also assessed for single symptoms and composite symptoms (i.e., cough, dyspnea, and chest pain), defined as the time from randomization to the earliest time with a ≥10–point increase from baseline for the symptom of interest (or any component of a composite symptom), and evaluated as a time-to-event outcome using Kaplan Meier methods.[2]

Table 6: Baseline patient characteristics in the ALUR trial.[1,2]

ALUR Trial	Treatment Groups (n randomized)	
Baseline Characteristics, n (%) unless otherwise specified	**Alectinib (n=72)**	**Chemotherapy[a] (n=35)**
Median age, years (range)	56 (21-82)	59 (37-80)
Age category (years), % 18-64 ≥65	 60 (83) 12 (17)	 25 (71) 10 (29)
Sex, n (%) Male Female	 41 (57) 31 (43)	 17 (49) 18 (51)
Race, n (%) White Asian Unknown Native Hawaiian or other Pacific Islander	 61 (85) 5 (7) 5 (7) 1 (1)	 28 (80) 7 (20) 0 0
Smoking status, n (%) Never Current Previous	 35 (49) 2 (3) 35 (49)	 16 (46) 2 (6) 17 (49)
ECOG PS, n (%) 0 1 2	 29 (40) 37 (51) 6 (8)	 11 (31) 19 (54) 5 (14)
Disease stage at baseline, n (%) Stage IIIB Stage IV	 3 (4)[2] 69 (96)[2]	 1 (3)[2]34 (97)[2]
Number of site/organs involved, n (%) 1 2 >2	 2 (3)[2] 8 (11)[2] 62 (86)[2]	 2 (6)[2] 4 (11)[2] 29 (83[2]
CNS metastases at baseline, n (%) No Yes CNS metastases treated	 25 (35) 47 (65) 28 (60)	 9 (26) 26 (74) 15 (58)
Previous crizotinib[2] Time on crizotinib, median (range) in days Time since last dose, median (range) in days Response on crizotinib, n (%) CR PR SD PD NE NA	 353 (22-1424) 16.5 (-15-422)[b] 1 (1) 27 (38) 20 (28) 21 (29) 2 (3) 1 (1)	 356 (59-1173) 27 (-1-329)[b] 1 (3) 10 (29) 12 (34) 12 0 0
History of radiotherapy and CNS metastases at baseline, n (%) No prior radiotherapy With prior radiotherapy	 21 (29) 26 (36)	 12 (34) 14 (40)
Abbreviations: CNS – central nervous system; **ECOG** – Eastern Cooperative Oncology Group; **NA** – not available; **NE** – not evaluable; **PS** – performance status.		
Notes: [a] – patients received either docetaxel (n=25) or pemetrexed (n=9). [b] – negative values likely attributable to missing data (i.e., 14 of 107 end dates were imputed with last day of the month because of missing data).		

Table 7: Patient disposition in the ALUR trial.[2]

ALUR Trial	Treatment Groups		
Primary Analysis Date: January 26, 2017	**Alectinib, n (%)**	**Chemotherapy[a], n (%)**	
Screened	136		
Randomized	107		
	72 (100)	35 (100)	
Treated	70 (97)[c]	34 (97)[c]	
Included in primary efficacy analysis	72 (100)	35 (100)	
Included in safety analysis[b]	70 (97)	34 (97)	
		Docetaxel	Pemetrexed
Discontinuing treatment	26 (36)	22 (63)	7 (20)
Progressive disease	20 (28)	16 (46)	7 (20)
Death	3 (4)	3 (9)	0
Withdrawal by subject	2 (3)	1 (3)	0
Other	1 (1)	1 (3)	0
Adverse event	0	1 (3)	0
Continuing treatment (at clinical cut-off)	44 (61)	5 (14)	
Continuing alectinib post-progression	5 (7)[d]	-	
Crossed over to receive alectinib post-progression	-	24 (69)[e]	
Other therapy post-progression	1 (1)	1 (3)[f]	
Gemcitabine	-	1 (3)	
Carboplatin	-	1 (3)	
Ceritinib	1 (1)	-	

Abbreviations: CNS – central nervous system; **ECOG** – Eastern Cooperative Oncology Group; **PS** – performance status.

Notes:
[a] – Patients received either docetaxel (n=25) or pemetrexed (n=9).
[b] – Patients who received at least one dose of study drug.
[c] – There were a total of three patients who did not receive any study treatment; two were due to withdrawal of consent (one patient in each treatment group), and one due to death (one patient in the alectinib treatment group).
[d] – Of the five patients in the alectinib treatment group continuing alectinib post-progression, one patient (20%) discontinued due to "other: loss of clinical benefit".
[e] – Of the 24 patients in the chemotherapy treatment group that crossed over to receive alectinib post-progression, six patients (25%) discontinued alectinib due to progression of disease (4 patients), death (1 patient), and adverse event (1 patient).
[f] – Patients reporting more than one therapy are only counted once.

Efficacy Outcomes

The median time on treatment for patients in the ALUR trial was 20 weeks for patients in the alectinib group and six weeks for patients in the chemotherapy group; median follow-up time at primary analysis was 6.5 months and 5.8 months, respectively.[1] The key efficacy results of the ALUR trial are summarized in Table 8; refer to the notes section of this table for definitions of the efficacy outcomes assessed in the trial.

Systemic Efficacy[1]

PFS by INV (primary outcome)

At primary analysis, a statistically significant improvement in PFS by INV, of approximately eight months, was demonstrated in the alectinib treatment group compared to chemotherapy; median PFS by INV was 9.6 months with alectinib and

1.4 months with chemotherapy (HR=0.15, 95% CI, 0.08-0.29; p<0.001). The Kaplan-Meier PFS curves showed a pronounced and persistent separation between the two treatment groups starting at approximately one month of follow-up. A similar treatment benefit, albeit of slightly lower magnitude, was observed for PFS by IRC (Table 8). The results of subgroup analyses were consistent with the primary analysis results across all patient subgroups examined (HRs ranged from 0.06-0.25), with the exception of patients of Asian race and those with an ECOG status of 2. Results were not estimable for patients aged ≥65 years. In these three subgroups the confidence limits surrounding the estimates obtained were very wide, resulting in unreliable estimates most likely due to low event rates and small sample sizes (n range, 6-22).

ORR, DOR, and DCR

The ORR by INV was higher in patients treated with alectinib (38%) compared to chemotherapy (3%), with ORRs in both treatment groups comprised of all partial responses. The ORR by IRC was similar to that obtained by investigator assessment (36% versus 11%, Table 8).

Duration of response was longer in patients treated with alectinib compared to chemotherapy (median DOR in months, 9.3 versus 2.7). These estimates are based on 27 partial responses and one partial response observed in the alectinib and chemotherapy groups, respectively. The DOR by IRC was similar for the alectinib treatment group and not estimable for the chemotherapy group (Table 8). Similarly, the DCR was higher with alectinib; the rates by INV were 81% versus 29%. Compared to the investigator assessment of DCR, the assessment by IRC showed a similar result for alectinib (76%) but higher rate for chemotherapy (49%).[2]

Overall Survival

Data on OS were deemed immature at the date of primary analysis, at which time, 69% of patients (n=24) in the chemotherapy group had crossed over to receive alectinib post-progression. Data on OS are expected after 24 months of follow-up or when 50% of patients in the trial have died.[2]

CNS Efficacy[1,4]

CNS efficacy outcomes were assessed in the subgroups of patients who had measurable (mC-ITT, n=40) and measurable/non-measurable (C-ITT, n=76) CNS metastases at baseline, as well as in all patients (ITT, n=107) for assessment of time-to-CNS progression (Table 8).

CNS ORR by IRC (key secondary outcome), CNS DOR, CNS DCR, and PFS

The CNS ORR among patients with measurable CNS metastases at baseline (mC-ITT) was 54% in the alectinib group versus 0% in the chemotherapy group (p<0.001), demonstrating a significant treatment benefit in the CNS with alectinib compared to chemotherapy. There were one complete and 12 partial CNS responses in patients treated with alectinib. Duration of response was not estimable in either patient subgroup due to no CNS response in the chemotherapy group. The CNS DCR by IRC also favoured alectinib (79% versus 31%). A similar result was observed in the subgroup of patients with measurable and non-measurable CNS metastases at baseline (C-ITT) but of lower magnitude (Table 8). In this subgroup, the median PFS by INV was longer in patients treated with alectinib (median 9.7 months versus 1.4 months; HR=0.12, 95% CI, 0.05-0.27, p<0.001);[4] a result consistent with the primary outcome analysis results.

Time-to-CNS Progression

Considering all patients (ITT), the risk of CNS progression was significantly reduced in patients treated with alectinib compared with chemotherapy (median not estimable for alectinib versus 2.4 months with chemotherapy;[2] HR=0.14, 95% CI, 0.06-0.36, p<0.001). At six months, the cumulative incidence rate of CNS progressive disease was 11% in the alectinib treatment group and 48% in the chemotherapy group.[1] Similar results were observed in patients with CNS metastases (C-ITT) at baseline (median time-to-CNS progression was not estimable for alectinib versus 1.6 months with chemotherapy; HR=0.16, 95% CI, 0.06-0.43);[2] six month CNS metastases incidence rate, 15% versus 52%. In patients without CNS metastases at baseline, the median time-to-CNS metastases was not estimable for either treatment group;[2] the six month CNS metastases incidence rate was 0% for patients treated with alectinib and 39% for patients treated with chemotherapy.

Quality of Life[3]

Analysis of patient-reported QOL was assessed in both the ITT and C-ITT populations. As the results from these two analysis sets closely aligned, the ITT analyses are summarized and presented. Questionnaires were administered at baseline, week three and six, and every six weeks until PD, death or withdrawal. It was reported that both treatment groups reported minimal lung cancer symptom burden and moderate impact of disease on functioning and QOL at baseline. Mean symptom and functioning scores were generally comparable between treatment groups; the largest observed difference was for dyspnea, which was worse in the alectinib group at baseline [mean score (standard deviation), 28.3 (31.6) for alectinib and 19.4 (24.0)]. Compliance in completing questionnaires was high at baseline for both treatment groups (92% in the alectinib group versus 89% in the chemotherapy group). For the remainder of the trial compliance was ≥70% in the alectinib group, but steadily declined in the chemotherapy group, with very few patients completing questionnaires; for example, at weeks 6, 12 and 18 compliance rates were 64% (n=18), 78% (n=7), and 67% (n=4), respectively.

EORTC-QLQ-C30

Compared to chemotherapy patients, a greater proportion of patients treated with alectinib reported clinically meaningful improvements in global health status and all but one function scale (emotional functioning), with the greatest improvements observed in the global health status scale (35% versus 20%)[2] and cognitive function (19% versus 3%). These improvements, however, were not significantly different between groups.[2] Differences in the mean change from baseline in global health status and each function scale numerically favoured alectinib over chemotherapy; however, only cognitive function met the MCID threshold (least squares mean difference=10.0, 95% CI, 2.2-17.7).

For symptom scales, a greater proportion of patients treated with alectinib reported clinically meaningful improvements over chemotherapy in every symptom scale with the exception of constipation. Differences in the mean change from baseline numerically favoured alectinib for scales including fatigue, nausea/vomiting, insomnia, appetite loss, and diarrhea; but favoured chemotherapy for pain, dyspnea (multi-item) and constipation, with constipation being the only symptom scale to reach the MCID (least squares mean difference=17.1, 95% CI, 3.3-30.9).

EORTC QLQ-LC13

More patients treated with alectinib reported clinically meaningful improvements in lung cancer symptoms including dyspnea (single-item), cough, sore mouth, peripheral neuropathy, chest pain, arm and shoulder pain, and pain in other parts, while, hemoptysis was improved with chemotherapy. However, the only significant difference between the treatment groups was in patient-reported worsening of alopecia in patients treated with chemotherapy (39% versus 8%).[2] Differences in mean changes from baseline in lung symptoms numerically favoured alectinib for scales including cough, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, and pain in chest but these differences were not significant between treatment groups; alopecia was the only scale that met the MCID (least squares mean difference -20.8, 95% CI, -33.6—8.0).

Time-to-deterioration of lung symptoms was assessed for all single- and composite scales. Only TTD in patient-reported fatigue and arm/shoulder pain were significantly delayed with alectinib compared to chemotherapy (TTD in arm/shoulder pain: median TTD 8.1 versus 1.9 months; TTD in fatigue: 2.7 versus 1.4 months); the remaining scales showed no differences in TTD between treatment groups.

EORTC BN20

Compared to patients treated with chemotherapy, a greater proportion of patients treated with alectinib reported improvements in the incidence of headaches (14% versus 12%) and improvements in coordination (18% versus 4%) and communication (18% versus 8%).

Harms Outcomes[1,2]

Adverse Events

Adverse events were assessed in the safety population, which included all patients who received at least one dose of study treatment (n= 104); there were three patients who did not receive any study drug. Duration of treatment was significantly longer in the alectinib treatment group compared with chemotherapy (20 weeks versus 6 weeks). The relative dose intensity was 86%, 84%, and 78% for alectinib, docetaxel and pemetrexed, respectively.[2] The incidence of all-cause AEs occurring in the ALUR trial at the time of primary analysis are summarized in Table 9.

Overall, AEs of any grade and AEs of grade 3 or higher occurred less frequently in patients treated with alectinib compared to chemotherapy (any grade: 77% versus 85%; grade ≥3: 27% versus 41%). The most common all grade AEs associated with alectinib were constipation (19%), anemia (14%), asthenia (10%),[2] and dyspnea (9%)[2] (Table 9). There were three AEs that occurred in greater frequency in alectinib-treated patients compared to chemotherapy, which included constipation (19% versus 12%), dyspnea (9% versus 0%),[2] and blood bilirubin increased (6% versus 0%).[2] It was reported that the majority of grade 3 or greater AEs in the alectinib group occurred in a single patient (n=19); those occurring in two or more patients included anemia (n=1, 1%), pneumonia (n=2, 3%), asthenia (n=2, 3%), syncope (n=2, 3%), and acute kidney injury (n=2, 3%). AEs were deemed related to study drug in 50% and 65% of patients treated with alectinib and chemotherapy, respectively.[2]

The incidence of serious AEs (SAEs) was higher in patients treated with alectinib compared to chemotherapy (19% versus 15%); of those patients in the alectinib

group, 6% of SAEs (n=4) occurred in more than one patient and included pneumonia (n=2) and acute kidney failure (n=2, one of which was deemed related to study drug). [2] One patient in the chemotherapy group experienced a fatal AE attributed to bacterial pneumonia.

It was reported that the incidence and type of all grade and grade 3-5 AEs in the C-ITT population were consistent with those observed in the ITT population.[4]

Treatment with alectinib led to a higher frequency of treatment interruption compared to chemotherapy (19% versus 9%); however, the chemotherapy group had a greater frequency of dose reductions (12% versus 4%) and treatment discontinuation (9% versus 6%).

Deaths

During the treatment period of the ALUR trial six patients discontinued study treatment due to death. One patient receiving docetaxel died from pneumonia deemed unrelated to study treatment, while the remainder in either group were due to disease progression and also unrelated to study treatment.[2]

Table 8: Efficacy outcomes in the ALUR trial.[1,2,4,23]

Efficacy Outcomes	Alectinib	Chemotherapy
Median follow-up time in months	6.5	5.8
Median time on treatment in weeks (range)	20 (0.4-62.1)	6 (1.9-47.1)
Systemic Efficacy (ITT, n=107)[1,2]		
n	72	35
PFS[a] by INV (primary outcome)		
Events, n (%)	24 (33)	28 (80)
Median in months (95% CI)	9.6 (6.9-12.2)	1.4 (1.3-1.6)
HR (95% CI); p-value[g]	0.15 (0.08-0.29); p<0.001	
PFS[a] by IRC		
Events, n (%)	28 (39)	21 (60)
Median in months (95% CI)	7.1 (6.3-10.8)	1.6 (1.3-4.1)
HR (95% CI); p-value[g]	0.32 (0.17-0.59); p<0.001	
ORR[b] by INV, % (95% CI)	38 (26-50)	3 (0-15)
CR, n (%)	0	0
PR, n (%)	27 (38)	1 (3)
SD, n (%)	31 (43)	9 (26)
PD, n (%)	4 (6)	20 (57)
ORR[b] by IRC, % (95% CI)	36 (25-48)	11 (3-27)
CR, n (%)	0[2]	0[2]
PR, n (%){	26 (36)[2]	4 (11)[2]
SD, n (%)	29 (40)[2]	13 (37)[2]
PD, n (%)	6 (8)[2]	12 (34)[2]
NE, n (%)	11 (15)[2]	6 (17)[2]
DCR[c] by INV, % (95% CI)	81 (70-89)	29 (15-46)
DCR[c] by IRC, % (95% CI)	76 (0.65-0.86)[2]	49 (0.31-0.66)[2]
DOR[d] by INV, median in months (95% CI)	9.3 (6.9-NE)	2.7 (NE)
DOR[d] by IRC, median in months (95% CI)	9.7 (5.6-NE)[2]	NE[2]
OS	NE	NE
CNS Efficacy in Patients with Measurable CNS Metastases (mC-ITT, n=40)[1,4]		
n	n=24	n=16
CNS ORR[e] by IRC (key secondary outcome)		
% (95% CI)	54 (33-74)	0 (0-21)
p-value[h]	p<0.001	
CR, n (%)	1 (4)	0
PR, n (%)	12 (50)	0
SD, n (%)	6 (25)	5 (31)
PD, n (%)	3 (13)	8 (50)
Not evaluable	2 (8)	3 (19)
CNS DCR[e] by IRC, % (95% CI)	79 (58-93)	31 (11-59)
p-value[h]	p<0.001	
CNS DOR[f] by IRC, median (95% CI)	NE (3.6-NE)	0
CNS Efficacy in Patients with Measurable/Non-measurable CNS Metastases (C-ITT, n=76)[4,23]		
n	50	26
CNS ORR[e] by IRC		
% (95% CI)	36 (23-51)	0 (0-13)
p-value[h]	p<0.001	
CNS DCR[e] by IRC, % (95% CI)	80 (66-90)	27 (12-48)
p-value[h]	p<0.001	

Efficacy Outcomes	Alectinib	Chemotherapy
CNS DOR[f] by IRC, median (95% CI)	NE (6.2-NE)	0
PFS[f] by INV, median in months (95% CI)	9.7 (6.9-NE)[2]	1.4 (1.2-1.6)[2]
HR (95% CI); p-value[g]	0.12 (0.05-0.27); p<0.001[2]	
PFS[f] by IRC, median in months (95% CI)	8.1 (6.3-NE)[2]	1.5 (1.2-4.1)[2]
HR (95% CI); p-value[g]	0.26 (0.12-0.55); p<0.001[2]	
Time-to-CNS progression[i,2,4]		
All patients, n	72[2]	35[2]
No. events, n (%)	9 (13) [2]	15 (43) [2]
Median (95% CI)	NE (8.1-NE) [2]	2.4 (1.4-NE) [2]
HR (95% CI); p-value	0.14 (0.06-0.36); p<0.001	
Patients with CNS metastases at baseline, n	50[2]	26[2]
No. events, n (%)	9 (18) [2]	13 (50) [2]
Median (95% CI)	NE (6.8-NE)	1.6 (1.3-9.9)
HR (95% CI)	0.16 (0.06-0.43); p=NR	
Patients without CNS metastases, n	22[2]	9[2]
No. events, n (%)	0[2]	2 (22) [2]
Median (95% CI)	NE[2]	NE[2]

Abbreviations: CI – confidence interval; **C-ITT** – analysis population comprised of patients with CNS metastases at baseline; **CNS** – central nervous system; **CR** – complete response; **DCR** – disease control rate; **DOR** – duration of response; **HR** – hazard ratio; **INV** – investigator assessment; **IRC** – independent review committee; **mC-ITT** – analysis population comprised of patients with measurable CNS metastases at baseline; **NE** – not estimable; **NR** – not reported; **ORR** – overall response rate; **OS** – overall survival; **PFS** – progression-free survival; **PD** – progressive disease; **PR** – partial response; **SD** – stable disease; **ITT** – intent-to-treat.

Notes:

[a] – PFS defined as the time from randomization to the first documented disease progression (as determined by RECIST version 1.1) or death, whichever occurred first.

[b] – ORR defined as the percentage of patients who obtained a CR or PR, as determined by RECIST v1.1.

[c] - DCR defined as percentage of patients who attained a CR, PR or SD of at least five weeks as determined by RECIST version 1.1.

[d] – DOR defined as the time from when CR or PR was first documented to first documented disease progression or death, which ever occurred first.

[e] – Outcome is defined the same way as in the ITT population but applied to lesions in the CNS only. Patients with non-measurable disease can only achieve a CR and SD, and not a PR.

[f] – Outcome is defined the same way as in the ITT population but takes into account all lesions in the body.

g -Hazard ratios derived from stratified Cox model using treatment as a covariate (HR <1.00 favour alectinib); the treatment groups were compared using a log-rank test at a two-sided α=0.05.

[h] – The difference between treatment groups was compared using a Chi-square test at a one-sided α=0.05.

[i] – Defined as the time from randomization to the first documented disease progression in the CNS.

Table 9: Adverse events in the ALUR trial.[1,2]

AEs, n (%)[a]	Alectinib (n=70)		Chemotherapy (n=34)	
	All grade	Grade ≥3	All grade	Grade ≥3
Any AE	54 (77)	19 (27)[2]	29 (85)	14 (41)
Constipation	13 (19)	0	4 (12)	1 (3)
Anemia	10 (14)	1 (1)	4 (12)	2 (6)
Asthenia	7 (10)[2]		5 (15)[2]	
Dyspnea	NR (9)[2]		0[2]	
Fatigue	4 (6)	0	9 (27)	3 (9)
Blood bilirubin increased	NR (6)[2]		0[2]	
Neutropenia	2 (3)	0	5 (15)	4 (12)
Nausea	1 (1)	0	6 (18)	1 (3)
Alopecia	0[2]		6 (18)[2]	
AEs related to study drug, any grade	35 (50)[2]		22 (65)[2]	
SAE	13 (19)[b]		5 (15)	
Fatal AE	0		1 (3)[c]	
AEs leading to treatment discontinuation	4 (6)		3 (9)	
AEs leading to dose reduction	3 (4)		4 (12)	
AEs leading to dose interruption	13 (19)		3 (9)	
Selected AEs, n (%)[2]	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Diarrhea	2 (3)	0	3 (9)	1 (3)
Headache	3 (4)	0	2 (6)	0
Myalgia	6 (9)	0	3 (9)	0
Peripheral edema	1 (1)	0	2 (6)	0
Increase in ALT	2 (3)	0	0	0
Increase in AST	1 (1)	0	0	0
Pneumonitis	1 (1)	0	0	0

Abbreviations: AE (s)– adverse event (s); **ALT** – alanine aminotransferase; **AST** – aspartate aminotransferase; **SAE** – serious adverse event.

Notes:
[a] – Treatment emergent adverse events occurring in ≥10% of patients who received at least one dose of assigned study medication.
[b] – SAEs reported in > one patient: pneumonia (n=2, both unrelated to study drug), acute kidney injury (n=2, one related and one unrelated to study drug).
[c] – Fatal event was bacteria pneumonia, which occurred during post-progression treatment period.

6.4 Ongoing Trials

No ongoing trials were identified that met the selection criteria of this review.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of alectinib:

- Critical appraisal of the Manufacturer's submitted indirect treatment comparison (ITC) and network meta-analysis (NMA) comparing alectinib to ceritinib in patients with ALK-positive metastatic NSCLC who have progressed on crizotinib.
- Critical appraisal of the Manufacturer's submitted ITC of alectinib phase 2 data versus ceritinib real world data (RWD).

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical Appraisal of the Manufacturer's Submitted ITC and NMA[2]

7.1.1 Objective

There are no randomized trials that directly compare the efficacy of alectinib to another available ALK-inhibitor, ceritinib. Therefore, the manufacturer conducted meta-analyses using different methods (Direct Meta-analysis, ITC and NMA) to examine the comparative efficacy of these two treatments.[2] The objective of this section is to summarize and critically appraise the methods and results of the performed meta-analyses, which compared alectinib, ceritinib and chemotherapy as treatment for patients with metastatic NSCLC who have progressed on chemotherapy and crizotinib (target population) in order to inform the pCODR clinical and economic evaluations of alectinib compared to relevant comparators.

7.1.2 Findings

Rationale and Objectives

Data recently became available from the phase 3 ALUR trial,[1] which compared alectinib to chemotherapy in the target population. The objectives of the manufacturer-submitted ITC and NMA were to compare the available treatments in order to derive estimates of treatment effect and use them as supportive evidence for the pCODR submission.

Systematic Review

The evidence informing the ITC and NMA was identified through a systematic review that was very broad in scope since it served multiple purposes; it included multiple lines of treatment, study designs, and outcomes. The methods followed PRISMA guidelines for reporting, and appeared comprehensive; however, the full systematic review in its entirety was not provided to pCODR. Details were provided on the inclusion criteria used for the review, the specific evidence sources searched (i.e., data bases, conference proceedings, hand searches), the literature search strategies performed, and the methods used for trial selection (i.e., independent and blinded reviewers, with discrepancies adjudicated by a third reviewer) and data extraction (i.e., prospectively determined data fields and independent data auditing). Included trials were assessed for quality (risk of bias) using multiple quality assessment tools (e.g., Cochrane risk of bias checklist, NICE checklist) and the results of these assessments were provided.

Scope of Meta-analyses

The meta-analyses were restricted to the patient population in the ALUR trial. Any treatment groups from randomized trials (phase 2 or 3) conducted in the target population that could be connected to either alectinib (600 mg twice daily), ceritinib (750 mg every day), or chemotherapy (pemetrexed 500mg/m^2 every three weeks or docetaxel 75 mg/m^2 every three weeks) were included. The outcomes of interest included PFS, OS, ORR, DCR, health-related QOL, grade 3 or higher AEs, SAE, SADR, and treatment discontinuation and treatment interruption due to AEs.

Systematic Review Results

The literature search, which was current to February 2017, identified two phase 3, open label, randomized trials that met the inclusion criteria. A list of the trials excluded from the review was not provided. The two included trials, ALUR[1] and ASCEND-5,[11] compared alectinib and ceritinib, respectively, to identical active control chemotherapy regimens (investigator's choice of docetaxel or pemetrexed).

Study Quality

The quality assessments performed of each trial (i.e., internal and external validity) were generally judged as good. The most notable source of bias cited for both trials was the open-label trial design, which could have influenced the higher dropout rates observed in the chemotherapy groups of each trial. However, for both trials, it was noted that the majority of patients dropped out due to progressive disease, and attempts were made to reduce bias through the use of blinded, independent central review of outcomes. At the time of the quality assessment, the ALUR trial was unpublished and no data were in the public domain, and the ASCEND-5 trial had only been published in preliminary form.

Feasibility of Meta-analysis and Assessment of Heterogeneity

Prior to conducting any analyses, the extracted data were assessed for suitability for meta-analysis, which included an assessment of potential study heterogeneity. The specific factors considered as possible sources of heterogeneity, however, did not appear to be identified a priori and were investigated informally using non-statistical approaches (e.g. tabular summaries of trial data). In regards to patient and disease characteristics (Table 10), it was cited that no concerning differences between the two trials were identified. It was noted that compared to ALUR, the ASCEND-5 trial had a lower proportion of patients with CNS metastases at baseline (and thus a higher frequency of brain radiation) and included a proportion of patients with two prior lines of chemotherapy (versus only one in ALUR). In terms of patient disposition and follow-up (Table 11), more patients in ASCEND-5 had discontinued treatment and median follow-up time was much longer when compared to ALUR. However, it was noted that the majority of the follow-up difference was in the post-progression period, and time-to-progression or death was comparable among the trial treatment groups as was treatment exposure for chemotherapy and ALK inhibitors. There was a higher proportion of patients in the ALUR chemotherapy group treated with docetaxel compared to ASCEND-5, but the difference was tested and found to be non-significant. Considering these differences and the study quality assessment (risk of bias), it was concluded that the trials were similar enough to be connected in an evidence network (Figure 1).

Meta-analysis was deemed feasible since the outcomes of interest were defined similarly in the ALUR and ASCEND-5 trials, and data were available for all outcomes with the exception of health-related QOL. The QOL data were judged as incomparable between trials for some patient-reported endpoints or sample sizes were too small to provide estimates. As well, the analyses of OS were considered to be limited (but included for economic analysis purposes)

since they could not be adjusted for treatment crossover and the data were considered immature (median OS had not been observed for some treatment groups).

Table 10. Baseline characteristics of patients by treatment group in the ALUR and ASCEND-5 trials.[2]

Baseline Characteristics	ALUR		ASCEND-5	
	Alectinib	Chemotherapy	Ceritinib	Chemotherapy
N, randomized	72	35	115	116
Age, median (range)	55.5 (21-82)	59.0 (37-80)	54 (30-77)	54 (28-84)
Male, n (%)	41 (56.9)	17 (48.6)	47 (40.9)	55 (47.4)
Race, n (%)				
White	61 (84.7)	28 (80)	81 (70.4)	68 (58.6)
Asian	5 (6.9)	7 (20)	30 (26.1)	38 (32.8)
Other/unknown	6 (8.3)	0 (0)	4 (3.5)	10 (8.6)
ECOG/WHO PS, n (%)				
0	29 (40.3)	11 (31.4)	56 (48.7)	51 (44.0)
1	37 (51.4)	19 (54.3)	50 (43.5)	60 (51.7)
2	6 (8.3)	5 (14.3)	9 (7.8)	5 (4.3)
Stage at baseline, n %				
IIIB	3 (4.2)	1 (2.9)	1 (0.9)	1 (0.9)
IV	69 (95.8)	34 (97.1)	114 (99.1)	115 (99.1)
Histology/cytology, n (%)				
Adenocarcinoma	72 (100)	35 (100)	111 (96.5)	113 (97.4)
Other	0 (0)	0 (0)	4 (3.5)	3 (2.6)
Smoking history, n (%)				
Current/ex-smoker	37 (51.4)	19 (54.3)	43 (37.4)	52 (44.8)
Never smoker	35 (48.6)	16 (45.7)	71 (61.7)	61 (52.6)
Missing	0 (0)	0 (0)	1 (0.9)	3 (2.6)
Time since diagnosis, median in months (range)	21.6 (5.8-67.2)	22.7 (6.3-88.7)	19.4 (5.55-153.3)	19.8 (6.5-115.9)
Brain/CNS metastasis, n (%)	47 (65.3)	26 (74.3)	65 (56.5)	69 (59.5)
Previous CRZ, n (%)	72 (100)	35 (100)	115 (100)	116 (100)
Previous CHEMO, n (%)	NR	NR	114 (99.1)7	116 (100)
1 line	68 (94.4)	34 (97.1)	101 (87.8)	102 (87.9)
2 lines	-	-	13 (11.3)	13 (11.2)
Previous therapy line, other	4 (5.6)	1 (2.9)	-	-

Abbreviations: CNS – central nervous system; CHEMO – chemotherapy; CRZ – crizotinib; ECOG – Eastern Co-operative Oncology Group; PS – performance status; WHO – World Health Organization.

Table 11. Patient disposition by treatment group in the included ALUR and ASCEND-5 trials.[2]

Patient Disposition	ALUR		ASCEND-5	
	Alectinib	Chemotherapy	Ceritinib	Chemotherapy
Randomized, n	72	35	115	116
Randomized and treated, n (%)	70 (97.2)	34 (97.1)	115 (100)	113 (97.4)
Received CHEMO	-	34	-	113
Treated with PEM, n (%)	-	9 (26.5)	-	40 (35.4)
Treated with DOC, n (%)	-	25 (73.5)	-	73 (64.6)
Discontinued treatment, n (%)	26 (37.1)	29 (85.3)	82 (71.3)	108 (93.1)
Median follow-up, median in months	6.5	5.8	16.5	16.5
Treatment exposure, median in weeks	39.6	5.6	30.3	6.3
Cross-over to ALK inhibitor at PD, n (%)	NA	24 (70.6)	NA	75 (64.7)

Abbreviations: ALK - anaplastic lymphoma kinase; **CHEMO** – chemotherapy; **CRZ** – crizotinib; **DOC** – docetaxel; **PEM** – pemetrexed; **PD** – progressive disease

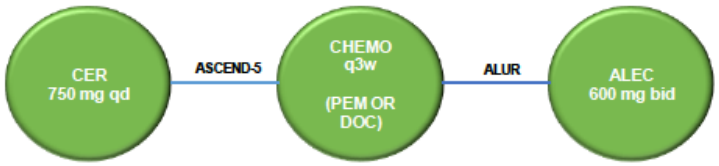


Figure 1: Meta-analysis evidence network.

Meta-analysis Methodology

Overall, the approaches used to synthesize the trial data, including underlying statistical assumptions and the statistical programs used, were well reported and aligned with recommended practice. Treatments were compared using three different analytic methods. The first was a pairwise direct meta-analysis (Direct MA) comparing the treatments that have been evaluated head-to-head in RCTS (i.e., alectinib versus chemotherapy; ceritinib versus chemotherapy); with Bucher indirect comparisons estimated for treatments (Bucher ITC) that have not been evaluated in head-to-head RCTs (i.e., alectinib versus ceritinib). An NMA using Bayesian methods was also performed to simultaneously estimate both direct and indirect comparisons of all treatments in the network (i.e., alectinib versus ceritinib and versus chemotherapy, and ceritinib versus chemotherapy). Each method was conducted using fixed effects analyses, with appropriate justification for the choice of analysis (versus random effects). Analyses were carried out by ITT for efficacy outcomes and in the safety patient population for safety outcomes. The primary efficacy analyses used outcomes determined by investigator assessment (INV), and outcomes by independent review committee (IRC) were assessed in sensitivity analyses. Consistency between direct and indirect evidence was not assessed in the NMA as the network did not contain a closed loop (Figure 1). It was reported that all analyses were pre-specified in a statistical analysis plan (SAP), however, the SAP was not provided to pCODR; from the analysis details that were provided it is unclear whether statistical approaches to investigate heterogeneity (e.g., sensitivity analyses) were planned. It was mentioned that a subgroup analysis of patients with CNS metastases at baseline was of

interest but could not be performed due to lack of subgroup endpoint data in the ASCEND-5 trial.

The results of individual trials were provided and presented in tabular form and as Forest plots [hazard ratios (HR) estimated for continuous outcomes and odds ratios (OR) estimated for dichotomous outcomes, with corresponding 95% confidence intervals (CIs)]. The same statistics were reported for the Bucher ITC and summarized in tabular form. For the NMA, a tabular summary and caterpillar plots were provided for each outcome with estimates of treatment effect for all pairwise comparisons (direct and indirect) in the network [HRs and ORs, with corresponding 95% credible intervals (CrI)]. Other effect measures, although not the focus of this report, were reported and included different measures of treatment rankings (i.e., probability best, median rankings, and SUCRA (surface under the cumulative ranking curve).

Meta-analysis Results

The efficacy and safety results, summarized by outcome and meta-analytic method, can be found in Tables 12and 13, respectively.

Efficacy

PFS
Alectinib significantly improved PFS (INV and IRC) compared to chemotherapy by Direct MA and NMA. Using Bucher ITC and NMA, alectinib resulted in significantly improved PFS by INV assessment compared to ceritinib (NMA HR=0.38, 95% CrI, 0.19-0.76) but no difference between the treatment groups was detected by IRC assessment (NMA HR=0.65, 95% CrI, 0.32-1.31).

OS
All analyses conducted on unadjusted OS (Direct MA, Bucher ITC, and NMA) showed no differences between treatment groups. It was noted that the OS results were not adjusted for treatment crossover and data were deemed immature.

Response
Alectinib significantly improved ORR and DCR (INV and IRC) compared to chemotherapy using Direct MA and NMA. Using Bucher ITC and NMA, no significant differences between alectinib and ceritinib were detected for ORR or DCR (INV and IRC). Ceritinib significantly improved ORR and DCR (INV and IRC) compared to chemotherapy using Direct MA and NMA.

Safety

There were no differences in any safety outcomes (SAE, SADR, grade ≥3 AEs, treatment discontinuations due to AEs, treatment interruption due to AEs and dose reduction) between alectinib and chemotherapy using Direct MA or NMA. Alectinib was associated with significantly fewer grade ≥3 AEs (NMA OR=0.27, 95% CrI, 0.10-0.77) and dose reductions (NMA OR=0.15, 95% CrI, 0.02-0.88) compared to ceritinib using Bucher ITC and NMA; and no differences were detected for the other safety outcomes assessed (i.e., SAE, SADR, treatment discontinuations due to AEs, and treatment interruption due to AEs). Ceritinib was associated with significantly more grade ≥3 AEs, treatment interruptions, and dose reductions compared to chemotherapy using Direct MA and NMA.

Table 12: Meta-analysis results (Direct Meta-analysis, Indirect Treatment Comparisons and Network Meta-analysis) of efficacy outcomes.[2]

Method	Comparison	Efficacy Outcomes						
		PFS by INV	PFS by IRC	OS	ORR by INV	ORR by IRC	DCR by INV	DCR by IRC
Direct MA		**HR (95% CI)**			**OR (95% CI)**			
ALUR	ALEC vs. CHEMO	0.15 (0.08-0.28)*	0.32 (0.17-0.60)*	0.89 (0.35-2.27)	20.4 (2.64-157-68)*	4.38 (1.39-13.79)*	10.36 (4.06-26.44)*	3.43 (1.45-8.07)*
ASCEND-5	CER vs. CHEMO	0.40 (0.29-0.55)*	0.49 (0.36-0.67)*	1.00 (0.68-1.48)	11.56 (4.95-27.02)*	8.68 (3.86-19.51)*	6.55 (3.62-11.82)*	5.74 (3.24-10.19)*
BUCHER ITC		**HR (95% CI)**			**OR (95% CI)**			
	ALEC vs. CER	0.38 (0.19-0.76)*	0.65 (0.32-1.32)	0.89 (0.32-2.46)	1.76 (0.19-16.15)	0.50 (0.12-2.06)	1.58 (0.52-4.79)	0.60 (0.21-1.67)
NMA		**HR (95% CrI)**			**OR (95% CrI)**			
	ALEC vs. CHEMO	0.15 (0.08-0.28)*	0.32 (0.17-0.60)*	0.89 (0.35-2.26)	25.23 (4.63-651.2)*	4.58 (1.60-17.32)*	10.93 (4.31-29.40)*	3.51 (1.48-8.60)*
	ALEC vs. CER	0.38 (0.19-0.76)*	0.65 (0.32-1.31)	0.89 (0.32-2.44)	2.12 (0.30-58.72)	0.51 (0.13-2.40)	1.64 (0.54-5.14)	0.60 (0.21-1.75)
	CER vs. CHEMO	0.40 (0.29-0.55)*	0.49 (0.36—0.68)*	1.00 (0.67-1.49)	1.08 (5.37-31.10)*	8.95 (4.10-21-96)*	6.69 (3.72-12.28)*	5.84 (3.20-10.55)*

Abbreviations: ALEC – alectinib; **DCR** – disease control rate; **CER** – ceritinib; **CHEMO** – chemotherapy; **CI** – confidence interval; **CrI** – credible interval; **IRC** – independent review committee assessment; **ITC** - indirect treatment comparison; **INV** – investigator assessment; **MA** – meta-analysis; **NMA** – network meta-analysis; **OR** – odds ratio; **OS** – overall survival; **PFS** – progression-free survival.

Notes:
*Statistically significant difference at p<0.05; HRs < 1.00 represent significantly lower hazard for treatment vs. comparator, and ORs > 1.00 represent significantly higher odds of event for treatment vs. comparator.

Table 13: Meta-analysis results (Direct Meta-analysis, Indirect Treatment Comparisons, and Network Meta-analysis) of safety outcomes.[2]

Method	Comparison	Safety Outcomes					
		SAE	SADR	Grade ≥3 AEs	TRT Discontinuation due to AE	TRT Interruption due to AE	Dose Reduction
Direct MA		**OR (95% CI)**					
ALUR	ALEC vs. CHEMO	1.32 (0.43-4.07)	0.45 (0.11-1.94)	0.53 (0.22-1.26)	0.89 (0.33-2.35)	2.36 (0.62-8.91)	0.34 (0.07-1.59)
ASCEND-5	CER vs. CHEMO	1.59 (0.92-2.73)	1.07 (0.47-2.46)	1.95 (1.09-3.49)*	0.74 (0.25-2.21)	8.63 (4.75-15.68)	2.13 (1.18-3.85)
BUCHER ITC		**OR (95% CI)**					
	ALEC vs. CER	0.83 (0.24-2.90)	0.42 (0.08-2.26)	0.27 (0.10-0.77)*	1.19 (0.28-5.16)	0.27 (0.06-1.17)	0.16 (0.03-0.83)*
NMA		**OR (95% CrI)**					
	ALEC vs. CHEMO	1.35 (0.45-4.58)	0.45 (0.10-2.13)	0.53 (0.22-1.26)	0.90 (0.34-2.53)	2.54 (0.72-12.00)	0.32 (0.06-1.67)
	ALEC vs. CER	0.85 (0.25-3.23)	0.42 (0.07-2.45)	0.27 (0.09-0.77)*	1.25 (0.28-5.76)	0.29 (0.07-1.52)	0.15 (0.02-0.88)*
	CER vs. CHEMO	1.59 (0.92-2.77)	1.06 (0.46-2.5)	1.97 (1.10-3.57)*	0.73 (0.23-2.22)	8.81 (4.90-16.46)*	2.14 (1.20-3.91)*

Abbreviations: AE– adverse events; **ALEC** – alectinib; **CER** – ceritinib; **CHEMO** – chemotherapy; **CI** – confidence interval; **CrI** – credible interval; **ITC** - indirect treatment comparison; **MA** – meta-analysis; **NMA** – network meta-analysis; **OR** – odds ratio; **SADR** – serious adverse drug reaction; **SAE** – serious adverse event; **TRT** – treatment.

Notes:
*Statistically significant difference at p<0.05; ORs <1.00 represent significantly lower hazard for treatment vs. comparator.

Critical Appraisal of Direct Meta-analysis with Bucher ITC and NMA

The quality of the manufacturer-submitted ITC and NMA were assessed according to the 2014 IPSOR (International Society of Pharmacoeconomics and Outcomes Research) Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire.[30] A summary of the quality assessment is provided in Table 14.

Overall, the relevance of the ITC and NMA was considered sufficient since the two included trials, ALUR and ASCEND-5, were well matched in terms of patient population, treatment comparators, outcomes of interest, and clinical context. The reporting of the methods used to conduct both the systematic review and meta-analyses were, for the most part, clear and comprehensive. There are concerns, however, in terms of credibility (i.e., internal validity, interpretation, and conflict of interest), which are summarized below:

- Due to the structure of the evidence network, only a fixed effects analysis could be performed. A fixed effects analysis, by definition, assumes no heterogeneity between trials with observed differences in relative treatment effects solely due to chance. There does, however, appear to be heterogeneity present between the ALUR and ASCEND-5 trials (i.e., differences in the proportion of patients with baseline CNS metastases, number of previous lines of chemotherapy, Asian race, smoking history, receipt of docetaxel in the chemotherapy group) that should not be ignored. It is assumed that this potential heterogeneity was not explored statistically (i.e., through sensitivity/subgroup analysis) because data were unavailable for the ASCEND-5 trial at the time. Thus the treatment estimates obtained are likely to be biased (i.e., not only due to treatment) since between study heterogeneity was not appropriately accounted for in analyses. The direction and magnitude of the bias is unclear, and therefore, the effect estimates obtained may over or under estimate the treatment effect associated with alectinib.
- A second concern relates to the preliminary nature of the data used for the meta-analyses. At the time they were conducted, data for ASCEND-5 came from conference abstracts and posters, and data for ALUR were not yet in the public domain. The use of these types of data can be problematic since selective reporting, data immaturity, and lack of peer-review have the potential to influence estimates of treatment effect and lead to invalid interpretations of the evidence network. It would make sense to conduct the ITC and NMA when published and longer follow-up (for OS) data become available, at which point it is also likely investigation of between study heterogeneity could be performed.
- In terms of specific outcomes, the analyses of OS should be considered with caution as they are limited by data immaturity and have not been adjusted for treatment cross-over, which occurred in both trials. Further, the results obtained have not been considered alongside impacts on health-related QOL.
- The submitted ITC and NMA was funded and performed by external consultancy groups hired by the manufacturer. Therefore, the results should be viewed considering this potential conflict of interest and lack of peer-review.

Table 14: Adapted ISPOR Questionnaire[30] to assess the relevance and credibility of an ITC or NMA.

IPSOR Questions	Details and Comments
1. Is the population relevant?	Yes. The patients included in the ALUR and ASCEND-5 trials closely align with the target population of interest: patients with metastatic NSCLC who have progressed on chemotherapy and crizotinib.
2. Are any critical interventions missing?	No. The ITC and NMA included all relevant treatment comparators at appropriate doses, schedules, and modes of administration.
3. Are any critical outcomes missing?	Yes. Although all relevant outcomes were considered, health-related QOL was not included because the manufacturer cited the data were incomparable between trials or were limited due to small samples for some QOL outcomes. Of note, although the two trials assessed different primary outcomes (ALUR: PFS by INV; ASCEND-5: PFS by IRC), each trial assessed PFS by both methods of assessment. The concordance between the methods (i.e., number of PFS events) was very high in each trial, which suggests no obvious bias related to open-label design in either trial and makes the use of either PFS endpoint acceptable.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Yes.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Yes, in part. The systematic review appeared comprehensive in terms of the approach used to search for evidence. However, a detailed list of the specific trials excluded from the review was not provided.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes. The included trials formed a connected network comprising of single trial connections with no closed loop.
7. Is it apparent that poor quality studies were included leading to bias?	No. The included trials were assessed for risk of bias using several different tools and the results of these assessments were provided. Considering all assessments, the overall quality of both included trials was judged as good (low risk of bias).
8. Is it likely that bias was introduced by selective reporting of outcomes in the studies?	Unclear. Although it was cited that all outcomes in both the ALUR and ASCEND-5 trials were accounted for in terms of reporting, neither trial were published in full at the time the ITC and NMA were conducted, and the ALUR trial data were not in the public domain. Neither trial, therefore, had undergone peer review, and the possibility of selective reporting cannot be eliminated.
9. Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	Yes. Differences between the trials in patient characteristics were identified but judged to be minor (e.g., proportion of patients with two previous lines of chemotherapy) or tested and deemed non-significant (i.e., proportion of patients receiving docetaxel). It is unclear why some of the observed differences between the trial treatment groups were tested for significance and others were not. It was reported that the higher proportion of patients with CNS metastases at baseline in the ALUR trial may have influenced outcomes in favour of the ASCEND-5 trial (ceritinib); however, it was unknown whether the imbalance acted as a treatment effect modifier. Other patient characteristics also appeared imbalanced (i.e., Asian race, smoking history).
10. If yes (i.e., there are such systematic differences in treatment effect	Not reported.

IPSOR Questions	Details and Comments
modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	
11. Were statistical methods used that preserve within-study randomization? (i.e. no naïve comparisons)	Yes. The Bucher method was used for ITC, and Bayesian methods were used for the NMA.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops, was agreement in treatment effects (i.e. consistency) evaluated or discussed?	Not applicable (no closed loop).
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable (no closed loop).
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias in the analysis?	No.
15. Was a valid rationale provided for the use of random effects or fixed effects models?	Yes. A fixed effects model was chosen for the Direct Meta-analysis and Bucher ITC since a random effects model could not be estimated (in the statistical program STATA) since there was only one trial per direct comparison. A fixed effects model was also used for the NMA due to a lack of informative priors to estimate between study variation.
16. If random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable (fixed effects analysis).
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	No.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes.
19. Are the individual study results reported?	Yes.
20. Are the results of direct comparisons reported separately from results of the indirect comparisons or NMA?	Yes.
21. Are all pairwise contrasts between interventions as obtained with the NMA reported along with measures of uncertainty?	Yes.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes.

IPSOR Questions	Details and Comments
23. Is the impact of important patient characteristics on treatment effects reported?	No.
24. Are the conclusions fair and balanced?	No. The conclusions cannot be considered fair and balanced due to differences in patient characteristics (heterogeneity) between trial treatment groups that were unaccounted for in analyses.
25. Were there any potential conflicts of interest?	Not reported.
26. If yes, were steps taken to address these?	Not applicable.

7.1.3 Summary

A manufacturer-submitted ITC and NMA,[2] which compared alectinib to ceritinib and chemotherapy as treatment for patients with advanced or metastatic NSCLC who progressed on were intolerant to crizotinib, was summarized and critically appraised using the ISPOR Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire.[30] The ITC and NMA found that alectinib significantly improved PFS by INV compared to ceritinib, but no difference in PFS by IRC was detected. Alectinib significantly improved PFS by INV and IRC compared to chemotherapy. No differences in OS were demonstrated between the treatment groups, however, OS data were considered immature and unadjusted for treatment crossover. There were no differences between alectinib and ceritinib for response outcomes including ORR and DCR (by INV and IRC); however, each ALK inhibitor showed significantly better response outcomes compared to chemotherapy. Alectinib was associated with significantly fewer grade ≥3 AEs and dose reductions when compared to ceritinib; and no differences in safety outcomes were observed when alectinib was compared to chemotherapy. Conversely, ceritinib was associated with significantly more grade ≥3 AEs, treatment interruptions, and dose reductions compared to chemotherapy. Health-related QOL data were available but not amenable to meta-analysis. The quality assessment judged the overall relevance of the ITC and NMA to be sufficient, but concerns were noted related to credibility (internal validity). The main limitations of the ITC/NMA included heterogeneity across the included studies that was not investigated in analyses due to constraints in the structure of the evidence network (e.g., single trial connections) and the use of preliminary and/or unpublished data. It was concluded that the comparative efficacy estimates obtained (alectinib versus ceritinib) are likely biased due to uncontrolled heterogeneity; however, the direction and magnitude of the bias is unclear, and therefore, the estimates obtained may over or under estimate the true treatment effect associated with alectinib.

7.2 Critical Appraisal of the Manufacturer's Submitted Indirect Comparison of Alectinib Phase 2 Data versus Ceritinib Real World Data[2,5]

7.2.1 Objective

The Manufacturer's submitted ITC and NMA described in section 7.1 was unable to provide an estimate of the comparative efficacy of alectinib versus ceritinib for OS due to immaturity of trial data. Therefore, data from two single-arm, phase 2 alectinib clinical trials (refer to section 8 for a brief summary of trials NP28673 and NP28761) and real world patient data (RWD) from an electronic health record (EHR) database were retrospectively analyzed to

indirectly compare OS in the target population and derive an estimate of treatment effect.[2,5] The objective of this section is to summarize and critically appraise the methods and results of the submitted analyses in order to inform the pCODR clinical and economic evaluations of alectinib compared to relevant comparators.

7.2.2 Findings

The two treatment groups were constructed retrospectively from two sources of individual patient data (IPD) for patients with ALK-positive NSCLC who had progressed on crizotinib. For the alectinib treatment group, data from the two previously mentioned alectinib trials were pooled. For the ceritinib treatment group, IPD were extracted from the Flatiron EHR database by applying the inclusion and exclusion criteria used in the alectinib trials to patients diagnosed between, January 1, 2011 and December 31, 2014, who received ceritinib following crizotinib failure. Follow-up data were available up to February 28, 2016. After the treatment groups were combined into a single cohort, additional criteria were applied in order to adjust for observed imbalances between the two treatment groups (i.e., stage of diagnosis and treatment with crizotinib post-progression).[2] A third data source, which included published summary data from a cohort of patients treated with ceritinib in the ASCEND-2 phase 2 trial,[31] were used in naïve treatment comparison with alectinib to assess the generalizability of results obtained using the ceritinib RWD. Further sensitivity analyses were performed to evaluate the robustness of the primary analysis and included the following: excluding patients with follow-up time in the top 10th percentile, missing covariates imputed (race and stage at diagnosis), including CNS metastases added as a prognostic variable, including Asian race as a prognostic variable, including patients with 1-3 lines of prior treatment (patients with >3 lines of treatment excluded), excluding stage at diagnosis as a prognostic variable, and including age as a continuous variable.[2]

Statistical Methods

The primary outcome of the analysis was OS, defined as the time from the date of initiation of alectinib or ceritinib until death from any cause. Patients were censored in the analysis on their date of last visit if they were still on their previous treatment at the end of the study period or if their death could not be confirmed.[2] A propensity score logistic regression model, which included baseline prognostic variables predicting treatment assignment, was used to generate a propensity score for each patient. The specific prognostic variables informing the model were age, gender, race, stage at initial diagnosis, and prior lines of therapy. Inverse probability treatment weighting with stabilized weights (IPTW) was used to produce weighted treatment groups based on propensity scores in order to achieve a balanced distribution of baseline variables between the treatment groups. To assess whether balance was achieved, standardized mean differences (SMD) were calculated for each variable in an unadjusted (i.e., no propensity scores) and adjusted (with propensity scores) model. Any differences greater than 10% in the SMD indicated an imbalance between groups. Graphical displays of the propensity score were also used to assess balance pre- and post-weighting.[2] Median OS, which was estimated from treatment initiation until death, loss to follow-up, or data cut-off, and 95% confidence intervals (CI) were calculated for the weighted treatment groups using the methods of Kaplan-Meier and compared with a log-rank test. A Cox proportional hazard model was used to estimate the hazard ratio and corresponding 95% CI.

Results

The primary analysis included a total of 250 patients; a pooled cohort of 183 patients who received alectinib in the two phase 2 trials and 67 patients who received ceritinib from the Flatiron database. Prior to propensity score weighting, baseline patient characteristics between the treatment groups were unbalanced (Table 15). Patients in the alectinib treatment group were younger, more heavily pretreated with chemotherapy (and radiation), and had a much higher prevalence of CNS metastases, with SMD ranging between 0.9% and 62.8% among the five variables included in the propensity score model. After weighting, the treatment groups appeared balanced with SMD ranging between 0.9 and 6.4% (all below the 10% balance threshold), with the largest difference (6.4%) observed for prior lines of treatment. Balance was also confirmed by visual graphical inspection of the propensity score distribution by treatment group.[2] Of note, while all patients treated with alectinib experienced failure on crizotinib, only 57% of patients treated with ceritinib received first-line crizotinib; of those patients, it was reported that 94% discontinued crizotinib due to disease progression.[5]

The median follow-up time of patients was 23 months and 12 months for the alectinib and ceritinib treatment groups, respectively. Median OS for the weighted treatment groups was 24.3 months (95% CI, 21-not reached) in the alectinib group and 15.6 months (95% CI, 16-19) for the ceritinib group. Alectinib was associated with a significantly reduced risk of death compared to ceritinib (HR=0.65, 95% CI, 0.48-0.88; p=0.006). These analyses were not adjusted for the subsequent treatments received by patients in both treatment groups. In the alectinib and ceritinib groups, 53 patients (42%) and 34 patients (54%), respectively, received at least one subsequent therapy.[2] The results of all sensitivity analyses performed were consistent with the primary analysis results.

For the naïve treatment comparison, when the alectinib data were compared to the ceritinib ASCEND-2 trial data, similar imbalances were seen in baseline patient characteristics. The median OS reported in ASCEND-2 (median OS=14.9 months, 95% CI, 14-not reached) was consistent with the ceritinib RWD (15.6 months, 95% CI, 12-not reached), and was inferior to alectinib (median OS=26 months, 95% CI, 21-not reached) in an unweighted analysis.

Table 15: Patient characteristics by treatment cohort prior to weighting using propensity scores.[5]

Patient Characteristics *n (%) unless otherwise noted*	**Alectinib Pooled Phase 2 Data (n=183)**	**Ceritinib RWD (n=67)**	**p-value**
Median age (SD)	52.5 (±11.2)	59.8 (±11.7)	<0.0001*
Age group			
<65 years	160 (87)	41 (61)	<0.0001*
≥65 years	23 (13)	26 (39)	
Gender			
Male	85 (47)	30 (45)	0.89
Female	98 (54)	37 (55)	
Race			
White	133 (73)	49 (73)	1.00
Other	50 (27)	18 (27)	
ACA histology	175 (96)	61 (91)	0.029*
ECOG performance status			
0	64 (35)	8 (12)	0.11
1	101 (55)	8 (12)	
2	18 (10)	5 (7)	
Missing	0	46 (69)	
Stage at diagnosis			
IIIB	13 (7)	8 (12)	0.3
IV	170 (93)	59 (88)	
CNS metastases			
Yes	112 (61)	23 (34)	0.0002*
No	71 (39)	44 (66)	
History of smoking			
Yes	62 (34)	30 (45)	0.14
No	121 (66)	37 (55)	
Prior chemotherapy	136 (74)	19 (28)	<0.0001*
Prior radiation	84 (46)	21 (31)	0.043*
Prior lines of treatment			
1	52 (28)	38 (57)	<0.0001
2	66 (36)	20 (30)	
≥3	66 (36)	9 (13)	
Range of prior lines	1-8	1-5	
Abbreviations: ACA – adenocarcinoma; **CNS** – central nervous system; **ECOG** – Eastern Cooperative Oncology Group; **RWD** – real world data; **SD** – standard deviation.			
Notes: *Statistically significant difference between treatment groups (p<0.05) using Wilcoxon rank sum test for continuous data and Chi-square test for categorical data.			

Critical Appraisal

The quality of the manufacturer-submitted ITC of alectinib phase 2 data and ceritinib RWD was assessed according to best practice principles, set out by Austin and Stuart (2015),[8] when using IPTW using the propensity score to estimate causal treatment effects from observational data.

Overall, the manufacturer-submitted ITC employed methods that align with best practice; however, important limitations in the analysis were noted, which raises uncertainty about both the relevancy and internal validity of the results obtained.

- Although it is implied in the manufacturer's ITC that all patients experienced crizotinib failure, just over half of the patients included in the ceritinib RWD treatment group (57%) received and discontinued treatment with crizotinib first-line.[5] The difference between the two treatment groups in the proportion of patients with first-line crizotinib failure (57% versus 100%) calls into question the relevancy of the analysis

performed, and whether or not it aligns to the target population of the pCODR review. In the ALUR trial, the criteria for inclusion was two previous lines of therapy consisting of one line of crizotinib and one line of platinum-based chemotherapy.

- The Submitter commented on the pCODR Expert Review Committee's (pERC's) Initial Recommendation that statements made regarding the ceritinib RWD patient population from the EHR database appear incorrect, leading to flawed conclusions. Specifically, the Submitter states that all patients (100%) in the ceritinib cohort derived from the RWD from the EHR database had prior treatment with crizotinib, and not 57% as reported by the pCODR Methods Team. The Submitter states in the feedback that it is incorrect to report that "although it is implied in the manufacturer's ITC that all patients experienced crizotinib failure, just over half of the patients included in the ceritinib RWD treatment group (57%) received and discontinued treatment with crizotinib". The Submitter explained that the NP28763 and NP28761 inclusion and exclusion criteria were used to extract patients diagnosed with a NSCLC between January 1, 2011 and December 31, 2014, who received ceritinib treatment following crizotinib failure.
- In response to the Submitter's feedback, the pCODR Methods Team acknowledges that all patients in the ceritinib cohort received ceritinib treatment following crizotinib failure. However, the Methods Team would like to clarify that the uncertainty about the relevancy and internal validity of the results is specific to the fact that 57% of patients in the ceritinib RWD treatment group, and not 100% of patients, received and discontinued treatment with crizotinib *first-line*. The Methods Team re-iterates that the submitted Davies et al poster[5] specifically reports that in the ceritinib RWD arm, 57% of patients had received crizotinib ***first-line*** (refer to table below). This suggests that 43% of patients in the ceritinib RWD group failed crizotinib in later lines of treatment (i.e., did not receive crizotinib in the first-line setting); and therefore, a substantial portion of patients may not align to the target population of the pCODR review: alectinib as second-line therapy for patients who have progressed on crizotinib.

Prior Lines, n (%)	Alectinib (n=183)	Ceritinib RWD (n=67)
1	52 (28)	38 (57)
2	66 (36)	20 (30)
≥ 3	65 (36)	9 (13)
Range	1-8	1-5

- Further to the point above, the pCODR review team, including its clinical members, were unfamiliar with the Flatiron EHR database. Background information provided on this data source, which was used to comprise the ceritinib RWD treatment group, was limited. The context in which patients were treated and information on the data source (e.g., types and methods of data capture) are important to know for the purpose of validity and generalizability of findings.
- For causal inferences using propensity score methods to be valid, the assumption of no important unmeasured prognostic variables or confounders must be met.[8] Five prognostic variables (age, gender, race, stage at diagnosis, and prior lines of treatment) were included in the primary analysis model to generate propensity scores and achieve balance between treatment groups. Beyond unavailability of performance status data, it was not thoroughly explained or justified why some important variables were excluded. Pre-weighting there were clear imbalances between the treatment

groups in proportions of patients with CNS metastases and previous chemotherapy but these variables were not accounted for in the primary analysis, while other variables less predictive of treatment outcome (e.g., race, gender) were included. A sensitivity analysis did explore the influence of CNS metastases on the result obtained but it did not provide an estimate that incorporated all important variables simultaneously in the model. The effect of previous chemotherapy was not explored in a sensitivity analysis. The reported OS estimate, therefore, is likely confounded since the effects of all important prognostic baseline variables were not controlled for in the primary analysis.

- The Submitter also commented on the pERC Initial Recommendation that an incorrect statement was made regarding the prognostic variables used in the propensity score analysis. Specifically, the Submitter stated that it is incorrect to state that the reported OS estimate is likely confounded since the effects of all important prognostic variables (CNS metastases and previous chemotherapy) were not controlled for in the primary analysis.
- In response to the Submitter's feedback, the Methods Team acknowledges that in addition to the primary analysis, multiple sensitivity analyses were conducted to assess the robustness of the primary analysis. The primary analysis included the following prognostic variables: age, gender, race, stage at diagnosis, and prior lines of treatment. However, the Methods Team re-iterates that the prognostic variable of CNS metastases was not included in the primary analysis model. This is because the Submitter claimed that "the screening for CNS metastases differs between the clinical trial and real world, which could lead to inconsistent definitions and impact the specification of the propensity score model".[2] Instead, a sensitivity analysis exploring the influence of CNS metastases as a prognostic factor on OS was conducted.[2,5] Furthermore, the Methods Team also acknowledges that the prognostic variable of prior lines of therapy was included in the primary analysis model, however, the prognostic variable of *previous chemotherapy* was not included and was *not* explored in a sensitivity analysis. The Methods Team notes that the types of prior lines of therapy included in this prognostic variable are unclear as these were not clearly defined in the submitted poster or manuscript, and could possibly include multiple types of therapy including, but not limited to, ceritinib, radiotherapy, immunotherapy or chemotherapy. Therefore, the prognostic variable of prior lines of therapy does not capture the influence of previous chemotherapy alone. Although multiple sensitivity analyses were conducted by the Submitter, the Methods Team re-iterates that *all* important prognostic variables were not controlled for *simultaneously in the primary analysis model, and* therefore, there is a possibility that the OS estimate may be confounded.
- Attributes of the ceritinib RWD patient cohort, including median follow-up time of patients compared to the alectinib treatment group (12 versus 24 months), and the size of the sample (n=67), also raise concern about the reliability of the OS estimates obtained. Further, OS estimates in both treatment groups were not adjusted for the use of subsequent treatments used after disease progression.

Summary

The Manufacturer's submitted ITC and NMA described in section 7.1 was unable to provide an estimate of the comparative efficacy of alectinib versus ceritinib for OS due to immaturity of trial data and heavy crossover. Therefore, data from two single-arm, phase 2 alectinib clinical trials[6,7] (refer to Section 8 for a brief summary of trials NP28673 and NP28761) and RWD from an electronic health record (EHR) database were retrospectively analyzed to indirectly compare OS in the target population and derive an estimate of treatment effect. The quality of the analysis was assessed according to best practice principles, set out by Austin and Stuart

(2015),[8] when using inverse probability of treatment weighting (IPTW) using propensity scores to estimate causal treatment effects from observational data. Overall, the ITC used methods that align with best practice; however, important limitations in the analysis were noted, including issues related to relevancy (a substantial proportion of patients in the ceritinib RWD treatment group did not experience crizotinib failure in the first-line setting)[5] and internal validity (important key prognostic baseline variables were left out of the model used to balance treatment groups for the primary analysis). Therefore, the reported OS estimate may be confounded since the effects of all important prognostic baseline variables were not controlled for simultaneously in the primary analysis model.

8 COMPARISON WITH OTHER LITERATURE

This section describes how the evidence and results summarized in the pCODR systematic review compare with published literature or other findings.

Prior to results of the phase 3 ALUR trial becoming available, clinical evidence for the efficacy and safety of alectinib in patients with ALK-positive, locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib (with or without CNS metastases), was limited to two single-group, open-label phase 2 trials (NP28761 and NP28673).[6,7] These phase 2 trials formed the evidence base for the May 2017 pCODR review (project number 10092) on alectinib for ALK-positive NSCLC.[22] Since the completion of that review, the data from these trials have been pooled and published.[24,25] The pooled analyses combined data from the most recent data cut-off date of each trial. The analyses performed were conducted post-hoc, and therefore should be viewed as exploratory in nature and interpreted with caution. For a detailed review of the phase 2 trials and their limitations, please refer to the full guidance report referred to above.[22] A brief summary of the trials and the pooled analyses performed are provided below.

In brief, NP28673 and NP2871 were both single-group multi-centred, open-labelled trials. NP28673 was a global trial conducted across 16 countries and 56 trial sites, and enrolled patients between June 2013 and April 2014. NP28761 was conducted in the US (26 sites) and Canada (1 site), and enrolled patients between May 2012 and August 2014. The trials were very similar in design and the outcomes assessed, and included patients based on the following criteria:

- Stage IIIB-IV, ALK-positive NSCLC determined by a FDA-approved FISH (fluorescence in situ hybridization)
- Disease progression (per RECIST) while receiving crizotinib (with a one-week wash-out period)
- ECOG performance status of 0-2
- Measurable disease at baseline (per RECIST)
- Brain or leptomeningeal metastases were allowed, treated or untreated, as long as metastases were asymptomatic and stable
- Previous treatment with an ALK inhibitor other than crizotinib, receipt of chemotherapy within four weeks (NP28761, NP28673) or radiotherapy within two weeks (NP28761) of study start was not permitted

Treatment with alectinib was administered at a dose of 600mg orally twice a day in both trials, in 21-day cycles in trial NP28761 and 28-day cycles in trial NP28673, and continued on treatment until disease progression, unacceptable toxicity or withdrawal of consent.

The primary outcome of the pooled analysis was objective response rate (ORR) by independent review committee (IRC), using RECIST version 1.1. The secondary outcomes of interest included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. Secondary outcomes also included CNS efficacy endpoints including CNS ORR, CNS DOR, and CNS DCR, which were published separately in abstract form.[25] Efficacy outcomes were assessed in the response evaluable (RE) population of patients, which comprised patients with measurable disease at baseline who received at least one dose of alectinib. Safety outcomes were assessed in patients who received at least one dose of alectinib. PFS and OS were assessed in the safety patient population.

The pooled analysis set included 225 patients (138 and 87 from trials NP28673 and NP28761, respectively). Of those patients, 189 (84%) comprised the RE population (122 and 67 from trials NP28673 and NP28761, respectively). Baseline characteristics (Table 16) were reported as similar across the two phase 2 trials, however, there appeared to be a few imbalances. In trial NP28673, there were higher proportions of patients of Asian race (26% versus 8%) and treated with crizotinib

plus one additional therapy (38% vs. 0%). In trial NP28761, there were more patients of white race (84% versus 67%), with past smoker smoking status (38% versus 28%), and treated with crizotinib plus two additional therapies (22% versus 12%). Considering all pooled patients, the median age was 53 years (range, 22-79), and the majority of patients were white (74%), had an ECOG performance status of 0 or 2 (67%), presented with CNS metastases (60%), and were previously treated with chemotherapy (77%). Of the patients with CNS metastases, 70% had received prior radiotherapy.

Outcomes
The results of the pooled analyses of efficacy and safety outcomes are summarized in Table 17. The median follow-up time for the pooled data set was 18.8 (range, 0.6-29.7) months.

Overall Efficacy
The pooled ORR by IRC in the RE population was 51% (95% CI, 44-59), which comprised of all partial responses. Subgroup analyses were performed to estimate the treatment effect of alectinib in patients based on different prognostic factors, including sex, race, ECOG status, CNS metastases at baseline, smoking status, prior chemotherapy, number of prior therapies, and best response to crizotinib. The ORR estimates in patients previously treated and treatment-naïve with chemotherapy were 49% (95% CI, 41-58) and 59% (95% CI, 42-74), respectively. In general, the ORR estimates among the patient subgroups were consistent with the analysis of all patients (ORR range, 29% to 66%), however, many groups included a small number of patients, which resulted in wide, overlapping confidence limits. The median DOR in the RE population was 14.9 (95% CI 11.1–20.4) months.

There were 156 patients (69%) in the RE population who had a PFS event; median PFS by IRC was 8.3 months (95% CI, 7-11.3). For OS, there were 96 patients (43%) who died at the data cut-off; the median OS was 26 months (95% CI, 21.4-NE).

CNS Efficacy
Among the 60% of patients who had CNS metastases at baseline, there were 136 patients who had measurable/non-measurable CNS disease and 50 patients who had measurable CNS disease; the pooled CNS ORR for these two groups of patients was 44% (95% CI, 36-53) and 64% (95% CI, 49-77), respectively.[25] Median CNS DOR was 11.1 months (95% CI, 7.1-not estimable) in patients with measurable CNS disease and 13.8 months (95% CI, 11-21.5) in patients with measurable/non-measurable CNS disease.[25]

Safety
Considering both trials, the mean dose intensity of alectinib was 94.1%. The most commonly occurring AEs of any grade were constipation (38%), fatigue (34%), peripheral edema (28%), myalgia (25%), nausea (23%), cough (21%), and headache (21%). Grade 3-5 AEs occurred in 40% of patients, and included dyspnea (4%) and elevated levels of blood creatine phosphokinase (4%), alanine transaminase (3%), and aspartate transaminase (3%). AEs led to study or treatment discontinuation in 6% of patients, and treatment dose modification or interruption 33% of patients.

There were seven patient deaths during both trials (two cases of hemorrhage, and one case each of dyspnea, endocarditis, intestinal perforation, pulmonary embolism, and unspecified cause), of which two were considered related study treatment (hemorrhage and intestinal perforation).

Table 16: Baseline patient characteristics of the pooled population of patients from trials NP28761 and NP28673.[24]

Baseline Characteristics	NP28761 (n=87)	NP28673 (n=138)	Pooled Population (n=225)
Median age (range) in years	54 (29-79)	52 (22-79)	53 (22-79)
Sex, n (%)			
Male	39 (45)	61 (44)	100 (44)
Female	48 (55)	77 (56)	125 (56)
ECOG PS, n (%)			
0	30 (34)	61 (44)	74 (33)
1	48 (55)	81 (59)	129 (57)
2	9 (10)	13 (9)	22 (10)
Race, n (%)			
White	73 (84)	93 (67)	166 (74)
Asian	7 (8)	36 (26)	43 (19)
Other	3 (3)	4 (3)	7 (3)
Black/African American	3 (3)	1 (0.2)	4 (2)
Multiple	1 (1)	0	7 (3)
Unknown	0	3 (2)	1 (0.4)
American Indian/Alaska native	0	1 (0.7)	1 (0.4)
CNS metastases, n (%)			
Yes	52 (60)	84 (61)	136 (60)
No	35 (40)	54 (39)	89 (40)
Histological subtype, n (%)			
Adenocarcinoma	82 (94)	133 (96)	215 (96)
Other	5 (6)	5 (4)	10 (4)
Prior chemotherapy, n (%)			
Yes	64 (74)	110 (80)	174 (77)
No	23 (26)	28 (20)	51 (23)
Crizotinib + prior therapies, n (%)			
Crizotinib only	23 (26)	28 (20)	51 (23)
+1 therapy	0	52 (38)	52 (23)
+2 therapies	19 (22)	16 (12)	35 (16)
+3 therapies	18 (21)	17 (12)	35 (16)
+4 therapies	14 (16)	16 (12)	30 (13)
+5 therapies	8 (9)	4 (3)	12 (5)
≥6 therapies	5 (6)	5 (4)	10 (4)
Smoking status, n (%)			
Active smoker	0	3 (2)	3 (1)
Past smoker	33 (38)	39 (28)	72 (32)
Never smoker	54 (62)	96 (70)	150 (67)

Abbreviations: CNS – central nervous system; **ECOG** – Eastern Cooperative Oncology Group; **PS** – performance status.

Source: Adapted from table 1 in the Journal of Thoracic Oncology, Yang JC, et al., pooled systemic efficacy and safety data from the pivotal phase II studies (NP28673 and NP28761) of alectinib in ALK-positive non-small cell lung cancer, October 2017.[24] Copyright ©2017 Elsevier. DOI: https://doi.org/10.1016/j.jtho.2017.06.070; under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND)

Table 17: Outcomes in the pooled population of patients from trials NP28761 and NP28673.[24,25]

OUTCOMES	Pooled Population (n=225)	
Data cut-off date	NP28761 – January 22, 2016 (n=87) NP28673 – February 1, 2016 (n=138)	
Efficacy[24]		
Median follow-up in months (range)	18.8 (0.6-29.7)	
Response evaluable	189	
ORR by IRC (RECIST), % (95% CI)	51 (44-59)	
CR, n (%)	97 (51)	
PR, n (%)	0	
SD, n (%)	52 (28)	
DOR, median in months	14.9 (11.1-20.4)	
DCR, n (%)	79 (72-84)	
PFS events, n (%)	156 (69)	
PFS, median in months (95% CI)	8.3 (7.0-11.3)	
OS events	96 (43)	
OS, median in months (95% CI)	26 (21.4-NE)	
CNS Efficacy[25]		
Patient subgroups	Measurable CNS metastases (n=50)	Measurable/non-measurable CNS metastases (n=136)
CNS ORR, n (%, 95% CI)	32 (64, 49-77)	60 (44, 36-53)[a]
CR, n (%)	11 (22)	39 (29)[a]
CNS DCR, n (%, 95% CI)	45 (90, 78-97)	117 (86, 79-91)
CNS DOR, median in months (95% CI)	11.1 (7.6-NE)	13.8 (11-21.5)
Safety		
Selected, any grade AEs, n (%)[b]		Grades 3-5
Patients with ≥1 AE	219 (97)	NR (40)
Constipation	85 (38)	NR
Fatigue	76 (34)	NR
Peripheral edema	63 (28)	NR
Myalgia	57 (25)	NR
Nausea	51 (23)	NR
Cough	48 (21)	NR
Headache	47 (21)	NR
Diarrhea	42 (19)	NR
Dyspnea	40 (18)	NR (4)
Increased aspartate transaminase	36 (16)	NR (3)
Anemia	33 (15)	NR
Weight increased	33 (15)	NR
Asthenia	32 (14)	NR
Upper respiratory tract infection	32 (14)	NR
Vomiting	32 (14)	NR
Increased alanine transaminase	31 (14)	NR (3)
Rash	30 (13)	NR
Back pain	28 (12)	NR
Increased bilirubin level	27 (12)	NR
Increased blood creatine phosphokinase level	26 (12)	NR (4)
AEs leading to withdrawal from study	14 (6)	
AEs leading to withdrawal from treatment	14 (6)	
AEs leading to dose modification/interruption	75 (33)	
SAE leading to withdrawal from treatment	9 (4)	
SAE leading to dose medication/interruption	22 (10)	
Abbreviations: AEs – adverse events; **CI** – confidence interval; **CNS** – central nervous system; **CR** – complete response; DCR – disease control rate; **DOR** – duration of response; **IRC** – independent review committee; **ORR** –		

objective response rate; **OS** – overall survival; **PFS** – progression-free survival; **PR** – partial response; **SAE** – serious adverse events; **SD** – stable disease.
Notes: [a] – Non-measurable disease response can only be classified as CR or non-CR/non-progressive disease (PD), or PD. [b] – AEs with an incidence rate higher than 10% in the pooled phase 2 studies.

Summary

Overall, the pooled analysis efficacy results (ORR, PFS, CNS ORR) are consistent with the results of the phase 3 ALUR trial,[1] and the pooled safety results demonstrate a similar safety profile to that observed in the alectinib treatment group of ALUR.

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 on alectinib for NSCLC. 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.

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.

The Lung Clinical Guidance Panel is comprised of three clinicians. 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 July 2017, **Embase** 1974 to 2017 August 31, **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

#	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).ti,ab,ot,kf,kw,hw,rn,nm.	1056
2	1 use ppez	253
3	1 use cctr	36
4	*Alectinib/	211
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.	689
6	or/4-5	694
7	6 use oemezd	415
8	6 and conference abstract.pt.	153
9	limit 8 to yr="2012 -Current"	150
10	7 not 8	265
11	2 or 3 or 10	554
12	remove duplicates from 11	317
13	9 or 12	464
14	limit 13 to english language	442

2. Literature search via PubMed

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

Search	Query	Items found
#3	Search #1 AND #2	8
#2	Search publisher[sb] OR 2017/08/28:2017/08/31[edat]	532174
#1	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]	220

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)

   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 Oncology (ESMO)
   http://www.esmo.org/

   Search: Alecensa (alectinib)
   - 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-) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (Sep 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 concept was Alecensa (alectinib).

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

The search is considered up to date as of January 4, 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. Two members 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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