CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Alectinib (Alecensaro) for Non-Small Cell Lung Cancer

May 4, 2017

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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) as monotherapy for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung carcinoma (NSCLC) who have progressed or are intolerant to crizotinib and have central nervous system (CNS) metastases. 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 the treatment of patients with ALK-positive locally advanced or metastatic NSCLC who have progressed or are intolerant to crizotinib and have CNS metastases conducted by the Lung Cancer Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on alectinib (Alecensaro) for the treatment of patients with ALK-positive locally advanced or metastatic NSCLC who have progressed or are intolerant to crizotinib and have CNS metastases, a summary of submitted Provincial Advisory Group Input on alectinib (Alecensaro) for the treatment of patients with ALK-positive locally advanced or metastatic NSCLC who have progressed or are intolerant to crizotinib and have CNS metastases, and a summary of submitted Registered Clinician Input on alectinib (Alecensaro) for the treatment of patients with ALK-positive locally advanced or metastatic NSCLC who have progressed or are intolerant to crizotinib and have CNS metastases, 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 ALK-positive locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib and have CNS metastases.

The appropriate comparators for alectinib in this setting include chemotherapy as second line treatment with whole brain radiation therapy (WBRT) or stereotactic radiation (SRS) therapy. The patient population is more narrow than the Health Canada approved indication in that market authorization has been granted with conditions (pending the results of studies to verify its clinical benefit) by Health Canada for patients with ALK-positive, locally advanced (not amenable to curative therapy) or metastatic NSCLC who have progressed on or are intolerant to crizotinib. The pCODR review only focuses on patients with ALK- positive, locally advanced or metastatic NSCLC who have progressed or are intolerant to crizotinib and have CNS metastases.

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

Trials

Two non-randomized, single-group, open-label phase 2 trials were identified that met the selection criteria of this review. Trials NP28761[1] and NP28673[2] both evaluated alectinib in patients with ALK-positive, locally advanced or metastatic NSCLC who progressed on or were intolerant to treatment with crizotinib, and were with or without CNS metastases. Both trials were multi-centred. Trial NP28761 was conducted in North America (26 sites in the US and one site in Canada) and trial NP28673 was an international trial (56 sites in 16 countries). The trials, which were very similar in design, applied the following patient eligibility criteria for study entry:

- Confirmed diagnosis of stage IIIB-IV, ALK-positive NSCLC determined by a FDA-approved FISH (fluorescence in situ hybridization) test
- Disease progression (per RECIST) while receiving crizotinib (with a one-week wash-out period)
- ECOG performance status of 0-2
- Previous treatment with chemotherapy for advanced/metastatic disease was permitted
- Measurable disease at baseline (per RECIST)
- Brain or leptomeningeal metastases were permitted, 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 trial start was not permitted

The primary outcome of both trials was overall response rate (ORR) by central independent review committee (IRC) using RECIST criteria. In trial NP28673 there were two primary endpoints: ORR by IRC in all patients and ORR by IRC in the subgroup of patients pre-treated with chemotherapy. The key secondary outcomes of both trials (for a complete list refer to section 6.3.2.1) included:

- Duration of response (DOR) by IRC
- Progression-free survival (PFS) by IRC
- Overall survival (OS)
- Central nervous system (CNS) ORR in patients with measurable disease at baseline
- CNS DOR by IRC
- Quality of life (QOL) measured by the EORTC quality of life questionnaire (QLQ)-C30 and LC-13 in trial NP28761
- Safety
- CNS ORR by IRC in patients with measurable or non-measurable metastases at baseline (exploratory)

Neither trial assessed the primary outcome (ORR by IRC) using an intent-to-treat (ITT) analysis since a percentage of patients in each trial, 21% (n=18) in trial NP28761 and 12% (n=16) in trial NP28673, were deemed not to have measurable disease upon IRC assessment. Therefore, the primary and some secondary efficacy analyses were carried out in a response-evaluable (RE) population. PFS, OS, and safety were the only outcomes evaluated by ITT. Subgroup analyses were pre-specified (for ORR by IRC) for chemotherapy naïve patients and those pre-treated with chemotherapy. The Submitter confirmed subgroup analyses were also pre-planned for age (<65 and ≥65), gender, race (white, Asian, other), ECOG status (0,1 and

2), and baseline CNS metastases (yes/no).[3] The results of these latter subgroup analyses were not reported in trial publications.

Trials NP28761 and NP28673 enrolled 87 and 138 patients, respectively; of those patients, 69 and 122, respectively, comprised the RE population in each trial. The distributions of demographic characteristics were similar between the two trials (NP28761 vs. NP28673), with the majority of patients being female (55% vs. 56%), white (84% vs. 67%), and never-smokers (62% vs. 70%). The median age of patients was approximately 53 years (54 years vs. 52 years). Almost all patients had metastatic disease (99% in both trials) and an ECOG status of 0 or 1 (90% vs. 91%). Lung (84% vs. 86%) and the CNS (60% vs. 61%) were the most common sites of metastasis. No patients in either trial had leptomeningeal metastases. CNS metastases were measurable in 18% (n=16) of patients in trial NP28761 and 25% (n=35) of patients in trial NP28673. Among patients with CNS metastases (measurable and non-measurable), 65% (NP28761) and 73% (NP28673) had received prior brain radiation, with 47% (NP28761) and 64% (NP28673) completing radiation more than six months prior to trial entry. The baseline characteristics of this patient subgroup were similar to the trial population in both trials. Both trials enrolled patients that had received crizotinib for approximately one year. The number of patients progressing on crizotinib was 31% (NP28761) and 20% (NP28673). The majority of patients in each trial had also been previously treated with chemotherapy (74% in NP28761 vs. 80% in NP28673).

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 in 28-day cycles in trial NP28673. Patients continued on alectinib until disease progression, unacceptable toxicity or withdrawal of consent. All patients were offered continued treatment with alectinib post-progression if it was deemed clinically beneficial to the patient. The Submitter confirmed that 49% and 52% of patients in NP28761 and NP28673 trials, respectively, continued to receive alectinib post-progression.[3] The median duration of treatment was 20 weeks in trial NP28761 and 27.1 weeks in trial NP28673. At the last update analysis of each trial, 66% of patients in trial NP28673 and 69% of patients in trial NP28761 had discontinued treatment, with 34% and 31% of patients, respectively, still alive on treatment.[3]

Key Outcomes

Both NP28761 and NP28673 trials are ongoing, and updated efficacy data continue to be published, primarily in abstract form. The most recent update analyses were performed after a median follow-up time of 17 months (data cut-off: January 22, 2016) in trial NP28761[4] and 21 months (data cut-off: February 1, 2016) in trial NP28673.[5] The key outcomes from these analyses are summarized in Table 1 and are described below.

Efficacy

All Patients

The primary endpoint of both trials, ORR by IRC, was defined as the proportion of patients achieving a best overall response of complete or partial response in the RE population by IRC based on RECIST criteria. An ORR greater than 35% was considered clinically relevant and statistically significant at the two-sided 5% significance level.[1,2]

In trial NP28761, the ORR by IRC was 52% (95% CI, 40-65%), which included 35 partial responses among 67 evaluable patients. The median DOR by IRC was 14.9 months (95% CI, 6.9-not estimable).

In trial NP28673, the ORR by IRC was 51% (95% CI, 42-60%), which included 62 partial responses among 122 evaluable patients. The median DOR by IRC was 15.2 months (95% CI, 11.2-24.9). In the subgroup of patients pre-treated with chemotherapy (n=96), the ORR by

IRC was 45% (95% CI, 35-55%). The analysis of this subgroup did not meet the pre-specified threshold for statistical significance as the lower boundary of the confidence interval included 35%.

In trial NP28761 (n=87), median PFS was 8.2 months and median OS was 22.7 months. In trial NP28673 (n=138), median PFS was 8.9 months and median OS was 26 months.

CNS Metastases (Measurable or Non-measurable) Patient Subgroup[3]
In trial NP28761, the ORR by IRC in this patient subgroup was 49% (95% CI, 32-65%), and the median DOR among the 19 patients with a response was 11.1 months (95% CI, 7.5-not estimable).

In trial NP28673, the ORR by IRC in this patient subgroup was 49% (95% CI, 37-61%) and the median DOR was 16.6 months (95% CI, 10.9-not estimable) among the 36 patients with a response.

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

CNS Efficacy

CNS Metastases (Measurable) Patient Subgroup
In trial NP28761,[4] 16 patients (18%) had measurable CNS metastases at baseline and include 11 patients previously treated with brain radiation. The CNS ORR by IRC for this patient subgroup was 75% (48-93%); four complete responses and eight partial responses contributed to the CNS ORR. The median CNS DOR was 11.1 months (95% CI, 5.5-NE).

In trial NP28673,[5] 35 patients (25%) had measurable CNS metastases at baseline and include 23 patients previously treated with brain radiation. The CNS ORR for this patient subgroup was 59% (41-75%); seven complete responses and 13 partial responses contributed to the CNS ORR. The median CNS DOR was 11.1 months (7.1-NE).

CNS Metastases (Measurable or Non-measurable) Patient Subgroup
In trial NP28761,[4] the CNS ORR was 40% (95% CI, 27-55%) in 52 patients with measurable or non-measureable CNS metastases, with 13 complete responses and 8 partial responses contributing to the CNS ORR. The median DOR in this patient subgroup was 15.5 months (95% CI, 11.1-21.5).

In trial NP28673,[5] the CNS ORR was 46% (95% CI, 36-58%) in 84 patients, with 26 complete responses and 45 partial responses (or stable disease) contributing to the CNS ORR. The median DOR was 11.2 months (95% CI, 9.1-not estimable).

Quality of Life

Patient–reported QOL was evaluated in the NP28761 trial[1] and was measured using the EORTC QLQ-C30 and the QLQ-LC-13. For both instruments, assessments were completed at baseline and every six weeks. A mean change from baseline of 10% or greater is considered the minimal clinically important difference (MCID), with lower scores indicative of improvement in symptoms and side effects.

The NP28761 trial publication reported very limited data on QOL outcomes, which included mean changes from baseline (provided in graph form) starting at week six to last visit at week 66, for the QLQ-C30 global health status and fatigue symptom scales. Mean baseline scores were not reported for either of these scales, nor were data reported for the remaining scales that comprise the QLQ-C30 or all scales comprising the QLQ-LC-13. For the QLQ-C30 global health status scale, the trial reported a MCID at the first assessment (week six), which was

maintained for at least two consecutive visits and generally sustained until the end of treatment. For the QLQ-C30 fatigue symptom scale, a MCID was reported at all assessment time points. For both scales patient compliance was approximately 93% at week six but declined substantially over time. [1]

Harms

Adverse Events

Overall, alectinib was well tolerated in both trials.[1,2] The majority of AEs were low grade, with the most common AEs (NP28761 vs. NP28673) being grade 1-2 constipation (36% vs. 33%), fatigue (33% vs. 26%), peripheral edema (23% vs. 24%), and myalgia (24% vs. 22%). The incidence of grade 3-4 AEs was below 5% for all AEs in both trials with the exception of elevations in blood creatine phosphokinase (8%), alanine aminotransferase (6%), and aspartate aminotransferase (5%) in trial NP28761. Serious AEs were reported in 15% of patients in trial NP28761 and 16% of patients and in trial NP28673.[3] The number of patients discontinuing treatment due to AEs was 2% and 8%, respectively.

The Submitter provided updated AE data for the most recent analysis of each trial.[3] These data appeared very similar to the AE data presented at primary analysis. In trial NP28671, grade ≥3 AEs were reported in 41% of patients, and AEs led to dose modifications or interruptions, reductions, or withdrawal from study in 28%, 18%, and 2% of patients, respectively. In trial NP28673, the incidence of grade ≥3 AEs was not reported. AEs led to dose modifications or interruptions, reductions, and withdrawal from trial in 25%, 11%, and 9% of patients, respectively.

A summary of grade 3-5 AEs by baseline CNS metastases status, provided by the Submitter, showed a similar AE profile between patients with and without CNS metastases at baseline.[3]

Deaths

Four deaths were reported in trial NP28761.[3] One patient on anticoagulants died from hemorrhage, which was judged related to study treatment. The second patient had disease progression and a history of stroke, which was not judged related to study treatment. The cause of death in the remaining two patients was unknown.

Eight deaths were reported in trial NP28637,[3] of which five were attributed to AEs including dyspnea, pulmonary embolism, hemorrhage, endocarditis, and an intestinal perforation judged related to study treatment. The cause of death in the remaining three patients was unknown.

Table 1: Highlights of Key Outcomes from Trials NP28761 and NP28673.

Key Outcomes	Shaw 2016 (NP28761)[3,4]	Ou 2016 (NP28673)[3,5]
Date of last update analysis	January 22, 2016	February 1, 2016
Median follow-up in months	17.0	21.0
Primary Outcome		
ORR by IRC in all patients	n=67	n=122
n	35	62
% (95% CI)	52 (40-65)	51 (42-60)
ORR by IRC in patients treated with chemotherapy	NA	n=96
n	NA	43
% (95% CI)	NA	45 (35-55)
Key Secondary Outcomes		
DOR by IRC	n=35	n=62
median in months (95% CI)	14.9 (6.9-NE)	15.2 (11.2-24.9)

Key Outcomes	Shaw 2016 (NP28761)[3,4]	Ou 2016 (NP28673)[3,5]
PFS by IRC	n=87	n=138
median in months (95% CI)	8.2 (6.3-12.6)	8.9 (5.6-12.8)
OS	n=87	n=138
median in months (95% CI)	22.7 (17.2-NE)	26.0 (21.5-NE)
CNS Key Secondary Outcomes		
Measurable Metastases	n=16	n=34
CNS ORR by IRC	n=16	n=34
n	12	20
%, 95% CI	75 (48-93)	59 (41-75)
CNS DOR by IRC	n=12	n=20
median (95% CI)	11.1 (5.5-NE)	11.1 (7.1-NE)
PFS by IRC	n=16	n=34
median (95% CI)	13.2 (8-NE)	9.2 (4.3-16.8)
OS	n=16	n=34
median (95% CI)	NE	26.0 (17.4-NE)
Measurable/Non-Measurable Metastases	n=52	n=84
CNS ORR by IRC	n=52	n=84
n	21	39
% (95% CI)	40 (27-55)	46 (36-58)
CNS DOR by IRC	n=21	n=39
median (95% CI)	15.5 (11.1-21.5)	11.2 (9.1-NE)
PFS by IRC	n=52	n=84
median (95% CI)	8.4 (6.1-16.3)	7.4 (5.6-15.4)
OS	n=52	n=84
median (95% CI)	22.7 (17.2-NE)	26.0 (21.7-NE)
Harms Outcome, n (%)		
Grade ≥3	NR (41)	NR
AE (any grade)	84 (97)	135 (98)
WDAE	2 (2)	12 (9)

Abbreviations: AE - adverse event, CI = confidence interval, CNS – central nervous system; DOR – duration of response; IRC – independent review committee; NA – not applicable; ORR – objective response rate; OS – overall survival; NR - not reported, PFS – progression-free survival; WDAE - withdrawal due to adverse event.

Limitations

Overall, the results of the alectinib trials are limited by the lack of randomized, comparative efficacy data for alectinib compared to an appropriate comparator (e.g. ceritinib, chemotherapy). The non-comparative design makes attributing efficacy, QOL and safety events to alectinib difficult since all patients received the same treatment. The two trials were also open-label and are therefore prone to different biases (e.g., patient selection and performance bias) that can affect the internal validity of a trial. Attempts were made in both trials, however, to mitigate such biases by using an IRC to assess response outcomes using standardized criteria.

Efficacy analyses of the primary endpoint, ORR by IRC, as well as other key secondary outcomes should have been analyzed by ITT as specified in the trial protocols and not the RE population. Post-hoc amendments to the statistical analysis plans (SAP) can compromise the integrity and interpretation of trial results.

Efficacy data on the funding population of ALK-positive NSCLC patients with CNS metastases are limited in the alectinib trials, as small numbers of patients had measurable CNS disease at baseline [16 patients (18%) in trial NP28761; and 35 patients (25%) in trial NP28673], and efficacy data on the larger subgroup of patients with measurable or non-measurable CNS metastases were based on unplanned exploratory analyses in both trials. As such, the results of these analyses should be interpreted with caution.

QOL outcomes in the NP28761 trial were difficult to interpret without a comparator treatment group and due to the open-label design. Patient compliance in completing questionnaire assessments was also poor. Further, both published and unpublished data made available to pCODR, were limited by incomplete reporting and short length of follow-up. [1] Given these factors, the QOL findings should be interpreted with caution.

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

From a patient's perspective, receiving a diagnosis of lung cancer can be devastating and specifically stage IV lung cancer patients experience the highest burden of symptoms. Symptoms such as fatigue or lack of energy for caregivers and patients was hardest to manage, and had the highest impact on 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, the options for patients are radiation or to go back to chemotherapy. According to LCC, stereotactic radiation can be used if patients have limited lesions. However, most patients may face whole brain radiation, which may carry significant risk of permanent cognitive damage. While treatments such as crizotinib seem to provide a good quality of life, and shrink or control their lung cancer. However, respondents reported needing another option when crizotinib 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. Respondents reported an uncertainty with differentiating between side effects from alectinib or from some other previous treatments. 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.

Provincial Advisory Group (PAG) Input

Input was obtained from the seven 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:

- Lack of comparative data
- Clarification of funding request on whether alectinib is for patients who have developed CNS metastasis while on crizotinib or for any patients with ALK+ NSCLC who have CNS metastasis and have previously been treated with crizotinib
- Indication creep into first-line treatment, particularly for patients who already have CNS metastasis upon diagnosis

Economic factors:

- Place in therapy

Registered Clinician Input

According to the Registered Clinician Input, alectinib would fill a gap in therapy for a very small number of patients with ALK positive lung cancer with brain metastases. Key benefits identified are that alectinib is an oral take-home medication that would relieve hospital resources in regards to chemotherapy and radiation services. Based on the clinicians' limited clinical experience with alectinib, it appears to be efficacious and well tolerated.

Summary of Supplemental Questions

No supplementary questions were identified during the development of this review.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

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

Table 2: Assessment of generalizability of evidence for alectinib in patients with ALK-positive, advanced/metastatic NSCLC who have progressed on or are intolerant to crizotinib.[1,2]

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	Stage of disease	In both trials, 99% of patients had stage IV disease and 1% of patients had stage IIIB disease.	Is this representative of how patients present in Canadian practice? Does this limit the interpretation of the trial results to stage IV patients?	The use of alectinib should be limited to patients with stage IV disease.
	ECOG Performance Status	Both trials limited eligibility to ECOG PS 0-2. Trial NP28761, n (%): ECOG 0: 30 (35) ECOG 1: 48 (55) ECOG 2: 9 (10) Trial NP28673, n (%): ECOG 0: 44 (32) ECOG 1: 181 (59) ECOG 2: 13 (9)	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.)?	The majority of patients enrolled in the trials had an ECOG PS of 0-1. Data on the efficacy and safety of alectinib in patients with an ECOG PS >1 was limited in both trials. 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 $\geq$2 may be appropriate and should be left to the discretion of the treating oncologist.
	Age	Both trials enrolled patients aged 18 years or older. The median age of patients was: Trial NP28761: 54 years Trial NP28673: 52 years The proportion of patients over age 65 is not known, but is likely small as this malignancy is more common in younger ALK-positive NSCLC patients.	Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?	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 in the trials is unknown. 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.

	Organ dysfunction	Both trials limited eligibility to patients with adequate hematological, renal and liver function.	Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	The use of alectinib should be limited to patients with adequate hematological, renal and liver function as determined by the treating oncologist.
	Ethnicity or Demographics	Trial NP28761 was conducted in North America (US and Canada); however, only one patient was enrolled from the one participating Canadian centre. Trial NP28673 was a global trial that enrolled patients from 16 countries: Australia, Belgium, Denmark, France, Germany, Italy, Luxenberg, Netherlands, Russia, Singapore, South Korea, Spain, Sweden, Taiwan, UK, and USA.	If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting?	Although only one patient was enrolled from the one participating Canadian centre, the CGP agrees that the ethnicity of the study populations would be comparable to the Canadian population and therefore the results of the trial would be generalizable to the Canadian population.
	Biomarkers	Both trials enrolled patients who had ALK-positive NSCLC ascertained by an FDA-approved FISH test.	Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the trial applicable to all subgroups equally? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?	Determination of ALK positivity in Canada is standard. It uses an immunohistochemistry test to screen advanced non-squamous NSCLC.

Intervention	Line of therapy	Both trials evaluated alectinib in patients who progressed on previous lines of therapy (chemotherapy and/or crizotinib). Both trials allowed for the inclusion of patients who had been previously treated with crizotinib and chemotherapy for advanced and/or metastatic disease. All patients were treated with crizotinib for approximately one year with 31% (NP28761) and 20% (NP28673) of patients who progressed on crizotinib. The majority of patients in each trial had been previously treated with chemotherapy (75% in NP28761 and 80% in NP28673).	Are the results of the trials generalizable to patients who have: • developed CNS metastasis while on crizotinib only • CNS metastasis and previously been treated with crizotinib • No CNS metastases • CNS metastasis and who have 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?	The CGP agree that in clinical practice, clinicians will want to treat with alectinib after failure of crizotinib, which is the current first-line treatment option. The CGP agree that alectinib may be effective in managing CNS disease. This includes those with CNS metastasis at initial presentation, those who developed CNS disease on first-line crizotinib or other systemic therapies. The CGP agree that they would treat patients with CNS metastases with alectinib before chemotherapy, due to the lack of efficacy of chemotherapy in CNS disease. However, the CGP acknowledge the absence of direct evidence to conclude on the efficacy of alectinib compared to chemotherapy. The CGP agree that in clinical practice for patients with new isolated CNS metastases or those whose CNS disease progresses, clinicians will want to treat with SRS therapy, followed by alectinib and then followed by WBRT. If targeted therapy (i.e., crizotinib) and SRS were not available to patients, then treatment with alectinib should be considered. The CGP acknowledges the absence of evidence to conclude on the efficacy of alectinib compared to chemotherapy. However, it is the opinion of the CGP that in practice, clinicians will treat with chemotherapy likely following failure on alectinib. Both trials 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.

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 the US, 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	The submitter confirmed that in both trials participating centres included both academic and community-based treatment centres.	If the trial was conducted only in academic centres are the results applicable in the community setting?	The CGP agree that the locations of participating centres would be comparable to Canadian treatment centres and therefore the results of the trial would be generalizable to the broader Canadian population.

	Supportive medications, procedures, or care	In trial NP28761, supportive care included: •Anti-emetics, anti-diarrheas, or laxative bowel regimen consistent with standard of care •Red blood cell transfusions as clinically indicated •Bone marrow colony-stimulating factors as clinically indicated There were no supportive care guidelines for trial NP28673.	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 in both trials. 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 trial NP28761 are generalizable to the majority of Canadian treatment centres.
Abbreviations: ALK+ – anaplastic lymphoma kinase positive; CNS – central nervous system; CGP – Clinical Guidance Panel; ECOG PS - Eastern Cooperative Oncology Group Performance Status; NSCLC – non-small cell lung cancer; FDA – Food and Drug Administration; SRS – stereotactic radiosurgery; WBRT – whole brain radiation therapy; FISH - Fluorescence in situ hybridization; AEs – adverse events				

1.2.4 Interpretation

Two non-randomized phase 2, multinational, open label, single arm trials, NP28761 and NP28673, evaluated the efficacy and safety of alectinib 600 mg orally twice daily in ALK mutation positive NSCLC, and were included in the pCODR systematic review. Eligibility criteria for both studies were nearly identical. All subjects had to have ALK mutation positive NSCLC, were previously treated with crizotinib and had progression of disease on treatment with that agent, and were performance status ECOG 0-2. Those with brain or leptomeningeal disease were allowed on study as long as those sites were asymptomatic and stable. The objective of this review is to assess 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 and who have CNS metastases. As patients without CNS metastases are outside of the scope of this review, the review focuses on the treatment of patients with CNS metastases. While the design of the trials affects the generalizability of the results, focusing on the subgroup of patients with central nervous system disease is another major limiting factor in interpreting the data. Therefore, the review needed to consider whether the overall trial results (including patients with CNS metastases as well as patients without CNS metastases) would be generalizable to a subgroup of patients who have CNS metastases.

The primary endpoint for both studies was objective response rate (ORR) assessed by independent radiologic review, although on study investigator assessment of response determined management. Secondary endpoints included duration of response, progression-free and overall survival, and, in NP28761, quality of life. Separate analyses were performed for those with measurable CNS disease and measureable or non-measureable CNS disease, with regards to CNS response rate, CNS duration of response, and CNS progression rate. Efficacy data on the funding population of ALK-positive NSCLC patients who have progressed on or are intolerant to crizotinib with CNS metastases are limited in the trials, as small numbers of patients had measurable CNS disease at baseline in both trials and efficacy data on the larger subgroup of patients with measurable or non-measurable CNS metastases were based on unplanned exploratory analyses. As such, the interpretation of such results should be done with caution.

Effectiveness

CNS Efficacy

In NP28761, 16 patients (18%) had measurable CNS metastases at baseline. The CNS ORR was 69% (95% CI, 41-89%), with an updated analysis demonstrating a CNS ORR of 75% (95%CI, 41-75%). The median CNS DOR at the last updated analysis was 11.1 months (95%CI, 5.5-NE).

In NP28673, 35 patients (25%) had measurable CNS metastases at baseline. The CNS ORR was 56% (95% CI, 38-73%), with an updated analysis demonstrating a CNS ORR of 59% (95%CI, 48-93%). The median CNS DOR at the last updated analysis was 11.1 months (95%CI, 7.1-NE).

At 12 months, the cumulative incidence of CNS progression events was 22% (n=18/87) in NP28761, and 24% (32/138) in NP28673. The cumulative incidence of non-CNS progression events at 12 months was 29% (n=23/87) and 31% (43/138), respectively.

An exploratory outcome in both trials was to assess CNS ORR activity in patients with measurable and non-measureable disease. In trial NP28761, at the updated analysis, the CNS ORR was 40% (95% CI, 27-55%) in 52 patients with 13 complete responses and 8 partial responses contributing to the CNS ORR. The median DOR in this patient subgroup was 15.5 months (95% CI, 11.1-21.5). In trial NP28673, at the updated analysis, the CNS ORR was 46% (95% CI, 36-58%) in 84, with 26 complete responses and 45 partial responses (or stable disease) contributing to the CNS ORR. The median DOR was 11.2 months (95% CI, 9.1-not estimable).

Overall Efficacy

In NP2871, the ORR for the full trial population was 48% (95%CI, 36-60%), with an updated analysis demonstrating an ORR of 52% (95%CI, 40-65%). In NP28673, the ORR for the full trial population was 49% (95%CI, 40-58%), with an updated analysis demonstrating an ORR of 51% (95%CI, 42-60%).

In the updated analyses, the median DOR was 14.9 months (95% CI, 6.9-not estimable) among the 35 partial responders in NP28761, and 15.2 months (95% CI, 11.2-24.9) among the 62 partial responders in NP28673.

In NP28761 (n=87), median PFS was 8.2 months and median OS was 22.7 months. In NP28673 (n=138), median PFS was 8.9 months and median OS was 26 months.

In the CNS metastases patient subgroup, in trial NP28761, the ORR by IRC was 49% (95% CI, 32-65%) and in trial NP28673, the ORR by IRC was 49% (95% CI, 37-61%) at the updated analyses.

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

Quality of Life

Quality of life (QOL) was assessed in only one trial (NP28761) using the EORTC QLQ-C30 and QLQ-LC13, however there was very limited data reported and poor compliance in completing questionnaire assessments.[1] For the QLQ-C30 global health status scale, the trial reported an improvement in overall health status from baseline of at least 10% at the first assessment, which was maintained for at least two consecutive visits and generally sustained until the end of treatment. For the QLQ-C30 fatigue symptom scale, an improvement in fatigue from baseline of at least 10% was reported at all assessment time points. In the CNS metastases patient subgroup, over the course of treatment, the mean changes from baseline in overall QOL status was generally similar to the patients without CNS metastases.

Safety

The incidence of grade 3 or 4 adverse events (AEs) was below 5% in both NP28761 and NP28673 with the exception of elevations in blood creatine phosphokinase (8%), alanine aminotransferase (6%), and aspartate aminotransferase (5%) in trial NP28761.The most frequent of these were elevations in the creatinine phosphokinase, transaminases and dyspnea. Serious AEs were reported in 15% of patients in NP28761, and 16% in NP28673. The number of patients discontinuing treatment due to AEs was 2% and 8%, respectively. A similar AE profile was seen between patients with and without CNS metastases at baseline.

Burden of Illness

The annual incidence of NSCLC is high. While the ALK positive population represents a small minority of all advanced or metastatic NSCLC, well validated ALK mutation testing is now established in the routine evaluation of NSCLC. Directed therapy based on testing of potential driver mutations is now standard of care in management of advanced or metastatic NSCLC. Furthermore, CNS involvement is a common occurrence in patients with ALK positive disease. The impact of neurologic symptoms on physical, role and social functioning is not inconsequential.

Need

In patients who develop CNS metastases or whose CNS metastases progress while receiving crizotinib (or who are intolerant to crizotinib), there are no effective systemic therapies available. Therefore, in patients with CNS disease, effective drug therapies to complement existing management strategies such as radiotherapy and neurosurgery are sorely needed. The availability of a reliable method to

detect the subpopulation of ALK positive patients is an important factor supporting a role for alectinib in the treatment of this subset of NSCLC. Of particular benefit is access to a therapy that is expected to be more efficacious and relatively less toxic than standard chemotherapy. The impact of agents such as alectinib on patients and their families is highlighted in the statements in the Patient Advocacy Group Input.

1.3 Conclusions

The conclusion of the Clinical Guidance Panel is that there may be a net overall clinical benefit to alectinib in the treatment of ALK mutation positive patients with NSCLC with CNS metastasis who have disease progression on crizotinib, based on subgroup analyses of the currently limited evidence. Alectinib may have superior response rates, PFS, and tolerability profile when considering historical data for standard second line chemotherapy.

The Clinical Guidance Panel acknowledges that there is a paucity of data from randomized clinical trials to clearly establish the superiority of alectinib to standard chemotherapy in the ALK inhibitor pretreated population; the results of such trials are awaited. The CGP considered the consistency of antitumour activity and superior tolerability of alectinib in the overall ALK inhibitor-pretreated population, in the trials available to date, as well as the pattern by which it targets the driver mutation. Despite the even more limited analyses regarding patients with CNS metastases, the CGP considered that the subgroup results for patients with CNS metastases were at least consistent with the overall trial results. Therefore, the CGP agreed that alectinib may satisfy the need for a drug therapy that is effective in managing CNS disease. This includes those with CNS metastasis at initial presentation, those who developed CNS disease on first-line crizotinib or other systemic therapies.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

In Canada, 2 out of every 5 people are expected to develop cancer in their lifetime. Furthermore, 1 out of 4 Canadians are expected to die of cancer. Lung cancer is the second-most commonly diagnosed cancer in both men and women, and is the leading cause of cancer deaths in Canada. Non-small cell lung cancers (NSCLC) are the most common type of lung cancers, comprising 85% of lung cancers. In 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.[7] 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. Approximately 4 % of all NSCLC have a 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.[8] Furthermore, these cancers tend to be quite sensitive to inhibitors of the ALK fusion protein. Finally, 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.[9] The development of brain metastases is associated with deterioration of quality of life (QOL) and shortened survival.[10-12] The development of brain metastases may be the initial or only site of treatment failure in those receiving crizotinib, a finding potentially related to the poor CNS penetrance of this drug.[13] Control of CNS disease thus is an important consideration in ALK-positive NSCLC.

Ceritinib has shown activity in the CNS, with investigator-determined response rates of between 19 and 39 %, depending on the study,[3,14] but this is based on relatively small numbers of patients. However, in studies of ceritinib, disease progression in the CNS occurred in 42% of patients, and was the sole site of relapse in 34%.[3] Both ceritinib and crizotinib are substrates for p-glycoprotein, which serves to pump drugs out of the CNS, thus also potentially explaining the low concentrations in the CNS of these agents.[15]

2.2 Accepted Clinical Practice

In patients with echinoderm microtubule-associated protein-like 4 (EML4)-ALK translocation, 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 III study that confirmed superior objective response rates [74% vs. 45%, (P<0.001)] and progression-free survival (PFS) [median 10.9 months vs. 7.0 months; hazard ratio for progression or death with crizotinib, 0.45; 95% confidence interval [CI], 0.35 to 0.60; P<0.001)] favouring crizotinib when compared to first-line platinum doublet chemotherapy; overall survival was not different between the two arms, likely due to the high rate of cross-over to crizotinib in the chemotherapy arm.[16] Crizotinib is continued in the absence of disease progression or unacceptable toxicity. However, resistance to crizotinib inevitably develops in the majority of patients. The second generation ALK inhibitor ceritinib has demonstrated ability to overcome resistance to crizotinib and is shown to provide durable responses and meaningful benefit in terms of progression free survival in both crizotinib resistant and crizotinib naive patients.[17] More recently, a press-release from Novartis has indicated that the first-line ASCEND-4 trial comparing ceritinib to chemotherapy (including

maintenance) was positive for the primary endpoint of progression-free survival suggesting that ceritinib may become a first-line treatment option.[18]

Alectinib is seeking funding approval for the treatment of those patients with ALK-positive NSCLC with CNS metastases that have previously received crizotinib and subsequently had progressive disease, or who were intolerant of crizotinib. The data suggests that brain metastases occur in a majority of patients with ALK-positive NSCLC at some point in their disease course. Thus the intended population represents about two-thirds of all patients with metastatic ALK-positive NSCLC.

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.[7] 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. Assuming that CNS metastases develop in two-thirds of ALK-positive NSCLC patients at some point in their disease course, this leads to an estimated 425 patients per year in Canada for whom treatment with alectinib may fit the requested funding criteria. 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.[19]

Alectinib has clinically meaningful activity in those patients whose disease has progressed on crizotinib. Phase II trials have shown independent review committee response rates of 47.8 % in study NP28716 (n=87 patients) and 49.2 % in study NP28673 (n=183). Both patients enrolled only those whose disease had progressed on prior crizotinib therapy; of the total, 60 % had CNS metastases at study entry. In updated analyses with longer follow-up, the median progression free survival seen on study NP28673 was 8.9 months (95% CI 5.6 – 11.3 months), which is also clinically meaningful, and similar to what is observed in ALK-positive, treatment naïve patients who receive crizotinib.

The Submitter commented on the pCODR Expert Review Committee's (pERC's) Initial Recommendation that the report estimated 650 patients with advanced ALK-positive NSCLC in Canada in 2015. The Submitter believes this to be an over estimate as it assumes that 100% of NSCLC patients are tested for the ALK rearrangement. The Submitter notes that an Ontario linked database study found that of patients diagnosed with advanced NSCLC only 70% have a consultation with a medical oncologist and are considered for ALK testing. (Sacher, A. et al. Cancer. 2015).

In response to the Submitter's feedback, the Clinical Guidance Panel considers the estimated numbers of patients with ALK positive NSCLC reasonable. The estimated number of approximately 650 cases considers the rising prevalence of new ALK positive cases as well as cases that may have been diagnosed at an earlier stage and then progressed to metastatic disease requiring testing. Furthermore, ALK testing uses an immunochemistry test to screen advanced non-squamous NSCLC and is considered standard practice in Canada.

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 who also have CNS metastases. However, the Health Canada indication is for those patients intolerant of or who have progressed following crizotinib, with no reference to the presence or absence of brain metastases. Thus, any second line patient could theoretically be prescribed the drug within indication. Furthermore, the results of the J-ALEX trial,

presented at the 2016 annual meeting of the American Society of Clinical Oncology, showed that in previously untreated ALK-positive NSCLC Japanese patients, alectinib was superior to crizotinib in progression-free survival. The results of the global ALEX study are expected in early 2017, and if positive, will likely lead to an immediate switch to alectinib as the preferred first-line treatment. Furthermore the data that suggests that alectinib can decrease the rate of the development of brain metastases may lead some prescribers to prefer this agent over other ALK-inhibitors currently available.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Lung Cancer Canada (LCC), provided input on alectinib (Alecensaro) for the treatment of non-small cell lung cancer (NSCLC), and their input is summarized below.

LCC gathered information from: (1) Faces of Lung Cancer Survey, (2) summary from previous submissions to the pCODR program (1st line crizotinib, 2nd line ceritinib, nivolumab and osimertinib), (3) environmental scan of online forums, and (4) an updated literature review.

Faces of Lung Cancer Survey was a national survey of lung cancer patients and caregivers conducted by Lung Cancer Canada in August 2015, which included 91 patients who have or have had lung cancer and 72 caregivers who are currently caring for or previously cared for patients living with lung cancer. With regards to the previous four submissions to pCODR submitted between 2015 and 2016, there were a total of 31 patients and 19 caregivers who were interviewed for these submissions. The patient and caregiver experiences on treatments and expectations from the four previous submissions have been included in this current submission. LCC also conducted an environmental scan of online forums to gather patient and caregiver experiences with alectinib. In total the opinions and perspectives of 22 patients and 19 caregivers, all with alectinib experience, have been included in this submission. To further probe and understand their alectinib experience, LCC conducted one-on-one interviews with three patients and one caregiver.

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. Symptoms such as fatigue or lack of energy for caregivers and patients was hardest to manage, and had the highest impact on 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, the options for patients are radiation or to go back to chemotherapy. According to LCC, stereotactic radiation can be used if patients have limited lesions. However, most patients may face whole brain radiation, which may carry significant risk of permanent cognitive damage. While treatments such as crizotinib seem to provide a good quality of life, and shrink or control their lung cancer. However, respondents reported needing another option when crizotinib 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. Respondents reported an uncertainty with differentiating between side effects from alectinib or from some other previous treatments. 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 groups. 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 Non-Small Cell Lung Cancer

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. When screening for ALK, LCC indicated that there may be as many as 30% of patients who may have ALK rearrangements if they never or are light smokers, have non-squamous NSCLC, and do not have EGFR mutations.

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 addition, LCC asserted that having brain metastases is a huge additional burden for lung cancer patients as it significantly diminishes their prognosis.

In one Canadian study, LCC noted that financial hardship was experienced by 41% of respondents in a Canadian study, and 69% of respondents believed their illness imposed a significant hardship on those close to them. LCC also found that lung cancer patients experience a high amount of stigma a social burden despite the fact that many who are diagnosed with lung cancer no longer or have never smoked.

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 Non-Small Cell Lung Cancer

LCC highlighted that when one line of treatment either begins to show progression or fails to respond, the only options for patients are radiation or to go back to chemotherapy. One respondent stated "*Chemo kicks the crap out of your body and mind. You feel absolutely horrible. (For a) half year of your life you feel like hell for a week, every three weeks. It's not for wimps!*" Another respondent noted "*I was thankful that I didn't need whole brain radiation*." Specifically, 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.

According to LCC, stereotactic radiation can be used if patients have limited lesions. However, most patients may face whole brain radiation (WBR), which may carry significant risk of permanent cognitive damage. Although WBR can be effective and there are fewer short term side effects than chemotherapy, the fear is that WBR will leave lasting long term effects such as memory loss, seizures, severe headaches and permanent damage to the brain. One respondent reported "*I opted not to have WBR because after doing my research I noticed that it's a harder treatment and the thought of having my whole brain radiated scared me*."

Respondents reported that receiving a diagnosis of lung cancer can be devastating. In particular, if you are told that due to metastasis to your brain you will have to undergo WBR. Respondents want to experience as much of life as possible but may suffer from memory loss or seizures or permanent cognitive impairment due to treatment; yet would still try to stay alive long enough to share milestones with your loved ones.

Other treatments such as crizotinib seem to provide a great quality of life while shrinking or controlling their lung cancer. However, respondents reported needing another option when crizotinib fails or cannot be tolerated.

3.1.3 Impact of Non-Small Cell Lung Cancer 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) The stigma unique to lung cancer places an additional emotional burden on caregivers.
LCC indicated that in the Faces of Lung Cancer Report (FOLCR), caregivers seemed to feel the stigma more acutely than patients. 38% of caregiver respondents felt that they had to advocate more strongly for their family members because of a lung cancer diagnosis. One caregiver respondent stated: *"Everyone assumes that lung cancer is self-inflicted and somehow people who get it deserve their lot. All I heard when people asked if my mom smoked was: "your mother deserves to die.' It is such an ignorant position and a stigma that doesn't affect any other disease that I can tell, including others with high lifestyle correlations (type II diabetes, heart disease etc.). It's frustrating that if my mom had been diagnosed with breast cancer, she would have been considered a hero, but because it was lung cancer, people don't even want to talk to me about it."*

2) Lung cancer is further handicapped by late diagnosis.
LCC noted that across Canada, most lung cancer is diagnosed in Stage IV [Statistics Canada, Canadian Cancer Registry] – potentially when the physical and emotional demands of caregiving are at their peak. The FOLCR indicates that 82% of caregivers said their caregiving experience was somewhat to very stressful.

3) Lung cancer carries a significant economic toll on household finances
LCC expressed that work and relationships often gave way to the challenge of providing care. 59% of caregiver respondents reduced the number of hours they worked and a further 8% of respondents quit their jobs. 50% of caregiver respondents reported a negative impact on their household financial situation.

4) High symptom burden of lung cancer is difficult to manage for both patients and caregivers.
According to LCC, one of the most common symptoms is fatigue or lack of energy. FOLCR also found that fatigue or lack of energy for caregivers and patients was hardest to manage, and had the highest impact on quality of life. Fatigue was also the top treatment side-effect that both patients (68%) and caregivers (43%) found most difficult to manage. This was followed by pain, concentration or memory issues and nausea – each with a combined patient and caregiver rating of 31%.

5) Anxiety and more anxiety when lung cancer turns into a waiting game.
LCC reported that the biggest stressor for caregivers is fear. The anxiety felt with a loved one's disease was the highest expressed by respondents (50%), more than any other impacts. This was reported by more caregivers (61%) than the patients themselves (42%) in the FOLCR. When a patient respondent was diagnosed with lung cancer and learned that it had spread to four lesions in his brain, one respondent said, "*my wife, who was 8 months pregnant, dropped to her knees. She*

thought I only had months to live." The fear and anxiety with lung cancer alone is stressful, but by adding wait times that fear and anxiety is compounded.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Alectinib

LCC indicated that 22 patients and 19 caregivers have experience with alectinib. To further probe and understand their alectinib experience, LCC also conducted one-on-one interviews with three patients and one caregiver.

1) Lung cancer patients have no time to wait
According to LCC, respondents who are made to wait for access to their treatment often express frustration and confusion. Respondents are understandably anxious; they do not have as much time as those with other forms of cancer and those with brain metastasis even have less than others with the same cancer. Many patients do their own research and are aware of treatments that have approval but remain unavailable to them or are required to wait for the results of a test. Respondents find it even more frustrating when they feel they have to advocate for treatment, or travel to another city to receive it. Two respondents who were interviewed noted that they had to endure "*abnormal delays*." Once they received alectinib, they expressed that it "*meant everything; I'm very grateful the trial was available, it breaks my heart that others can't get (alectinib).*"

For others, there is also anxiety while they wait, and hope that they will test positive for ALK and meet the requirements of a clinical trial. One respondent stated "*I am getting a little frustrated with the process of getting on alectinib. I want to get on it as soon as possible…the suffering has been out of the stratosphere*."

2) Alectinib works and 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!*"

3) Alectinib allows patients to avoid the permanent cognitive damage from WBR and treated their brain metastases
Brain metastases are a huge concern for lung cancer patients. Since brain metastases could be a common occurrence with lung cancer, respondents understand the implications of this diagnosis and are often quite frightened of them. Upon learning of her brain metastases, one respondent said "*I worked in the pharmaceutical industry, I knew the prognosis. I was devastated. My family was more devastated*." The majority of respondents that received radiation in the form of cyber knife, gamma knife, stereotactic radiation or WBR report that it has been effective at treating their brain metastases. Those who do not have to undergo radiation report being thankful and grateful. The main reason for the aversion is the fear of long term and even permanent side effects. Memory loss, seizures, headaches and changes to hair growth including hair loss are all reported from those that experienced WBR and the main reason to avoid WBR for those that opted not to receive it. Some even felt scared of progression and tumour growth during the "washout" period in between treatments. One respondent reported "*The requirement was a seven day washout from crizotinib…several tiny brain mets appeared. The washout was hard. Eight weeks (on alectinib), all brain lesions completely disappeared except for one. Alectinib is a great drug*."

Respondents who received alectinib reported relief that the treatment was effective not only for their lungs, but also for their brain tumours as well. One caregiver respondent reported that her friend's doctor wanted her to receive WBR but the patient did not, instead opting for alectinib. The respondent noted "*Her brain mets went from 2 to 10 small mets. They wanted to do WBR but she did not. Alectinib has controlled her cancer well and there are now only two small, not active, spots seen in the brain.*"

4) Alectinib was effective at treating the disease
Both patient and caregiver respondents have expressed surprise and delight at how well alectinib has controlled their disease. While a few respondents have mentioned that they experienced progression on alectinib, this was in the minority. Some of the respondents reported the following: "*shrinkage by 50% - 100%.*" "*No evidence of disease after the first two months on alectinib*!" "*I'm hoping to ride alectinib for a while.*" One caregiver respondent stated "*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 some treatments are only effective for a few months, 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.*"

5) The side effects of alectinib did not inhibit life
Of the 22 patient and 19 caregiver respondents who participated in this submission, eight respondents reported "no side effects" and 12 respondents reported "low side effects" from treatment with alectinib; while four respondents reported "moderate side effects" and eight respondents reported "high/intolerable side effects". The most commonly reported side effects were: fatigue, photosensitivity, constipation, weight gain/loss and edema. LCC submits that alectinib was tolerable for 24 out of 32 patients (including those that were reported indirectly via their caregivers). Even those who experienced moderate side effects expressed that it was "*worth it*," not only for extending their lives but by being another option and to "*buy time*" until another treatment is found.

6) Is this a side effect from alectinib or from something else?
In some cases, respondents reported there was an uncertainty with differentiating between side effects from alectinib or from some other previous treatments. The "washout" period between treatments not only left some respondents nervous of progression but made it difficult to distinguish if the side effects were a result of alectinib or not. One respondent indicated "*I am feeling good on alectinib. Getting off Xalkori – not so much. I had body aches and low grade fever for two weeks.*" Another respondent noted "*Going off of xalkori was very tough. Low grade fever, aches, pains, tired, chest congestion. Now on alectinib for five days and feeling fatigue and chest congestion. (I'm) wondering if this is withdrawl from xalkori or the alectinib?*" Even though ALK inhibitors are now a standard of care, LCC recommends patient education to address issues unique to this new treatment.

7) Alectinib allowed patients to experience life milestones and leave a legacy
LCC submits that one of the more important aspects of any treatment is that it allows a patient to experience the special events, such as, the birth of a child or grandchild, graduation, running in marathons or even just reaching a birthday. One respondent interviewed was diagnosed when his wife was 8 months pregnant. He went from simply hoping to stay alive long enough to see his daughter born, to relishing his time taking care of her as a stay-at-home dad. In his own words, alectinib "*has meant everything to me!*" The respondent's wife, parents and brothers are "*not worried any more. They are relieved. I look and act like a normal person. It's incredible*!" Other respondents reported having a more modest, but also touching achievements. One respondent stated

"*CT scan shows complete response. Wow! This Sunday is my birthday…I could not have wished for a better birthday gift than this. And a gift for my wife as well.*"

8) Alectinib gave patients the ability to believe in long-term benefits and to think long term
One respondent commented "*I was blessed with ALK targeted treatment; I hope they approve more (so I can) keep living." I'm grateful, and hopeful there is something in the works for when this stops.*" LCC reported that respondents have begun to think about their future, what they can accomplish and what they can do to continue living even beyond their current treatment while on alectinib. One respondent stated "*Starting with the other drugs (and then alectinib) gave us the most amount of time.*" Respondents reported that they hope as long as there are options, they can transition from one treatment to the next and stay ahead of their disease. These options help lung cancer patients believe that chronic stable disease can be a possibility.

9) Caregivers have the opportunity to believe in the future and line up new treatments
LCC found that caregivers often feel the stress of lung cancer more acutely than the patient. One respondent noted that "*My wife looks out for new treatments, she feels at ease and doesn't have to worry.*" It was reported that alectinib allows the patient to feel well; and this enables caregivers the time to consider other new treatments without the additional stress of their loved one's declining health.

10) The high price of lung cancer drug costs should not be a barrier to access
LCC submits that when you have cancer, perspective can be everything. One respondent 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, the respondent had paid approximately $10,000 CAD out-of-pocket. Even after she was able to obtain a prescription, the cost was approximately $18,000/month CAD. In total, she has paid more than $36,000 CAD for alectinib. The respondent noted that if she does not receive approval from her private insurance coverage, she will continue to pay next month, and indicated "*I'm not sure what will happen to those who can't afford it or have no insurance. I'm lucky.*" LCC asserts that 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.

3.3 Additional Information

Lung Cancer Canada indicated that ALK positive lung cancer patients with brain metastasis have no other option that specifically targets this condition. Chemotherapy is the only funded option upon progression on crizotinib. 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 seven 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:

- Lack of comparative data
- Clarification of funding request on whether alectinib is for patients who have developed CNS metastasis while on crizotinib or for any patients with ALK+ NSCLC who have CNS metastasis and have previously been treated with crizotinib
- Indication creep into first-line treatment, particularly for patients who already have CNS metastasis upon diagnosis

Economic factors:

- Place in therapy

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). At the time of the PAG input, ceritinib is not funded, nivolumab for NSCLC is not yet funded and pembrolizumab for NSCLC is undergoing review at pCODR.

PAG noted that the two phase 2 trials being submitted enrolled small number of patients and a subgroup of the patients enrolled had CNS metastasis. PAG is seeking data, if available, from phase 3 comparative trials comparing alectinib to intravenous chemotherapy. PAG noted that the lack of phase 3 trials provide comparative data and long term data on benefits and safety would be barriers to implementation

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 noted that the indication under review at Health Canada is broader and not restricted to patients with CNS metastasis as in the pCODR funding request. Thus, PAG is seeking clarification of the funding request and whether the eligible patient population are patients who have:

- developed CNS metastasis while on crizotinib only,
- CNS metastasis and previously been treated with crizotinib,
- ALK+ NSCLC and progressed on or are intolerant to crizotinib but do not have CNS metastasis
- CNS metastasis and who have received crizotinib first-line and subsequently treated with chemotherapy or immunotherapy

PAG identified there may be indication creep to first-line treatment:

- 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.
- There would be requests for alectinib in patients who already have CNS metastasis upon diagnosis. PAG noted that there is an ongoing phase 3 trial (ALEX trial) comparing alectinib to crizotinib in the first-line treatment and is seeking information on when this trial data would be submitted for review, as first-line treatment with alectinib would be out of scope of this current review.

If recommended for funding, PAG is seeking clarity on whether patients who have CNS metastasis and have started crizotinib but not further progressed would be eligible to switch to treatment with alectinib. PAG is also seeking data on whether patients who have been previously treated with ceritinib and with or without previous crizotinib therapy would be eligible for treatment with alectinib.

PAG is seeking guidance on sequencing of the oral targeted therapies, intravenous chemotherapy and immunotherapy 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).

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.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.6 Factors Related to Manufacturer

PAG is seeking comparative data on the long term benefits and safety of alectinib as compared to other available treatments for ALK+ NSCLC.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Four registered clinicians provided input as a joint submission on the behalf of the Medical Advisory Committee of Lung Cancer Canada. Their input is summarized below.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for Non-small Cell Lung Cancer

The oncologists providing input noted that the current treatment for ALK positive patients with brain metastases is systemic treatment with crizotinib (on public formulary) or ceritinib (not on public formulary) along with either stereotactic radiation or whole brain radiation (WBR).

The oncologists noted that the current therapeutic approach carries significant limitations and risks. Recent data from ESMO 2016 suggests that although ALK positive patients with brain metastases are still able to benefit from ceritinib and crizotinib, the magnitude of benefit in terms of ORR, DCR and PFS was significantly lower for patients with brain metastasis.

In addition, they noted that stereotactic radiation is only viable if there are limited metastases. WBR requires hospital resources and exposes the patient to the risk of long term memory loss and permanent cognitive side effects. Most patients that require WBR require 5-10 treatment sessions. Each session requires an hour of time. During this time the patients are immobilized with a vice-like device, making it a highly uncomfortable procedure. In addition, there is increasing data to show that WBR is not an effective option.

5.2 Eligible Patient Population

The oncologists providing input noted that ALK positive lung cancer represent 3-5 percent of the lung cancer population. Of those, it is estimated that 50% of patients may eventually develop brain metastases. Therefore, they noted that this indication and funding will only affect a very small number of patients.

5.3 Identify Key Benefits and Harms with Alectinib

The oncologists identified benefits of treatment with alectinib being an oral take-home medication and thus, relieves hospital resources in regards to chemotherapy and radiation services. Based on their limited clinical experience, it appears to be efficacious and well tolerated.

They noted that alectinib is currently positioned after crizotinib in patients with brain metastases. As these patients are ALK positive, their clinical outcome and quality of life tends to be better than those on traditional chemotherapy. ALK+ patients also tend to be younger. The permanent cognitive effects of whole brain radiation therapy on this younger population who may have a chance to live longer, will have a large negative impact on their quality of life.

5.4 Advantages of Alectinib Over Current Treatments

The oncologists providing input identified one randomized trial that has publically available data on alectinib. In the J-ALEX trial, alectinib was compared to crizotinib in untreated ALK+ Japanese NSCLC patients. In the subgroup with brain metastases at baseline the hazard ratio for progression free survival was 0.08 (95%CI, 0.01-0.61) dramatically favouring the patients treated with alectinib. However, it is

important to note that this randomized trial is outside of the scope for the funding request for this submission, since the funding request is for patients who have failed or are intolerant to crizotinib.

5.5 Sequencing and Priority of Treatments with Alectinib

The oncologists providing input indicated that alectinib will be used in those that have progressed on, or are intolerant to, crizotinib in those that have brain metastasis. It will replace whole brain radiation therapy or stereotactic radiation and chemotherapy as a second line of treatment.

5.6 Companion Diagnostic Testing

This treatment will not require additional companion diagnostics over current treatments.

5.7 Additional Information

The oncologists providing input identified that alectinib is a very well tolerated drug compared to crizotinib and ceritinib, which have significant risks of gastrointestinal toxicity including nausea, vomiting and diarrhea as well as liver dysfunction which affects patient's daily quality of life. The oncologists stated that alectinib has a completely different side effect profile than crizotinib and ceritinib with half the rate of severe adverse events which translated into half as many patients needing to stop drug due to toxic side effects in the one randomized trial (J-ALEX).

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 (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib and have central nervous system (CNS) metastases.

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.

Table 3. Study Selection Criteria.

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCTs, fully published non-comparative clinical trials evaluating alectinib**	Previously treated patients with ALK+, advanced or metastatic NSCLC who progressed on or are intolerant to crizotinib and CNS metastases Patient subgroups of interest: • No CNS metastases • CNS metastases and previously treated with crizotinib • Developed CNS metastases while on crizotinib only • CNS metastases and received crizotinib first-line and subsequently treated with chemotherapy or immunotherapy	Alectinib monotherapy at a dose of 600mg orally twice daily	• Platinum chemotherapy and pemetrexed • Ceritinib • WBRT*** • BSC	Primary: • PFS • **OS** • **QOL** • Safety Secondary: • ORR • DOR • CNS ORR • Disease control

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; **WBRT** – whole brain radiation therapy.

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.
***Currently indicated for ALK+ NSCLC patients with progressing CNS metastases.

6.3 Results

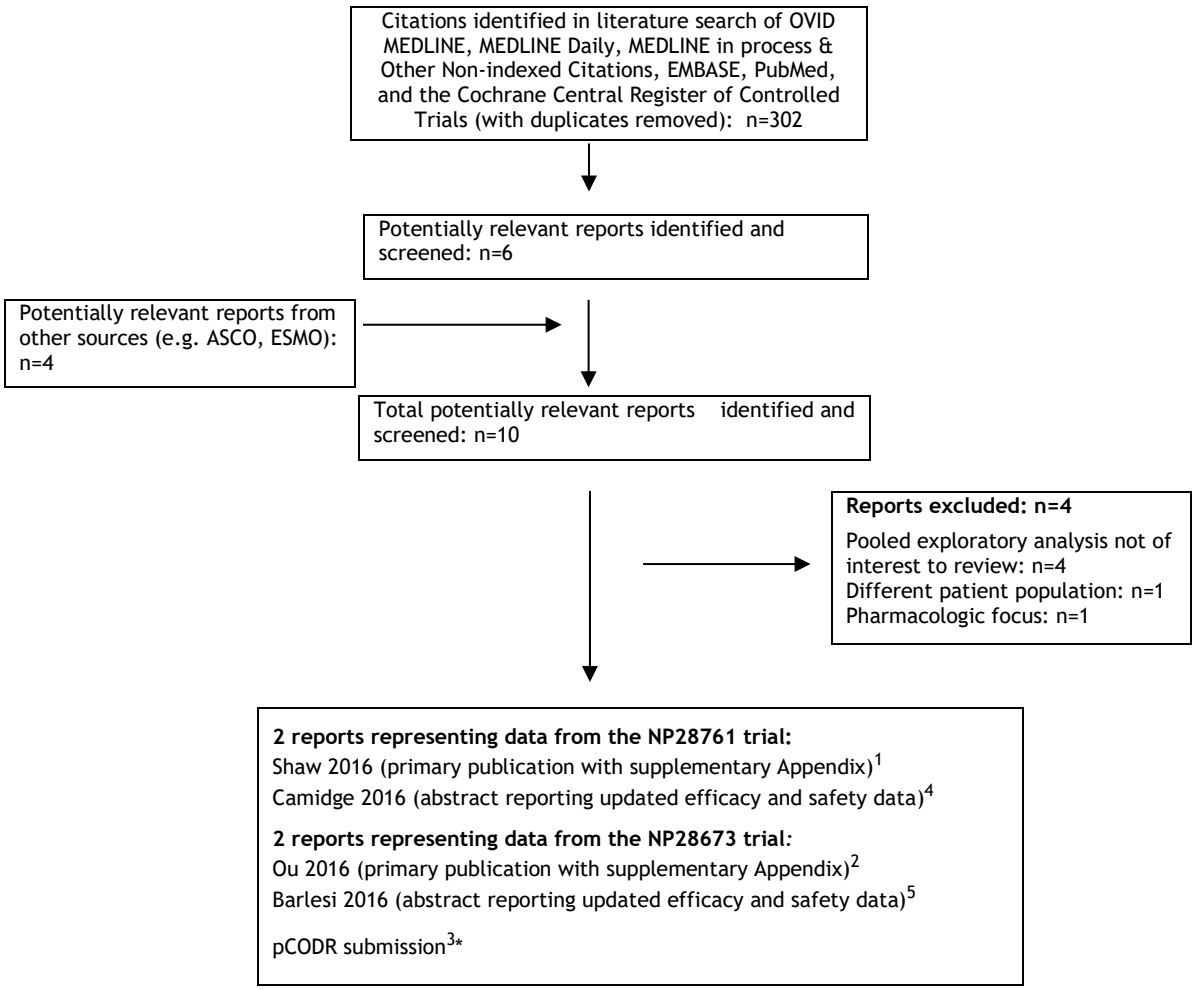
6.3.1 Literature Search Results

Of the ten potentially relevant reports identified, four reports[1,2,4,5] representing two unique trials were included in the pCODR systematic review and six reports[20-25] were excluded. Reports were excluded because they were pooled exploratory analyses of trial data that were not of interest to this review,[20-23] included a different population of ALK-positive NSCLC patients,[24] or had a pharmacologic focus.[25]

The Submitter commented on the pCODR Expert Review Committee's (pERC's) Initial Recommendation that all data from all available sources should be used to inform estimates of effectiveness, including pooled quantitative analyses to reflect the totality of the available evidence, and provide best estimates of outcomes and their uncertainties, citing the CADTH Guidelines for the Economic Evaluation of Health Technologies, 4th Edition (Draft, p.44).

It should be noted that the CADTH guidelines to which the Submitter refers, are referring to parameter estimation when estimating effectiveness and harms parameters specifically for an economic evaluation for synthesizing data from all available sources. That being said, the study selection criteria to be included in the pCODR systematic review was specifically clinical trials. The reports of the pooled analyses did not meet the inclusion criteria of the pCODR systematic review and therefore, were excluded. Considering this, it should be noted that the Methods Team and Clinical Guidance Panel (CGP) felt that it was inappropriate to pool the trial results, in agreement with the conclusions of the FDA Statistical Review, due to differences in regimens, tumor assessment, and baseline characteristics between trials NP28761 and NP28673. Furthermore, the CGP and Methods Team noted that no methodology has been reported for pooling the efficacy and safety data for patients with CNS disease from the phase II NP28761 and NP28673 trials, and expressed concern that multiple post-hoc analyses were performed and the pooled analyses for patients with measureable and non-measureable CNS disease at baseline were considered exploratory efficacy endpoints. Therefore, for these reasons, the CGP and Methods Team considered that pooled exploratory analyses of the data from the two phase II trials would not be appropriate and that any results from such an analysis would need to be interpreted with caution.

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



**Note: Additional data related to the NP28761 and NP28673 trials were also obtained through requests to the Submitter by pCODR.*

6.3.2 Summary of Included Studies

Two non-randomized, single-group, phase 2 trials were identified that met the selection criteria of this review. Trial NP28761[1] and trial NP28673[2] both evaluated alectinib in patients with ALK-positive locally advanced or metastatic NSCLC who progressed on or were intolerant to treatment with crizotinib. Key characteristics of the trials are summarized in Table 4 and specific aspects of trial quality are detailed in Table 5.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of trial characteristics of included trials evaluating alectinib in ALK-positive NSCLC who have progressed on or are intolerant to crizotinib.

Trial Design	Inclusion Criteria	Intervention	Trial Outcomes
Shaw 2016[1] (NP28761) Single-group, open-label phase 2 clinical trial N treated=87 26 centres in USA and 1 centre in Canada Patient enrolment dates: September 4, 2013 to August 4, 2014 Data cut-off for primary analysis: October 24, 2014 Data cut-off for updated analyses: April 27, 2015 and January 22, 2016 Funded by F. Hoffmann-La Roche	Key Inclusion Criteria: • Age ≥18 years • ECOG PS 0-2 • Stage IIIB-IV locally advanced or metastatic NSCLC and ALK-positive by FDA-approved FISH test • Progressed on crizotinib with a minimum 1-week washout period • Previous treatment with chemotherapy was permitted • Brain or leptomeningeal metastases, treated or untreated, as long as asymptomatic and stable • Measurable disease (RECIST version 1.1) at baseline • Adequate hematological, hepatic, and renal function Key Exclusion Criteria: • Previous treatment with ALK inhibitor other than crizotinib • Receipt of chemotherapy within 4 weeks, or radiotherapy within 2 weeks of trial start • History of MI, CHF, unstable angina or cardiac arrhythmia	Intervention: 600 mg alectinib orally twice daily in 21-day cycles until disease progression, withdrawal or death.	Primary: • ORR by IRC Key Secondary: • ORR by investigator assessment • DOR • QOL (EORTC QLQ-C30 and QLQ-LC13) • PFS • OS • CNS ORR • CNS DCR • CNS progression • Safety
Ou 2016[2] (NP28673) Single-group, open-label phase 2 clinical trial N treated=138	Key Inclusion Criteria: • Age ≥18 years • ECOG PS 0-2 • Histologically confirmed stage IIIB locally advanced or metastatic NSCLC and ALK-positive by FDA-approved FISH test	Intervention: 600 mg alectinib orally twice daily in 28-day cycles, until disease progression, unacceptable toxicity or	Primary: • ORR by IRC • ORR by IRC in subgroup of patients previously treated with chemotherapy

Trial Design	Inclusion Criteria	Intervention	Trial Outcomes
56 centres in 16 countries (not including Canada) Patient enrollment dates: June 2013 to April 2014 Data cut-off for primary analysis: August 18, 2014 Data cut-off for updated analyses: January 8, 2015 and February 1, 2016 Funded by F. Hoffman La Roche	• Disease progression on crizotinib (per RECIST version 1.1) with a minimum 1-week washout period • Life expectancy of at least 12 weeks • Chemotherapy naïve or received prior chemotherapy for advanced/metastatic disease • Brain or leptomeningeal metastases previously treated but stable (≥2 weeks) or untreated and asymptomatic (≥2 weeks) • Measurable disease according to RECIST version 1.1 • Adequate hematologic, hepatic, and renal function <u>Key Exclusion Criteria:</u> • Receipt of any other ALK inhibitor in addition to crizotinib • Receipt of chemotherapy within 4 weeks of trial start	withdrawal of consent.	<u>Key Secondary:</u> • ORR by investigator assessment • DOR • PFS • OS • CNS ORR • CNS DOR • CNS progression • Safety
Abbreviations: ALK – anaplastic lymphoma kinase; CHF – chronic heart failure; CNS – central nervous system; DCR – disease control rate; DOR – duration of response; ECOG – Eastern Cooperative Oncology Group; EORTC – European Organization for Research and Treatment of Cancer; FISH – fluorescence in situ hybridization; IRC – independent review committee; NSCLC – non-small cell lung cancer; MI – myocardial infarction; ORR – objective response rate; OS – overall survival; PFS – progression-free survival; PS – performance status; QLQ-C30- Quality of Life Questionnaire; QLQ-LC13 – Quality of Life Questionnaire lung cancer module.			

Table 5: Select quality features of trials NP28761 and NP28673 evaluating alectinib in ALK-positive advanced/metastatic NSCLC who progressed on or were intolerant to crizotinib.

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
Shaw 2016[1] (NP28761)	Alectinib No comparator	ORR by IRC	85 patients were required to provide 80% power to reject the null hypothesis of an ORR=35%,[A] and detect a 15% increase in ORR to 50% using a two-sided significance level of α=0.05[B]	87	NA	NA	NA	No[C]	No	No	Yes
Ou 2016[2] (NP28673)	Alectinib No comparator	ORR by IRC	130 patients were required to provide 93% power to reject the null hypothesis of an OR=35%, and detect a 15% increase in ORR to 50% using a two-sided significance level of α=0.05[D]	138	NA	NA	NA	No[E]	No	No	Yes

Abbreviations: IRC – independent review committee; ITT – intent-to-treat; NA – not applicable; ORR – objective response rate.

Notes:

[A] Based on the assumption that an ORR of 35% was clinically relevant. With 85 patients, the observed proportion of patients achieving an ORR of 46% (39 responses) would have a lower limit of the two-sided 95% confidence interval of 35%.

[B] The primary analysis was planned to occur when all patients had been followed a minimum of 12 weeks. An interim analysis of ORR (based on investigator assessment) for futility was planned after the first 30 patients were enrolled. If the ORR was not above or equal to 30% (9/30 responses) then the trial would be terminated.[6]

[C] The analysis of the primary outcome (ORR by IRC) was not performed in the ITT population. Due to discordance between the IRC and investigator assessment of measurable disease at baseline, the primary analysis population was defined as response-evaluable, which included patients with measurable disease at baseline by IRC who received at least one dose of study drug.[6]

[D] Based on the assumption that an ORR of 35% was clinically relevant. The sample size calculation (n=130) included enough patients to have sufficient power to test for treatment effect in subgroup of patients previously treated with chemotherapy (n=85); the remaining patients were chemotherapy naïve (n=45). Hierarchical testing was used such that the primary analysis was tested in all patients and if deemed clinically relevant, then testing was also performed in subgroup of patients previously treated with chemotherapy.

[E] The analysis of the primary outcome (ORR by IRC) was not performed in the ITT population. Sixteen patients did not have RECIST-measurable disease when assessed by the IRC, and were not included in efficacy analyses. Therefore, the primary analysis population was defined as response-evaluable, which included patients with measurable disease at baseline by IRC, and received at least one dose of study drug.

a) Trials

Trials NP28761[1] and NP28673[2] were both non-comparative, open-label, multi-centred phase 2 clinical trials. Trial NP28761 was conducted in North America and involved 26 sites in the US and one site in Canada; while NP28673 was an international trial conducted in 56 sites in 16 countries.[a] Study sites in each trial included both local and academic centres.[3] Patient enrolment for the trials overlapped, with accrual occurring between June 2013 and April 2014 for the global NP28673 trial, and between September 2013 and August 2014 for the North American NP28761 trial. Both trials evaluated the efficacy and safety of alectinib, at a dose of 600mg twice daily, in patients with ALK-positive advanced or metastatic NSCLC, with or without CNS metastases, who progressed on or were intolerant to crizotinib. The two trials, which were very similar in design, applied the following patient eligibility criteria (refer to Table 4 for a complete list) for study entry:

- Confirmed diagnosis of 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
- Previous treatment with chemotherapy for advanced/metastatic disease was allowed
- 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 (NP228761) of study start was not permitted

The Sponsor, F. Hoffman-La Roche, funded both trials and reported (NP28761) or confirmed to pCODR (NP28673) that for both trials they oversaw trial conduct, which included design, data collection, analysis, and interpretation, and final trial publication, in collaboration with the trial authors.

The primary outcome of each trial was overall response rate (ORR) by central independent review committee (IRC) using RECIST criteria (version 1.1) in all patients. In global trial NP28673 there were two primary endpoints: ORR by IRC in all patients and ORR by IRC in the subgroup of patients pre-treated with chemotherapy. The trial was appropriately powered to test for the treatment effect in all patients, and the previous chemotherapy and chemotherapy naïve patient subgroups (Table 5). For both trials, the trial publications did not clearly specify the key secondary outcomes of interest (versus those considered exploratory). According to the trial protocols and information supplied by the Submitter, the following were considered key secondary endpoints of each trial:

- ORR by investigator assessment
- Duration of response (DOR) by IRC and investigator assessment
- Progression-free survival (PFS) by IRC and investigator assessment
- Overall survival (OS)

[a] Australia, Belgium, Denmark, France, Germany, Italy, Luxemburg, Netherlands, Russia, Singapore, South Korea, Spain, Sweden, Taiwan, United Kingdom, USA.

- Central nervous system (CNS) ORR in patients with measurable disease at baseline
- CNS DOR by IRC
- CNS progression rate by IRC
- Quality of life (QOL) measured by the EORTC QOL questionnaire (QLQ)-C30 and LC13 in trial NP28761
- Safety

The following additional endpoints were considered exploratory in both trials:

- Disease control rate (DCR) by IRC
- CNS ORR by IRC in patients with measurable or non-measurable metastases at baseline

In trial NP28763, all patients underwent imaging at baseline, which included computed tomography (CT) of the chest and abdomen and CT or magnetic resonance imaging (MRI) of the brain. Restaging imaging was performed every eight weeks during treatment. Similar imaging was performed in trial NP28761; however, restaging was performed every six weeks during treatment cycles 1-6, and every nine weeks thereafter. In both trials, the IRC and investigators assessed systemic and CNS disease at baseline and subsequent visits using RECIST criteria; while a separate IRC, comprised of neuroradiologists, independently assessed CNS disease at baseline and CNS responses and progressions using both RECIST and Response Assessment in Neuro-oncology (RANO) criteria. The results of CNS efficacy analyses by RANO criteria were not reported for either trial. Investigator assessments guided all treatment decisions.[6]

More detailed information on aspects of trial quality, including sample size considerations, is summarized in Table 5. Neither trial assessed the primary outcome (ORR by IRC) using an intent-to-treat (ITT) analysis (i.e., including all patients treated with at least one dose of alectinib). Since a percentage of patients in each trial, 21% (n=18) in trial NP28761 and 12% (n=16) in trial NP28673, were deemed not to have measurable disease upon IRC assessment, the primary and key secondary efficacy analyses instead were carried out in a response-evaluable (RE) population. Time-to-event outcomes of PFS and OS, and safety were evaluated in the ITT population. The FDA Statistical Review Report indicated that the RE population analysis was actually inconsistent with the primary analysis population specified in each trial protocol, which was the ITT population. It also reported revisions to the statistical analysis plans (SAP) of both trials, including a change in the null hypothesis threshold for testing of clinical relevance (i.e., from an ORR of 50% to an ORR of 35%; refer to Table 5). It is not known whether these SAP changes were informed by examinations of the trial data.

The trial protocols of each trial indicated subgroup analyses were pre-specified (for ORR by IRC) for patients pre-treated with chemotherapy and chemotherapy naïve. However, the Submitter confirmed subgroup analyses were also pre-planned and performed by additional factors including age (<65 and ≥65), gender, race (white, Asian, other), ECOG status (0,1 and 2), and baseline CNS metastases (yes/no). The results of these latter subgroup analyses were not reported in trial publications.

b) Populations

Trials NP28761 and NP28673 enrolled 87 and 138 patients, respectively; of those patients, 69 and 122, respectively, comprised the RE population in each trial. The baseline characteristics of enrolled patients are summarized in Table 6. The distributions of demographic characteristics were similar between the two trials (NP28761 vs. NP28673), with the majority of patients being female (55% vs. 56%), white (84% vs. 67%), and never-smokers (62% vs. 70%). The median age of patients was approximately 53 years (54 years vs. 52 years). Almost all patients had metastatic disease (99% in both trials) and an ECOG status of 0 or 1 (90% vs. 91%). Lung (84% vs. 86%)[3] and the CNS (60% vs. 61%) were the most common sites of metastasis. No patients in either trial had leptomeningeal metastases. CNS metastases were measurable in 18% (n=16) of patients in trial NP28761 and 25% (n=35) of patients in trial NP28673. Among patients with CNS metastases (measurable and non-measurable), 65% (NP28761) and 73% (NP28673) had received prior brain radiation, with 47% (NP28761) and 64% (NP28673) completing radiation more than six months prior to study entry. The baseline characteristics of this patient subgroup were similar to the trial population in both trials. Both trials enrolled patients that had received crizotinib for approximately one year. The number of patients progressing on crizotinib was 31% (NP28761) and 20% (NP28673). Neither trial reported how many patients were deemed intolerant to crizotinib. The majority of patients in each trial had also been previously treated with chemotherapy (74% in NP28761 vs. 80% in NP28673). The Submitter confirmed that at the last data analysis of each trial, 49% and 51% of patients in NP28761 and NP28673 trials, respectively, continued to receive alectinib post-progression.[3]

c) Interventions

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. In both trials patients continued on treatment until disease progression, unacceptable toxicity or withdrawal of consent. All patients were offered continued treatment with alectinib post-progression if the investigator deemed treatment still clinically beneficial to the patient. The protocols of each trial allowed for dose reduction 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 selected AEs. If further dose reduction was required, withdrawal from study was considered. The median duration of treatment was 20 weeks in trial NP28761[26] and 27.1 weeks in trial NP28673. There were 83% (NP28761) and 89% (NP28673) of patients who received at least one concomitant medication (including medications to treat AEs) during each trial, with the most common types of medications being laxatives, stool softeners, corticosteroids and opioid analgesics.[26] The use of potent inducers (e.g., rifampin, rifabutin, St. John's wort) or inhibitors (e.g., ketoconazole) of CYP3A were prohibited in both trials, as were systemic immunosuppressive drugs or other anti-cancer therapies (e.g., chemotherapy, radiation).[27,28] At primary analysis, dose interruptions and reductions were required in 36% (n=31) and 16% (n=14) of patients in trial NP28761, respectively, and interruptions/reductions occurred in 21% (n=29) of patients in trial NP28673.

d) Patient Disposition

The disposition of patients in each trial is summarized in Table 7. As indicated previously, primary and secondary efficacy analyses were primarily carried out in

the RE population with the exception of time-to-event outcomes (PFS, OS). At the time of the primary efficacy analysis in both trials, 36% of patients had discontinued study treatment and 64% were alive remaining on treatment. Insufficient therapeutic response (i.e., progressive disease) was attributed as the main reason for treatment discontinuation in both trials. At the last update analysis of each trial, 66% of patients in trial NP28673 and 69% of patients in trial NP28761 had discontinued study treatment, with 34% and 31% of patients, respectively, still alive on treatment.[3]

Information on the major protocol deviations that occurred during the course of each trial was not reported in the publications of either trial. A request was made to the Submitter for this information and they indicated there were a total 21 (15%) and one (<1%) major protocol deviation(s) that occurred at baseline in trial NP28673 and NP28761, respectively. The multiple deviations in trial NP28673 were related to ALK status not being validated by an FDA approved FISH test (n=17), severe hematological renal or hepatic impairment (n=3), and one positive pregnancy test. The Submitter confirmed these patients were included in all efficacy analyses.[3] The FDA Medical Review Report reported that additional major protocol deviations occurred during the course of each trial beyond baseline.[26] In trial NP28761, ten major deviations occurred in eight patients (9%), and in trial NP28673, 26 major deviations occurred in 23 patients (17%). In both trials these deviations included violations related to prohibited medications or procedures and study drug not taken according to protocol. Considering the type and low frequency of these violations, they likely did not impact the overall efficacy findings of either trial.

Table 6: Baseline patient characteristics in phase 2 trials of alectinib in patients with ALK-positive, advanced/metastatic NSCLC who progressed on or were intolerant to crizotinib.

Trial	Shaw 2016[1] (NP28761)	Ou 2016[2] (NP28673)
No. patients enrolled	**87**	**138**
Baseline Characteristics, n (%) unless otherwise specified		
Median Age	54	52
Sex		
Male	39 (45)	61 (44)
Female	48 (55)	77 (56)
Ethnicity		
White	73 (84)	93 (67)
Asian	7 (8)	36 (26)
Other[A]	7 (8)	9 (7)
ECOG PS		
0	30 (35)	44 (32)
1	48 (55)	81 (59)
2	9 (10)	13 (9)
Disease stage		
IIIB	1 (1)	2 (1)[B]
IV	86 (99)	136 (99)[B]
Histology		
Adenocarcinoma[C]	82 (94)	133 (96)
Other	5 (6)	5 (4)
Baseline CNS metastases		
Yes	52 (60)	84 (61)
Measurable	16 (18)	35 (25)
Non-measurable	36 (41)	49 (36)
No	35 (40)	54 (39)
Previous treatment		
Chemotherapy	64 (74)	110 (80)
Radiotherapy		
Brain	36 (41)[B]	69 (50)
Bone	11 (13)[B]	30 (22)
Lung	8 (9)[B]	17 (12)
Previous crizotinib		
Time on crizotinib, median (range) in days	366 (16-1622)	364 (1-1428)
Time since last dose, median (range) in days	15 (7-733)	15 (7-676)
ORR on crizotinib	29 (33)	75 (54)
PD on crizotinib	27 (31)	27 (20)
Smoking status		
Never	54 (62)	96 (70)
Former	33 (38)	39 (28)
Current	NR	3 (2)

Abbreviations: CNS – central nervous system; ECOG – European Cooperative Oncology Group; NR – not reported; PS – performance status.

Notes:
[A] Other includes black or African American (n=3) and multiple or other ethnic origins (n=4).
[B] Source: Alecensa (alectinib) FDA Statistical Review.[6]
[C] Includes large-cell carcinoma (n=1), squamous-cell carcinoma (n=1), adenosquamous carcinoma (n=3), and poorly differentiated carcinoma (n=1)

Table 7: Patient disposition in phase 2 trials of alectinib in patients with ALK-positive, advanced/metastatic NSCLC who progressed on or were intolerant to crizotinib.

Trial	Shaw 2016 (NP28761)[1]	Ou 2016 (NP28673)[2]
Number of patients, n (%)		
Primary Analysis Date	**October 24, 2014**	**August 18, 2014**
Screened	125	176
Enrolled/treated	87 (100)	138 (100)
Included in primary efficacy analyses (response evaluable population)	69 (79)	122 (88)
Discontinuing treatment	31 (36)	49 (36)
Adverse event	2 (2)	11 (8)
Death	3 (3)	3 (2)
Physician decision	0	1 (<1)
Insufficient therapeutic response (PD)	22 (25)	33 (24)
Other	2 (2)	1 (<1)
Withdrawal by subject	2 (2)	1 (<1)
Alive on treatment	56 (64)	89 (64)
Last Update Analysis Date	**January 22, 2106[3]**	**February 1, 2016[3]**
Discontinuing treatment	60 (69)	91 (66)
Adverse event	2 (2)	12 (9)
Death	4 (5)	8 (6)
Physician decision	0	4 (3)
Insufficient therapeutic response (PD)	46 (53)	65 (47)
Other	3 (3)	1 (<1)
Withdrawal by subject	5 (6)	1 (<1)
Alive on treatment	27 (31)	47 (34)
Abbreviations: PD – progressive disease		

e) Limitations/Sources of Bias

Refer to Table 5 for a summary of quality-related features of the NP28761 and NP28673 trials.

Overall, the results of the two alectinib trials are limited by the level of evidence and the lack of randomized, comparative efficacy data for alectinib compared to an appropriate comparator (e.g. ceritinib, chemotherapy). The single-group, non-comparative design of the trials makes attributing efficacy, QOL and safety events to alectinib difficult since all patients received the same treatment. The two trials were also open-label, and as such are prone to different biases (e.g., patient selection and performance bias) that can affect the internal validity of a trial. The investigators, trial personnel, and patients were aware of the study drug administered, which can potentially bias outcome assessment in favour of alectinib if assessors (i.e., investigators or patients) believe the study drug is likely to provide benefit. Attempts were made in both trials, however, to mitigate such biases by using an IRC to assess response outcomes using standardized criteria.

When interpreting the efficacy results from NP28761 and NP28673, caution is advised in comparing the trial findings to other ALK inhibitors (e.g. ceritinib). Such comparisons are at a high-risk of bias since regimens have not been directly compared in a randomized trial. However, the two trials were very similar in design and statistical methodology, and thus can be evaluated for consistency of treatment effect.

Efficacy analyses of the primary endpoint, ORR by IRC, as well as other key secondary outcomes should have been analyzed by ITT as specified in the trial

protocols and not the RE population. Post-hoc amendments to the SAP of trials can compromise the integrity and interpretation of trial results. In their statistical review of the two trials,[6] the FDA re-analysed efficacy data by ITT and found that at the primary analysis for trial NP28761 the primary outcome was actually not statistically significant (ORR by IRC=38%, 95% CI, 27.7-49%) as the lower limit of the confidence interval did not exceed the null hypothesis threshold for statistical significance (i.e., 35%). In trial NP28673, the primary outcome was marginally statistically (ORR by IRC=44%, 95% CI, 35.8-52.9%). At the time of the FDA Statistical Review updated efficacy data were not available.

Efficacy data on the funding population of ALK-positive NSCLC patients with CNS metastases are limited in the alectinib trials, as small numbers of patients had measurable CNS disease at baseline [16 patients (18%) in trial NP28761; and 35 patients (25%) in trial NP28673], and efficacy data on the larger subgroup of patients with measurable or non-measurable CNS metastases were based on unplanned exploratory analyses in both alectinib trials. As such, the results of these analyses should be interpreted with caution.

QOL outcomes in the NP28761 trial were difficult to interpret without a comparator treatment group and due to the open-label trial design. Patient compliance in completing questionnaire assessments was also poor in the trial. [1] Further, both the published and unpublished data made available to pCODR was limited by incomplete reporting and length of follow-up, respectively. Given these factors, the QOL findings are very limited and should be interpreted with caution.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Both NP28761 and NP28673 trials are ongoing, and therefore updated efficacy data continues to be published at different follow-up times, primarily in abstract form.

In trial NP28761, the median follow-up time at primary analysis was 4.8 months (data cut-off: October 14, 2014);[1] and updated analyses were performed after a median follow-up time of 9.9 months (data cut-off: April 27, 2015)[1] and 17 months (data cut-off: January 22, 2016).[4]

In trial NP28673, the median follow-up time at primary analysis was 7.5 months (data cut-off: August 18, 2014);[2] and updated analyses were performed after a median follow-up time of 11.8 months (data cut-off: January 8, 2015)[2] and 21 months (data cut-off: February 1, 2016).[5]

For both trials, the reporting of efficacy results varied among trial reports (i.e., primary and updated analyses) and among documents provided by the Submitter as part of the pCODR submission. Key secondary outcomes in particular were inconsistently reported (i.e., partially reported or not at all). In order to fill gaps in the published data, pCODR requested the Submitter provide additional data for some outcomes,[3] which included data specific to the funding population (subgroup of ALK-positive NSCLC patients who progressed on crizotinib and had CNS metastases, measurable or non-measurable, at baseline). The efficacy analyses conducted on this patient subgroup were unplanned and exploratory,

and therefore the results should be interpreted within this context; the subgroup results presented below are from the most recent update analysis of each trial.

The key efficacy results from trials NP28761 and NP28673 are summarized in Table 8.

Efficacy Outcomes

Overall Efficacy

Objective Response Rate by Central Independent Review Committee (IRC)

All Patients
ORR was defined in both trials as the proportion of patients achieving a best overall response of complete response or partial response in the RE population by IRC based on RECIST criteria. Primary efficacy analyses were performed when all patients had been followed for a minimum of 12 weeks in trial NP28761 and a minimum of 16 weeks in trial NP28673, so that two tumour assessments could be completed to confirm any observed responses.[6]

At the primary analysis, both trials reported a clinically relevant ORR by IRC, such that the lower 95% confidence limit around the estimated ORR exceeded 35% (thus rejecting the null hypothesis).

In trial NP28761, the ORR by IRC was 48% (95% CI, 36-60%) and comprised all partial responses. At the most recent updated analysis, the ORR by IRC was 52% (95% CI, 40-65%).

In trial NP28673, the ORR by IRC at primary analysis was 49% (95% CI, 40-58%) and was comprised of all partial responses. At the most recent updated analysis, the ORR by IRC was 51% (95% CI, 42-60%). In the subgroup of patients pre-treated with chemotherapy (n=96), the ORR by IRC was 44% (95% CI, 34-54%) at primary analysis and 45% (95% CI, 35-55%) at the most recent update analysis. These analyses did not meet the pre-specified threshold for clinical relevance. In chemotherapy naïve patients (n=26), the ORR by IRC was 69% (95% CI, 48-86%; January 8, 2015 data cut-off).

For both trials the ORRs obtained by investigator assessment in the RE population were similar to the ORRs obtained by IRC (Table 8).

The results of additional preplanned subgroup analyses, which were provided by the Submitter for each trial,[3] showed most subgroup analyses performed failed to meet the threshold for clinical relevance. These results, however, should be considered in view of the small numbers of patients included in the subgroups examined. In trial NP28761, clinical relevance was demonstrated among patients who were <65 years of age, female, of white race, and who had an ECOG performance status of 0. In trial NP28673, clinical relevance was demonstrated among patients who were <65 years of age, male, of white and Asian race, and who had an ECOG performance status of 0.

CNS Metastases (Measurable or Non-measurable) Patient Subgroup[3]
At the most recent update analysis, there were 39 and 74 patients with CNS metastases in trials NP28761 and NP28673, respectively, who comprised the RE population. In trial NP28761, the ORR by IRC was 49% (n=19/39; 95% CI, 32-65%), and in trial NP28673, the ORR by IRC was 49% (n=36/74; 95% CI, 37-61%). The ORRs obtained by investigator assessment were higher in each trial, 58% (n=30/52; 95% CI, 43-71%) in trial NP28761 and 52% (n=44/84; 95% CI, 41-63%) in

trial NP28673. Data on the type of responses contributing to the ORRs in both trials were not provided.

Time-to Event Outcomes: Duration of Response, Progression-free Survival, and Overall Survival

All Patients

In both trials, time-to-event outcome data were immature at the time of primary analyses; however, estimates were reported for DOR and PFS. OS was reported in the most recent update analyses of both trials. The results described below focus on the most recent update analyses (median follow-up times of 17 and 21 months in trials NP28761[4] and NP28673,[5] respectively). Refer to Table 8 for estimates at other analysis time points.

Duration of response was reported for the number of patients achieving an ORR (i.e. partial response) in each trial. In trial NP28761, the median DOR by IRC was 14.9 months (95% CI, 6.9-not estimable) among the 35 partial responders. In trial NP28673, the median DOR by IRC was 15.2 months (95% CI, 11.2-15.9) among the 62 responders.

In both trials, median DOR by investigator assessment was slightly shorter compared to DOR by IRC (Table 8).

In both trials PFS and OS were assessed in the ITT population. In trial NP28761 (n=87), median PFS was 8.4 months[3] and median OS was 22.7 months. In trial NP28673 (n=138), median PFS was 8.9 months and median OS was 26 months.

CNS Metastases (Measurable or Non-measurable) Patient Subgroup[3]

In trial NP28761, the median DOR among the 19 patients with a response was 11.1 months (95% CI, 7.5-not estimable) and was 16.6 months (95% CI, 10.9-not estimable) in trial NP28673 among the 36 patients with a response. The median DOR by investigator assessment was 11.1 months in both trials.

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

Disease Control Rate

All Patients

DCR by IRC was an exploratory endpoint of both trials, and defined as the percentage of patients with a best overall response of complete response, partial response, or stable disease lasting for at least 12 weeks in trial NP28761 or 16 weeks in trial NP28673. In trial NP28761, the DCR was 80% (95% CI, 68-88%) at the primary analysis and 79% (67-88%) at the most recent update analysis. In trial NP28673, the DCR was 64% (95% CI, 55-72%) at the primary analysis and 79% (70-86%) at the most recent update analysis.

CNS Metastases (Measurable or Non-measurable) Patient Subgroup[3]

Among patients with CNS metastases, the DCR by IRC was 80% (n=31/39; 95% CI, 64-91%) in trial NP28761, and 80% (n=59/74; 95% CI, 69-88%) in trial NP28673.

CNS Efficacy

The following CNS efficacy endpoints were considered key secondary outcomes in both trials: CNS ORR, CNS DOR, and CNS progression rate. All CNS efficacy analyses were based on IRC assessment in each trial.

In trial NP28761, 16 patients (18%) had measurable CNS metastases at baseline and include 11 patients previously treated with brain radiation. The CNS ORR for this patient subgroup was 69% (95% CI, 41-89%) at primary analysis and 75% (48-93%) at both update analyses. In the updated analyses, four complete responses and eight partial responses contributed to the CNS ORR. The median CNS DOR among this patient subgroup at the last updated analysis was 11.1 months (95% CI, 5.5-not estimable).

In trial NP28673, 35 patients (25%) had measurable CNS metastases at baseline and include 23 patients previously treated with brain radiation.[3] The CNS ORR for this patient subgroup was 56% (95% CI, 38-73%) at primary analysis, 57% (39-74%) at the January 8, 2015 update analysis, and 59% (48-93%) at the February 1, 2016 update analysis. In both update analyses, seven complete responses and 13 partial responses contributed to the CNS ORR. The median CNS DOR among this patient subgroup at the last updated analysis was 11.1 months (7.1-note estimable).

CNS progression was defined as any new CNS lesion or progression of pre-existing CNS lesions, as assessed by IRC. At 12 months, the cumulative incidence of CNS progression events was 22% (n=18/87) in trial NP28761 and 24% (32/138) in trial NP2867;[3] while the cumulative incidence of non-CNS progression events at 12 months was 29% (n=23/87) and 31% (43/138), respectively.[3]

<u>CNS Metastases (Measurable or Non-measurable) Patient Subgroup</u>
In trial NP28761, the CNS ORR was 40% (95% CI, 27-55%) in 52 patients with measurable or non-measureable CNS metastases, with 13 complete responses and 8 partial responses contributing to the CNS ORR. The median DOR in this patient subgroup was 15.5 months (95% CI, 11.1-21.5).

In trial NP28673, the CNS ORR was 46% (95% CI, 36-58%) in 84 patients, with 26 complete responses and 45 partial responses (or stable disease) contributing to the CNS ORR. The median DOR was 11.2 months (95% CI, 9.1-not estimable).

Quality of Life

Patient–reported QOL was evaluated in the NP28761 trial[1] and was measured using the EORTC QLQ-C30 and the QLQ-LC-13. 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/vomiting), a global health status scale, and six single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, and financial difficulties). The QLQ-LC13 is specific to lung cancer, and assesses lung cancer symptoms (coughing, hemoptysis, dyspnea, and pain in chest, arm or shoulder, or other) and side effects from treatment (hair loss, neuropathy, sore mouth and dysphagia). For both instruments, assessments were completed at baseline and every six weeks up to week 66 (last visit). A mean change from baseline of 10% or greater (for continuous endpoints) is considered the minimal clinically important difference (MCID), with lower scores indicative of improvement in symptoms and side effects.

All Patients

The NP28761 trial publication reported very limited data on QOL outcomes, which included mean changes from baseline (provided in graph form) starting at week six to last visit at week 66, for the QLQ-C30 global health status and fatigue symptom scales. Mean baseline scores were not reported for either of these scales, nor were data reported for the remaining scales that comprise the QLQ-C30 or all scales comprising the QLQ-LC-13. For the QLQ-C30 global health status scale, the trial reported a MCID (i.e., improvement in overall health status from baseline of at least 10%) at the first assessment (week six), which was maintained for at least two consecutive visits and generally sustained until the end of treatment. For the QLQ-C30 fatigue symptom scale, a MCID (i.e., improvement in fatigue from baseline of at least 10%) was reported at all assessment time points. For both scales patient compliance was approximately 93% at week six but declined over time to approximately 74%, 57%, 48%, 25% and 4% at weeks 12, 24, 36, 48 and 60, respectively, and then increased to 100% at week 66 (last visit). [1]

Due to the limited QOL data reported in the trial report, pCODR requested the Submitter provide complete QOL data, including mean baseline scores for both QOL instruments. In response, the Submitter provided mean QOL outcome scores and mean changes from baseline, at week six only, for the scales comprising each instrument.[3] The data cut-off for these data was April 27, 2015.

For the QLQ-C30, two of five function scales (social and role functioning), two of three symptom scales (fatigue and pain) and two of six single symptom items (dyspnea, appetite loss) showed improvements from baseline at week six that exceeded the MCID. For the QLQ-LC13, three of ten lung cancer symptoms (coughing, pain in chest, and pain in other parts) showed improvements from baseline at week six that exceeded the MCID.[3]

CNS Metastases (Measurable or Non-measurable) Patient Subgroup[3]

In documents provided with the pCODR submission, the Submitter graphically compared QOL outcomes, in terms of the QLQ-C30 global health status score, between patients with (n=52) and without (n=35) CNS metastases at baseline. Over the course of treatment, the mean changes from baseline in overall QOL health status were generally similar between the two groups of patients.

Harms Outcomes

Grade 3 or 4 Adverse Events

In both trials, analysis of AEs was based on the safety population that included all patients treated with at least one dose of study drug. A summary of the all-cause AEs occurring at the time of primary analysis in trials NP28761 and NP28673 is provided in Table 9.[1,2]

The median duration of treatment was 20 weeks in trial NP28761 and 27.1 weeks in trial NP28673; dose intensity was 92% and 97%, respectively. Overall, alectinib was well tolerated in both trials. The majority of AEs were low grade, with the most common AEs (NP28761 vs. NP28673) being grade 1-2 constipation (36% vs. 33%), fatigue (33% vs. 26%), peripheral edema (23% vs. 24%), and myalgia (24% vs. 22%). The incidence of grade 3-4 AEs was below 5% for all AEs in both trials with the exception of elevations in blood creatine phosphokinase (8%), alanine aminotransferase (6%), and aspartate aminotransferase (5%) in trial NP28761. Serious AEs were reported in 15% of patients in trial NP28761 and 16% of patients

and in trial NP28673.[3] The number of patients discontinuing treatment due to AEs was 2% and 8%, respectively.

The Submitter provided updated AE data for the most recent update analysis of each trial (January 22, 2016 for NP28761 and February 1, 2016 for NP28673).[3] These data (all grade and selected grade ≥3 AEs for trial NP28761; all grade for trial NP28673) appear very similar to the AE data presented at primary analysis but with less detail by grade. In trial NP28671, grade ≥3 AEs were reported in 41% of patients, and AEs led to dose modifications/interruptions, reductions, or withdrawal from study in 28%, 18%, and 2% of patients, respectively. In trial NP28673, the incidence of grade ≥3 AEs was not reported. AEs led to dose modifications/interruptions, reductions, and withdrawal from trial in 25%, 11%, and 9% of patients, respectively.

A summary of grade 3-5 AEs by baseline CNS metastases status, provided by the Submitter, showed a similar AE profile between patients with and without CNS metastases at baseline.[3]

Deaths

Four deaths were reported in trial NP28761 at the last update analysis.[3] One patient on anticoagulants died from hemorrhage, which was judged related to study treatment; and the second patient had disease progression and a history of stroke, which was not judged related to study treatment. The cause of death in the remaining two patients was unknown.

Eight deaths were reported in trial NP2863 at the last update analysis,[3] of which five were attributed to AEs including dyspnea, pulmonary embolism, hemorrhage, endocarditis, and an intestinal perforation judged related to study treatment. The cause of death in the remaining three patients was unknown.

Table 8: Efficacy outcomes in phase 2 trials of alectinib in patients with ALK-positive, advanced/metastatic NSCLC who progressed on or were intolerant to crizotinib.

Trial	Shaw 2016 (NP28761)[1,3,4]			Ou 2016 (NP28673)[2,3,5]		
	Primary analysis	*Updated analyses*		*Primary analysis*	*Updated analyses*	
Data Cut-off Date	*October 24, 2014*	*April 27, 2015*	*January 22, 2016*	*August 18, 2014*	*January 8, 2015*	*February 1, 2016*
Median follow-up time in months	4.8	9.9	17.0	7.5	11.8	21.0
Primary Outcomes						
n	*n=69*[A]	*n=67*[B]	*n=67*	*n=122*	*n=122*	*n=122*
ORR by IRC, n (%, 95% CI)	33 (48, 36-60)	35 (52, 40-65)	35 (52, 40-65)	60 (49, 40-58)	61 (50, 41-59)	62 (51, 42-60)
CR, n (%)	0	0	0	0	0	NR
PR, n (%)	33 (48)	35 (52)	35 (52)	60 (49)	61 (50)	NR
SD, n (%)	22 (32)	18 (27)	18 (27)	37 (30)	35 (29)	NR
PD, n (%)	11 (16)	11 (16)	11 (16)	20 (16)	22 (18)	NR
n				*n=96*	*n=96*	*n=96*
ORR by IRC in patients treated with chemotherapy, n (%, 95% CI)	NA	NA	NA	42 (44, 34-54)	43 (45, 34-55)	43 (45, 35-55)
CR, n (%)				0	0	0
PR, n (%)				42 (44)	43 (45)	43 (45)
SD, n (%)				33 (34)	31 (32)	31 (32)
PD, n (%)				17 (18)	18 (19)	NR
Secondary Outcomes						
n	*n=33*[A]	*n=35*[B]	*n=35*	*n=60*	*n=61*	*n=62*
DOR by IRC, median in months (95% CI)	7.5 (4.9-NE)	13.5 (6.7-NE)[C]	14.9 (6.9-NE)	9.2 (NE)	11.2 (9.6-NE)	15.2 (11.2-24.9)
n	*n=69*[A]	*n=67*[B]	*n=67*			
DCR by IRC, n (%, 95% CI)	55 (80, 68-88)	53 (79, 67-88)	53 (79, 67-88)	78 (64, 55-72)	96 (79, 70-86)	96 (79, 70-86)
n	*n=87*	*n=87*	*n=87*	*n=138*	*n=138*	*n=138*
ORR by INV, n (%, 95% CI)	40 (46, 35-57)	44 (51, 40-61)	46 (53, 42-64)	66 (48, 39-57)	69 (50, 41-59)	71 (51, 43-60)
DOR by INV, median in months	NR	NR	13.3 (8.8-18.2)	7.8 (7.4-9.2)	11.0 (9.1-NE)	13.7 (11.0-20.3)
PFS by IRC, median in months (95% CI)	6.3 (5.5-NE)	8.1 (6.2-12.6)[D]	8.2 (6.3-12.6)	7.5 (5.9-11.2)	8.9 (5.6-11.3)	8.9 (5.6-12.8)
PFS by INV, median in months (95% CI)	NR	NR	8.4 (5.5-12.7)	NR	NR	9.3 (7.4-12.8)
OS, median in months (95% CI)	NR	NE	22.7 (17.2-NE)	NR	NE	26.0 (21.5-NE)
CNS Secondary Outcomes						
Measurable metastases, n	*n=16*[E]	*n=16*[E]	*n=16*[E]	*n=34*	*n=35*	*n=34*
CNS ORR by IRC[F], n (%, 95% CI)	11(69, 41-89)	12 (75, 48-93)	12 (75, 48-93)	19 (56, 38-73)	20 (57, 39-74)	20 (59, 41-75)
CR, n (%)	2 (13)	4 (25)	4 (25)	5 (15)	7 (20)	7 (21)
PR, n (%)	9 (56)	8 (50)	8 (50)	15 (41)	13 (37)	13 (38)
SD, n (%)	5 (31)	4 (25)	4 (25)	10 (29)	10 (29)	9 (27)

Trial	Shaw 2016 (NP28761)[1,3,4]			Ou 2016 (NP28673)[2,3,5]		
	Primary analysis	*Updated analyses*		*Primary analysis*	*Updated analyses*	
Data Cut-off Date	*October 24, 2014*	*April 27, 2015*	*January 22, 2016*	*August 18, 2014*	*January 8, 2015*	*February 1, 2016*
CNS DOR, median in months (95% CI)	NR	11.1 (5.8-11.1)	11.1 (5.5-NE)	11.1 (5-8-NE)	9.1 (5.8-NE)	11.1 (7.1-NE)
CNS DCR, n (%, 95% CI)	16 (100, 79-100)	16 (100, 79-100)	16 (100, 79-100)	29 (85, 69-95)	30 (86, 70-95)	(85, 68.9-95.1)
PFS by IRC, median in months (95% CI)	NR	12.4 (8-NE)	13.2 (8-NE)	NR	NR	9.2 (4.3-16.8)
OS, median in months (95% CI)	NR	NE	NE	NR	NR	26.0 (17.4-NE)
Measurable or Non-measurable metastases, n	*n=52*	*n=52*	*n=52*	*n=83*	*n=84*	*n=84*
CNS ORR[D] by IRC, n (%, 95% CI)	20 (39, 25-53)	21 (40, 27-55)	21 (40, 27-55)	32 (39, 28-50)	36 (43, 32-54)	39 (46, 36-58)
CR, n (%)	11 (21)	13 (25)	13 (25)	18 (22)	23 (27)	26 (31)
PR, n (%)	9 (17)	NR	8 (15.4)	14 (17)	13 (16)	13 (16)
SD, n (%)	26 (50)	NR	25 (48)	37 (45)	34 (41)	32 (38)
CNS DOR, median in months (95% CI)	NR	11.1 (10.8-NE)	15.5 (11.1-21.5)	15.5 (11.1-21.5)	10.3 (7.6-11.2)	11.2 (9.1-NE)
CNS DCR, n (%, 95% CI)	46 (89, 77-96)	46 (89, 77-96)	46 (89, 77-96)	69 (83, 73-91)	70 (83, 74-91)	71 (85, 78-91.5)
PFS by IRC, median in months (95% CI)	NR	8.3 (5.1 – 14.9)	8.4 (6.1-16.3)	NR	NR	7.4 (5.6-15.9)
OS, median in months (95% CI)	NR	14.9 (14.9 – NE)	22.7 (17.2-NE)	NR	NR	26.0 (24.2-NE)

Abbreviations: CI – confidence interval; CNS – central nervous system; CR – complete response; DCR – disease control rate; DOR – duration of response; INV – investigator; IRC – central independent review committee; NA – not applicable; NE – not estimable; NR – not reported; ORR – objective response rate; OS – overall survival; PD – progressive disease; PFS – progression-free survival; PR – partial response; SD – stable disease.

Notes:

[A] Response evaluable population, which includes patients who had measurable disease at baseline according to the IRC. For 3 (4%) patients, response was not known because of missing or non-assessable restaging scans.

[B] The primary analysis was extended in an updated analysis to achieve more stable time-to-event estimates, and additional restaging scans were available to IRC for the update analysis. The number of patients for the primary and update analyses are different because additional update assessments required adjudication between scan readers, and in some instances use of a different assessment of baseline disease.

[C] Assessment of DOR includes the 35 patients achieving an ORR; data for 21 of these patients (60%) were censored at the time of data cut-off.

[D] Data for 38 patients (44%) were censored at the time of data cut-off.

[E] CNS ORR by RECIST.

[F] Eleven of the 16 patients with measurable CNS disease were previously treated with brain radiation therapy.

Table 9: Adverse events in phase 2 trials of alectinib in patients with ALK-positive, advanced/metastatic NSCLC who progressed on or were intolerant to crizotinib.

All Cause AEs, n (%)	Shaw 2016 (NP28761)[1] n=87		Ou 2016 (NP28673)[2] n=138	
	Grade 1-2[A]	Grade 3-4	Grade 1-2[A]	Grade 3-4
Any AE	87 (100)		134 (97)[B]	
Blood creatine phosphokinase increased	12 (14)	7 (8)		
AST increased	14 (16)	4 (5)	14 (10)	2 (1)
ALT increased	11 (13)	5 (6)	12 (9)	2 (1)
Constipation	31 (36)	0	45 (33)	0
Fatigue	29 (33)	0	34 (26)	0
Myalgia	21 (24)	0	30 (22)	1 (1)
Nausea	19 (22)	0	16 (12)	0
Peripheral edema	20 (23)	0	33 (24)	1 (1)
Asthenia	NR	NR	24 (17)	1 (1)
Headache	18 (21)	0	20 (15)	2 (1)
Diarrhea	18 (21)	0	13 (9)	1 (1)
Rash	NR	NR	16 (12)	0
Anemia	15 (17)	1 (1)*	NR	NR
Cough	15 (17)	0	19 (14)	0
Weight increased	14 (16)	0	NR	NR
Dyspnea	13 (15)	3 (3)	13 (10)	4 (3)**
Blood alkaline phosphatase increased	11 (13)	0	NR	NR
Vomiting	10 (11)	0	14 (10)	1 (1)
Insomnia	10 (11)	0	NR	NR
Back pain	9 (10)	0	NR	NR
Dizziness	9 (10)	0	NR	NR
Upper-respiratory tract infection	9 (10)	0	NR	NR
Photosensitivity reaction	9 (10)	0	NR	NR
Blood bilirubin increased	6 (7)	1 (1)	NR	NR
Hypokalemia	6 (7)	2 (2)	NR	NR
Hypertriglyceridemia	5 (6)	2 (2)	NR	NR
Hypoalbuminemia	4 (5)	1 (1)	NR	NR
Activated partial thromboplastin time prolonged	4 (5)	1 (1)	NR	NR
Neutropenia	3 (3)	1 (1)	NR	NR
Hyponatremia	2 (2)	1 (1)*	NR	NR
Hypophosphatemia	2 (2)	2 (2)	NR	NR
Hypocalcemia	2 (2)	1 (1)	NR	NR
Seizure	2 (2)	1 (1)	NR	NR
Lymphopenia	1 (1)	1 (1)	NR	NR
Hemiparesis	1 (1)	1 (1)	NR	NR
Lung infection	1 (1)	1 (1)	NR	NR
Electrocardiogram QT prolonged	0	1 (1)	NR	NR
Generalized edema	0	1 (1)	NR	NR
Intestinal obstruction	0	1 (1)	NR	NR
Brain edema	0	1 (1)*	NR	NR
Cerebral ventricle dilatation	0	1 (1)	NR	NR
Cerebrovascular accident	0	1 (1)	NR	NR
Embolic stroke	0	1 (1)*	NR	NR
Obstructive airways disorder	0	1 (1)	NR	NR
Influenza	0	1 (1)	NR	NR
Staphylococcal sepsis	0	1 (1)	NR	NR
Glucose tolerance impaired	0	1 (1)	NR	NR
Hyperammonemia	0	1 (1)	NR	NR

All Cause AEs, n (%)	Shaw 2016 (NP28761)[1] n=87		Ou 2016 (NP28673)[2] n=138	
	Grade 1-2[A]	Grade 3-4	Grade 1-2[A]	Grade 3-4
Malnutrition	0	1 (1)	NR	NR
Confusional state	0	1 (1)	NR	NR
Drug induced liver injury	0	1 (1)	NR	NR
SAE	13 (15)		22 (16)	
Abbreviations: AEs – adverse events; ALT - alanine aminotransferase; AST - aspartate aminotransferase; SAE – serious adverse event.				
Notes: [A] Grade 1-2 adverse events occurring in ≥10% of patients. [B] Source: Health Canada Summary of Clinical Safety. Section 2.7.4.[3] *Grade 4 only. **One patient had a grade 5 event that was unrelated to treatment.				

6.4 Ongoing Trials

One ongoing trial of alectinib in patients with ALK-positive, advanced or metastatic NSCLC was identified.[29] The randomized phase 3 trial compares alectinib to docetaxel or pemetrexed in patients who have received two prior lines of systemic therapy including platinum-based chemotherapy and crizotinib. The estimated completion date of the trial is April 2019.

Table 10: Ongoing trial of alectinib in patients with ALK-positive NSCLC who progressed on or were intolerant to crizotinib.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NCT02604342[29] Randomized, open-label, phase 3 Estimated enrolment: 120 patients 54 centres in 15 countries Trial start date: November 2015 Estimated completion date: April 2019 Sponsor: Hoffmann-La Roche	Key Inclusion Criteria: • Histologically confirmed stage IIIB locally advanced or stage IV metastatic NSCLC and ALK-positive by FISH or ICH test • Received two prior systemic lines of therapy including one line of platinum-based chemotherapy and one line of crizotinib. • Prior CNS or leptomeningeal metastases permitted if asymptomatic; symptomatic metastases permitted if radiotherapy not a treatment option • Measurable disease by RECIST (version 1.1) • ECOG 0-2 Key Exclusion Criteria: • Previous treatment with ALK inhibitor other than crizotinib • Previous malignancy within past 3 years (with the exception of curatively treated basal cell carcinoma of the skin, early GI cancer by endoscopic resection or in situ cancer of the cervix) • Any GI disorder affecting absorption of oral medications	600mg alectinib orally twice daily until disease progression, unacceptable toxicity, withdrawal of consent or death vs. 500mg pemetrexed or 75mg docetaxel every 3 weeks, until disease progression, unacceptable toxicity, withdrawal of consent or death	Primary: • PFS Secondary: • OR (CR + PR) • Disease control (CR + PR + SD of at least 5 weeks) • DOR • OS • Time-to-CNS progression • QOL (EORTC QLQ-C30, QLQ-LC-13, EQ-5D-5L) • Safety

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were identified.

8 COMPARISON WITH OTHER LITERATURE

No comparisons were performed to other available literature.

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. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Lung Clinical Guidance Panel is comprised of three 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

See Appendix B for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** September 2016**, Embase** 1974 to 2016 October 11**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	(alectinib* or alecensa* or CH5424802 or CH 5424802 or RO5424802 or RO 5424802 or RG7853 or RG 7853 or AF802 or AF 802 or 1256580-46-7 or 1416163-60-4 or LIJ4CT1Z3Y).ti,ab,ot,kf,kw,hw,rn,nm.	656
2	1 use pmez	142
3	1 use cctr	6
4	*alectinib/ or (alectinib* or alecensa* or CH5424802 or CH 5424802 or RO5424802 or RO 5424802 or RG7853 or RG 7853 or AF802 or AF 802 or LIJ4CT1Z3Y).ti,ab,kw.	410
5	4 use oemezd	268
6	5 and conference abstract.pt.	91
7	limit 6 to yr="2011 -Current"	91
8	5 not 7	177
9	2 or 3 or 7 or 8	416
10	remove duplicates from 9	272
11	limit 10 to english language	256

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 publisher[sb]** Filters: **English**	20
#2	Search **#1 AND publisher[sb]**	20
#1	Search **alectinib*[tiab] OR alecensa*[tiab] OR CH5424802[tiab] OR CH 5424802[tiab] OR RO5424802[tiab] OR RO 5424802[tiab] OR RG7853[tiab] OR RG 7853[tiab] OR AF802[tiab] OR AF 802[tiab] OR 1256580-46-7[tiab] OR 1416163-60-4[tiab] OR LIJ4CT1Z3Y[tiab]**	148

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
http://www.esmo.org/

Search: Alecensa/alectinib - last 5 years

APPENDIX B: DETAILED METHOLODGY OF LITERATURE REVIEW

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-present) with in-process records & daily updates via Ovid; Embase (1974- 2016 October 11) via Ovid; The Cochrane Central Register of Controlled Trials (September 2016) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were alectinib and alecensa/alecensar/alecensaro.

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

The search is considered up to date as of February 2, 2017.

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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