pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Ceritinib (Zykadia) for Metastatic Non-Small Cell Lung Cancer

December 3, 2015

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of ceritinib (Zykadia) monotherapy, as compared to an appropriate comparator in patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have disease progression on or with intolerance to crizotinib.

Ceritinib is an oral, small-molecule, ATP-competitive, tyrosine kinase of ALK. Ceritinib has a Health Canada indication with conditions which is the same as the indication under pCODR review. Ceritinib is available in a 150 mg capsule, it has Health Canada approval with conditions for 750 mg taken orally once daily until disease progression.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Two non-randomized phase one/two multi-centre, open-label, single-arm trials, ASCEND-1 and ASCEND-2 evaluating the efficacy and safety of ceritinib 750 mg orally daily in ALK-positive NSCLC were included in the pCODR systematic review. The single-arm, non-randomized designs make interpreting the efficacy and safety results difficult, especially when assessing outcomes such as response rate and progression-free survival which are more open to subjective bias. ASCEND-1 included a dose-escalation phase followed by an expansion phase while ASCEND-2 included only one phase where all patients received the recommended dose of 750 mg per day and had been pretreated with crizotinib as their last prior therapy.

The primary endpoint for both studies was objective response rate (ORR) as evaluated by the investigator, with confirmatory assessment conducted by an independent review committee. Secondary outcomes included progression-free survival (PFS), overall survival (OS), intracranial response rate, safety and tolerability.

Of the 246 patients in ASCEND-1, 163 (66%) patients were treated with a prior ALK inhibitor (ALKi) and 83 (34%) patients were ALKi naïve. In ASCEND-2, all patients' (n=140) last prior therapy was crizotinib and had at least one line of platinum-based therapy.

Efficacy

In ASCEND-1, the ORR was 56.4% (95%CI: 48.5-64.2) patients with prior ALKi treatment. In ASCEND-2, the ORR was 38.6% (95%CI: 30.5-47.2). The median duration of response was 8.3 months in ASCEND-1 for patients with prior ALKi treatment and 9.7 months ASCEND-2. The median PFS was 6.9 (95%CI: 5.6-8.7) and 5.7 months (95%CI: 5.4-7.6) in ASCEND-1 for patients with prior ALKi treatment and ASCEND-2, respectively.

Data on patient-reported outcomes was assessed in ASCEND-2 using the European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC-QLQC30) and lung cancer specific questionnaire (QLQ-LC13) and the Lung Cancer Symptom Scale (LCSS). Throughout the treatment period, the change from baseline in global health status remained close to zero which suggested quality of life was maintained and did not worsen during ceritinib treatment. Patients reported consistent but not

clinically important improvements in lung-related symptoms (i.e. cough, pain in chest and dyspnea) and no worsening of cancer symptoms while on treatment.

Harms

The most frequent grade 3 or 4 adverse event was increased alanine aminotransferase levels which is associated with liver damage, this occurred in 29.8% and 13.6% of patients in ASCEND-1 and ASCEND-2, respectively. Other commonly reported grade 3 or 4 adverse events included but were not limited to nausea, diarrhea, and fatigue. Seventeen (10.4%) and 10 (7.1%) of patients discontinued treatment due to adverse events in ASCEND-1 and ASCEND-2, respectively.

1.2.2 Additional Evidence

pCODR received input on ceritinib from one patient advocacy group (Lung Cancer Canada). Provincial Advisory Group input was obtained from nine of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. No supplemental issues were identified during the development of the review.

1.2.3 Interpretation and Guidance

The expansion cohort of ASCEND-1 and the ASCEND-2 trial demonstrated early onset of response, improved efficacy in terms of tumour response and progression-free survival for ceritinib. Quality of life was reported in ASCEND-2 and noted to be maintained throughout the treatment period. This appears to be superior when compared to historical comparisons to standard second line chemotherapy of docetaxel and pemetrexed monotherapy.

The benefits of ceritinib were consistent with those seen in subgroup analyses of the ASCEND-1 trial for inter-ethic variations in response, for patients with ALKi naïve disease or previously untreated brain metastases NSCLC.

Targeting a driver mutation such as ALK with ceritinib appears to be a successful strategy. Ceritinib, a more novel and potent ALKi than crizotinib, has demonstrated activity against crizotinib resistant tumour models and this is supported by the clinical data from ASCEND-1 and ASCEND-2. A pooled analysis comparing crizotinib and ceritinib suggest ceritinib has significantly improved progression-free survival and overall survival, however this is limited by its methodology and differing patient characteristics in the trials.

The safety profile of ceritinib appears favourable, with the spectrum and incidence of adverse effects in keeping with other oral molecularly targeted agents used in the management of NSCLC. The frequency of adverse effects leading to discontinuation of treatment in the two reported trials was low.

Although the ALK-positive population represents a small proportion of all advanced or metastatic NSCLC, the annual incidence of NSCLC is large and therefore the absolute number of patients eligible for ceritinib on an annual basis is not inconsequential.

A major limitation of the available data regarding ceritinib is that the phase I and II trials do not establish its effectiveness improving overall survival and quality of life outcomes compared to standard systemic therapy options. There remains uncertainty in terms of correlation between response rates and overall survival in this setting. Nevertheless, improvement in overall response rates, progression-free survival, maintained quality of life, and tolerable safety profile would suggest ceritinib is superior and preferred to alternative standard chemotherapy in the setting of ALKi pretreated NSCLC.

1.3 Conclusions

The conclusion of the Clinical Guidance Panel is that there may be a net overall benefit to ceritinib in the treatment of ALK+ve patients with advanced or metastatic NSCLC who have disease progression on crizotinib, based on the currently limited evidence. Ceritinib has demonstrated superior response rates, progression free survival and tolerability profile when compared to historical comparisons to 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 ceritinib to standard chemotherapy in the ALKi pretreated population. The data from two ongoing phase III, randomized, multicenter trials evaluating the efficacy of ceritinib in comparison to platinum doublet and second line chemotherapy agents, respectively, are expected to provide better clarity in this regard. Both trials are expected to be completed in 2018. Nonetheless, the consistency of antitumour activity and superior tolerability of ceritinib in this population, in trials available up to date, as well as the pattern by which it targets the driver mutation argue in favor of its use prior to chemotherapy in this previously ALKi treated population.

Data from ongoing clinical trials are expected to further clarify the role of ceritinib in patients with ALK+ve NSCLC who present with brain metastases. The results of other pending trials may further clarify the role of ceritinib in other lines of therapy or with tumours that harbor alternative aberrations such as ROS1 or ALK-over expression. In addressing PAG input, patients would likely receive platinum-doublet therapy after the use of two ALKis (crizotinib and ceritinib).

2 CLINICAL GUIDANCE

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 Ceritinib (Zykadia) for Metastatic Non-Small Cell Lung Cancer. 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 pCODR website, www.cadth.ca/pcodr.

This Clinical Guidance is based on: a systematic review of the literature regarding ceritinib conducted by the Lung Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; 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. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on ceritinib and a summary of submitted Provincial Advisory Group Input on ceritinib are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths globally for both men and women, with the majority of patients presenting with non-curable disease.[1] In Canada it is estimated that 20,900 Canadians will die from lung cancer in 2015, representing 27% of all cancer deaths. NSCLC is the most common type of lung cancer, accounting for about 85 percent of all cases (ref- Canadian Cancer Society: Lung Cancer Statistics 2015).[2] In its early stages (Stage I and II), NSCLC can be largely asymptomatic, resulting in most cases (greater than 70%) being diagnosed at an advanced stage.[3] There is evidence to support that ALK+ tumours present at a more advanced clinical stage at diagnosis compared to non-ALK tumours.[4] If left untreated, patients with advanced NSCLC have poor survival outcomes and a median survival from diagnosis of 4-5 months.[3,4]

Targeted therapy has transformed the treatment of patients with NSCLC by incorporating tumour genotyping into clinical decision making. The identification of oncogenic drivers and selecting matched targeted therapies accordingly has the possibility of increasing survival, although randomized trials are required to definitively confirm this association.[5]

Among patients with advanced, ALK rearranged NSCLC, crizotinib has been associated with response rates of approximately 60% across multiple studies and a median progression-free survival of 8-10 months. However, despite the initial responses to crizotinib, a majority of patients have a relapse within 12 months due to the development of resistance.[6]

Ceritinib is an oral, small-molecule, ATP-competitive, tyrosine kinase inhibitor of ALK. In enzymatic assays, ceritinib is 20 times as potent as crizotinib against ALK. Ceritinib is also a more specific ALK inhibitor than crizotinib and does not inhibit the kinase activity of MET. However, ceritinib does inhibit the IGF-1receptor, although the inhibition of IGF-1 is substantially less potent than the inhibition of ALK (i.e., by a factor of 50).These preclinical studies suggested that ceritinib may be active in patients with NSCLC who have

not received crizotinib, as well as in patients who have experienced progressive disease after receiving crizotinib.[6]

2.1.2 Objectives and Scope of pCODR Review

To evaluate the safety and efficacy of ceritinib on patient outcomes, in the treatment of patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have disease progression on or with intolerance to crizotinib.

See Table 5 in Section 6.2.1 for outcomes of interest and appropriate comparators.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

Two non-randomized trials evaluating the safety and efficacy of ceritinib on patient outcomes, in the treatment of patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have disease progression on or with intolerance to crizotinib were identified and included in this clinical guidance report.[7-13] For a more detailed description of the trials' designs and patient characteristics, please see Table 6 in the *Systematic Review* (Section 6.3.2.1). The two trials were not of similar design.

ASCEND-1 was a phase I trial and ASCEND-2 was a phase II trial. ASCEND-1 included a dose-escalation followed by an expansion phase. All patients (n=255) in the expansion phase received the recommended dose of 750 mg/day, including 9 patients that had tumours with genetic alternations of ALK other than NSCLC. The remaining 246 patients with ALK+NSCLC tumours were stratified into two groups that were ALK inhibitor treated (n=163) and ALK inhibitor naïve (n=83).[9]

ASCEND-2 included only one phase where all ALK+ NSCLC patients (n=140) received ceritinib at the recommended dose of 750 mg/day and all patients been pretreated with crizotinib as the last prior antineoplastic therapy.[8]

Both trials enrolled adult patients diagnosed with a locally advanced or metastatic non-small cell lung cancer that have disease progression despite standard therapy, or for which no effective standard therapy exists. Both studies required documented ALK-positive status, in ASCEND-1 based on validated ALK assay and in ASCEND-2 based on the FDA-approved, ALK break-apart fluorescence in situ hybridization (FISH) assay. Additionally, both trials also allowed patients with asymptomatic or neurologically stable central nervous system disease at baseline to enroll. Of the 246 patients in ASCEND-1 with ALK+NSCLC treated with ceritinib at 750 mg/day, 50.4% (n=124) had brain metastases at study entry. Of the 140 ALK+NSCLC enrolled patients in ASCEND-2, 71.4% (n=100) presented with brain metastases at study entry.[9,10]

Treatment with ceritinib continued in both trials until the patient experienced unacceptable toxicity that precluded any further treatment, disease progression, and/or treatment was discontinued at the discretion of the investigator or by patient request. A brief summary of the key trial quality characteristics can be found in Table 1.

Table 1. Select quality characteristics of included studies of ceritinib in patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC who have disease progression on or with intolerance to crizotinib. [8,9]

Study	Treatment	Primary outcome	Required sample size	Sample size N	Randomization method	Allocation concealment	Blinding	Final analysis	Early termination	Ethical Approval
X2101 (ASCEND-1)[9]	Ceritinib	MTD ORR DOR	NR	246	Not randomized study	NR	Open-label	Yes	No	NR
A2201 (ASCEND-2)[8]	Ceritinib	ORR	137 patients were required to test a null hypothesis of ORR ≤ 25% with a one-sided alpha of 0.025 and 90% power, based on the exact binomial distribution	140	Not randomized study	NR	Open-label	Yes	No	NR

Notes: N = number of patients; ITT = intention-to-treat; ORR = overall response rate; N/A = not applicable; NR = not reported; MTD = maximum tolerated dose; DOR = duration of response; NSCLC = non-small cell lung cancer

The primary outcome/efficacy endpoint in both trials was to demonstrate the antitumour activity of ceritinib as measured by ORR by investigator assessment according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. In the ASCEND-1 study, the primary objective was also to determine the maximum tolerable dose (MTD) of ceritinib in adult patients with tumours harbouring a genetic alteration in ALK. Another primary efficacy outcome in ASCEND-1 was duration of response (DOR), which was defined as the time from first documented response (PR to CR) to the date of first documented disease progression (PD) or death due to any cause, among patients with a confirmed PR or CR. Secondary efficacy outcomes were progression-free survival (PFS) and overall survival (OS).[14] In the ASCEND-2 study, secondary objectives included ORR as assessed by BIRC, duration of response (DOR), disease control rate (DCR), time to response (TTR), overall intracranial response rate (OIRR), progression-free survival as assessed by both investigator and BIRC, overall survival (OS) and safety profile.[8,9]

Both studies were described as being open-label, multicentre studies that were conducted globally across several sites and were funded by Novartis Pharmaceuticals.

Due to both trials being open-label, they are at risk of several biases that can affect the internal validity of a trial. Examples of such biases are patient selection as part of inclusion criteria for eligibility and performance bias due to knowledge of the study treatment. In open-label trials, the assessment of measures such as HR-QoL in ASCEND-2 and the reporting of adverse events are also likely to be subjectively biased. It is important to also note that investigators, study personnel, clinicians and patients involved in both the trials were aware of the study drug treatment assigned, which can introduce the potential to bias results and outcomes in favour of whether the assessor (investigator or patient) believes the study drug is

likely to provide a benefit. For ASCEND-1, assessment of tumour response and for ASCEND-2, assessments of best overall response, PFS and intracranial response were conducted via a blinded independent review committee (BIRC), which could reduce the potential for biased results of these outcomes.

The key efficacy results for both studies are summarized in Table 2. The results for patients with ALK+NSCLC and brain metastases as per investigator assessment are summarized in Table 3.

Table 2: Key efficacy results of included studies of ceritinib in patients with ALK+NSCLC who have disease progression on or with intolerance to crizotinib[8,9]

Study	ORR % [95%CI]	DOR Median [95%CI]	PFS Median [95%CI]	OS Median [95%CI]	Median follow-up
ASCEND-1 prior ALK inhibitor n=163 [95% CI]	56.4% [48.5, 64.2]	8.3 months [6.8, 9.7]	6.9 months [5.6, 8.7]	16.7 months [14.8, NE]	10.2 months
ASCEND-2 n=140*	38.6% [30.5, 47.2]	9.7 months [7.1, 11.1]	5.7 months [5.4, 7.6]	14.9 months [13.5, NE]	11.3 months

Notes: *FAS investigator assessed; NE = not estimable; CI = confidence interval
Results in this table for ASCEND-1 only include the previously treated with an ALKi population (n=163)

Table 3: Systemic response to ceritinib treatment in patients with ALK+NSCLC and brain metastases at baseline* as per investigator assessment[8,10]

	ASCEND-1 (n=124)[10]		ASCEND-2 (n=100)[8]
	ALK inhibitor treated (n=98)	ALK inhibitor naïve (n=26)	
ORR, n (%) (95% CI)	50.0 (51%) (40.7,61.3)	19 (73.1%) (52.2,88.4)	33.0 (33%) (23.9,43.1)
DOR (95% CI)	6.9 months (5.4, 8.3)	12.6 months (5.5, NE)	9.2 months (5.5, 11.1)
PFS (95% CI)	6.9 months (4.9, 8.4)	9.7 months (4.6, NE)	5.4 months (4.7, 7.2)
DCR, n (%) (95% CI)	NR (not an outcome of interest in ASCEND-1)	NR (not an outcome of interest in ASCEND-1)	74.0 (74%) (64.3,82.3)

*Systemic response denotes best overall response in all sites of disease, including brain; ALK= anaplastic lymphoma kinase; CI= confidence interval; NSCLC= non-small cell lung cancer (RECIST v1.0)

ASCEND-2 assessed quality-of-life using the European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC-QLQC30, version 3.0), lung cancer specific questionnaire (QLQ-LC13) and the Lung Cancer Symptom Scale (LCSS). For

most of the time points during the study, the compliance was high with over 90% of patients completing the EORTC-QLQ-C30/LC13.Throughout the treatment period, the change from baseline in global health status remained close to zero, which suggested that HRQoL was maintained and did not worsen during ceritinib treatment. Patients reported consistent but not clinically important improvements in lung related symptoms based on the cut-off date of August 12th 2014 (i.e. cough, pain in chest and dyspnea). At the end of treatment, worsening outcomes were reported for both the QLQ-C30 and LCSS, suggesting quality of life declined off treatment due to disease progression.[8] However, it is important to note that the sample size at the end of treatment visit was relatively small.

Key grade 3 or 4 AEs for both studies can be found in Table 4.

Table 4. Grade 3/4 Adverse Events (≥20% for all Grades) among patients with ALK+NSCLC and Brain Metastases at Baseline

	X2101 (ASCEND-1)[10] n =124		A2201 (ASCEND-2)[8] n= 140
	NSCLC with prior ALKi (n=98) n (%)	NSCLC ALKi naïve (n=26) n (%)	
Nausea	6(6.1)	1(3.8)	9(6.4)
Diarrhea	5(5.1)	1(3.8)	9(6.4)
Vomiting	8(8.2)	1(3.8)	6(4.3)
Alanine Aminotransferase increased	26(26.5)	10(38.5)	24(17.1)
Fatigue	7(7.1)	0(0.0)	9(6.4)
Abdominal pain	0(0.0)	1(3.8)	2(1.4)
Headache	4(4.1)	0(0.0)	NR
Aspartate aminotransferase increased	10(10.2)	2(7.7)	7(5.0)
Weight decreased	1(1.0)	2(7.7)	6(4.3)
Asthenia	1(1.0)	0(0.0)	NR
Dyspnoea	4(4.1)	3(11.5)	8(5.7)
Back pain	1(1.0)	0(0.0)	NR
Blood alkaline phosphatase increased	6(6.1)	0(0.0)	NR
Hypokalemia	5(5.1)	2(7.7)	NR

The most frequent grade 3/4 AEs assessed as related to study drug in both trials were related to hepatotoxicity and gastrointestinal toxicity, specifically alanine aminotransferase increased (ALT), aspartate aminotransferase increased (AST), gamma-glutamyltransferase increased (GGT), blood alkaline phosphatase increased, diarrhoea, nausea, vomiting and fatigue.[14] GI toxicity occurred in almost all patients with 246/255 (96.5%) patients in ASCEND-1 and 134/140(95.7%) patients in ASCEND-2.[14]

Adverse events of special interest to the Clinical Guidance Panel included GI toxicity (i.e., nausea, vomiting and diarrhoea), hepatoxicity, pneumonitis, and QT interval prolongation. Please see the Systematic Review section on adverse events for more details.

In the ASCEND-1 trial, 13 patients (10.5%) discontinued treatment due to AEs. The most frequent reason for treatment discontinuation among all 124 patients with brain metastases at baseline was disease progression in 45.2% of patients. There was a slightly higher treatment discontinuation observed among the ALK inhibitor-pretreated than the ALK inhibitor-naïve patients (46.9% and 38.5%, respectively).[10] Serious AEs in ASCEND-1 were reported in 121 (47.5%) patients. 4.7% (12/255) of patients developed interstitial lung disease/pneumonitis.[9] The most common SAEs among the 124 patients with brain metastases were convulsion (n=9), pneumonia (n=9), dyspnoea (n=5) and hyperglycaemia (n=5).[10]

In the ASCEND-2 trial, eleven patients (7.9%) discontinued due to AEs, with no one type of AE predominating and 4 patients discontinued due to gastrointestinal AEs.[8] SAEs suspected to be study drug related were: pneumonia, nausea, and vomiting (each reported in 2.1% of patients); pericarditis, abdominal pain, pyrexia, and pneumonitis (each reported in 1.4% of patients). A total of 58 (41.4%) patients required a dose adjustment or interruption. Dose adjustment/interruption due to vomiting, nausea, and diarrhoea were reported in 39 (27.9%), 34 (24.3%), and 24 (17.1%) out of 140 patients, respectively.[8]

2.1.4 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.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

2.1.6 Other Considerations

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

Patient Advocacy Group Input

According to LCC, lung cancer patients appear to have the highest symptom burden of all cancer patients. LCC noted that from the Canadian Cancer Statistics 2015, lung cancer is the leading cause of cancer death in Canadian men and women, killing more Canadians than breast, prostate and colorectal cancer combined. LCC reported that while the average 5-year survival rate for all cancers is 63%, the 5-year survival rate for lung cancer is approximately 17% [Canadian Cancer Statistics 2015]. The key symptoms associated with lung cancer include fatigue, loss of appetite, shortness of breath, cough, pain, and blood in sputum. LCC reported that most Canadians with advanced lung cancer get chemotherapy for first-line treatment of NSCLC, irrespective of their ALK status. While response rates are approximately 20%-30%, with temporary improvement in symptoms and quality of life in up to two thirds of patients, LCC reported that chemotherapy is associated with severe side effects including nausea, vomiting, hair loss, fatigue and the risk of fever and infection. There was also the inconvenience of multiple blood tests, intravenous treatment and multiple visits (with long wait times) to hospital for chemotherapy. LCC submitted that this poses a tremendous burden on patients and their caregivers, who must take time off

from work to receive treatment, and then additional time off to manage chemotherapy toxicity, including frequent admission to hospital.

For patients who have not experienced ceritinib, but have or are currently on crizotinib, respondents stated that they saw fast response and felt better with crizotinib. As such, the expectation was that ceritinib would be the same if not better. For patients who have experienced ceritinib, they have a perception that crizotinib did not cross the blood/brain barrier while ceritinib does, and thus ceritinib would be efficacious against brain metastasis. Like crizotinib, ceritinib had manageable side effects and improved outcomes. Common side effects reported include elevated liver enzymes and heart palpitations. Other side effects were nausea and diarrhea that in most cases, were less frequent, or lasted a shorter duration than those experienced with crizotinib. LCC indicated that many of these patients continue to be feeling great and are highly functional. Additionally, patients are staying out of chemotherapy clinics and hospital, and both they and their caregivers are living more active lives because of these new treatments.

PAG Input

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

Overall Summary

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

Clinical factors:

- Standard of care is intravenous chemotherapy and crizotinib
- Lack of comparative data and/or phase 3 trials

Economic factors:

- Extend treatment options with another line of therapy, if third line
- If approved for second line, replacement of intravenous chemotherapy

2.2 Interpretation and Guidance

The expansion cohort of the non-randomized phase I study (ASCEND-1), as well as the phase II trial (ASCEND-2) demonstrated early onset of response within six weeks and significant efficacy in terms of tumour responses in ALK inhibitor (ALKi) pre-treated populations. Improvements in terms of progression free survival (PFS) and trend towards improved quality of life (QoL) in lung symptoms as well as maintained global QoL have been noted. QoL benefits reflected the antitumour activity of ceritinib and its modest toxicity profile. A subgroup analysis of the ASCEND-1 trial to evaluate inter-ethnic variations in response, identified high and durable antitumour activity as well as manageable tolerability with low discontinuation rates in both Asian and Caucasian patients with ALK+ve NSCLC (Felip et al. J Clin Oncol 33, 2015(suppl; abstr 8060).

Consistent benefits with ceritinib were seen in an open label phase II trial (ASCENÐ-3) which demonstrated significant response rates and progression free survival benefits in

ALKi naïve populations, as suggested by the expansion cohort of the ASCEND-1 trial. Notably, in addition to whole body responses, the ASCEND-2 and ASCEND-3 trials demonstrated intracranial responses to previously untreated brain metastases. This is being further evaluated in the currently accruing ASCEND-7 trial.

The strategy of targeting specific driver mutations has consistently been shown to be successful with respect to a variety of targeted agents currently in use in NSCLC. Crizotinib, such an inhibitor of the EML4-ALK pathway, is currently approved in the second line setting of ALK+ve NSCLC. Ceritinib, a more novel and potent ALKi has demonstrated activity against crizotinib resistant tumour models and this is supported by the clinical data obtained from the ASCEND-1 and ASCEND-2 trials. An indirect comparison between crizotinib and ceritinib performed by pooling individual data from the PROFILE series and the ASCEND series of trials, respectively, demonstrated significantly improved PFS and overall survival (OS) for ceritinib. This analysis, while thought provoking and worthy of further exploration, is limited by its methodology, as well as the inability to balance for ethnicity as well as prior lines of therapy. (Tan et al. J Clin Oncol 33, 2015 (suppl; abstr 8058) There are currently no head-to-head trials comparing ceritinib and crizotinib in the ALK+ve NSCLC population.

The tumour response rates seen with ceritinib in the ALKi pretreated as well as naïve populations are superior to those associated with existing standard systemic therapy, regardless of the line of therapy. The safety profile of ceritinib as well as the incidence and spectrum of adverse events, appear to be favorable. The frequency of adverse events leading to treatment discontinuation has been consistently low.

The availability of a well validated ALK companion laboratory test to establish ALK mutation status allows for the early selection of the appropriate treatment population.

The annual incidence of NSCLC is high. The ALK +ve population represents a small minority of all advanced or metastatic NSCLC (approximately 850 patients per year in Canada). The availability of a reliable method to detect this small sub-population of ALK+ve patients that would benefit from a significantly more efficacious and relatively less toxic regimen than standard chemotherapy would support a definite role for ceritinib in the treatment of this subset of NSCLC.

There remains uncertainty in terms of correlation between response rates and overall survival in this setting. Nevertheless, the improvement in overall response rates, progression free survival as well as QoL noted with ceritinib coupled with the improved tolerability of this agent would suggest that ceritinib is the superior and preferred alternative to standard chemotherapy in the setting of ALKi pretreated NSCLC.

2.3 Conclusions

The conclusion of the Clinical Guidance Panel is that there may be a net overall benefit to ceritinib in the treatment of ALK+ve patients with advanced or metastatic NSCLC who have disease progression on crizotinib, based on the currently limited evidence. Ceritinib has demonstrated superior response rates, progression free survival and tolerability profile when compared to historical comparisons to 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 ceritinib to standard chemotherapy in

the ALKi pretreated population. The data from two ongoing phase III, randomized, multicenter trials evaluating the efficacy of ceritinib in comparison to platinum doublet and second line chemotherapy agents, respectively, are expected to provide better clarity in this regard. Both trials are expected to be completed in 2018. Nonetheless, the consistency of antitumour activity and superior tolerability of ceritinib in this population, in trials available up to date, as well as the pattern by which it targets the driver mutation argue in favor of its use prior to chemotherapy in this previously ALKi treated population.

Data from ongoing clinical trials are expected to further clarify the role of ceritinib in patients with ALK+ve NSCLC who present with brain metastases. The results of other pending trials may further clarify the role of ceritinib in other lines of therapy or with tumours that harbor alternative aberrations such as ROS1 or ALK-over expression. In addressing PAG input, patients would likely receive platinum-doublet therapy after the use of two ALKis (crizotinib and ceritinib).

3 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.

3.1 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 most common type of cancer 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.[15] The majority of new cases of lung cancer are expected to arise in people over 60 years of age, with estimated 16,300 new cases in the age group between 60 years and 79 years and 12,300 associated deaths in 2015.[15,16] The advanced age group and advanced stage population contain a disproportionately greater number of patients with poor performance status as well as a higher likelihood of significant co-morbidities that might impact their ability to tolerate conventional chemotherapy regimens.[17]

3.2 Accepted Clinical Practice

The goals of treatment for patients with advanced stage NSCLC are primarily palliative and aim to prolong life while also prolonging quality of life. Factors that influence the choice of initial therapy depend on the clinical condition (performance status, co-morbidities, etc.) of the patient, the histological subtype of NSCLC and the presence of driver mutations for which a specific inhibitor may be available.

In the setting of NSCLC without an eligible driver mutation, platinum based doublet chemotherapy combinations remain the mainstay for first life systemic treatment. Platinum combinations have provided palliative benefit with modest incremental improvements in median survival in the magnitude of months over the course of the last few decades.[18-21] A variety of first-line platinum doublets have shown comparable efficacy in terms of response rates, modest survival improvements and improvements in quality of life. Third generation cytotoxic agents such as vinorelbine, gemcitabine, pemetrexed, paclitaxel and docetaxel when paired with platinum agents have shown modest incremental gains over historical controls.[21-23] Histological sub-classifications of NSCLC have proven to have implications for therapy. The use of pemetrexed combinations appear to preferentially benefit treatment of non-squamous histologies. Alternatively, this agent appears to be inferior to gemcitabine in the first line setting of the treatment of squamous NSCLC when combined with a platinum agent.[24] This difference has been attributed to differential levels of thymidylate synthase expression.[25,26] The addition of maintenance therapy in the first line setting with pemetrexed and the Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR TKI), erlotinib, have demonstrated modest incremental gains in survival.[27,28] Platinum doublets in combination with targeted therapy in the form of bevacizumab have demonstrated an improvement in progression free survival without consistently translating into an overall survival benefit in the first line setting.[29,30] While a meta-analysis identified an improvement in overall survival with this strategy, there remains uncertainty if the identified survival gains are superior to that provided by the addition of maintenance chemotherapy to the first-line setting.[31,32] Furthermore, the cost of bevacizumab and associated toxicities have dissuaded the widespread adoption of such triplet therapies in clinical practice.

Activating mutations have been increasingly recognized as key drivers in certain histological subtypes. Epidermal Growth Factor Receptor (EGFR) activating mutations and EML4-ALK mutations have well elucidated roles in the pathogenesis of NSCLC.[33,34] Agents that selectively target these pathways have been shown to induce superior response rates and progression free survival benefits in patients whose cancers harbour these mutations. Several trials and a meta-analysis confirmed the benefit of EGFR TKI therapy in the front line, second line and maintenance therapy in patients with EGFR mutated tumours without demonstrating an advantage to overall survival - attributable to the extensive cross over in this population.[35] The exact sequencing of these agents in relation to chemotherapy is, hence, not yet clearly established.[36] Nevertheless, there is increasing clinical consensus that the utilization of these agents upfront provides improved quality of life and delays the necessity of initiating cytotoxic chemotherapy with its inferior tolerability profile in well-selected populations.

In patients with EML4-ALK mutated tumours, crizotinib — an oral small molecule inhibitor of ALK, MET and ROS1 kinase - has demonstrated objective responses as high as 60% and progression free survival as high as 7-10 months in pretreated populations.[37,38] An open label, phase III study confirmed superior objective response rates [65% vs. 20%, (P<0.001)] and Progression Free Survival (PFS) [median 7.7 months vs. 3.0 months; hazard ratio for progression or death with crizotinib, 0.49; 95% confidence interval [CI], 0.37 to 0.64; P<0.001)] favouring crizotinib when compared to second line chemotherapy (docetaxel or pemetrexed).[39] More recently, an open label phase III study confirmed superior objective response rates [74% vs. 45%, (P<0.001)] and 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.[40] The current funding model supports the use of crizotinib in the second line treatment of stage IV lung cancer, following chemotherapy.

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.

The classical paradigm for the second line treatment of NSCLC consists of chemotherapy especially in patients with good performance status. A role for single agent therapy with pemetrexed or docetaxel was suggested based on the improvement in survival as well as quality of life when compared to best supportive care.[41,42] Recent data from the Checkmate 017 and 057 trials have suggested a role for immunotherapy in the second line setting. Nivolumab, a Programmed Cell Death Receptor 1 (PD-1) antibody has demonstrated improved survival when compared to docetaxel in the second line treatment of squamous and non-squamous NSCLC respectively.[43,44]

Third line and subsequent therapy is typically dependent on patient performance status as well as patient motivation. In the era of targeted therapies, Gefitinib demonstrated non-inferiority to docetaxel in the second or subsequent line of treatment.[45] Erlotinib has shown improved survival and symptom control in the second or subsequent line treatment when compared to best supportive care.[46] More recently, afatinib has been shown to provide greater benefit than erlotinib in the treatment of squamous cell cancers.[47] A trial of a previously unused agent is reasonable in the absence of contraindications and if a suitable clinical trial is unavailable. Supportive care therapy including palliative radiation and early referral to the palliative care team along with psychosocial and spiritual supportive care are considered appropriate throughout the spectrum of treatment.[12]

3.3 Evidence-Based Considerations for a Funding Population

Echinoderm microtubule associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) gene rearrangements have a well-established role in the pathway leading to the development of NSCLC.[48-50] ALK gene rearrangements appear to be mutually exclusive of EGFR and KRAS mutations and occur in approximately 4% of lung cancers.[51] These mutations are more common in adenocarcinomas and never/light smokers.[52] The multi targeted small molecule tyrosine kinase inhibitor, crizotinib, has demonstrated superior objective response rates and progression free survival in patients whose tumours harbour the EML4-ALK mutation.[37-40] This agent has been approved in the second line setting of the treatment of these tumours following the use of platinum doublet chemotherapy. The duration of treatment with crizotinib is until there is evidence of disease progression. Almost all patients develop resistance to the drug within the first few year of treatment. A few distinct mechanisms of resistance include acquisition of a secondary mutation within the ALK tyrosine kinase domain and amplification of the ALK fusion gene. Ceritinib, a second generation TKI of ALK is approximately twenty times more potent than crizotinib and has activity against cells with the most common resistance mutations to crizotinib. Accelerated FDA approval was granted in 2014, for the treatment of patients with Stage IV ALK positive NSCLC who had experienced disease progression or who were intolerant to crizotinib.[53] A phase 1 study established the maximum tolerated dose as 750 mg orally daily. The dose expansion cohort of that study included crizotinib naive and pre-treated subjects and demonstrated an objective response rate of 58% with a median duration of response of 10 months.[54] A multicenter, single-arm, open-label phase II clinical trial demonstrated durable responses of large magnitude with duration of response greater than 9 months, objective response rate >38% and disease control rate greater than 77% in pretreated patients.[8] An acceptable safety profile was demonstrated on safety evaluation based on 255 patients with ALK positive tumours. The clinical trial data published and reviewed in this clinical guidance report supports the use of this drug in the setting of advanced NSCLC (defined as stage IIIb or Stage IV [AJCC 7th edition] harbouring ALK rearrangement defined as 15% or more positive tumour cells as assessed by the FDA-approved FISG test [Abbott Molecular Inc.) using Vysis break-apart probes. In the province of Ontario, testing for the presence of EML4-ALK fusion protein is well established and available to practitioners to allow identification of patients who would benefit from ALK inhibitor therapy. In the current model, Ceritinib is likely to benefit the treatment of ALK - positive tumours following use of crizotinib and as a third line option. With the publication of the PROFILE 1014 clinical trial results and increasing expert consensus favouring the use of crizotinib in the first line treatment of ALK positive tumours, it is likely that ceritinib may evolve to find a role in the second line setting of these tumours prior to the use of chemotherapy.[40]

3.4 Other Patient Populations in Whom the Drug May Be Used

Currently there is no level 1 evidence for the use of this drug in indications other than advanced NSCLC. It is being studied in proof-of-concept trials in terms of anti-tumour activity, safety and tolerability in advanced ALK positive tumours other than NSCLC.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Lung Cancer Canada (LCC), provided input on the ceritinib (Zykadia) submission as monotherapy in patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have disease progression on or with intolerance to crizotinib, and their input is summarized below.

LCC conducted focus groups of patients on crizotinib and their caregivers in February 2015. Five (5) patients and four (4) caregivers participated. LCC also conducted one on one interviews with an additional three (3) patients and two (2) caregivers; and one (1) additional patient provided written feedback. All patients were ALK+ and all caregivers were caring for those with ALK+ lung cancer. Between May and June 2015, LCC conducted one on one interviews with an additional five (5) patients and four (4) caregivers. LCC re-interviewed two (2) patients and one (1) caregiver from February 2015 specifically for the current submission. In total, LCC received input from fourteen (14) patients and ten (10) caregivers who provided their perspectives into the current submission. Of those patients, seven (7) patient respondents had experiences with ceritinib, and all of whom had previously experienced crizotinib. All (14) patient respondents were under 70 years old, three (3) were the primary income earner for their family, and three (3) patient respondents had infant or very young children.

In addition, LCC included findings based on supporting materials from Lung Cancer Canada Faces of Lung Cancer report, which was released in November 2014, as well as literature review.

According to LCC, lung cancer patients appear to have the highest symptom burden of all cancer patients. LCC noted that from the Canadian Cancer Statistics 2015, lung cancer is the leading cause of cancer death in Canadian men and women, killing more Canadians than breast, prostate and colorectal cancer combined. LCC reported that while the average 5-year survival rate for all cancers is 63%, the 5-year survival rate for lung cancer is approximately 17% [Canadian Cancer Statistics 2015]. The key symptoms associated with lung cancer include fatigue, loss of appetite, shortness of breath, cough, pain, and blood in sputum. LCC reported that most Canadians with advanced lung cancer get chemotherapy for first-line treatment of NSCLC, irrespective of their ALK status. While response rates are approximately 20%-30%, with temporary improvement in symptoms and quality of life in up to two thirds of patients, LCC reported that chemotherapy is associated with severe side effects including nausea, vomiting, hair loss, fatigue and the risk of fever and infection. There was also the inconvenience of multiple blood tests, intravenous treatment and multiple visits (with long wait times) to hospital for chemotherapy. LCC submitted that this poses a tremendous burden on patients and their caregivers, who must take time off from work to receive treatment, and then additional time off to manage chemotherapy toxicity, including frequent admission to hospital.

For patients who have not experienced ceritinib, but have or are currently on crizotinib, respondents stated that they saw fast response and felt better with crizotinib. As such, the expectation was that ceritinib would be the same if not better. For patients who have experienced ceritinib, they have a perception that crizotinib did not cross the blood/brain barrier while ceritinib does, and thus ceritinib would be efficacious against brain metastasis. Like crizotinib, ceritinib had manageable side effects and improved outcomes. Common side effects reported include elevated liver enzymes and heart palpitations. Other side effects were nausea and diarrhea that in most cases, were less frequent, or lasted a shorter duration than those experienced with crizotinib. LCC indicated that many of these patients continue to be feeling great and are highly functional. Additionally, patients are staying out of chemotherapy clinics and hospital, and both they and their caregivers are living more active lives because of these new treatments.

Please see below for a summary of specific input received from the patient advocacy group. Cited quotes and statistics are not corrected for spelling or grammar.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Advanced or Metastatic NSCLC

LCC highlighted that lung cancer is currently the leading cause of cancer-related mortality in Canadians, causing more death than breast, ovarian, prostate, and colorectal cancer combined.

A study reported by LCC highlighted that a high proportion of patients experienced lung cancer symptoms: fatigue (100 %), loss of appetite (97 %), shortness of breath (95 %), cough (93 %), pain (92 %), and blood in sputum (63 %). Loss of appetite, cough, pain, and shortness of breath were found to be significant quality of life predictors.

LCC reported on the challenges experienced by lung cancer patients compared to other cancers. According to LCC, about 2 – 7% of NSCLC patients are considered to be ALK+. Compared to the general NSCLC population, ALK+ patients tend to be younger and are never smokers. LCC indicated that lung cancer patients and their families also carry a heavy burden of stigma. As smoking is the leading cause of lung cancer, the stigma associated with this diagnosis is overwhelming. A 2010 national poll showed more than one in five Canadians (22%) said they feel less sympathy for people with lung cancer than those with other cancers because of its link to smoking. Participants of the LCC focus group of patients and their families conducted in October 2014 expressed that they felt the burden of that judgement.

One responded noted: "*"Often when I tell people that I have lung cancer, the first thing they ask me is not "How are you?" but "Did you smoke?"*"

4.1.2 Patients' Experiences with Current Therapy for Advanced or Metastatic NSCLC

LCC reported that most Canadians with advanced lung cancer get chemotherapy for first-line treatment of NSCLC, irrespective of their ALK status. Response rates are approximately 20%-30%, with temporary improvement in symptoms and quality of life in up to two thirds of patients.

LCC indicated that chemotherapy is associated with severe side effects including nausea, vomiting, hair loss, fatigue and the risk of fever and infection. Other side effects may include dehydration, kidney damage, hearing loss and nerve damage. There is also the inconvenience of multiple blood tests, intravenous treatment and multiple visits (with long wait times) to hospital for chemotherapy. LCC submitted that this poses a tremendous burden on patients and their caregivers, who must take time off from work to receive treatment, and then additional time off to manage chemotherapy toxicity, including frequent admission to hospital (>10%).

According to the respondents, the burden of chemotherapy was felt during all stages of the treatment.

1. Diagnosis: Chemotherapy carried a psychologic burden even before receiving the first dose. Those that did not have to go through chemotherapy expressed it as a "*relief*". One respondent stated: "*When I was first diagnosed, the fear of traditional chemotherapy and radiation was overwhelming.*" Patients of the focus group used words such as "*cytotoxic killer*" and "*poison*" to describe chemotherapy.

2. Infusion: The infusions themselves presented challenges beyond travel time and hospital visits. During the infusion, some patients were asked to wear "*ice*" mittens and socks to in an attempt to minimize the effects of chemotherapy on finger and toe nails. This made the experience of chemotherapy even more challenging and as one respondent described it "painful".

3. Recovery: Significant recovery time was needed after each chemotherapy infusion. For one respondent, this meant "*two bad weeks and one good week.*" "*Walking and activity were difficult. I was so so sick on infusion chemo. I wasn't functional*," stated another respondent. According to LCC, all of the patients who were on chemotherapy mentioned that chemotherapy took away precious time that they could spend with loved ones due to the side effects. Even when the more acute side effects subsided, their susceptibility to infections due to low white blood counts made spending time with friends and family difficult. The effects were cyclical for many. One respondent stated: "*I had one good week and then the next two were in bed."*

4. Lasting effects of chemotherapy: One respondent that was on chemotherapy felt that you never recover. To this date, 4 years after chemotherapy she still experiences fatigue and has not yet been able to return to work.

5. "Looking sick": LCC reported that not only did respondents feel sick on chemotherapy, they also looked sick. On chemotherapy, they tended to stay at home and some experienced hair loss. In contrast, LCC reported that respondents felt and looked well on oral therapies. One respondent stated: "*No one even knew I had cancer*."

In addition to the above, LCC indicated that the cost of travel is a further burden, more so in rural communities. Hospital appointments are difficult to obtain and access to chemotherapy suites is limited in both urban and rural areas, and more so in outlying areas.

LCC also noted that some patients may be deemed unsuitable of chemotherapy, for reasons of performance status, age or other illnesses, further shortening their survival and ability to fight their advanced lung cancer. One respondent, who was in her 60's before she passed away, was on chemotherapy and was having a very difficult time; however, she persevered and her reasons to persevere summed up the thoughts of many patients and involved three parts: Time to spend with her grandchildren and husband. Hope to beat the disease and, promise of a better treatment (more effective and more tolerable) on the horizon. LCC submitted that ceritinib represents that treatment.

4.1.3 Impact of Advanced or Metastatic NSCLC and Current Therapy on Caregivers

LCC received input from both caregivers from families that were interviewed for a previous pCODR submission (for crizotinib) and those that were interviewed for the current submission.

Caregivers play an important role in making decisions about treatment and care. During the brief, intense and relentlessly progressive course of advanced lung cancer, caregivers report difficulties in juggling the competing demands of providing emotional and tangible support to patients while meeting the ongoing obligations of home, work, and family. The demands of providing transportation, scheduling and making hospital visits, arranging for home nursing and oxygen support, and managing family finances are physically and emotionally devastating for both cancer patients and their caregivers. Persistent psychological distress and role adjustment problems experienced by caregivers have been reported up to a year after patients have completed treatment for cancer, with levels of distress far higher than those found in healthy controls.

In addition, the physical and emotional demands of care giving reach their peak as lung cancer progresses. Many caregivers and all lung cancer patients must take time off – most people affected by lung cancer are of lower socioeconomic status, and many families are devastated by the loss of one or both earners as patient and caregiver. Intensive chemotherapy requires caregivers both to attend hospital and treatment sessions, as well as to support patients at home through nausea and vomiting, fever and other toxicities.

To help illustrate the experiences of caregivers, below are some of the key responses reported by LCC:

1. High management burden of lung cancer – all caregivers felt a high physical burden prior to treatment and while they were on other treatments. This was reflected in all aspects, from the hospital visits to the support of patients at home. "*When* [redacted] *was not feeling well, all of a sudden, I went from having three children to four children.*" Chemotherapy often left caregivers feeling helpless as the side effects carried a high level of unpredictability. Everyone spoke to the challenge of constantly "*trying this, or that*" to make the patient more comfortable. One respondent stated: "*I was running a short order kitchen. Constantly we would be trying something and then she would have one bite and throw up. Crizotinib has allowed me to have a spouse and not a patient. It's allowed me someone I can spend time with instead of taking care off.*" The respondent's wife has since experience progression and is on ceritinib. LCC noted that ceritinib has allowed them to continue to spend quality time together as a couple.

2. Psychological burden of maintaining positivity – All the caregivers felt the need to maintain positivity - to try to stay positive so that their loved ones would not lose hope. One respondent, whose mother is living with lung cancer felt that burden as his mother became depressed after diagnosis. "*She didn't want to live.*" Chemotherapy and other treatments made that burden even harder due to the harsh side effects. Another respondent stated: "*Being the caregiver it's hard to be positive around someone that is feeling so horribly.*" "*You can't be happy and it's impossible to make them happy.*"

3. Time – This concept was very important. This is something that both crizotinib and ceritinib were able to give to the families. The length of time their loved ones were on crizotinib varied, from a low of 4 months to over a year. One continues to be on crizotinib at the time of the call with a duration of 4 years. Another respondent participated in the original 2011 crizotinib submission to pCODR is still doing well on crizotinib. She and her husband provided their thoughts in the one-on-one interview as they were spending time together on a road trip. Caregivers felt that crizotinib gave them time with loved ones to do "*normal*" things. "*Living with lung cancer takes away all normal, but crizotinib gave us a new normal.*" They all expressed that it gave them much valued time as a family, to travel to visit with friends. All expressed the idea of a "*good*" time, even if it was short.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to date with Ceritinib

According to LCC, respondents who received crizotinib saw fast response and felt better. In view of this, the expectation was that ceritinib would be the same if not better. Patients have a perception that crizotinib did not cross the blood/brain barrier while ceritinib does, and thus ceritinib would be efficacious against brain metastasis.

LCC stated that for ALK+ NSCLC patients, crizotinib revolutionized their treatment and outcomes and that ceritinib continued that hope and quality of life.

LCC also noted that like crizotinib, ceritinib had manageable side effects and improved outcomes. According to LCC, patients continue to be feeling great and are highly functional. Also, patients are staying out of chemotherapy clinics and hospital, and both they and their caregivers are living more active lives because of these new treatments.

According to LCC, all seven (7) of the patients that had experience with ceritinib had previously been on crizotinib. LCC also reported that four (4) of the respondents interviewed who are presently on ceritinib had previously experienced chemotherapy and the past experience left a deep impression of a harsher treatment. Chemotherapy made them feel sick, whereas targeted therapy made them feel well. Five (5) of the respondents that have been interviewed since February 2015, have lived more than five years on targeted therapy. They feel like they have beat the five year survival rate generally associated with lung cancer.

Below are key findings and comments that were reported by LCC based on patients' experience with ceritinib:

1. Ceritinib had manageable side effects

Those living with ceritinib reported that side effects differed from both chemotherapy and crizotinib. Of those interviewed the most commonly reported side effects were elevated liver enzymes and heart palpitations. Other side effects were nausea and diarrhea that in most cases, were less frequent, or lasted a shorter duration than those experienced with crizotinib.

One respondent stated: "*The difference between crizotinib and ceritinib is that crizotinib's side effects lasted longer but were more "mild" and the ceritinib side effects were more intense.*"

LCC noted that all the patients on ceritinib started on 5 pills per day and all underwent dose reductions. When this occurred the patients stated that the heart palpitations resolved and liver enzymes returned to normal.

2. Ceritinib allowed me to continue to have confidence in my treatment

Like crizotinib, this confidence came from two aspects. LCC reported that ceritinib helped achieve dramatic tumour shrinkages in the vast majority of respondents that were interviewed. According to LCC, one respondent had 10 small tumours in her brain. She started on ceritinib and 6 – 8 weeks later, all the tumours had disappeared. Today she is living with no evidence of disease.

Psychologically, continuing on an oral targeted therapy helped all the patients feel better and believe in treatment, and the possibility of a future. For many, disease progression on crizotinib differed from disease progression after chemotherapy as many did not feel "sick" when they found out that crizotinib was no longer working.

One respondent stated: "*Going back on chemotherapy would be devastating.*"

3. Ceritinib continued "*normal*"

One respondent stated: "*Its amazing to have the drug. It's unbelievable. I am not working anymore but it allows me to be almost bored! I go to the gym several times a week. It's amazing!*"

Another respondent stated: "*There is no comparison – it is a life saving drug and gives you a life. I take care of my grandchildren and enjoy time with my family.*"

LCC noted that like crizotinib, after the side effects were managed, all felt that they could "*function normally.*" "*Sometimes I forget I have cancer – Its bizarre!*" stated one responded.

Another respondent stated: "*Day to day, I continue to feel good.*" LCC noted that the respondent is able to come back home at night and "*roll around with their baby*" on the floor. "*I don't feel like I have lost anything.*"

4. Ceritinib meant hope continued

One respondent stated: "*I feel like I can live for a long time and I feel like I can become an old lady!*"

Another respondent expressed: "*It's important to me be able to continue on a targeted therapy. Going to chemo would be demotivating. It was a relief to stay on the targeted path.*"

A third respondent stated: "*Ceritinib has made this [lung cancer] doable.*"

One respondent reported: "*Because ceritinib is so effective at it gives us good measurable time – It made a huge impact and it completely worth it!" "With this drug you get substantial time balanced with ability to live your life, which is amazing!*"

"For those of us that are on crizotinib, ceritinib gives us hope for the future as there is another treatment that will allow us to avoid chemotherapy and radiation once crizotinib fails." "I just got married this weekend and the option of ceritinib leads me to truly believe that there is a future to come," stated another respondent.

4.3 Additional Information

LCC highlighted that there would only be a small population of patients eligible to receive ceritinib, as only 2-7% of patients with NSCLC have ALK positive disease.

LCC indicated that ALK+ patients in Canada currently have one line of publically funded targeted therapy, while people living with other cancers have more than one line of publically funded targeted therapy. LCC stated that funding ceritinib for ALK+ lung cancer will allow patients and families of this disease to have equality in terms of access to efficacious treatment choices and standard of care.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group at the beginning of the review as factors that potentially affect the feasibility of implementing a funding recommendation for ceritinib (Zykadia) for metastatic non-small cell lung cancer. The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr).

Overall Summary

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

Clinical factors:

- Standard of care is intravenous chemotherapy and crizotinib
- Lack of comparative data and/or phase 3 trials

Economic factors:

- Extend treatment options with another line of therapy, if third line
- If approved for second line, replacement of intravenous chemotherapy

Please see below for more details.

5.1 Factors Related to Comparators

PAG noted that the standard first-line therapy for patients with EGFR mutation-positive NSCLC would be gefitinib or afatinib and standard second-line therapy would be erlotinib. Cisplatin plus pemetrexed is the standard first-line treatment and crizotinib is the standard second-line treatment for patients who are not EGFR mutation-positive but are ALK positive.

PAG is seeking information on the long term data and on comparative data with intravenous chemotherapy and crizotinib in the second-line treatment of NSCLC. PAG noted that submission only includes a phase 1 trial and interim results of a phase 2 trial that do not provide comparative data with current standard of care. PAG noted that the precedence set by the original submission for crizotinib which included non-comparative trials for first-line and second-line treatment and pERC recommended to not fund due to limitations in the data available at the time of the review. At the time of the PAG input, the second pCODR resubmission for crizotinib (in first-line treatment of NSCLC is still under review and PAG indicated that if it is eventually recommended for funding in the first-line setting), crizotinib would be the standard of care in the first-line and intravenous chemo would be the standard of care in the second-line setting for ALK positive NSCLC. Thus, PAG is seeking comparative data for ceritinib versus cisplatin/pemetrexed.

5.2 Factors Related to Patient Population

Although NSCLC is a common cancer, PAG noted that ceritinib would only be indicated for patients who were ALK positive and who were previously treated with ALK inhibitor. The overall numbers of patients accessing ceritinib is likely to be small. This is an enabler to implementation.

PAG noted that there may be indication creep for use of ceritinib in the first-line setting.

At the time of the PAG input, crizotinib is funded in the second-line treatment and thus, ceritinib would be used in the third-line setting. In this scenario, ceritinib would be an additional line of therapy, extending treatment options for patients.

PAG noted that if crizotinib were to be used in the first-line setting, ceritinib would be used in the second-line setting. PAG is seeking guidance on sequencing of intravenous chemotherapy in the third-line setting after treatment with two ALK inhibitors.

5.3 Factors Related to Dosing

PAG noted that the drug's once daily, continuous dosing schedule and the flat dose of 750mg would be an enabler to implementation. However, a barrier to implementation is the need for patients to take five capsules for the dose.

There is one capsule strength available and dose adjustment is made by adjusting the number of capsules per dose. PAG noted this reduces wastage and is easier for patients to manage.

5.4 Factors Related to Implementation Costs

As ceritinib is administered orally, PAG noted that chemotherapy units and chair time would not be required.

PAG noted that there may be a small incremental cost with the addition of a third-line of therapy and a possible shift in costs if ceritinib was used as second-line therapy after crizotinib in first-line.

PAG also noted that additional health care resources may be required to monitor and treat toxicities and monitor drug-drug interactions.

5.5 Factors Related to Health System

PAG noted that ALK testing is already available in all provinces. Since ceritinib is indicated for use after prior treatment with ALK inhibitor, ALK testing for the patient would already be completed. This is an enabler to implementation. PAG also noted that in some cases, patients would start therapy prior to receiving the results of their ALK testing due to the delayed turn-around times for test results.

PAG noted that ceritinib 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 is 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.

5.6 Factors Related to Manufacturer

The high cost of ceritinib is a barrier to implementation.

PAG is seeking trial data comparing ceritinib to crizotinib in the first-line and in the second-line setting. The lack of comparative data from a phase 3 clinical trial is noted as a barrier to implementation.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the safety and efficacy of ceritinib as a monotherapy on patient outcomes, in the treatment of patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have disease progression on or with intolerance to crizotinib.

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

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel 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 5. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*†	Outcomes
Published and unpublished RCT or non RCTs	Patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have disease progressioned on or who were intolerantwith intolerance to Crizotinib. Subgroups: • Histologic type • ECOG PS (0—1 vs. ≥2) • EGFR mutation status • Age (< 65 years vs. ≥65 years) • Ethnicity (Asian vs. non-Asian) • Sex • Smoking status (never or light vs. current/heavy smokers) • Brain metastases vs. no brain metastases	Ceritinib monotherapy at recommended dose of 750 mg orally once daily	Cytotoxic Chemotherapies: • Combinations of treatment options for patients with ALK + NSCLC treated with platinum doublet agents • Pemetrexed • Docetaxel • Best supportive care • Placebo	Efficacy • **OS** • **PFS** • **HRQoL** • ORR • DOR • DCR Safety • **AEs** • **SAEs** • WDAEs

ALK=anaplastic lymphoma kinase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EGFR=epidermal growth factor receptor; HRQoL=Health related quality of life; RCT=randomized controlled trial; SAE=serious adverse events; AE=adverse events; WDAE=withdrawals due to adverse events; DCR=disease control rate; ORR=objective response rate; DOR=duration of response

** All treatments in combination with supportive care.*

† Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).

6.2.2 Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (May 2015) 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 Zykadia and ceritinib.

No methodological filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but not limited by publication year. The search is considered up to date as of September 2, 2015.

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. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were limited to the last five years. 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.

6.2.3 Study Selection

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

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

6.2.4 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.

6.2.5 Data Analysis

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

6.2.6 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 overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

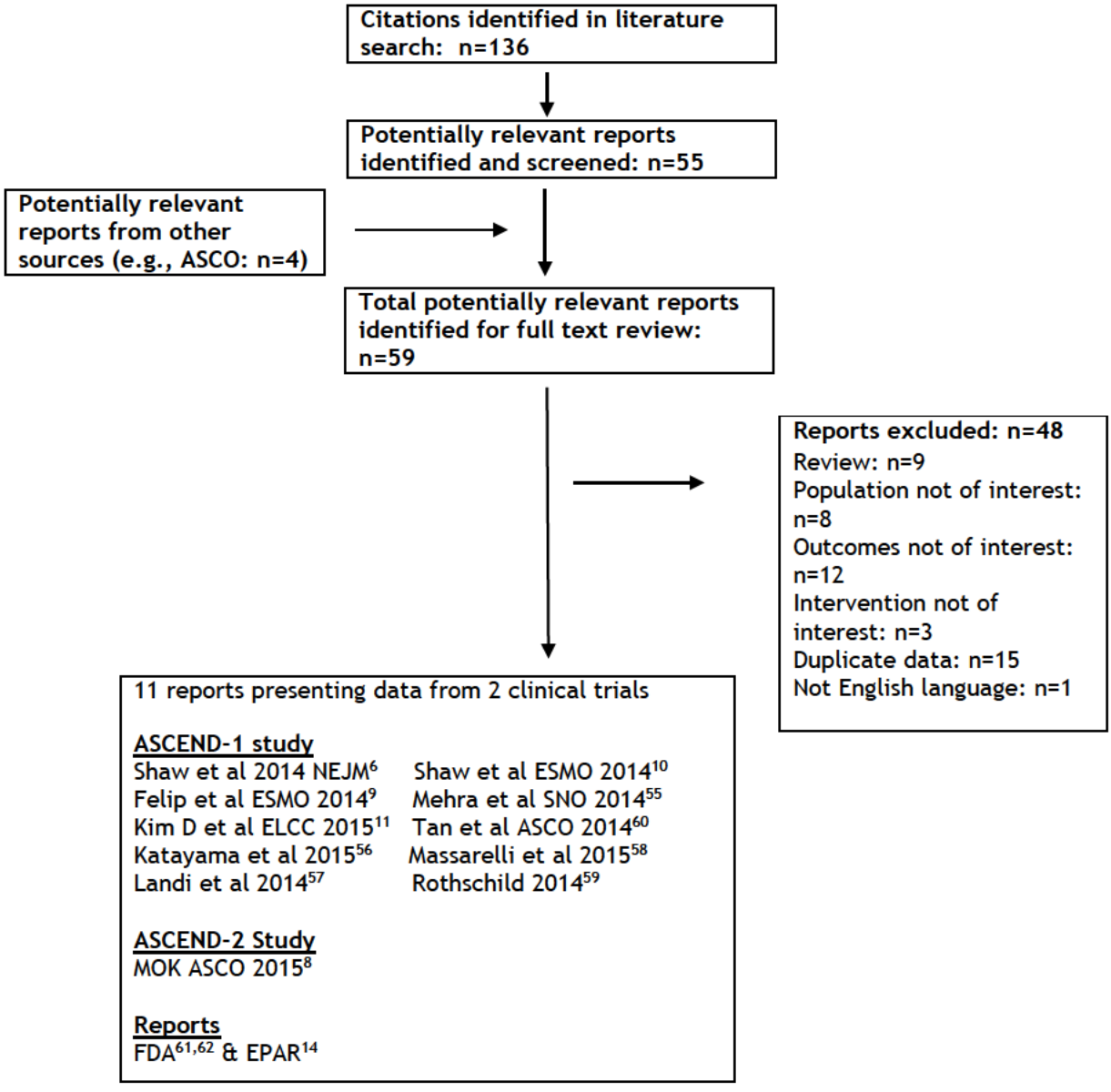
6.3.1 Literature Search Results

Of the 131 potentially relevant reports identified, 11 reports presenting data from 2 unique clinical trials were included in the pCODR systematic review [6,8-11,55-60]

The submitter commented on the pCODR Expert Review Committee's (pERC's) Initial Recommendation that one study included in their submission to pCODR was not reviewed. As it was included in the pCODR submission as a part of the economic evaluation, a description and assessment was completed in the accompanying pCODR Economic Guidance Report for ceritinib (Zykadia) for metastatic NSCLC. Furthermore, the retrospective observational study was not published and was excluded during the screening phase as it did not meet the criteria of the protocol which was set a priori. Evidence from phase II studies was of the highest quality available.

Retrospective case series were not included in this systematic review as they are generally considered low quality evidence that is susceptible to many forms of bias, including, but not limited to, incomplete data collection and selection bias. In addition, the inclusion of studies in this systematic review was based on a pre-specified protocol in order to prevent bias in the selection of studies for inclusion. Choosing to include studies that do not meet the pre-specified eligibility criteria of the systematic review has the potential to bias the results in the direction that is of interest to the author while also negating the reason for having eligibility criteria.

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



Note: Additional data related to studies ASCEND-1 and ASCEND-2 were also obtained through requests to the Submitter by pCODR

6.3.2 Summary of Included Studies

Two non-randomized interventional trials were identified that met the eligibility criteria of this systematic review (see Tables 2 & 6).

6.3.2.1 Detailed Trial Characteristics

Table 6. Summary of Trial characteristics of the included studies of ceritinib in patients with locally advanced or metastatic NSCLC who have disease progression on or with intolerance to crizotinib.

X2101 Study [6,9-11,63]			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
NCT01283516 ASCEND-1 Data cut-off: 14 April 2014 Phase 1, global, single-arm, open-label, multicentre, dose- escalation and expansion trial Non randomized Expansion Phase: N=246 patients with ALK+NSCLC tumours ALK inhibitor treated N=163 & ALK inhibitor naïve N=83 Funded by Novartis Pharmaceuticals	Adult patients' ≥ 18 years with locally advanced or metastatic progressive ALK+ NSCLC who had investigator-identified brain metastases at baseline Presence of at least one measurable lesion as per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 in expansion phase Patients who were ALK inhibitor naïve & patients who had received prior treatment with an ALK inhibitor ECOG PS ≤ 2 & life expectancy of ≥ 12 weeks In the group of patients with NSCLC, ALK translocation had to be detected by FISH in ≥ 15% of tumour cells	**Intervention:** Ceritinib 50 mg to 750 mg/day (dose escalation phase) and 750 mg/day (expansion phase) MTD and recommended ceritinib dose for the expansion phase was set at 750 mg once daily in continuous 21-day cycles, until unacceptable toxicity, disease progression, or withdrawal of consent **Comparator:** N/A	**Primary:** MTD of ceritinib (during dose Escalation phase) ORR, DOR as per RECIST criteria & by BIRC assessment **Secondary:** PFS OS PK parameters Safety & tolerability
A2201 Study[8,13,64]			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
NCT01685060 ASCEND-2 Data cut-off: 13 August 2014 Phase 2, global, single-arm, open-label, multicentre	Adult patients ≥ 18 years with histologically or cytologically confirmed diagnosis of stage IIIB or IV NSCLC that carries an ALK rearrangement, as per the FDA-approved FISH assay. Progression on standard therapy and crizotinib (1-3 lines of cytotoxic chemotherapy)	**Intervention:** Ceritinib at 750 mg once daily in continuous 28-day cycles, until unacceptable toxicity, discontinuation of treatment at the discretion of the	**Primary:** ORR by investigator assessment & per RECIST 1.1 **Secondary:** DOR DCR

Table 6. Summary of Trial characteristics of the included studies of ceritinib in patients with locally advanced or metastatic NSCLC who have disease progression on or with intolerance to crizotinib.			
X2101 Study [6,9-11,63]			
trial Non-randomized N= 140 Funded by Novartis Pharmaceuticals	ECOG PS 0-2 Measurable disease as per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.	investigator or patient, initiation of new anticancer therapy and/or death **Comparator:** N/A	TTR ORR by BIRC assessment PFS OS OIRR Safety profile & AEs
Notes: ECOG = Eastern Cooperative Oncology Group; **PS** = performance status; **QOL** = quality of life; **RECIST** = Response Evaluation Criteria in Solid Tumours; **AEs** = adverse events **BIRC**=Blinded Independent Review Committee; **DCR**=disease control rate; **DOR**=duration of response; **OIRR**= overall intracranial response rate; **ORR**= objective response rate; **OS**=overall survival; **TTR**=time to response; **PFS**= progression-free survival; **EORTC-QLQ-C30**= European Organization for Research and Treatment of Cancer's core quality of life questionnaire.			

a) Trials

Two non-randomized interventional trials met the inclusion criteria for this systematic review, ASCEND-1[7,9-11] and ASCEND-2.[8] Characteristics of the trials' designs can be found in Table 6 and select study quality-related characteristics can be found in Table 1.

ASCEND-1 was a phase I trial and ASCEND-2 was a phase II trial. ASCEND-1 enrolled adult patients diagnosed with a locally advanced or metastatic non-small cell lung cancer that has disease progression despite standard therapy, or for which no effective standard therapy exists.

The ASCEND-1 study design included a dose-escalation phase, followed by an expansion phase in which all patients received treatment at the maximum dose established in the dose-escalation phase (750 mg). In ASCEND-2, adult patients with locally advanced or metastatic ALK-positive NSCLC who were previously treated with cytotoxic chemotherapy (one to three prior lines, of which 1 must have been a platinum doublet) and crizotinib must have been the last prior systemic antineoplastic therapy before ceritinib initiation were eligible to enroll.[8]

Both studies required documented ALK-positive status, in ASCEND-1 based on validated ALK assay and in ASCEND-2 based on the FDA-approved, ALK break-apart fluorescence in situ hybridization (FISH) assay. Additionally, both ASCEND-1 and ASCEND-2 allowed patients with asymptomatic or neurologically stable central nervous system disease at baseline to enroll. Select quality characteristics of each study are summarized in Table 1; however, as the ASCEND-2 study was reported in abstract form only, many of the study details have not been reported.

Both studies were described as being open-label.[8,10] Both trials were multicentre studies: the ASCEND-1 study[14] was conducted at 20 centres in 11 countries: Australia (1 centre), Belgium (1 centre), Germany (4 centres), Italy (2 centres), Netherlands (1 centre), Spain (1 centre), UK (1 centre), Canada (1 centre), Singapore (1 centre), Korea (1 centre), and US (6 centres) and the ASCEND-2 study[8] was conducted globally across 51 sites. Both studies were funded by Novartis Pharmaceuticals.[63,64]

The primary outcome/efficacy endpoint in both trials was to demonstrate the antitumour activity of ceritinib as measured by ORR by investigator assessment according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. In the ASCEND-1 study,[14] the primary objective was also to

determine the maximum tolerable dose (MTD) of ceritinib in adult patients with tumours harbouring a genetic alteration in ALK. The overall response rate (ORR) was defined as the proportion of patients with a best overall response of CR or PR. Another primary efficacy outcome in ASCEND-1 was duration of response (DOR), which was defined as the time from first documented response (PR to CR) to the date of first documented disease progression (PD) or death due to any cause, among patients with a confirmed PR or CR. Secondary efficacy outcomes were progression-free survival (PFS) and overall survival (OS). In the ASCEND-2 study, secondary objectives included ORR as assessed by BIRC, duration of response (DOR), disease control rate (DCR), time to response (TTR), overall intracranial response rate (OIRR), progression-free survival as assessed by both investigator and BIRC, overall survival (OS) and safety profile.

In the ASCEND-1 trial, the efficacy analyses included only patients with ALK+ NSCLC; all patients treated with ceritinib 750 mg/day, including those with other tumour types, were included in the safety analyses. DOR and PFS efficacy data were estimated using Kaplan Meier method, with associated 95% CI. Safety data were summarised for all patients who received ≥1 dose of ceritinib 750 mg/day. Efficacy data were analysed for all patients with NSCLC who received ≥1 dose of ceritinib 750 mg/day, and also by prior ALK inhibitor treatment status.[9]

No formal statistical power calculations to determine sample size were performed for the ASCEND-1 study. During the expansion phase, up to 310 patients could be enrolled (including all patients treated at the recommended dose (RD) during the dose-escalation phase who were eligible for the safety set) with at least 25 and up to 100 patients in each of NSCLC arms (Arms 1A, 1B and 2), and approximately 10 patients in Arm 3. Arm 1A included patients with NSCLC that had disease progression during treatment with a prior ALK inhibitor or within 2 weeks of the last dose of a prior ALK inhibitor, and the first dose of ceritinib was expected to be ≤ 60 days since the last dose of the prior ALK inhibitor. Arm 1B included patients with NSCLC that had disease progression since treatment with a prior ALK inhibitor, but that need not have been the last prior therapy, and they did not meet the criteria for Arm 1A. Arm 2 included patients with NSCLC that had not been previously treated with an ALK inhibitor. Lastly, Arm 3 included patients with a malignancy other than NSCLC, and there was no requirement regarding therapy with a prior ALK inhibitor.[14]

In ASCEND-1, protocol deviations were reported in 23.2% of the 246 ALK-positive NSCLC patients at 750 mg. The deviations reported were use of prohibited concomitant medications in 8.9% (n=22) patients, patients did not follow dosing of ceritinib as per the protocol in 8.1% (n=20) patients, selection criteria not adhered to in 3.3% (n=8) patients where ALK translocation was detected by a method other than the FISH assay, 1 patient did not have a tumour with evidence of ALK expression and key procedures were not performed as per the protocol in 2.8% (n=7) patients.[14]

The study protocol for ASCEND-1 was amended six times and this was mainly to increase the sample size and facilitate a representation of further efficacy and safety of ceritinib. These amendments included basing patients' eligibility on ALK translocation as assessed by FISH, removing the criteria of confirmatory ALK testing by a central laboratory, increasing the number of allowed dose reductions from 2 to 3, updating the exclusion criteria to exclude patients taking concomitant medications with a known risk of prolonging the QT interval or inducing Torsade de pointes. In addition, the definition of duration of response (DOR) was also amended from first documented response to the date of first documented disease progression or death due to underlying cancer to the date of first documented disease progression or death due to any cause.[14]

The sample size requirement in the ASCEND-2 study was 137 patients to test a null hypothesis of ORR ≤ 25% with a one-sided alpha of 0.025 and 90% power, based on the exact binomial distribution (see Table 1).[8]

In the ASCEND-2 trial, the Full Analysis Set (FAS) consisted of all patients who received at least one dose of study drug, and was the default analysis set used for all analyses including the primary analysis. The Safety Set consisted of all patients who received at least one dose of study drug. All safety data were analyzed using the Safety Set.[14]

b) Populations

In the ASCEND-1 study, a total of 255 patients received at least one dose of ceritinib at the recommended 750 mg dose. Of these 255 patients, 246 had ALK+NSCLC; 83 of these had received no prior treatment with an ALK inhibitor and 163 had received prior ALK inhibitor therapy. Within the subgroup of 246 patients with ALK+NSCLC, 124 patients were identified with brain metastases at study entry and 122 patients had no brain metastases. Of these 124 brain metastases patients, 98 had been previously treated with an ALK inhibitor and 26 were identified as being ALK inhibitor naïve.[10]

The majority of ALK+ NSCLC patients recruited were never/ex-smokers, Caucasian or Asian and had an ECOG performance status ≤1. The number of prior treatment regimens was also higher in patients who were previously treated with an ALK inhibitor than those who were ALK inhibitor naïve.[9]

In the ASCEND-2 study, a total of 140 ALK+ NSCLC patients with metastatic disease previously treated with at least 1 platinum doublet and crizotinib as the last therapy received at least 1 dose of ceritinib 750 mg/day. The majority of patients (n = 100) presented with brain metastases at study entry (71.4%), of whom 72 (72.0%) patients had received prior brain radiation (BRT). All patients received at least 1 platinum-based regimen and crizotinib as the last treatment before starting ceritinib. 43.6% patients received doublet chemotherapy, 34.3% patients received triplet, and 22.1% patients received multiple lines of prior chemotherapy.[8] Baseline characteristics were similar between the ASCEND-1 and ASCEND-2 trials (see Tables 7 and 8).

Table 7: Baseline Patient Characteristics in the included studies of ceritinib in patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC who havef disease progression on or with intolerance to crizotinib.[8-10]

Characteristic	X2101 (ASCEND-1)[9,10]			A2201 (ASCEND-2)[8]
	NSCLC with prior ALK inhibitor* 750 mg n=163	NSCLC ALK inhibitor naïve patients 750 mg n=83	All NSCLC patients 750 mg n=246	750 mg n=140
Sex (female; n [%])	88(54.0)	44(53.0)	132(53.7)	70(50.0)
Age (median) years (range)	52(24-80)	55(22-80)	53(22-80)	51(29-80)
ECOG performance status, n (%)				
0	38(23.3)	25(30.1)	63(25.6)	42(30.0)
1	104(63.8)	51(61.4)	155(63.0)	78(55.7)
2	20(12.3)	7(8.4)	27(11.0)	20(14.3)
>2	1(0.6)	0	1(0.4)	0
Smoking status, n (%)				
Never/Ex-smoker	158(96.9)	82(98.8)	240(97.6)	NR

Current smoker	5(3.1)	1(1.2)	6(2.4)	NR
Tumour histology/cytology, n (%)				
Adenocarcinoma	152(93.3)	76(91.6)	228(92.7)	129(92.1)
Other	11(6.7)	7(8.4)	18(7.3)	11(7.9)
No. of prior medication regimens, n (%)				
0	0	16(19.3)	16(6.5)	0
1	26(16.0)	38(45.8)	64(26.0)	0
2	45(27.6)	16(19.3)	61(24.8)	61(43.6)
3	35(21.5)	7(8.4)	42(17.1)	48(34.3)
>3	57(35.0)	6(7.2)	63(25.6)	31(22.1)
Site of metastases, n (%)				
Brain	98(60.1)	26(31.3)	NR	100(71.4)
Liver	68(41.7)	30(36.1)	NR	52(37.1)
Bone	69(42.3)	26(31.3)	NR	81(57.9)
Predominant race, n (%)				
Asian	47(28.8)	35(42.2)	NR	53(37.9)
Caucasian	108(66.3)	48(57.8)	NR	84(60.0)

ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer
*All received crizotinib (in addition, 5 patients received the investigational ALK inhibitor alectinib & alectinib was the last ALK inhibitor)

Table 8: Baseline Patient Characteristics in the included studies of ceritinib in patients with ALK+NSCLC and Brain Metastases.[8,10]
data cut-off: April 2014 for ASCEND-1 & August 2014 for ASCEND-2

	X2101 (ASCEND-1)[9,10]			A2201 (ASCEND-2)[8] n=140
Characteristic	NSCLC with prior ALK inhibitor n=98	NSCLC ALK inhibitor naïve patients n=26	All NSCLC patients n=124	
Sex (female; n [%])	57(58)	17(65)	74(60)	70(50)
Age (median) years (range)	51(24-80)	53(27-73)	51(24-80)	51(29-80)
ECOG performance status, n (%)				
0	16(16)	6(23)	22(18)	42(30.0)
1	68(69)	16(62)	84(68)	78(55.7)
2	13(13)	4(15)	17(14)	20(14.3)
>2	1(1)	0	1(1)	0
Smoking status, n (%)				
Never/former or current	65/33(66/34)	17/9(65/35)	82/42(66/34)	NR
Tumour histology/cytology, n (%)				
Adenocarcinoma	92(94)	24(92)	116(94)	129(92.1)
Other	6(6)	2(8)	8(6)	11(7.9)
No. of prior medication regimens, n (%)				
0	0	3(12)	3(2)	0
1	11(11)	13(50)	24(19)	0
2	28(29)	4(15)	32(26)	61(43.6)
3	59(60)	6(23)	65(52)	48(34.3)
>3	68(69)	15(58)	83(67)	31(22.1)
Extra cranial metastatic lesions				
Lung	66(67)	20(77)	86(69)	47(33.6)

Lymph nodes Bone Liver	93(95) 61(62) 43(44)	22(85) 13(50) 12(46)	115(93) 74(60) 55(44)	73(52.1) 81(57.9) 52(37.1)
Predominant race, n (%) Asian Caucasian	 35(36) 60(61)	 14(54) 12(46)	 49(40) 72(58)	 53(37.9) 84(60.0)
Prior radiotherapy to the brain, n (%)	68(69)	15(58)	83(67)	72/100(72%)
Time elapsed from prior radiotherapy to the brain to first dose of ceritinib, months (range)	6.5(0-38)	4.6(1-21)	6.1(0-38)	6.2(0.5-54)
ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer				

c) Interventions

Details of the dosing and administration of the study drug used in the treatment of each trial can be found in Table 6. In both trials, treatment regimens were given until disease progression, unacceptable toxicity or withdrawal of consent.[8,9]

ASCEND-1 was a single-arm study, thus all patients in the expansion phase were assigned to oral ceritinib 750 mg once daily, further details can be found in the trials section. The dose for ASCEND-2 was selected on the basis of Study ASCEND-1, where the maximum tolerated dose (MTD) of ceritinib and recommended dose for the expansion phase were determined to be 750 mg once daily. Dose adjustments were permitted for intolerable grade 2 or 3 treatment-related toxicities or for any grade 4 toxicity. Dosing was interrupted until resolution to at least grade 1, followed by dose reduction or treatment discontinuation (in the case of grade 4 toxicity only). Once the dose of ceritinib was reduced, it could not be re-escalated. A maximum of three dose modifications were allowed after which the patient was discontinued from treatment with ceritinib.[14]

Median ceritinib treatment exposure in ASCEND-1 among all 124 patients with ALK+NSCLC and brain metastases at baseline was 36 weeks. In the ALK inhibitor-pretreated cohort median treatment exposure was 36 weeks and 43 weeks in the ALK inhibitor-naïve cohort. The median dose intensity for patients with ALK+ NSCLC and brain metastases at baseline was 628 (range, 311-750) mg/day in the total cohort, 570 (range, 362-750) mg/day in the ALK inhibitor-naïve and 637 (range, 311-750) mg/day in the ALK inhibitor-pretreated cohort. The most frequent reason for treatment discontinuation amongst all patients with brain metastases at baseline (n=124) was disease progression in 45.2% of patients. There was a slightly higher treatment discontinuation observed among the ALK inhibitor-pretreated than the ALK inhibitor-naïve patients (46.9% and 38.5%, respectively).[10]

In ASCEND-2, median ceritinib treatment exposure was 8.8 months (range 0.1-19.4). The median relative dose intensity was 84.9% (range 37.5-100.00). Dose interruptions of ≥1 day of treatment occurred in 75.7% (106/140) patients and 85.8% (91/106) of all dose interruptions recorded on study were attributable to AEs. There was ≥1 dose reduction required in 54.3% (74/106) patients and 84.2% (64/76) of all dose reductions reported on study were due to AEs.[8]

Patient Disposition

In the ASCEND-1 trial, there were a total of 255 patients who were treated with ceritinib at the recommended dose of 750 mg/day. Of these patients, 246 had ALK-positive NSCLC with a median duration of follow-up of 11.1 months. Among these patients, a total of 163 had been previously treated with an ALK inhibitor with a median duration of follow up of 10.2 months and a total of 83 patients were classified as ALK inhibitor naïve with a median duration of follow-up of 12.5 months. In the previously treated with an ALK inhibitor group, 52 (31.9%) patients had treatment ongoing and 111(68.1%) patients discontinued treatment at the primary analysis cut-off date. The reasons for study drug treatment discontinuation were 17 (10.4%) patients had an adverse event, death in 4 (2.5%) patients, and disease progression in 74 (45.4%) patients. In addition, there was consent withdrawal in 15(9.2%) patients and a loss of follow-up in 1(0.6%) patient.[9]

Of the 83 patients in the ALK inhibitor naïve group, 47 (56.6%) had treatment ongoing, and 36(43.4%) discontinued treatment at the primary analysis cut-off date. The reasons for study drug treatment discontinuation were adverse events in 7 (8.4%) patients, death in 4 (4.8%), disease progression in 24 (28.9%), and consent withdrawal in 1(1.2%) patient.

In the ASCEND-1 trial, of the 246 patients with ALK+ NSCLC treated with ceritinib at 750 mg/day, there were 124 (50.4%) patients identified with brain metastases at study entry with a median duration of follow-up of 10.5 months and 122 patients identified with no brain metastases at study entry. Among the group of patients with brain metastases, 98 had been previously treated with an ALK inhibitor with a median duration of follow-up of 9.8 months and 26 patients were ALK inhibitor naïve with a median duration of follow-up of 12.3 months.[65]

In the ASCEND-2 trial, there were a total of 140 patients who were treated with ceritinib at the recommended dose of 750 mg/day. Of these patients, 51(36.4%) had treatment ongoing and 89(63.6%) had discontinued treatment at the primary analysis cut-off date. The primary reasons for study drug treatment discontinuation were an adverse event in 10 (7.1%) patients, death in 5(3.6%) patients and progressive disease in 56(40.0%). In addition, 6 (4.3%) patients discontinued due to a physician decision, 11(7.9%) patients due to a guardian decision and 1(0.7%) patient was lost to follow-up.[8] Please see Tables 13 and 13.1 for more details on adverse events.

d) Limitations/Sources of bias

Refer to Table 1 for a summary of quality-related features of both trials.

Overall, results from both ASCEND-1 and ASCEND-2 are limited by their level of evidence and ability to inform comparative efficacy against relative comparators in the ALK+NSCLC setting.

Both ASCEND-1 and ASCEND-2 are single-arm non-randomized open-label trials that lack blinding of all participants and investigators in the trial. Therefore, the following biases and limitations should be noted:

- The trial was open-label, and thus is at risk for a number of different biases that can affect the internal validity of a trial. Examples of such biases are patient selection as part of inclusion criteria for eligibility and performance bias due to knowledge of the study

treatment. In open-label trials, the assessment of measures such as HR-QoL in ASCEND-2 and the reporting of adverse events are also likely to be subjectively biased. It is important to also note that investigators, study personnel, clinicians and patients involved in both the trials were aware of the study drug treatment assigned, which can introduce the potential to bias results and outcomes in favour of whether the assessor (investigator or patient) believes the study drug is likely to provide a benefit. In ASCEND-2, assessments of best overall response, PFS and intracranial response were conducted via a blinded independent review committee (BIRC), which could reduce the potential for biased results of these outcomes.

- The single-arm, non-randomized design for both ASCEND-1 and ASCEND-2 makes interpreting the efficacy and safety/adverse events attributable to ceritinib difficult, since all patients received the same treatment in both studies. In particular, the lack of a randomized comparison treatment group greatly limits the robustness of the preliminary overall survival and progression-free survival results. The overall survival data should also be considered exploratory given the small sample sizes and no power calculation for PFS and OS.
- The adequacy of the objective response rate as a primary efficacy endpoint is also unclear. Objective response rate appears to be correlated with median overall survival, but a statistical correlation does not necessarily equate to the prediction of a survival benefit from the response rate.
- Both ASCEND-1 and ASCEND-2 had multiple secondary outcomes which increase the risk of type 1 error
- There were six protocol amendments in the ASCEND-1 trial. This could have introduced selection bias in the enrolled patients by selecting patients that would fare better on the study drug. For example, one of the protocol amendments was updating the exclusion criteria to exclude patients who are taking concomitant medications with a known risk of prolonging the QT interval. This would remove the applicability aspect of this study drug to a real ALK+NSCLC patient scenario in which patients are on several medications and can experience adverse events tied to one or more drug interactions.
- In ASCEND-1, protocol deviations were reported in 23.2% of the 246 ALK+NSCLC patients receiving ceritinib at 750 mg/day. The deviations reported were use of prohibited concomitant medications in 22(8.9%) patients, not following dosing of ceritinib as per the protocol in 20 (8.1%) patients and selection criteria not adhered to in 8 (3.3%) patients. Such deviations limit the validity of the safety and efficacy results and add uncertainty into the measurable endpoints of this trial.
- In the ASCEND-1 subgroup of 163 patients who had received a prior ALK inhibitor, all had received crizotinib except for 5 patients that had received alectinib as the last ALK inhibitor prior to starting ceritinib therapy. This introduces a confounding factor into the investigational efficacy and safety analysis of ceritinib as it is difficult to delineate the effects of ceritinib and alectinib when looking at the ORR and OS data. However, given the few number of patients treated with alectinib as the last ALK inhibitor, the overall results are unlikely to be confounded.
- The sponsor Novartis Pharmaceuticals funded both the trials, and sponsor employees/stock-holders were involved in all aspects of conducting the trial and the extent of their involvement in performing data analyses is unclear. In addition, the extent to which the use of independent review committees may have influenced the results and the reporting of the trial is also uncertain.
- Both trials included patients with an ECOG performance status of ≤ 2. Performance status is a well-established prognostic factor in advanced/metastatic NSCLC. Consequently, the

beneficial effects of ceritinib may have been overestimated among a study population with better survival probabilities than typically seen in practice.[66]

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

A summary of efficacy results can be found in Tables 9-10.

Table 9: Key efficacy results of included studies of ceritinib in patients with ALK+NSCLC who have disease progression on or with intolerance to crizotinib [8,9]

Study	ORR % [95%CI]	DOR Median [95%CI]	PFS Median [95%CI]	OS Median [95%CI]	Median follow-up
ASCEND-1 prior ALK inhibitor n=163	56.4% [48.5, 64.2]	8.3 months [6.8, 9.7]	6.9 months [5.39, 8.41]	16.7 months [14.8, NE]	10.2 months
ASCEND-2 n=140*	38.6% [30.5, 47.2]	9.7 months [7.1, 11.1]	5.7 months [5.4, 7.6]	14.9 months [13.5, NE]	11.3 months

Notes: *FAS investigator assessed; NE = not estimable; CI = confidence interval

Table 10: Systemic response to ceritinib treatment in patients with ALK+NSCLC and brain metastases at baseline* as per investigator assessment[8,10]

	ASCEND-1 (n=124)		ASCEND-2 (whole body response) (n=100)
	ALK inhibitor treated (n=98)	ALK inhibitor naïve (n=26)	
ORR, n (%) (95% CI)	50 (51.0%) (40.7,61.3)	19 (73.1%) (52.2,88.4)	33 (33%) (23.9,43.1)
DOR (95% CI)	6.9 months (5.4, 8.3)	12.6 months (5.5, NE)	9.2 months (5.5, 11.1)
PFS (95% CI) (95% CI)	6.9 months (4.9, 8.4)	9.7 months (4.6, NE)	5.4 months (4.7, 7.2)
DCR, n (%) (95% CI)	NR (not an outcome of interest in ASCEND-1)	NR (not an outcome of interest in ASCEND-1)	74 (74%) (64.3, 82.3)

*Systemic response denotes best overall response in all sites of disease, including brain; ALK= anaplastic lymphoma kinase; CI= confidence interval; NSCLC= non-small cell lung cancer (RECIST v1.0)

Table 11: Overall survival (OS) in patients with ALK+NSCLC treated with prior ALK inhibitor[14]		
	ASCEND-1 study ceritinib 750 mg, N=163	ASCEND-2 study ceritinib 750 mg, N=140
Number of deaths, n (%)	**63(38.7)**	**39(27.9)**
Number of patients censored, n (%)	**100(61.3)**	**101(72.1)**
Reason for censoring Alive Lost to follow-up	 73(44.8) 27(16.6) [a]	 100(71.4) 1(0.7)
Median (month) (95% CI) 12 month OS rate (95% CI)	16.7 (14.8, NE) 67.2 (58.9, 74.1)	14.9 (13.5, NE) 54.9 (38.5, 68.6)
NE = not estimable. [a] 2 patients classified by the investigator as lost to follow-up, and 24 patients for whom no survival information was available within 14 weeks prior to the cut-off date.		

Table 12: Response of measurable brain metastases patients to ceritinib evaluable by MRI.[8,10]				
	ASCEND-1		ASCEND-2	
Endpoint	NSCLC with Prior ALK Inhibitor(n=24)	NSCLC ALK Inhibitor Naïve (n=5)	Investigator Review (FAS) n=20	BIRC (FAS) n=33
CR, n (%)	0	0	2(10.0)	1(3.0)
PR, n (%)	7(29.2)	3(60.0)	7(35.0)	12(36.4)
SD, n (%)	7(29.2)	0	7(35.0)	15(45.5)
PD, n (%)	6(25.0)	0	3(15.0)	0
Unknown, n (%)	4(16.7)	2(40.0)	1(5.0)	5(15.2)
OIRR, n (%) [95% CI]	7(29.2) [12.6, 51.1]	3(60.0) [14.7, 94.7]	9(45.0) [23.1, 68.5]	13(39.4) (22.9, 57.9]
IDCR, n (%) [95% CI]	14(58.3) [36.6, 77.9]	3(60.0) [14.7, 94.7]	16(80.0) [56.3, 94.3]	28(84.8) [68.1, 94.9]
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; OIRR = overall intracranial response rate; IDCR = intracranial disease control rate				

Tumour Response

The primary efficacy endpoint for trials, ASCEND-1 and ASCEND-2 was the overall response rate (ORR) defined as the proportion of patients with a best overall confirmed complete response (CR) or partial response (PR), as assessed by RECIST 1.1 criteria. Based on the August 2014 cut-off for ASCEND-2, the primary efficacy objective of ORR was met, as per investigator assessment.

Secondary efficacy endpoints included duration of response (DOR), disease-control rate (DCR), time to treatment response (TTR), overall intra-cranial response rate (OIRR) and ORR by BIRC assessment.

In the ASCEND-1 study, the overall response rate was 56.4% (95% CI: 48.5, 64.2) among patients previously treated with an ALK inhibitor and 72.3% (95% CI: 61.4, 81.6) in ALK inhibitor naïve patients.[9]

In the ASCEND-2 study, the ORR by investigator review was 38.6% (95% CI: 30.5, 47.2) with a similar ORR reported by BIRC (35.7%). The ORR by BIRC, excluding patients who had 0 target

lesions at baseline (and no major protocol violations) was 49.0%. The median time to first response was 1.8 months (range: 1.6–5.6) by investigator review. Among patients with measurable disease at baseline and ≥ 1 post-baseline assessment, 75.2% (94/125) patients had a decrease in tumour burden from baseline by investigator review.[8]

In the ASCEND-1 study, the median duration of response in patients previously treated with an ALK inhibitor (n=163) was 8.3 months (95% CI: 6.8, 9.7) and in the ASCEND-2 study the median duration of response was 9.7 months (95% CI: 7.1, 11.1) by investigator review.[8,9]

Key efficacy results for patients with ALK+NSCLC and brain metastases

In ASCEND-1, patients who presented with brain metastases (n=124) at study entry had an overall response rate (ORR) of 51% (95% CI: 40.7, 61.3) as per investigator assessment in the previously treated with an ALK inhibitor population and an ORR of 73.1% (95 CI: 52.2, 88.4) in the ALK inhibitor naïve population.[10]

Among responding patients, the median DOR in the previously treated with an ALK inhibitor group was 6.9 months (95% CI: 5.4, 8.3) and in the ALK inhibitor naïve group was 12.6 months (95 CI: 5.5, NE). The median PFS in previously treated with an ALK inhibitor group was 6.9 months (95% CI: 4.9, 8.4) and in the ALK inhibitor naïve group 9.7 months (95 CI: 4.6, NE).[10]

In ASCEND 2, patients who presented with brain metastases (n=100) at study entry had an overall response rate (ORR) of 33% (95% CI: 23.9, 43.1) as per investigator review and a similar ORR of 32% (95% CI: 23.0, 42.1) by BIRC assessment.[8]

Disease control rate (DCR) was 74% (95% CI: 64.3, 82.3) as per investigator assessment and 64% (95% CI: 53.8, 73.4) by BIRC assessment.[8]

Median duration of response (DOR) was 9.2 months (95% CI: 5.5, 11.1) as per investigator assessment, with a similar DOR reported by BIRC of 9.3 months (95% CI: 5.5, 12.9).[8]

Median progression-free survival (PFS) was 5.4 months (95% CI: 4.7, 7.2) as per investigator review and 6.8 months (95% CI: 5.4, 7.4) by BIRC assessment.[8] Please see Table 10.

Intracranial Efficacy[8,10]

Of the 124 ALK+NSCLC patients in ASCEND-1 with brain metastases at baseline, 74 patients had MRI scans available for central evaluation according to RECIST v1.1 and the remaining either had CT scans or scans that were unavailable. For the 74 patients with MRI scans available, 59 were previously ALK inhibitor treated and 15 were ALK inhibitor naïve. The baseline disease characteristics in the 74 patients were similar to those in the overall patient subgroup with brain metastases (n=124). Among the 29 patients with measurable brain lesions by MRI, (see table 13) 24 were previously ALK inhibitor treated and 5 were ALK inhibitor naïve. Ceritinib achieved an overall intracranial response rate (OIRR) of 29% and 60% in the 24 patients who were previously ALK inhibitor treated and those were ALK inhibitor naïve, respectively. Intracranial disease control rate (IDCR) was 58% in ALK inhibitor previously treated (n=24) and 60% in ALK inhibitor naïve patients (n=5).[10]

In the ASCEND-2 trial, of patients with brain metastases at study entry (n=100), 20 had investigator-assessed brain lesions selected as active target lesions and 33 patients had brain lesions selected as target lesions by BIRC assessment.[8] (Please see Table 12).

The OIRR by investigator assessment was 45.0% (95% CI: 23.1, 68.5) by investigator review and 39.4% (95% CI: 22.9, 57.9) by BIRC assessment. The intracranial disease control rate (IDCR) was 80% (95% CI: 56.3, 94.3) by investigator review with a similar number of 84.8% (95% CI: 68.1, 94.9) reported by BIRC assessment

The OIRR and IDCR by investigator assessment is considered to be of significant clinical importance, however due to the small number of patients with brain metastases at baseline considered as target lesions, there is uncertainty associated with these results and they should be interpreted with caution.

Ethnicity (Asian vs. Caucasian patients)[60]

In the ASCEND-1 trial, 82 patients identified as Asian, 156 as Caucasian and 8 as other out of the total of 246 with ALK+NSCLC. The baseline demographics and duration of ceritinib exposure between Asian and Caucasian patients were similar but their prior ALK inhibitor status differed. 108 (66%) patients who were Caucasian had been previously treated with an ALK inhibitor compared to only 47(29%) of Asian patients.

In ASCEND-1, no dose reductions were reported for 42.7% of Asian compared to 51.9% of Caucasian patients, while 29.3% vs 38.5% and 24.4% vs 7.1% had 1 and 2 dose reductions, respectively.

Grade 3/4 AEs were reported in 55% of Asian and 72% of Caucasian patients. Discontinuations due to AEs were reported in 4 (5%) Asian and 18 (12%) Caucasian patients.

Of the 173 patients in this subgroup analyzed for efficacy the ORR was 69% (95% CI: 55.2, 80.9) in Asian (38/55) and 57% (95% CI: 47.3, 65.9) in Caucasian patients (67/118).

The median duration of response (DOR) among responders was 10.1 months (95% CI: 7.3, not reached) and 6.9 months (95% CI: 4.5, 11.4) in the Asian and Caucasian patients, respectively.

Progression-Free Survival (PFS)

In the ASCEND-1 subgroup of 163 patients who had received prior treatment with an ALK inhibitor, median PFS was 6.9 months (95% CI: 5.39, 8.41). In the subgroup of 83 patients who had not received prior treatment with an ALK inhibitor, median PFS was not yet estimable (95% CI: 8.31, NE). In the ASCEND-2 study, the median PFS (95% CI) was 5.7 months [5.4, 7.6] (data cut-off 13 Aug 2014) by investigator assessment and 7.2 months [5.4, 9.0] by BIRC assessment.[14]

Overall Survival (OS)

ASCEND-1 reported a median OS of 16.7 months and ASCEND-2 reported a median OS of 14.0 months in the prior ALK inhibitor treated group as of the data cut-off.[14] However, because OS was assessed an exploratory endpoints in both trials, these results should be interpreted with caution.

Health-related Quality of Life[8]

Health-related quality of life was not assessed in the ASCEND-1 study and was assessed in the ASCEND-2 study as an exploratory endpoint.

Quality of life data was reported in ASCEND-2 using the European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC-QLQC30, version 3.0), lung cancer specific questionnaire (QLQ-LC13) and the Lung Cancer Symptom Scale (LCSS). Compliance to patient reported outcomes was high with more than 90% of patients completing the EORTC-QLQ-C30/LC13 at most of the different time points during the study. LCSS showed an improvement in symptom burden (-1.4 to -6.2) and global quality of life score (QLQ-C30) was maintained on treatment, with no substantial change from baseline (-1.5 to +4.6).[8]

The change from baseline in global health status remained close to zero throughout the treatment period, which implied the maintenance of HRQoL with no worsening during ceritinib treatment.[8]

Patients reported consistent improvements in lung-related symptoms (i.e. cough, pain in chest and dyspnoea) and no worsening of cancer symptoms while on treatment as of the August 13th 2014 cut-off date. This data suggests that the patients' overall HRQoL was maintained during treatment as measured by both the QLQ-C30 and LCSS.[8]

Dose Intensity & Dose Interruptions/Reductions

In ASCEND-1, AE's were listed as the primary cause of dose interruptions and/or reductions. Among patients with ALK+ NSCLC, 185 patients (75.2%) had at least one dose interruption, and 152 (61.8%) had at least one dose reduction.[9]

In the ASCEND-2 study, dose interruptions of ≥ 1 day of treatment occurred in 75.7% (106/140) patients; 85.8% (91/106) of all dose interruptions recorded on the study were attributable to AEs. Greater or equivalent to 1 dose reduction was required in 54.3% (76/140) patients. 84.2% (64/76) of all dose reductions reported on the study were due to AEs.[8]

Of the total number of patients in ASCEND-2 (N=140), a total of 58 (41.4%) patients required a dose adjustment or interruption. Dose adjustment/interruption due to vomiting, nausea, and diarrhoea were reported in 39/140 (27.9%), 34/140 (24.3%), and 24/140 (17.1%) patients, respectively.[8]

Grade 3 or 4 Adverse Events

In both the ASCEND-1 and ASCEND-2 trials, all patients experienced ≥1 adverse event, regardless of study drug relationship.

The most common adverse events in the 124 patients with brain metastases in ASCEND-1 were nausea, diarrhoea, vomiting, alanine aminotransferase increase, fatigue, aspartate aminotransferase increase, blood alkaline phosphatase increase and hypokalemia.

In the ASCEND-1 trial, 13 patients (10.5%) discontinued treatment due to AEs. The most frequent reason for treatment discontinuation among all 124 patients with brain metastases

at baseline was disease progression in 45.2% of patients. There was a slightly higher treatment discontinuation observed among the ALK inhibitor-pretreated than the ALK inhibitor-naïve patients (46.9% and 38.5%, respectively).[10]

The incidence of grade 3/4 adverse events listed in table 14 below were higher in the group of patients that had received a prior ALK inhibitor as compared to ALK inhibitor-naïve patients, with the exception of abdominal pain and weight decrease. This indicates toxicity profiles of ceritinib differ according to prior ALK inhibitor treatment status.

In the ASCEND-2 trial, eleven patients (7.9%) discontinued due to AEs, with no one type of AE predominating and 4 patients discontinued due to gastrointestinal AEs.

Serious adverse events in ASCEND-2 suspected of being study-drug related were seen in 24(17.1%) patients. Grade 3/4 Hyperglycemia was reported in 13% of 255 patients in ASCEND-1. There was a 6-fold increased risk of grade 3-4 hyperglycemia in patients with diabetes or glucose intolerance and a 2-fold increase risk in patients taking corticosteroids.[67]

The most common study drug related adverse events were: pneumonia, nausea and vomiting, each of which was reported in 3(2.1%) patients, and pericarditis, abdominal pain, pyrexia, and pneumonitis (each reported in 2(1.4%) patients.

The most frequent grade 3-4 AEs assessed as related to study drug in both trials were related to hepatotoxicity and gastrointestinal toxicity, specifically alanine aminotransferase increased (ALT), aspartate aminotransferase increased (AST), gamma-glutamyltransferase increased (GGT), blood alkaline phosphatase increased, diarrhoea, nausea, vomiting and fatigue.[14] Please see Tables 13 and 13.1.

Table 13. Adverse Events (≥20% for all Grades) among patients with ALK+NSCLC and Brain Metastases at Baseline

	X2101 (ASCEND-1)[10] n =124 (patients with brain metastases at baseline)		A2201 (ASCEND-2)[8] n= 140
	NSCLC with prior ALKi (n=98) Grade 3/4 n (%)	NSCLC ALKi naïve (n=26) Grade 3/4 n (%)	Grade 3/4 n (%)
Nausea	6(6.1)	1(3.8)	9(6.4)
Diarrhea	5(5.1)	1(3.8)	9(6.4)
Vomiting	8(8.2)	1(3.8)	6(4.3)
Alanine Aminotransferase increased	26(26.5)	10(38.5)	24(17.1)
Fatigue	7(7.1)	0(0.0)	9(6.4)
Abdominal pain	0(0.0)	1(3.8)	2(1.4)
Headache	4(4.1)	0(0.0)	NR
Aspartate	10(10.2)	2(7.7)	7(5.0)

aminotransferase increased			
Weight decreased	1(1.0)	2(7.7)	6(4.3)
Asthenia	1(1.0)	0(0.0)	NR
Dyspnoea	4(4.1)	3(11.5)	8(5.7)
Back pain	1(1.0)	0(0.0)	NR
Blood alkaline phosphatase increased	6(6.1)	0(0.0)	NR
Hypokalemia	5(5.1)	2(7.7)	NR
Table 13.1[%] Frequent Adverse Events (All patients pool) >2.0% of patients	**X2101 (ASCEND-1) Ceritinib 750 mg n=255*** n (%)		**A2201 (ASCEND-2) Ceritinib 750 mg n=140** n (%)
Nausea	15(5.9)		9(6.4)
Diarrhea	15(5.9)		9(6.4)
Vomiting	12(4.7)		6(4.3)
Alanine Aminotransferase increased	76(29.8)		19(13.6)
Decreased Appetite	4(1.6)		5(3.6)
Fatigue	13(5.1)		9(6.4)
Abdominal pain	3(1.2)		2(1.4)
Headache	4(1.6)		0
Aspartate aminotransferase increased	25(9.8)		7(5.0)
Weight decreased	5(2.0)		6(4.3)
Asthenia	2(0.8)		6(4.3)
Dyspnoea	11(4.3)		7(5.0)
Back pain	1(0.4)		1(0.7)
Blood alkaline phosphatase increased	13(5.1)		4(2.9)
Hypokalemia	11(4.3)		4(2.9)
Arthralgia	0		0
Oedema Peripheral	0		0
Gamma-Glutamyltransferase increased	7(2.7)		17(12.1)
Pneumonia	12(4.7)		5(3.6)
Upper Respiratory Tract Infection	0		0
Hyperglycaemia	15(5.9)		3(2.1)
Musculoskeletal Chest pain	0		0
Nasopharyngitis	0		0
Pruritus	1(0.4)		0
Dry Skin	0		0
Electrocardiogram QT Prolonged	3(1.2)		0

Hypomagnesaemia	0	0
Productive cough	0	0
Dysgeusia	0	0
Anxiety	2(0.8)	0
Stomatitis	0	0
Non-cardiac chest pain	2(0.8)	2(1.4)
Anaemia	13(5.1)	3(2.1)
Insomnia	0	0
Dizziness	0	0
Musculoskeletal Pain	0	0
Dyspepsia	1(0.4)	0
Hypophosphatemia	8(3.1)	2(1.4)
Pain in extremity	0	0
Urinary Tract infection	2(0.8)	0
Lipase Increased	16(6.3)	0
Hyponatremia	11(4.3)	0
%The following grade 3/4 adverse events are taken from the pooled safety set[14] * Includes 9 Non-NSCLC patients		

Adverse events of special interest

Adverse events of special interest to the Clinical Guidance Panel included GI toxicity (i.e., nausea, vomiting and diarrhoea), hepatoxicity, pneumonitis, and QT interval prolongation.

Gastrointestinal (GI) toxicity

GI toxicity occurred in almost all patients with 246/255 (97%) patients in ASCEND-1 and 134/140(95.7%) patients in ASCEND-2.[14] In ASCEND-1, diarrhoea, nausea, vomiting, or abdominal pain occurred in 96% of the 255 patients including severe grade 3/4 adverse events in 14% of patients treated with ceritinib. Thirty-three patients out of 163 (20.2%) who received a prior ALK inhibitor reported grade 2 diarrhoea while receiving treatment with ceritinib. Dose modification due to these adverse events occurred in 38% of patients.[67]

Hepatotoxicity

Hepatotoxicity occurred in 126 (49%) patients and 73 (52%) patients in ASCEND-1 and ASCEND-2, respectively. Elevations in alanine aminotransferase (ALT) greater than 5 times the upper limit of normal (ULN) occurred in 27% of 255 patients in ASCEND-1. One patient required permanent discontinuation due to elevated transaminases, and jaundice.[67]

Interstitial Lung Disease (ILD)/Pneumonitis

In ASCEND-1, pneumonitis was reported in 4% of 255 patients treated with ceritinib. Grade 3/4 ILD/pneumonitis was reported in 3% of patients and fatal ILD/pneumonitis was reported in 1 patient (0.4%).[67]

QT interval prolongation

QT interval prolongation occurred in 16(6.3%) patients in ASCEND-1 and 9(6.4%) in ASCEND-2. Three percent (3%) of 255 patients experienced a QTc interval increase over baseline greater

than 60 msec in ASCEND-1. Pharmacokinetic analysis has suggested that ceritinib causes concentration-dependent increases in the QTc interval.[67]

Harms and Deaths

The pooled dataset in ASCEND-1 included 255 patients. There were 41(16.1%) on treatment deaths of which 26 (10.2%) were due to study indication. The pooled dataset for ASCEND-2 included 140 patients. There were 17(12.1%) on treatment deaths of which 15(10.7%) were due to study indication.[14]

6.4 Ongoing Trials

Three ongoing randomized trials investigating the efficacy of ceritinib in patients with previously treated ALK positive NSCLC met the eligibility criteria for this review. The primary objective of the phase 3 study (NCT01828112) is to investigate progression-free survival (PFS), defined as the time from the date of randomization to the date of the first radiologically documented disease progression or death due to any cause. The primary objective of the phase 2 study (NCT02336451) evaluating the efficacy of ceritinib in patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges is overall response rate (ORR), defined as the proportion of patients with a best overall confirmed response of CR or PR in the whole body as assessed per RECIST 1.1 by the investigator. The primary objective of the phase 2 trial (NCT02513667) of ceritinib in combination with stereotactic ablative radiation in ALK-rearranged Metastatic Lung Adenocarcinoma is to investigate progression-free survival (PFS) in a time frame of up to 10 months. A summary of the three trials is provided in the table below.

Table 15: Ongoing trials of ceritinib in patients with previously treated ALK positive NSCLC[68-70]

Trial Design	Key Inclusion Criteria	Interventions and Comparators	Outcomes
Trial NCT01828112 Phase III, Multicenter, Randomized, Open-label Study Start date: June 2013 Expected completion date: June 2018 Status: Last verified June 2015, currently recruiting patients Estimated enrolment: 236 Sponsor: Novartis Pharmaceuticals	• Histologically or cytologically confirmed diagnosis ALK+ NSCLC assessed by FISH • stage IIIB or IV diagnosis and must have received one or two prior regimens (including platinum-doublet) of cytotoxic chemotherapy • At least one measurable lesion as defined by RECIST 1.1	<u>Intervention:</u> Oral ceritinib 750 mg once daily <u>Comparator:</u> • Pemetrexed: 500 mg/m2 IV every 21 days • Docetaxel: 75 mg/m2 every 21 days	<u>Primary</u>: PFS <u>Secondary</u>: OS ORR DOR DCR TTR

Trial NCT02336451 Phase II, multi-center, open-label, five-arm study Start date: April 2015 Expected completion date: July 2018 Status: Last verified June 2015, currently recruiting patients Estimated enrolment: 125 patients Sponsor: Novartis Pharmaceuticals	• Histologically or cytologically confirmed diagnosis of metastatic NSCLC • At least one extra cranial measurable lesion as defined by RECIST 1.1. • Be neurologically stable within at least 1 week prior to the first dose of study drug. • Patients may have received prior chemotherapy, crizotinib, biologic therapy or other investigational agents including other ALK Inhibitors • Life expectancy ≥ 6 weeks. • ECOG PS 0-2	Oral ceritinib 750 mg once daily (five 150 mg capsules) on a continuous dosing schedule	<u>Primary:</u> ORR <u>Secondary</u>: DCR OIRR IDCR TTIR DOIR OERR EDCR TTER DOER ORR (whole body) DCR (whole body) TTR (whole body) DOR (whole body) PFS (whole body) OS Overall Safety AEs, ECGs and laboratory abnormalities
Trial NCT02513667 Phase II, non-randomized, open-label, two-cohort protocol study Start date: August 2015 Expected completion date: August 2019 Status: last verified July 2015, not yet open for participant recruitment Estimated enrollment: 33 patients Sponsor: University of Texas Southwestern Medical Center	• Histologically or cytologically confirmed diagnosis of lung adenocarcinoma that demonstrates ALK rearrangement as detected by the approved FISH test • Patients with no prior ALK-inhibitor therapy will be placed in cohort A, those treated with one prior line of ALK-inhibitor (at any time) will enter cohort B. • Patients will not have any other curative therapeutic option, such as radiation or surgery • Patients must have recovered from all toxicities related to any prior anticancer therapies to ≤ Grade 2 (CTCAE v 4.03), provided that any concomitant medication is given	<u>Intervention:</u> Patients will receive ceritinib at a dose of 750 mg (150 mg capsules times 5 capsules once a day) for 10 weeks. Patient will stop taking Ceritinib 72 hours before SABR radiation. The patient may start taking Ceritinib again 72 hours after radiation is complete. Patient will continue to take ceritinib for up to 8 months. Radiation:	<u>Primary</u>: Cohort A & B: median PFS <u>Secondary</u>: OS Report time to 2nd SABR time from start of systemic therapy to first day of second course of SABR Report time to 3rd SABR time from start of therapy to

Collaborator: Novartis Pharmaceuticals	prior to initiation of treatment with ceritinib • ECOG performance status 0-2. • Age ≥18 years • Adequate organ function (lab criteria must have been met)	Stereotactic ablative body radiation Patients will receive study drug for 10 weeks.	first day of third course of SABR Report proportion of patients CR/PR/stable disease at 6 & 12 months Safety of ceritinib followed by SABR compared to historical controls
ECOG= Eastern Cooperative Oncology Group; **QoL**= quality of life; **RECIST**= Response Evaluation Criteria in Solid Tumours; **RCT**= randomized controlled trial; **PS**= performance status; **ORR**= overall response rate; **DCR**= disease control rate; **OIRR**= overall intracranial response rate; **IDCR**= intracranial disease control rate; **TTIR**= time to intracranial tumour response; **DOIR**= duration of intracranial response; **OERR**= overall extra cranial response rate; **EDCR**= extra cranial disease control rate; **TTER**= time to extra cranial tumour response; **DOER**= duration of extra cranial response			

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 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 ceritinib (Zykadia) for Metastatic Non-Small Cell Lung Cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR 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. Personal identifying information has been removed from the registered patient advocacy group section, to the Clinical Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Lung Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR 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 section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** May 2015, **Embase** 1974 to 2015 June 23, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

#	Searches	Results
1	(Zykadia* or ceritinib* or LDK 378 or LDK378 or 1032900-25-6 or 1431456-10-8 or K418KG2GET).ti,ot,ab,sh,rn,hw,nm,kw.	334
2	1 use pmez	75
3	1 use cctr	0
4	*ceritinib/ or (Zykadia* or ceritinib* or LDK 378 or LDK378).ti,ab.	169
5	4 use oemezd	104
6	2 or 3 or 5	179
7	limit 6 to English language	173
8	remove duplicates from 7	124

2. Literature search via PubMed

Search	Query	Items found
#6	Search **#4 OR #5**	11
#5	Search **ceritinib[Supplementary Concept] OR ceritinib*[tiab] OR Zykadia*[tiab] OR LDK 378[tiab] OR LDK378[tiab] OR K418KG2GET[rn] OR 1032900-25-6[rn] OR 1431456-10-8[rn] OR Zykadia*[ot] OR ceritinib*[ot]** Filters: **Publication date from 2015/06/08; English**	4
#4	Search **#3 AND publisher[sb]** Filters: **English**	9

Search	Query	Items found
#3	Search **ceritinib[Supplementary Concept] OR ceritinib*[tiab] OR Zykadia*[tiab] OR LDK 378[tiab] OR LDK378[tiab] OR K418KG2GET[rn] OR 1032900-25-6[rn] OR 1431456-10-8[rn] OR Zykadia*[ot] OR ceritinib*[ot]** Filters: **English**	75

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 terms: Zykadia/ceritinib

Select international agencies including:

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

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

Search terms: Zykadia/ceritinib

Conference abstracts:

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

European Society for Medical Oncology
http://www.esmo.org/

Search terms: Zykadia/ceritinib / last 5 years

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