CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

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

March 21, 2017

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

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1 GUIDANCE IN BRIEF

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

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

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

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy ceritinib (Zykadia) for the treatment of patients locally advanced or metastatic ALK+ NSCLC who have progressed on or who were intolerant to crizotinib.

The appropriate comparators for ceritinib include single agent cytotoxic chemotherapies. The patient population under review is similar to the population for whom Health Canada market authorization has been granted.

The recommended dose for ceritinib is 750 mg taken orally once daily until disease progression or until no clinical benefit is derived.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one multicenter, open-label, phase III RCT that assessed the efficacy and safety of ceritinib in patients with locally advanced or metastatic ALK+ NSCLC who have progressed on or who were intolerant to crizotinib (ASCEND-5; N= 231). Patients were randomized (1:1) to receive ceritinib 750mg daily or chemotherapy. Those randomized to the chemotherapy arm were treated with either docetaxel (75 mg/m^2, 1 hour infusion IV every 21 days) or pemetrexed (500 mg/m^2, 10 minute IV infusion every 21 days) based on the opinion of the investigator. Patients continued to be treated with their assigned therapy until disease progression confirmed by a Blinded Independent Review Committee (BIRC) or other withdrawal criteria were met. Patients with documented disease progression in the ceritinib arm could continue receiving ceritinib or discontinue treatment and enter the survival follow-up phase of the study. In contrast, patients who were randomized to the chemotherapy arm were given the option to enter the extension phase, where they received treatment with ceritinib, or they could discontinue their assigned treatment and enter the survival follow-up phase.

The primary outcome assessed in the ASCEND-5 Trial was progression-free survival (PFS) assessed by BIRC according to the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. The trial was designed to have 90% power to reject the null hypothesis of an HR of 0.60 (161 progressive events) using a one-sided significance level of α=0.025.[1] The key secondary outcome was overall survival, and exploratory outcomes included objective response rate (ORR); duration of response (DOR); disease control rate (DCR), time to response (TTR), overall intracranial response rate (OICR), intracranial disease control rate (IDCR), duration of intracranial response (DOIR); patient reported outcomes (PROs); safety profiles and pharmacokinetic (PK) parameters.

A larger proportion of patients in the chemotherapy arm discontinued treatment as compared to the ceritinib arm (93.1% vs. 71.3%, respectively),[2] and at the time of data cut-off, 28.7% of patients in the ceritinib arm and 6.9% of patients in the chemotherapy arm were still receiving treatment.[2] Sixty-four (63.8%) of patients treated with chemotherapy crossed over and received ceritinib.[1] More deaths were reported in the ceritinib arm as compared to the chemotherapy arm (13.0% vs. 4.4%).[1]

Efficacy

At the time of data cut-off, a total of 172 patients (74.5%) had progressive disease as assessed by BIRC or died (ceritinib: 72.2% and chemotherapy: 76.7%).[2] Median PFS was 5.4 months (95% CI, 4.1 to 6.9) for patients treated with ceritinib and 1.6 months (95% CI, 1.4 to 2.8) for patients treated with chemotherapy.[2] Treatment with ceritinib was associated with a statistically significant prolongation of PFS as compared to chemotherapy in patients with ALK+ NSCLC (HR = 0.49; 95% CI, 0.36 to 0.67; long-rank P < 0.001).[2]

Overall survival was a key secondary endpoint in the ASCEND-5 trial. It was defined as the time from the date of randomization to the date of death due to any cause.[3] At the time of the data cut-off for the primary PFS analysis, the data for overall survival was immature. At the reported time point, 98 deaths (42.4%) had been documented, where 48 patients (41.7%) and 50 patients (43.1%) died in the ceritinib and the chemotherapy groups, respectively.[1,2] Median overall survival in the ceritinib group was 18.1 months (95% CI, 13.4 to 23.9) and 20.1 months (95% CI, 11.9 to 25.1) in the chemotherapy group.[2] There was no difference between treatment groups for overall survival (HR = 1.00; 95% CI, 0.67 to 1.49; P= 0.496).[2] However, the reported effect estimate was immature at the time of analysis and it may also be confounded by patient cross-over.

Patients in the ceritinib group were more likely to demonstrate an ORR assessed by BIRC compared with those in the chemotherapy group (39.1% [95% CI, 30.2 to 48.7] vs. 6.9% [95% CI, 3.0 to 13.1]).[2] Similar patterns were observed for DCR assessed by BIRC, DOR assessed by BIRC and TTR. However, due to limited sample size in the chemotherapy arm, some of these estimates may be unpowered and should be interpreted with caution.

Table 1: Summary of the Key Outcomes from the ASCEND-5 Trial

Treatment Groups	Ceritinib N = 115	Chemotherapy N =116
Median follow-up, months	16.5	
No. patients on treatment, n (%)	33 (28.7)	8 (6.9)
Primary Outcome - BIRC Assessed PFS[A]		
No. PFS events (%)	83 (72.2)	89 (76.7)
Median PFS, months (95% CI)	5.4 (4.1-6.9)	1.6 (1.4 - 2.8)
Hazard ratio (95% CI; one-sided p-value)	0.49 (0.36 - 0.67; P < 0.001)	
Key Secondary Outcome - Overall Survival[B]		
No. deaths events (%)	48 (41.7)	50 (43.1)
Median overall survival months (95% CI)	18.1 (13.4-23.9)	20.1 (11.9-25.1)

Treatment Groups	Ceritinib N = 115		Chemotherapy N =116	
Hazard ratio (95% CI; one-sided p-value)	1.00 (0.67 - 1.49; P = 0.496)			
Other Secondary Outcomes				
Investigator Assessed PFS				
No. PFS events (%)	83 (72.2)		96 (82.8)	
Median PFS, months (95% CI)	6.7 (4.4 - 7.9)		1.6 (1.4-2.6)	
Hazard ratio (95% CI; one-sided p-value)	0.40 (0.29-0.54; P < 0.001)			
	BIRC	**Investigator**	**BIRC**	**Investigator**
Objective Response Rate[C] , n	45/115	49/115	8/116	7/116
% (95% CI)	39.1 (30.2-48.7)	42.6 (33.4-52.2)	6.9 (3.0-13.1)	6.0 (2.5-12.0)
Disease Control Rate[D], n	88/115	92/115	42/116	44/116
% (95% CI)	76.5 (67.7-83.9)	80.0 (71.5-86.9)	36.2 (27.5-45.6)	37.9 (29.1-47.4)
Time to Response[E], n	45/45	49/49	8/8	7/7
Median time to response in weeks (95% CI)	6.7 (5.3-52.3)	6.4 (4.9-45.4)	7.4 (5.4-12.1)	12.14 (6.3-22.9)
Duration of Response[F] , n	29/45	35/49	4/8	5/7
Median duration in months (95% CI)	6.9 (5.4-8.9)	5.9 (5.4-9.7)	8.3 (3.5-NR)	4.3 (2.8-NR)

Abbreviations: BICR - blinded independent central review; **CI** - confidence interval; **NA** - not available; **NR** - not reached; **PFS** - progression-free survival.

Notes:
A: Time from date of randomization to date of PD per BIRC or death due to any cause.
B: Time from date of randomization to date of death due to any cause.
C: Defined as the sum of complete plus partial responses.
D: Defined as the sum of patients with best response rate of complete response, partial response, stable disease or Non-complete response or non PD per RECIST 1.1 for patients with non-measurable disease only at baseline
E: Time from date of randomization to date of in documented complete or partial response in patients with confirmed complete or partial response.
F: Time from date of documented complete or partial response in patients to the date of PD or death to any cause with confirmed complete or partial response.
G: Patients with measurable and/or non-measurable disease in the brain at baseline as per an independent neuro-radiology review.
H: Defined as the sum of complete plus partial responses in the brain per modified RECIST 1.1.
I: Defined as the sum of patients with best response rate of complete response, partial response, stable disease or Non-complete response or non PD per RECIST 1.1 for patients with non-measurable disease only at baseline
J: Defined as the DCR based on target and non-target lesions in the brain and defined as the proportion of patients with a best overall confirmed response of CR or PR or a response of SD in the brain per modified RECIST 1.1.

Data source: CSR[1] and Scagliotti et al.[2]

Harms

The population evaluable for safety in the ASCEND-5 Trial consisted of 228 patients who received at least one dose of their assigned therapies (115 in the ceritinib group and 113 in the chemotherapy group).[2] As compared to the placebo group, patients in the ceritinib group experienced more all grades adverse event (100% vs. 99.1%), grade 3 to 4 adverse event (77.4% vs. 63.7%), serious adverse event (42.6% vs. 31.9%), adverse events leading to a dose interruption (73.0% vs. 23.9%) and death (13.0% vs. 4.4%).[2] Similar results were observed for adverse events of special interest. Here, a higher proportion of adverse events of interest occurred in the ceritinib group compared to the placebo group and include: hyperglycemia (8.7% vs. 3.5%), GI toxicity (93.0% vs. 34.5%), hepatotoxicity (53.0% vs. 13.3%) and QT prolongation (12.2% vs. 0.9%). However, there were more ILD/pneumonitis events in the chemotherapy arm as compared to the ceritinib arm (2.7% vs. 1.7%).[1]

Limitations

The ASCEND-5 trial was an open-label RCT design. This design was used because a double-blinding would have been difficult to implement owing to the administration of the study interventions (ie oral vs. intravenous) and assignment of the chemotherapy agents (ie docetaxel or pemetrexed). To account for the open-label design of ASCEND-5, a Blinded Independent Review Committee was used to assess objective outcomes like PFS. However, for the assessment of subjective outcomes, such as the PROs and reporting of adverse events, there is a greater risk of detection bias because patients and the study investigators were aware of treatment status.

Additionally, the data for overall survival were immature at the data cut-off. Since the trial protocol allowed patients who were randomized to chemotherapy and had documented disease progression to cross over and receive open-label treatment with ceritinib, the overall survival effect estimates could be confounded.

The study used a hierarchical testing approach to control for type 1 error in the study. The protocol stipulates that overall survival could be assessed if the effect estimate of PFS as assessed by BIRC was significant. However, there was no adjustment for multiplicity of analyses of the other secondary endpoints, which increases the risk of type 1 error in these reported estimates. Therefore, these results should be interpreted with caution. Furthermore, the effect of ceritinib as compared to chemotherapy on the change in PROs was performed using an exploratory analysis and had no statistical testing. In addition, a protocol amendment was made to include measuring intracranial anti-tumour activity as a secondary outcome and these results may be underpowered to detect an effect.

The funding request made by the submitter was to evaluate the use of ceritinib as monotherapy in patients with ALK+ locally advanced (not amenable to curative therapy) or metastatic NSCLC who have progressed on or who were intolerant to crizotinib. Indeed, ASCEND-5 included patients with histologically or cytologically confirmed diagnosis of stage IIIB or IV NSCLC carrying an ALK rearrangement and who had received cytotoxic chemotherapy and crizotinib. Notably, there were two amendments made to the protocol which permitted patients who had received one or two prior chemotherapy regimens and more than one course of crizotinib to be included in the study as well as to allowing any sequence of prior crizotinib or chemotherapy. Therefore the inclusion criteria used in ASCEND-5 does not reflect the submitter's funding indication. However, it has been noted that at the time of the conception and the execution of ASCEND-5, crizotinib had not yet been approved as a first-line therapy for patients with ALK+ NSCLC. Thus, the differences in the study patient population and the funding request should be considered when interpreting the generalizability of the ASCEND-5 data.

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

According to Lung Cancer Canada (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%. 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 receive 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 experienced a 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.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Ceritinib is a targeted therapy that would provide another oral treatment option
- Clarity whether ceritinib is only for patients who have been treated with crizotinib and platinum-based chemotherapy as per ASCEND-5 trial
- Place in therapy amongst other available agents and upcoming agents, including anti-PD1 agents and other targeted therapies, and sequencing of all available treatments

Economic factors:

- Extend treatment options with another line of therapy

Registered Clinician Input

Overall, clinicians providing input noted that patients with ALK mutation positive NSCLC comprise only 3-5% of the general NSCLC population and the population of patients eligible for ceritinib will be even smaller. Clinicians acknowledge a need for patients who progress following treatment with crizotinib and who would otherwise be eligible for treatment with a platinum doublet as patients have rapid progression and treatment options with limited benefit. Based on trial evidence and clinical experience of clinicians providing input, ceritinib is more effective and has better tolerability than chemotherapy agents currently available. Thus, the registered clinicians believe that patients should have first line crizotinib, then ceritinib on progression. Ceritinib would replace chemotherapy such as platinum/pemetrexed doublets, pemetrexed maintenance and likely patients would not need downstream

chemotherapy with docetaxel, which can be even more toxic. As an oral treatment option, ceritinib also provides ease of administration to patients.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

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

[Table 2]: Assessment of generalizability of evidence for ceritinib for advances or metastatic NSCLC

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="3">Population</td><td>Performance Status</td><td>Patients had a WHO PS ranging from 0 to 2. Subgroup analysis of WHO PS and brain metastases were specified a priori.

WHO PS (n [%]) based on the ASCEND 5 trial
<table>
<tr><th></th><th>Ceritinib</th><th>Chemo</th><th>HR (95% CI) for PFS</th></tr>
<tr><td>0</td><td>56 (48.7)</td><td>51 (44.0)</td><td>0.38 (0.24-0.6)</td></tr>
<tr><td>1</td><td>50 (43.5)</td><td>60 (51.7)</td><td rowspan="2">0.63 (0.41-0.97)</td></tr>
<tr><td>2</td><td>9 (7.8)</td><td>5 (4.3)</td></tr>
</table></td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>While data on the efficacy and safety of using ceritinib in patients with an ECOG PS of >2 was very limited, the CGP agreed that use of ceritinib in this population may be appropriate and should be left to the discretion of the treating oncologist. The CGP acknowledged the increased toxicity with ceritinib compared to chemotherapy and note that in patients with lower performance status (ECOG PS 2), clinicians may start patients at a lower dose.</td></tr>
<tr><td>Metastatic Sites</td><td>Patients were stratified based on brain metastases at baseline in the ASCEND 5 trial.

<table>
<tr><th></th><th>Ceritinib, n=115</th><th>Chemo, n=116</th></tr>
<tr><td colspan="3">Patients with brain metastases at baseline</td></tr>
<tr><td></td><td>65 (56.5%)</td><td>69 (59.5)</td></tr>
<tr><td>HR (95% CI) for PFS</td><td colspan="2">0.54 (0.36-0.80)</td></tr>
</table>
Anti-tumour intracranial activity was an exploratory outcome in the ASCEND-5 Trial. Patients were included in the analyses if they had up to five brain lesions at baseline. Please see Section 6.3.2.2 for details</td><td>Are the results in the overall trial generalizable to patients with brain metastases?</td><td>Based on the ASCEND-5 trial, nearly 60% of patients in either treatment group had asymptomatic and neurologically stable brain metastases at baseline. Results in these patients were similar to overall trial results. The CGP agreed this was a reasonable number to generalize the overall trial results and conclude that ceritinib is effective in patients with brain metastases.</td></tr>
<tr><td>Line of therapy</td><td>No specified line of therapy in ASCEND-5. Patients were included if they had been treated with one to two regimens of chemotherapy (including platinum doublet) and crizotinib.

The majority of patients in the trial, 97% in both arms, had received prior platinum based doublet therapy.</td><td>Are the results of the trial generalizable to patients who have only had prior crizotinib and progressed?

Are the results of the trial generalizable to patients who are intolerant to crizotinib?</td><td>The inclusion criteria of the ASCEND-5 clinical trial allowed for patients who had been pretreated with crizotinib and cytotoxic chemotherapy. At the time of trial conception and execution, crizotinib was approved only in the second line setting following a platinum doublet for patients with EML4-ALK mutated tumors. The tumour response rates seen with</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		There was no evidence available on the efficacy of ceritinib in patients who are intolerant to crizotinib or in patients who had previously progressed on crizotinib but had not received treatment with a platinum doublet.		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. Therefore the CGP agree that in clinical practice, clinicians will want to use ceritinib after first line crizotinib, which has since become available as a first line option. The CGP acknowledged that this is becoming the accepted standard of care in the light of evolving data comparing ceritinib to a platinum doublet. Therefore the use of a platinum doublet will likely follow failure on ceritinib. The CGP agreed that there would be few instances where patients would be intolerant to crizotinib. In instances where patients may develop intolerance to crizotinib, the CGP agreed that ceritinib would be a reasonable treatment alternative as long as patients have previously been treated with a systemic therapy. In the opinion of the CGP, it is also unlikely that ceritinib will move up to first line in view of the lack of clinical data with ceritinib as opposed to other agents being studied in this space.
Setting	Location	The study was conducted in Belgium, Canada, France, Germany, Hong Kong, Ireland, Israel, Italy, Japan, Lebanon, Netherlands, Portugal, Republic of Korea, Russia, Singapore, Spain, Switzerland, Turkey, UK and USA	If the trial was conducted in other countries, is there any known difference in the practice pattern between those countries and Canada? Differences in the patterns of care might impact the clinical outcomes or the resources used to achieve the outcomes.	The CGP agreed that the locations where the trial was conducted would be comparable to Canadian treatment setting and therefore the results of the trial would be generalizable to the Canadian population.
	Academic centres	Was the trial conducted in academic centres only or were community treatment facilities also involved?	If the trial was conducted only in academic centres are the results applicable in the community setting?	

1.2.4 Interpretation

Burden of Illness and Need

Although the annual incidence of NSCLC is high, the number of patients with an ALK translocation is only a very small minority (3-5%) of all locally advanced or metastatic NSCLC. The number of annual, newly diagnosed patients with an ALK gene rearrangement is estimated to be approximately 850 patients per year in Canada). Based on clinical expert opinion, it is estimated that approximately 80% of patients pre-treated with crizotinib would be likely to proceed to second line therapy with ceritinib.

Effectiveness

Results of the ASCEND 5 trial: The phase III open-label trial, ASCEND-5, compared ceritinib to second line chemotherapy (Pemetrexed or Docetaxel) in ALK inhibitor and platinum doublet pretreated patients with metastatic NSCLC. The trial demonstrated a statistically significant prolongation of median PFS with ceritinib (5.4 months vs. 1.6 months, HR 0.49 (95%CI 0.36 - 0.67; P < 0.001)) compared to chemotherapy and achieved its predefined primary endpoint of improvement in PFS. Other trial endpoints, including ORR and DCR were superior with ceritinib when compared to chemotherapy. Notably, the clinical benefit of ceritinib was consistent across geographic regions and racial groups, age and gender distributions, performance status, status of brain metastases and smoking history. The interpretation of these subgroup analyses is nevertheless considered exploratory given the post hoc nature of these analyses. The time to response with ceritinib was comparable to chemotherapy but the duration of response was shorter. However, the interpretation of this result was limited by the small number of responding patients in the chemotherapy arm. Overall survival, a secondary endpoint, was not statistically different between the groups [18.1 months (95% CI, 13.4 to 23.9) and 20.1 months (95% CI, 11.9 to 25.1) for ceritinib and chemotherapy, respectively HR: 1.00 (95% CI 0.67 - 1.49; P = 0.496)] but may have been influenced by the immaturity of the survival data and confounding due to extensive crossover from the chemotherapy arm to ceritinib. Despite this, the CGP noted that there was a slight trend in survival benefit favouring chemotherapy.

An exploratory outcome in the ASCEND-5 trial was to assess anti-tumour intra-cranial activity. In patients with both measurable disease and non-measurable intra-cranial disease, as well as in the subset of those with measurable disease who had been previously treated with radiation to the brain, the overall intracranial response rate (OIRR) was superior with ceritinib when compared to chemotherapy. Results on intracranial disease control rates was not made available by the submitter. The interpretation of this result is limited by the small number of patients with measurable disease and the sizable proportion of these patients that did not have a valid post-baseline tumor assessment.

The results of this study are congruent with the results from the expansion cohort of the non-randomized phase I study (ASCEND-1), as well as the phase II trial (ASCEND-2), which demonstrated early onset of response to treatment and responses in ALK inhibitor (ALKi) pre-treated populations. In both the phase II ASCEND-2 (ALKi pretreated populations) and ASCEND-3 trial (ALKi naïve populations) intracranial responses were noted in previously untreated brain metastases. The efficacy of ceritinib in previously untreated ALK +ve intra-cranial metastases is being further evaluated in the currently accruing ASCEND-7 trial and cannot be concluded upon based on the current evidence.

Safety

The safety profile of ceritinib in ASCEND -5 and the spectrum of adverse events are consistent with prior studies. The majority of treatment related Serious Adverse Events were related to the NSCLC and not to the study treatment. The most common adverse events with ceritinib were diarrhea, nausea and vomiting. The most common Grade 3 or higher adverse event in the ceritinib group was elevation of the serum transaminase. However, there were more serious adverse events with ceritinib compared to chemotherapy and more patients in the ceritinib arm had an adverse event that led to dose discontinuation compared to chemotherapy. This observation needs to be considered against the fact that the median exposure time to ceritinib was much longer than for chemotherapy (30 weeks for ceritinib vs. 6 weeks for Docetaxel; 14 weeks for Pemetrexed). More patients were also continued on Ceritinib beyond progressive disease. Furthermore, there were fewer dose reductions for Grade 3 or 4 adverse events in the ceritinib arm compared to chemotherapy. This is in contrast to the greater proportion of ceritinib dose interruptions for adverse events compared to chemotherapy. These imbalances with respect to the time on treatment (five times longer on ceritinib vs. Docetaxel chemotherapy; two times longer on ceritinib vs. Pemetrexed chemotherapy), a tendency to maintain patients on Ceritinib beyond initial progression, as well as the difference in the management of adverse events, limits the interpretation of the tolerability of this regimen when compared to chemotherapy in the real world setting. It could be hypothesized that earlier institution of dose reductions and improved supportive care management may result in greater tolerability. This remains to be validated in a prospective study.

In the 30 days after study drug was discontinued, there were more deaths in the ceritinib arm of the trials. Interpretation of this is limited due to cross over. Interpretation of this is limited by the immature data for overall survival analysis at the time of reporting as well as the opportunity to cross over in those who progressed on chemotherapy.

Other relevant considerations

Generalizability: Although the majority of patients in ASCEND-5 had a good performance status (ECOG 0, 1), there were some patients with ECOG PS 2. Given the manageable toxicity profile of ceritinib and the generally prompt response to treatment, it is the opinion of the CGP that the results can be generalized to the ECOG 2 population. The cumulative experience with Ceritinib in the ASCEND trials, including ASCEND-5 indicates that Ceritinib can induce tumour regression in patients with previously treated. Therefore, ceritinib can be considered as a therapeutic option in patients with previously treated ALK translocation positive NSCLC with brain metastases. The CGP did not identify any subpopulations of ALK positive NSCLC that would not potentially benefit from Ceritinib following disease progression on Crizotinib when categorized by age, gender, ethnicity or smoking status.

Sequencing:

In the context of ALK inhibition:

Crizotinib is currently the only approved first line therapy for ALK+ NSCLC in Canada. Ceritinib has demonstrated activity against Crizotinib resistant tumour models and in the ASCEND-5 trial demonstrated a statistically significant and clinically meaningful improvement in progression free survival compared to chemotherapy following disease progression after one or more chemotherapy regimens including a platinum doublet and Crizotinib. Therefore, the CGP recommends that Ceritinib be used in the second-line setting after disease progression on Crizotinib.

In the context of chemotherapy:
At the time the ASCEND-5 trial was undertaken, Crizotinib was approved only in the second line setting following a platinum doublet for patients with ALK mutated tumours. Now that Crizotinib is approved as a first-line therapy, the CGP recommends that Ceritinib be used following disease progression on Crizotinib and before treatment with systemic chemotherapy. It makes this recommendation on the basis of the results of the ASCEND-5 trial, as well as the fact that Ceritinib is an oral agent and more easily administered than chemotherapy. Furthermore, it is the opinion of the CGP that the toxicities of Ceritinib are manageable and generally less than those of platinum –based chemotherapy.

ALK testing: The availability of a validated ALK companion laboratory test to establish ALK mutation status is necessary to select the appropriate population of NSCLC patients for treatment.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit with the use of ceritinib in patients with ALK+ locally advanced or metastatic NSCLC who have progressed on or who were intolerant to crizotinib. The CGP based this conclusion on the evidence of a statistically significant and clinically meaningful improvement in progression free survival without a decline in quality of life in patients receiving ceritinib compared with chemotherapy after disease progression on crizotinib in the ASCEND-5 trial. Although the Clinical Guidance Panel acknowledges that there are some limitations to the ASCEND-5 trial given its open label design, inclusion of patients who progressed on both chemotherapy and crizotinib and some minor imbalances in patient subgroups, the CGP concluded that Ceritinib following disease progression on crizotinib addresses an unmet clinical need and achieves a net overall clinical benefit in the treatment of good performance status, ALK+, locally advanced or metastatic NSCLC.

In making this conclusion, the Clinical Guidance Panel also considered that:

- There is a paucity of randomized data to guide sequencing of crizotinib in relation to ceritinib or ceritinib in relation to other second generation ALKi agents. However, based on currently available data, it is the CGP's expert opinion that the most appropriate use of ceritinib is following disease progression on crizotinib and prior to the use of chemotherapy doublet.
- Studies have demonstrated the benefit of anti-PD1 agents when compared to single agent chemotherapy in patients following failure on a platinum doublet. The CGP agree that the expected place of therapy for ceritinib would be prior to the use of a platinum doublet. The CGP also acknowledged evidence available for the use of anti-PD1 agents in the first line setting however it must be noted that patients with EGFR- and ALK-mutated tumors were not included.
- Ceritinib has demonstrated anti-tumour activity against previously treated and treatment-naïve patients with brain metastases and who have ALK+ NSCLC. . The CGP therefore agreed there was a reasonable number of patients with brain metastasis at baseline to generalize the overall trial results and conclude that ceritinib is effective in patients with brain metastasis. Data from ongoing clinical trials are expected to further clarify the role of ceritinib in patients with ALK+ NSCLC who present with brain metastases (previously untreated). The results of ongoing trials may further clarify the role of ceritinib in other lines of therapy or with tumours that harbor alternative gene alterations such as ROS1 or ALK-over expression.

- While data on the efficacy and safety of using ceritinib in patients with an ECOG PS of >2 was very limited, the CGP agreed that use of ceritinib in this population may be appropriate and should be left to the discretion of the treating oncologist.
- In instances where patients may develop intolerance to crizotinib, which are expected to be very few, the CGP agreed that ceritinib would be a reasonable treatment alternative as long as patients have previously been treated with a systemic therapy. In the opinion of the CGP, it is also unlikely that ceritinib will move up to first line in view of the lack of clinical data with ceritinib as opposed to other agents being studied in this space.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

In Canada, 2 out of every 5 people are expected to develop cancer in their lifetime. Furthermore, 1 out of 4 Canadians are expected to die of cancer. Lung cancer is the 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 2016, it is estimated that there will be 28,400 new cases of lung cancer diagnosed and 20,800 deaths associated with lung cancer, with age-standardized incidence and mortality rates of 71.4/100,000 and 52.1/100,000 respectively.[4] The majority of new cases of lung cancer are expected to arise in people over 60 years of age, with estimated 17,700 new cases in the age group between 60 years and 79 years and 12,400 associated deaths in 2016.[4,5] The advanced age of patients and the high frequency of advanced disease, poor performance status and other significant co-morbidities of this patient population limit their ability to tolerate conventional chemotherapy regimens.[6]

2.2 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. Presently, 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. More recently, molecular signatures related to the tumor and tumor microenvironment such a Programmed Cell Death Ligand (PD-L1) expression have been shown to be predictive in the context of certain types of immunotherapies.[7,8]

In the setting of NSCLC without an eligible driver mutation, platinum based doublet chemotherapy combinations remain the mainstay for first line systemic treatment. Platinum combinations have provided palliative benefit with modest incremental improvements in median survival measured in months over the course of the last few decades.[9-12] 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.[12-14] Histological sub classifications of NSCLC have proven to have implications for therapy. The use of pemetrexed combinations appears to preferentially benefit patients with non-squamous histologies. Alternatively, pemetrexed appears to be inferior to gemcitabine in the first line treatment of squamous NSCLC when combined with a platinum agent.[15] This difference has been attributed to differential levels of thymidylate synthase expression.[16,17] 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.[18,19] 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.[20,21] 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.[22,23] Furthermore, the cost of bevacizumab and associated toxicities has 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.[24,25] Agents that selectively target these pathways have been shown to induce superior response rates and progression free survival benefits in patients whose cancers harbor these mutations. Several trials and a meta-analysis confirmed the benefit of EGFR TKI therapy in the first line, second line and maintenance therapy in patients with EGFR mutated tumors without demonstrating an advantage to overall survival - attributable to extensive treatment cross over in this population.[26] The exact sequencing of these agents in relation to chemotherapy is, hence, not yet clearly established.[27] Nevertheless, there is increasing clinical consensus that the utilization of these agents upfront in well-selected populations provides improved quality of life and delays the necessity of initiating cytotoxic chemotherapy with its inferior tolerability profile.

In patients with EML4-ALK mutated tumors, 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.[28,29] 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)] favoring crizotinib when compared to second line chemotherapy (docetaxel or pemetrexed).[30] 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)] favoring crizotinib when compared to first-line platinum doublet chemotherapy.[31] The current funding model supports the use of crizotinib in the first line treatment of stage IV lung cancer followed by chemotherapy.

A few second and latter generation ALK inhibitors have been evaluated and some have been approved for use clinically. 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. Furthermore, there is accruing evidence that ceritinib has activity in inducing intracranial responses in patients with brain metastases.[32-34] Ceritinib has regulatory approval from both the FDA and Health Canada for use in ALK mutation positive locally advanced or metastatic NSCLC patients who have progressed or are intolerant of Crizotinib. Alectinib, another second generation ALK inhibitor also has regulatory approval for this indication and is currently under review with pCODR-CADTH. Other agents are also under investigation and include brigatinib, an ALK inhibitor that is currently being investigated for activity in crizotinib – resistant patients. Lorlatinib, an investigational ALK inhibitor has shown promise in overcoming resistance to second generation ALK inhibitors such as ceritinib, alectinib and brigatinib. These advances afford patients with ALK mutation positive advanced NSCLC not only targeted but also more tolerable and effective treatment options when compared with conventional chemotherapy.

Recent data presented at the European Society of Medical Oncology suggest a role for Pembrolizumab, a Programmed Cell Death Receptor 1 (PD-1) inhibitor, in the first line treatment of advanced NSCLC. A phase III trial demonstrated a survival benefit when compared to treatment with a platinum doublet in patients with high (≥50%) expression of PD-L1.[8] It must be noted that patients with EGFR- and ALK- mutated tumors were not included. This benefit was however not demonstrated in the Checkmate 026 phase III first line trial of a similar agent, Nivolumab, also a PD-1 inhibitor, albeit in a less selected patient population. A progression free survival benefit to the addition of Pembrolizumab to first line chemotherapy was further suggested in a randomized Phase II trial.[35] Phase III trials are ongoing to further evaluate this effect. These data are gradually transforming the treatment paradigms in patients with advanced NSCLC without driver mutations.

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.[36,37] Recent data from the Checkmate 017, Checkmate 057 and the Keynote 010 trials have established a role for immunotherapy in the second line setting. The Checkmate studies demonstrated that nivolumab, a Programmed Cell Death Receptor 1 (PD-1) antibody confers improved survival when compared to docetaxel in the second line treatment of squamous and non-squamous NSCLC respectively.[38,39] The Keynote 010 established that Pembrolizumab, another Programmed Cell Death Receptor 1 (PD-1) antibody confers improved survival when compared to docetaxel in the second line treatment of NSCLC and that the response was most pronounced in patients with high (≥50%) expression of PD-L1. In this context, single agent therapy with pemetrexed or docetaxel may be considered in the third line setting if not already utilized in earlier lines of therapy.

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.[40] Erlotinib has shown improved survival and symptom control in the second or subsequent line treatment when compared to best supportive care.[41] More recently, afatinib has been shown to provide greater benefit than erlotinib in the treatment of squamous cell cancers.[42] 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.[43]

2.3 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.[44-46] ALK gene rearrangements appear to be mutually exclusive of EGFR and KRAS mutations and occur in approximately 4% of lung cancers.[47] These mutations are more common in adenocarcinomas and never/light smokers.[48] The multi targeted small molecule tyrosine kinase inhibitor, crizotinib, has demonstrated superior objective response rates and progression free survival in patients whose tumors harbor the EML4-ALK mutation.[28-31] This agent has been approved in the first line setting of the treatment of these tumors. 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.[49] A phase 1 study (ASCEND-1) established the maximum tolerated dose as 750 mg po 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.[50] A multicenter, single-arm, open-label phase II clinical trial (ASCEND-2) 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.[51] An acceptable safety profile was demonstrated on safety evaluation based on 255 patients with ALK positive tumors. In a 2015 review with pCODR-CADTH, evidence from these two non-randomized trials (the expansion cohort of ASCEND-1 and the ASCEND-2 trial) was evaluated. In addition to whole body responses mentioned above, the ASCEND-2 trial demonstrated intracranial responses to previously untreated brain metastases (overall intracranial response rate: 45%; intracranial

disease control rate: 80%).[64] At the time, the pCODR Expert Review Committee (pERC) recommendation was to not fund ceritinib due to lack of confidence in the net clinical benefit with ceritinib. pERC was confident that ceritinib produces a tumour response, however it was unable to determine how ceritinib compares with other treatments including best supportive care alone with regards to outcomes important to decision-making such as overall survival, progression-free survival and quality of life. The current review is a resubmission for ceritinib based on the results of ASCEND 5 trial, evaluating ceritinib compared to chemotherapy (pemetrexed or docetaxel) in patients with ALK positive NSCLC who had been pretreated with crizotinib and one or two prior regimens of cytotoxic chemotherapy (including a platinum doublet).

A recent randomized Phase III trial (ASCEND 5) evaluated the role of ceritinib in ALK positive patients who had been pretreated with crizotinib and one or two prior regimens of cytotoxic chemotherapy (including a platinum doublet). Ceritinib was noted to improve progression free survival (5.4 months vs. 1.6 months) when compared to single agent Pemetrexed or Docetaxel (HR 0.49; P<0.001 one-sided). The ASCEND 5 trial is the focus of the current review.

An additional benefit of Ceritinib appears to be it's effect on intracranial responses in patients with pre-existing brain metastases. Patients with brain metastases in the context of Stage IV NSCLC, have a particularly poor prognosis.[52] The ASCEND -1 study as well as the ASCEND-3 trial identified that patients with baseline brain metastases benefitted from therapy. A recent pooled analysis of data from both these trials identified an intracranial overall response rate of 60% and an Intracranial Disease Control Rate of 76%.[34] These results appear to be clinically important. The results of the ASCEND 7 trial is expected to provide further information in this regard.

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] harboring ALK rearrangement defined as 15% or more positive tumor cells as assessed by the FDA-approved FISH 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.

The data from the phase III randomized trial supports the use of ceritinib following crizotinib and a platinum doublet regimen. With the publication of the PROFILE 1014 clinical trial results, crizotinib is funded and is increasingly used in the first line treatment of ALK positive tumors. Hence, it is likely that ceritinib will find a role following disease progression on crizotinib and prior to patients receiving systemic chemotherapy.[31]

2.4 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-tumor activity, safety and tolerability in advanced ALK positive tumors other than NSCLC.

ROS1 is a receptor tyrosine kinase of the insulin receptor family that acts as a driver oncogene in approximately 1 % of patients with NSCLC.[53,54] Both Crizotinib and Ceritinib have inhibitory effect on the ROS1 pathway. Currently, the lack of routinely available testing for ROS1 preclude the use of these agents in the clinical setting.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Input on ceritinib (Zykadia) resubmission for treatment 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 progressed on or who were intolerant to crizotinib was provided by Lung Cancer Canada (LCC). Their input is summarized below.

In February 2015, LCC conducted focus groups with patients on crizotinib and their caregivers; five patients and four caregivers had participated. LCC also conducted one on one interviews with an additional three patients and two caregivers. LCC also received written feedback from one other patient. LCC noted that all of these patients were ALK+ and all of the caregivers were caring for those patients with ALK+ lung cancer. Then between May 2015 and June 2015, LCC conducted one on one interviews with another five patients and four caregivers. Two patients from February 2015 were re-interviewed specifically for the ceritinib submission. In total, fourteen ALK+ patients and ten caregivers with experience in ALK+ lung cancer provided input into this submission. Specifically, seven patients with ceritinib experience provided input into this submission. LCC submitted that ALK+ patients represent between 2% and 7% of the NSCLC population, and therefore it was difficult to obtain a large sample size for this submission. LCC also stated that all of the patients were under 70 years old, three were the primary income earner for their family, and three had infant or very young children.

LCC also gathered information from a presentation of findings from Lung Cancer Canada Faces of Lung Cancer Report; this report was compiled from roundtable discussions with physicians, caregivers and patients, and was released in November 2014. Moreover, LCC updated a literature review from a previous pCODR submission for this submission. As well, for this ceritinib re-submission, LCC attempted to follow up with the seven patients that contributed to the original ceritinib submission to provide an update. LCC received an update from two of the seven patients, but was unable to find four of the seven patients, and for one patient, their journey had ended. Lastly, LCC included findings from the Lung Cancer Canada 2015 Faces of Lung Cancer Report, which was compiled from a questionnaire with 91 patients and 72 caregivers.

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

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Advanced or Metastatic Non-Small Cell Lung Cancer

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. According to LCC, most Canadians (~70%) are diagnosed at an advanced stage, and many diagnosed at or in an earlier potentially curable stage will subsequently relapse. LCC noted that while the average 5 year survival rate for all cancers is 63%, the five year survival rate for lung cancer is 17% [Canadian Cancer Statistics 2015].

LCC stated that lung cancer patients appear to have the highest symptom burden of all cancer patients. 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%). LCC reported that loss of appetite, cough, pain, and shortness of breath were significant quality of life predictors (Iyer et al. Support Cancer Care, 2014). [Patel et al. Proc ASCO 2003; Zawisza et al. WCLC 2013]. As well, LCC noted that in a survey of Canadian patients with advanced lung cancer, two-thirds of patients feel that their symptoms interfere with daily activities; for instance, anxiety or worry was common. According to LCC, rates of depression in advanced lung cancer patients vary from 16%-50%, and is consistently higher than other cancer sites [Aass et al. 1997, Hopwood et al 2000, Akechi et al 1998]. Financial hardship was also experienced by 41% of patients in the Canadian study. 69% of respondents believed that their illness imposed a significant hardship on those close to them.

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?""*

3.1.2 Patients' Experiences with Current Therapy for Advanced or Metastatic Non-Small Cell Lung Cancer

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. According to LCC, currently in Canada, ALK+ lung cancer patients may receive first line chemotherapy and then a targeted therapy (crizotinib) as second line. Once a patient progresses on crizotinib, the current standard of care is chemotherapy.

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.*" Respondents 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 as "*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: (i) time to spend with her grandchildren and husband, (ii) hope to beat the disease and, (iii) promise of a better treatment (more effective and more tolerable) on the horizon. LCC submitted that ceritinib represents that treatment.

3.1.3 Impact of Advanced or Metastatic Non-Small Cell Lung Cancer and Current Therapy on Caregivers

LCC received input from caregivers that were interviewed for previous pCODR submissions (crizotinib and ceritinib). In total, ten caregivers with experience in ALK+ lung cancer provided input.

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. LCC noted that 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 progressed 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.

3.2 Information about the Drug Being Reviewed

3.2.1 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 indicated that all seven of the patients respondents that had experience with ceritinib, had been previously treated with crizotinib.

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 were 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.

   LCC indicated that 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, progression on crizotinib differed from 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 respondent.

   Another respondent stated: "*Day to day, I continue to feel good.*" LCC indicated 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.

LCC attempted to follow up with these seven patient respondents that contributed to the original 2015 ceritinib submission to provide an update. LCC received an update from two of the seven patients, but was unable to find four of the seven patient respondents, and for one patient respondent, their journey had ended. The two respondents from the original 2015 ceritinib submission have both moved onto alectinib. LCC noted that both respondents started on crizotinib, then were on ceritinib prior to taking alectinib.

LCC included one respondent's experience. As a teacher, this respondent shared her life with students and she hopes her lung cancer journey will inform a whole new audience of survivors. After retiring from a long teaching career in 2010, she was diagnosed with lung cancer in 2011. According to LCC, everything appeared to be on the right track, she was receiving the 'gold-standard' of chemotherapy and remained hopeful. Unfortunately, the chemotherapy treatments were unsuccessful and the tumours continued to grow in her lung.

As a result, the respondent looked at biomarker testing in the United States to determine which mutation of lung cancer she had, and which of the newly targeted treatments might work, if she had a mutation for which there was a targeted drug. She was successful, received the right tests and had the marker she was looking for. Unfortunately, the right drug was crizotinib and it was not approved or available in Canada at that time. The respondent purchased her initial dose through her physician in the United States of America, while her Canadian doctor began to work with Health Canada and the pharmaceutical company to get crizotinib to her on compassionate grounds in Canada. This route was successful and some months later, crizotinib was finally approved for treatment in Canada.

According to LCC, this targeted treatment (crizotinib) worked well; the respondent was able to see her daughter complete her course of study to become a Clinical Psychologist, attend her son's wedding, and experience the birth of her first grandson. After about fourteen months, she needed to examine a new option, as crizotinib had stopped working. The respondent was then enrolled in a new clinical trial with ceritinib and again she saw success with treatment, this time for a period of three years. After that, while ceritinib continued to control the cancer in her lung, brain metastases were now detected.

The respondent is now taking alectinib.

3.3 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+ disease.

LCC indicated that ALK+ patients in Canada currently have one line of publicly funded targeted therapy, while people living with other cancers have more than one line of publicly 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.

LCC recognized that funding and overall burden on the public health system is a concern. LCC stated that all stakeholders, including the manufacturer, must work together to find solutions. One caregiver stated, "*I'm disappointed that it costs so much. I understand that money spent to produce and market these drugs is high, but the cost is insane."* According to LCC, cost is an issue that must be globally addressed; however despite the cost, funding this patient population will not be overly burdensome on the healthcare budget given that ALK+ lung cancer patients are 2-7% of the overall lung cancer population and these treatments offer substantial benefits over chemotherapy.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- Ceritinib is a targeted therapy that would provide another oral treatment option
- Clarity whether ceritinib is only for patients who have been treated with crizotinib and platinum-based chemotherapy as per ASCEND-5 trial
- Place in therapy amongst other available agents and upcoming agents, including anti-PD1 agents and other targeted therapies, and sequencing of all available treatments

Economic factors:

- Extend treatment options with another line of therapy

Please see below for more details.

4.1 Factors Related to Comparators

For patients who are not EGFR mutation-positive but are ALK positive, crizotinib is the standard first-line treatment and cisplatin plus pemetrexed is the standard second-line treatment.

PAG noted that anti-PD1agents and other oral targeted therapies could potentially become the standard second-line treatment, if and when they are funded. Thus, PAG is seeking if there is information available comparing ceritinib to anti-PD1 agents and other oral targeted therapies in patients who were previously treated with crizotinib.

4.2 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. Ceritinib would be another oral targeted therapy option for patients.

PAG is seeking clarity on the inclusion criteria as it was noted that the patients in the ASCEND-5 trial are those who have failed crizotinib and platinum-doublet chemotherapy. PAG is seeking data on the use of ceritinib in patients who were treated with crizotinib in the first-line setting but have not received platinum-doublet chemotherapy.

In addition, PAG noted that there are patients who have failed treatment with crizotinib and then were treated with anti-PD1 agents, available through clinical trials or compassionate access programs. As such, PAG is seeking information, if available, on the use of ceritinib after the use of crizotinib and an anti-PD1 agent.

PAG is seeking guidance on ceritinib's place in therapy and sequencing of all available treatments, including anti-PD1 agents, and upcoming targeted oral therapies for ALK

positive NSCLC. PAG noted that alectinib is also under review and is seeking advice on the place of therapy of ceritinib in comparison to alectinib.

4.3 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.

4.4 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 oral therapy for patients who have had two prior treatments. There would be a shift in costs if ceritinib was used as second-line therapy after crizotinib in first-line and additional costs of subsequent treatments upon progression on ceritinib.

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

4.5 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.

4.6 Factors Related to Manufacturer

The high cost of ceritinib is a barrier to implementation.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were provided on ceritinib for NSCLC: one from an individual oncologist and one joint submission.

Overall, clinicians providing input note that patients with ALK mutation positive NSCLC comprise only 3-5% of the general NSCLC population and the population of patients eligible for ceritinib will be even smaller. Clinicians acknowledge a need for patients who progress following treatment with crizotinib and who would otherwise be eligible for treatment with a platinum doublet as patients have rapid progression and treatment options with limited benefit. Based on trial evidence and clinical experience of clinicians providing input, ceritinib is more effective and has better tolerability than chemotherapy agents currently available. Thus, in the opinion of the clinicians providing input patients would have first line crizotinib, then ceritinib on progression. Ceritinib would replace chemotherapy such as platinum/pemetrexed doublets, pemetrexed maintenance and likely patients would not need downstream chemotherapy with docetaxel, which can be even more toxic. As an oral treatment options, ceritinib also provides ease of administration to patients.

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

5.1 Current Treatment(s) for this Advanced or Metastatic Non-Small Cell Lung Cancer

The current treatment for ALK positive patients that progress on, or are intolerant to crizotinib is chemotherapy (platinum doublet chemotherapy, most commonly pemetrexed/cisplatin). Patients may also be presented with an option to participate in a clinical trial of another ALK inhibitor in development.

After progression on first line crizotinib, ALK positive non small cell lung cancer can progress explosively. Chemotherapy can be used second line but responses tend to be slow, modest and unpredictable. By the time progression on chemotherapy is confirmed, most patients decline rapidly and may not have the chance to try more effective targeted therapies such as ceritinib or alectinib.

5.2 Eligible Patient Population

The clinicians providing input noted that ALK positive lung cancer represents approximately 3 - 5 percent of the non-small cell lung cancer population. It is estimated that about 80% of the crizotinib patients will be eligible for treatment with ceritinib.

While overall this may seem to be a very small number of patients, as there are 28,000+ lung cancer new cases a year in Canada, there will be a low but consistent number of patients in each cancer centre. When physicians that are part of this submission estimated the number of patients that would be placed on ceritinib in their institution/year, the answers ranged from 5 to 15. These physicians are representative of many academic cancer centres across Canada.

Given the limited life expectancy of lung cancer, very few prevalent cases would be anticipated. If they do well, they could be on therapy for longer durations of time (i.e. more than one year), increasing the prevalence of the population on treatment, however the group as a whole should be small. The approaches used however should also be applicable to ROS mutation patients as well.

5.3 Identify Key Benefits and Harms with Ceritinib

Ceritinib is an oral take-home medication. In the opinion of clinicians providing input, it has been clearly demonstrated to be efficacious and well tolerated. It is currently indicated as second-line therapy in ALK+ patients, who progress on, or are intolerant to crizotinib.

In the opinion of clinicians providing input, ceritinib is generally very well tolerated, with a side effect profile similar to crizotinib. Clinicians that are part of this submission unanimously agree that ceritinib has a higher response rate (tumour shrinkage) and durability of response (longer disease control) when compared to chemotherapy. Physicians also see significant and rapid symptom improvement on treatment.

Chemotherapy may carry challenging quality of life limiting side effects for patients that are more burdensome for patients and their families. For patients who used crizotinib as their first line treatment, ceritinib allows them to maintain a similar quality of life as on crizotinib.

The benefits when compared with chemotherapy are clear – a targeted drug, targeting the known driver mutation, is more effective and better tolerated than chemotherapy in this population which is often older and has comorbidities. The oral route is clearly preferable.

Chemotherapy often requires dose reductions or early discontinuation because of toxicity and ancillary and supportive care costs can be substantial. Patients enjoying responses and improved progression free survival, in our observations, are less likely to be hospitalized.

5.4 Advantages of Ceritinib Over Current Treatments

Ceritinib is an oral therapy with a superior therapeutic index. This carries significant resource advantages over chemotherapy in terms of less hospital visits, reduced load on chemotherapy units which frees up chair time for other patients. It also reduces the number of hospital visits that patients are required to make.

Currently patients are only able to access ceritinib through clinical trial or Special Access programs. Involvement in clinical trials may involves long travel times and distances for patients, and extra visits for study-related procedures. Further, not all patients are eligible for the available clinical trials, or are not willing to participate, and indeed these clinical trial programs will be coming to an end anyway. Placing ceritinib on public formulary also allows clinicians to focus on treating patients as Special Access requests require a significant amount of time to complete and takes away from clinical time.

5.5 Sequencing and Priority of Treatments with Ceritinib

Ceritinib will be used for ALK+ positive patients that progress or are intolerant to crizotinib. The clinicians providing input noted that other ALK inhibitors are also in development, with alectinib having recently been submitted to pCODR for funding consideration.

Once a patient progresses on crizotinib, the clinicians would like to be able to use ceritinib for those without brain metastasis and alectinib for those with brain metastasis (where specific research has been conducted). Ideally clinicians would like to have both drugs available for use. Ceritinib and alectinib have different side effect profiles and access to both agents allows clinicians to choose the most appropriate drug based on their patients symptoms and co-morbidities.

Ceritinib would replace chemotherapy in this patient population. There is currently a gap in the standard of care as both ceritinib and alectinib have demonstrated that they are superior to chemotherapy and are used in many other countries, but are not yet publicly covered in Canada.

In this application, a funding recommendation is sought for second line. Thus, patients would have first line crizotinib, then ceritinib on progression. Ceritinib would replace chemotherapy such as platinum/pemetrexed doublets, pemetrexed maintenance and likely patients would not need downstream chemotherapy with docetaxel, which can be even more toxic.

5.6 Companion Diagnostic Testing

The companion testing for ALK or ROS mutations is inherently required but will not require additional companion diagnostics over current treatments.

5.7 Additional Information

It was noted by one oncologist that clinicians feel that ceritinib (or its successors) will likely be optimal in the first line setting, given better toxicity and likely benefits eventually. However, this is out of scope of this funding request.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of ceritinib as a 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 progressed on or who were intolerant to crizotinib.

No supplemental questions were identified that were relevant to the pCODR review

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below (Table 3). Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A and Appendix B.

Table 3: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators[A]	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of ceritinib should be included.	Patients with locally advanced or metastatic ALK+ NSCLC who have progressed on or who were intolerant to crizotinib <u>Subgroups:</u> • Histologic type • ECOG PS (0 vs. 1 to 2) • WHO PS (0—1 vs. ≥2) • 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	<u>Cytotoxic Chemotherapies:</u> • Single agent (i.e. pemetrexed, docetaxel) • Platinum doublet <u>Targeted Therapies</u> • Alectinib[B]	<u>Primary</u> • OS • PFS • HRQoL <u>Secondary</u> • ORR • DOR • DCR • OCRR • IDCR • DOIR Safety • AEs • SAEs • WDAEs • GI toxicity • Hepatotoxicity • QT interval prolongation • ILD/pneumonitis • Hyperglycemia

ALK=anaplastic lymphoma kinase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; WHO PS = World Health Organization Performance Status; 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

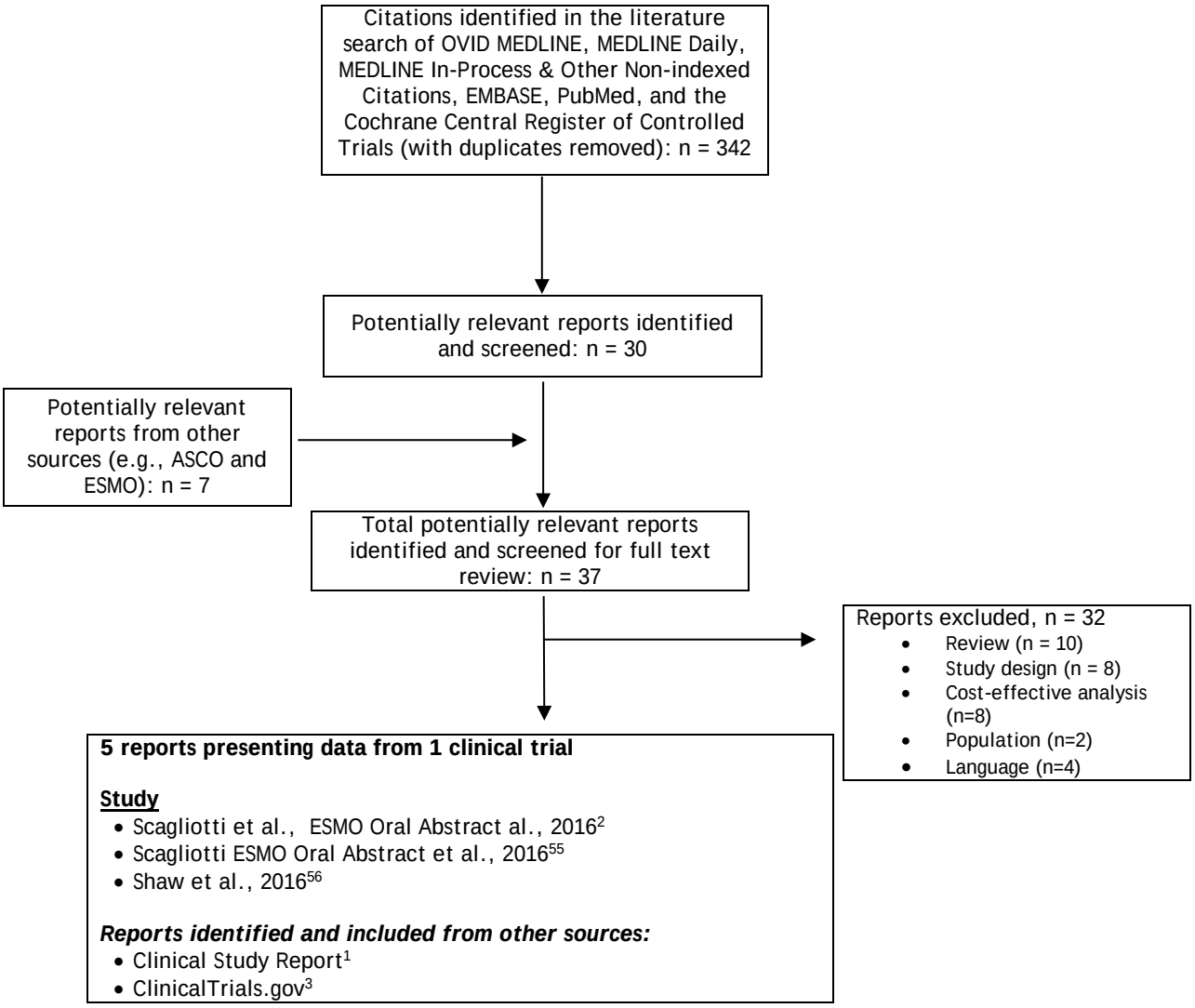
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators[A]	Outcomes
control rate; ORR=objective response rate; DOR=duration of response; ORR = overall response rate; OCRR = overall cranial response rate; IDCR = intracranial disease control rate; DOIR = duration of intracranial response; GI = gastrointestinal; ILD = Interstitial lung disease				
Notes: A: Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions). B: Alectinib is not currently a reimbursed option				

6.3 Results

6.3.1 Literature Search Results

Of the 37 potentially relevant reports identified, one study (ASCEND-5), reported in 5 citations[1-3,55,56], was included in the pCODR systematic review and 32 studies were excluded. Studies/reports excluded included the following: reviews, ineligible study design, cost-effective analyses, ineligible population of interest and language.

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



Note: Additional reports related to the ASCEND-5 were obtained from the Submitter.[57]

6.3.2 Summary of Included Studies

The pCODR systematic review identified one phase III, open-label, randomized controlled trial (RCT) that assessed the efficacy and safety of ceritinib in patients with locally advanced or metastatic ALK+ NSCLC who have progressed on or who were intolerant to crizotinib. The summary of the trial and select quality characteristics are presented in Table 4 and Table 5.

Table 4: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
ASCEND-5 **Other identifiers:** CLDK378A2303 NCT01828112 **Characteristics:** Phase 3, open-label, RCT **Sample size:** Randomized: 231 **Locations:** 99 sites in 20 countries and includes Belgium, Canada, France, Germany, Hong Kong, Ireland, Israel, Italy, Japan, Lebanon, Netherlands, Portugal, Republic of Korea, Russia, Singapore, Spain, Switzerland, Turkey, UK and USA **Patient Enrolment Dates:** 07/2013 to 11/2015 **Primary Analysis Data cut-off:** 01/2016 **Final Analysis Date:** 08/2018 **Sponsor:** Novartis Pharmaceuticals	<u>Key Inclusion Criteria:</u> Adult patients ≥ 18 years with histologically or cytologically confirmed diagnosis of stage IIIB or IV NSCLC carrying an ALK rearrangement assessed with an FDA-approved FISH assay and scoring algorithm WHO PS of 0 to 2 and a life expectancy of ≥ 12 weeks Patients with documented disease progression at study enrollment At least one measurable lesion as defined by RECIST 1.1 Patients who received 1 to 2 prior regimens of cytotoxic chemotherapy and crizotinib <u>Key Exclusion Criteria:</u> Patients with a known hypersensitivity to ceritinib, docetaxel and/or pemetrexed Patients with symptomatic CNS metastases who are neurologically unstable	**Intervention:** Ceritinib at 750 mg once daily **Comparator:** Pemetrexed at 500 mg/m^2 in a 21-day cycle OR Docetaxel at 75 mg/m^2 in a 21-day cycle	**<u>Primary:</u>** PFS by BIRC **<u>Secondary:</u>** OS **<u>Exploratory:</u>** ORR, DOR, DCR and TTR by BIRC and by IA OIRR, IDCR and DOIR per BIRC neuro-radiology review PFS by IA Safety and tolerability PROs PK parameters

RCT = Randomized controlled trial; **ALK** = anaplastic lymphoma kinase; **WHO PS** = World Health Organization Performance Status; **RECIST** = Response Evaluation Criteria In Solid Tumours; **CNS** = central nervous system; **PFS** = Progression-free survival; **BICR** = Blinded Independent Review Committee; **OS** = Overall Survival; **IA** = Investigator assessment; **ORR** = Overall response rate; **DOR** = Duration of response; **DCR** = Disease control rate; **TTR** = Time to response; **OIRR** = Overall intracranial response rate; **IDCR** = Intracranial disease control rate; **DOIR** = Duration of intracranial response; **PRO** = Patient reported outcome; **PK** = pharmacokinetics.

Table 5: Select quality characteristics of included studies of ceritinib in patients with ALK+ locally advanced or metastatic NSCLC

Study	Treatment vs. Comparator	Primary outcome	Required sample size [A]	Sample size	Randomization method [B]	Allocation concealment	Blinding [C]	ITT Analysis	Final analysis [D]	Early termination	Ethics Approval
ASCEND-5	Ceritinib versus chemotherapy	PFS assessed by BIRC	236 (based on 161 progression events)	231	IVRS, stratified	Yes	BIRC	Yes	No	No	Yes

Abbreviations: ITT = intention to treat; IVRS = interactive voice response service; PFS = progression-free survival

[A] 236 patients were required to provide 90% power to reject the null hypothesis of an HR of 0.60 (161 progressive events) using a one-sided significance level of α=0.025. In addition, a power calculation was also done for overall survival, where 236 patients were required to provide 80% power for the final analysis to reject the null hypothesis of HR of 0.667 (196 deaths) using a one-sided significance level of α=0.025.

[B] Randomization was stratified by WHO performance status (0 vs. 1 to 2) and brain metastases (present vs. absent).

[C] Investigators and patients were not blinded to treatment assignment. In fact, chemotherapy treatment was guided by the Investigator; however, a BIRC was used to assess PFS and all other secondary outcomes and was also confirmed using an Investigator assessment.

[D] The primary analysis was planned to occur when 161 PFS events were documented by BIRC and all patients had completed at least 12 weeks of follow-up or discontinued early. In addition, three interim analyses were also planned for OS, which include: 1) time of the primary PFS analysis, 2) when 171 deaths had occurred and 3) when 196 deaths had occurred. The estimated primary completion date is August 2018 (Final data collection date for primary outcome measure)

6.3.2.1 Detailed Trial Characteristics

a) Trials

One phase III RCT met the inclusion criteria of the pCODR systematic review, ASCEND-5 (N = 231). Characteristics of the trial design are presented in Table 4.

ASCEND-5 is an ongoing, multicenter, open-label, phase III RCT that assessed the efficacy and safety of ceritinib in patients with locally advanced or metastatic ALK+ NSCLC who have progressed on or who were intolerant to crizotinib (ASCEND-5; N= 231). The trial was conducted in 99 centres in 20 countries and includes Belgium, Canada, France, Germany, Hong Kong, Ireland, Israel, Italy, Japan, Lebanon, Netherlands, Portugal, Republic of Korea, Russia, Singapore, Spain, Switzerland, Turkey, UK and USA.[57] For the primary analysis, the data cut-off date was January 26th 2016[2]. The trial was funded by Novartis Pharmaceuticals.

Patient enrolment occurred between July 2013 and November 2015.[2] The trial included patients aged 18 years and older who had a histologically or cytologically confirmed diagnosis of stage IIIB or IV NSCLC and were carrying an ALK rearrangement assessed by an FDA-approved fluorescent in situ hybridization (FISH) assay and scoring algorithm (positivity criteria).[2] Patients must have had documented disease progression and had at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.[3] Furthermore, patients must have received one or two prior regimens of cytotoxic chemotherapy (including one platinum doublet) and one or more regimens of crizotinib. No particular treatment sequence was required for enrollment. However, patients were ineligible if they had received prior treatment with both pemetrexed and docetaxel. Patients were excluded from the study if they had hypersensitivity to ceritinib,

pemetrexed and/or docetaxel and they had symptomatic central nervous system (CNS) metastases.

Eligible patients were randomized (1:1) to receive ceritinib 750mg daily or chemotherapy. Randomization was stratified by WHO performance status and brain metastases at baseline. For those randomized to the chemotherapy arm, patients were treated with either docetaxel (75 mg/m^2) or pemetrexed (500 mg/m^2) based on the opinion of the Investigator. Patients continued to be treated with their assigned therapy until death, lost to follow-up, pregnancy or disease progression confirmed by a blinded Independent Review Committee (BIRC).[1]

In the treatment phase, once disease progression had been confirmed by BIRC or other withdrawal criteria were met, patients randomized to the ceritinib arm could enter the survival follow-up phase. In this phase, patients could continue to receive ceritinib therapy or a subsequent antineoplastic agent and were followed for survival. In contrast, patients who were randomized to the chemotherapy arm were given the option to enter the extension phase, where they received treatment with ceritinib, or they could discontinue their assigned treatment and enter the survival follow-up phase.

The primary outcome assessed in the ASCEND-5 Trial was progression-free survival (PFS) assessed by BIRC according to the RECIST v1.1. The trial was designed to have 90% power to reject the null hypothesis of a hazard ratio (HR) of 0.60 (161 progressive events) using a one-sided significance level of α=0.025. The key secondary outcome was overall survival. Exploratory outcomes included PFS assessed by the Study Investigator; measures of anti-tumour activity (ie. objective response rate (ORR), duration of response (DOR), disease control rate (DCR) and time to response (TTR)) assessed by BIRC and the Study Investigator; measures of intracranial anti-tumour activity (i.e. overall intracranial response rate (OICR), Intracranial disease control rate (IDCR), duration of intracranial response (DOIR)) assessed by BIRC and the Study Investigator; patient related outcomes (PROs); safety profiles and pharmacokinetic (PK) parameters.

The study protocol for the ASCEND-5 Trial was amended four times. These amendments were made in order to help increase sample size and to better understand the efficacy and safety of ceritinib as compared to chemotherapy.[1] These amendments include: adjusting eligibility criteria, updating safety information, providing clarifications and clinical guidance, addressing cross-over time periods, increasing the length of follow-up for PFS and adding secondary objectives and related endpoints to assess anti-tumour intracranial activity.

b) Populations

The study baseline characteristics are presented in Table 6. Patient characteristics were generally balanced between the ceritinib and chemotherapy groups with the exception of sex (59.1% vs. 52.6% females), ethnicity (70.4% vs. 58.6% Caucasians) and smoking history (61.7% vs. 52.6% never smokers).[2]

Table 6: Baseline characteristics of patients in the ASCEND-5 Trial

Characteristics	Ceritinib n = 115	Chemotherapy n = 116	Total n = 231
Sex (Female; n [%]))	68 (59.1)	61 (52.6)	129 (55.8)
Age (median [range])	54.0 (30-77)	54.0(28-84)	54.0 (28-84)
Ethnicity (n [%])			
Asian	30 (26.1)	38 (32.8)	68 (29.4)
Caucasian	81 (70.4)	68 (58.6)	149 (64.5)
Other/unknown	4(3.5)	10 (8.6)	14 (6.1)
WHO PS (n [%])			

Characteristics	Ceritinib n = 115	Chemotherapy n = 116	Total n = 231
0	56. (48.7)	51 (44.0)	107(46.3)
1	50 (43.5)	60 (51.7)	110 (47.6)
2	9 (7.8)	5 (4.3)	14 (6.1)
Smoking history (n [%])			
Current smoker or Ex-smoker	43 (37.4)	52 (44.8)	95 (41.1)
Never smoker	71 (61.7)	61 (52.6)	132 (57.1)
Missing	1 (0.9)	3 (2.6)	4 (1.7)
Histology Cytology (n [%])			
Adenocarcinoma	111 (96.5)	113 (97.4)	224 (97.0)
Other	4 (3.5)	3 (2.6)	7 (3.0)
Metastatic site of cancer (n [%])			
Lung[1]	115 (100)	115 (99.1)	230 (99.6)
Stage at time of study entry (n [%])			
IIIB	1 (0.9)	1 (0.9)	2 (0.9)
IV	114 (99.1)	115 (99.1)	229 (99.1)
Brain metastases per BIRC			
Absent	50(43.5)	47 (40.5)	97(42.0)
Present	65(56.5)	69 (59.5)	134(58.0)
Median time from primary diagnosis to randomization, months (range)	19.4 (5.5-153.3)	19.8 (6.5-115.9)	19.5 (5.5-153.3)[1]
SD = standard deviation; WHO PS = World Health Organization Performance Status.			

Data source: Scagliotti et al. ESMO 2016 Oral[2]

All patients enrolled in the ASCEND-5 Trial had received prior treatment with crizotinib and one to two regimens of chemotherapy (including platinum doublet). Table 7 represents the prior antineoplastic therapies all patients received in the ASCEND-5 Trial. Notably, two amendments were made to the trial protocol which altered the inclusion criteria of the trial.[1] The first amendment was to include patients who had received one or two prior chemotherapy regimens and more than one course of crizotinib and the second amendment was to allow any sequence of prior crizotinib or chemotherapy.

A large proportion of patients in ASCEND-5 received crizotinib as their last treatment (81.7% in the ceritinib group and 81.9% in the chemotherapy group) and only a few patients received crizotinib more than once (1.3% of all patients).[1] Moreover, most patients in this trial received chemotherapy treatment for advanced disease (97.4% for all patients) and had only one prior chemotherapy regimen (ceritinib: 86.1% and chemotherapy: 85.3%).[1] The most common therapies patients received were crizotinib (100%), pemetrexed (70.6%), cisplatin (63.6%) and carboplatin (42.4%).[1] Furthermore, the majority of patients received cisplatin or carboplatin and pemetrexed as a prior platinum-based doublet for advanced disease (67.8% for ceritinib and 65.5% for chemotherapy).[1]

Table 7: Prior antineoplastic therapies at baseline for patients in the ASCEND-5 Trial

Therapy	Ceritinib n = 115	Chemotherapy n = 116	Total n = 231
Radiotherapy to the brain	41 (35.7)	42 (36.2)	83 (35.9)
Any chemotherapy[A]			
Advanced disease [B]	112 (97.4)	113 (97.4)	225 (97.4) [C]
Crizotinib	115 (100)	116 (100)	231 (100)
>1 prior regimen	1 (0.9)	2 (1.7)	3 (1.3)
As last treatment	94 (81.7)	95 (81.9)	189 (81.8)
Number of prior chemotherapy			

regimens in advanced disease [B]			
0	3(2.6)[D]	3(2.6)	6(2.6) [C]
1	99 (86.1)	99 (85.3)	198 (85.7)
2	13 (11.3)	14 (12.1)	27 (11.7)
Prior anti-cancer medications			
Bevacizumab	12 (10.4)	19 (16.4)	31 (13.4)
Carboplatin	48 (41.7)	50 (43.1)	98 (42.4)
Cisplatin	76 (66.1)	71 (61.2)	147 (63.6)
Crizotinib	115 (100)	116 (100)	231 (100)
Docetaxel	4 (3.5)	5 (4.3)	9 (3.9)
Erlotinib	0	3 (2.6)	3 (1.3)
Etoposide	2 (1.7)	1 (0.9)	3 (1.3)
Gefitinib	1 (0.9)	1 (0.9)	2 (0.9)
Gemcitabine	16 (13.9)	23 (19.8)	39 (16.9)
Investigational drug	2 (1.7)	1 (0.9)	3 (1.3)
Irinotecan	0	1 (0.9)	1 (0.4)
Paclitaxel	13 (11.3)	20 (17.2)	33 (14.3)
Pemetrexed	82 (71.3)	81 (69.8)	163 (70.6)
Vinorelbine	11 (9.6)	8 (6.9)	19 (8.2)
Prior platinum-based doublet therapies in advance disease[B]	111 (96.5)	113 (97.4)	224 (97.0) [C]
cisplatin or carboplatin + pemetrexed	78 (67.8)	76 (65.5)	154 (66.7)
cisplatin or carboplatin + paclitaxel	13 (11.3)	18 (15.5)	31 (13.4)
cisplatin or carboplatin + docetaxel	2 (1.7)	1 (0.9)	3 (1.3)
cisplatin or carboplatin + emcitabine	14 (12.2)	20 (17.2)	34 (14.7)
cisplatin or carboplatin + vinorelbine	8 (7.0)	5 (4.3)	13 (5.6)
cisplatin or carboplatin + other[D]	2 (1.7)	1 (0.9)	3 (1.3)

[A] May have received prior therapy in more than one setting.
[B] Includes therapeutic, metastatic or palliative setting and neo-/adjuvant setting with relapse ≤ 12 months from end of therapy
[C] 6 out of 7 patients with "0" chemotherapy regimen in the metastatic setting were confirmed after database lock to have received chemotherapy for metastatic disease (not protocol deviations) and one patient in the ceritinib arm had no prior chemotherapy which was a protocol deviation (excluded from Per-Protocol Set)
[D] Includes one patient who had no prior chemotherapy and which was a protocol deviation.

Data source: CSR and Scagliotti et al. ESMO 2016 Oral[1,2]

c) Interventions

In the ASCEND-5 Trial, patients received either an oral 750 mg dose of ceritinib once daily or an intravenous 75 mg/m^2 docetaxel per 21 day cycle or an intravenous 500 mg/m^2 pemetrexed per 21 day cycle.[3] Patients continued receiving their assigned therapy for a 12 week period until they progressed or withdrew from the study. Patients in the ceritinib group were able to remain on ceritinib beyond disease progression as part of a survival follow up phase; however, those randomized to the chemotherapy group were allowed to cross-over and receive ceritinib after disease progression.

Dose adjustment and dose interruptions were allowed for patients who were unable to tolerate the study dosage. Dose reduction for patients treated with ceritinib could not be re-escalated and only three dose reductions were permitted or the patient was discontinued from treatment.[1] Furthermore, dose reductions for patients treated with chemotherapy were based on local clinical guidelines and only two dose modifications were permitted or the patient was discontinued from treatment.[1]

d) Patient Disposition

Patient disposition for ASCEND-5 is presented in Table 8. In total, 326 patients were enrolled in the trial, and 231 patients were randomized on a 1:1 ratio to receive ceritinib (N = 115) or chemotherapy (N = 116; docetaxel arm N = 73 and pemetrexed arm N = 40).[2] Three patients in the

chemotherapy arm did not receive treatment.[2] The median duration from follow-up from randomization to data-cut off was 16.5 months.[2]

A larger proportion of patients in the chemotherapy arm discontinued treatment as compared to the ceritinib arm (93.1% vs. 71.3%, respectively) , and at the time of data cut-off, 28.7% of patients in the ceritinib arm and 6.9% of patients in the chemotherapy arm were still receiving treatment.[2] The primary reason for discontinuation was due to disease progression (48.7% in ceritinib group and 70.7% in the chemotherapy group).[2] Among the patients in the ceritinib group who discontinued treatment due to disease progression, more than three-quarters continued to receive ceritinib therapy beyond progression. In addition, more patients in the ceritinib arm (7.8%) had a treatment-related death as compared to chemotherapy (4.3%).[2]

In the ceritinib group, the majority of patients in the treatment phase entered the survival follow-up phase (53.0%).[1] In this phase, patients could continue to receive ceritinib therapy or a subsequent antineoplastic agent and were subsequently followed up for survival every 12 weeks until death, lost to follow-up or study withdrawal.[1] Additionally, 12.2% of patients discontinued from the study and 6.1% entered the post-treatment follow-up phase.[1] The post-treatment follow-up phase consisted of patients who discontinued from the treatment phase for reasons other than PD assessed by BIRC, death or lost to follow-up and were followed-up for tumor assessment and PROs until PD by BIRC or they withdrew from the study.[1] In contrast, patients in the chemotherapy group entered the extension treatment phase (63.8.0%) or the survival follow-up phase (34.6%).[1] In the extension treatment phase, only patients who were randomized to chemotherapy and had PD as assessed by BIRC could cross-over and receive ceritinib (Table 8).

- Extension treatment phase: for patients who crossed-over from chemotherapy to ceritinib treatment.
- Post-treatment follow up phase: patients who discontinued their assigned treatment during the treatment phase for reasons other than death, lost to follow-up, or disease progression. These patients were monitored for tumour and PRO assessments until they had disease progression assessed by BIRC, they withdrew, they were lost to follow-up, they died or the study was terminated by the sponsor.
- Survival follow up phase: patients who had disease progression assessed by BIRC and/or withdrew consent. These patients were followed by the study investigator for survival information and subsequent antineoplastic therapies until death, lost to follow-up or withdrawal of consent for survival.

At the time of data cut-off, 0.9% of study participants were in the post-treatment phase.[1] However, in the extension phase, 75 patients randomized to chemotherapy with disease progression assessed by BIRC crossed over and received ceritinib treatment (docetaxel N = 48 and pemetrexed N = 27). Of note, one patient did not have disease progression assessed by BIRC and was reported as a protocol deviation. At the time of data cut-off, 47/75 patients who had crossed into the ceritinib arm discontinued treatment, primarily due to disease progression (20.7%) or death (12.9%).[1]

In ASCEND-5, the Manufacturer reported that at least one protocol deviation occurred in 48.7% of patients in the ceritinib arm and in 47.4% of patients in the chemotherapy arm.[1] In the ceritinib arm, 8.7% of patients had a protocol deviation based on inclusion criteria compared to 11.2% in the chemotherapy arm.[1] Five patients were excluded from the study due to protocol deviations. These patients were excluded because three had been identified as ALK negative using the FISH test and scoring algorithm before their first study dose (ceritinib: 2 and chemotherapy: 1), one patient had not been treated with crizotinib nor cytotoxic chemotherapy and one patient had not received any previous chemotherapy treatments.[1]

Table 8: Summary of patient disposition in the ASCEND-5 Trial

	Ceritinib N = 115	Chemotherapy N = 116	Total N = 231
Patients randomized			
Treated	115 (100)	113 (97.4)	228 (98.7)
Treatment phase			
Ongoing[A]	33 (28.7)	8 (6.9)	41 (17.7)
Discontinued from treatment phase	82 (71.3)	108 (93.1)	190 (82.3)
Entered extension treatment phase[B]	0	74 (63.8)	74 (32.0)
Entered post-treatment follow-up phase[C]	7 (6.1)	5 (4.3)	12 (5.2)
Entered survival follow-up phase[D]	61 (53.0)	19 (16.4)	80 (34.6)
Discontinued from study	14 (12.2)	10 (8.6)	24 (10.4)
Primary reason for discontinuation from treatment phase			
Adverse event	6 (5.2)	8 (6.9)	14 (6.1)
Death	9 (7.8)	5 (4.3)	14 (6.1)
Physician decision[E]	5 (4.3)	5 (4.3)	10 (4.3)
Progressive disease	56 (48.7)	82 (70.7)	138 (59.7)
Subject guardian decision	6 (5.2)	8 (6.9)	14 (6.1)
Extension treatment phase[B]			
Ongoing[A]	0	28 (24.1)	28 (12.1)
Discontinued extension treatment phase	0	47 (40.5)	47 (20.3)
Entered survival follow-up phase	0	28 (24.1)	28 (12.1)
Discontinued from study	0	19 (16.4)	19 (8.2)
Primary reason for discontinuation from extension treatment phase			
Adverse event	0	3 (2.6)	3 (1.3)
Death	0	15 (12.9)	15 (6.5)
Physician decision	0	1 (0.9)	1 (0.4)
Progressive disease	0	24 (20.7)	24 (10.4)
Subject guardian decision	0	4 (3.4)	4 (1.7)

A: Patients ongoing at the time of the cut-off 26-Jan-2016.
B: Extension treatment phase is for patients who crossed-over from chemotherapy to ceritinib treatment.
C: This phase consists of patients who discontinued their assigned treatment during the treatment phase for reasons other than death, lost to follow-up, or disease progression. These patients were monitored for tumour and PRO assessments until they had disease progression assessed by BIRC, they withdrew, they were lost to follow-up, they died or the study was terminated by the sponsor.
D: This phase consists of patients who had disease progression assessed by BIRC and/or withdrew consent. These patients were followed by the study investigator for survival information and subsequent antineoplastic therapies until death, lost to follow-up or withdrawal of consent for survival.
E: Includes eight patients with local disease progression by RECIST not confirmed by BIRC, or clinical disease progression.

Data source: CSR and Scagliotti et al. ESMO 2016 Oral [1,2]

e) Limitations/Sources of Bias

ASCEND-5 was a multicentre, open-labeled phase III, randomized controlled trial. Overall, the trial was well designed; however, there are a few limitations that need to be considered:

- The ASCEND-5 trial was open-label RCT design. A double-blinded design would have been very difficult to implement due to the administration of the study interventions (ie oral versus intravenous) and assignment of the chemotherapy agents (ie docetaxel or pemetrexed). To account for the open-label design of ASCEND-5, an independent, blinded review committee was used to assess objective outcomes like PFS. However, for the assessment of subjective outcomes, such as PRO and reporting adverse events, there is a greater risk of detection bias because patients and Study Investigators would be aware of which treatment was being administered.

- Although the Manufacturer provided comprehensive regulatory and summary reports, the only published material provided for ASCEND-5 was in conference abstract form. Thus it is unclear whether the results of ASCEND-5 have undergone peer-review or whether the data for the reported results are complete. Furthermore, more follow-up data is required to provide a more comprehensive understanding of the effect of ceritinib as compared to chemotherapy in patients with ALK+ NSCLC.

- Patients were generally balanced between the two treatment groups, with the exception of ethnicity and smoking status. Here, there were more Caucasians in the ceritinib group compared to the chemotherapy arm (70.4% vs. 58.6%) and more never smokers in the ceritinib arm as compared to the chemotherapy arm (61.7% vs. 52.6%). Although similar frequencies of ALK+ NCSLS occur in both Asian and Western countries[47], never smokers have a higher risk of ALK+ NSCLC[48,58,59] and these imbalances may introduce bias.

- The effect estimate for overall survival was immature at the data cut-off. Since the trial protocol allowed patients who were randomized to chemotherapy and had documented disease progression to cross over and receive open-label treatment with ceritinib, the overall survival effect estimates are likely confounded. However, the direction of confounding is unclear, and therefore, the reported effect estimate for survival may be over or underestimated.

- The Manufacturer reported that the overall compliance rate was not assessed during the trial.

- The study used a hierarchical testing approach to control for type 1 error in the study. The protocol stipulated that overall survival could be assessed if the effect estimate of PFS as assessed by BIRC was significant. However, there was no adjustment for multiplicity in analyses of other the secondary endpoints, such as PFS assessed by Investigator, ORR, DOR, DCR, TTR and PROS. The lack of adjustment increases the risk of type 1 error in these reported estimates and should be interpreted with caution.
- For the PRO analyses, the Manufacturer reported that they used nominal p-values and did not adjust for type 1 error. In addition, the Manufacturer stated that compliance rates for the different PRO instruments were high, but as the trial progressed, there were fewer patients on the chemotherapy arm at later treatment cycles. However, the compliance rate varied throughout the trial in both treatment arms, which may indicate that there is a high degree of incomplete reporting and the presented results do not fully capture the quality of life for all patients in the trial.
- A protocol amendment added measurement of intracranial anti-tumour activity as an exploratory secondary outcome. These estimates may be underpowered to detect an effect owing to missing post-baseline data and lack of adjustment for type 1 error.

- The funding request made by the Manufacturer was to evaluate the use of ceritinib as monotherapy in patients with ALK+ locally advanced (not amenable to curative therapy) or metastatic NSCLC who have progressed on or who were intolerant to crizotinib. Indeed, ASCEND-5 included patients with histologically or cytologically confirmed diagnosis of stage IIIB or IV NSCLC carrying an ALK rearrangement and who had received cytotoxic chemotherapy and crizotinib. However, only two patients (0.9%) enrolled in the trial had stage IIIB NSCLC at the time of study entry.[1] Furthermore, two amendments were made to the protocol which permitted patients who had received one or two prior chemotherapy regimens and more than one course of crizotinib to be included in the study as well as allowing any sequence of prior crizotinib or chemotherapy. Therefore the inclusion criteria used in ASCEND-5 does not reflect the Manufacturer's funding indication.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Progression-free Survival

The primary endpoint in the ASCEND-5 trial was PFS assessed by BIRC using the RECIST 1.1 guidelines. PFS was defined as the time from the date of randomization to the date of the first radiologically documented disease progression per BIRC assessment or death due to any cause[3].

In order to have 90% power for a one-sided 2.5% level of significance, a total of 161 progressive events were expected.[1] No interim analysis was planned for this outcome.[1] This analysis used an intention-to-treat (ITT) approach and PFS distributions were estimated using Kaplan-Meier methods and a log-rank test stratified by WHO performance status and presence or absence of brain metastases. The Manufacturers also used Cox regression models to estimate the hazard ratio (HR) of PFS and 95% confidence intervals (CI).

The cut-off date for the primary PFS analysis assessed by BIRC was on January 26th 2016[2] . At the time of data cut-off, a total of 172 patients (74.5%) had disease progression as assessed by BIRC or died (ceritinib: 72.2% and chemotherapy: 76.7%).[2] Median PFS was 5.4 months (95% CI, 4.1 to 6.9) for patients treated with ceritinib and 1.6 months (95% CI, 1.4 to 2.8) for patients treated with chemotherapy.[2] Treatment with ceritinib was associated with a statistically significant prolongation of PFS as compared to chemotherapy in patients with ALK+ NSCLC (HR = 0.49; 95% CI, 0.36 to 0.67; long-rank P < 0.001).[2] The Manufacturer confirmed the robustness of these results using supportive and sensitivity analyses.

As an exploratory outcome, PFS was assessed by the Study Investigator. At the time of data cut-off, the Study Investigator identified 83 (72.2%) events in the ceritinib group and 96 (82.8%) events in the chemotherapy group.[2] The median PFS was 6.7 months (95% CI, 4.4 to 7.9) in the ceritinib group and 1.6 months (95% CI, 1.4 to 2.6) in the chemotherapy group. Similar to the estimates obtained from the BIRC assessment, the Manufacturer reported treatment with ceritinib was associated with a statistically significant prolongation of PFS as compared to chemotherapy (HR=0.40; 95% CI, 0.29 to 0.54; *P* < 0.001).

Additionally, for this review, the CGP identified several subgroups of interest to explore the effect of ceritinib as compared to chemotherapy on the risk of PFS, and include: histological type, WHO performance status, age, ethnicity, sex, smoking status and brain metastases at baseline. The results of the subgroup analysis are presented in Figure 2. Overall, the Manufacturer showed that the protective effect of ceritinib as compared to chemotherapy was consistent among all groups.[2,57]

Figure 2: The association between ceritinib as compared to chemotherapy on the effect of PFS as assessed by BIRC stratified by geographic region, age, sex, race, WHO performance status, brain metastases and smoking history[2]

Estimate	Ceritinib (N = 115)	Chemotherapy (N = 116)	HR (95% CI)
Geographic Region			
North America	8 (88.9)	8 (72.7)	1.56(0.39−6.24)
Europe	51 (63.8)	53 (74.6)	0.45(0.3−0.68)
Asia Pacific	24 (92.3)	28 (75.6)	0.4(0.21−0.75)
Age			
< 65 years	63 (70.8)	65 (73)	0.53(0.37−0.77)
> 65 years	20 (76.9)	24 (88.9)	0.26(0.12−0.58)
Sex			
Male	35 (74.5)	40 (72.7)	0.43(0.26−0.71)
Female	48 (70.6)	49 (80.3)	0.51(0.34−0.79)
Race			
Caucasian	53 (65.4)	50 (73.5)	0.49(0.33−0.74)
Asian	27 (90)	31 (81.6)	0.46(0.26−0.82)
Other	1 (50)	1 (50)	
WHO performance status			
0	40 (71.4)	43 (84.3)	0.38(0.24−0.6)
=>1	43 (72.9)	46 (70.8)	0.63(0.41−0.97)
Brain metastases			
Absent	36 (65.4)	41 (71.9)	0.41(0.24−0.69)
Present	47 (78.3)	48 (81.3)	0.54(0.36−0.8)
Smoking history			
Never smoked	52 (73.2)	49 (80.3)	0.45(0.27−0.68)
Ex−smoker or current smoker	30 (70)	37 (71.1)	0.68(0.4−1.14)
Total	**83 (72.2)**	**89 (76.7)**	**0.49(0.36−0.67)**

Overall Survival

Overall survival was a key secondary endpoint in the ASCEND-5 trial. It was defined as the time from the date of randomization to the date of death due to any cause.[3] A total of 196 deaths were required for the final analysis to have 80% power with a one-sided 2.5% level of significance.[1] Three interim analyses for overall survival were planned: 1) at the time of the final PFS analysis; 2) following 171 deaths; and 3) following 196 deaths[1]. Furthermore, for this analysis, the Manufacturer used a hierarchical testing approach to control for Type I error.[1] Overall survival could be assessed only if PFS was statistically significant between treatment groups. Similar to the primary analysis of PFS, this analysis used an ITT approach, Kaplan-Meier methods and a stratified log-rank test. A Cox regression model was also used to estimate the HR of overall survival and 95% CI.

At the time of the data cut-off for the primary PFS analysis, the data for overall survival was immature. At the reported time point, 98 deaths (42.4%) had been documented, where 48 patients (41.7%) and 50 patients (43.1%) died in the ceritinib and the chemotherapy groups, respectively.[1,2] Among the 98 events that occurred, the median overall survival in the ceritinib group was 18.1 months (95% CI, 13.4 to 23.9) and 20.1 months (95% CI, 11.9 to 25.1) in the chemotherapy group.[2] Given that 50% of events have not occurred, the median OS estimate is

uncertain and may change. The Manufacturer reported that there was no difference between treatment groups for overall survival (HR = 1.00; 95% CI, 0.67 to 1.49; P= 0.496). However, this effect estimate was immature at the time of the data cut-off and it may also be confounded by patient cross-over.

The Manufacturer also conducted various supportive and sensitivity analyses to confirm the PFS and OS effect estimates; however, within the current review only the results of the sensitivity analysis will be presented. For this analysis, the Manufacturers conducted a rank-preserving structural failure time (RPSFT) model to correct for confounding that may have resulted from patient cross over. The effect estimate from the RPSFT was similar to the original analysis (HR: 0.97, 95% CI, 0.65 to 1.45).[1] Although the supportive analyses showed similar estimates, the Manufacturer has acknowledged that at the time of the primary analysis, only half of the required overall survival events had been reached (i.e. 50% information fraction) and there was a limited follow-up time after crossover in the ASCEND-5 trial. Thus the interim overall survival results are immature and confounded by the high rate of cross-over, and should therefore be interpreted with caution.

Anti-tumour Activity Measures

In the ASCEND-5 trial, anti-tumour activity was measured by overall response rate (ORR), disease control rate (DCR), duration of response (DOR) and time to response (TTR). Table 9 represents the results of the effect of ceritinib as compared to chemotherapy on the risk of anti-tumour activity endpoints. It should be noted that no formal statistical testing was performed for these exploratory outcomes.

Table 9. The association of ceritinib and chemotherapy on the risk of anti-tumour activity endpoints assessed by BIRC

Outcome	Ceritinib N = 115	Chemotherapy N = 116
Best overall response		
Complete Response, n (%)	0	0
Partial Response, n (%)	45 (39.1)	8 (6.9)
Stable Disease, n (%)	35 (30.4)	28 (24.1)
Progressive Disease, n (%)	19 (16.5)	60 (51.7)
Non-CR/Non-PD, n (%)	8 (7.0)	6 (5.2)
Unknown, n (%)	8 (7.0)	14 (12.1)
ORR, % (95% CI)[A]	39.1 (30.2, 48.7)	6.9 (3.0, 13.1)
DCR, % (95% CI)[B]	76.5 (67.7, 83.9)	36.2(27.5, 45.6)
DOR, median in months (95% CI)[C]	6.9(5.4, 8.9)	8.3(3.5, NE)
TTR, median in weeks (range)[D]	6.7(5.3 to 52.3)	7.4(5.4, 12.1)

CR = complete response; ORR = overall response rate; DCR = disease control rate; DOR = duration of response; TTR = time to response.
A: Defined as the sum of complete plus partial responses.
B: Defined as the sum of patients with best response rate of complete response, partial response, stable disease or Non-complete response or non PD per RECIST 1.1 for patients with non-measurable disease only at baseline
C: Time from date of documented complete or partial response in patients to the date of PD or death to any cause with confirmed complete or partial response.
D: Time from date of randomization to date of in documented complete or partial response in patients with confirmed complete or partial response.

Overall Response Rate

ORR was defined as the proportion of patients with the best overall response, which was measured as the sum of complete response (CR) and partial response (PR).[3] Tumour assessment for best overall response was performed before patients received any additional antineoplastic therapies. Patients in the ceritinib group were more likely to demonstrate an ORR assessed by BIRC compared with those in the chemotherapy group (39.1% [95% CI, 30.2 to 48.7] vs. 6.9% [95% CI, 3.0 to 13.1]).[2] No patients demonstrated a complete response.

Additionally, the Manufacturer noted that 7.0% of patient in the ceritinib group and 12.1% of patients in the chemotherapy group had an unknown response.[1] Patients were most likely to have an unknown response because they did not have a post-baseline assessment owing to early discontinuation (62.5% in ceritinib vs. 64.3% in chemotherapy).[1] The effect estimates of ORR by Investigators assessment was similar to that of ORR by BIRC assessment (42.6% [95% CI, 33.4 to 52.2] in ceritinib and 6.0% [95% CI, 2.5 to 12.0] in chemotherapy).[1]

Disease control rate

DCR was defined as the sum of patients with best response rate of complete response, partial response, stable disease or Non-complete response or non-disease progression per RECIST 1.1 for patients with non-measurable disease only at baseline.[3] DCR assessed by BIRC was higher in patients treated with ceritinib as compared to those treated with chemotherapy (76.5% [95% CI, 67.7 to 83.9] vs. 36.2% [95% CI, 27.5 to 45.6]).[2]

Duration of Response

DOR was defined as the time from first documented response of either CR or PR, in patients with confirmed PR or CR, to the date of first documented disease progression or death due to any cause.[3] Patients randomized to the ceritinib arm had a shorter median DOR assessed by BIRC as compared to those randomized to the chemotherapy arm (6.9 months [95% CI, 5.4 to 8.9; N= 45] and 8.3 months [95% CI, 3.5 to NR; N = 8], respectively).[1] However, given than only 8 events were available in the chemotherapy arm to determine duration of response, these estimates may be under powered and should be interpreted with caution.

Time to Response

TTR was defined as the time from the date of randomization to the date of the first documented CR or PR only in patients with confirmed CR or PR.[3] The TTR was 6.7 weeks (range: 5.3 to 52.3 weeks; N = 45) for patients treated with ceritinib and 7.4 weeks (range: 5.4 to 12.1 weeks; N = 8) treated with chemotherapy.[1]

Anti-tumour Intracranial Activity Measures

Another exploratory outcome in the ASCEND-5 Trial was anti-tumour intracranial activity, which was measured by overall intracranial response rate (OIRR), intracranial disease response rate (IDCR) and duration of intracranial response (DOIR) assessed by BIRC neuro-radiologist per modified RECIST 1.1. These endpoints were included in as a protocol amendment.[1] The Manufacturer indicated that the results of IDCR are non-disclosable because they may be included in a future, peer-reviewed publication; however, the Manufacturer did not provide any information on the current state of this manuscript.

Patients were included in the anti-tumour intracranial activity analyses if they had up to five brain lesions at baseline. For this analysis, measurable disease was classified as the presence of at least

one measurable lesion while non-measurable disease was classified as previously irradiated lesions unless there was evidence of progression after radiotherapy[1].

Overall, the ASCEND-5 trial enrolled 133 patients who had brain metastases (both measurable and non-measurable) at baseline (ceritinib: 66 and chemotherapy: 67).[1] Among those with brain metastases, 23 patients in both the ceritinib and chemotherapy groups had measurable lesions and were included in the aforementioned intracranial tumor activity assessments. However, the Manufacturer stated that 21.7% of these patients with measurable disease did not have a valid post-baseline tumour assessment, and were therefore, not included in the analysis.[1] In addition, 56.0% patients in the ceritinib arm and 56.7% of patients in the chemotherapy arm with brain metastases at baseline had prior radiation therapy to the brain.[1] Although this is a relative subgroup of the ASCEND-5 trial, this is a small population which may have limited power to detect an effect.

OIRR was defined as the proportion of patients with a best overall confirmed response of CR or PR in the brain as assessed by BIRC neuro-radiologist per modified RECIST 1.1. Patients with measurable lesions at baseline and who were randomized to ceritinib had a higher OIRR as compared to those randomized to chemotherapy (26.1% [95% CI, 10.2 to 48.4] vs. 4.3% [95% CI, 0.1 to 21.9], respectively).[1] A similar trend was observed for a subgroup of patients with measurable disease at baseline who did not have prior radiotherapy (data not shown).[57] OIRR was also measured in patients with measurable and non-measurable disease; however, the Manufacturer did not disclose these results. It is notable that the OIRR in the ceritinib arm for all patients with brain metastases at baseline (measurable and non-measurable) was lower than what was observed among patients with only measurable disease (23 patients in each arm). Although this data was in a comparatively larger patient population, limitation still exist regarding the interpretation of results due to the small sample size and limited power to detect an effect.

Notably, 26.1% of patients in both the ceritinib and chemotherapy arms had unknown response rates.[1] Unknown response rates were most likely due to no valid baseline assessment (ceritinib N = 6 and chemotherapy N =3). As a sensitivity analysis, the Manufacturer excluded patients with no post-baseline assessments and reported similar results for OIRR in the ceritinib and chemotherapy arms (35.3% [95% CI, 14.2 to 61.7] vs. 5.0% [95% CI, 0.1 to 24.9], respectively).[1]

Additionally, the OIRR as assessed by BIRC for patients with measurable and non-measurable disease at baseline was also reported. The OIRR was higher in patients treated with ceritinib (10.6%, 95% CI, 4.4 to 0.6) as compared to those treated with chemotherapy (3.0%, 95% CI, 0.4, 10.4).1 As reported previously, there was a higher proportion of unknown response rates, which was most likely to due to no valid post-baseline assessment (66.7% in ceritinib and 62.5% in chemotherapy). [1]

Finally, DOIR was defined as the time from first documented complete or partial intracranial response to the date of first documented disease progression or death to any cause only in patients with a confirmed intracranial response of PD or CR.[1] For this analysis, six patients in the ceritinib arm and one patient in the chemotherapy arm had confirmed intracranial response of PR or CR. The median duration of intracranial response for patients with measure disease at baseline in the ceritinib group was 6.9 months (95% CI, 2.7 to 8.3) and not reached (NR) in chemotherapy arm.1 Similar estimates were reported for patients with measurable and non-measurable disease at baseline, where the DOIR for patients treated with ceritinib was 8.3 months (95% CI, 2.7 to 8.8) and NR for those in the chemotherapy arm. [1]

Quality of Life

Patient related outcomes (PROs) were reported in the ASCEND-5 Trial to assess the effect of ceritinib as compared to chemotherapy on the patients' health related quality of life (HRQoL).The

following instruments were used: lung cancer symptom scale (LCSS), European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30) and lung cancer specific questionnaire (LC13) and EuroQOL five dimensions questionnaire (EQ-5D-5L) with EQ visual analog scale (VAS). The Manufacturer's also reported that completion rates were high, where more than 75% of patients completed a questionnaire at all time points. However, it should be noted that the Manufacturer did not provide completion time rates for all scales.

LCSS

LCSS assesses the effect a therapeutic agent has on lung symptoms and HRQoL. It is a disease- and site-specific instrument that measures changes in six major lung cancer symptoms and three summary items using 100mm VAS.[60] The scale ranges from 0 (best) to 100 (worse). The minimally important difference (MID) used for the LCSS was a 15 mm or higher increase/decrease from baseline.[57] The Manufacturers reported that there was no deterioration in quality of life for patients treated with ceritinib as compared to chemotherapy.[61]

The Manufacturer also created a composite endpoint to assess time to definitive symptom deterioration, which was based on scores of cough, pain and dyspnea. Time to definitive deterioration was defined as the time from randomization to the earliest date a patient shows a ≥ 15mm increase from baseline with no later change below this threshold.[61] Patients were censored at the date they last completed the questionnaire. The authors reported that those in the ceritinib arm had a longer median time to deterioration (18 months [95% CI: 13.4 to NE]) as compared to those randomized to chemotherapy (4.4 months [95% CI: 1.6 to 8.6]).[61] Furthermore, patients assigned to ceritinib had a prolonged time to deterioration as compared to chemotherapy (HR=0.40; 95% CI=0.25 to 0.65).[61] However, it should be noted that this was a descriptive analysis and no adjustment for multiplicity was made.

EORTC QLQ-C30 and EORTC QLQ-LC13

The EORTC-QLQ-C30 and the EORTC- QLQ-LC13 questionnaires measure QoL, function, dyspnea and disease related symptoms. The EORTC QLQ-C30 specifically measured nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale.[62] The EORTC QLQ-LC13 is a disease specific module that complements the EORTC QLQ-C30 and it evaluates different aspects of lung cancer symptoms and side-effects from chemotherapy and radiotherapy.[63] In the EORTC-QLQ-LC13 and the EORTC- QLQ-C30 questionnaires a lower score over time indicates a better performance.

The MID for the EORTC QLQ-C30 and the EORTC QLQ-LC13 was a 10 points increase for the symptom scales and 10 points decrease for the QoL/functional scales.[57] The Manufacturers used a repeated measure model to compare the treatment differences between ceritinib and chemotherapy for both instruments. For the EORTC QLQ-C30, the Manufacturers stated that treatment with ceritinib as compared to chemotherapy appeared to improve fatigue, dyspnea, insomnia, financial difficulties as well as physical, role and social functioning.[61] However, there was no difference in the scores of diarrhea, nausea, vomiting or quality of life.[61] Additionally, using the EORTC QLQ-LC13, the Manufacturers reported that ceritinib therapy was associated with improvements in dyspnea, cough, sore mouth, dysphagia, peripheral neuropathy, alopecia, chest pain, and other pain as compared to chemotherapy.[61] However, it is unclear to the Methods Team whether the MID was met.

For the EORTC QLQ-LC13, the Manufacturer created a composite endpoint of cough, pain and dyspnea to assess time to definitive symptom deterioration. This was defined as the time from the date of randomization to the earliest date when the patient's score shows a ≥ 10 point increase from baseline in any of the QLQ -LC13 scores related to pain in chest, cough or dyspnoea or

death.[61] Here, the ceritinib arm had a higher median time to deterioration (11.1 months, 95% CI: 7.1 to 14.2) as compared to those randomized to chemotherapy (2.1 months, 95% CI: 1.0 to 5.6).[61] Furthermore, patients assigned to ceritinib had a prolonged time to deterioration as compared to chemotherapy (HR: 0.34, 95% CI: 0.22 to 0.52).[61] However, these results were reported using nominal p-values and should be interpreted with caution because they do not account for Type I error.

EQ-5D-5L

The EQ-5D-5L provides a standardized measure of health status for five dimensions of health. The EQ-5D-5L also includes an assessment of VAS, which measures patient's health status using a vertical VAS scale that ranges from "Best imaginable health state" to "Worst imaginable health state".[1] The MID of the EQ-5D-5L was a change in 10 points.[57] Using a repeated measures model, the Manufacturers stated that ceritinib was associated with an improvement in overall health status as compared to chemotherapy ($P < 0.001$) while the effect on the EQ-5D-5L VAS was modest.[61] However, these results are difficult to interpret because it is unclear whether the MID was met and the Manufacturer used an exploratory repeated measures model and nominal p-values.

Harms Outcomes

The safety set of ASCEND-5 consisted of 228 patients who received at least one dose of their assigned therapies (115 in the ceritinib group and 113 in the chemotherapy group).[1] Three patients were excluded in the safety set because they did not receive their assigned treatment.[2]

Deaths

During the 30 day study drug discontinuation period, 15 patients in the ceritinib group died (13.0%).1 Thirteen of these patients died as a result of disease progression and two died of "other causes" that were not related to the study treatment. Similarly, in the chemotherapy group, five patients died (4.4%) as a result of disease progression (docetaxel N = 3 and pemetrexed N = 2). The Manufacturer also noted that the frequency of deaths during the first six weeks of treatment was similar between the two treatment arms.

Serious Adverse Events

In the ASCEND-5 Trial, patients treated with ceritinib experienced more serious adverse events as compared to those treated with chemotherapy (42.6% vs. 31.9%).[2] The most frequently reported serious adverse event in the ceritinib treatment group was dyspnea (6.1%), followed by nausea (5.2%), general physical health deterioration, pleural effusion, pneumonia, and vomiting (4.3% for all), pericardial effusion and pyrexia (3.5% for all), and respiratory failure (2.6%).[1] In contrast, dyspnea (4.4%) and asthenia (2.7%) were more commonly reported in the chemotherapy group. The Manufacturer also reported that 39.1% of patients in the ceritinib group and 30.1% in the chemotherapy arm reported a grade 3 to 4 serious adverse event.[1] To address the serious adverse event rate in the ASCEND-5 Trial, the Manufacturer provided the following statement: "The difference in the duration of treatment exposure between the two treatment arms was five times longer in the ceritinib arm than in the chemotherapy arm (30.3 weeks vs 6.3 weeks), which may have contributed to the accumulation of adverse events observed in the ceritinib arm." In addition, the Manufacturer also stated that for treatment-related serious adverse events, most of the serious adverse events were a result of underlying disease and not related to the study treatment.

All Grades and Grade 3 or 4 Adverse Events

All patients treated with ceritinib (100%) and 99.1% of patients treated with chemotherapy experienced an adverse event[1]. Furthermore, compared to patients treated with chemotherapy, more patients treated with ceritinib experienced a grade 3 or 4 adverse event (77.4% vs. 63.7%).[2]

All grades adverse events that were reported in ≥20% of patients in the ASCEND-5 Trial are presented in Table 10. The adverse events that were reported in more than 25% randomized to the certinib group were diarrhoea (72.2%), nausea (66.1%), increase in alanine aminotransferase (ALT) (42.6%), decreased appetite (41.7%), increase in aspartate aminotransferase (AST) (36.5%) and fatigue (27.0%). In contrast, the adverse event that occurred in more than 25% of patients in the chemotherapy group was fatigue (28.3%).[2] Furthermore, the most commonly reported grade 3 or 4 adverse events that occurred in the ceritinib group was ALT increased (20.9%), GGT increased (20.9%), and AST increased (13.9%) while the most frequent was neutropenia (15.0%) in the chemotherapy group.[2] Also more patients in the ceritinib group had elevated creatinine levels as compared to the chemotherapy group (19.1% vs. 0%). However, CGP has stated that these grade 3 to 4 adverse events, such as nausea, vomiting, diarrhea, were infrequent and varied according to the patients' experience.

Table 10. All and grade 3 to 4 adverse events, regardless of study drug relationship by treatment group (≥ 20% for all grades and greater than 10% in grade 3 to 4 in either groups)

	Ceritinib (N=115)		Chemotherapy (N=113)		Pemetrexed (N =40)		Docetaxel (N=73)	
Preferred term	All grades (n [%])	Grade 3/4 (n [%])	All grades (n [%])	Grade 3/4 (n [%])	All grades (n [%])	Grade 3/4 (n [%])	All grades (n [%])	Grade 3/4 (n [%])
Total	115 (100)	89 (77.4)	112 (99.1)	72 (63.7)	40 (100)	18 (45.0)	72 (98.6)	54 (74.0)
Diarrhoea	83 (72.2)	5 (4.3)	20 (17.7)	1 (0.9)	1 (2.5)	0	19 (26.0)	1 (1.4)
Nausea	76 (66.1)	9 (7.8)	26 (23.0)	2 (1.8)	14 (35.0)	1 (2.5)	12 (16.4)	1 (1.14)
Vomiting	60 (52.2)	9 (7.8)	6 (5.3)	1 (0.9)	2 (5.0)	1 (2.5)	4 (5.5)	0
ALT increased	49 (42.6)	24 (20.9)	10 (8.8)	2 (1.8)	8 (20.0)	2 (5.0)	2 (2.7)	0
Decreased appetite	48 (41.7)	2 (1.7)	22 (19.5)	3 (2.7)	5 (12.5)	17 (23.3)	3 (4.1)	0
AST increased	42 (36.5)	16 (13.9)	5 (4.4)	1 (0.9)	3 (7.5)	1 (2.5)	2 (2.7)	0
Weight decreased	34 (29.6)	3 (2.6)	7 (6.2)	1 (0.9)	1 (2.5)	0	6 (8.2)	1 (1.4)
Fatigue	31 (27.0)	6 (5.2)	32 (28.3)	5 (4.4)	14 (35.0)	2 (5.0)	18 (24.7)	3 (4.1)
Asthenia	26 (22.6)	6 (5.2)	21 (18.6)	7 (6.2)	8 (20.0)	4 (10.0)	13 (17.8)	3 (4.1)
Blood ALP increased	26 (22.6)	7 (6.1)	1 (0.9)	0	0	0	1 (1.4)	0
GGT increased	26 (22.6)	24 (20.9)	2 (1.8)	1 (0.9)	0	0	2 (2.7)	1 (1.4)
Abdominal pain	25 (21.7)	1 (0.9)	11 (9.7)	1 (0.9)	5 (12.5)	0	6 (8.2)	1 (1.4)
Back pain	25 (21.7)	1 (0.9)	8 (7.1)	3 (2.7)	3 (7.5)	1 (2.5)	5 (6.8)	2 (2.7)
Blood creatinine increased	22 (19.1)	0	0	0	0	0	0	0
Constipation	22 (19.1)	0	15 (13.3)	0	6 (15.0)	0	9 (12.3)	0
Headache	22 (19.1)	1 (0.9)	17 (15.0)	2 (1.8)	6 (15.0)	1 (2.5)	11 (15.1)	1 (1.4)
Dyspnoea	20 (17.4)	6 (5.2)	21 (18.6)	7 (6.2)	7 (17.5)	2 (5.0)	14 (19.2)	5 (6.8)
Pyrexia	19 (16.5)	2 (1.7)	17 (15.0)	0	4 (10.0)	0	13 (17.8)	0
Abdominal pain upper	18 (15.7)	1 (0.9)	5 (4.4)	0	1 (2.5)	0	4 (5.5)	0
Cough	16 (13.9)	0	18 (15.9)	1 (0.9)	6 (15.0)	0	12 (16.4)	1 (1.4)

Non-cardiac chest pain	15 (13.0)	1 (0.9)	4 (3.5)	0	2 (5.0)	0	2 (2.7)	0
Electrocardiogram QT prolonged	13 (11.3)	1 (0.9)	0	0	0	0	0	0
Rash	13 (11.3)	0	12 (10.6)	0	6 (15.0)	0	6 (8.2)	0
Arthralgia	12 (10.4)	0	13 (11.5)	3 (2.7)	3 (7.5)	2 (5.0)	10 (13.7)	1 (1.4)
Nasopharyngitis	12 (10.4)	0	1 (0.9)	0	1 (2.5)	0	0	0
Alopecia	6 (5.2)	0	24 (21.2)	0				
Anaemia	6 (5.2)	0	19 (16.8)	5 (4.4)	5 (12.5)	4 (10.0)	14 (19.2)	1 (1.4)
Stomatitis	5 (4.3)	0	15 (13.3)	0	6 (15.0)	0	9 (12.3)	0
Myalgia	4 (3.5)	0	13 (11.5)	0	2 (5.0)	0	11 (15.1)	0
Neutropenia	4 (3.5)	1 (0.9)	23 (20.4)	17 (15.0)	3 (7.5)	0	20 (27.4)	17 (23.3)

ALT=alanine aminotransferase; ALP=alkaline phosphatase, AST=aspartate aminotransferase; GGT=gamma-glutamyltransferase
Preferred terms are sorted in descending frequency of all grades column, as reported for the ceritinib treatment group.
A patient with multiple adverse events was counted only once in the total row. Missing grades are included under 'All grades' column.
Data source: CSR and Scagliotti et al.[1, 2]

Adverse Events of Special Interest

For this review the CGP identified hyperglycemia, gastrointestinal (GI) toxicity, hepatotoxicity, QT prolongation and interstitial lung disease (ILD)/pneumonitis as adverse events of special interest. The details of these special adverse events of interest are presented in Table 11. Overall, more patients in the ceritinib group experienced all grades and grade 3 or 4 hyperglycemia, GI toxicity, hepatotoxicity and QT prolongation as compared to the chemotherapy group. On the other hand, patients in the chemotherapy arm were more likely to experience all grades and grade 3 or 4 ILD/pneumonitis than the ceritinib arm.

Table 11: Summary of the Adverse Events of Special Interest

Adverse event	Severity	Ceritinib (N = 115)	Chemotherapy (N = 113)
Hyperglycemia	All AEs	10 (8.7)	4 (3.5)
	Hyperglycaemia	8 (7.0)	3 (2.7)
	Diabetes mellitus	2 (1.7)	0
	Blood glucose increased	0	1 (0.9)
	AE of CTC Grade ≥3	6 (5.2)	2 (1.8)
	Hyperglycaemia	6 (5.2)	2 (1.8)
	SAEs	1 (0.9)	0
	Hyperglycaemia	1 (0.9)	0
	WDAE	0	0
GI toxicity	All AEs	107 (93.0)	39 (34.5)
	Diarrhoea	83 (72.2)	20 (17.7)
	Nausea	76 (66.1)	26 (23.0)
	Vomiting	60 (52.2)	6 (5.3)
	AE of CTC Grade ≥3	15 (13.0)	3 (2.7)
	Diarrhoea	9 (7.8)	2 (1.8)
	Nausea	9 (7.8)	1 (0.9)
	Vomiting	5 (4.3)	1 (0.9)
	SAEs	8 (7.0)	0
	Diarrhoea	6 (5.2)	0
	Nausea	5 (4.3)	0
	Vomiting	2 (1.7)	0
	WDAE	1 (0.9)	0
	Vomiting	1 (0.9)	0

Adverse event	Severity	Ceritinib (N = 115)	Chemotherapy (N = 113)
Hepatotoxicity	All AEs	61 (53.0)	15 (13.3)
	AE of CTC Grade ≥3	44 (38.3)	4 (3.5)
	SAE	1 (0.9)	1 (0.9)
	WDAE	2 (1.7)	2 (1.7)
QT prolongation	All AEs	14 (12.2)	1 (0.9)
	AE of CTC Grade ≥3	2 (1.7)	1 (0.9)
	SAE	2 (1.7)	1 (0.9)
	WDAE	0	1 (0.9)
ILD/Pneumonitis	All AEs	2 (1.7)	3 (2.7)
	ILD	1 (0.9)	1 (0.9)
	Lung infiltration	1 (0.9)	0
	Pneumonitis	0	2 (1.8)
	AE of CTC Grade ≥3	2 (1.7)	3 (2.7)
	ILD	1 (0.9)	1 (0.9)
	Lung infiltration	1 (0.9)	0
	Pneumonitis	0	2 (1.8)
	SAE	2 (1.7)	3 (2.7)
	ILD	1 (0.9)	1 (0.9)
	Lung infiltration	1 (0.9)	0
	Pneumonitis	0	2 (1.8)
	WDAE	2 (1.7)	1 (0.9)
	ILD	1 (0.9)	0
	Lung infiltration	1 (0.9)	0
	Pneumonitis	0	1 (0.9)

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events; n = number of patients with events; SAE = serious adverse event; WDAE = withdrawal due to adverse event. **Data source: CSR[1]**

In the ceritinib group, 8.7% patients reported an adverse hyperglycemia event as compared to 3.5% of patients in the chemotherapy arm.[1] Furthermore, as compared to the chemotherapy group, patients in the ceritinib group reported a greater number of hyperglycemia CTC grade 3 to 4 event (1.8% vs. 5.2%) or serious adverse event (0% vs. 0.9%).[1] No patients reported that an adverse event that led to discontinuation of the study medications. For these adverse events, the Manufacturer stated that: "many cases are confounded by brain metastasis/brain radiotherapy, steroids or other underlying conditions. One patient with serious adverse event ("hyperglycemia") had new brain metastasis at the time of event treated with brain RT and dexamethasone; the event was not suspected to be study drug related."

Compared to chemotherapy, a larger proportion of patients treated with ceritinib reported a GI toxicity event (34.5% vs. 93%).[1] In addition, patients treated with ceritinib reported more GI toxicity CTC grade 3 to 4 adverse events (13.0% vs. 2.7%) and serious adverse events (7.0% vs. 0%) as compared to the chemotherapy group.[1] One patient reported that an adverse GI toxicity event led to discontinuation of the study medications while none were reported in the chemotherapy arm. The Manufacturer also provided this following statement to pCODR: "the one patient who discontinued due to vomiting the event was not suspected to be study drug related". However, given the provided statement, the CGP are still uncertain whether this serious adverse event is study drug related.

Hepatotoxicity was more commonly reported in patients treated with ceritinib (53.0%) as compared to those treated with chemotherapy (13.3%).[1] These results were consistent for patients experiencing CTC grade 3 to 4 adverse event (ceritinib: 38.3% vs. chemotherapy: 3.5%). Furthermore, there was no difference between treatment groups for those reporting serious adverse events (ceritinib: 0.9% vs. chemotherapy: 0.9%); however, 1.7% in the ceritinib group

reported an adverse event leading to discontinuation while no events occurred in the chemotherapy group.[1] The Manufacturer provided the following statement to pCODR: "the patient with a serious adverse event had grade 3 jaundice due to biliary obstruction on Day 668. This event was not suspected to be related to the study drug and resolved upon biliary stent placement. There were no Hy's law cases".

QT prolongation adverse events were more frequently reported in the ceritinib group as compared to the chemotherapy group (12.2% vs. 0.9%). This was also consistent for CTC grade 3 to 4 adverse events (1.7% and 0.9%) and serious adverse events (1.7% vs. 0.9%).[1] No patients experienced an adverse event that led to study drug discontinuation. Additionally, the Manufacturer submitted this statement to pCODR: "one of the two serious adverse event cases ("QT prolongation") was confounded by Grade 4 hypokalemia, one corrected the event resolved and the other serious adverse event was due to "loss of consciousness" occurred in the context of disease progression and was not suspected to be study drug related". However, upon review, the CGP felt that the description of these serious adverse events was not informative enough to make any definitive conclusions.

In the ceritinib group, two (1.7%) patients reported an adverse ILD/pneumonitis event.[1] The Manufacturer noted that the two adverse ILD/ pneumonitis events were classified as serious adverse events and the patients were subsequently discontinued from the study.[1] In contrast, 2.7% of patients in the chemotherapy group had an adverse ILD/ pneumonitis event, where 0.9% had ILD and 1.8% had pneumonitis. The Manufacturer also provided this statement to pCODR: "one of the two serious adverse event cases ("lung infiltration") was suspected to be of infectious origin and not related to study drug."

Adverse events leading to dose interruption, adjustment and discontinuation

The median ceritinib treatment exposure was 30.3 weeks while the median treatment period for docetaxel was 6.1 weeks and 14.1 weeks for pemetrexed.[1] The median dose intensity for ceritinib was 614.9 mg (range: 265.2 to 750.0), 73.8 mg/m^2 (range: 40.9 to 77.3) for docetaxel and 492.7 mg/m^2 (range: 312.6 to 564.6) for pemetrexed.

In ASCEND-5, patients in the ceritinib group (60.9%) were more likely to have at least one dose reduction as compared to those in the pemetrexed and the docetaxel groups (17.5% and 26.0%).[1] The most common cause of at least one dose reduction for all treatment groups was due to an adverse event (90.0% for ceritinib, 100% for pemetrexed, and 94.7% for docetaxel).[1] There were more adverse events that led to a dose adjustment in the ceritinib arm as compared to the chemotherapy arm (36.5% vs. 21.2%, respectively). [1] However, less patients in the ceritinib arm (9.6%) had a grade 3 to 4 adverse event that required a dose reduction compared to 18.6% of patient in the chemotherapy arm.[1]

Additionally, a greater proportion of patients treated with ceritinib (76.5%) required at least one dose interruption as compared to those treated with chemotherapy (25.0% for pemetrexed and 5.5% for docetaxel).[1] As well, adverse events were the most frequently reported cause of dose interruptions for ceritinib (96.6%), pemetrexed (90.0%) and docetaxel (75.0%).[1] A greater proportion of patients treated with ceritinib experienced an adverse event that led to a dose interruption as compared to those treated with chemotherapy (73% vs. 23.9%).[2]

Finally, more patients in the ceritinib arm had an adverse event that led to dose discontinuation as compared those treated with chemotherapy (15.7% vs. 9.7%, respectively).[1] Similar results were observed for those reporting grade 3 to 4 adverse events (13% vs. 8.0%, respectively).[1]

6.4 Ongoing Trials

No ongoing trials meeting the review's inclusion criteria were found.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 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.

9 ABOUT THIS DOCUMENT

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

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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

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

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** September 2016, **Embase** 1974 to 2016 October 24, **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results	Annotations
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,kf.	901	
2	1 use ppez	210	
3	1 use cctr	3	
4	*ceritinib/ or (Zykadia* or ceritinib* or LDK 378 or LDK378).ti,ab,kw.	539	
5	4 use oemezd	339	
6	conference abstract.pt.	2360104	
7	5 and 6	122	
8	limit 7 to yr="2011 -Current"	122	
9	5 not 6	217	
10	2 or 3 or 8 or 9	552	
11	limit 10 to english language	534	
12	remove duplicates from 11	358	

2. **Literature search via PubMed**

Search	Add to builder	Query	Items found	Time
#4	Add	Search **#1 AND #2** Sort by: **PublicationDate** Filters: **English**	12	14:21:09
#3	Add	Search **#1 AND #2**	12	14:21:03
#2	Add	Search **publisher[sb]**	517510	14:20:55
#1	Add	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]**	196	14:20:39

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

REFERENCES

1. Novatris Pharmaceuticals. Clinical Study Report: CLDK378A2303. A Phase III, multi-center, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with ALK rearranged (ALK-positive) advanced non-small cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib. [CONFIDENTIAL internal manufacturer's report]. Dorval (QC): Novatris Pharmaceuticals; 2016.

2. Scagliotti G, Kim TM, Crino L, Liu G, Gridelli C, Novello S, et al. Ceritinib versus chemotherapy in patients with advanced alk+ nsclc previously treated with chemotherapy and crizotinib: results from the confirmatory phase iii ASCEND-5 study [Slide deck].2016.

3. Novatris Pharmaceuticals. LDK378 versus chemotherapy in ALK rearranged (ALK positive) patients previously treated with chemotherapy (platinum doublet) and crizotinib. 2013 Apr 2 [cited 2016 Dec 13]. In: ClinicalTrials.gov [Interent]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT01828112 Identifier: NCT01828112.

4. Canadian Cancer Society. Canadian cancer statistics 2016 [Internet]. Ottawa (ON): Public Health Agency of Canada; 2016. [cited 2017 Jan 20]. Available from: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2016-EN.pdf

5. Herbst RS, Heymach JV, Lippman SM. Lung cancer. N Engl J Med. 2008 Sep 25;359(13):1367-80.

6. Weiss J, Stinchcombe TE. Treatment of elderly patients with stage IV non-small-cell lung cancer. Expert Rev Anticancer Ther. 2012 Jan;12(1):111-20.

7. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016 Apr 9;387(10027):1540-50.

8. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016 Nov 10;375(19):1823-33.

9. Rajeswaran A, Trojan A, Burnand B, Giannelli M. Efficacy and side effects of cisplatin- and carboplatin-based doublet chemotherapeutic regimens versus non-platinum-based doublet chemotherapeutic regimens as first line treatment of metastatic non-small cell lung carcinoma: a systematic review of randomized controlled trials. Lung Cancer. 2008 Jan;59(1):1-11.

10. Ardizzoni A, Boni L, Tiseo M, Fossella FV, Schiller JH, Paesmans M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. J Natl Cancer Inst. 2007 Jun 6;99(11):847-57.

11. Delbaldo C, Michiels S, Syz N, Soria JC, Le Chevalier T, Pignon JP. Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: a meta-analysis. JAMA. 2004 Jul 28;292(4):470-84.

12. Smit EF, Dingemans AC. Secondary resistance to systemic treatment [abstract]. Ann Oncol [Internet]. 2014 [cited 2015 Jul 9];25 Suppl 4:iv23. Available from: http://annonc.oxfordjournals.org/content/25/suppl_4/iv23.3.full.pdf+html (Presented at 20140625;-20140628. Conference Publication: (var.pagings). 25 ()(pp iv23), 2014. Date of Publication: June 2014).

13. Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol. 2003 Aug 15;21(16):3016-24.

14. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med. 2002 Jan 10;346(2):92-8.

15. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008 Jul 20;26(21):3543-51.

16. Maus MK, Mack PC, Astrow SH, Stephens CL, Zeger GD, Grimminger PP, et al. Histology-related associations of ERCC1, RRM1, and TS biomarkers in patients with non-small-cell lung cancer: implications for therapy. J Thorac Oncol. 2013 May;8(5):582-6.

17. Sun JM, Ahn JS, Jung SH, Sun J, Ha SY, Han J, et al. Pemetrexed plus cisplatin versus gemcitabine plus cisplatin according to thymidylate synthase expression in nonsquamous non-small-cell lung cancer: a biomarker-stratified randomized phase II trial. J Clin Oncol. 2015 Aug 1;33(22):2450-6.

18. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol. 2012 Mar;13(3):247-55.

19. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczesna A, Juhasz E, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2010 Jun;11(6):521-9.

20. Herbst RS, Lynch TJ, Sandler AB. Beyond doublet chemotherapy for advanced non-small-cell lung cancer: combination of targeted agents with first-line chemotherapy. Clin Lung Cancer. 2009 Jan;10(1):20-7.

21. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol [Internet]. 2010 Sep [cited 2015 Aug 14];21(9):1804-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2924992

22. Soria JC, Mauguen A, Reck M, Sandler AB, Saijo N, Johnson DH, et al. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. Ann Oncol. 2013 Jan;24(1):20-30.

23. Zinner RG, Obasaju CK, Spigel DR, Weaver RW, Beck JT, Waterhouse DM, et al. PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab in patients with advanced nonsquamous non-small-cell lung cancer. J Thorac Oncol [Internet]. 2015 Jan [cited 2015 Aug 14];10(1):134-42. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4276572

24. Vincent MD, Kuruvilla MS, Leighl NB, Kamel-Reid S. Biomarkers that currently affect clinical practice: EGFR, ALK, MET, KRAS. Curr Oncol [Internet]. 2012 Jun [cited 2015 Aug 14];19(Suppl 1):S33-S44. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3377752

25. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med [Internet]. 2010 Oct 28 [cited 2015 Aug 14];363(18):1693-703. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3014291

26. Lee CK, Brown C, Gralla RJ, Hirsh V, Thongprasert S, Tsai CM, et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. J Natl Cancer Inst. 2013 May 1;105(9):595-605.

27. Ellis PM, Coakley N, Feld R, Kuruvilla S, Ung YC. Use of the epidermal growth factor receptor inhibitors gefitinib, erlotinib, afatinib, dacomitinib, and icotinib in the treatment of non-small-cell lung cancer: a systematic review. Curr Oncol [Internet]. 2015 Jun [cited 2015 Aug 14];22(3):e183-e215. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4462541

28. Camidge DR, Bang YJ, Kwak EL, Iafrate AJ, Varella-Garcia M, Fox SB, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol [Internet]. 2012 Oct [cited 2015 Aug 14];13(10):1011-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3936578

29. Kim D-W, Ahn M-J, Shi Y, De Pas TM, Yang P-C, Riely GJ, et al. Results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol. 2012;30(suppl; abstr 7533). (Presented at 2012 ASCO Annual Meeting; June 1-5, 2015; Chicago, Illinois).

30. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013 Jun 20;368(25):2385-94.

31. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014 Dec 4;371(23):2167-77.

32. Shaw AT, Engelman JA. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med [Internet]. 2014 Jun 26 [cited 2015 Jul 9];370(26):2537-9. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMc1404894

33. Novatris Pharmaceuticals. LDK378 in crizotinib naive adult patients with ALK-activated non-small cell lung cancer. 2012 Sep 4 [cited 2017 Jan 20; last updated 2016 Aug 31]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/show/NCT01685138 Identifier: NCT01685138.

34. Felip E, Tan DSW, Kim D-W, Mehra R, Orlov S, Park K, et al. Whole body and intracranial efficacy of ceritinib in ALK-inhibitor (ALKi)-naive patients (pts) with ALK-rearranged (ALK+) NSCLC and baseline (BL) brain metastases (BM): Results from ASCEND-1 and -3 [abstract]. J Clin Oncol. 2016;34(Suppl.).

35. Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016 Nov;17(11):1497-508.

36. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol. 2000 May;18(10):2095-103.

37. Hanna N, Shepherd FA, Fossella FV, Pereira JR, de Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol. 2004 May 1;22(9):1589-97.

38. Spigel DR, Reckamp KL, Rizvi NA, Poddubskaya E, West HJ, Eberhardt WEE, et al. A phase III study (CheckMate 017) of nivolumab (NIVO; anti-programmed death-1 [PD-1]) vs docetaxel (DOC) in previously treated advanced or metastatic squamous (SQ) cell non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol. 2015;33(suppl; abstr 8009). (Presented at 2015 ASCO Annual Meeting; May 29-June 2, 2015; Chicago, Illinois).

39. Paz-Ares L, Horn L, Borghaei H, Spigel DR, Steins M, Ready N, et al. Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol. 2015;33(15 May 20 suppl; abstr LBA109). (Presented at 2015 ASCO Annual Meeting; May 29-June 2, 2015; Chicago, Illinois).

40. Kim ES, Hirsh V, Mok T, Socinski MA, Gervais R, Wu YL, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet. 2008 Nov 22;372(9652):1809-18.

41. Shepherd FA, Rodrigues PJ, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005 Jul 14;353(2):123-32.

42. Soria J-C, Felip E, Cobo M, Lu S, Syrigos KN, Lee KH, et al. Afatinib (A) vs erlotinib (E) as second-line therapy of patients (pts) with advanced squamous cell carcinoma (SCC) of the lung following platinum-based chemotherapy: overall survival (OS) analysis from the global phase III trial LUX-Lung 8 (LL8) [abstract]. J Clin Oncol. 2015;33(suppl; abstr 8002). (Presented at 2015 ASCO Annual Meeting; May 29-June 2, 2015; Chicago, Illinois).

43. A guide to palliative or supportive care [Internet].American Cancer Society; 2014. [cited 2017 Jan 20]. Available from: http://www.cancer.org/treatment/treatments-and-side-effects/palliative-care/supportive-care-guide.html

44. Mano H. The EML4-ALK oncogene: targeting an essential growth driver in human cancer. Proc Jpn Acad Ser B Phys Biol Sci. 2015;91(5):193-201.

45. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007 Aug 2;448(7153):561-6.

46. Soda M, Takada S, Takeuchi K, Choi YL, Enomoto M, Ueno T, et al. A mouse model for EML4-ALK-positive lung cancer. Proc Natl Acad Sci U S A [Internet]. 2008 Dec 16 [cited 2015 Aug 14];105(50):19893-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2605003

47. Solomon B, Varella-Garcia M, Camidge DR. ALK gene rearrangements: a new therapeutic target in a molecularly defined subset of non-small cell lung cancer. J Thorac Oncol. 2009 Dec;4(12):1450-4.

48. Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB, Heist RS, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol [Internet]. 2009 Sep 10 [cited 2015 Aug 14];27(26):4247-53. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2744268

49. FDA approves ceritinib [Internet]. Silver Spring (MD): U.S. Food & Drug Administration; 2014. [cited 2017 Jan 20]. Available from: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm395386.htm

50. Shaw AT, Kim D-W, Mehra R, Tan DS, Felip E, Chow LQ, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med [Internet]. 2014 Mar 27 [cited 2015 Jul 8];370(13):1189-97. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4079055

51. Mok T, Spigel D, Felip E, de Marinis F, Ahn M-J, Groen HJM, et al. ASCEND-2: A single-arm, open-label, multicenter phase II study of ceritinib in adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) previously treated with chemotherapy and crizotinib (CRZ) [abstract]. J Clin Oncol. 2015;33(suppl; abstr 8059). (Presented at 2015 ASCO Annual Meeting; May 29-June 2, 2015; Chicago, Illinois).

52. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol. 2012 Feb 1;30(4):419-25. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3269967

53. Bergethon K, Shaw AT, Ou SH, Katayama R, Lovly CM, McDonald NT, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol. 2012 Mar 10;30(8):863-70. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3295572

54. Jurmeister P, Lenze D, Berg E, Mende S, Schaper F, Kellner U, et al. Parallel screening for ALK, MET and ROS1 alterations in non-small cell lung cancer with implications for daily routine testing. Lung Cancer. 2015 Feb;87(2):122-9.

55. Scagliotti G, Kim TM, Crino L, Liu G, Gridelli C, Novello S, et al. Ceritinib vs chemotherapy (CT) in patients (pts) with advanced anaplastic lymphoma kinase (*ALK*)-rearranged (ALK+) non-small cell lung cancer (NSCLC) previously treated with CT and crizotinib (CRZ): results from the confirmatory phase 3 ASCEND-5 study [abstract] [Internet]. Abstract presented at: ESMO 2016 Congress. 2016 Oct 9; Copenhagen (Denmark). [cited 2016 Dec 14]. Available from: http://oncologypro.esmo.org/Meeting-Resources/ESMO-2016/Ceritinib-vs-chemotherapy-CT-in-patients-pts-with-advanced-anaplastic-lymphoma-kinase-ALK-rearranged-ALK-non-small-cell-lung-cancer-NSCLC-previously-treated-with-CT-and-crizotinib-CRZ-Results-from-the-confirmatory-phase-3-ASCEND-5-study

56. Shaw A, Tan DS-W, Crino L, Felip E, Mok T, Nishio M, et al. Two phase III studies evaluating ceritinib in patients (pts) with anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC): ASCEND-4 and ASCEND-5. Poster presented at: European Society for Medical Oncology (ESMO). 2014 Sep; Madrid.

57. [Pr]Zykadia®/ceritinib for treatment 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 progressed on or who were intolerant to crizotinib. Respnse to pCODR record of decisions, part 1 of 2. Dorval (QC): Novatris Pharmaceuticals; 2016 Dec 23.

58. Shaw AT, Solomon B. Targeting anaplastic lymphoma kinase in lung cancer. Clin Cancer Res. 2011 Apr 15;17(8):2081-6.

59. Ou SH. Lung cancer in never-smokers. Does smoking history matter in the era of molecular diagnostics and targeted therapy? J Clin Pathol. 2013 Oct;66(10):839-46.

60. Hollen PJ, Gralla RJ, Kris MG, Potanovich LM. Quality of life assessment in individuals with lung cancer: testing the Lung Cancer Symptom Scale (LCSS). Eur J Cancer. 1993;29A Suppl 1:S51-S58.

61. Mok TSK, Scagliotti G, Kim TM, Crino L, Liu G, Gridelli C, et al. Patient-reported outcomes in ASCEND-5: a randomized, phase III study of ceritinib versus chemotherapy in patients with advanced anaplastic lymphoma kinase rearranged NSCLC previously treated with chemotherapy and crizotinib. Poster presented at: European Society for Medical Oncology Asia (ESMO Asia). 2016 Dec; Singapore.

62. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76.

63. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer. 1994;30A(5):635-42.

64. pCODR Final Clinical Guidance Report. Ceritinib (Zykadia) for Metastatic Non-Small Cell Lung Cancer [Internet]. Toronto (ON): Canadian Agency for Drugs and Technologies in Health; Dec 3, 2015. [cited 2017 Feb 01]. Available from: https://www.cadth.ca/sites/default/files/pcodr/pcodr_ceritinib_zykadia_nsclc_fn_cgr.pdf

65. pCODR Final Recommendation. Ceritinib (Zykadia) for Metastatic Non-Small Cell Lung Cancer [Internet]. Toronto (ON): Canadian Agency for Drugs and Technologies in Health; Dec 3, 2015. [cited 2017 Feb 01]. Available from: https://www.cadth.ca/sites/default/files/pcodr/pcodr_ceritinib_zykadia_nsclc_fn_rec.pdf