pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

Providing Feedback on this Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pERC will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug:
Ceritinib (Zykadia)

Submitted Funding Request:
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.

Submitted By:
Novartis Pharmaceuticals Canada Inc.

Manufactured By:
Novartis Pharmaceuticals Canada Inc.

NOC Date:
March 27, 2015

Submission Date:
June 5, 2015

Initial Recommendation Issued: October 1, 2015

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) does not recommend funding ceritinib (Zykadia) monotherapy for patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have disease progression on or with intolerance to crizotinib. pERC made this recommendation because the Committee was not confident of the net clinical benefit of ceritinib due to limitations in the evidence from available clinical trials. While pERC was confident that ceritinib produces a tumour response pERC 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. pERC noted that ceritinib aligned with patient values as there is a need for more effective treatment options for patients with ALK-positive NSCLC who have disease progression on or with intolerance to crizotinib. The Committee concluded that ceritinib was likely not cost-effective based on the uncertainty of clinical data included in the submitted economic evaluation.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps were identified.

SUMMARY OF pERC DELIBERATIONS

pERC discussed the burden of illness of advanced NSCLC and the proportion of patients expected to have the ALK gene mutation. It was noted that NSCLC is the leading cause of cancer-related deaths and that approximately 4% of patients with NSCLC are expected to have the ALK mutation. Standard treatment for patients with ALK-mutation positive advanced NSCLC is crizotinib, which has recently been approved for funding in Canada. For patients with disease progression on or with intolerance to crizotinib, current standard treatment includes intravenous chemotherapy with platinum-based doublet therapy, such as cisplatin or carboplatin combined with one of gemcitabine, vinorelbine, paclitaxel, docetaxel, or pemetrexed. pERC considered that there is an unmet need for effective treatments for patients with ALK positive NSCLC who have disease progression on or with intolerance to crizotinib.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of two non-randomized, non-comparative studies evaluating ceritinib (ASCEND-1 and ASCEND-2). The Committee was not satisfied that the available evidence clearly demonstrated a net overall clinical benefit of treatment with ceritinib. While pERC considered that the ASCEND-1 and ASCEND-2 trials were appropriately conducted non-randomized studies, the Committee noted that only limited conclusions could be drawn from these studies. While pERC considered that the magnitude of objective tumour response observed with ceritinib in the two trials was important, pERC did not consider it sufficient evidence of effectiveness. pERC was concerned about the strength of the evidence due to inherent biases of non-comparative studies, and reliance on tumour response as the principal measure of benefit. pERC has considered evidence from non-comparative studies in previous submissions, however, in this situation, pERC was not confident that the magnitude and duration of response were sufficient to conclude that there was a net clinical benefit of ceritinib. pERC further noted that there are ongoing randomized comparative trials with ceritinib in this patient population which may provide clarity on the comparative effectiveness of ceritinib in relation to standard of care options (docetaxel and pemetrexed monotherapy) in previously treated patients. pERC noted that objective response rate is an uncertain surrogate for overall survival and that neither trial provided any comparative evidence on overall survival, which has been a standard outcome in lung cancer studies. pERC noted that the quality of life results reported in the ASCEND-2 study were maintained across the course of the study and that patients tolerated ceritinib generally well with an acceptable toxicity profile. The most frequently observed adverse events included elevated liver enzymes, nausea, vomiting, and diarrhea. However, given the lack of a comparator arm in the ASCEND-1 and ASCEND-2 trials, pERC considered the safety data to be preliminary.

pERC discussed input from a patient advocacy group on ceritinib. It was noted that ceritinib is an oral treatment, which would be easier for patients to take and would not require as much personal and caregiver time and resources (e.g., trips to the hospital) as receiving intravenous chemotherapies. pERC also noted that patients valued additional treatment options relevant to their genotype. pERC considered patient input that highlighted data suggesting that ceritinib crosses the blood-brain-barrier, and may, therefore, have activity in brain metastases. pERC noted that although this is an interesting finding, it is preliminary and more evidence is required to assess the effectiveness of ceritinib in the treatment of patients with NSCLC and brain metastases. pERC considered that ceritinib aligns with patient values.

pERC deliberated upon the cost-effectiveness of ceritinib. Because of the limitations in the available clinical information of ceritinib from non-randomized studies, pERC concluded that it was challenging to draw conclusions on the cost-effectiveness of ceritinib. In addition, pERC noted that the Economic Guidance Panel's estimates of cost-effectiveness were somewhat higher than the manufacturer's estimates. pERC considered that the Economic Guidance Panel's estimates and assumptions were more realistic.

pERC also discussed the feasibility of implementing a funding recommendation for ceritinib. The Provincial Advisory Group noted that there are a small number of patients with the ALK-mutation. They also noted that if crizotinib is funded in the first line setting, then ceritinib would replace intravenous chemotherapy for ALK+ NSCLC in the second line setting. pERC noted, however, that it is unclear if this change in the sequencing of treatment is effective as well as cost effective.

EVIDENCE IN BRIEF

pERC deliberated upon a pCODR systematic review, other literature in the Clinical Guidance Report providing clinical context, an evaluation of the manufacturer's economic model and budget impact analysis, guidance from pCODR's clinical and economic review panels, input from one patient advocacy group (Lung Cancer Canada) and input from pCODR's Provincial Advisory Group.

OVERALL CLINICAL BENEFIT

pCODR review scope

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

Studies included: Two non-comparative studies

The pCODR systematic review included two open-label, non-randomized studies (ASCEND-1 and ASCEND-2) evaluating the safety and efficacy of ceritinib in patients with ALK positive NSCLC who had disease progression despite previous treatment with crizotinib. ASCEND-1 (N=255) included a dose-escalation phase followed by an expansion phase while all patients in the ASCEND-2 (N=140) study received the recommended dose of 750 mg per day and had been pre-treated with crizotinib as their last prior therapy. pERC noted that the non-randomized designs made interpreting the efficacy and safety results difficult, especially when assessing outcomes such as response rate and progression-free survival, endpoints that are more open to subjective bias.

Patient populations: Majority of patients had brain metastases in both studies

Both trials enrolled adult patients diagnosed with documented ALK-positive status locally advanced or metastatic NSCLC who had disease progression despite standard therapy. Both trials allowed patients with asymptomatic or neurologically stable central nervous system disease at baseline to be enrolled. Of the 246 patients in ASCEND-1 with ALK+NSCLC treated with ceritinib at 750 mg/day, 50.4% (n=124) had brain metastases at study entry. Of the 140 ALK+NSCLC enrolled patients in ASCEND-2, 71.4% (n=100) had brain metastases at study entry.

Key efficacy results: Objective response rate, magnitude of comparative benefit unclear

The key efficacy outcome deliberated on by pERC was objective response rate (ORR). In ASCEND-1, the ORR was 56.4% (95%CI: 48.5-64.2) for patients who had received prior therapy targeted against ALK. In ASCEND-2, the ORR was 38.6% (95%CI: 30.5-47.2). The median duration of response was 8.3 months in ASCEND-1 and 9.7 months in ASCEND-2. The median PFS was 6.9 (95%CI: 5.6-8.7) and 5.7 months (95%CI: 5.4-7.6) in ASCEND-1 and ASCEND-2, respectively. Overall intracranial response rate (OIRR) among patients who had received prior therapy targeted against ALK was 29.2% in ASCEND-1 (n=7) and 45.0% in ASCEND-2 (n=9). However, given the small numbers and subjectivity of OIRR, pERC noted it was challenging to interpret the magnitude of benefit among patients with brain metastases. pERC noted that although there is anti-tumour activity with ceritinib, the magnitude of the effect was uncertain given the lack of comparative and long term outcome data. Overall, pERC considered these results promising but insufficient to confirm an overall clinical benefit.

Quality of life: No deterioration in quality of life

Data on patient-reported outcomes were assessed in ASCEND-2 using the European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC-QLQC30) and lung cancer specific questionnaire (QLQ-LC13) and the Lung Cancer Symptom Scale (LCSS). Throughout the treatment period, the change from baseline in global health status remained close to zero which suggested quality of life was maintained by patients and did not worsen during ceritinib treatment. Patients reported consistent improvements in lung-related symptoms (i.e. cough, pain in chest and dyspnea) and no worsening of cancer symptoms while on treatment, however, improvements did not meet the threshold for statistical significance.

Safety: Preliminary evidence suggests manageable toxicity

The most frequent grade 3 or 4 adverse event was an increase in alanine aminotransferase levels; this occurred in 29.8% and 13.6% of patients in ASCEND-1 and ASCEND-2, respectively. Other commonly reported grade 3 or 4 adverse events included but were not limited to nausea, diarrhea, and fatigue. Seventeen (10.4%) and 10 (7.1%) patients discontinued treatment due to adverse events in ASCEND-1 and ASCEND-2, respectively. pERC considered that ceritinib appeared to have a manageable toxicity profile, however, the non-comparative design of the studies made it challenging to assess the adverse events against a relevant comparator.

Limitations: No comparative or OS data

pERC discussed several limitations in the two studies using ceritinib in ALK+ NSCLC. Both studies were non-comparative, thus there is substantial uncertainty regarding the magnitude of benefit with ceritinib compared to other therapies. In addition, these trials were open label by design which is subject to bias, especially when assessing outcomes such as response rate and progression-free survival. Overall survival data were not reported and there is uncertainty as to whether response rate is a reliable surrogate outcome for overall survival. pERC noted that there are ongoing randomized trials that may address some of the limitations noted and provide more certainty on the effectiveness of ceritinib.

Need: Unmet need for patients with ALK+ NSCLC

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths globally for both men and women. The majority of patients present with non-curable disease. In Canada it is estimated that 20,900 Canadians will die from lung cancer in 2015, representing 27% of all cancer deaths. NSCLC is the most common type of lung cancer, accounting for about 85 percent of all cases. There is evidence that ALK+ tumours present at a more advanced clinical stage compared to non-ALK tumours. If left untreated, patients with advanced NSCLC have a short survival with a median survival from diagnosis of 4-5 months. pERC acknowledged that there is a need for effective treatments for these patients, as there is a need for all patients with NSCLC with progressive disease on treatment.

PATIENT-BASED VALUES

Values of patients with non-small cell lung cancer: Current therapies have high toxicity and burden

The key symptoms associated with lung cancer include fatigue, loss of appetite, shortness of breath, cough, pain, and blood in sputum. They also noted the stigma associated with a diagnosis of lung cancer. The patient group reported that most Canadians with advanced lung cancer receive chemotherapy for first-line treatment of NSCLC, irrespective of their ALK status. The patient group reported that chemotherapy is associated with severe side effects including nausea, vomiting, hair loss, fatigue and the risk of fever and infection. Patient also experience the inconvenience of multiple blood tests, intravenous treatment and multiple visits to hospital for chemotherapy often associated with long wait times. The patient group submitted that this imposes 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.

Patient values on treatment: Perception that ceritinib may treat brain metastases

The patients who had direct experience with ceritinib, have a perception that crizotinib does not cross the blood/brain barrier while ceritinib does, and thus ceritinib would be efficacious against brain metastases. pERC also discussed that ceritinib may have activity in brain metastases, but noted that the data are not available yet to draw any conclusions on the magnitude of effect of ceritinib on brain metastases due to NSCLC.

Like crizotinib, patients reported that 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 time than those experienced with crizotinib. The patient group indicated that many of these patients continue to feel well 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.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis, partitioned survival model
The submitter provided a partitioned survival economic model which was comprised of 3 states: stable disease; progressive disease; and death. pERC noted that the model was adequately designed and the limitations of the model were related to the paucity of the effectiveness inputs (that is, lack of comparative efficacy data) rather than the model's structure. pERC noted that in partitioned survival models it is not possible to explicitly examine the impact of post-progression survival, which is a limitation when trying to assess the downstream effect of a treatment.

Basis of the economic model: Ceritinib vs four comparators
The economic analysis provided by the submitter compared ceritinib to 1) best supportive care, 2) pemetrexed, 3) Canadian historical controls in patients with ALK-positive NSCLC who were previously treated with an ALK inhibitor, and 4) docetaxel.

Drug costs: Ceritinib more expensive than all comparators
Ceritinib costs $67.47 per 150mg tablet. At a dosing regimen of 750mg/day, ceritinib costs $337.33 per day, and $9,445.32 per 28 day course.

Pemetrexed costs $4.29 per mg, $173.64 per day, and $4,862.00 per 28 day course. Of note, the price provided is the list price which may be higher than provinces are currently paying.

Docetaxel costs $4.46 per mg, $27.05 per day, and $757.35 per 28 day course.

Cisplatin costs $5.86 per mg, $35.57 per day, and $996.10 per 28 day course.

Clinical effect estimates: Considerable uncertainty in clinical estimates
The clinical inputs used in the submitted model were the best currently available. However, pERC discussed that the clinical estimates were not based on data from head-to-head trials. The historical control group that was used in the model was taken from a chart review from 6 oncology centres across Canada and may not be generalizable to the rest of Canada because of the limited sample size.

Cost-effectiveness estimates: Overall the cost inputs were reasonable
pERC agreed with the Economic Guidance Panel (EGP) that the majority of costs considered were reasonable. However, they also considered that the Clinical Guidance Panel (CGP) identified that the cost of treating neutropenia is very unlikely to be the same as febrile neutropenia which results in hospitalization and, therefore, the EGP reduced this cost to zero in the best case estimate. pERC agreed with the EGP's reanalyses and the limitations identified in the submitted economic model.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Small patient population with ALK mutation
pERC discussed the feasibility of implementing a funding recommendation for ceritinib. The Provincial Advisory Group noted that there is a small number of patients with the ALK-mutation. They also noted that if crizotinib is funded in the first line setting, then ceritinib would replace intravenous chemotherapy for ALK+ NSCLC in the second line setting. pERC noted however that it is unclear whether this change in treatment sequencing would be cost effective.

DRUG AND CONDITION INFORMATION

Drug Information	• Anaplastic Lymphoma Kinase (ALK) Tyrosine Kinase Inhibitor • Recommended dosage of 750mg per day administered orally. Treatment continues until disease progression.
Cancer Treated	• 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 disease progression on or with intolerant to crizotinib
Burden of Illness	• NSCLC is the leading cause of cancer-related mortality in Canadians • Approximately 4% of patients with NSCLC are ALK-positive.
Current Standard Treatment	• Pemetrexed • Docetaxel • Platinum-based doublet
Limitations of Current Therapy	• Response rates to chemotherapy are approximately 20% and responses generally last only a few months. Disease progression typically occur within three to four months and patients then require alternative treatment options.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Matthew Cheung, Oncologist
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Wasney, Pharmacist
Carole McMahon, Patient Member
Jo Nanson, Patient Member Alternate
Dr. Tallal Younis, Oncologist
Dr. Kelvin Chan, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Drs. Bill Evans and Allan Grill who were not present for the meeting
- Jo Nanson who did not vote due to her role as a patient member alternate

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of Ceritinib

(Zykadia) for Metastatic Non-Small Cell Lung Cancer, through their declarations, no members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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