pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH 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 reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

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:** October 19, 2016
Initial Recommendation: March 3, 2017	**Final Recommendation:** March 21, 2017

pERC Final Recommendation
This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation. Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

pERC RECOMMENDATION

pERC recommends reimbursement of 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 intolerance to crizotinib conditional on the cost-effectiveness being improved to an acceptable level.

pERC made this recommendation because the Committee was confident of the net clinical benefit of ceritinib, based on statistically significant and clinically meaningful improvements in progression-free survival (PFS) compared to chemotherapy. The Committee acknowledged that quality of life with ceritinib was similar to chemotherapy; however, ceritinib is associated with manageable but not insignificant toxicity compared with chemotherapy. pERC agreed that ceritinib aligned with patient values, as there is a clear unmet need for more effective treatment options. However, the increased toxicity profile compared with chemotherapy tempered pERC's conclusions with respect to alignment with patient values.

The Committee also concluded that, at the submitted price, ceritinib was not cost-effective compared with chemotherapy and would require a substantial price reduction.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Generalizability of results regarding patients with World Health Organization Performance Status ≥ 2 and central nervous system metastases
pERC considered the generalizability of the trial results in patients with a World Health Organization Performance Status (WHO PS) of ≥ 2. Given that the trial included a small number of patients with PS ≥ 2, pERC agreed that the decision to use ceritinib in these patients should be at the discretion of the treating oncologist. pERC also noted that nearly 60% of patients in the

trial had stable CNS metastases at baseline. Subgroup analysis in these patients demonstrated that the treatment effect seen in the overall trial population was maintained in patients with central nervous system (CNS) metastases. pERC therefore agreed that the available evidence is sufficient to conclude that ceritinib is effective in this population.

Time-limited need for patients who are currently on or have recently completed treatment with chemotherapy or an immune checkpoint inhibitor

At the time of implementing a reimbursement recommendation for ceritinib, jurisdictions may want to consider addressing the short-term, time-limited need for ceritinib for patients who meet the reimbursement criteria and who are currently on or have recently completed treatment with chemotherapy, or patients who are currently on or have recently completed treatment with an immune checkpoint inhibitor.

Optimal Sequencing of Ceritinib and Other Therapies

pERC noted that there is no clinical trial evidence to inform the optimal sequencing of ceritinib and other treatments now available for the treatment of patients with ALK-positive locally advanced or metastatic NSCLC . Although the ASCEND-5 trial included patients who had previously been treated with crizotinib and a platinum doublet, pERC agreed that treatment with ceritinib is likely to be used as a second line option following crizotinib, followed by doublet chemotherapy as third line treatment and subsequently with immune checkpoint inhibitors. Upon implementation of ceritinib reimbursement, pERC recognized that collaboration among provinces to develop a common approach for treatment sequencing would be of value.

Pricing arrangements to improve cost-effectiveness

Given that pERC was satisfied that there is a net clinical benefit with ceritinib compared with chemotherapy, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of ceritinib.

SUMMARY OF pERC DELIBERATIONS

In Canada, an estimated 28,400 new cases and 20,800 deaths occurred in 2016 from lung cancer, with a five-year survival rate of 15% to 18%. Treatment decisions for advanced or metastatic NSCLC are typically dependent on the presence or absence and type of driver mutation status of patients in the first-line setting. 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 the front-line setting in Canada. For patients who have disease progression on or intolerance to crizotinib, current standard treatment includes intravenous chemotherapy with platinum-based doublet therapy. Third-line options include single-agent chemotherapies (i.e., docetaxel or pemetrexed). pERC noted that instances of intolerance to crizotinib will be few. Patients with brain metastases in the context of stage IV NSCLC have a particularly poor prognosis. pERC therefore agreed that there is a continued need for more effective treatment options with more manageable toxicity profiles for patients with ALK-positive NSCLC who have disease progression on or intolerance to crizotinib.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of one randomized controlled trial (RCT; ASCEND-5) evaluating ceritinib compared with single-agent chemotherapy in patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC who have disease progression on or intolerance to crizotinib. The Committee was satisfied that the available evidence demonstrated a net overall clinical benefit of treatment with ceritinib. ASCEND-5 demonstrated a statistically significant and clinically meaningful improvement in PFS in favour of ceritinib. The trial did not report an overall survival (OS) benefit. This could be due to the immaturity of the data and the large number of patients who crossed over from the chemotherapy group to receive ceritinib upon disease progression. Although no minimally important differences were reported, ceritinib was not associated with a deterioration or improvement of quality of life compared with chemotherapy. pERC noted that the toxicity profile of ceritinib was increased compared with chemotherapy. The frequency of grade 3 or 4 adverse events (AEs) and serious AEs were increased in the ceritinib group, and more patients in the ceritinib group experienced AEs leading to treatment discontinuation than patients in the chemotherapy group. AEs leading to death were also increased in the ceritinib group; however, none of the deaths were attributed to the treatment. All grades, grades 3 or 4, and serious AEs for gastrointestinal (GI) toxicities, occurred more frequently in the ceritinib group compared with chemotherapy. pERC therefore agreed that GI toxicities are a concern with ceritinib that will need to be managed during treatment. pERC acknowledged that the longer median duration of exposure to treatment with ceritinib compared with chemotherapy may be a contributing factor to the increased toxicities observed with ceritinib. pERC also considered the fact that the AEs appeared to be manageable for many patients through dose reductions. Overall, based on the improvement in PFS, the maintenance of quality of life compared with chemotherapy, and the manageable (but not insignificant) toxicity profile, pERC concluded that there is a net clinical benefit with the use of ceritinib in patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC who have disease progression on or with intolerance to crizotinib. pERC considered the generalizability of the trial results in patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≥ 2 and noted that the available evidence from ASCEND-5 was limited; however, the Committee agreed that the decision to use ceritinib in these patients should be left to the discretion of the treating oncologist. pERC also considered the fact that the majority of patients in the trial had stable CNS metastases at baseline, and subgroup analysis demonstrated that the treatment effect seen in the overall population was maintained in patients with CNS metastases.

pERC discussed input from a patient advocacy group on ceritinib. pERC considered patient input that described a desire for effective oral treatment options that better manage the tremendous disease- and treatment-related burden. pERC noted that toxicities associated with chemotherapy were especially difficult for patients. As an effective oral treatment option, ceritinib 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 although patients preferred to have an oral

treatment option, there is a notable pill burden at five tablets per day. pERC also noted that patients valued additional treatment options relevant to their genotype. pERC, however, noted that the increased but manageable toxicity profile of ceritinib compared with chemotherapy may be challenging for patients. However, despite the increase in toxicity, pERC concluded that ceritinib aligns with patient values because it offers patients an effective, oral treatment option after disease progression on (or intolerance to) crizotinib.

pERC deliberated upon the cost-effectiveness of ceritinib compared with chemotherapy based on the submitted economic evaluation and reanalysis estimates provided by the pCODR Economic Guidance Panel (EGP). The largest impact on the incremental cost-effectiveness ratio (ICER) was related to duration of treatment and the method of extrapolating OS data. pERC noted that there may be a clinical rationale for continuing treatment beyond Response Evaluation Criteria in Solid Tumors (RECIST)–defined progression (to maintain disease control) and agreed with the EGP's estimate exploring the impact of treatment beyond disease progression. As the model did not allow the EGP to remove the modelled OS benefit, the EGP used an alternative parametric distribution that better fit the clinical trial data to extrapolate long-term benefit with ceritinib. This approach reduced the quality-adjusted life-year (QALY) gains seen in the post-progression state. pERC acknowledged that patients going on to subsequent treatments with chemotherapy (platinum doublet) are likely to have QALYs gained in the post-progression state; however, the Committee did not agree that more than half of this gain would be post-progression. Lastly, the EGP explored the cost associated with the use of generic pemetrexed and 50% of patients going onto subsequent therapy with platinum doublet. When all of the above factors were combined, pERC noted that the ICER was increased substantially. pERC agreed that the true ICER is likely at the upper end of the EGP's reanalysis estimate, as uncertainties related to the presence of an OS benefit and use of equal utilities between treatment groups could not be explored. Overall, pERC concluded that ceritinib is not cost-effective.

pERC discussed the feasibility of implementing a funding recommendation for ceritinib. The pCODR Provincial Advisory Group (PAG) noted that there are a small number of patients with the ALK mutation. pERC noted that ceritinib would be followed by combination chemotherapy as third-line treatment and immune checkpoint inhibitors thereafter. pERC did acknowledge a short-term, time-limited need for ceritinib for patients who meet the reimbursement criteria and who are currently on or who recently completed treatment with chemotherapy or patients who are currently on or who recently completed treatment with an immune checkpoint inhibitor. pERC acknowledged the inclusion criteria of the ASCEND-5 trial (patients previously treated with crizotinib and a platinum doublet) is not similar to the population in which the reimbursement recommendation is being made. In considering input from the CGP and registered clinicians pERC agreed that ceritinib is expected to be a treatment option in the second line after failure of crizotinib. pERC agreed that ceritinib would be followed by combination chemotherapy as third-line therapy, and checkpoint inhibitors thereafter. pERC noted the concern of both PAG and registered clinicians regarding the relative place in therapy of ceritinib compared with other new therapies that are currently being reviewed by pCODR. pERC concluded that an overview of all available therapies for NSCLC may be helpful at a future date to understand the comparative effectiveness. The Committee, however, noted that the current review is based on the evidence presented for ceritinib and must be considered on its own merits.

CONTEXT OF THE RESUBMISSION

On June 5, 2015, the CADTH pan-Canadian Oncology Drug Review received a submission for ceritinib (Zykadia) 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 progressed on or who were intolerant to crizotinib. The pCODR Expert Review Committee (pERC) Final Recommendation was issued on December 3, 2015.

- The pERC Final Recommendation was to not recommend funding ceritinib (Zykadia) monotherapy for patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC who have disease progression on or intolerance to crizotinib.
- The resubmission made by the submitter provided new information on ceritinib. The new information included:
    - New efficacy and safety data from an ongoing randomized controlled trial (RCT; ASCEND-5)
    - A revised economic evaluation incorporating the new data.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from the pCODR clinical and economic review panels
- Input from one patient advocacy group (Lung Cancer Canada)
- Input from an individual oncologist and one joint submission from Lung Cancer Canada Medical Advisory Committee
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, (Lung Cancer Canada)
- One clinician group, (Lung Cancer Canada Medical Advisory Committee)
- The PAG
- The submitter (Novartis Pharmaceuticals Canada Inc.)

The pERC Initial Recommendation was to recommend reimbursement of 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 intolerance to crizotinib conditional on the cost-effectiveness being improved to an acceptable level.

Feedback on the pERC Initial Recommendation indicated that the patient advocacy group, and registered clinician group disagreed with the Initial Recommendation, while the submitter and PAG agreed with the Initial Recommendation.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

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 ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC who have disease progression on or intolerance to crizotinib.

Studies included: One randomized trial

The pCODR systematic review included one multi-centre, open-label, phase III RCT that assessed the efficacy and safety of ceritinib in patients with locally advanced or metastatic ALK-positive NSCLC who have progressed on or who were intolerant to crizotinib (ASCEND-5; N = 231).

Key inclusion criteria specified that patients be 18 years or older with histologically or cytologically confirmed diagnosis of stage IIIB or IV NSCLC, carrying an ALK rearrangement assessed with an FDA-approved fluorescence in situ hybridization (FISH) assay and scoring algorithm; have a World Health Organization Performance Status (WHO PS) of 0 to 2 and a life expectancy of ≥ 12 weeks; have received one to two prior treatments of cytotoxic chemotherapy (including one platinum doublet) and crizotinib. No particular treatment sequence was required for enrolment. Patients with asymptomatic and stable central nervous system (CNS) metastases were also allowed to enrol in the trial.

Patient populations: Central nervous system metastases

Patients enrolled in the trial were randomized (1:1) to receive ceritinib 750 mg daily or chemotherapy (docetaxel [75 mg/m^2] or pemetrexed [500 mg/m^2] based on the opinion of the investigator). Randomization was stratified by WHO PS and CNS metastases at baseline. Patients in the ceritinib group could continue to receive ceritinib beyond Response Evaluation Criteria in Solid Tumors (RECIST)-defined disease progression. In the trial, 58% of patients in the ceritinib group continued treatment with ceritinib beyond disease progression. Additionally, 63.8% of patients in the chemotherapy groups crossed over to receive ceritinib upon RECIST-defined disease progression. pERC noted input from the pCODR Clinical Guidance Panel (CGP) that suggested RECIST-defined progression may not always indicate deterioration in patients, as continued treatment may provide disease control and reduced disease burden for patients. Given this, pERC was comfortable with concluding that treatment with ceritinib should be continued until clinically meaningful progression occurs, based on the judgment of the treating oncologist.

Baseline characteristics were mostly balanced between treatment groups, with the exception of sex (59.1% versus [vs.] 52.6% females), ethnicity (70.4% vs. 58.6% Caucasians), and smoking history (61.7% vs. 52.6% never-smokers). Among patients enrolled in ASCEND-5, the majority of patients in both groups had a WHO PS of 0 (46.3%) or 1 (47.6%) and 6.1% had a WHO PS of 2. CNS metastases was present in 56.5% and 59.5% of patients in the ceritinib and chemotherapy groups, respectively. pERC noted that patients enrolled in the trial were previously treated with crizotinib and a platinum doublet (100% and 97%, respectively). In considering ceritinib's place in therapy, pERC noted input from the CGP and registered clinicians. pERC also considered the fact that the ASCEND-5 trial was conducted at a time when crizotinib was available only as a second-line treatment; therefore, at the time, all patients would have received a platinum doublet in the first-line setting. pERC noted input from registered clinicians indicating that, following progression on chemotherapy, most patients decline rapidly and may not have the chance to try more effective targeted therapies. Given the shift in treatment patterns and current availability of crizotinib as a first-line treatment, pERC agreed with the CGP and the registered clinician input that the use of ceritinib in the second line following failure of crizotinib would be reasonable.

Key efficacy results: Significant improvement in progression-free survival; overall survival immature

The key efficacy outcome deliberated on by pERC was progression-free survival (PFS), assessed by a blinded independent review committee (BIRC). pERC agreed that treatment with ceritinib was associated with a statistically significant prolongation of PFS as compared with chemotherapy in patients with ALK-positive NSCLC (median 5.4 and 1.6 months, respectively; hazard ratio [HR] = 0.49; 95% confidence interval [CI], 0.36 to 0.67; log-rank $P < 0.001$). Investigator-assessed PFS was similar to the BIRC. The protective effect of ceritinib was also consistent across all subgroups for PFS. Overall survival (OS) was a key secondary outcome. At the time of the data cut-off for the primary PFS analysis, the data for OS was immature, with 41.7% and 43.1% deaths occurring in the ceritinib and the chemotherapy groups, respectively. Median OS in the ceritinib group was 18.1 and 20.1 months in the chemotherapy group. Given the immaturity of the results and the allowance for patients from the chemotherapy group to cross over and receive ceritinib upon progression, pERC acknowledged that it is likely the OS results are cofounded. However, the direction of confounding is unclear, and therefore the reported effect estimate for survival may be over- or underestimated.

pERC considered the generalizability of the trial results in patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≥ 2 and noted that the ASCEND-5 trial enrolled 6.1% with a WHO PS of 2. pERC considered the fact that the available evidence in this population was limited; however, the

Committee agreed that the decision to use ceritinib in these patients should be left to the discretion of the treating oncologist. Given the increased toxicity profile of ceritinib compared with chemotherapy, pERC agreed with the CGP that treating oncologists may need to start patients who have lower PS at a lower dose. pERC also considered that nearly 60% of patients in the trial had stable CNS metastases at baseline (56.5% and 59.5% of patients in the ceritinib and chemotherapy groups, respectively). Subgroup analysis in these patients demonstrated that the treatment effect seen in the overall population was maintained in patients with CNS metastases (HR, 0.54; 95% CI, 0.36 to 0.80). pERC therefore agreed that the available evidence is sufficient to conclude that ceritinib is effective in this population. pERC noted that there was no evidence presented for the efficacy of ceritinib in patients who are intolerant to crizotinib. pERC noted input from the CGP acknowledging that crizotinib is generally well tolerated and intolerance occurs in few cases. Overall, pERC agreed with the CGP that it would be reasonable to use ceritinib in patients who experience intolerance to crizotinib.

Quality of life: Limited reporting for quality of life

Patient-reported outcomes were measured using the Lung Cancer Symptom Scale (LCSS), the European Organization for Research and Treatment of Cancer Core 30-item Quality of Life Questionnaire (EORTC QLQ-C30), the 13-item Quality of Life Questionnaire Lung Cancer Module (QLQ-LC13), and the EuroQol 5-Dimensions questionnaire, 5-Levels (EQ-5D-5L) with EQ visual analogue scale (VAS). Minimally important differences were defined as follows: a 15 mm or higher increase or decrease from baseline for the LCSS, a 10-point increase for the symptom scales (LC13) and 10-point decrease for the quality of life or functional scales (QLQ-C30). Two composite end points were created based on scores of cough, pain, and dyspnea to assess time to symptom deterioration using the LCSS scale and the LC13 scale.

Although it was not clear whether minimally important differences (MIDs) were met, the manufacturer reported that ceritinib was associated with improvements in a number of symptoms for both the QLQ-C30 and -LC13 scales. Similarly, the EQ-5D-5L results were difficult to interpret, given the lack of clarity on whether the MIDs were met. Based on the LCSS-derived composite end points, the manufacturer reported that patients in the ceritinib arm had a longer median time to deterioration compared with chemotherapy (18 months and 4.4 months, respectively). Using the LC13-derived composite end point, the ceritinib arm had a higher median time to deterioration compared with chemotherapy (11.1 months and 2.1 months, respectively). pERC agreed that there was some uncertainty in the interpretation of the patient-reported outcomes as MIDs (improvement or decline) were not reported. Overall, ceritinib did not result in a deterioration or improvement of patients' quality of life compared with chemotherapy.

Safety: Increased toxicity with ceritinib

pERC discussed the toxicity profile of ceritinib based on the results of the ASCEND-5 trial. The frequency of grade 3 or 4 adverse events (AEs) (77.4% and 63.7%) and serious AEs (42.6% and 31.9%) were increased in the ceritinib group. AEs leading to death (13.0% and 4.4%) were also increased in the ceritinib group; however, none of the deaths were attributed to the treatment. A higher proportion of patients in the ceritinib groups also experienced the following AEs and grade 3 or 4 AEs of special interest: hyperglycemia, QT prolongation, gastrointestinal (GI) toxicity, and hepatotoxicity. A between-group difference of more than 10% was reported for grade 3 or 4 GI toxicity (13.0% and 2.7%) and hepatotoxicity (38.3% and 3.5%) in the ceritinib and chemotherapy groups, respectively. More patients in the ceritinib group also experienced serious AEs for GI toxicity (7% and 0%). pERC noted that GI toxicities are a concern with ceritinib that will need to be managed during treatment. pERC acknowledged that the longer median duration of exposure to treatment (30.3 weeks for ceritinib and 6.1/14.1 weeks for pemetrexed/docetaxel) with ceritinib compared with chemotherapy may be a contributing factor for the increased toxicities observed with ceritinib.

pERC also acknowledged that AEs appeared to be manageable for many patients through dose reductions. A greater proportion of patients in the ceritinib compared with the pemetrexed/docetaxel group required dose reductions (60.9% and 17.5%/26.0%) and at least one dose interruption (76.5% and 25.0%/5.5%). However, more patients in the ceritinib group experienced AEs (15.7% vs. 9.7%) or grade 3 or 4 AEs (13% vs. 8.0%) leading to dose discontinuation compared with those treated with chemotherapy, respectively.

Need: Continued need in patients with ALK-positive non-small cell lung cancer

Lung cancer 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 20,800 Canadians will die from lung cancer in 2016. NSCLC is the most common type of lung cancer, accounting for about 85% of all cases. Approximately 4% of patients with NSCLC are expected to have the ALK mutation and there is evidence that ALK-positive tumours present at a more advanced clinical stage than non-ALK-positive tumours. Standard treatment for patients with ALK mutation–positive advanced NSCLC is

crizotinib, which has recently been approved for funding in the front-line setting in Canada. For patients with disease progression on or intolerance to crizotinib, current standard treatment includes intravenous chemotherapy (platinum-based doublet therapy) such as cisplatin or carboplatin combined with one of gemcitabine, vinorelbine, paclitaxel, docetaxel, or pemetrexed. Third-line options include single-agent chemotherapies (i.e., docetaxel or pemetrexed). The advanced age of patients and the high frequency of advanced disease, poor PS, and other significant comorbidities of this patient population limit their ability to tolerate conventional chemotherapy regimens. Patients with CNS metastases in the context of stage IV NSCLC have a particularly poor prognosis. pERC therefore agreed that there is a need for effective and more tolerable treatment options for these patients.

Registered clinician input: Ceritinib more effective than chemotherapy in this population
Clinicians providing input noted that ALK-positive NSCLC can progress explosively following progression on first-line crizotinib. 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 have declined rapidly and may not have the chance to try more effective targeted therapies. Given the limited life expectancy of patients with lung cancer, clinicians providing input anticipate very few prevalent cases; however, these cases might be expected to be on therapy for a longer duration (i.e., more than one year).

Clinicians noted that ceritinib is more effective and better tolerated than chemotherapy in this population, which is often older and has comorbidities. Clinicians providing input also noted significant and rapid symptom improvement on treatment. Clinician input noted that ceritinib maintains quality of life, similar to that experienced by patients on front-line crizotinib. Based on the results of the ASCEND-5 trial, pERC agreed that ceritinib is more effective than standard chemotherapy, while the toxicity profile appears to be higher than chemotherapy. In the absence of evidence, pERC was, however, unable to comment on the similarity of ceritinib with crizotinib as it relates to the safety profile and quality-of-life impact. pERC also agreed with the CGP that the results of ongoing trials may further clarify the role of ceritinib in other lines of therapy or with tumours that harbour alternative gene alterations, such as ROS1 or ALK overexpression.

pERC noted input from registered clinicians regarding the relative place in therapy of ceritinib compared with other new therapies that are currently being reviewed by pCODR. pERC concluded that an overview of all available therapies for NSCLC may be helpful at a future date to understand the optimal use of therapies. The Committee, however, noted that the current review is based on the evidence presented for ceritinib and must be considered on its own merits.

PATIENT-BASED VALUES

Values of patients with non-small cell lung cancer: High symptom burden; 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. Patient input indicated that lung cancer patients appear to have the highest symptom burden of all cancer patients, among which loss of appetite, cough, pain, and shortness of breath were significant predictors of quality of life. Additionally, rates of depression in advanced lung cancer patients vary from 16% to 50%, and are consistently higher than other cancer sites. Compared with the general NSCLC population, ALK-positive patients also tend to be younger and never-smokers. However, patients and their families carry a heavy burden of stigma associated with their lung cancer diagnosis, which is typically associated with smoking.

The patient group reported that most Canadians with advanced lung cancer receive chemotherapy for first-line treatment of NSCLC, irrespective of their ALK status. Chemotherapy is associated with severe side effects, including nausea, vomiting, hair loss, fatigue, and the risk of fever and infection. Patients also experience the inconvenience of multiple blood tests, intravenous treatment, and multiple visits to hospital for chemotherapy, which are 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 assist patients with treatment, and then additional time off to manage chemotherapy toxicity, including frequent admission to hospital. According to patients, the burden of chemotherapy was felt during all stages of the treatment. Because of the significant burden of toxicities, some patients may be

deemed unsuitable for chemotherapy, for reasons related to PS, age, or other illnesses, which further shortens their survival and ability to fight their advanced lung cancer. Caregivers described the course of disease as intense and relentlessly progressive, and that juggling competing demands with respect to providing emotional and tangible support to patients while meeting the ongoing obligations of home, work, and family becomes difficult.

pERC considered both patient and caregivers experiences with lung cancer and agreed that as an effective oral treatment option that maintains patients' quality of life, ceritinib aligns with patient values. However, pERC considered the toxicity profile of ceritinib and noted the increased grade 3 or 4 AEs, serious AEs, and AEs of interest compared with chemotherapy. In considering the tremendous burden of disease and treatment-related side effects, pERC agreed that the increased but manageable toxicity profile of ceritinib tempered the Committee's conclusions on alignment with patient values.

Patient values on treatment: Brain metastases, manageable toxicities

Patients reported that ceritinib had manageable side effects and improved outcomes, likening it to their experiences with crizotinib. Patients noted that the side effects of crizotinib lasted longer but were mild, while ceritinib had more intense side effects. 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. Patients also have a perception that crizotinib does not cross the blood–brain barrier while ceritinib does, and thus patients expressed that they feel ceritinib would be efficacious against CNS metastases. Based on the results of the ASCEND-5 trial, pERC agreed that ceritinib is effective in patients with CNS metastases.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility and cost-effectiveness analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-utility analysis comparing ceritinib to single-agent chemotherapy in patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC who have progressed on or who were intolerant to crizotinib.

Basis of the economic model: Clinical and cost inputs

Costs considered in the analysis included the drug acquisition cost, drug administration and premedication costs, pre- and post-progression resource use costs of AE management, best supportive care, subsequent treatment costs, and end-of-life costs.

The clinical effects considered in the analysis include the ASCEND-5 trial for PFS and OS estimates. Given the high rate of crossover in the trial, OS data for the chemotherapy group were inferred from the general NSCLC populations. pERC noted input from the CGP indicating that the prognosis of patients with ALK-positive NSCLC is better than the general NSCLC population; therefore, the submitted inputs for chemotherapy likely underestimate the effect of chemotherapy in patients with ALK-positive NSCLC. Other clinical inputs include utilities in the progression-free (derived from the ASCEND-5 trial) and utilities in the post-progression states from the literature.

Drug costs: Ceritinib more expensive than all comparators

Ceritinib costs $67.47 per 150 mg tablet. At a dosing regimen of 750 mg/day, ceritinib costs $337.33 per day, and $9,445.32 per 28-day course.

At the list generic price, pemetrexed costs $0.8318 per mg, $33.67 per day, and $942.66 per 28-day course. Docetaxel costs $11.42 per mg, $69.36 per day, and $1,942.00 per 28-day course. pERC noted that the submitted analysis incorporated costs for pemetrexed based on the brand price, which did not reflect the current availability of generic pemetrexed at a significantly lower cost.

Cost-effectiveness estimates: Overall, the cost inputs were reasonable

pERC deliberated upon the cost-effectiveness of ceritinib compared with chemotherapy based on the submitted economic evaluation and reanalysis estimates provided by the EGP. pERC noted that the ASCEND-5 trial data did not report mature OS results; however, uncertainty with respect to the OS benefit

could not be explored by the EGP, given the lack of an option in the submitted model to assess the impact of having no OS benefit. pERC also noted uncertainty related to the utilities modelled. pERC agreed that the clinical trial data suggested increased toxicities with ceritinib compared with chemotherapy; however, utilities were based on pooled data from both treatment arms. pERC agreed that these two uncertainties, which could not be altered in the EGP's reanalysis estimates, could have a substantial impact on the incremental cost-effectiveness ratio (ICER).

The EGP was able to alter other parameters to explore uncertainty in clinical and cost estimates. The largest impact on the ICER was related to duration of treatment and the method of extrapolating OS data. pERC noted that patients on the trial continued treatment beyond progression as there may be a clinical rationale for continuing treatment beyond RECIST-defined progression (to maintain disease control). The EGP demonstrated that treatment beyond progression had the largest impact on the ICER. As the model did not allow the EGP to remove the modelled OS benefit, the EGP used an alternative parametric distribution that better fit the clinical trial data to extrapolate long-term benefit with ceritinib. This approach helped reduce quality-adjusted life-year (QALY) gains seen in the post-progression state. pERC acknowledged that patients going on to subsequent treatments with chemotherapy (platinum doublet) are likely to have QALYs gained in post-progression; however, the Committee did not agree that more than half of this gain would be post-progression. pERC noted that the EGP was unable to further reduce the large gains in the post-progression state that were present in the reanalysis estimates. Lastly, the EGP explored costs associated with the use of generic pemetrexed and 50% of patients going on to subsequent therapy with platinum doublet. When all of the above factors were combined, pERC noted that the ICER was increased between $159,750/QALY and $208,377/QALY. Both the upper and lower bounds of the estimates were significantly higher than the submitted estimates. pERC agreed that the true ICER is likely at the upper end of this estimate as uncertainties related to the presence of an OS benefit and use of equal utilities between treatment groups could not be explored. Overall, pERC agreed that ceritinib is not cost-effective.

ADOPTION FEASIBILITY

pERC discussed the feasibility of implementing a funding recommendation for ceritinib. The PAG noted that there are a small number of patients with the ALK mutation. pERC acknowledged the inclusion criteria of the trial (patients previously treated with crizotinib and a platinum doublet) and in considering input from the CGP and registered clinicians and agreed that ceritinib is expected to be a treatment option in the second line after failure of crizotinib. pERC agreed that ceritinib would be followed by combination chemotherapy as third-line and checkpoint inhibitors thereafter. pERC did acknowledge a short-term, time-limited need for ceritinib for patients who meet the reimbursement criteria and who are currently on or have recently completed treatment with chemotherapy or patients who are currently on or who have recently completed treatment with an immune checkpoint inhibitor. pERC noted the PAG's concern and registered clinician input regarding the relative place in therapy of ceritinib compared with other new therapies that are currently being reviewed by pCODR. pERC concluded that an overview of all available therapies for NSCLC may be helpful at a future date to understand the comparative effectiveness. The Committee, however, noted that the current review is based on the evidence presented for ceritinib and must be considered on its own merits.

pERC acknowledged that the oral route of administration of ceritinib is an enabler; however, patients would be faced with the burden of taking five tablets per day. In jurisdictions in which applications are required for pharmacare programs, which can be associated with co-payments and deductibles, pERC noted that patients may experience some limited accessibility and financial burden.

DRUG AND CONDITION INFORMATION

Drug Information	• Anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor • Recommended dosage of 750 mg per day, administered orally. Treatment continues until disease progression
Cancer Treated	• For treatment as monotherapy in patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have disease progression on or are 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	• Platinum-based doublet • Pemetrexed • Docetaxel
Limitations of Current Therapy	• Response rates to chemotherapy are approximately 20%, and responses generally last only a few months. Disease progression typically occurs within three to four months and patients then require alternative treatment options.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Paul Hoskins, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy Thompson, Pharmacist
Valerie McDonald, Patient Member Alternate
Carole McMahon, Patient Member
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Dr. Marianne Taylor, Oncologist
Danica Wasney, Pharmacist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Craig Earle, Allan Grill, and Danica Wasney, who were not present for the meeting
- Anil Abraham Joy, who was excluded from voting due to a conflict of interest
- Valerie McDonald, who did not vote due to her role as a patient member alternate.

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of pERC 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) resubmission for metastatic non-small cell lung cancer, through their declarations, seven members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting.

Information sources used

pERC 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 its 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 pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. Novartis Pharmaceuticals Canada Inc., as the primary data owner, did not agree to the disclosure of certain clinical information; therefore, this information has been redacted in the Recommendation and publicly available Guidance Reports.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers 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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