pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

NOTE: This recommendation supersedes the pERC Final Recommendation for this drug and indication dated October 4, 2012

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.

pERC Final Recommendation
This 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.

Drug: Crizotinib (Xalkori) **Submitter's Funding Request:** As monotherapy for use in patients with anaplastic lymphoma kinase (ALK)-positive advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC)	
Submitted By: Pfizer Canada Inc.	**Manufactured By:** Pfizer Canada Inc.
NOC Date: April 25, 2012	**Resubmission Date:** October 23, 2012
Initial Recommendation: March 7, 2013	**Final Recommendation:** May 2, 2013

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) recommends funding crizotinib (Xalkori) as a second-line therapy for patients with ALK-positive advanced non-small cell lung cancer (NSCLC) with ECOG performance status $\leq$ 2, conditional on the cost-effectiveness of crizotinib being improved to an acceptable level. The Committee made this recommendation because the Committee was confident of the net clinical benefit of crizotinib in patients who received one prior chemotherapy and because it aligns with patient values. However, the Committee noted that, at the submitted price and best estimates of the incremental cost-effectiveness ratio, crizotinib may not be cost-effective compared with standard care given the continuing uncertainty in the range of cost-effectiveness estimates. Funding crizotinib as a first-line therapy for patients with ALK-positive advanced NSCLC was not recommended because the Committee was not confident of the net clinical benefit of crizotinib due to limitations in the evidence currently available from clinical trials.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given pERC was satisfied there is a net clinical benefit of crizotinib, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of crizotinib to an acceptable level. pERC noted that jurisdictions may want to consider the impact of dose adjustments on tablet burden since crizotinib is priced per tablet and not per milligram (e.g. a reduction from 250 mg to 200 mg would not result in a price reduction) and actual use in clinical practice may significantly increase costs. **Implementation of Crizotinib and ALK Testing** Because use of crizotinib requires patients to have ALK-positive advanced or metastatic NSCLC, diagnostic testing for ALK will need to be implemented side-by-side with funding for crizotinib. **Time-Limited Need for Crizotinib** At the time of implementing a funding recommendation for crizotinib, jurisdictions may consider addressing the short-term, time-limited need for crizotinib for patients who are currently receiving second line treatment; who have recently relapsed on a second-line treatment; or who have recently completed a second line treatment. pERC noted that this time-limited access should be for patients who otherwise meet the eligibility criteria of PROFILE 1007.

SUMMARY OF pERC DELIBERATIONS

For patients with advanced NSCLC, including those with ALK-mutation positive disease, standard treatments in both the first-line and second-line setting include intravenous chemotherapy with platinum-based doublet therapy, such as cisplatin or carboplatin combined with one of gemcitabine, vinorelbine, paclitaxel, docetaxel, or pemetrexed. One randomized controlled trial, PROFILE 1007, was included in the systematic review, comparing crizotinib with standard of care in previously treated patients. Two non-randomized studies, PROFILE 1001 and PROFILE 1005, evaluating crizotinib in untreated and previously treated patients were also included. Neither of the non-randomized studies included a comparison group, although a retrospective analysis with crizotinib-naïve historical controls was conducted for PROFILE 1001.

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

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberations for this resubmission focused upon the results of the randomized controlled trial, PROFILE 1007 conducted with patients who had received one prior chemotherapy treatment. Based on the clinically and statistically significant improvement in progression-free survival, pERC considered that there was a net clinical benefit associated with crizotinib in previously treated patients. pERC also discussed safety data from the randomized controlled trial. pERC noted that crizotinib generally appeared to be well-tolerated by patients, with an acceptable toxicity profile; adverse events that were more frequently observed in the crizotinib group included nausea, vomiting, dizziness, visual disturbances and edema. pERC also considered updated clinical data from the non-randomized studies, PROFILE 1001 and PROFILE 1005, which provided information on the use of crizotinib in untreated patients. However, the Committee was not satisfied that these data provided sufficient evidence of comparative effectiveness and the information did not change pERC's original assessment that the available evidence was insufficient to demonstrate a net overall clinical benefit of treatment with crizotinib in untreated patients. Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the manufacturer on the use of crizotinib in the first line setting. pERC noted that there is an ongoing trial evaluating crizotinib in the first line setting (PROFILE 1014). To date, pre-specified criteria (i.e. stopping rules) have not been met that would provide a strong enough reason to stop PROFILE 1014 early and accept crizotinib as the standard first-line treatment for all patients in the trial. . Therefore, given the existing equipoise, pERC considered it ethical to wait for the results of this trial to inform any potential use of crizotinib in the first-line setting. pERC also noted that patient advocacy group feedback on the pERC Initial Recommendation indicated that patients were awaiting results of the trial in the first-line setting.

pERC discussed input from patient advocacy groups on crizotinib and noted that improving quality of life was important to patients. PROFILE 1007 demonstrated a clinically and statistically significant improvement in quality of life for patients receiving crizotinib compared with standard of care. It was also noted that crizotinib is an oral treatment, which may be easier for patients to take and would not require as much personal and caregiver time and resources (e.g., trips to the hospital) compared with intravenous chemotherapies. Therefore, pERC considered that crizotinib aligns with patient values.

pERC deliberated upon the cost-effectiveness of crizotinib, focusing on the estimates of cost-effectiveness in the second-line setting since the Committee was confident that there is a net overall clinical benefit of crizotinib in previously treated patients. pERC considered estimates submitted by the manufacturer and reanalyses conducted by the pCODR Economic Guidance Panel. pERC noted that there was some uncertainty around the utility values and the time horizon applied to the analysis but concluded that within the range of possible estimates and at the submitted price, crizotinib was not cost-effective. Upon reconsideration, pERC discussed feedback from the manufacturer, which disagreed with the cost-effectiveness estimates upon which the pERC Initial Recommendation was based. pERC further discussed the time horizon and utility values used in the cost-effectiveness analyses. Based on these discussions, the range of cost-effectiveness estimates considered by pERC changed to include those based on a time horizon of three to four years and those that used either trial-based utility values or literature-based

utility values. However, because of continuing uncertainty in the precise cost-effectiveness estimate, pERC concluded that over the range of estimates that were considered applicable, crizotinib may not be cost-effective.

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 but that <5% of NSCLC patients are expected to have the ALK mutation. pERC further discussed these estimates in the context of the feasibility of implementing a funding recommendation for crizotinib. It was noted that there was no new information provided that was relevant to ALK mutation testing, therefore pERC reiterated its previous concerns. pERC noted that the small number of patients with the ALK-mutation and the large number of patients who would need to be tested for the ALK mutation may lead to challenges in implementation, i.e. the testing burden is large compared with the small number of patients who would be ALK-positive. While there is uncertainty around testing costs, pERC noted that some estimates suggested that the cost of screening all patients with NSCLC for ALK-mutation may actually be greater than the cost of treatment. pERC noted that implementation of a cost-effective testing algorithm incorporating reliable testing methods and quality assurance steps could help to reduce the budget impact. Upon reconsideration, pERC discussed that the cost-effectiveness of crizotinib will also be impacted by the cost-effectiveness of testing for the ALK mutation and noted that it was challenging to determine this impact in the absence of a complete review of the cost-effectiveness of ALK mutation testing.

CONTEXT OF THE RESUBMISSION

A submission for crizotinib (Xalkori) for patients with anaplastic lymphoma kinase-(ALK) positive advanced non-small cell lung cancer (NSCLC) was previously received by pCODR on March 26, 2012 and the pERC Final Recommendation was issued on October 4, 2012.

- The pERC Final Recommendation was to not recommend funding crizotinib (Xalkori) for patients with ALK-positive advanced non-small cell lung cancer. The Committee made this recommendation because they were not confident of the net clinical benefit of crizotinib due to limitations in the evidence available from clinical trials.
- As a potential next step for stakeholders, pERC noted the possibility for a Resubmission using data from PROFILE 1007, a recently completed randomized controlled trial comparing crizotinib with current standard of care in previously treated patients, which was expected to report results in the near future. pERC considered that a randomized study would provide more robust information on the efficacy of crizotinib that might lead to a different recommendation for crizotinib in patients with ALK-positive advanced NSCLC. Feedback from the manufacturer on the pERC Initial Recommendation indicated their intent to resubmit crizotinib with data from PROFILE 1007 as soon as possible.
- The resubmission that was made by the manufacturer provided New Information on crizotinib. The New Information included:
    - clinical data from the randomized controlled trial (PROFILE 1007), identified by pERC as potentially being able to address points previously raised in the Final Recommendation
    - updated efficacy and safety data from two non-randomized studies included in the original submission (PROFILE 1001 and PROFILE 1005).
    - a revised economic evaluation

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 clinical and economic review panels
- input from one patient advocacy group (Lung Cancer Canada), received as part of the original submission for crizotinib (Xalkori)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- one patient advocacy group (Lung Cancer Canada)
- the Submitter (Pfizer Canada Inc.)

The pERC Initial recommendation was to fund crizotinib as a second-line therapy for patients with ALK-positive advanced non-small cell lung cancer conditional on the cost-effectiveness of crizotinib being improved to an acceptable level. Feedback on the pERC Initial Recommendation indicated that the manufacturer agreed in part with the pERC initial recommendation while the patient advocacy group and pCODR's Provincial Advisory Group agreed with the pERC initial recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

To evaluate the effect of crizotinib on patient outcomes compared with standard therapies or placebo in the treatment of patients with anaplastic lymphoma kinase (ALK) positive advanced or metastatic non-small cell lung cancer.

Studies included: one randomized controlled trial in previously treated patients

The pCODR systematic review included one randomized controlled trial, PROFILE 1007 and updated information on two previously submitted open-label single-arm trials, PROFILE1001 and PROFILE1005. pERC deliberations focused upon the results of the randomized controlled trial, PROFILE 1007.

- PROFILE 1007 was an open-label, randomized controlled trial of crizotinib versus second-line standard of care chemotherapy (pemetrexed or docetaxel), in ALK-positive, advanced NSCLC patients who had received one prior chemotherapy regimen that was platinum-based.
- PROFILE 1001 and PROFILE 1005 were non-randomized studies that included previously treated patients and some untreated patients. Neither study included a comparison group although a retrospective analysis with crizotinib-naïve historical controls was conducted for PROFILE 1001.

The pCODR review also provided contextual information on ALK mutation testing. pERC noted that no new information on testing was provided in the resubmission.

Patient populations: Most patients with ECOG performance status 0 or 1

The majority of patients across all three studies had an ECOG performance status of 0 or 1, although a small number of patients with ECOG performance status 2 were also included.

Patients in PROFILE 1007 and in PROFILE 1005 had received prior systemic treatment. Only 13% (n=15) of patients in PROFILE 1001 received crizotinib as a first-line treatment.

Key efficacy results: improved progression-free survival in previously treated patients, benefit for untreated patients unclear

The key efficacy outcomes deliberated on by pERC were progression-free survival, the primary outcome in PROFILE 1007, and overall survival. A median progression-free survival of 7.7 months versus 3.0 months was observed in PROFILE 1007 for patients randomized to crizotinib compared with current standard of care (HR=0.49, 95% CI: 0.37 to 0.64), as determined by independent radiology review. pERC considered that this improvement in progression-free survival was both statistically significant and clinically meaningful. pERC also discussed results from a pre-specified interim overall survival analysis but no statistically significant difference was observed. pERC noted that a substantial proportion of patients from the standard of care chemotherapy group (64%) had crossed over to the crizotinib group upon disease progression; therefore, overall survival results were likely biased by confounding.

pERC also considered updated clinical data from the non-randomized studies, PROFILE 1001 and PROFILE 1005, which provided some information on the use of crizotinib in untreated patients. pERC noted that the updated data were consistent with previous evidence from the original pCODR systematic review. However, the Committee was not satisfied that these data provided sufficient evidence of effectiveness and the information did not change pERC's original position that the available evidence was insufficient to demonstrate a net overall clinical benefit of treatment with crizotinib in untreated patients. While pERC

considered that PROFILE 1001 and PROFILE 1005 were appropriately conducted non-randomized studies, the conclusions the Committee could draw from these studies were limited. pERC considered that the magnitude of objective tumour response rate observed with crizotinib in the two trials was substantial, however, pERC did not consider it sufficient evidence of effectiveness. pERC was concerned about the strength of the evidence due to inherent biases in such a study design. pERC noted that objective response rate is an uncertain surrogate for overall survival and that PROFILE 1001 and PROFILE 1005 did not provide any comparative evidence on overall survival or progression-free survival, which are standard outcomes in lung cancer studies.

Quality of life: clinically meaningful improvement in quality of life

pERC discussed input from patient advocacy groups on crizotinib and noted that improving quality of life was important to patients. In PROFILE 1007, crizotinib was associated with a statistically significantly greater improvement from baseline in global quality of life in patients treated with crizotinib compared with chemotherapy (estimated difference 9.84, 95% CI: 5.39–14.28) and a statistically significantly greater improvement from baseline in symptoms and functioning (except for cognitive functioning) on the EORTC QLQ-C30/QLQ-LC13 questionnaire compared with chemotherapy. pERC considered that this was a clinically and statistically significant improvement in quality of life for patients receiving crizotinib compared with standard of care.

Safety: acceptable toxicity profile

pERC deliberated upon the adverse events observe in PROFILE 1007 and considered that they were consistent with those reported in the original pCODR systematic review. Serious adverse events were greater in the crizotinib group compared with the chemotherapy group (37.2% versus 23.4%, respectively) Overall, adverse events that were more frequently observed in the crizotinib group included nausea, vomiting, dizziness, visual disturbances and edema. However, pERC considered that crizotinib generally appeared have an acceptable toxicity profile and was tolerated by patients as supported by the improvements in quality of life.

Limitations: insufficient comparative data in untreated patients

pERC discussed the limitations of non-randomized studies and considered that, although the non-randomized studies PROFILE 1001 and 1005 were appropriately conducted, key questions could not be answered using this study design. pERC noted that there was no evidence from randomized controlled trials on the effectiveness of crizotinib in untreated patients since PROFILE 1007 only included previously treated patients. In addition, from the non-randomized studies, no patients in PROFILE 1005 and only 13% (n=15) of patients in PROFILE 1001 were untreated. Therefore pERC considered that there was insufficient data to establish the effectiveness of crizotinib in untreated patients when compared to standard treatments.

Ongoing trials: randomized study evaluating crizotinib in untreated patients

There is one ongoing randomized controlled trial in untreated patients evaluating crizotinib compared with pemetrexed plus a platinum agent, for which the primary endpoint is progression-free survival (PROFILE 1014). pERC considered that these comparative data would be of interest to the Committee. Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the manufacturer on the use of crizotinib in the first line setting. pERC noted that there is an ongoing trial evaluating crizotinib in the first line setting. To date, pre-specified criteria (i.e. stopping rules) have not been met that would provide a strong enough reason to stop PROFILE 1014 early and accept crizotinib as the standard first-line treatment for all patients in the trial. Therefore, given the existing equipoise, pERC considered it ethical to wait for the results of this trial to inform any potential use in first line patients. pERC also noted that patient advocacy group feedback on the pERC Initial Recommendation indicated that patients were awaiting results of the trial in the first-line setting.

Need: Only modest benefit with systemic therapy therefore alternative therapies needed

pERC noted that while the chemotherapies used in the treatment of NSCLC are associated with improvements in overall survival and quality of life, these improvements are modest and most patients with metastatic disease experience disease progression with a median time to progression of approximately four months. NSCLC is the leading cause of cancer-related deaths globally with the majority of patients presenting with non-curable disease. pERC noted that although a large number of patients would need to be screened for the ALK mutation, only a small number of patients are expected to be ALK positive and, therefore, candidates for treatment with crizotinib. pERC noted that prior to the identification of the ALK mutation, patients with this mutation would have been treated in the same

manner as other lung cancer patients and there is no evidence to suggest that patients with the ALK mutation do not respond to these other, standard of care treatments.

PATIENT-BASED VALUES

Values of patients with advanced NSCLC: Extending life and improving quality of life
Patient advocacy group input indicated that current chemotherapies only extend life expectancy to a limited extent and that many patients are not considered fit enough for chemotherapy treatments. pERC noted that for many patients, lung cancer symptoms interfere with their daily activities and that treatments that improve quality of life or other patient-relevant outcomes such as overall survival would be of value. pERC noted that improvements in quality of life were important to patients and that a clinically meaningful and statistically significant improvement in quality of life was observed in PROFILE 1007, which aligns with patient values.

Patient values on treatment: Improved efficacy, side effect profile and convenience valued
Input from the patient advocacy group indicated that treatments for advanced NSCLC that improve efficacy, convenience, or side effect profile over currently available therapies are important considerations. Patient input also noted that crizotinib is associated with minimal side effects, which appear to be manageable. pERC noted that crizotinib is an oral therapy, which would improve convenience of treatment for patients with ALK-positive advanced NSCLC. Oral treatments may 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 intravenous chemotherapies.

pERC also noted that input from patient advocacy group was based on a limited number of patients with direct experience of receiving crizotinib. pERC considered that other approaches for identifying patients with such experience, such as contacting global collaborations, may be appropriate when there are only a small number of patients in Canada who have had experience with a drug at the time of evaluation by pERC.

Upon reconsideration of the pERC Initial Recommendation, pERC considered patient advocacy group feedback on the pERC Initial Recommendation indicating that there is a need for crizotinib in patients beyond the second-line setting and that, overall, the number of patients who would be candidates crizotinib is very small. pERC discussed the use of crizotinib in a broader population of previously treated patients and also considered feedback from the pCODR Provincial Advisory Group indicating that there may be a need for time-limited access to crizotinib for patients that have recently failed second line therapy or are currently on second-line therapy prior to the availability of provincially-funded crizotinib. pERC was sensitive to the needs of this specific group of patients who may have used other second-line treatments before crizotinib was available as a second-line treatment. Therefore, pERC considered that, for a time-limited period, it would be clinically reasonable for these patients to have access to crizotinib, if they would otherwise meet the eligibility criteria of PROFILE 1007.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness and cost-utility
The pCODR Economic Guidance Panel assessed an economic evaluation of the cost-effectiveness and cost-utility of crizotinib with current standard of care for patients with locally advanced or metastatic ALK-positive Non-Small Cell Lung Cancer (NSCLC). The primary economic analysis involved the use of crizotinib as a first-line therapy. Scenario analyses were also submitted evaluating the cost-effectiveness of crizotinib as a second-line treatment.

Basis of the economic model: Clinical and economic inputs
Costs included drug costs and costs associated with drug administration and monitoring, management of adverse events, disease progression and palliative care.

In the first-line setting, key clinical effects included progression-free survival and overall survival estimates from PROFILE 1001 and utility values derived from the literature. In the second-line setting, key clinical effects included progression-free survival and overall survival estimates from PROFILE 1007 and

health utility values obtained from PROFILE 1007. In both settings, the two largest influences on both QALYs and life years were the model's post progression probability of mortality and its time horizon.

Drug costs: dose adjustments may lead to higher drug costs and wastage

At the list price, crizotinib costs $146.67 per 200 and 250 mg tablets; and at the recommended dose of 250 mg twice daily, the average cost per day of crizotinib is $293.33 and the average cost per 28-day course is $8,213.34.

Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from the pCODR Provincial Advisory Group, who had concerns that the price of crizotinib tablets is the same regardless of dose rather than being priced per milligram. As such, dose reductions would not lead to a corresponding reduction in drug costs because the costs of the 200 mg and 250 mg tablets are the same. pERC noted that dose escalations or dose reductions that result in multiple tablets may lead to substantial increases in drug costs and potential for wastage of previously dispensed tablets.

Cost-effectiveness estimates: time horizon and utilities uncertain in second-line setting

pERC deliberated upon the cost-effectiveness of crizotinib, focusing on the estimates of cost-effectiveness in the second-line setting since the Committee was confident that there is a net overall clinical benefit of crizotinib in previously treated patients. pERC noted that many of the strengths and limitations of the cost-effectiveness analysis in the first-line setting also applied to the analyses conducted in the second-line setting. pERC considered estimates submitted by the manufacturer and reanalyses conducted by the pCODR Economic Guidance Panel. pERC noted that a time horizon of six years had been used in the manufacturer's analyses but that in the EGP's analyses, a time horizon of two to three years had been applied after consultation with the pCODR Clinical Guidance Panel. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the manufacturer indicating that a two-year time horizon was too short and not appropriate. While pERC considered that a time horizon of five or six years, which the manufacturer applied in their analyses was likely too long for patients with metastatic lung cancer, pERC considered that a time horizon of three to four years would ensure that all potential costs and benefits were captured in the analysis.

pERC also discussed that the use of utility values from PROFILE 1007 rather than from the literature may have biased the cost-effectiveness estimates in favour of crizotinib. It was noted that the pCODR Economic Guidance Panel had limited information available to them on these utility values and so were unable to be validated. In the absence of this information, pERC considered that the utility values from published literature may be more reliable. Upon reconsideration, pERC discussed feedback from the manufacturer indicating that, calculating utilities using trial-based quality of life data is preferred to using utilities from previously published literature. pERC acknowledged that using trial-based estimates is a standard and preferred methodology. However, the large difference in trial-based mean utility values ([redacted] for crizotinib and [redacted] for standard care) compared with the literature-based mean utility values (0.673) created uncertainty for pERC (*Non-disclosable information was provided to pERC in the pCODR economic guidance report for deliberation on a recommendation and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed)*. pERC noted that the utility estimates based on PROFILE 1007 were considerably higher than those based on established literature and higher than what might be expected for patients with metastatic lung cancer and no rationale was provided for this considerable difference. Therefore, without additional information allowing the pCODR Economic Guidance Panel to validate these estimates, pERC was concerned that estimates from PROFILE 1007 may be outliers compared with established literature or that there may be biases associated with the trial-based estimates. To balance these issues, when making a recommendation, pERC considered cost-effectiveness estimates informed by both trial-based utility values and those informed by literature-based utility values.

Based on reconsideration of the pERC Initial Recommendation, the range of cost-effectiveness estimates considered by pERC changed due to discussions around the appropriate time horizon and source of utility values. However, due to continuing uncertainty in the precise cost-effectiveness estimate, pERC concluded that over the range of estimates that were considered applicable, crizotinib may not be cost-effective.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: High proportion of patients to be screened for ALK mutation

Input from pCODR's Provincial Advisory Group indicated that molecular testing for ALK positive mutations may impact on the feasibility of adopting a funding recommendation for crizotinib. It was noted that there was no new information provided that was relevant to ALK mutation testing, therefore pERC reiterated its previous concerns.

pERC discussed various aspects of testing and noted that the number of patients with NSCLC who would need to be screened for the ALK mutation (i.e. thousands of patients in Canada), relative to the number of patients likely to be positive (i.e. approximately 500 patients in Canada), is large. The small number of patients with the ALK-mutation and the large number of patients who would need to be tested for the ALK mutation may lead to challenges for implementation, that is the testing burden is large compared with the small number of ALK positive patients. In addition, while there is uncertainty around the cost of ALK-mutation testing, pERC noted that some estimates suggested that the cost of screening patients for the ALK-mutation may actually be greater than the cost of treatment, due to the large number of patients who need to be screened. pERC also noted that ALK mutation testing is not currently available throughout Canada. As such, pERC considered that the feasibility of adoption was low but that implementation of a cost-effective testing algorithm incorporating reliable testing methods and quality assurance steps could help to reduce the budget impact. Upon reconsideration, pERC discussed that the cost-effectiveness of crizotinib will be impacted by the cost-effectiveness of testing for the ALK mutation and noted that it was challenging to determine this impact in the absence of a complete review of the cost-effectiveness of ALK mutation testing.

DRUG AND CONDITION INFORMATION

Drug Information	• Anaplastic lymphoma kinase (ALK) inhibitor • 200 mg and 250 mg tablets reviewed by pCODR • Recommended dosage of 250 mg administered orally twice daily • Validated diagnostic test for determining ALK-mutation status required
Cancer Treated	• ALK positive advanced non-small cell lung cancer (NSCLC).
Burden of Illness	• NSCLC is the leading cause of cancer-related mortality in Canadians • Approximately <5% of patients with NSCLC are ALK-positive.
Current Standard Treatment	• Standard treatments in both the first-line and second-line setting include intravenous chemotherapy with platinum-based doublet therapy, such as cisplatin or carboplatin combined with one of gemcitabine, vinorelbine, paclitaxel, docetaxel, or pemetrexed. • Other therapies in patients who progress after one or two lines of prior chemotherapy include the molecular targeted therapies erlotinib and gefitinib.
Limitations of Current Therapy	• Response rates to chemotherapy are approximately 20% but responses last only a few months, with progression occurring within three to four months and patients requiring alternative treatment options in both the first-line and second-line settings.

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. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
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 Lister, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:
- Dr. Bill Evans and Jo Nanson who were absent from the meeting

All members participated in deliberations and voting on the final recommendation except:
- Dr. Bill Evans who was absent from the meeting
- Carol McMahon 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 crizotinib (Xalkori) resubmission for advanced NSCLC, through their declarations, seven members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, but 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*. Pfizer Canada Inc., as the primary data owner, did not agree to the disclosure of some economic information; therefore, this information will remain redacted until notification by manufacturer that it can be publicly disclosed.

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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