

pCODR EXPERT REVIEW COMMITTEE (pERC) FINAL 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.

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: Patients with anaplastic lymphoma kinase-(ALK) positive advanced non-small cell lung cancer (NSCLC)	
Submitted By: Pfizer Canada Inc.	Manufactured By: Pfizer Canada Inc.
NOC Date: April 25, 2012	Submission Date: March 26, 2012
Initial Recommendation: August 2, 2012	Final Recommendation: October 4, 2012

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) does not recommend funding crizotinib (Xalkori) for patients with ALK-positive advanced non-small cell lung cancer. The Committee made this recommendation because the Committee was not confident of the net clinical benefit of crizotinib due to limitations in the evidence available from clinical trials. Although the pertinent studies were appropriately conducted, pERC considered that the conclusions that could be drawn from non-randomized phase two studies were limited. While pERC was confident that crizotinib produces a tumour response, based on the observed magnitude of response, pERC was unable to determine how crizotinib compares with other treatments on outcomes important to decision-making such as overall survival, progression-free survival and quality of life.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Possibility of Resubmission to Support Funding PROFILE 1007, a recently completed randomized controlled trial comparing crizotinib with standard of care in previously treated patients, is expected to report results in the near future. A randomized study will provide more robust information on the efficacy of crizotinib that may 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.

SUMMARY OF pERC DELIBERATIONS

Standard treatment for patients with advanced NSCLC, including those with ALK-mutation positive disease, include intravenous chemotherapy with platinum-based doublet therapy, such as cisplatin or carboplatin combined with one of gemcitabine, vinorelbine, paclitaxel, docetaxel, or pemetrexed. No randomized controlled trials were identified for inclusion in the pCODR systematic review. Two non-randomized studies evaluating crizotinib were included, PROFILE 1001 and PROFILE 1005. Neither study included a comparison group although a retrospective analysis with crizotinib-naive historical controls was conducted for PROFILE 1001. A randomized controlled trial, PROFILE 1007 was identified. Although it has been recently completed, results are not yet available and so it was not included in the pCODR systematic review. pERC considered that results from this trial would be key to determining the safety and effectiveness of crizotinib. Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the manufacturer indicating their intent to resubmit crizotinib to pCODR with data from PROFILE 1007 as soon as possible. It was noted that pCODR had requested data from PROFILE 1007 during this review of crizotinib but at that time the manufacturer had indicated the data were unavailable.

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 PROFILE 1001 and PROFILE 1005 but was not satisfied that the available evidence clearly demonstrated a net overall clinical benefit of treatment with crizotinib. While pERC considered that PROFILE 1001 and PROFILE 1005 were appropriately conducted non-randomized studies, the Committee concluded that the conclusions that can be drawn from these studies were limited. While pERC considered that the magnitude of objective tumour response observed with crizotinib in the two trials was substantial, 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 further noted that results of a randomized controlled trial comparing crizotinib with standard of care in previously treated patients (PROFILE 1007) will soon be available and may provide additional clarity on the effectiveness of crizotinib. 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. Furthermore, pERC found it difficult to assess the impact of crizotinib on patient-reported outcomes and quality of life as only abstract-level data were available and these could not be adequately appraised. pERC reviewed safety evidence for crizotinib from PROFILE 1001 and PROFILE 1005. pERC noted that there were a number of deaths due to hepatotoxicity and that QT prolongation had been observed. pERC noted that crizotinib generally appeared to be tolerated by patients with an acceptable toxicity profile; the most frequently observed adverse events included nausea, vomiting, dizziness and visual disturbances. However, given the lack of a comparator arm in PROFILE 1001 and PROFILE 1005, pERC considered the safety data to be preliminary.

pERC discussed input from a patient advocacy group on crizotinib. It was 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) as receiving intravenous chemotherapies. Therefore, pERC considered that crizotinib aligns with patient values.

pERC deliberated upon the cost-effectiveness of crizotinib. Overall, pERC considered that because of the limitations in the available clinical information on crizotinib from non-randomized studies, it was challenging to draw conclusions on the cost-effectiveness of crizotinib. In addition, when discussing the cost-effectiveness estimates, pERC noted that the Economic Guidance Panel's estimates were substantially larger than the manufacturer's estimates but considered that the Economic Guidance Panel's estimates and assumptions were more realistic and clinically valid.

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

only approximately 4% 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 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.

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)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- one patient advocacy group who provided input at the beginning of the review (Lung Cancer Canada)
- pCODR's Provincial Advisory Group
- the Submitter (Pfizer Canada Inc.)

The pERC Initial Recommendation was to not recommend funding crizotinib (Xalkori) for patients with ALK-positive advanced non-small cell lung cancer. Feedback on the pERC Initial Recommendation indicated that the pCODR's Provincial Advisory Group agreed with the recommendation while Lung Cancer Canada and Pfizer Canada Inc. disagreed with the 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: Two non-randomized, single-arm studies

The pCODR systematic review included two open-label non-randomized single-arm trials, PROFILE1001 and PROFILE1005.

- PROFILE1001 was a published phase 1/phase 2, open-label, dose-escalation study evaluating crizotinib in ALK-positive patients with advanced malignancies (i.e., not limited to patients with NSCLC). In addition, a retrospective analysis comparing crizotinib-treated patients in PROFILE 1001 with crizotinib-naive historical controls was conducted.
- PROFILE1005 was an unpublished, abstract-only, phase 2, open-label, single-arm study of the efficacy and safety of crizotinib in patients with ALK- positive advanced NSCLC.

The pCODR review also provided contextual information on ALK mutation testing.

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

The majority of the patients from both studies had an ECOG performance status of 0 or 1, although a small number of patients with ECOG performance status 2 were also included. Only 13% (n=15) patients in PROFILE1001 received crizotinib as a first-line treatment; all other patients in the two studies had received prior systemic treatment.

Key efficacy results: Magnitude of tumour response promising but insufficient

The primary efficacy endpoint for both non-randomized studies was tumour response as assessed by the investigators. Based on the investigator assessments, the objective response rate in PROFILE 1001 was 61.2% (2 complete and 69 partial responses) and in PROFILE 1005 was 49.6% (1 complete and 67 partial responses). An assessment was also conducted by an independent review committee and lower responses were reported. pERC noted that the magnitude of the tumour response rates seen with crizotinib was considerable, indicating activity of crizotinib. pERC also reviewed tumour response rates in various patient subgroups and noted that high response rates were observed in patients with lower performance status who are more challenging to treat. Overall, pERC considered these results promising but insufficient to confirm an overall clinical benefit.

pERC discussed that median overall survival time has not yet been reached in either PROFILE 1001 or PROFILE 1005 and comparative data on progression-free survival were not available from PROFILE 1001 or PROFILE 1005. Furthermore, pERC noted that the relationship of objective response rate as a surrogate endpoint for overall survival in advanced NSCLC is unclear. pERC discussed these results and considered that further comparative information on quality of life, progression-free survival and overall survival, which are standard endpoints that are considered in oncology trials would be important to informing their assessment of clinical benefit.

Quality of life: Insufficient details on patient-reported outcomes

pERC discussed data on patient reported outcomes and global quality of life from PROFILE 1005 that were available in abstract form. However, pERC considered that the limited details provided in the abstract prevented a full description and complete assessment of this data. In particular, there was no information on the demographic or clinical characteristics of the subset of evaluable patients. In addition, pERC considered that the lack of comparative data made it challenging to assess the benefits of crizotinib on patient reported outcomes and quality of life.

Safety: Preliminary evidence suggests acceptable toxicity but comparative data unavailable

pERC discussed the adverse events observed in PROFILE 1001 and PROFILE 1005 and the resulting toxicity profile of crizotinib. pERC noted that 45 deaths occurred among patients receiving crizotinib in PROFILE 1001 and PROFILE 1005 combined. Grade 3 to 4 adverse events occurred in 40.8% of patients across both studies and QT prolongation was observed in some patients. Frequently reported adverse events included visual disorders, nausea, vomiting, diarrhea, and constipation. pERC considered that crizotinib appears to have an acceptable toxicity profile, which may be comparable to standard chemotherapy, however, the non-randomized design of the studies makes it challenging to determine the adverse events attributable to crizotinib.

Limitations: Insufficient comparative data on outcomes important to patients

pERC discussed the limitations of non-randomized studies and considered that, although the non-randomized studies were appropriately conducted, key questions could not be answered using this study design. pERC considered that, given the lack of a comparator arm, the magnitude of crizotinib response is uncertain and may overestimate the magnitude of clinical benefit associated with crizotinib. Due to the lack of comparative data for crizotinib, there is also uncertainty as to its place in the overall management of advanced or metastatic NSCLC. pERC considered that while the results of PROFILE 1001 and PROFILE 1005 are promising and demonstrate crizotinib activity, they do not establish its effectiveness in improving overall survival and quality of life outcomes compared to standard treatments.

Ongoing trials: Comparative PFS results to be available shortly from randomized studies

There are two phase 3 randomized clinical trials evaluating crizotinib that are either recently completed or ongoing, for which the primary endpoint is progression-free survival. pERC considered that these ongoing trials indicated that conducting randomized controlled trials in this small population of ALK-positive patients with advanced NSCLC is feasible and that it would be of value for the Committee to review these comparative data.

- PROFILE 1007 comparing crizotinib with either docetaxel or pemetrexed as a second-line therapy for ALK-positive patients was recently completed and results are expected to be reported later in 2012.
- PROFILE 10014 comparing crizotinib with pemetrexed plus a platinum agent as first-line therapy is ongoing.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the manufacturer indicating their intent to resubmit crizotinib to pCODR with data from PROFILE 1007 as soon as possible. It was noted that pCODR had requested data from PROFILE 1007 during this review of crizotinib but at that time the manufacturer had indicated the data were unavailable.

Need: 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 experience disease progression with a median time to progression of approximately four months. NSCLC is the leading cause of cancer-related deaths 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.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the patient advocacy group that disagreed with the initial recommendation because they felt crizotinib is the only treatment that can benefit patients with ALK positive lung cancer. pERC considered that this is not the case as prior to the identification of the ALK mutation, these patients 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.

Patient values on treatment: Improved efficacy, side effect profile and convenience valued

Input from patient advocacy groups 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. While pERC was not satisfied with the information available on crizotinib to support overall clinical benefit, pERC noted that crizotinib is an oral therapy, which would improve convenience of treatment for patients with ALK-positive advanced NSCLC.

pERC also discussed the fact that input from patient advocacy groups was based on a limited number of patients with direct experience of receiving crizotinib. pERC noted 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 experience with a drug at the time of evaluation by pERC.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility in untreated patients

The pCODR Economic Guidance Panel assessed an economic evaluation of the cost-effectiveness and cost-utility of crizotinib as first line therapy compared 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 previously untreated patients with additional analyses conducted for the use of crizotinib as a second-line or third-line therapy.

Basis of the economic model: Clinical and economic inputs

Costs include drug costs and costs associated with drug administration and monitoring, management of adverse events, disease progression and palliative care.

Key clinical effects included progression-free survival and overall survival estimates from PROFILE 1001 and utility values derived from the literature. 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: Lower confidential price submitted

At the confidential submitted price, crizotinib costs \$██████ per 200 mg and 250 mg tablets. At the recommended dose of 250 mg twice daily, the average cost per day in a 28-day course of crizotinib is \$██████ and the average cost per 28-day course is \$██████ (*Non-disclosable information was provided to pERC in the pCODR guidance reports 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*).

At a wholesale acquisition price, crizotinib costs \$146.67 per 200 mg and 250 mg tablets; and at the recommended dose of 250 mg twice daily, the average cost per day in a 28-day course of crizotinib is \$293 and the average cost per 28-day course is \$8,213.

Cost-effectiveness estimates: Estimates limited by available clinical data

pERC deliberated upon the cost-effectiveness of crizotinib and discussed the Economic Guidance Panel's critique and re-analyses of the submitted economic evaluation. Overall, pERC considered that because of the limitations in the available clinical information for crizotinib from non-randomized studies, it was challenging to draw conclusions on the cost-effectiveness of crizotinib.

In discussing the cost-effectiveness estimates, pERC noted that the EGP estimates were substantially larger than the manufacturer's estimates but considered that the EGP estimates and assumptions were more realistic and clinically valid. The EGP assumed that the risk of death before tumour progression differs from the risk of death after tumour progression. In addition, the EGP, in consultation with the CGP, assumed a shorter time horizon of two years compared with the six year time horizon used by the manufacturer.

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. pERC discussed various aspects of testing and noted that the number of patients who would need to be screened for the ALK mutation, 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, i.e. the testing burden is large compared with the small number of ALK positive patients. In addition, while there is uncertainty around testing costs, 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 of the initial recommendation, pERC noted feedback from the patient advocacy group indicating that ALK mutation testing is available in Canada. pERC clarified that while ALK mutation testing is available and conducted in some centres, the Committee is aware that it may not be broadly accessible to all patients in all jurisdictions.

DRUG AND CONDITION INFORMATION

Drug Information	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	Anaplastic lymphoma kinase-(ALK) positive advanced non-small cell lung cancer (NSCLC).
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	Intravenous chemotherapy with platinum-based doublet therapy, such as cisplatin or carboplatin combined with one of gemcitabine, vinorelbine, paclitaxel, docetaxel, or in select provinces, pemetrexed
Limitations of Current Therapy	Response rates to first-line chemotherapy are approximately 20% but improvement only lasts a few months, with progression occurring within three to four months

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

- Dr. Tallal Younis who was not present for this part of the meeting
- Dr. Bill Evans who was excluded from voting due to a conflict of interest
- Carole McMahon who did not vote due to her role as a patient member alternate

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

- Dr. Chaim Bell, Mario de Lemos, Bryson Brown, Dr. Paul Hoskins and Dr. Tallal Younis who were not present
- Dr. Bill Evans who was excluded from voting due to a conflict of interest

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 crizotinib (Xalkori) for advanced NSCLC through their declarations, four 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

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 has been redacted in this recommendation and publicly available guidance reports.

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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