pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Crizotinib (Xalkori) Resubmission for NSCLC

May 2, 2013

Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	XALKORI is indicated as monotherapy for the use in patients with anaplastic lymphoma kinase (ALK)-positive advanced (not amenable for curative therapy) or metastatic non-small cell lung cancer (NSCLC).
Role in Review (Submitter and/or Manufacturer):	Submitter and manufacturer
Organization Providing Feedback	Pfizer Canada Inc.

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees _X_ agrees in part ____ disagree

Please explain why the Submitter (or the Manufacturer of the drug under review, if not the Submitter) *agrees, agrees in part or disagrees with the initial recommendation.*

Pfizer Canada agrees in part with the pCODR recommendation mainly because pERC recognized the net clinical benefit of Xalkori in patients who received one prior chemotherapy. However, the reasons why we partly disagree are listed below.

1- Health Canada approved Xalkori for ALK positive advanced NSCLC regardless of the line of therapy:
- The basis of approval is Xalkori's remarkable clinical efficacy and favourable tolerability profile determined in earlier phase studies: PROFILE 1001 and 1005. Health Canada granted market authorization (NOC/c) on April 25, 2012.[1]
- Xalkori has become the first targeted agent approved for use as a monotherapy in patients with ALK positive advanced (not amenable to curative therapy) or metastatic NSCLC in Canada.1
- In addition to Canada, Xalkori received market authorization in more than 20 countries for ALK+ advanced NSCLC in 1st line.

2- Screening patients in personalized medicine to determine/confirm driver mutations is the basis for targeted therapy identification. Patients are screened for oncogene not line of therapy. For Xalkori, patients are screened for ALK status to determine whether they qualify to be treated and to derive the benefits of treatment, not to be assigned to a treatment based on line of therapy:
- Multiple publications on patient datasets suggest that ALK-positive advanced NSCLC is more aggressive than a wild-type ALK lung cancer including the ones with oncogenic drivers other than ALK.[2,3,4]
- ALK positive advanced lung cancers have shown inferior responses to standard therapies, particularly EGFR TKIs and platinum-based chemotherapy.4
- As reported in the PROFILE 1001 updated publication, patients receiving first-line Xalkori (N=24), reached a median PFS of 18.3 months (95% CI: 8.3, upper bound not reached), far surpassing the 3-5 months PFS that has been reported for first-line standard chemotherapy. [5]
- The body of evidence for Xalkori currently highlights the critical value of identifying ALK

positive advanced patients very early in the course of their clinical management to select the treatment to which these severely ill patients will optimally respond and eliminate therapies which these patients are very likely to fail on or not respond to.

- ALK testing is available in Canada and is being routinely conducted by several pathology laboratories established in the vast majority of Provinces.

3- There is an evolving phenotypic portrait of the ALK positive patient, which may guide screening:

- Evidence to date suggests that ALK positivity is not only a predictive factor for an unfavourable response to standard approved NSCLC treatments but also a predictor for worse survival.[2,3,4]
- *ALK* aberrations are more prevalent in adenocarcinomas, never-smokers, and younger patients (median age 50), but clinical features are not sufficiently sensitive to be used to select patients for ALK testing. [2,4,5]Reducing or truncating the population to be tested towards line of therapy is against the interests of the patient and clinician and potentially unethical.
- If the biopsy is done early on (1st line) and patients are found to be ALK+, ethically and legally, it's the physicians obligation to inform patients that a treatment is indicated and shown to work for them but is not publicly funded until a first treatment fails. This could create a difficult situation for both the physicians and the patients. Failure to inform ALK+ patients of the availability of Xalkori for 1st line treatment may constitute a negligent failure on the part of the healthcare systems and may negate a patient's informed consent, because the patient's ultimate treatment decision would not be based on knowing all the information that would be "material to a reasonable patient in the same circumstances".[6]

4- Some patients (potentially ALK positive) will be placed at higher risk of death before reaching to 2nd line either due to progression of disease or worsening of the performance status :

- A total of 40-50% of patients who receive conventional chemotherapy in the frontline setting are not suitable to receive more advanced lines of therapy due to either disease progression, or poor performance status as a result of severe adverse events caused by chemotherapy.[7] Therefore, it is of upmost importance to detect ALK alterations early in the course of the disease in order for patients to receive the best available treatment with the highest expected benefits.

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

- There are two main reasons that pCODR relies on to state that the cost effectiveness of Xalkori needs to be improved: use of utility from the 1007 trial for 2nd line and the time horizon. We respectfully disagree with these reasons that do not hold any scientific or logical weight.
- Choice of time horizon: pCODR suggests that a 2 year time horizon be used while we argue, based on clinical trial data, that a 6 year time horizon for 1st line and a 5 year time horizon for 2nd line allows capturing all of the clinical outcomes and costs associated with the economic simulation.[8,9] As explained within the submitted economic dossier, the observed median PFS for patients on Xalkori in 1st line in PROFILE 1001 was 18.3 months,[10] therefore at least 50% of our cohort was still alive at month 18. How can we then consider a 2 year time horizon and assume that all patient events (mortality and progression) have been captured? Even in 2nd line, by applying the probability of mortality post-regression calculated from the phase 3 trial PROFILE 1007, it can be shown that 26%, 17%, 11%, and 7% of the cohort would be still alive as per simulation respectively 3, 4, 5, and 6 years after the start of the treatment. Median OS from PROFILE 1001 is 29.6 months *(note to pCODR, please sever, confidential data), which does* not support adopting a time horizon no greater than 24 months.[11] It is concerning that pCODR and the pERC concluded on the validity of such a limited time horizon in light of this data.
- The use of EQ-5D from PROFILE 1007 to calculate the utilities for 2nd line analyses instead of

published literature data was challenged by pCODR because of lack of methodology information and pCODR's preference for using data from outside the trial for utilities. It is generally preferred to use Quality of Life results from the in-trial population rather than figures from the literature, the latter may represent a completely different patient population (and treatments). As for lack of detailed information around the methodology, we respectfully argue that it's not the first time that the EQ-5D has been used in an oncology trial and that pCODR could have simply asked for more information as allowed during their review process (i.e. checkpoint meeting). This would have enabled a more rapid and accurate appraisal of the economic calculations.

We are disappointed with the outcome of the assessment by the pERC. We believe that there are significant ethical concerns to deny patients who are ALK+ a medicine that can truly improve their quality and length of life early on. The implementation of such second line reimbursement criteria as recommended by pCODR could lead to medical malpractice should health care professionals fail to inform patients about the availability of Xalkori and the administrative necessity to fail on another agent before qualifying for reimbursement despite an observed ALK+ test.[12]

We are also confident in the results of our cost-effectiveness analysis in 2nd line and we believe it's closer to the true value of Xalkori than pCODR's assessment. However, we will not challenge pERC's initial recommendation. We are accepting to convert this decision only because patients can't afford not to have access to Xalkori through adequate reimbursement.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

_X_	Support conversion to final recommendation.	____	Do not support conversion to final recommendation.
	Recommendation does not require reconsideration by pERC.		Recommendation should be reconsidered by pERC.

About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.

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1 Xalkori™ (Crizotinib) Product Monograph, Pfizer Canada Inc.

2 Yang P et al. Worse disease-free survival in never-smokers with *ALK*+ lung adenocarcinoma. J Thorac Oncol 2012;7:90-97.

3 Kim DW et al. Comparative analyses of overall survival of anaplastic lymphoma kinase-positive advanced non-small cell lung cancer (NSCLC) patients who did not receive *ALK* inhibitors. Presented at: 47th American Society of Clinical Oncology (ASCO) Annual Meeting, June 3-7, 2011, Chicago, Illinois.

4 Shaw AT et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-*ALK*. J Clin Oncol 2009;27(26):4247-53.

5 Camidge R et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol 2012;13(10):1011-9.

6 Reibl v. Hughes [1980] 2 S.C.R. 880 Supreme Court of Canada

7 Fidias P et al. Strategies for prolonged therapy in patients with advanced non-small-cell lung cancer. J Clin Oncol 2010;28(34):5116-23.

8 NICE guidance for manufacturers' submissions. London,UK, 2004 http://www.nice.org.uk/niceMedia/pdf/TAP_Methods.pdf

[9] Mittmann N et al. Addendum to CADTH's Guidelines for the Economic Evaluation of Health Technologies: Specific Guidance for Oncology Products. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009

[10] Camidge R et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol 2012[Epub].

[11] Pfizer Inc. Data on file

[12] Margaret A. Somerville, "Structuring the Issues in Informed Consent" (1981) 26:4 McGill Law Journal 740-808.