



pan-Canadian Oncology Drug Review Final Economic Guidance Report

Crizotinib (Xalkori) Resubmission for Advanced Non-Small Cell Lung Cancer

July 21, 2015

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FUNDING

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This section outlines the technical details of the pCODR Economic Guidance Panel’s evaluation of the economic evidence that is summarized in Section 1. Pursuant to the <i>pCODR Disclosure of Information Guidelines</i> , this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.	
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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The economic analysis submitted to pCODR by Pfizer compares crizotinib as first line therapy to current standard of care in Canada for patients with locally advanced or metastatic Anaplastic Lymphoma Kinase (ALK) positive Non-Small Cell Lung Cancer (NSCLC) patients. The patient population reflects the expanded cohort of ALK positive NSCLC (PROFILE 1014 study, Solomon et al. 2014). PROFILE 1014 is an ongoing phase 3 randomized open-label study of crizotinib (n=172) versus pemetrexed-plus-platinum chemotherapy (n=171), in ALK-positive, advanced non-squamous NSCLC patients who had received no previous systemic treatment for advanced NSCLC. Patients were also included if they had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 . Patients with treated brain metastases were eligible for inclusion if the metastases were neurologically stable for at least two weeks before enrollment and if the patient had no ongoing requirement for glucocorticoids. Crizotinib is administered orally. Current standard of care in Canada for NSCLC includes pemetrexed/platinum (administered intravenously) as 1st line, to be followed by crizotinib (administered orally) as 2nd line and docetaxel (administered intravenously) as 3rd line.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate.

The present economic analysis is an updated resubmission of a previously submitted economic analysis of crizotinib by the manufacturer to pCODR for a second line indication. Most of the economic model's input parameters have remained unchanged; however, the probabilities for progression and mortality have been updated from the PROFILE 1014 study.

Patient advocacy groups considered the following factors important in the review of crizotinib, which are relevant to the economic analysis: improvement in treatment efficacy and patient's quality of life, convenience and fewer hospital visits and time off from work with oral administration of crizotinib. A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

- The submitted economic analysis explicitly considered improvements in quality of life by applying utility scores and measuring outcomes in quality-adjusted life years.
- The model has not considered whether crizotinib will enable patients to save more time off of work - the model adopts the perspective of the publicly funded health care system which is appropriate for pCODR because drug funding recommendations must be considered from a health system perspective.
- The benefits of oral administration were considered in the submitted analysis in terms of cost of administration as crizotinib was compared to intravenous drug comparators.

The Provincial Advisory Group (PAG) considered that the following factors would be important to consider if implementing a funding recommendation for crizotinib, and which are relevant to the economic analysis: treatment sequence after progression on crizotinib first-line and oral administration and dosing of crizotinib for NSCLC. A full summary of Provincial Advisory Group input is provided in the pCODR Clinical Guidance Report.

- Cost savings associated with oral administration of crizotinib were considered in the submitted model, however, dosage reductions with crizotinib were not explicitly considered in the submitted model.
- Although oral administration of crizotinib was identified as an enabler to implementation; oral medications are not funded in the same mechanism as

intravenous cancer medications in some jurisdictions. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program which can be associated with co-payments and deductibles. Co-payments and deductibles were not incorporated in the submitted analysis.

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 in a 28-day course of crizotinib is \$293.33 and the average cost per 28-day course is \$8,213.34.

At the list price, pemetrexed cost \$4.2900 per mg. At the recommended dose of 500mg/m² on day 1 of every 21 day cycle, pemetrexed costs \$173.64 per day and \$4862.00 per 28-day course.

At the list price, cisplatin cost \$5.8594 per mg. At the recommended dose of 75 mg/m² IV day 1 every 21 days, cisplatin costs \$35.57 per day and \$996.10 per 28-day course.

At the list price, carboplatin cost \$0.10 per mg. At the recommended dose of AUC 5 IV on day 1 every 21 days, carboplatin costs \$2.38 per day and \$66.67 per 28-day course.

1.2 Summary of Results

The Economic Guidance Panel's best estimate of the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) for 1st line crizotinib is between \$173,570 per QALY and \$285,299 per QALY when compared to standard of care (defined as 1st pemetrexed/platinum followed by 2nd line crizotinib and 3rd line docetaxel). These estimates are based on reanalyses conducted by the Economic Guidance Panel using the list price and the model submitted by Pfizer.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect ($\Delta QALY$ or ΔLY). For 1st line crizotinib, the Economic Guidance Panel's best estimate of:

- The extra cost (ΔC) of crizotinib is between \$36,548 and \$37,387. Costs included drug costs and drug administration and monitoring costs, disease progression, and palliative care. Costs associated with management of adverse events were also considered.
- The extra clinical effect ($\Delta QALY$ or ΔLY) of crizotinib is between 0.131 QALYs (6.81 weeks) and 0.211 QALYs (10.97 weeks) or between -0.015 (1 week less) and 0.117 (6.08 weeks) life years. Key clinical effects included progression-free survival and overall survival estimates from PROFILE 1014 trial (Solomon et al. 2014) and utility values derived from the PROFILE 1014 trial. The biggest influence on both QALYs and life years was the post progression probability of mortality, time horizon, extrapolation method of survival effects, and utility values.

The EGP based these estimates on the model submitted by Pfizer and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that:

- The upper estimate of the range (ICER of \$285,299) assumed that the time horizon of the model was reduced to 4 years versus the 6 years modeled by the manufacturer and using individual post-progression probabilities of mortality for each subsequent treatment. The extra costs associated with crizotinib were \$37,387 and the extra QALYs associated with crizotinib were 0.131 (6.81 weeks).
- The lower estimate of the range (ICER of \$173,570) assumed that the time horizon of the model was reduced to 4 years versus the 6 years used by the manufacturer and

using the manufacturer's assumption that subsequent treatments do not affect overall survival. The extra costs associated with crizotinib were \$36,548 and the extra QALYs associated with crizotinib were 0.211 (10.97 weeks).

The Economic Guidance Panel's estimated differed from the submitted estimates. This is primarily because in the submitted model, progression-free survival and overall survival were extrapolated using short term data. The Clinical Guidance Panel had previously determined that survival benefits with crizotinib as 1st line treatment would not be anticipated beyond the 36 months clinical trial duration (PROFILE 1014). In addition, 1st line crizotinib was significantly influenced by assumptions on post-progression probability of mortality for subsequent treatments. Therefore, in the Economic Guidance Panel reanalyses, time horizon was shortened to align with the clinical data, and individual post-progression probabilities of mortality for each subsequent treatment were applied. This reduces the extra QALY gains for crizotinib and leads to a decrease in the extra healthcare-associated costs for crizotinib.

According to the economic analysis that was submitted by the manufacturer; crizotinib, was used as 1st line therapy (base-case analysis) and compared to standard of care in previously untreated patients over a 6-year time horizon.

- The extra cost (ΔC) of crizotinib was \$37,366. Costs included drug treatment acquisition cost, molecular diagnostic testing cost, and administration and monitoring costs. The model also incorporated costs of adverse events (grade 3 or 4) as well as cost of palliative care.
- The extra clinical effect (ΔE) of crizotinib is 0.243 QALYs or 0.166 life years gained (LYG). Key efficacy outcomes considered in the model provided by the submitter were overall survival, progression-free survival and utilities
- Incremental costs and effects for crizotinib were based on the assumption that survival benefits are extended beyond the trial duration.

So, the Submitter estimated that, based on a submitted list price (\$146.67 per tablet), the incremental cost-effectiveness ratio ($\Delta C/\Delta E$) was \$153,597 per QALY or \$224,872 per LYG.

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC , ΔE and the ICER differ from the Submitter's, what are the key reasons?

The manufacturer submitted a model that assumed survival benefits extending beyond the clinical trial duration or median follow-up periods. The Clinical Guidance Panel had previously determined that assuming such benefit effect may not be a realistic expectations and that survival benefits would not be anticipated beyond the 36 month trial duration for PROFILE 1014. The Economic Guidance Panel estimate for 1st line crizotinib is based on a reanalysis which assumed that the time horizon of the model was reduced to align with the short term data for progression free survival and overall survival. To estimate the life-year gain, post-progression mortality risk was obtained from Kaplan-Meier curves of observed survival data from the PROFILE 1014 study and applied to subsequent treatments. This approach assumed that second-line mortality risk is dependent on the first-line treatment. For example, in the case of crizotinib in 1st line followed by pemetrexed/platinum in 2nd line, both the pre and post-progression mortality rates are obtained from the same crizotinib calibrated survival curve; the pre-progression mortality rate is used for crizotinib during the first-line phase, and the post-progression mortality

rate is applied when the patient is treated with pemetrexed/platinum 2nd line and docetaxel 3rd line treatment. The Economic Guidance Panel estimate for 1st line crizotinib is based on a reanalysis that separately modelled the contribution of each subsequent treatment to overall survival.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

Yes. Based on patient advocacy group input, patients considered the following factors important in the review of crizotinib and which were relevant to the economic analysis: improvement in treatment effect and patient's quality of life, treatment that will enable them to save more time-off from work, and oral administration of crizotinib. These factors were addressed in the economic analysis when possible and appropriate.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

Yes. The model structure was adequate and no changes in structure are required.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

In the submitted economic model, for 1st line crizotinib, the submitter assumes that over a 6-year period, a patient's risk of dying following tumour progression would be improved with crizotinib even though treatment with crizotinib would have been stopped early in the 6-year time period. The time horizon of the data collected from the PROFILE 1014 trial is short (36 months) in comparison with the 6 year time horizon of the model. Based on input from the CGP, there would be a lack of any meaningful clinical benefit beyond the 3 years of the trial period, and therefore a shorter time horizon was used until longer term data is available to suggest more prolonged benefit. Therefore, assumptions around extrapolation using short term data could have an unrealistic effect on clinical effect estimates. Overall, this has an impact on the cost-effectiveness estimates and the Economic Guidance Panel conducted reanalyses to address these limitations, which led to higher estimates of the ICUR for crizotinib.

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

Estimates of the long term survival gains with treatment were uncertain due to an assumption relating to the selection of subsequent treatment not having an effect on overall survival. The EGP relied on the pCODR Clinical Guidance Panel to inform assumptions on survival once disease progression is observed and attempted to conduct reanalyses where it is assumed that a patient's risk of dying after tumour progression differ were related to the subsequent treatment.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The manufacturer's one-way sensitivity analyses indicated that estimating for the number of ALK positive NSCLC patients, varying attrition rates, and % of population covered by public drug plans resulted in the most impact on the results. The manufacturer's model also considered the use of crizotinib as 2nd line treatment.

What are the key limitations in the submitted budget impact analysis?

The submitted budget impact analysis is well-designed with standard methods to calculate incidence and prevalence. Methods to elicit numbers of eligible patients appear to be appropriate. The major limitations are the accuracy over the estimates of above factors in addition to market share being key drivers to the results.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

- long term data to evaluate these assumptions are needed as a focus of further research
- Availability of crizotinib data from clinical trials with longer term follow-up periods should be a focus of further research. Such long-term data can improve the determination of efficacy of crizotinib beyond 36 months and the estimation of patients' risk of dying after tumour progression is detected.

Is there economic research that could be conducted in the future that would provide valuable information related to crizotinib in this context?

If crizotinib becomes a standard treatment option for ALK positive NSCLC patients, an assessment of effectiveness and cost-effectiveness of treatment sequences of crizotinib and other treatments for ALK positive NSCLC would also provide a more accurate reflection of real-world cost-effectiveness and may improve estimates of budget impact.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Lung Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of crizotinib (Xalkori) resubmission for NSCLC. A full assessment of the clinical evidence of crizotinib (Xalkori) resubmission for NSCLC is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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