PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

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

October 4, 2012

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis submitted to pCODR by Pfizer Canada Inc. compared 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. This patient population reflects the expanded cohort of ALK positive NSCLC (Study A8081001, Camidge et al. 2011). Study A8081001 was a two-part phase 1/2 trial, originally designed as a phase 1 dose-escalation study in patients with any tumor type (except leukemia) to evaluate the safety and pharmacokinetics of the maximum tolerated dose of crizotinib. However, an expanded cohort (recommended phase 2 dose cohort) enrolling patients with ALK-positive NSCLC was established following evidence of improvements among patients with ALK-positive NSCLC treated with crizotinib. Crizotinib is administered orally. Current standard of care in Canada for NSCLC includes gemcitabine/cisplatin (administered intravenously) as 1st line, to be followed by pemetrexed (administered intravenously) as 2nd line and erlotinib (administered orally) as 3rd line.

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

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: molecular testing for ALK mutation in NSCLC patients, crizotinib's place in current treatment algorithms for NSCLC, dosing and oral administration of crizotinib. A full summary of Provincial Advisory Group input is provided in the pCODR Clinical Guidance Report.

- Costs of molecular testing for ALK mutation in NSCLC were not included in the base case analysis, but as part of a scenario analysis in the submitted model.
- 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.

At the confidential price, crizotinib costs $[redacted] per 200 mg and 250 mg tablets. *(Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by*

manufacturer that it can be publicly disclosed). At the recommended dose of 250 mg twice daily, the average cost per day in a 28-day course of crizotinib is $[redacted] and the average cost per 28-day course is $[redacted]. (*Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure 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 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.

1.2 Summary of Results

The Economic Guidance Panel's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $240,972 per QALY and $255,976 per QALY when 1st line crizotinib is compared to standard of care (defined as 1st line gemcitabine/cisplatin followed by 2nd line pemetrexed and 3rd line erlotinib). This estimate is based on reanalyses conducted by the Economic Guidance Panel using the confidential 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 (ΔQALY or ΔLY). The Economic Guidance Panel's best estimate of:

- The extra cost (ΔC) of crizotinib is between $82,752 and $83,118.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 (ΔQALY or ΔLY) of crizotinib is between 0.323 QALYs (16.8 weeks) and 0.345 QALYs (17.9 weeks) or between 0.464 (24.1 weeks) and 0.502 (26.1 weeks) life years. Key clinical effects included progression-free survival and overall survival estimates from A8081001 trial (Camidge et al.) and utility values derived from the literature. The biggest influence on both QALYs and life years was the post progression probability of mortality and time horizon.

This range is based on Economic Guidance Panel reanalyses that assumed the model's time horizon to be shorter than the proposed lifetime time horizon modelled by the manufacturer. The assumption that the time horizon should be reduced was supported by the pCODR Lung Clinical Guidance Panel.

- The upper estimate of the range (ICER of $255,976) assumed that the time horizon of the model was reduced to 2 years versus the 6 years modelled by the manufacturer in addition to increasing the monthly post-progression probability of crizotinib by 50% as suggested by the CGP. The extra costs associated with crizotinib were $82,752 and the extra QALYs associated with crizotinib were 0.323.

- The lower estimate of the range (ICER of $240,972) assumed that the time horizon of the model was reduced to 2 years versus the 6 years used by the manufacturer without varying the monthly post-progression probability of mortality. The extra costs associated with crizotinib were $83,118 and the extra QALYs associated with crizotinib were 0.345.

Using the **wholesale price of crizotinib ($146.67 per tablet)**; the EGP's best estimate of the incremental cost-effectiveness ratio (ΔC/ΔE) is **between $283,303 per QALY and $301,141 per QALY**.

The Economic Guidance Panel's estimates differed from the submitted estimates. This is primarily because in the submitted model, it was assumed that a patient's risk for dying before tumour progression is equal to the patient's risk of dying after tumour progression, and that progression-free survival and overall survival were extrapolated using short term data. The Lung Clinical Guidance Panel determined that assuming equal or similar risks of dying pre and post progression did not appropriately reflect realistic clinical practice and that survival benefits would not be anticipated beyond the 24 months clinical trial duration. Therefore, in the Economic Guidance Panel reanalyses where the time horizon was shortened to align with clinical data and a 50% increase in probability of dying post-progression was applied, extra QALY gains for crizotinib are lower and lead 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 (base-case analysis) and compared to standard of care in previously untreated patients over a 6-year time horizon with mortality probabilities assumed to be equal pre and post-progression.

- The extra cost (ΔC) of crizotinib was $[redacted]. (*Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed*). Incremental costs for crizotinib were based on the assumption that a patient's risk of dying before tumour progression is equal to the patient's risk of dying after tumour progression.
- The extra clinical effect (ΔE) of crizotinib is 0.908 QALYs or 1.492 life years gained (LYG). This was largely driven by the assumption that a patient's risk of dying before tumour progression is equal to the patient's risk of dying after tumour progression.

So, the Submitter estimated that, based on a **confidential price ($[redacted] per tablet)**, the incremental cost-effectiveness ratio (ΔC/ΔE) was **$[redacted] per QALY or $[redacted] per LYG**. (*Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed*).

Using the **wholesale price of crizotinib ($146.67 per tablet)**; the Submitter's best estimate of the incremental cost-effectiveness ratio (ΔC/ΔE) of crizotinib as 1st line treatment in ALK positive patients was **$141,787 per QALY or $86,336 per LYG**.

In addition, **according to a sensitivity analysis submitted by the manufacturer**, crizotinib was used as 2nd line treatment in *ALK* positive patients in comparison with pemetrexed single agent under the same assumptions as in the base-case (i.e. time horizon and mortality probability).

- The extra cost (ΔC) of crizotinib was $[redacted]. (*Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed*). Incremental costs for crizotinib were also based on the assumption that a patient's risk of dying before tumour progression is equal to the patient's risk of dying after tumour progression.
- The extra clinical effect (ΔE) of crizotinib is [redacted] QALYs or [redacted] life years gained (LYG). (*Non-disclosable economic information was used in this pCODR Guidance Report*

and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed). This too was largely driven by the assumption that a patient's risk of dying before tumour progression is equal to the patient's risk of dying after tumour progression.

Therefore, use of crizotinib as 2nd line in *ALK* positive patients resulted in an estimated incremental cost-effectivess ratio (ΔC/ΔE) of $[redacted] per QALY or $[redacted] per LYG. *(Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).*

Using the **wholesale price of crizotinib ($146.67 per tablet)**; the Submitter's best estimate of the incremental cost-effectiveness ratio (ΔC/ΔE) of crizotinib as 2nd line treatment in ALK positive patients was **$[redacted] per QALY or $[redacted] per LYG** *(Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).*

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 a patient's risk of dying before tumour progression and the patient's risk of dying after tumour progression are equivalent, hence the model implicitly assumed that patients continued to benefit from the drug as if there was carry-over beneficial effect of the drug even after tumour progression has occurred and the drug has been stopped. The Clinical Guidance Panel determined that assuming such a beneficial effect may not be a realistic expectation and that survival benefits would not be anticipated beyond the 24 months clinical trial duration. The Economic Guidance Panel estimate 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 while also changing the risk of death after tumour progression to be different from the risk of death before tumour progression.

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, it was assumed that a patient's risk of dying before tumour progression is equal to the patient's risk of dying after tumour progression. However, the pCODR Lung Clinical Guidance Panel supported that these risks may differ. 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 model implicitly assumed that patients continued to benefit from the drug as if there was carry-over beneficial effect of the drug even after tumour progression has occurred and the drug has been stopped. The time horizon of the data collected from the A8081001 trial is short (24 months) in comparison with the 6 year time horizon of the model. Therefore, assumptions around extrapolation using short term data could have a pronounced 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 ICER.

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?

The utility data used were adequate and the EGP would have used similar data. However, the cost data were uncertain due to a probable underestimation in the cost of ALK-mutation testing and associated systems costs. In addition, estimates of the long term survival gains with treatment were uncertain due to an assumption relating to improved survival post progression and the EGP would have used more recently available clinical data which might have accounted for differences in risk of death before and after tumour progression. In the absence of this data, the EGP relied on the pCODR Lung Clinical Guidance Panel to inform assumptions and clinical estimates, and attempted to conduct reanalyses where it is assumed that a patient's risk of dying before tumour progression and the patient's risk of dying after tumour progression differ.

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 disease prevalence, tissue availability, uptake of ALK testing, dose intensity, 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. The submitted model did not consider the variation in the cost of ALK mutation testing. 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 and uptake of ALK testing which are key drivers to the results.

1.5 Future Research

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

- The economic evaluation of crizotinib as 1st line treatment could have been improved by including efficacy data from clinical trials that included a sufficient patient population size of previously untreated NSCLC patients.
- Long term data to evaluate the clinical assumptions are needed.
- 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 24 months and the estimation of patients' risk of dying after tumour progression has occurred.

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

- A proper estimation of the costs of the ALK test would allow for cost-effectiveness analyses that include both crizotinib costs and ALK-testing costs. In addition to the ALK test costs, there are costs involved in the production and reporting of the ALK test results such as technician, technologist and pathologist work. This information varies from province to province and from institution to institution.

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. A full assessment of the clinical evidence of crizotinib 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.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from this publicly available Guidance Report.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final 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.pcodr.ca). 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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