PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

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

May 2, 2013

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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 1001 study, Camidge et al. 2012). PROFILE 1001 study is an ongoing 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 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 similar indication. Most of the economic model's input parameters have remained unchanged; however, some changes are noted as follows:

- Probabilities for progression and mortality have been updated from the PROFILE 1001 study.
- Pre-progression mortality has been increased by 50% upon progression in accordance with previous EGP recommendations.
- The unit cost of crizotinib used in the economic analysis has been increased from $[redacted] per 200 and 250 mg tablets to $146.67 per 200 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).*

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 included in the base case analysis. As these were assumed equal in both arms (crizotinib/pemetrexed/docetaxel vs. gemcitabine/platinum agent/pemetrexed/erlotinib), there is no incremental impact of testing in the base case analysis.
- 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 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 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) for 1st line crizotinib is between $124,472 per QALY and $246,117 per QALY when compared to standard of care (defined as 1st line gemcitabine/cisplatin followed by 2nd line pemetrexed and 3rd line erlotinib). For 2nd line crizotinib, the Economic Guidance Panel's best estimate of the incremental cost-effectiveness ratio is between $140,561 per QALY and $216,050 per QALY when compared to pemetrexed. 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 (ΔQALY or ΔLY).

For 1st line crizotinib, the Economic Guidance Panel's best estimate of:

- The extra cost (ΔC) of crizotinib is between $118,764 and $180,973.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 0.483 QALYs (25 weeks) and 1.454 QALYs (76 weeks) or between 0.712 (37 weeks) and 2.385 (124 weeks) life years. Key clinical effects included progression-free survival and overall survival estimates from PROFILE 1001 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 Clinical Guidance Panel.

- The upper estimate of the range (ICER of $246,117) assumed that the time horizon of the model was reduced to 2 years versus the 6 years modeled by the manufacturer.

The extra costs associated with crizotinib were $118,764 and the extra QALYs associated with crizotinib were 0.483.

- The lower estimate of the range (ICER of $124,472) assumed that the time horizon of the model was maintained at 6 years used by the manufacturer without any variation of the monthly post-progression probability of mortality by the Economic Guidance Panel. The extra costs associated with crizotinib were $180,973 and the extra QALYs associated with crizotinib were 1.454.

For 2nd line crizotinib, the Economic Guidance Panel's best estimate of:

- The extra cost (ΔC) of crizotinib is $23,260. 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 0.108 QALYs (5.6 weeks) and 0.165 QALYs (8.6 weeks) or 0.154 (8 weeks) life years. Key clinical effects included progression-free survival and overall survival estimates from PROFILE 1007 trial (Shaw et al. 2012) and *utility values derived from the literature*. The biggest influence on both QALYs and life years were the health state utility values 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. This conservative assumption that the time horizon should be reduced was supported by the pCODR Clinical Guidance Panel

The upper estimate of the range (ICER of $216,050) assumed that the time horizon of the model was reduced to 2 years versus the 5 years modeled by the manufacturer and that health utilities from the literature were applied before and after progression. The extra costs associated with crizotinib were $23,260 and the extra QALYs associated with crizotinib were 0.108.

The lower estimate of the range (ICER of $140,561) assumed that the time horizon of the model was reduced to 2 years versus the 5 years used by the manufacturer but with health utilities obtained from the PROFILE 1007 trial until progression occurs, after which the utilities from the literature will be used. The extra costs associated with crizotinib were $23,260 and the extra QALYs associated with crizotinib were 0.165.

At the request of pERC, additional analyses were conducted in the 2nd line setting using a time horizon of 3 and 4 years:

- Using a 3 year time horizon, the resulting ICER ranges from $114,993 per QALY (using utility values from PROFILE 1007) to $157,671 per QALY (using published utility values)
- Using a 4 year time horizon, the resulting ICER ranged from $98,834 per QALY (using utility values from PROFILE 1007) to $127,920 per QALY (using published utility values).

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 24 months clinical trial duration (PROFILE 1001). This was also applied for crizotinib as 2nd line treatment (PROFILE 1007). In addition, 2nd line crizotinib

was significantly influenced by health utility values obtained from the PROFILE 1007 trial. Therefore, in the Economic Guidance Panel reanalyses, time horizon was shortened to align with the clinical data, and for 2nd line crizotinib, health utilities from the literature 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** (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 $180,973.
- The extra clinical effect (ΔE) of crizotinib is 1.454 QALYs or 2.385 life years gained (LYG).
- 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 wholesale list price ($146.67 per tablet)**, the incremental cost-effectiveness ratio (ΔC/ΔE) was **$124,472 per QALY or $75,882 per LYG**.

According to the economic analysis that was submitted by the manufacturer; crizotinib, when used **as 2nd line** (scenario analysis) and compared to standard of care over a 5-year time horizon.

- 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).*
- 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).*
- The incremental costs and effects were largely driven by the assumptions that survival benefits extend beyond the duration of the clinical trial and that crizotinib is associated with significant improvements to quality of life.

So, the Submitter estimated that, based on a **submitted wholesale list price ($146.67 per tablet)**, the incremental cost-effectiveness ratio (ΔC/ΔE) was **$88,982 per QALY or $67,762 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 24 months PROFILE 1001 clinical trial duration or the 33 week median treatment duration for PROFILE 1007. 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. For 2nd line crizotinib, in addition to the extended time horizon of 5 years, the manufacturer had applied EQ-5D utility values obtained from the PROFILE 1007 study. Quality of life was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and its 13-item lung-cancer specific module (EORTC QLQ-LC13) and was converted to EQ-5D utilities. Quality of life results from in-trial populations are acknowledged to be more reliable than published figures. However, with insufficient information provided on the methodology used in the collection of quality of life information and the calculations applied to convert them to EQ-5D values, concerns of uncertainty and possible introduction of bias become apparent and warrant careful consideration when applying these values in the economic evaluation of 2nd line crizotinib. The Economic Guidance Panel's estimates for 2nd line crizotinib were based on reducing the time horizon in addition to applying utility values from published literature.

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 1001 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. This assumption is also evident in the analysis for 2nd line crizotinib in which the submitter used a 5-year time horizon, a duration that extends beyond the trial's median treatment duration of 33 weeks (range of 3 to 111 weeks). 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 in both lines of therapy.

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 for 1st line crizotinib was adequate and the EGP would have used similar data. However, for 2nd line crizotinib, the utility data used by the manufacturer was obtained from the trial but raises uncertainty due to lack of information on the methodology used to calculate the utilities; the EGP would have used utility values from published literature instead. The cost data was 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 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. 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 these assumptions are needed as a foci 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 24 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?

- 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 (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.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.

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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