CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

# pan-Canadian Oncology Drug Review
# Final Economic Guidance Report

# Ceritinib (Zykadia) Resubmission for Metastatic Non-Small Cell Lung Cancer

**March 21, 2017**

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# FUNDING

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## INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

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# 1 ECONOMIC GUIDANCE IN BRIEF

## 1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Novartis Pharmaceuticals Canada Inc.** compared ceritinib monotherapy to standard second-line chemotherapy (pemetrexed or docetaxel) for patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have progressed on or who were intolerant to crizotinib.

**Table 1. Submitted Economic Model**

| | |
|---|---|
| Funding Request/Patient Population Modelled | *Yes for patients who have progression following crizotinib. For those intolerant to crizotinib, no the funding request does not match the trial population, however, the CGP thinks that there would be few instances where a patient would be intolerant to crizotinib.* |
| Type of Analysis | *CUA & CEA* |
| Type of Model | *Semi-Markov three-state partitioned survival model* |
| Comparator | *Standard second-line chemotherapy (pemetrexed or docetaxel) or best supportive care or historical controls* |
| Year of costs | *2016* |
| Time Horizon | *5 years* |
| Perspective | *Public health payer* |
| Cost of ceritinib | At the list price ceritinib costs $67.47 per 150mg capsule. At the recommended dose of 750 mg per day, ceritinib costs<br>• $337.35 per day<br>• $9445.80 per 28-day course |
| Cost of pemetrexed<br>** Price Source: QuintilesIMS accessed [November 7, 2016]* | At the list generic price pemetrexed costs $0.8318 per mg. At the recommended dose of 500 mg/$m^2$ every 21 days, pemetrexed costs<br>• $33.67 per day<br>• $942.66 per 28-day course |
| Cost of docetaxel<br>** Price Source: QuintilesIMS accessed [November 7, 2016]* | At the list price docetaxel costs $11.42per mg. At the recommended dose of 75 mg/$m^2$ every 3 weeks, docetaxel costs<br>• $69.36 per day<br>• $1,942.00 per 28-day course |
| Model Structure | The model was comprised of three health states: stable disease, progression and death. Patients were defined to be in the stable disease if they were treated with initial treatment and had not yet progressed. They could then transition to progressive disease or death, or remain in stable disease. Patients were defined to be in progressive disease if they had progressed during or after treatment. Patients in progressive disease state could transition to death or remain in progressive disease. |
| Key Data Sources | *ASCEND-5*<br>*Literature for alternative comparators* |
| **Drug costs for all comparators in this table are based on costing information under license from QuintilesIMS concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian* | |

| | |
|---|---|
| Funding Request/Patient Population Modelled | *Yes for patients who have progression following crizotinib. For those intolerant to crizotinib, no the funding request does not match the trial population, however, the CGP thinks that there would be few instances where a patient would be intolerant to crizotinib.* |
| *Agency for Drugs and Technologies in Health and not those of QuintilesIMS.* | |

## 1.2 Clinical Considerations

**According to the pCODR Clinical Guidance Panel (CGP)**, this comparison is appropriate. (*If applicable:* Relevant issues identified included:

- There is a net overall clinical benefit with the use of ceritinib in patients with ALK+ locally advanced or metastatic NSCLC who have progressed on or who were intolerant to crizotinib.
- Based on currently available data, it is the CGP's expert opinion that the most appropriate use of ceritinib is following disease progression on crizotinib and prior to the use of chemotherapy doublet.
- The CGP agree that the expected place of therapy for ceritinib would be prior to the use of a platinum doublet.
- The CGP agreed there was a reasonable number of patients with brain metastasis at baseline to generalize the overall trial results and conclude that ceritinib is effective in patients with brain metastasis. Data from ongoing clinical trials are expected to further clarify the role of ceritinib in patients with ALK+ NSCLC who present with brain metastases (previously untreated). The results of ongoing trials may further clarify the role of ceritinib in other lines of therapy or with tumours that harbor alternative gene alterations such as ROS1 or ALK-over expression.
- In instances where patients may develop intolerance to crizotinib, which are expected to be very few, the CGP agreed that ceritinib would be a reasonable treatment alternative as long as patients have previously been treated with a systemic therapy. In the opinion of the CGP, it is also unlikely that ceritinib will move up to first line in view of the lack of clinical data with ceritinib as opposed to other agents being studied in this space.

**Summary of registered clinician input relevant to the economic analysis**
Registered clinicians considered the oral administration of ceritinib and favourable adverse event profile as benefits to patients. The lack of drug administration costs and the adverse event profile of ceritinib were considered in the economic analysis.

**Summary of patient input relevant to the economic analysis**
**Patients** considered a fast response and feeling better as important in their treatment for non-small cell lung cancer. Quality of life and increased survival were considered in the economic analysis.

**Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis**
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for ceritinib, which are relevant to the economic analysis.

<u>Enablers to implementation:</u>

- Oral treatment option, meaning less resources for drug administration compared to chemotherapy; and
- Flat dosing, easy to adjust doses which reduces wastage.

Barriers to implementation:

- Addition of a third-line of oral therapy, with additional costs of subsequent treatments upon progression on ceritinib; and
- High cost of ceritinib.

## 1.3 Submitted and EGP Reanalysis Estimates

**Table 2 Submitted and EGP Estimates**

| Estimates (range/point) | Submitted | EGP Reanalysis Lower Bound | EGP Reanalysis Upper Bound |
|---|---|---|---|
| ΔE (LY) | 1.11 | 0.85 | 0.85 |
| Progression-free | 0.34 | 0.34 | 0.34 |
| Post-progression | 0.76 | 0.51 | 0.51 |
| ΔE (QALY) | 0.59 | 0.47 | 0.47 |
| Progression-free | 0.24 | 0.24 | 0.24 |
| Post-progression | 0.35 | 0.23 | 0.23 |
| ΔC ($) | $70,293 | $75,766 | $98,829 |
| ICER estimate ($/QALY) | $118,676 | $159,750 | $208,377 |

**The main assumptions and limitations with the submitted economic evaluation were:**

- *Source of efficacy data: the overall survival estimates for the chemotherapy arm are taken from the general NSCLC population due to lack of mature data from the ASCEND 5 trial. However, the population in the ASCEND 5 trial is for ALK+ NSCLC population. The EGP, in consultation with the CGP, noted that ALK+ NSCLC patients live longer than general NSCLC patients, and the use of data from the general NSCLC population, which is modeled here, is therefore considered to be inappropriate and may underestimate overall survival in the comparator arm.*
- *Overall survival benefit and impact of cross-over in clinical trial: Based on the clinical trial data, the OS results were immature and likely to be confounded by extensive crossover of patients from the chemotherapy group, upon disease progression. A scenario analysis was presented to adjust for confounding due to crossover however, the approach did not have a significant impact on the HR estimate for overall survival. The CGP also noted that there is currently no evidence to support an OS benefit with the use of ceritinib. The economic model does not have, however, an option to examine overall survival using a hazard ratio model, therefore the impact of using an alternative HR for overall survival on the results could not be examined.*
- *Utility values: The submitter assumed that health utilities in the model depend only on health state and adverse events, and pooled results from the ASCEND-5 from both treatment arms to inform this. This method may over or under-estimate the utility for either of the treatment arms if the adverse event profile differs between treatments. For example, the ASCEND 5 trial reported higher rates of all grades, grade 3 or 4 and serious grade 3 or 4 adverse events in the ceritinib arm compared to the chemotherapy arm. Therefore using a pooled utility value overestimates the utility of ceritinib in the economic model, while underestimating the utility in the chemotherapy arm. Finally, the CGP expressed concerns about the high relative values of the utilities, given the adverse event profile observed in the trial, and the disease (NSCLC) itself. The EGP was unable to do reanalysis using separate utility values for each treatment group as the model did now have this function.*
- *Post-progression benefit: The submitted base case analysis had a large incremental gain in effectiveness for ceritinib compared to combined chemotherapy in the post progression health state. Given the lack of clinical rational to support a larger post progression gain I*

*QALY's than when patients are on treatment, the EGP attempted to minimize this post-progression gain in QALY's by using the Gompertz parametric curve for the modelling of overall survival.*

- *Subsequent therapies: Based on the clinical population in whom the CGP made a conclusions, the EGP considered that ceritinib is likely to be used as a second line therapy, following failure on crizotinib but prior to the use of a platinum doublet. This sequencing would then allow for treatment following ceritinib with a platinum-doublet. To account for this scenario, which may likely represent the clinical population, the EGP considered a scenario analysis where 50% of patients following progression on ceritinib received a platinum doublet as a subsequent treatment.*
- *Treatment duration: Based on CGP opinion, the EGP considered two scenarios to present treatment duration.*
    - *Patients in the trial were allowed to continue treatment beyond disease progression; however, treatment duration in the submitted base case economic model did not consider the possibility of patients receiving treatment beyond progression. The EGP therefore explored a scenario where patients continue ceritinib treatment beyond progression (a reflection of the clinical trial data); or*
    - *Based on input from the CGP, patients in the clinical setting may not be given the option to continue ceritinib beyond progression as the expected place in therapy for ceritinib is likely to be considered second line following crizotinib. Following that, patients would be eligible to receive a platinum doublet as a third line treatment. The EGP therefore explored a second scenario where patients would cease treatment with ceritinib at disease progression and 50% of patients would receive a platinum doublet (a reflection of using ceritinib as a second line therapy following crizotinib).*
- *Cost of pemetrexed: The cost used for pemetrexed in the model is significantly higher than the generic list price of pemetrexed, which is currently available. The EGP used the generic list price in their re-analysis estimates.*

## 1.4 Detailed Highlights of the EGP Reanalysis

**The EGP made the following changes to the submitted economic model:**

**The EGP made the following changes to the economic model:**

- Subsequent therapy for ceritinib: In the clinical trial, only 3.5% of patients in the ceritinib went on to receive a platinum doublet therapy. Based on input from the CGP, and in alignment with the expected clinical population in whom ceritinib is likely to be used (ie patients who have been previously treated with crizotinib only and naïve to a platinum doublet), patients would then be eligible to receive a platinum doublet following progression on ceritinib. Input from the CGP suggested that the proportion of patients who would be eligible for subsequent combination chemotherapy would be around 50%. In order to accommodate the increase in the proportion of ceritinib patients receiving platinum doublet, the proportion of those receiving best supportive care was reduced.
- Treatment duration. In the economic model, treatment is continued until discontinuation or progression. In the clinical trial, a large proportion of patients continued on ceritinib post-progression, as allowed in the trial protocol, based on the judgement of the investigators. Based on conclusions made by the CGP, ceritinib is likely to be discontinued following disease progression as patients could benefit from treatment with the platinum doublet post-progression and therefore treatment with ceritinib may be appropriate only until progression. This would be in alignment with the CGP's conclusion that ceritinib is likely to be used following failure on crizotinib and before a platinum doublet. The EGP reanalyses examined

both ceritinib treatment until disease progression and ceritinib treatment beyond disease progression as part of the upper and lower bounds of its re-analysis estimates.

- OS parametric curve for ceritinib: The exponential has a higher AIC than the Gompertz function, and visually does not fit the clinical course of the disease as well. Further, using a Gompertz curve reduces the gains seen in the post-progression state. The EGP and CGP acknowledged that a gain in the post progression state may be possible given that a large number of patients who continued to receive ceritinib beyond progression. However, it is unlikely to have more QALY gains in the post-progression state than on treatment for ceritinib, as is reported for the base case analysis.
- Reduction in cost of comparator. The cost used for pemetrexed in the model is significantly higher than the generic list price of pemetrexed. The EGP therefore used the generic list price of pemetrexed in their reanalysis.

**Table 3. EGP Reanalysis Estimates**

| Description of Reanalysis | ΔC | ΔE QALYs | ICUR (QALY) | Δ from baseline submitted ICER |
|---|---|---|---|---|
| *Submitted base case* | $70,293 | 0.59 | $118,676 | ----- |
| **EGP's Reanalysis for the Best Case Estimate** | | | | |
| *1. Generic cost of pemetrexed* | $74,913 | 0.59 | $126,476 | $7,800 |
| *2. Overall survival parametric curve - Gompertz* | $70,041 | 0.47 | $147,678 | $29,002 |
| *3. Subsequent therapy ceritinib - 50% platinum doublet* | $71,992 | 0.59 | $121,544 | $2,868 |
| **LOWER BOUND** | | | | |
| *4. Treatment duration - treatment until progression* | $69,085 | 0.59 | $116,636 | -$2,040 |
| Best case estimate of lower bound (1+ 2 + 3 + 4) | $75,766 | 0.47 | $159,750 | $41,074 |
| **UPPER BOUND** | | | | |
| *5. Treatment duration - treatment until discontinuation* | $95,131 | 0.59 | $160,610 | $41,934 |
| Best case estimate of upper bound (1+ 2 + 3 + 5) | $98,829 | 0.47 | $208,377 | $89,701 |

## 1.5 Evaluation of Submitted Budget Impact Analysis

Secondary to drug costs, the factors that most influence the budget impact analysis include the prevalence of lung cancer and the % of adenocarcinoma with ALK+ NSCLC.

Key limitations of the BIA model include the use of the most expensive chemotherapy in the comparator arm, at brand pricing. Should cheaper chemotherapies (ie. docetaxel) have been included, this would have impacted the BIA and increased the incremental cost between the reference scenario and the treatment-funded scenario, increasing the magnitude of the 3-year budgetary impact.

## 1.6 Conclusions

**The EGP's best estimate of ΔC and ΔE for ceritinib when compared to chemotherapy (pemetrexed or docetaxel) is:**

- Between $159,750/QALY and $208,377/QALY, depending on whether treatment is until progression or until discontinuation, respectively.
- The extra cost of ceritinib is between $75,766 and $98,829. *The main factors that most influence ΔC are treating until discontinuation and the relative dose intensity.*
- The extra clinical effect of ceritinib is 0.47 (ΔE). *The main factors that most influence ΔE are the time horizon and the parametric curve used to model overall survival.*

**Overall conclusions of the submitted model:**

- *The main limitation in the model is the inability of the EGP to adjust assumptions for overall survival benefit. Based on the trial data and the CGP opinion, there is currently no evidence to support an OS benefit with ceritinib. The EGP was however unable to alter this parameter to model no OS benefit. In addition, the EGP was unable to adjust utility values based on treatment option, given the evidence from the ASCEND-5 trial that found that ceritinib is more toxic than chemotherapy (pemetrexed or docetaxel). The magnitude of impact on the ICER of using the same utility values across treatment options is however unknown.*
- *The use of the brand price of pemetrexed favours ceritinib. Using the generic price of pemetrexed raises the ICER.*

# 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 ceritinib (Zykadia) resubmission for metastatic non-small cell lung cancer. A full assessment of the clinical evidence of ceritinib (Zykadia) resubmission for metastatic non-small cell lung cancer 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 Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

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.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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