pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

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

December 3, 2015

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Novartis Pharmaceuticals Canada Inc.** compared ceritinib to pemetrexed, best supportive care, a combination of treatments found through a chart review of patients treated with crizotinib ("historical controls") and docetaxel for patients with anaplastic lymphoma kinas (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC). Ceritinib is administered orally. Pemetrexed and docetaxel are administered intravenously. The historical controls contains a mixture of drugs, with a variety of administrations.

The submitter commented on the pCODR Expert Review Committee's (pERC's) Initial Recommendation that one study included in their submission to pCODR was not reviewed. However, pERC had initially reviewed this information in Section 2 (Detailed Technical Report) of the Economic Guidance Report. In this Final Economic Guidance Report, this information has now also been summarized below (Section 1, Economic Guidance in Brief) as Section 2 is not publically available.

A retrospective chart study was conducted to identify treatment patterns, outcomes, and healthcare resource utilization among patients with locally advanced or metastatic ALK+ NSCLC who failed crizotinib in Canada. Data were collected from six oncology centres in Canada, from 2010 to 2015. The economic evaluation included 45 (58.4%) patients who failed crizotinib treatment only. The majority of patients were female, Caucasian, with a median age at primary diagnosis of NSCLC of approximately 54.7 years. The most commonly administered therapy after crizotinib were ceritinib, pemetrexed, and no further systemic treatment (best supportive care). Progression-free survival and overall survival was longer for those who were treated with ceritinib compared to patients who did not receive ceritinib post crizotinib failure. As clinical care for NSCLC varies across Canada, given that the chart review was not representative of all Canadian centres, the generalizability of the results of this comparator is limited. Retrospective case studies are generally considered low quality evidence that are susceptible to many forms of bias, including, but not limited to, incomplete data collection and selection bias.

According to the pCODR Clinical Guidance Panel (CGP), these comparators are appropriate, though there is no standard of care in Canada for the treatment of ALK+ NSCLC in the second-line.

Patients considered the following factors important in the review of ceritinib, which are relevant to the economic analysis: side effects profile, quality of life and access to additional therapies to extend life. The economic model incorporated adverse events, as well as survival and quality of life.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for ceritinib, and which are relevant to the economic analysis:

- Lack of comparative data, including phase III trials;
- Replacement of intravenous therapies (and therefore less costly);
- Extended treatment options with another line of therapy;
- Overall number of patients to be treated with ceritinib is likely to be small;
- Sequencing of drugs if crizotinib were to be first-line and ceritinib in second line (or first-line);
- Wastage is a minimal factor given that there are five capsules to be taken and dose reductions can be managed with reducing the number of capsules; and
- The high cost of ceritinib.

Ceritinib costs $67.47 per 150 mg tablet. At the recommended dose of 750 mg orally once daily until progression, the cost of ceritinib is $337.35 per day and $9,445.32 per 28-day course. Pemetrexed costs 4.29 per mg. At the recommended dose of 500 mg/m^2 on day one every 21 days and using the standard pCODR reporting of a body surface area of 1.7m^2, the cost of pemetrexed is $173.64 per day and $4,862.00 per 28-day course.df Docetaxel costs $4.46 per mg. At the recommended dose of 75 mg/m^2 on day one every 21 days, the cost of docetaxel is $27.05 per day and $757.35 per 28-day course. Cisplatin cost $5.86 per mg. At the recommended dose of 75 mg/m^2 on day one every 21 day (in combination with pemetrexed), the cost of cisplatin is $35.57 per day and $996.10 per 28-day course.

1.2 Summary of Results

Ceritinib vs pemetrexed

According to the economic analysis that was submitted by Novartis Pharmaceuticals Inc., when ceritinib is compared with pemetrexed:

- the extra cost of ceritinib is $34,906 (ΔC). Costs considered in the analysis included drug acquisition costs, drug administration costs, resource use, adverse event costs and terminal care costs.
- the extra clinical effect of ceritinib is 0.44 quality-adjusted life years gained (ΔE). The clinical effect considered in the analysis was based on progression-free survival, overall survival, treatment duration, adverse events, utilities and disutilities.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $80,100.

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $196,335 and $211,759 when ceritinib is compared with pemetrexed.

The EGP conducted reanalyses based on the model submitted by Novartis Pharmaceuticals Inc.

For ceritinib vs pemetrexed, the EGP's best estimate reflects changes to multiple variables at the same time. However, when varying each individual variable, the reanalysis conducted by the EGP using the submitted model showed that when:

- The therapies used post-progression for those on ceritinib was changed to 17.6% pemetrexed and 50% single-arm chemotherapy (from 17.6% pemetrexed and 8.8% single-arm chemotherapy), the extra cost of certinib is $40,353 ($\Delta C_1$), and the extra clinical effect is 0.44 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $92,598 (from $80,100).
- The utility used in the model was unadjusted (instead of adjusting for overall response rate), the extra cost of ceritinib is $34,906 ($\Delta C_2$), and the extra clinical effect is 0.43 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $80,830 (from $80,100).
- The mean treatment duration is increased by 20% (as per guidance from the CGP), the extra cost of ceritinib is $68,951 ($\Delta C_3$), and the extra clinical effect is 0.44 (ΔE_3), which increases the estimated incremental cost-effectiveness ratio to $158,222 (from $80,100).

- The cost of treating neutropenia is set to $0 (as per guidance from the CGP), the extra cost of ceritinib is $35,313 ($\Delta C_4$), and the extra clinical effect is 0.44 (ΔE_4), which increases the estimated incremental cost-effectiveness ratio to $81,033 (from $80,100).
- The cost of pemetrexed is lowered by 50% (as per guidance from the CGP, reflecting varying prices across the provinces), the extra cost of ceritinib is $53,839 ($\Delta C_6$), and the extra clinical effect is 0.44 (ΔE_5), which increases the estimated incremental cost-effectiveness ratio to $123,547 (from $80,100).
- The cost of pemetrexed is lowered by 30% (as per guidance from the CGP, reflecting varying prices across the provinces), the extra cost of ceritinib is $46,266 ($\Delta C_5$), and the extra clinical effect is 0.44 (ΔE_5), which increases the estimated incremental cost-effectiveness ratio to $106,168 (from $80,100).

The EGPs estimates differed from the submitted estimates.

Ceritinib vs historical control

According to the economic analysis that was submitted by Novartis Pharmaceuticals Inc., when ceritinib is compared with historical control:

- the extra cost of ceritinib is $72,083 (ΔC). Costs considered in the analysis included drug acquisition costs, drug administration costs, resource use, adverse event costs and terminal care costs.
- the extra clinical effect of ceritinib is 0.69 quality-adjusted life years gained (ΔE). The clinical effect considered in the analysis was based on progression-free survival, overall survival, treatment duration, adverse events, utilities and disutilities.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $104,436.

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $164,503 and 166,201 when ceritinib is compared with historical control.

The EGP conducted reanalyses based on the model submitted by Novartis Pharmaceuticals Inc.

For ceritinib vs historical control, the reanalysis conducted by the EGP using the submitted model showed that when:

- The therapies used post-progression for those on ceritinib was changed to 17.6% pemetrexed and 50% single-arm chemotherapy (from 17.6% pemetrexed and 8.8% single-arm chemotherapy), the extra cost of certinib is $77,529 ($\Delta C_1$), and the extra clinical effect is 0.68 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $112,327 (from $104,436).
- The utility used in the model was unadjusted (instead of adjusting for overall response rate), the extra cost of ceritinib is $72,083 ($\Delta C_2$), and the extra clinical effect is 0.68 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $105,365 (from $104,436).
- The mean treatment duration is increased by 20% (as per guidance from the CGP), the extra cost of ceritinib is $109,180 ($\Delta C_3$), and the extra clinical effect is 0.69 (ΔE_3),

which increases the estimated incremental cost-effectiveness ratio to $158,185 (from $104,436).

- The cost of treating neutropenia is set to $0 (as per guidance from the CGP), the extra cost of ceritinib is $72,598 ($\Delta C_4$), and the extra clinical effect is 0.69 (ΔE_4), which increases the estimated incremental cost-effectiveness ratio to $105,184 (from $104,436).
- The cost of pemetrexed is lowered by 50% (as per guidance from the CGP, reflecting varying prices across the provinces), the extra cost of ceritinib is $73,072 ($\Delta C_5$), and the extra clinical effect is 0.69 (ΔE_5), which increases the estimated incremental cost-effectiveness ratio to $105,869 (from $104,436).
- The cost of pemetrexed is lowered by 30% (as per guidance from the CGP, reflecting varying prices across the provinces), the extra cost of ceritinib is $72,676 ($\Delta C_6$), and the extra clinical effect is 0.69 (ΔE_5), which increases the estimated incremental cost-effectiveness ratio to $105,296 (from $104,436).

The EGPs estimates differed from the submitted estimates.

Ceritinib vs best supportive care

According to the economic analysis that was submitted by Novartis Pharmaceuticals Inc., when ceritinib is compared with best supportive care:

- the extra cost of ceritinib is $79,055 ($\Delta C$). Costs considered in the analysis included drug acquisition costs, drug administration costs, resource use, adverse event costs and terminal care costs.
- the extra clinical effect of ceritinib is 0.53 quality-adjusted life years gained (ΔE). The clinical effect considered in the analysis was based on progression-free survival, overall survival, treatment duration, adverse events, utilities and disutilities.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $149,117.

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $219,353 and $222,335 when ceritinib is compared with best supportive care.

The EGP conducted reanalyses based on the model submitted by Novaris Pharmaceuticals Inc.

For ceritinib vs best supportive care, the reanalysis conducted by the EGP using the submitted model showed that when:

- The therapies used post-progression for those on ceritinib was changed to 17.6% pemetrexed and 50% single-arm chemotherapy (from 17.6% pemetrexed and 8.8% single-arm chemotherapy), the extra cost of certinib is $84,501 ($\Delta C_1$), and the extra clinical effect is 0.53 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $159,390 (from $149,117).
- The utility used in the model was unadjusted (instead of adjusting for overall response rate), the extra cost of ceritinib is $79,055 ($\Delta C_2$), and the extra clinical effect is 0.52 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $151,010 (from $149,117).

- The mean treatment duration is increased by 20% (as per guidance from the CGP), the extra cost of ceritinib is $113,295 ($\Delta C_3$), and the extra clinical effect is 0.53 (ΔE_3), which increases the estimated incremental cost-effectiveness ratio to $213,703 (from $149,117).
- The cost of treating neutropenia is set to $0 (as per guidance from the CGP), the extra cost of ceritinib is $79,055 ($\Delta C_4$), and the extra clinical effect is 0.53 (ΔE_4), which has no impact on the estimated incremental cost-effectiveness ratio.
- The cost of pemetrexed is lowered by 50% (as per guidance from the CGP, reflecting varying prices across the provinces), the extra cost of ceritinib is $77,529 ($\Delta C_5$), and the extra clinical effect is 0.53 (ΔE_5), which decreases the estimated incremental cost-effectiveness ratio to $146,240 (from $149,117).
- The cost of pemetrexed is lowered by 30% (as per guidance from the CGP, reflecting varying prices across the provinces), the extra cost of ceritinib is $78,140 ($\Delta C_6$), and the extra clinical effect is 0.53 (ΔE_6), which decreases the estimated incremental cost-effectiveness ratio to $147,391 (from $149,117).

The EGPs estimates differed from the submitted estimates.

Ceritinib vs docetaxel

According to the economic analysis that was submitted by Novartis Pharmaceuticals Inc., when ceritinib is compared with docetaxel:

- the extra cost of ceritinib is $67,541 ($\Delta C$). Costs considered in the analysis included drug acquisition costs, drug administration costs, resource use, adverse event costs and terminal care costs.
- the extra clinical effect of ceritinib is 0.45 quality-adjusted life years gained (ΔE). The clinical effect considered in the analysis was based on progression-free survival, overall survival, treatment duration, adverse events, utilities and disutilities.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $149,780.

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $241,396 and $244,906 when ceritinib is compared with docetaxel.

The EGP conducted reanalyses based on the model submitted by Novartis Pharmaceuticals Inc.

For ceritinib vs docetaxel, the reanalysis conducted by the EGP using the submitted model showed that when:

- The therapies used post-progression for those on ceritinib was changed to 17.6% pemetrexed and 50% single-arm chemotherapy (from 17.6% pemetrexed and 8.8% single-arm chemotherapy), the extra cost of certinib is $72,987 ($\Delta C_1$), and the extra clinical effect is 0.45 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $161,858 (from $149,780).
- The utility used in the model was unadjusted (instead of adjusting for overall response rate), the extra cost of ceritinib is $67,541 ($\Delta C_2$), and the extra clinical effect is 0.44 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $151,891 (from $149,780).

- The mean treatment duration is increased by 20% (as per guidance from the CGP), the extra cost of ceritinib is $102,781 ($\Delta C_3$), and the extra clinical effect is 0.45 (ΔE_3), which increases the estimated incremental cost-effectiveness ratio to $227,929 (from $149,780).
- The cost of treating neutropenia is set to $0 (as per guidance from the CGP), the extra cost of ceritinib is $79,563 ($\Delta C_4$), and the extra clinical effect is 0.45 (ΔE_4), which increases the estimated incremental cost-effectiveness ratio to $156,481 (from $149,780).
- The cost of pemetrexed is lowered by 50% (as per guidance from the CGP, reflecting varying prices across the provinces), the extra cost of ceritinib is $66,016 ($\Delta C_5$), and the extra clinical effect is 0.45 (ΔE_5), which decreases the estimated incremental cost-effectiveness ratio to $146,397 (from $149,780).
- The cost of pemetrexed is lowered by 30% (as per guidance from the CGP, reflecting varying prices across the provinces), the extra cost of ceritinib is $66,626 ($\Delta C_6$), and the extra clinical effect is 0.45 (ΔE_6), which decreases the estimated incremental cost-effectiveness ratio to $147,750 (from $149,780).

The EGPs estimates differed from the submitted estimates.

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 EGP estimates differed from the submitter's due to the changes as mentioned above. These include changing the proportion of patients on single-arm chemotherapy post-progression on ceritinib, using unadjusted utility estimates, increasing the mean treatment duration, setting the cost of neutropenia to $0 and varying the cost of pemetrexed.

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

Yes, factors important to patients were adequately addressed. These include adverse events, quality of life and overall survival, through access to ceritinib as an additional therapy.

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

The design of the submitted economic model is adequate. It should be noted that in partitioned survival models, it is not possible to examine the impact of post-progression survival. The partitioned survival approach ignores that mortality at any given time is a function of the proportion of the alive population in the post-progression state, which is bounded to 1.

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?

The variables that were assumptions that had the most important effect on the results depended on the comparator chosen. The EGP was able to modify these and produced the best estimates as per above.

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?

Clinical inputs were the best currently available. However, it should be noted that there are no head-to-head clinical trials of ceritinib vs the comparators presented in this analysis. Further, the historical control group was taken from a chart review which represented six oncology centres across Canada and may not be generalizable to current standard of care. The majority of costs considered were reasonable, however, the CGP identified that the cost of treating neutropenia is very unlikely to be the same as febrile neutropenia, and therefore the EGP considered this cost $0 in the best case estimate.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The budget impact analysis was most sensitive to the percent of patients with ALK+ NSCLC with adenocarcinoma. Increasing the proportion of these patients by 3% increased the budget impact by over 50%. The BIA was also sensitive to the prevalence of lung cancer and the proportion of patients with adenocarcinoma (of those with lung cancer).

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

The budget impact analysis excluded the cost of IV drugs and palliative treatments. As all patients under the currently funded scenario receive IV treatments, and the cost of palliative treatments was assumed to be minimal, this resulted in a cost of $0 in the current scenario for years 1, 2, and 3. Excluding the cost of IV treatments assumes that the use of any IV treatments for NSCLC would not differ between the current scenario and a scenario where ceritinib is funded.

1.5 Future Research

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

In the absence of head-to-head clinical trial data, a chart review that is representative of treatment across Canada would increase the generalizability of the results.

Is there economic research that could be conducted in the future that would provide valuable information related to ceritinib for the treatment of ALK+ NSCLC?

Developing clinical trials that include the current standard of care as comparator would greatly inform the cost-effectiveness of ceritinib. PAG identified a trial comparing ceritinib to crizotinib would be particularly useful.

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) for Metastatic Non-Small Cell Lung Cancer. A full assessment of the clinical evidence of Ceritinib (Zykadia) 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.

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.

REFERENCES

1. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *The New England journal of medicine.* Jul 14 2005;353(2):123-132.

2. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *The New England journal of medicine.* Jun 20 2013;368(25):2385-2394.

3. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* May 2000;18(10):2095-2103.

4. Hollander MJ. Costs of end-of-life care: findings from the province of Saskatchewan. *Healthcare quarterly (Toronto, Ont.).* 2009;12(3):50-58.

5. Chouaid C, Agulnik J, Goker E, et al. Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: a prospective cross-sectional patient survey in a real-world setting. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer.* Aug 2013;8(8):997-1003.

6. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health and quality of life outcomes.* 2008;6:84.