PAN-CANADIAN ONCOLOGY DRUG REVIEW

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

# Afatinib (Giotrif) for Advanced Non-Small Cell Lung Cancer

May 2, 2014

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# TABLE OF CONTENTS

# 1 ECONOMIC GUIDANCE IN BRIEF

## 1.1 Background

The main economic analysis **submitted to pCODR by Boehringer Ingelheim** compared afatinib to three comparators – pemetrexed/cisplatin, gefitinib and erlotinib – for first line treatment of locally advanced or metastatic NSCLC with EGFR mutation(s). Afatinib is administered orally. Erlotinib and gefitinib are administered orally. Pemetrexed/cisplatin is administered intravenously.

According to the pCODR Clinical Guidance Panel (CGP), gefitinib and erlotinib would be the most appropriate comparators representing real world clinical practice in Canada. However, there is no direct evidence for either of these as comparators, and the evidence of clinical benefit versus these agents was derived through a Network Meta-Analysis (NMA). In addition, both the EGP and CGP considered that some of the model assumptions derived from the NMA lacked face validity. There was direct evidence of clinical benefit versus pemetrexed/cisplatin from the LUX-3 and gemcitabine-cisplatin from the LUX-Lung 6 trial. However, the CGP did not feel that these would be the most relevant comparison in real world clinical practice. It was also noted that although direct clinical evidence was available from the LUX-Lung 6 trial, the submitter did not provide economic information assessing the cost-effectiveness of afatinib in comparison with cisplatin-gemcitabine in this population of patients. The EGP noted that erlotinib is not funded as a first-line treatment in most provinces, therefore, the EGP focused on cost-effectiveness estimates compared with gefitinib.

**Patients** considered the following factors important in the review of afatinib, which are relevant to the economic analysis: 1. Oral availability, which means reduced time in hospitals receiving infusions; 2. Minimal side effects compared to chemotherapy; 3. Having an additional option in case other EGFR-TKIs were not effective. The EGP noted that adverse events were considered in the economic model and the submitted economic analyses compared afatinib with both chemotherapy (pemetrexed plus cisplatin) and other EGFR-TKIs (gefitinib and erlotinib). The model explicitly considers the following AEs: diarrhea, rash/acne, fatigue, anemia, neutropenia, and febrile neutropenia.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for afatinib, and which are relevant to the economic analysis: 1. As an oral drug it can easily be delivered in the community setting. However, oral drugs are not funded through the same mechanisms as intravenous cancer drugs which may limit accessibility in some jurisdictions; 2. There is potential use in second or third line settings or for other solid tumours without supporting data from appropriate trials; however, the pCODR review and the economic analysis were limited to the first-line setting. 3. PAG expressed concern about the flat pricing per tablet and indicated a preference for pricing per mg; Although the pricing is flat across all available tablets, the EGP does not expect that dose reductions could lead to higher costs as dose reduction would not likely lead to more than 1 tablet once daily given the available dosage strengths.4. PAG noted that EGFR mutation testing is already established. Testing was not considered in the economic evaluation and is not expected to increase costs because it has been established.

At the submitted confidential price, afatinib costs $[redacted] per 20mg, 30mg, 40mg or 50mg tablet. At the recommended dose of 40 mg once daily, afatinib costs $[redacted] per day and $[redacted] per 28-day course. The cost of afatinib is based on a confidential price submitted by the manufacturer and cannot be disclosed to the public according to the

*pCODR Disclosure of Information* guidelines. At the list price, afatinib costs $80.00 per 20mg, 30mg, 40mg or 50mg tablet. At the recommended dose of 40mg once daily, afatinib costs $80.00 per day and $2240.00 per 28-day course. Although the starting dose is 40 mg, patients are able to increase to 50 mg after the first cycle if tolerated; however only a small proportion of patients in each trial had this increase (6.1% in LUX-Lung 3 and 15.9% in LUX-Lung 6). This potential increase in the dose is not expected to impact the cost-effectiveness as the 50mg tablet is available and all tablets are flat priced.

The list price of the most relevant comparator, gefitinib, is $73.30 per 250mg tablet. At the recommended dose of 250mg once daily, gefitinib costs $73.30 per day and $2052.40 per 28-day course. The effective price of gefitinib may vary across jurisdictions and be lower than the list price if it is based on a confidential price that is unknown to pCODR. In the main economic analysis, the manufacturer of afatinib assumed similar drug costs by using the list price of gefitinib to demonstrate its cost-effectiveness compared with afatinib.

At the list price pemetrexed costs $514.80 and $2145.00 per 100mg and 500mg vial, respectively. Assuming use of the 500mg vial, at the recommended dose of 500mg/$m^2$ on day 1 of every 21 day cycle, the average daily cost is $174 and the average cost per 28-day course is $4862. Assuming use of the 100mg vial, at the recommended dose of 500mg/$m^2$ on day 1 of every 21 day cycle, the average daily cost is $208 and the average cost per 28-day course is $5834. Cisplatin cost $5.86 per 1mg/ml. At the recommended dose of 75 mg/$m^2$ IV day 1 every 21 days, cisplatin costs $35.57 per day and $996.10 per 28-day course.

## 1.2 Summary of Results

**The EGP has presented two sets of results: the first using pemetrexed/cisplatin as the comparator, the second using gefitinib as the comparator. The reason for this presentation of results is that there is direct clinical evidence for pemetrexed/cisplatin from the LUX-3 clinical trial; however, there is only indirect evidence for gefitinib, the more clinically relevant comparator. The EGP noted that although there was direct clinical evidence from the LUX-Lung 6 trial assessing the safety and efficacy of afatinib compared with cisplatin-gemcitabine, the manufacturer did not provide an economic model or evaluation comparing afatinib with cisplatin-gemcitabine. As such, the EGP was not able to provide any cost-effectiveness reanalysis estimates to address this comparison.**

**First, using <u>pemetrexed/cisplatin</u> as the comparator:**

**The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is $25,069 per QALY gained when afatinib is compared with pemetrexed/cisplatin. This is the value submitted by the manufacturer.**

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate of:

- the extra cost of afatinib is $4387. The main driver of incremental cost is the cost of disease management. Note that because pemetrexed is more expensive than afatinib there are some cost savings to offset the drug costs.
- the extra clinical effect of afatinib is .017 QALYS (2.1 QALM, or .8 life-months). The main driver of incremental benefit is a small increase in OS (.8 life months) and an 8.1 month increase in progression free life months (which drives the increases in quality of life).

**Second, using gefitinib as the comparator:**

**The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) varied widely. In terms of $/QALY gained, the range was from $39,000 to $211,000. In terms of $/LY gained estimates included $39,000/LY gained to cost increasing (i.e., increase in cost but no increase in health outcomes).**

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate of:

- In the base case submitted by the manufacturer the incremental benefit was 0.21 QALY or 0.39 LY. In reanalysis the EGP set the HR for OS and PFS equal to 1 (i.e., no benefit in terms of survival or progression free survival) resulting in an incremental benefit of 0.003 QALY and no benefit in terms of LY.
- In the base case submitted by the manufacturer the incremental cost was $15,153. In reanalysis the EGP set the HR for OS and PFS equal to 1 (i.e., no benefit in terms of survival or progression free survival) resulting in an incremental cost of $540.
- The main factor contributing to these wide ranges is uncertainty in the clinical benefit of afatinib relative to gefitinib. Note that the credible intervals for both OS and PFS contain 1 suggesting the possibility of no benefit in either outcome.

**The EGP based these estimates on the model submitted by Boehringer Ingelheim (model produced by IMS Health) and reanalyses conducted by the EGP. The EGP's re-analysis assumes similar pricing of afatinib and gefitinib. These estimates are extremely sensitive to the relative price of afatinib and gefitinib.** The reanalysis conducted by the EGP using the submitted model showed that when:

- The time horizon was reduced to 5 years from 10 years, based on input from the Clinical Guidance Panel, the incremental cost of afatinib was $12,590, and the incremental benefit of afatinib is 0.18 QALY. These changes decreased the estimated incremental cost-effectiveness ratio to $71,905/QALY gained.
- The hazard ratio for OS was set equal to 1, the incremental cost of afatinib was $574, and the incremental benefit of afatinib is 0.015 QALY (= 5.36 quality-adjusted life days). These changes decreased the estimated incremental cost-effectiveness ratio to $39,060/QALY gained.
- The hazard ratio for PFS was set equal to 1, the incremental cost of afatinib $15,118 and the incremental benefit of afatinib is 0.20 QALY. These changes increased the estimated incremental cost-effectiveness ratio to $76,660/QALY gained.
- The hazard ratios for both OS and PFS were set equal to 1, the incremental cost of afatinib $540, and the incremental benefit of afatinib is 0.0026 QALY (= 0.93 quality-adjusted life days). These changes increase the estimated incremental cost-effectiveness ratio to $211,189/QALY gained.
- The hazard ratios for both OS and PFS were set equal to 1 and the time horizon was reduced to 5 years, the incremental cost of afatinib $540, and the incremental benefit of afatinib is 0.0026 QALY (= 0.93 quality-adjusted life days). These changes increase the estimated incremental cost-effectiveness ratio to $211,189/QALY gained.

**The EGPs estimates varied over a very wide range and included the submitted estimates as a possibility. The main reason for this is because of the uncertainty in the clinical effects that are based on an indirect comparison.**

According to the economic analysis that was submitted by Boehringer Ingelheim (model produced by IMS Health), when afatinib is compared with gefitinib:

- the extra cost of afatinib is $15,153 (ΔC). Costs considered in the analysis included drug costs, drug administration costs, AE management costs, and other health care costs (i.e., disease management costs). The extra clinical effect of afatinib is 0.21 QALY (0.39 LY) (ΔE). The clinical effect considered in the analysis was based on survival pre- and post-progression, AE rates and AE severity.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $72,153/QALY gained and $38,450/LY gained.

## 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?**

When pemetrexed/cisplatin was the comparator the EGP estimates were close to the submitted by the manufacturer. The EGP noted that jurisdictions may be purchasing pemetrexed at a lower confidential price. When a one way sensitivity analysis is conducted using a price reduction in the cost of pemetrexed, the ICER increases and doubles (approximately $50,000) at a price reduction of 40%.

With regards to the gemcitabine/cisplatin comparator, the EGP noted that although head-to-head clinical efficacy data was available in the LUX-Lung 6 trial, the submitter did not provide a cost-effectiveness analysis estimate comparing afatinib to gemcitabine/cisplatin. In addition, the EGP could not provide a rough estimate of the ICER for the comparison to gemcitabine as such an estimate would require that various assumptions be made regarding the adverse events rates, all non-drug related costs and post-progression survival. Estimates would also need to rely on immature OS results from the LUX-Lung 6 trial. As such, the EGP noted that a rough estimate would be a crude approximation and is likely very unreliable.

When gefitinib was the comparator the EGP estimates varied widely. The main reason was uncertainty about the clinical benefits of afatinib relative to gefitinib. The base case hazard ratios of afatinib suggest a modest benefit for afatinib versus gefitinib in terms of PFS and OS. However, these hazard ratios were derived from indirect evidence, and the credible intervals for the hazard ratio estimates include 1, which indicates that there could be no benefit on either PFS or OS.

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

Adverse event rates were explicitly included in the model. Other factors (e.g., preference for an oral drug relative to intravenous and availability of alternate treatment options) were not explicitly modeled.

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

The submitted models are partitioned survival models in which the overall survival curve and the progression free survival curve were modeled independently. When properly calibrated to ensure clinical validity, the results of a partitioned survival model and a Markov model should result in the same findings in the base case.

In the comparison between afatinib and cisplatin/pemetrexed, it was expected that the post-progression survival curves would be different between the two arms because the second line treatments were expected to be different between the two arms. The EGP felt that the submitted model is reasonable for this comparison.

In the comparisons between afatinib versus other EGFR inhibitors, the submitted models resulted in differences in post-progression survival in favour of the afatinib arm (by 7.4 months when compared with erlotinib and by almost 5 months when compared with gefitinib). When attempting to perform sensitivity analyses for this, it appeared to be more challenging to isolate the post-progression survival health state to perform sensitivity analysis independent of other health states, given the structure of the partitioned survival models.

On the balance, the EGP felt that it was able to perform reasonable sensitivity analyses based on the submitted model given the above clinical and theoretical considerations.

**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?**

As mentioned previously, for the comparison of afatinib versus gefitinib the evidence of clinical benefit are indirect and derived through a Network Meta-Analysis. The base case hazard ratios of afatinib suggest a modest benefit for afatinib versus gefitinib in terms of PFS and OS. However, these hazard ratios were derived from indirect evidence, and the credible intervals for the hazard ratio estimates include 1, which indicates that there could be no benefit on either PFS or OS. In addition, both the EGP and CGP considered that some of the model assumptions derived from the NMA lacked face validity.

**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 EGP was satisfied with the unit cost estimates in the model. **However, in consultation with the CGP, the EGP felt that some of the model assumptions derived from the NMA lacked face validity. In particular:**

1. The results from the Network Meta-Analysis (NMA) showed longer survival if pemetrexed/cisplatin was used in first line, followed by erlotinib second line, than if either gefitinib or erlotinib were used in first line followed by pemetrexed/cisplatin in second line. 2. Survival after progression was longer if afatinib used in first line compared to erlotinib or gefitinib (18.7 months for afatinib, 11.3 months for erlotinib, and 13.8 months for gefitinib).

## 1.4 Summary of Budget Impact Analysis Assessment

**What factors most strongly influence the budget impact analysis estimates?**

The Budget Impact Analysis (BIA) is influenced by four important assumptions:

1. In several provinces (BC, AB, SK, MB, ON, QC) afatinib is strictly a substitute for gefitinib. In others (NB, PE, NS, NL) afatinib is a substitute for a platinum-based chemotherapy regimen (gemcitabine/cisplatin).

2. the confidential price of afatinib relative to the price of gefitinib

3. the market share of TKIs in first line NSCLC.

4. the peak market share of afatinib within the TKI class.

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

1. The market share assumption is not well justified.

2. In provinces where gefitinib is the main comparator there may still be some substitution from pemetrexed/cisplatin to afatinib. This hybrid substitution is not modeled.

3. A very limited range of sensitivity analysis is considered.

## 1.5 Future Research

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

This analysis would benefit from direct clinical evidence comparing afatinib versus other TKIs. LUX lung 7 which has now completed enrollment compares first generation TKI gefitinib to afatinib in the first line setting of patients with advanced EGFR positive NSCLC. Further information on this question may be obtained when the results of this trial are available.

**Is there economic research that could be conducted in the future that would provide valuable information related to afatinib?**

Although there was direct clinical evidence from the LUX-Lung 6 trial assessing the safety and efficacy of afatinib compared with cisplatin-gemcitabine, the manufacturer did not provide an economic model or evaluation comparing afatinib with cisplatin-gemcitabine. The EGP also noted that there were no published reports available assessing the cost effectiveness of afatinib in comparison with cisplatin-gemcitabine.

In the absence of better clinical data no other cost effectiveness or cost utility analyses are needed.

# 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 Final 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 afatinib (Giotrif) for advanced non-squamous non-small cell lung cancer. A full assessment of the clinical evidence of afatinib (Giotrif) for advanced non-squamous 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.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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