pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

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

May 2, 2014

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Giotrif – Advanced Non Small Cell Lung Cancer
Role in Review (Submitter and/or Manufacturer):	Manufacturer
Organization Providing Feedback	Boehringer Ingelheim Canada Ltd.

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees __x__ agrees in part ____ disagree

Boehringer Ingelheim Canada Ltd (BICL) commends pERC on the thoroughness of its review of afatinib. pERC's recognition of afatinib's overall clinical benefit over pemetrexed/cisplatin in the first-line treatment of advanced or metastatic adenocarcinoma of the lung is fully agreed to by Boehringer Ingelheim. There are, however, a number of aspects of pERC's initial recommendation with which Boehringer Ingelheim does not agree and BICL welcomes the opportunity to present its rational.

1. **Uncertainty in the efficacy and safety of afatinib compared with gefitinib**

pERC did not recommend funding afatinib in provinces where a TKI (gefitinib) is funded in the first-line setting because:

> ***"…as yet, there is no evidence from randomized controlled trials that directly compare afatinib to other tyrosine kinase inhibitors. Therefore, there is too much uncertainty regarding net clinical benefit and the cost-effectiveness of afatinib compared with other tyrosine kinase inhibitors." (pCODR Initial Recommendation: p1, paragraph 2)***

Although BICL acknowledge that uncertainty exists in the absence of a direct comparison of afatinib to gefitinib or erlotinib, the degree of uncertainty is not great and we believe that this was also the conclusion of the Clinical Guidance Panel (CGP) as indicated in their report:

> ***"The Panel concluded that there is currently insufficient evidence to recommend the use of one EGFR TKI over the other for the first-line treatment of locally advanced or metastatic EGFR mutation positive NSCLC…" (CGP Report: p4, paragraph 4)***

From a net clinical benefit perspective, BICL believes that, at present, neither afatinib nor gefitinib demonstrate a net clinical benefit over the other. Consequently, Boehringer Ingelheim believes that both treatments should be made available as a treatment option for patients and clinicians.

Further, the Economics Guidance Panel (EGP) tested the baseline assumptions of the submitted model with a number of sensitivity analyses. There were no scenarios tested in which afatinib was assumed to be less efficacious than gefitinib. This implies that the EGP also considered afatinib to be at least as efficacious as gefitinib. Assuming no difference in efficacy, the cost

effectiveness would be based on a comparison of adverse events. The sensitivity analysis that explores this scenario is:

> ***"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." (EGP Report: p3, paragraph 11)***

In this scenario, it is assumed that there are no differences in efficacy, but differences in AEs are preserved and drive the differences in cost and outcomes. If this is considered the boundary of the uncertainty, or the worst case scenario for the value proposition of afatinib, there still remains ground for a positive recommendation based on the willingness to improve the cost effectiveness.

While the initial recommendation was reluctant to accept the comparative efficacy of afatinib versus gefitinib based on a network meta analysis (NMA), this reluctance did not appear to extend to the cross trial comparisons of toxicity.

> ***"There is however concern that there may be greater toxicity with afatinib compared to the first generation TKIs gefitinib and erlotinib. The rate of grade ≥3 rash, grade ≥3 diarrhea, rate of discontinuation and dose reductions were all higher in patients receiving afatinib in the LUX-Lung 3 and 6 trials as compared to the trials used as part of the network meta-analysis which were evaluating the efficacy of gefitinib and erlotinib." (CGP Report: p 4, paragraph 2)***

> ***"…The NMA had limitations with regard to the heterogeneity of patients in the different studies included in the analysis. A recent network analysis in patients with EGFR mutation positive NSCLC only found no difference in PFS between afatinib, gefitinib and erlotinib. Therefore, at present the benefit of one EGFR TKI over the other is uncertain." (CGP Report: p 3, paragraph 6)***

BICL would respectfully submit that there is an inconsistency of approach in relation to the use of the data from the NMA. BICL would also like to point out that the rates of AEs reported in LUX-Lung 6 were lower than those reported in Lux-Lung 3, and are closer to levels reported for gefitinib and erlotinib.

In several places in the initial recommendation and the CGP report, the suggestion is made that a head-to-head trial would address much of the uncertainty, and that LUX-Lung 7 would provide this information. There are a number of important considerations around LUX-Lung 7 that BICL would like to bring to pERC's attention:

1. Trial design and robustness of data: LUX-Lung 7 is a Phase IIb exploratory trial, meaning that it is not powered as either a superiority trial or a non-inferiority trial. It has no pre-defined hypothesis and no formal sample size calculation. As such, LUX-Lung 7 may or may not be able to address the current levels of uncertainty.

2. Timeliness of data: While it is currently anticipated that data lock for the primary outcome measure (PFS) for LUX-Lung 7 will occur in September 2014, the study is not expected to be fully completed until December 2016. Assuming that data lock for PFS occurs in September 2014, clinical trial data will not be available until Q1 2015. Taking into account the time required to develop the submission and the pCODR review time, the reimbursement recommendation based on this new evidence would not be expected until late 2015 or early 2016. This is nearly a two year delay from now and from a patient care

perspective could not be considered timely.

Finally, it should be noted that other HTA organizations have also had to face the issue of uncertainty of the efficacy of afatinib in relation to other TKIs and have concluded that in the absence of evidence of superiority of one TKI over another, all should be listed. This was the conclusion of the Pharmaceutical Benefits Advisory Committee (Australia)[1], the Scottish Medicines Consortium[2] and the National Institute for Health and Care Excellence in the UK (NICE)[3].

2. **The value of Patient Choice and Equity**

Boehringer Ingelheim believes that the patient's best interests should be a key component of HTA reviews and that historically, pERC has shown exemplary commitment to patient values. However, there are two dimensions of the initial recommendation on afatinib where BICL believes that the recommendation falls short in addressing patient values - patient choice and patient equity.

As stated by the Patient Advocacy group:

> ***"The patient advocacy group submits that having multiple EGFR Tyrosine-kinase inhibitors ("EGFR-TKIs") to choose from will promote greater competition in pricing, yield more options to choose from for both patients and practitioners." (CGP Report: p 15, paragraph 3)***

Patient and physician choice in therapies is undeniably a benefit to patient care. pERC's recommendation to not list afatinib in provinces where a TKI is funded in first line does not acknowledge this benefit.

Patient equity is another significant shortcoming of the initial recommendation. By recommending that afatinib only be listed in provinces where cisplatin-pemetrexed is funded as the 1st line treatment for advanced or metastatic NSCLC (i.e., no TKI), pERC is implicitly stating that only patients in Nova Scotia should be able to access afatinib. Boehringer Ingelheim believes that all patients in Canada should have access to afatinib as a first-line treatment option for advanced or metastatic EGFR mutation positive adenocarcinoma.

3. **Comparator Selection for Afatinib**

Afatinib's pivotal study, LUX-Lung 3, was designed and began recruitment in 2009. At that time, the recommended therapy for patients with adenocarcinoma (which is the histology where EGFR mutations are most likely to be found) was pemetrexed/cisplatin. This recommendation was based on the 2008 Scagliotti *et al*., study that found that pemetrexed/cisplatin significantly extended overall survival over gemcitabine/cisplatin. The magnitude of benefit of afatinib over the best chemotherapy regimen for adenocarcinoma, pemetrexed/cisplatin, in LUX Lung 3 is impressive in the setting of advanced NSCLC and increases PFS on average by 4.2 months to 6.8 months (in all mutations and common mutations respectively). Notwithstanding the fact that the standard of care for adenocarcinoma patients has changed due to Scagliotti *et al*., the LUX-Lung 6 trial was designed to meet the registration requirements for China, which required the platinum doublet (gemcitabine/cisplatin) as the control arm. Subsequent to the design of LUX-Lung 3, Mok *et al*., (2009) established the efficacy of EGFR TKIs over platinum doublets in 1st line EGFR mutation positive NSCLC and gefitinib became the standard of care in this patient population. As current standard of care, it is our belief that gefitinib is the most appropriate comparator for afatinib. Pemetrexed/cisplatin was also included as a comparator since it is the control arm of afatinib's pivotal study, LUX-Lung 3.

4. **Overarching Theme**

As articulated in the clinical and economic panel guidance reports, and outlined above, it is difficult to establish the superiority of any one EGFR TKI over another based on the current level of evidence. Given that plus the relative economic impact of afatinib and gefitinib, it is hard to justify the current recommendation not to list afatinib in the majority of provinces. Therefore, BICL respectfully requests that pERC amend its initial recommendation for provinces where a TKI is funded in the first line setting for the treatment of advanced or metastatic NSCLC to recommend the funding of afatinib in a similar manner to gefitinib in patients with EGFR mutation positive adenocarcinomas of the lung.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

____ Support conversion to final recommendation.

Recommendation does not require reconsideration by pERC.

__x__ Do not support conversion to final recommendation.

Recommendation should be reconsidered by pERC.

---

[1] http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-07/afatinib-first-line
[2] http://www.scottishmedicines.org/SMC_Advice/Advice/920_13_afatinib_Giotrif/afatinib_Giotrif
[3] http://guidance.nice.org.uk/TAG/341/FAD

About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

1 Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer

of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½″ by 11″ paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.