pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Afatinib (Giotrif) **Submitted Funding Request:** For the first line treatment of EGFR Mutation Positive, Advanced Non-Small Cell Lung Cancer patients	
Submitted By: Boehringer Ingelheim Canada Ltd.	**Manufactured By:** Boehringer Ingelheim Canada Ltd.
NOC Date: November 1, 2013	**Submission Date:** June 7, 2013
Initial Recommendation: March 6, 2014	**Final Recommendation:** May 2, 2014

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding afatinib (Giotrif) if cisplatin-pemetrexed is currently the main treatment option. pERC also recommends funding afatinib as an alternative treatment option to gefitinib, conditional on the cost-effectiveness of afatinib being improved to an acceptable level. Funding should be in the first-line setting for patients with EGFR mutation positive advanced or metastatic adenocarcinoma of the lung and with an ECOG performance status 0 or 1. pERC made this recommendation because it was satisfied that there is a net clinical benefit of afatinib compared with cisplatin-pemetrexed. In addition, although there were substantive deliberations and various opinions expressed, the majority of pERC members considered that there could be similar clinical benefit of afatinib and gefitinib, despite the lack of evidence from head-to-head randomized controlled trials. In addition, providing access to afatinib aligns with patient values of having access to more treatment options. Also, at the submitted price, afatinib is cost-effective compared with cisplatin-pemetrexed but may not be considered cost-effective compared with gefitinib.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-effectiveness** Although afatinib is cost-effective compared with cisplatin-pemetrexed it may not be cost-effective compared with gefitinib. Given that pERC was satisfied that there could be similar clinical benefit of afatinib and gefitinib for the treatment of EGFR mutation positive, advanced or metastatic adenocarcinoma of the lung in the first-line setting, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of afatinib to an acceptable level compared with gefitinib. pERC noted that, if one accepts a similar clinical benefit of afatinib and gefitinib, the cost-effectiveness of afatinib would require that the effective prices of the two drugs also be at least comparable. **Cost-Effectiveness Unknown vs. Cisplatin-Gemcitabine and Other Doublets** For provinces where cisplatin-pemetrexed in the first-line setting for the treatment of advanced or metastatic NSCLC is not funded but cisplatin-gemcitabine or other cisplatin-based doublets are funded in this setting, pERC was unable to make an informed recommendation on funding afatinib for patients with EGFR mutation positive, advanced or metastatic adenocarcinoma of the lung. Although pERC acknowledged that there was a net clinical benefit of afatinib compared with cisplatin-gemcitabine based on the LUX-Lung 6 study, in the absence of an economic evaluation comparing afatinib with cisplatin-gemcitabine, the cost-effectiveness is unknown. Information on the cost-effectiveness of afatinib compared with cisplatin-gemcitabine in this clinical setting could inform a resubmission for afatinib **Guideline Needed to Inform Optimal Treatment Sequencing** pERC noted that there is variability across provinces in the availability and sequencing of treatments for patients with EGFR mutation positive advanced adenocarcinoma of the lung. pERC discussed that the optimal sequencing of agents in this setting is currently unknown. However, pERC recognized that provinces may need to address this issue upon implementation of afatinib funding and noted that the development and implementation of an evidence-based guideline would be of value.

SUMMARY OF pERC DELIBERATIONS

pERC noted that the burden of illness associated with epidermal growth factor receptor (EGFR) mutation positive, metastatic or advanced adenocarcinomas of the lung is considerable and that the number of patients in Canada who could potentially receive afatinib is not inconsequential. pERC discussed the availability of treatments for this patient population. Cisplatin-pemetrexed, cisplatin-gemcitabine, other cisplatin-based doublets and other tyrosine kinase inhibitors (gefitinib and erlotinib) are all possible treatment options in the first-line setting. pERC noted that the availability of these therapies varies across Canada, leading to heterogeneity in treatment approaches and uncertainty in the most appropriate comparator for afatinib. As a result, pERC deliberated upon a number of scenarios, taking into consideration possible preferred first-line treatments in various provinces.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

The pCODR systematic review included two randomized controlled trials, LUX-Lung 3 (Sequist 2013), comparing afatinib with cisplatin-pemetrexed, and LUX-Lung 6 (Wu 2014), comparing afatinib with cisplatin-gemcitabine. pERC noted that in both studies afatinib demonstrated a clinically meaningful improvement in progression-free survival compared with chemotherapy. When quality of life outcomes were considered, pERC considered that in both the LUX-Lung 3 and LUX-Lung 6 studies, the outcomes generally favored afatinib compared with chemotherapy. pERC also discussed the toxicity profile of afatinib compared with cisplatin-pemetrexed and cisplatin-gemcitabine. It was noted that afatinib's side effects were distinct from those of the chemotherapies but were consistent with the type of adverse events generally associated with tyrosine kinase inhibitors. Afatinib was associated with substantially more diarrhea and dermatologic side effects such as rash or acne and stomatitis, all of which appeared to be manageable. pERC considered that the degree of toxicity also appeared to be manageable as both the rate of treatment discontinuation and treatment-related mortality were low (<1%). Considering all of these factors, pERC was satisfied that there is a net clinical benefit of afatinib when compared with either cisplatin-pemetrexed or cisplatin-gemcitabine.

pERC also discussed the net clinical benefit of afatinib compared with other tyrosine kinase inhibitors such as gefitinib and erlotinib. During deliberations on the Initial Recommendation, pERC had concluded that there was too much uncertainty in the net clinical benefit of afatinib compared with other tyrosine kinase inhibitors. This was because of the lack of randomized controlled trials comparing afatinib and gefitinib, the methodological limitations and limited clinical validity of the submitted indirect comparison, the inability to identify a clinical need or therapeutic gap for afatinib compared with other tyrosine kinase inhibitors and the potential for the ongoing LUX-Lung 7 study to provide more information on the direct comparative efficacy of these treatments. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the manufacturer, from pCODR's Provincial Advisory Group (PAG) and from a patient advocacy group regarding the desire to have access to afatinib as another treatment option in provinces already funding an EGFR tyrosine kinase inhibitor. The Committee noted that because gefitinib is currently funded in the majority of provinces, patients in most provinces would not be able to access afatinib based on the pERC Initial Recommendation. Therefore, the Committee re-deliberated upon whether or not there was sufficient reason to recommend funding afatinib as an alternative treatment option to gefitinib in all provinces. There were substantive deliberations and the Committee identified both reasons to fund afatinib and reasons to not fund afatinib in this context, as summarized below.

Some pERC members did not support funding afatinib as an alternative to gefitinib. In considering the clinical benefit, it was reiterated that there are no head-to-head trials comparing these treatments and the indirect comparison was flawed, which led to a lack of face validity for this analysis. pERC members also noted that based on known toxicity profiles of EGFR tyrosine kinase inhibitors, afatinib may potentially have higher rates of diarrhea and dermatologic adverse events than gefitinib, which would be a disadvantage to patients. In addition, some pERC members were not satisfied that there was a therapeutic gap or patient need that afatinib would address. The only subset of the population that was discussed as potentially benefiting from afatinib was that with rare EGFR mutations (e.g. Exon 20, T790M)

but this was considered insufficient reason to support funding, in light of the pCODR Clinical Guidance Panel's (CGP) perspectives on the low unmet need in this subpopulation. In considering patient values, it was noted that afatinib and gefitinib were both oral therapies in the same drug class and the CGP were unable to identify substantive reasons why they would prescribe one therapy over another (e.g. improved efficacy, reduced toxicity, improved convenience or accessibility). Therefore, although generally supportive of choice as an important patient value, some pERC members expressed the view that funding afatinib would not provide a meaningful choice of different therapies to patients. Some pERC members also noted that because of the uncertainty in the clinical effectiveness of afatinib versus gefitinib, in part due to the limitations of the indirect comparison, the incremental effect and resulting cost-effectiveness is uncertain in this setting. This was reflected by a wide range of potential incremental cost effectiveness ratios estimated by the EGP, not all of which would be considered cost-effective by pERC.

However, some pERC members also identified reasons to fund afatinib as an alternative to gefitinib. In considering the clinical benefit, it was noted that although, there is no head-to-head trial comparing afatinib with gefitinib, afatinib demonstrated a meaningful benefit with a historically-appropriate comparator, cisplatin-based chemotherapy. In addition, the ongoing comparative study, LUX-Lung 7, is a phase two study that is not statistically powered to adequately answer pERC's questions around the relative efficacy of afatinib and gefitinib. Some pERC members also noted that the CGP rejected the results of the indirect comparison claiming that afatinib is superior to gefitinib. However, from a clinical perspective, the CGP considered it unlikely that afatinib would be less efficacious than gefitinib in terms of progression-free survival. In addition, pERC members noted the CGP considered that if differences in toxicity profiles exist between afatinib and gefitinib, these would still be clinically manageable given their type and the ability to make dose modifications. It was also noted that afatinib is currently the only tyrosine kinase inhibitor to provide prospective data on rare EGFR mutations (e.g. Exon 20, T790M), which some pERC members considered an advantage. Some pERC members also discussed that providing funding for afatinib would align with patient values because it would provide access to more treatment options. pERC also deliberated on cost-effectiveness and noted that if one accepts that afatinib and gefitinib have a similar clinical benefit, a cost-minimization approach could be applied. In this case, the relative price of afatinib and gefitinib would be critical to cost-effectiveness during implementation and pricing negotiations. The feasibility of adoption was discussed and it was noted that stakeholders who must manage implementation issues had provided feedback asking pERC to reconsider its recommendation as it relates to other provincially-funded tyrosine kinase inhibitors in this setting and some pERC members considered this a reason to fund afatinib as an alternative treatment option to gefitinib.

Various opinions were expressed during deliberations and each of the above factors were valued differently by pERC members. Following voting, the majority of pERC members considered that there was sufficient reason to recommend funding afatinib as an alternative to gefitinib, conditional on cost-effectiveness being improved to an acceptable level. This was primarily because there could be a similar clinical benefit of afatinib and gefitinib and providing access to afatinib aligns with patient values of providing access to more treatment options, when assuming that the cost of the two treatments is at least comparable.

pERC deliberated upon patient advocacy group input. pERC noted that patients value oral therapies, greater accessibility and having a choice of therapies. pERC considered that providing access to afatinib aligns with these patient values and ensures that most patients in Canada have access to tyrosine kinase inhibitors as a first-line treatment option, reducing the heterogeneity of existing funding policies in this therapeutic area. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback received from the patient advocacy group during its deliberations on the pros and cons of funding afatinib in provinces that already have access to gefitinib. During these re-deliberations, pERC carefully considered the value of patient choice and the potential need for treatment options in patients with rare EGFR mutations, as discussed above.

pERC deliberated upon the cost-effectiveness of afatinib compared with other possible therapies. It was noted that when afatinib was compared with cisplatin-pemetrexed, the manufacturer's estimates and the pCODR Economic Guidance Panel's (EGP's) best estimates were the same. Based on this estimate and additional sensitivity analyses, including analyses on the price of pemetrexed, pERC considered that afatinib was cost-effective at the submitted confidential price compared with cisplatin-pemetrexed. An economic evaluation comparing afatinib with cisplatin-gemcitabine or other cisplatin-based chemotherapy doublets was not provided by the Submitter. Therefore, pERC considered that the cost-effectiveness of afatinib compared with cisplatin-gemcitabine or other cisplatin-based chemotherapy doublets is unknown and pERC was unable to make an informed funding recommendation in the absence

of information on cost-effectiveness. pERC recognized that this may create implementation challenges in provinces where cisplatin-gemcitabine is the most relevant funded comparator. However, pERC noted that information on the cost-effectiveness of afatinib compared with cisplatin-gemcitabine in this clinical setting could inform a resubmission for afatinib. pERC maintained this position following redeliberations on the Initial Recommendation.

pERC also considered the cost-effectiveness of afatinib compared with other tyrosine kinase inhibitors, including gefitinib, based on a submitted economic evaluation. During deliberations on the Initial Recommendation, pERC had concluded that there was too much uncertainty in the cost-effectiveness of afatinib compared with gefitinib due to the uncertainty in the network meta-analysis and the absence of a randomized controlled trial comparing afatinib with another tyrosine kinase inhibitor. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback received from stakeholders on the desire to have access to afatinib as another treatment option in provinces already funding a tyrosine kinase inhibitor. During its re-deliberations on the pros and cons of funding afatinib in provinces that already have access to gefitinib, as summarized above, pERC discussed that the relative cost-effectiveness of the two drugs is highly dependent on their relative clinical benefit. If one accepts that afatinib and gefitinib have similar clinical effects (including both effectiveness and safety), a cost-minimization approach could be applied. pERC noted that, in this clinical scenario, at the list prices of afatinib and gefitinib, afatinib costs more than gefitinib but at the submitted confidential price of afatinib and the list price of gefitinib, afatinib could be considered cost-effective compared with gefitinib. However, 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.

pERC considered the feasibility of implementing a funding recommendation for afatinib. pERC noted the heterogeneity of comparators and funding policies in the first-line setting for patients with EGFR mutation positive adenocarcinoma of the lung. pERC considered that the optimal sequencing of agents in this setting is currently unknown. However, pERC recognized that provinces may need to address this issue upon implementation of funding and noted that the development and implementation of an evidence-based guideline would be of value to guide consistency in drug funding. pERC also noted that the heterogeneity of comparators also resulted in uncertainty in budget impact as it will depend on the first-line treatment that afatinib would be replacing. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from pCODR's Provincial Advisory Group on the challenges of implementing separate recommendations that depend on what therapies each province is currently funding and noted this when formulating the pERC Final Recommendation. pERC also discussed that different recommendations for different provinces presented an implementation barrier, as this scenario could prevent provinces from negotiating drug prices as one body.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from one patient advocacy group (Lung Cancer Canada)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- pCODR's Provincial Advisory Group.
- one patient advocacy group (Lung Cancer Canada)
- the Submitter (Boehringer Ingelheim Canada Ltd.)

The pERC Initial Recommendation was to fund afatinib in provinces where no tyrosine kinase inhibitor is funded in the first-line setting for the treatment of advanced or metastatic non-small cell lung cancer (NSCLC) and cisplatin-pemetrexed is funded in this setting. For provinces where a tyrosine kinase inhibitor is funded in the first-line setting for the treatment of advanced or metastatic NSCLC, pERC did not

recommend funding afatinib (Giotrif) in patients with EGFR mutation positive adenocarcinomas of the lung.

Feedback on the pERC Initial Recommendation indicated that the manufacturer and pCODR's Provincial Advisory Group agreed in part with the pERC Initial Recommendation while the patient advocacy group disagreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the safety and efficacy of afatinib compared to appropriate comparators, in patients with previously untreated EGFR mutation positive, metastatic or locally advanced adenocarcinomas of the lung.

Studies included: two RCTs comparing afatinib to cisplatin-based chemotherapy

The pCODR systematic review included two randomized controlled trials, LUX-Lung 3 (Sequist 2013) and LUX-Lung 6 (Wu 2014), comparing the use of afatinib to cisplatin-based chemotherapy in patients with previously untreated locally advanced or metastatic adenocarcinoma of the lung with EGFR mutations. LUX-Lung 3 (N=345) was an international trial, with patients primarily from East Asia, that randomized patients 2:1 to afatinib or cisplatin-pemetrexed. LUX-Lung 6 (N=364) randomized patients 2:1 to afatinib or cisplatin-gemcitabine and enrolled patients solely from Asia. Both studies administered afatinib at a dose of 40 mg per day until disease progression. Cisplatin (75 mg/m^2 iv) and gemcitabine (1000 mg/m^2 iv, on days 1 and 8) or pemetrexed (500 mg/m^2 iv) were administered every 21 days for a maximum of six cycles. In both studies, patients were permitted to cross over to an EGFR tyrosine kinase inhibitor (including erlotinib or gefitinib) following progression on chemotherapy.

The pCODR review also provided contextual information on a critical appraisal of a network meta-analysis comparing afatinib with other treatments, including tyrosine kinase inhibitors for the first-line treatment of locally advanced or metastatic NSCLC.

Patient populations: ECOG performance status 0 or 1, rare EGFR mutations

In LUX-Lung 3, the majority of patients in the afatinib and cisplatin-pemetrexed group respectively had an ECOG performance status of 0 (40% and 35.7%) or 1(60% and 63.5%). In LUX-Lung 6, a higher proportion of patients in the cisplatin-gemcitabine arm had an ECOG performance status of 0 at baseline than in the afatinib arm (33.6% vs 19.8%, respectively). pERC discussed the use of afatinib in patients with an ECOG performance status of 2 or greater. While pERC noted that there was a need for effective therapies in these patients, they were excluded from the LUX-Lung 3 and LUX-Lung 6 studies and, therefore, pERC was unable to make an informed recommendation for this population in the absence of any data. It was noted that collection of prospective evidence on the use of afatinib in patients with ECOG performance status of 2 or greater could be of benefit if there is clinical interest in using afatinib in these patients.

Upon reconsideration of the Initial Recommendation, pERC discussed feedback received from the patient advocacy group regarding treatment options currently available to patients with rare mutations. pERC noted that afatinib is currently the only EGFR tyrosine kinase inhibitor with prospective efficacy data in this subpopulation of patients with rare EGFR mutations (e.g. Exon 20, T790M). However, pERC also discussed that this only affected a small proportion of patients and testing for these mutations was not even widely available. It was also noted that the pCODR Clinical Guidance Panel (CGP) had suggested that clinicians would likely extrapolate data from the LUX-Lung 3 and LUX-Lung 6 trials, and consider that rare mutations are likely sensitive to all EGFR tyrosine kinase inhibitors, including gefitinib. While some pERC members considered that the prospective data on rare EGFR mutations was an advantage for afatinib, other pERC members did not consider this sufficient reason to fund afatinib as an alternative to gefitinib, given the clinical perspectives on the lack of unmet need in this subpopulation.

Key efficacy results: clinically and statistically significant improvements in PFS

Key efficacy outcomes deliberated on by pERC included overall survival and independently assessed progression-free survival, which was the primary outcome of LUX-Lung 3 and LUX-Lung 6. After a median follow up of 16.4 (LUX-Lung 3) and 16.6 (LUX-Lung 6) months, both studies reported statistically and clinically significant differences in both independently- and investigator-assessed progression-free survival in favour of the afatinib arm compared to cisplatin-based chemotherapy. Independently assessed PFS was

11.1 vs. 6.9 months (HR 0.58 95%CI 0.43-0.78 p=0.001) in LUX-Lung 3 and 11.0 vs. 5.6 months (HR 0.28 95%CI 0.20-0.39 p<0.0001) in LUX-Lung 6 in the afatinib vs. cisplatin-based chemotherapy groups, respectively. pERC considered that both studies demonstrated a clinically meaningful improvement in progression-free survival in favour of afatinib compared with cisplatin-based chemotherapies.

Neither study demonstrated a statistically significant difference in overall survival. However, the pCODR Clinical Guidance Panel had noted that this was likely due to the rate of cross over to an EGFR tyrosine kinase inhibitor following progression on chemotherapy (65% in LUX-Lung 3 and 63% in LUX-Lung 6), which confounded the analysis.

Quality of life: similar to or better than cisplatin-based chemotherapy

Quality of life was assessed in both LUX-Lung 3 and LUX-Lung 6, using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and a lung cancer-specific module (QLQ-LC13). All patient-reported symptoms and health-related quality of life were either improved or unchanged when compared to chemotherapy. Both studies reported a clinically meaningful improvement in dyspnea and a delay in time to deterioration in cough and dyspnea favouring afatinib compared to cisplatin-based chemotherapy. pERC acknowledged that based on patient advocacy group input, quality of life was an outcome important to patients and that improvements in quality of life with afatinib, or at least no worsening relative to chemotherapy, aligned with patient values.

Safety: expected and manageable tyrosine kinase inhibitor toxicities

pERC discussed the toxicity profile of afatinib compared with cisplatin-pemetrexed and cisplatin-gemcitabine and noted that afatinib's side effects were distinct from those of the chemotherapies. Afatinib was associated with substantially more diarrhea and dermatologic side effects such as rash or acne and stomatitis, all of which are expected adverse events with tyrosine kinase inhibitors and appeared to be manageable. Overall grade 3 /4 adverse events were similar between afatinib and chemotherapy groups. pERC considered that the degree of toxicity also appeared to be manageable as the rate of discontinuation was low and treatment related mortality was also low (<1%).

Comparator Information: clinical benefit could be similar to gefitinib but robust evidence lacking

pERC also discussed the net clinical benefit of afatinib compared with other tyrosine kinase inhibitors such as gefitinib and erlotinib. pERC noted that there are no randomized controlled trials comparing afatinib with either therapy, therefore, the relative efficacy and harms of these treatments are uncertain. pERC also discussed a network meta-analysis conducted by the manufacturer that indirectly compared these treatments but noted the limitations of relying on indirect and cross-trial comparisons. Furthermore, the pCODR Clinical Guidance Panel had noted that the results of the analysis lacked clinical validity ~~and~~ as uncertainty was created by the heterogeneity of patients' EGFR mutation status across the trials being compared. pERC noted that there is currently an ongoing randomized controlled trial, LUX-Lung 7, comparing afatinib with gefitinib, which could provide more robust information in the future Therefore, during deliberations on the Initial Recommendation pERC determined there was too much uncertainty to draw conclusions regarding the relative efficacy of afatinib compared with other tyrosine kinase inhibitors.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the manufacturer, from Provincial Advisory Group and from a patient advocacy group regarding the clinical benefit of afatinib relative to gefitinib. Therefore, the Committee re-deliberated upon whether or not there was sufficient reason to recommend funding afatinib as an alternative treatment option to gefitinib. Some pERC members did not support funding afatinib as an alternative to gefitinib and maintained that there was too much uncertainty in the clinical benefit of afatinib compared with gefitinib for the reasons outlined below. It was reiterated that there are no head-to-head trials comparing these treatments and the indirect comparison was flawed, which led to a lack of face validity for this analysis. pERC members also noted that based on known toxicity profiles of EGFR tyrosine kinase inhibitors, afatinib may potentially have higher rates of diarrhea and dermatologic adverse events than gefitinib, which would be a disadvantage to patients.

However, some pERC members also identified reasons to fund afatinib as an alternative to gefitinib and considered that the clinical benefit could be similar between the two treatments. It was noted that although there is no head-to-head trial with gefitinib, afatinib demonstrated a meaningful benefit with a historically-appropriate comparator, cisplatin-based chemotherapy. In addition, the ongoing comparative

study, LUX-Lung 7, is a phase two study that is not statistically powered to adequately answer pERC's questions around the relative efficacy of afatinib and gefintib. Some pERC members also noted that the CGP rejected the results of the indirect comparison claiming that afatinib is superior to gefitinib. However, from a clinical perspective, the CGP considered it unlikely that afatinib would be less efficacious than gefitinib in terms of progression-free survival. In addition, pERC noted that the CGP considered that if differences in toxicity profiles exist between afatinib and gefitinib, these would still be manageable clinically given their type and the ability to make dose modifications.

Need: access to a first-line tyrosine kinase inhibitor for all patients

pERC noted that the burden of illness associated with EGFR mutation positive, advanced non-small cell lung cancer is considerable and that the number of patients in Canada who could potentially receive afatinib is not inconsequential. It is estimated that in 2012 there will be 25,600 new cases of NSCLC and 20,100 deaths from NSCLC in Canada with an incidence and mortality rate of 54/100,000 and 42/100,000 in the population, respectively. If left untreated, patients with metastatic NSCLC have a median survival after diagnosis of only 4-5 months. EGFR activating mutations exist in 12% of the NSCLC population and although this represents a small proportion of all locally advanced or metastatic NSCLC, the annual incidence of NSCLC is large and therefore the absolute number of patients eligible for afatinib on an annual basis is potentially large.

pERC discussed the availability of treatments for this patient population. Cisplatin-pemetrexed, cisplatin-gemcitabine, other cisplatin-based doublets and tyrosine kinase inhibitors (gefitinib and erlotinib) are all possible treatment options in the first-line setting. Cisplatin-pemetrexed, the preferred platinum-doublet for first-line treatment of those patients whose cancer is of non-squamous histology and who do not have an activating EGFR mutation, is accompanied by significant toxicity. Therefore, due to advanced age, poor performance status and/or co-morbidities many patients do not receive treatment in the first-line setting. Two EGFR tyrosine kinase inhibitors, gefitinib and erlotinib, have regulatory approval for first-line therapy for advanced EGFR mutation positive adenocarcinoma of the lung due to improved progression free survival, response rates and quality of life compared to chemotherapy. However, gefitinib is only funded in some provinces as a first-line therapy and erlotinib is currently only funded as a second- or third-line treatment in all provinces. pERC noted that the variation in the availability of these therapies across Canada has led to heterogeneity in treatment approaches and uncertainty as to the most appropriate comparator for afatinib. As a result, pERC deliberated upon a number of scenarios, taking into consideration the current preferred first-line treatments in various provinces. pERC also discussed the need for another tyrosine kinase inhibitor. pERC noted that not all provinces currently provide funding for a tyrosine kinase inhibitor in the first-line setting; in those provinces that do not fund a first-line tyrosine kinase inhibitor, afatinib would offer a benefit over cisplatin-based chemotherapies and fulfills a clinical need.

During deliberations on the Initial Recommendation, pERC concluded that in provinces where a tyrosine kinase inhibitor is already funded first-line, pERC was unable to identify a clinical need for afatinib, in the absence of robust comparative data with a relevant tyrosine kinase inhibitor. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the manufacturer, from pCODR's Provincial Advisory Group (PAG) and from a patient advocacy group regarding the desire to have access to afatinib as another treatment option in provinces already funding an EGFR tyrosine kinase inhibitor. The Committee noted that gefitinib is currently funded in the majority of provinces and based on the pERC Initial Recommendation to not fund afatinib in provinces that already fund an EGFR tyrosine kinase inhibitor, patients in most provinces would not be able to access afatinib. Therefore, the Committee re-deliberated upon whether or not there was sufficient reason to recommend funding afatinib as an alternative treatment option to gefitinib. There were substantive deliberations and the Committee identified both reasons to fund afatinib and reasons to not fund afatinib in this context, as described elsewhere in this document.

Patient advocacy group feedback also noted that afatinib is currently the only EGFR tyrosine kinase inhibitor to provide prospective data on rare mutations (e.g. Exon 20, T790M), which some pERC members considered an advantage. However, this was considered by some pERC members an insufficient reason to support funding in light of the CGP's perspectives on the low unmet clinical need in this subpopulation. No other therapeutic gap or clinical need was identified that afatinib would address if other EGFR tyrosine kinase inhibitors are funded.

PATIENT-BASED VALUES

Values of patients with advanced non-small cell lung cancer: survival and quality of life
Patient input indicated that patients with advanced lung cancer have at least one severe symptom, such as severe cough, pain, shortness of breath and/or coughing up blood, and many have three or more of these symptoms. Survival is short, ranging from 4 to 8 months on average, and quality of life in lung cancer is directly related to tumour control. Patient input suggested that the availability of afatinib will help improve the quality of life of patients with NSCLC compared to first-line chemotherapy. Results from the LUX-Lung 3 and LUX-Lung 6 studies demonstrated improvements in progression-free survival and quality of life outcomes, which aligns with these patient values.

Patient values on treatment: oral therapy, choice of treatments, more tolerable therapies
Most Canadians with EGFR mutation positive, advanced or metastatic adenocarcinoma of the lung who receive treatment are treated with chemotherapy as the first-line approach. Chemotherapy is associated with severe side effects including nausea, vomiting, hair loss, fatigue and the risk of fever and infection. Also, patients can also experience dehydration, kidney damage, hearing loss and nerve damage, as well as the inconvenience of multiple blood tests, intravenous treatment and multiple visits (with long wait times) to hospital for chemotherapy. Some patients may however be deemed unsuitable for chemotherapy, for reasons of age or other illnesses, further shortening their survival and ability to fight their advanced lung cancer. Side-effects of the treatment pose a tremendous burden on patients and their caregivers. Patient input indicated that the availability of afatinib will help improve the quality of life of Canadians with NSCLC compared to first-line chemotherapy and improve the control of symptoms for patients with advanced lung cancer. pERC noted that the side effect profile of afatinib was distinct from chemotherapy and manageable.

pERC noted that patients value oral therapies, greater accessibility and having a choice of therapies. As afatinib is an oral medication and more convenient to take than intravenous chemotherapy and has a more favourable side effect profile than chemotherapy, patients would not require frequent visits to the hospital or take as much time off work in order to receive lengthy chemotherapy treatments. The cost of travel is an additional burden for patients, especially in rural communities. Hospital appointments are often difficult to obtain and access to chemotherapy suites is limited in urban areas, and even more so in outlying areas. Patient input considered that having multiple EGFR Tyrosine-kinase inhibitors to choose from may promote greater competition in pricing and yield more options to choose from for both patients and practitioners. pERC considered that providing access to afatinib aligns with patient values and ensures that most patients in Canada have access to this class of drugs as a first-line treatment option, in spite of the heterogeneity of existing funding policies in this therapeutic area. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback received from the patient advocacy group during its deliberations on the pros and cons of funding afatinib in provinces that already have access to gefitinib. During these re-deliberations, pERC carefully considered the value of patient choice and the potential need for treatment options in patients with rare EGFR mutations.

In considering patient values, it was noted that afatinib and gefitinib were both oral therapies in the same drug class and the CGP were unable to identify substantive reasons why they would prescribe one therapy over another (e.g. improved efficacy, reduced toxicity, improved convenience or accessibility). Therefore, although generally supportive of choice as an important patient value, some pERC members considered that funding afatinib would not provide a meaningful choice of different therapies to patients. It was also noted that the CGP had indicated that, from a clinical perspective, the afatinib data on rare EGFR mutations (e.g. Exon 20, T790M) would likely be generalized to other tyrosine kinase inhibitors. However, some pERC members also discussed that providing funding for afatinib would align with patient values because it would provide access to more treatment options.

pERC also noted that the patient advocacy group input included only a small number of patients with direct experience with afatinib. While recognizing the difficulty patient advocacy groups may have in accessing a large number of patients who have had experience with a drug that has only recently received regulatory approval in Canada, pERC considered that it would be helpful to get input from a larger number of patients who may have had both positive and negative experiences with afatinib.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel assessed a cost-effectiveness and cost-utility analysis of afatinib as first line treatment of patients with locally advanced or metastatic NSCLC with EGFR mutations as compared to pemetrexed/cisplatin (LUX-Lung 3), gefitinib or erlotinib (via network meta-analysis using LUX-Lung 3 and LUX-Lung 6 and other clinical data). As erlotinib is not funded as a first-line treatment in most provinces, the EGP focused on cost-effectiveness estimates compared with gefitinib.

Basis of the economic model: clinical and economic inputs

Costs considered in the analysis included drug acquisition costs, drug administration costs, adverse event management costs, and other health care costs (i.e., disease management costs).

The clinical effects considered in the analysis were based on pre- and post-progression survival, adverse event rates and adverse event severity.

Drug costs: confidential price, effective price of comparators and flat pricing

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. *(Non-disclosable information was provided to pERC in the pCODR guidance reports for deliberation on a recommendation and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.)* 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.

Input from PAG noted the flat pricing for all four strengths of afatinib. PAG stressed the importance of pricing being per mg and indicated that the flat pricing for all tablet strengths is a barrier to implementation. The pCODR Clinical and Economic Guidance Panels considered the potential impact of flat pricing and dose reductions. However, the Panels considered that in this specific instance, applying standard dose reductions (decreases in 10mg decrements to a minimum of 20mg per day) or escalations (to 50 mg per day) would likely not lead to higher costs as one tablet per day could still be administered given the availability of the appropriate tablet strengths for afatinib

At the list price, 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.

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. The effective price of pemetrexed may vary across jurisdictions and be lower than the list price if it is based on a confidential price that is unknown to pCODR.

Cost-effectiveness estimates: cost-effective when compared to cisplatin-pemetrexed

pERC deliberated upon the cost-effectiveness of afatinib compared with other possible therapies. It was noted that when comparing afatinib with cisplatin-pemetrexed, the manufacturer's estimates and the EGP's best estimates were the same. Based on this estimate, and additional sensitivity analyses, pERC considered that afatinib was cost-effective at the submitted confidential price compared with cisplatin-pemetrexed. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the Provincial Advisory Group regarding potential differences between the list price and the effective price of pemetrexed, which could impact the cost-effectiveness of afatinib. pERC discussed additional sensitivity analyses conducted by the EGP and noted that, even at lower prices of pemetrexed, afatinib is likely still within a range that could be considered cost-effective.

Cost-effectiveness estimates: unknown when compared to cisplatin-gemcitabine

An economic evaluation comparing afatinib with cisplatin-gemcitabine or other cisplatin-based chemotherapy doublets was not provided by the Submitter. Therefore, pERC considered that the cost-effectiveness of afatinib compared with cisplatin-gemcitabine or other cisplatin-based chemotherapy doublets is unknown and pERC was unable to make an informed funding recommendation in the absence of information on cost-effectiveness. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the patient advocacy group suggesting that pCODR's EGP should estimate the cost-effectiveness of afatinib compared with cisplatin-gemcitabine. However, pERC agreed with the EGP that conducting such an analysis without an appropriate economic model provided by the submitter would not yield credible results. This would require too many assumptions by the EGP and would not provide a reasonably robust estimate that could be used for decision-making purposes. pERC also noted that the EGP had not identified any published cost-effectiveness analyses comparing afatinib with cisplatin-gemcitabine that could be used to inform cost-effectiveness in the Canadian setting. pERC recognized that this may create implementation challenges in provinces where cisplatin-gemcitabine is the most relevant comparator. However, pERC noted that information on the cost-effectiveness of afatinib compared with cisplatin-gemcitabine could inform a resubmission for afatinib

Cost-effectiveness estimates: when compared to gefitinib, depends on similar clinical benefit and effective drug prices that are at least comparable

pERC also considered the cost-effectiveness of afatinib compared with other tyrosine kinase inhibitors, including gefitinib, based on a submitted economic evaluation. The EGP's best estimates produced a very large range of incremental cost-effectiveness estimates. pERC noted that small differences in QALYs resulting from differences in adverse event profiles could lead to high incremental cost effectiveness ratios if one were willing to assume that the efficacy of the different tyrosine kinase inhibitors was similar. During deliberations on the Initial Recommendation, pERC had concluded that there was too much uncertainty to be able to determine the cost-effectiveness of afatinib compared with gefitinib or other tyrosine kinase inhibitors, due to the uncertainty in the network meta-analysis and the absence of a randomized controlled trial directly comparing afatinib with a tyrosine kinase inhibitor.

Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback received from all stakeholders on the desire to have access to afatinib as another treatment option in provinces already funding an EGFR tyrosine kinase inhibitor. During its re-deliberations, pERC discussed that the relative cost-effectiveness of the two drugs is highly dependent on their relative clinical benefit. Some pERC members reiterated that because of the uncertainty in the comparative effectiveness of afatinib versus gefitinib and the limitations of the submitted indirect comparison, the incremental effect and resulting cost-effectiveness is uncertain. This was reflected in the EGP's best estimates by a wide range of incremental cost effectiveness ratios, not all of which would be considered cost-effective by pERC. However, other pERC members noted that if one accepts that afatinib and gefitinib have similar effects (including both effectiveness and safety), a cost-minimization approach could be applied. pERC noted that, in this clinical scenario, at the list prices of afatinib and gefitinib, afatinib costs more than gefitinib but at the submitted confidential price of afatinib and the list price of gefitinib, afatinib could be considered cost-effective compared with gefitinib. However, the effective price of gefitinib may vary across jurisdictions and be lower than the list price. In this case, the relative effective prices of afatinib and gefitinib are critical to cost-effectiveness, which could be a potential advantage to consider during implementation and pricing negotiations.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: heterogeneity of comparators across provinces and the need to determine optimal sequencing

pERC considered the feasibility of implementing a funding recommendation for afatinib. pERC noted the heterogeneity of comparators and funding policies in the first-line setting for patients with EGFR mutation positive advanced or metastatic adenocarcinoma of the lung across Canada. pERC discussed that the optimal sequencing of agents is this setting is currently unknown. However, pERC recognized that provinces may need to address this issue upon implementation of funding and noted that the development and implementation of an evidence-based guideline would be of value to guide consistency in drug funding. pERC also noted that the heterogeneity of comparators also resulted in uncertainty in budget impact as it will depend on the first-line treatment that afatinib is replacing. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from pCODR's Provincial Advisory Group on the challenges of implementing separate recommendations that depend on what therapies each

province is currently funding and noted this when formulating the pERC Final Recommendation. pERC also discussed that different recommendations for different provinces presented an implementation barrier, as this scenario could prevent provinces from negotiating drug prices as one body.
The feasibility of adoption into the health system was also discussed. It was noted that stakeholders who must manage implementation issues had provided feedback asking pERC to reconsider its recommendation as it relates to other tyrosine kinase inhibitors and some pERC members considered this a reason to fund afatinib as an alternative to gefitinib.

pERC discussed the use of afatinib in patients with an ECOG performance status of 2 or greater, which may be a factor upon implementation of a funding recommendation for afatinib. While pERC noted that there was a need for effective therapies in these patients, they were excluded from the LUX-Lung 3 and LUX-Lung 6 studies and, therefore, pERC was unable to make an informed recommendation for this population in the absence of any data. It was noted that collection of prospective evidence on the use of afatinib in patients with ECOG performance status of 2 or greater could be of benefit if there is clinical interest in using afatinib in these patients.

DRUG AND CONDITION INFORMATION

Drug Information	• Tyrosine kinase inhibitor, irreversible Erb-B family blocker • 20mg, 30mg, 40mg and 50 mg tablet • 40 mg per day until disease progression
Cancer Treated	• Advanced or metastatic, non-small cell lung cancer • EGFR-mutation positive adenocarcinoma • First-line setting
Burden of Illness	• In 2012 there will be 25,600 new cases and 20,100 deaths associated with NSCLC in Canada. EGFR activating mutations exist in 12% of this population.
Current Standard Treatment	• Tyrosine kinase inhibitors, gefitinib and erlotinib, are first-line options. However, erlotinib, is currently only funded as a second- or third-line treatment in all provinces. • If platinum-doublets are used, Cisplatin-pemetrexed has become the preferred platinum-doublet for first-line treatment
Limitations of Current Therapy	• Platinum doublet chemotherapy is accompanied by significant toxicity.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Matthew Cheung, Oncologist
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Wasney, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Dr. Bill Evans, Dr. Chaim Bell and Carole McMahon who were not present for the meeting.

All members participated in deliberations and voting on the final recommendation except:

- Dr. Maureen Trudeau and Dr. Chaim Bell who were not present for the meeting.
- Dr. Bill Evans who was excused from deliberations and voting due to a conflict of interest
- Carole McMahon who was excluded from voting due to her role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of afatinib (Giotrif) for advanced non-small cell lung cancer, through their declarations, eight members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, However, one of the attending members was excluded from deliberations and voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. Boehringer Ingelheim Canada Ltd., as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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