pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL 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.

Providing Feedback on this Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pERC will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this 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 Issued:
March 6, 2014

pERC RECOMMENDATION	**For 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,** the pCODR Expert Review Committee (pERC) recommends funding afatinib (Giotrif). Funding should be for patients with EGFR mutation positive adenocarcinoma of the lung and with an ECOG performance status 0 or 1 when afatinib is used as a replacement therapy to first-line cisplatin-pemetrexed. pERC made this recommendation because it was satisfied that there is a net clinical benefit of afatinib compared with cisplatin-pemetrexed and that at the submitted prices, afatinib is cost-effective when used as a replacement therapy for cisplatin-pemetrexed. **For provinces where a tyrosine kinase inhibitor is funded in the first-line setting for the treatment of** advanced or metastatic NSCLC, pERC does not recommend funding afatinib (Giotrif) in patients with EGFR mutation positive adenocarcinomas of the lung. pERC made this recommendation 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 the net clinical benefit and the cost-effectiveness of afatinib compared with other tyrosine kinase inhibitors.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**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 platinum-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.

Possibility of a Resubmission to Support Broader Funding
There is one ongoing randomised controlled trial, LUX-Lung 7 (Study NCT01466660), comparing afatinib to gefitinib as first-line treatment in patients with EGFR mutation positive advanced adenocarcinoma of the lung. This study may provide more robust information on the comparative effectiveness of afatinib versus gefitinib that could inform a resubmission for afatinib in this setting. Also, information on the cost-effectiveness of afatinib compared with cisplatin-gemcitabine 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 is 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 burden of illness associated with epidermal growth factor receptor (EGFR) mutation positive, metastatic or advanced non-small cell lung cancer (NSCLC) 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 platinum-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 and noted that afatanib's side effects were distinct from those of the chemotherapies but were those expected for 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. 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. pERC noted that there are currently no completed 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 that uncertainty was created by the heterogeneity of included patients' EGFR mutation status. pERC noted that there is currently an ongoing randomized controlled trial, LUX-Lung 7, comparing afatinib with gefitinib, which could provide more robust comparative information in the future. pERC also discussed whether there was a clinical 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 these provinces not offering a first-line tyrosine kinase inhibitor afatinib would offer a greater benefit over platinum-based chemotherapies and fulfill a clinical need. However, 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. Therefore, pERC concluded there was too much uncertainty in the net clinical benefit of afatinib compared with other tyrosine kinase inhibitors.

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 in provinces that currently do not fund a tyrosine kinase inhibitor in the first-line setting, aligns with patient values. If afatinib were to be funded, this also ensures that all patients in Canada have access to this class of drugs as a first-line treatment option, reducing the heterogeneity of existing funding policies in this therapeutic area.

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, 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 platinum-based chemotherapy doublets was not provided by the Submitter. Therefore, pERC considered that the cost-effectiveness of afatinib compared with cisplatin-gemcitabine or other platinum-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 comparator. However, pERC noted that information on the cost-effectiveness of afatinib compared with cisplatin-gemcitabine could inform a resubmission for afatinib.

pERC also considered the cost-effectiveness of afatinib compared with other tyrosine kinase inhibitors, including gefitinib, based on a submitted economic evaluation. However, due to the uncertainty in the network meta-analysis and the absence of a randomized controlled trial comparing afatinib with a tyrosine kinase inhibitor, there was too much uncertainty in the cost-effectiveness of afatinib compared with gefitinib or other tyrosine kinase inhibitors.

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 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.

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) and input from pCODR's Provincial Advisory Group.

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 locally advanced or metastatic NSCLC with EGFR mutations.

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) 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 pharmacological interventions, including tyrosine kinase inhibitors for the first-line treatment of locally advanced or metastatic NSCLC.

Patient populations: ECOG performance status 0 or 1

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.

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 platinum-based chemotherapies.

Neither study demonstrated a statistically significant difference in overall survival. However, it was 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. All patient-reported symptoms and health-related quality of life was seen to be either an improvement or no difference as 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 appeared to be manageable and are expected adverse events with tyrosine kinase inhibitors. 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: indirect analysis vs tyrosine kinase inhibitors lacks clinical validity

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 uncertainty was created by the heterogeneity of patients' EGFR mutation status. 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, pERC determined there was too much uncertainty to draw conclusions regarding the relative efficacy of afatinib compared with other tyrosine kinase inhibitors.

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

pERC noted that 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 population, respectively. If left untreated, patients with metastatic NSCLC have a median survival after diagnosis of only 4-5 months. EGFR activating mutations exists 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 platinum-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 been approved 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. These agents are now established as standard of care in this patient population. However, gefitinib is only funded in some provinces as a first-line therapy and erlotinib is currently funded only as second-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 platinum-based chemotherapies and fulfills a clinical need. However, 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.

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 demonstrating improvements in progression-free survival and quality of life outcomes align with these patient values.

Patient values on treatment: oral therapy, choice of treatments, more tolerable therapies

Most Canadians with advanced NSCLCL 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, more so 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 in provinces that currently do not fund a tyrosine kinase inhibitor in the first-line setting, aligns with patient values; if afatinib were to be funded, this ensures that all 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. 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 or 40mg 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 three 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) 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.

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.

An economic evaluation comparing afatinib with cisplatin-gemcitabine or other platinum-based chemotherapy doublets was not provided by the Submitter. Therefore, pERC considered that the cost-effectiveness of afatinib compared with cisplatin-gemcitabine or other platinum-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 comparator. However, pERC noted that information on the cost-effectiveness of afatinib compared with cisplatin-gemcitabine could inform a resubmission for afatinib

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. However, 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, there was too much uncertainty to be able to determine the cost-effectiveness of afatinib compared with gefitinib or other tyrosine kinase inhibitors.

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.

pERC discussed the use of afatinib in patients with an ECOG performance status of 2 or greater 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, and 40mg tablet • 40 mg per day until disease progression
Cancer Treated	• Advanced or metastatic, EGFR-mutation positive non-small cell lung cancer • 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	• Cisplatin-pemetrexed has become the preferred platinum-doublet for first-line treatment for NSCLC if EGFR mutation status is unknown • Tyrosine kinase inhibitors, gefitinib and erlotinib, are first-line options. Erlotinib is however currently funded as a second-line treatment only in all provinces.
Limitations of Current Therapy	• Platinum doublet chemotherapy is however 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.

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, none of the attending members were excluded from 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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