pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

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

May 2, 2014

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of single-agent therapy with afatinib compared to an appropriate comparator, in patients with previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations.

Afatinib is an irreversible ErbB-family blocker with ability to block signaling from EGFR (ErbB1), human epidermal growth factor receptor 2 (HER2/ErbB2), ErbB4, and all relevant ErbB family dimers.[1,2] Health Canada recently approved afatinib for use in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s).

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two randomized controlled trials, LUX-Lung 3[3] and LUX-Lung 6[4], comparing the use of afatinib to cisplatin-based chemotherapy in patients with previously untreated locally advanced or metastatic NSCLC with EGFR mutations. The trials were very similarly in designed with some important distinctions:

- LUX-Lung 3 randomized patients 2:1 to afatinib or cisplatin-pemetrexed and enrolled 345 patients worldwide. The majority of patients in the afatinib and cisplatin-pemetrexed group respectively had an ECOG PS of 0 (40% and 35.7%) or 1(60% and 63.5%). Patients also had an exon 19 (49.1% and 49.6%), L858R (39.6% and 40.9%) or other (11.9% and 9.6%) EGFR mutation, in the afatinib and cisplatin-pemetrexed group, respectively.
- LUX-Lung 6 randomized patients 2:1 to afatinib or cisplatin-gemcitabine and enrolled 364 patients solely from Asia. The trial reported that the study was balanced at baseline for EGFR mutations on exon19 (51.2% and 50.8%) and L858R (38% and 37.7%) in the afatinib and cisplatin-gemcitabine group, respectively. 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).[4]

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.

Efficacy

The primary outcome in both studies was independently assessed progression-free survival (PFS) with overall survival (OS) as secondary outcomes.

After a median follow up of 16.4 (LUX-Lung 3)[3] and 16.6 (LUX-Lung 6)[4] months, both studies reported statistically 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. In LUX-Lung 3 pre-specified subgroup by L858R mutation did not show a statistically significant difference in progression-free survival between the two arms and was likely underpowered to detect a difference.[3]

Neither study demonstrated a statistically significant difference in OS.

Quality of Life

A statistically significant higher proportion of patients in the afatinib arm experienced a clinically meaningful improvement in dyspnea compared to cisplatin-based chemotherapy in both trials (Table 3). Patients in the afatinib arm in both studies experienced a statistically significantly longer time to deterioration in cough and dyspnea scores than patients in the cisplatin-based chemotherapy arm (Table 3). In addition, patients in the afatinib arm in both studies had a statistically significant difference in mean symptom score over time for both dyspnea and cough scores compared to the cisplatin-based chemotherapy arm (Table 3).

Harms

In both trials, the proportion of patients who experienced grade 3 or higher neutropenia, leukopenia, and anemia was higher in the cisplatin-based chemotherapy arm compared to the afatinib arm (Table 4). In contrast, more patients in the afatinib arms experienced grade 3 or higher diarrhea, rash or acne, or stomatitis or mucositis than in the cisplatin-based chemotherapy arm, in both trials (Table 4). Neither study reported statistical comparisons for differences between the treatment arms in the rates of adverse events.

Treatment was discontinued due to a treatment-related adverse event in 8% vs. 12% of patients in LUX-Lung 3[3] and 8.8% vs. 39.8% of patients in LUX-Lung 6[4] in the afatinib compared to cisplatin-based chemotherapy arm, respectively.

Fatal adverse event were reported in 6.1% vs. 2.7% (LUX-Lung 3) and 6.3% vs. 4.4% (LUX-Lung 6) of patients who received afatinib compared to cisplatin-based chemotherapy.[5] In LUX-Lung 3, 4 vs. 0 deaths were considered potentially treatment-related by the investigators the afatinib compared to cisplatin-pemetrexed arms.[5] In the LUX-Lung 6 study, one death in each arm was considered treatment-related.[4]

1.2.2 Additional Evidence

pCODR received input on afatinib (Giotrif) for advanced non-small cell lung cancer from one patient advocacy group, Lung Cancer Canada. Provincial Advisory group input was obtained from nine of the nine provinces participating in pCODR.

In addition, one supplemental question was identified during development of the review protocol as relevant to the pCODR review of afatinib and is discussed as supporting information:

- Critical Appraisal of a Network Meta-Analysis Comparing Afatinib with Other Pharmacological Interventions for the First-Line Treatment of Locally Advanced or Metastatic NSCLC

1.2.3 Interpretation and Guidance

Burden of Illness and Need

It is estimated that in 2012 there will be 25,600 new cases and 20,100 deaths associated with NSCLC in Canada with an incidence and mortality rate of 54/100,000 and 42/100,000 population, respectively. The 5 year survival across all stages of NSCLC is 15% and a majority of patients present with advanced stage disease. If left untreated, patients with metastatic NSCLC have a median survival after diagnosis of 4-5 months.

EGFR activating mutations exists in 12% of the NSCLC population and although this population 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 not inconsequential.

Cisplatin-pemetrexed has become the preferred platinum-doublet for first-line treatment of those non-squamous patients who do not have an activating EGFR mutation. Platinum doublet chemotherapy is however accompanied by significant toxicity and 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 (TKIs), gefitinib and erlotinib, have been approved for first-line therapy for advanced EGFR mutation positive NSCLC due to improved progression free survival (PFS), response rates (ORR) and QoL compared to chemotherapy. These agents are now established as standard of care in this patient population. Erlotinib is however currently funded in all provinces for second-line treatment only.

Effectiveness

LUX-Lung 3 and LUX-lung 6, have demonstrated a statistically and clinically significant improvement in PFS and ORR in favour of afatinib versus standard platinum doublet chemotherapy for untreated, locally advanced or metastatic EGFR mutation positive NSCLC. The preliminary analysis for OS in both studies did not demonstrate a benefit with afatinib and can likely be attributed to the rate of cross over to an EGFR TKI following progression on chemotherapy which confounds the analysis. Recent data on the activity of afatinib in rare mutations demonstrated that in rare mutations, other than exon 20 insertions and T790M mutations (reported to be low at 8% and 14% respectively), PFS and OS are similar to those reported with the common mutations.[6]

Quality of life was assessed in both phase III studies and all patient-reported symptoms and health-related QoL had seen either an improvement or no difference with afatinib compared to chemotherapy. Both studies reported a clinically meaningful improvement in dyspnea and a delay in time to deterioration in cough and dyspnea with afatinib compared to cisplatin-based chemotherapy.

A critical appraisal of a network multivariate analysis comparing afatinib with gefitinib and erlotinib was presented. 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.[7] Therefore, at present the benefit of one EGFR TKI over the other is uncertain.

Safety

Afatinib had an expected toxicity profile of increased diarrhea, stomatitis and rash compared to chemotherapy and overall comparable grade 3 /4 adverse events to chemotherapy. The degree of toxicity also appeared to be manageable as the rate of discontinuation was low and treatment related mortality was low (<1%). Despite the adverse events noted with afatinib there was improvement of clinically meaningful global health status compared to both cisplatin-based chemotherapy regimens.

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 use as part of the network meta-analysis which were evaluating the efficacy of gefitinib and erlotinib.

In response to feedback received from stakeholders regarding the comparative efficacy of afatinib to gefitinib, the CGP noted that from a clinical perspective, is unlikely that afatinib would be considered less efficacious than gefitinib or erlotinib in terms of PFS, the primary outcome in these trials. As such the CGP considered that from a clinical perspective, clinicians should have the option to prescribe either EGFR TKI in the first line setting. From a clinical perspective, afatinib may be considered to have higher rates of toxicities; however, all of these are manageable. The CGP also noted that the most important data that will be generated from the LUX-Lung 7 trial will be direct comparative evidence regarding toxicities and QoL between afatinib and gefitinib. Although direct comparative efficacy data will also be made available from LUX-Lung 7, the trial may not be powered to detect statistically significant differences among the two arms (see section 6.4).

The CGP noted that patients with rare mutation represent a small minority of the patient population. Access to testing for these rare mutations varies across the country; therefore, not all patients may be tested. The CGP also noted that except for the exon 20 insertion and T790M mutation, patients with the other rare mutations appeared to have the same clinical benefit from afatinib as patients with the common mutations. The CGP considered that from a clinical perspective, it is likely that clinicians will extrapolate data from the LUX-Lung 3 and 6 trials evaluating afatinib, to gefitinib and erlotinib and consider that rare mutations are sensitive to all EGFR TKI inhibitors. As such, in clinical practice patients with rare mutations are likely to be treated with gefitinib or erlotinib, as well as afatinib, as a first line therapy.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to afatinib over chemotherapy as first-line treatment of locally advanced or metastatic EGFR mutation positive NSCLC. This conclusion is based on two phase III randomized clinical trials, LUX-Lung 3 and LUX-Lung 6, which demonstrated an improvement of progression free survival, overall response rate and quality of life with afatinib compared to standard cisplatin based chemotherapy in previously untreated locally advanced or metastatic EGFR mutation positive NSCLC. With appropriate companion EGFR mutation testing, the panel concluded that afatinib is a new and reasonable option over chemotherapy for first-line systemic therapy for locally advanced or metastatic EGFR mutation positive NSCLC. The Clinical Guidance Panel acknowledged that there are two EGFR TKIs, gefitinib and erlotinib, available for the first-line treatment of locally advanced or metastatic EGFR mutation positive NSCLC. 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 as there are no head to head clinical trials comparing these agents. The CGP noted that from a clinical perspective, is unlikely that afatinib would be considered less efficacious than gefitinib or erlotinib in terms of PFS and any potential differences in harms would be manageable. As such the CGP considered that clinicians should have the option to prescribe either EGFR TKI in the first line setting. Afatinib may be associated with increased toxicity leading to dose modification; however these are cross-trial comparisons, and at present there are no head-to-head data available to inform which EGFR TKI may be the superior agent in this setting. The results of pending trials may further clarify this.

The Clinical Guidance Panel also considered that:

- No overall survival advantage has been demonstrated with afatinib however, limited follow up and a high rate of crossover to EGFR TKI inhibitors following progression of chemotherapy in the two phase III trials are potential confounding factors that limit the assessment of afatinib's impact on overall survival. The Panel felt it would have been unethical to deny an EGFR TKI to patients with a known mutation after progressing from chemotherapy.
- The use of afatinib beyond first-line therapy including patients who had received a prior EGFR TKI was beyond the scope of this review and it would be inappropriate to draw conclusions in this patient population.
- The CGP noted that the most important data that will be generated from the LUX-Lung 7 trial will be direct comparative evidence regarding toxicities and QoL between afatinib and gefitinib. Although direct comparative efficacy data will also be made available from this trial, it may not be powered to detect statistically significant differences among the two arms.
- Although patients with rare mutation represent a small minority of the patient population, from a clinical perspective, it is likely that clinicians will extrapolate data from the LUX-Lung 3 and 6 trials evaluating afatinib, to gefitinib and erlotinib and consider that rare mutations are sensitive to all EGFR TKI inhibitors. As such, in clinical practice, patients with rare mutations are likely to be treated with gefitinib or erlotinib, **as well as afatinib,** as first line therapy.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding afatinib (Giotrif) for advanced non-small cell lung cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding afatinib (Giotrif) conducted by the Lung Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on afatinib (Giotrif) and a summary of submitted Provincial Advisory Group Input on afatinib (Giotrif) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths globally for both men and women, with the majority of patients presenting with non-curable disease.[8,9] If left untreated, patients with advanced NSCLC have a median survival after diagnosis of 4-5 months.[10]

First-line treatments for advanced stage NSCLC include palliative platinum-based chemotherapy doublets. The introduction of newer agents, such as vinorelbine, gemcitabine, pemetrexed, paclitaxel, or docetaxel, paired with platinum agents in this setting has resulted in small improvements in patient outcomes; however, the majority of patients still experience disease progression, with a median time to progression of four months and a median survival of 8-10 months.[11-13]

In 2004, two pivotal studies showed that the presence of somatic activating mutations in the kinase domain of the epidermal growth factor receptor (EGFR) of NSCLC tumours, particularly small in frame deletions in exon 19 (deletion 19) and L858R missense mutation in exon 21 (L858R) which accounts for 90% of the EGFR mutations, strongly correlated with increased responsiveness to EGFR tyrosine kinase inhibitors (TKIs).[14-16] First generation small molecule reversible EGFR TKIs, gefitinib and erlotinib are now standard first-line treatment for patients with advanced NSCLC whose tumours harbour activating EGFR mutations.

Afatinib is an irreversible ErbB-family blocker with ability to block signaling from EGFR (ErbB1), human epidermal growth factor receptor 2 (HER2/ErbB2), ErbB4, and all relevant ErbB family dimers.[1,2] Afatinib has shown preclinical activity against cancer cells harbouring activating EGFR mutations, including the common mutations (deletion 19 and L858R) but in addition mutations in exon 20 of the kinase domain of EGFR and HER2. This includes the gatekeeper T790M mutation that is generally found to be resistant to EGFR TKIs and is responsible for acquired resistance to erlotinib and gefitinib in 60% of cases.[17-20] LUX lung 2, the phase II study with afatinib in advanced EGFR mutation positive NSCLC included 129 patients that were treatment naïve or had progressed following

chemotherapy.[21] ORR of afatinib by independent review was 61% with a median PFS of 10.1 months (95% CI 8.1-13.8) and median OS of 24.8 months (95% CI 22.0–38·7).

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness of single-agent therapy with afatinib compared to an appropriate comparator, in patients with previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations.

See Table 5 in Section 6.2.1 for outcomes of interest and appropriate comparators.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

Two randomized controlled trials comparing the use of afatinib to cisplatin-based chemotherapy in patients with previously untreated locally advanced or metastatic NSCLC with EGFR mutations were identified and included in this clinical guidance report.[3,4] A brief summary of the key trial quality characteristics can be found in Table 1. For a more detailed description of the trials' designs and patient characteristics, please see Table 6 in the *Systematic Review* (Section 6.3.2.1). The trials were very similarly designed, with two important distinctions: LUX-Lung 3 randomized patients 2:1 to afatinib or cisplatin-pemetrexed while LUX-Lung 6 randomized patients 2:1 to afatinib or cisplatin-gemcitabine; and, LUX-Lung 3 enrolled 345 patients worldwide, while LUX-Lung 6 enrolled 364 patients solely from Asia. In both trials afatinib was administered at a dose of 40 mg per day until disease progression and the dose could be increased to 50 mg per day after the first 21 days if the patient did not experience Grade 2 or higher drug-related adverse events. The dose could be decreased, in 10 mg per day increments (to a minimum of 20 mg per day) to manage Grade 3 or higher or select and prolonged Grade 2 adverse events. In LUX-Lung 3, cisplatin (75 mg/m^2 iv) and pemetrexed (500 mg/m^2 iv) were administered every 21 days for a maximum of six cycles. In the LUX-Lung 6 study, cisplatin (75 mg/m^2 iv) and gemcitabine (1000 mg/m^2 iv) were administered every 21 days for a maximum of six cycles.

Table 1. Select quality characteristics of included RCTs of afatinib in patients with previously untreated locally advanced or metastatic NSCLC with EGFR mutations.

Study	Treatment	Primary outcome	Required sample size (80% power, α=0.05)	Sample size N	Randomization method	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Ethical Approval
LUX-Lung 3 Study[3]	Afatinib Vs. Cis-Pem	PFS	330 patients required for 217 events to provide 90% power to detect a HR=0.64 using a two-sided overall alpha=0.05, assuming median PFS of 7 months for Cis-Pem arm and 11 months for afatinib arm.	Afatinib: 230 Cis-Pem: 115	Central (appropriate), stratified[A,*]	Yes*	Outcome assessors[B] and data analysts*	Yes	Yes	No	Yes*
LUX-Lung 6 Study[4]	Afatinib Vs. Cis-Gem	PFS	330 patients required for 217 events to provide 90% power to detect a HR=0.64 using a two-sided overall alpha=0.05, assuming median PFS of 7 months for Cis-Gem and 11 months for afatinib arm.	Afatinib: 242 Cis-Gem: 122	Central (appropriate), stratified[C]	Yes	Outcome assessors[B] and data analysts	Yes	Yes	No	Yes

Notes: Cis = cisplatin; **Gem** = gemcitabine; **ITT** = intention-to-treat; **N** = number of patients randomized; **NR** = not reported; **Pem** = pemetrexed; **PFS** = progression-free survival; **TTP** = time-to-progression.
[A]Stratification was by type of EGFR mutation (L858R, exon 19 deletion, or other) and by race (Asian or non-Asian).
[B]Tumour response (and disease progression) was assessed by an independent and blinded review committee.
[C]Stratification was by type of EGFR mutation (L858R, exon 19 deletion, or other).
*Information was obtained through a request to the submitter from pCODR.[5]

The primary outcome in both studies was independently assessed progression-free survival with overall survival as a secondary outcome. Both studies enrolled a sufficient number of patients to meet the pre-specified sample size requirement. Both studies used an appropriate method of randomization to prevent prediction of treatment assignment. In both studies, a blinded and independent review committee assessed tumour response and disease progression. In addition, data analysts were also blinded to treatment assignment. Both studies included all randomized patients as assigned in their final analysis, and neither study was terminated early.

In both studies, the study personnel, treating physicians, and patients were not blinded to treatment assignment. There is a potential for bias in the results, especially for patient-reported outcomes such as quality of life, in favour of whichever arm the assessor (either study personnel or the patient in the case of quality-of-life outcomes) felt was likely to provide benefit. Importantly, in both studies, tumour assessments were conducted by a blinded and independent committee, which would have resulted in unbiased assessments for tumour response and the primary outcome, progression-free survival.

The LUX-Lung 3 study was conducted worldwide; however approximately 70% of the study population was defined as East Asian. In addition, the LUX-Lung 6 study was conducted solely in Asia. If this population has a different disease course or responds differently to treatment than other populations, the results of both studies may be difficult to generalize to a Canadian population.

The key efficacy results for both studies are summarized in Table 2. Both studies reported statistically significant differences in both independently- and investigator-assessed progression-free survival in favour of the afatinib arm compared to cisplatin-based chemotherapy (Table 2). In interim analyses, neither study demonstrated a statistically significant difference in overall survival (Table 2). Both studies reported a statistically significant difference in objective response rate in favour of the afatinib arm compared to the cisplatin-based chemotherapy arm (Table 2).

Table 2. Efficacy outcomes reported in included studies of afatinib in patients with previously untreated locally advanced or metastatic NSCLC with EGFR mutations.

Study	Tumour assessment	Treatment arms	OS, median (mos)	PFS, median (mos)	Objective response, n (%)	Follow-up, median (mos)
LUX-Lung 3 Study[3,5]	Independent	Afatinib, n=230 Cis-Pem, n=115	NYR NYR HR 1.12 95%CI 0.73-1.73 p=0.60	11.1 6.9 HR 0.58 95%CI 0.43-0.78 p=0.001	129* (56%) 26* (23%) p=0.001	16.4
	Investigator	Afatinib, n=230 Cis-Pem, n=115	N/A	11.1 6.7 HR 0.49 95%CI 0.37-0.65 p=0.001	NR (69%) NR (44%) p=0.001	
LUX-Lung 6 Study(ref-Wu 2014 Lancet)	Independent	Afatinib, n=242 Cis-Gem, n=122	22.1 22.2 HR 0.95 95%CI 0.68-1.33 p=0.76	11.0 5.6 HR 0.28 95%CI 0.20-0.39 p<0.0001	162 (66.9%) 28 (23.0%) p<0.0001	16.6
	Investigator	Afatinib, n=242 Cis-Gem, n=122	N/A	13.7 5.6 HR 0.26 95%CI 0.19-0.36 p<0.0001	180 (74.4) 38 (31.1) p<0.0001	

Notes: 95%CI=95% confidence interval; **Cis-Gem**=cisplatin+gemcitabine; **Cis-Pem**=cisplatin+pemetrexed; **HR**=hazard ratio with HR<1 favouring afatinib; **mos**=months; **n**=number of patients; **N/A**=not applicable; **NR**=not reported; **NYR**=not yet reached; **OS**=overall survival; **PFS**=progression-free survival.

*Information was obtained through a request to the submitter from pCODR.[5]

Both studies assessed quality-of-life 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).[4,22,23] Baseline questionnaires were completed by more than 90% of patients in LUX-Lung 3 and by more than 85% of patients in LUX-Lung 6.[4,22] Clinically meaningful symptom improvement or worsening was defined as a change in baseline score of more than or less than 10 points, respectively. A summary of the quality-of-life outcomes that were pre-specified for both studies can be found in Table 3. Of note, a statistically significant higher proportion of patients in the afatinib arm experienced a clinically meaningful improvement in dyspnea compared to cisplatin-based chemotherapy in both trials (Table 3). Patients in the afatinib arm in both studies experienced a statistically significantly longer time to deterioration in cough and dyspnea

scores than patients in the cisplatin-based chemotherapy arm (Table 3). In addition, patients in the afatinib arm in both studies had a statistically significant difference in mean symptom score over time for both dyspnea and cough scores compared to the cisplatin-based chemotherapy arm (Table 3).

Table 3. Pre-specified analyses of clinically meaningful changes patient-reported outcomes for included studies of afatinib in patients with previously untreated locally advanced or metastatic NSCLC with EGFR mutations.

Trial	Treatment arms	Proportion of patients with clinically meaningful improvement in symptoms (%)			Time to deterioration of symptom, Median (months)			Differences in mean symptom score over time (adjusted mean difference)		
		Cough	Dyspnea	Pain	Cough	Dyspnea	Pain	Cough	Dyspnea	Pain
LUX-Lung 3 Study[22]	Afatinib, n=230 Cis-Pem, n=115	67.0 60.0 p=0.2444	64.0* 50.0* p=0.0103*	59.0* 48.0* p=0.0513*	NE 8.0 HR 0.60 95% CI: 0.41 to 0.87 p=0.007	10.3 2.9 HR 0.68 95% CI: 0.50 to 0.93 p=0.015	4.2 3.1 HR 0.83 95% CI: 0.62 to 1.10 p=0.19	-5.73 95% CI: -8.49 to -2.96 p<0.001	-5.77 95% CI: -8.11 to -3.43 p<0.001	0.77 95% CI: -2.08 to 3.62 p=0.598
LUX-Lung 6 Study[4,23]	Afatinib, n=242 Cis-Gem, n=122	76 55 p=0.0003	71 48 p<0.0001	64 47 p=0.003	NE 10.3 HR 0.45 95% CI: 0.30 to 0.68 p=0.0001	7.7 1.7 HR 0.54 95% CI: 0.40 to 0.73 p<0.0001	6.4 3.4 HR 0.70 95% CI: 0.51 to 0.96 p=0.0265	-6.34 95% CI: -9.10 to -3.58 p<0.0001	-9.89 95% CI: -12.13 to -7.66 p<0.0001	-5.89 95% CI: -8.50 to -3.27 p<0.0001

Notes: Cis-Gem=cisplatin+gemcitabine; **Cis-Pem**=cisplatin+pemetrexed.
*Data was obtained through requests to the submitter from pCODR.[5]

Key Grade 3 or higher adverse events can be found in Table 4. Neither study reported statistical comparisons for differences between the treatment arms in the rates of adverse events. Of note, LUX-Lung 3 reported a similar rate of any Grade 3 or higher adverse events for afatinib compared to cisplatin-pemetrexed, whereas the LUX-Lung 6 study reported that more patients in the cisplatin-gemcitabine arm experienced any grade 3 or higher adverse event compared to the afatinib arm (Table 4). In both trials, the proportion of patients who experienced grade 3 or higher neutropenia, leukopenia, and anemia was higher in the cisplatin-based chemotherapy arm compared to the afatinib arm (Table 4). In contrast, more patients in the afatinib arms experienced grade 3 or higher diarrhea, rash or acne, or stomatitis or mucositis than in the cisplatin-based chemotherapy arm, in both trials (Table 4).

In the LUX-Lung 3 study, treatment was discontinued due to a treatment-related adverse event in 8% of 229 patients in the afatinib arm and 12% of 111 patients in the cisplatin-pemetrexed arm.[3] In the LUX-Lung 6 study, 8.8% of 242 patients in the afatinib arm and 39.8% of 122 patients in the cisplatin-gemcitabine arm discontinued treatment due to a treatment-related adverse event.[4]

In the LUX-Lung 3 study, 14 of 229 patients (6.1%) who received afatinib had a fatal adverse event compared to three of 111 patients (2.7%) who received cisplatin-pemetrexed.[5] Four deaths in the afatinib arm were considered potentially treatment-related by the investigators.[5] No deaths in the cisplatin-pemetrexed arm were considered treatment-related.[5] In the LUX-Lung 6 study, 15 of 239 patients (6.3%) who received afatinib had a fatal adverse event compared to five of 113 patients (4.4%) who received cisplatin-gemcitabine.[5] One death in each arm was considered treatment-related.[4]

Table 4. Number of patients (percent) with Grade 3 or higher treatment-related adverse events that occurred in 5% or more of patients in either arm of the included studies of afatinib in patients with previously untreated locally advanced or metastatic NSCLC with EGFR mutations.

Grade 3 or Higher Adverse Event	LUX-Lung 3 Study[3]		LUX-Lung 6 Study[4]	
	Afatinib, n=229 n (%)	Cis-Pem, n=111 n (%)	Afatinib, n=239 n (%)	Cis-Gem, n=113 n (%)
Any adverse event, n (%)	112 (49)	53 (48)	86 (36.0)	68 (60.2)
Hematologic **Neutropenia**, n (%) **Leukopenia**, n (%) **Anemia, n (%)** **Thrombocytopenia, n (%)**	 1 (0.4) 1 (0.4) 1 (0.4) -	 20 (18.0) 9 (8.1) 7 (6.3) -	 1 (0.4) 1 (0.4) 1 (0.4) 1 (0.4)	 30 (26.5) 17 (15.0) 10 (8.8) 11 (9.7)
Hypokalemia, n (%)	-	-	3 (1.3)	9 (3.8)
Diarrhea, n (%)	33 (14.4)	0	13 (5.4)	0
Rash/acne, n (%)	37 (16.2)	0	35 (14.6)	0
Stomatitis/mucositis, n (%)	20 (8.7)	1 (0.9)	13 (5.4)	0
Paronychia, n (%)	26 (11.4)	0	0	0
Dry skin, n (%)	1 (0.4)	0	-	-
Decreased appetite, n (%)	7 (3.1)	3 (2.7)	3 (1.3)	2 (1.8)
Prutitis, n (%)	1 (0.4)	0	1 (0.4)	0
Nausea, n (%)	2 (0.9)	4 (3.6)	0	9 (8.0)
Fatigue, n (%)	3 (1.3)	14 (12.6)	1 (0.4)	1 (0.9)
Vomiting, n (%)	7 (3.1)	3 (2.7)	2 (0.8)	22 (19.5)
Epistaxis, n (%)	0	1 (0.9)	1 (0.4)	0

Notes: "**-**"=not reported; **Cis-Gem**=cisplatin-gemcitabine; **Cis-Pem**=cisplatin-pemetrexed; **n**=number of patients.

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel identified an abstract, reported by Yang et al[6] and presented at the 15th World Conference on Lung Cancer, that provided data on the activity of afatinib in patients with uncommon EGFR mutations (i.e., mutations other than Del19 or L858R) who were enrolled in the LUX-Lung 3, LUX-Lung 6 or the LUX-Lung 2 trials (LUX-Lung 2 was a non-comparative phase II study that treated patients with stage IIIB or IV adenocarcinoma of the lung with EGFR mutations who had received no more than one prior chemotherapy regimen for advanced disease, with afatinib monotherapy). Uncommon

mutations were classified as *de novo* T790M (alone or in combination with other mutations), exon 20 insertions, and other. For the LUX-Lung 3 and LUX-Lung 6 trials, only patients who received afatinib were included in this analysis. A total of 75 patients (LUX-Lung 2, n=23; LUX-Lung 3, n=26; LUX-Lung 6, n=26) had uncommon mutations (T790M, n=14; exon 20 insertions, n=23; other, n=38).[6] For the 14 patients with de novo T790 mutations, an objective response occurred in two patients (14.3%), with a median progression-free survival of 2.9 months (95% CI, 1.2-8.3), and a median overall survival of 14.9 months (95% CI, 8.1-24.9). For the 23 patients with exon 20 insertions, an objective response occurred in two patients (8.7%), with a median progression-free survival of 2.7 months (95% CI, 1.8-4.2), and a median overall survival of 9.4 months (95% CI, 4.1-21.0). For the 38 patients with other mutations (e.g., L861Q, G719X, G719X+S7681, G719X+L861Q), an objective response occurred in 27 patients (71.1%), with a median progression-free survival of 10.7 months (95% CI, 5.6-14.7), and a median overall survival of 18.6 months (95% CI, 16.4-not estimable).[6]

2.1.5 Summary of Supplemental Questions

Critical Appraisal of a Network Meta-Analysis Comparing Afatinib with Other Pharmacological Interventions for the First-Line Treatment of Locally Advanced or Metastatic NSCLC

The network meta-analysis provided by the manufacturer that investigated afatinib compared to any other pharmacological intervention reported that for patients with locally advanced or metastatic NSCLC, using a random effects model, the indirect comparison of afatinib to gefitinib for investigator-assessed progression-free survival demonstrated a HR of 0.70 with a 95% credible interval of 0.43 to 1.10.[24] Using independently assessed progression-free survival data, the HR was 0.78 (95% credible interval 0.47 to 1.20). The indirect comparison of afatinib to erlotinib for investigator-assessed progression-free survival demonstrated a HR of 0.82, 95% credible interval 0.50 to 1.30. For independently assessed progression-free survival, the HR was 0.91, 95% credible interval 0.53 to 1.50. Grade 3/4 adverse events of diarrhea, rash/acne and fatigue were also modeled but due to the low number of events in treatment arms, the results of the analyses were highly uncertain and uninformative.

There is uncertainty with respect to the estimated HR's and credible intervals for the indirect comparisons due to several limitations of the NMA. The inclusion of studies that reported only combined data for EGFR mutation-positive and mutation-negative locally advanced or metastatic NSCLC with studies that included only patients with EGFR mutation-positive disease introduces a potential for bias in the estimates of the indirect comparisons. In addition, there is uncertainty in the HR's and credible intervals for the indirect comparisons for investigator-assessed progression-free survival as investigator assessments have the potential to be biased in favour of the treatment that the investigator feels is superior. It is not possible to estimate the magnitude or direction of that potential bias given the complexity of the network. Of note, the estimates of the HR's and credible intervals calculated based on the independent assessments of progression-free survival were similar to the estimates based on investigator assessments. Although the authors reported the results using both the fixed and random effects models, the random effects model may be more appropriate given the inclusion of studies with different patient groups (some had EGFR-positive patients, some had both EGFR-positive and negative patients). As the effect of any of the identified treatments may be different for EGFR mutation-positive disease compared to EGFR mutation-negative disease, there is

likely to be more than one true treatment effect for each given treatment (e.g., one for EGFR mutation-positive patients and one for EGFR mutation-negative patients).

Of note, Lopes and Haaland reported, in abstract form at the 15th World Conference on Lung Cancer, the results of a network meta-analysis investigating the comparative effectiveness of gefitinib, erlotinib, afatinib, and chemotherapy in the first-line treatment of advanced NSCLC with EGFR mutations.[7] As this network meta-analysis has been published in abstract form only, insufficient information was reported in order to make any determinations regarding the study's potential limitations or risk of bias. What is notable is that the authors included randomized controlled trials that compared erlotinib, gefitinib, or afatinib to chemotherapy or to each other in the first-line treatment of advanced NSCLC. Studies were included only if the trial included only patients with EGFR activating mutations or if the study reported efficacy data separately for the subgroup of patients with EGFR activating mutations. Eight trials were included (OPTIMAL, EURTAC, LUX-Lung 3, LUX-Lung 6, IPASS, West Japan, North-east Japan, and First-SIGNAL). The pooled HR for progression-free survival for erlotinib vs. afatinib was 0.57 (95% CI, 0.26-1.23; 95% predictive interval, 0.21-1.55), and for afatinib vs. gefitinib was 1.02 (95% CI, 0.52-2.00; 95% predictive interval, 0.41-2.58).[7] The authors indicated that there was moderately high heterogeneity between studies (Q-statistic, p=0.003; I^2=72%).[7] For objective response rates, the pooled odds ratio for erlotinib vs. afatinib was 1.5 (95% CI, 0.7-3.3; 95% predictive interval, 0.6-3.7), and for afatinib vs. gefitinib was 1.3 (95% CI, 0.7-2.5; 95% predictive interval, 0.6-2.8), with moderate heterogeneity between studies (Q-statistic, p=0.198; I^2=32%).[7] No statistically significant differences were demonstrated for overall survival; however, no data were reported.[7]

See section 7.1 for more information.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient perspective, the availability of afatinib will help improve the quality of life of Canadians with NSCLC compared to first-line chemotherapy and improve the controlling of symptoms for patients with advanced lung cancer. Because afatinib is administered orally, respondents reported that the side effects were minimal, and the respondents were not required to undergo frequent visits to the hospital. 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.

PAG Input

Input on afatinib (Giotrif) for advanced non-small cell lung cancer was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, afatinib has enablers that include being an oral therapy that can be easily delivered in the community setting and EGFR testing being in place in many jurisdictions. Barriers include the potential for use of afatinib in the second-line treatment of NSCLC and for the treatment of other solid tumours, ahead of clinical trial data being available.

Other

The final product monograph[25] provided by the manufacturer (Boehringer Ingelheim Canada Ltd.) provides the following serious warnings and precautions:

General

Assessment of EGFR mutation status

EGFR mutation-status must be confirmed prior to starting GIOTRIF therapy. When assessing the EGFR mutation status a well-validated and robust methodology is necessary to avoid false negative or false positive determinations.

Clinical data supporting the efficacy of GIOTRIF in EGFR TKI naïve patients with uncommon EGFR mutations including the T790M mutation are limited. Although individual responses were observed in some patients with uncommon mutations, evidence for activity in patients with tumours harbouring de novo T790M mutations appears to be more limited in the pivotal LUX- Lung 3 study.

GIOTRIF contains lactose. Patients with rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ocular adverse reactions, including blurred vision and keratitis, have been reported in patients treated with GIOTRIF and may impact patients' ability to drive or operate machines.

Diarrhea

Diarrhea, including severe diarrhea, has been reported during treatment with GIOTRIF (see ADVERSE REACTIONS). Diarrhea has resulted in dehydration, clinically significant hypokalemia and/or renal impairment, and in rare cases fatal outcomes (see ADVERSE REACTIONS). In the pivotal trial, 96.1% of the patients in the GIOTRIF arm experienced diarrhea during the course of the study, of which 14.8% were CTCAE Grade 3 diarrhea. Diarrhea usually occurred within the first 2 weeks of treatment. Grade 3 diarrhea most frequently occurred within the first 6 weeks of treatment. Serious diarrhea occurred in 6.6% of patients. Diarrhea led to dose reduction and permanent discontinuation of GIOTRIF in 19.7% and 1.3% of patients, respectively. The majority of patients with diarrhea (92.7%) were treated with anti-propulsives.

Close monitoring and proactive management of diarrhea is essential for successful GIOTRIF treatment. Early and appropriate intervention can prevent the development of more severe diarrhea. In the protocol of LUX-Lung 3 study, it was recommended that loperamide should be made available at the start of GIOTRIF therapy and kept with the patient at all times. The recommendations for diarrhea management were as follows:

If any diarrhea is experienced (CTCAE Grade 1), 2 tablets of 2 mg loperamide should be taken immediately, followed by 1 tablet of 2 mg loperamide with every loose bowel movement, up to a maximum daily dose of 10 tablets, i.e., 20 mg loperamide.

Patients should be advised to avoid lactose-containing products or any foods known to aggravate diarrhea.

Oral hydration is essential regardless of severity; appropriate rehydration (1.5

L/m2/day plus equivalent of actual fluid loss) and electrolyte replacement has to be ensured for CTCAE Grade 2 and 3 diarrhea.

For CTCAE Grade 3 diarrhea or CTCAE Grade 2 diarrhea lasting ≥ 48 hours despite adequate anti-diarrheal treatment, GIOTRIF must be paused until recovery to CTCAE Grade ≤ 1. Upon recovery, GIOTRIF should be resumed at a reduced dose according to the dose reduction scheme.

If diarrhea does not resolve to CTCAE ≤ 1 within 14 days despite optimal supportive care and GIOTRIF treatment interruption, the patient must not receive further GIOTRIF treatment.

Close monitoring and proactive management of diarrhea including adequate hydration combined with anti-diarrheal agents (e.g., loperamide) is essential for successful GIOTRIF treatment of patients. Antidiarrheal agents should be readily available to the patients so that treatment can be initiated at first signs of diarrhea and if necessary, their dose should be escalated to the highest recommended approved dose. Antidiarrheal agents should be continued until loose bowel movements cease for 12 hours. Patients with severe diarrhea will require interruption and dose reduction or discontinuation of GIOTRIF therapy (see DOSAGE AND ADMINISTRATION). Patients should also be advised to drink an adequate amount of fluids to make up for the fluid lost through diarrhea. Patients who become dehydrated may require hospitalization and administration of intravenous electrolytes and fluids.

Prior to the start of GIOTRIF therapy, prescribers should ensure that patients are well informed of the risk of diarrhea and are able to proactively manage this side effect. Patients should be provided with contact information of a physician experienced in cancer treatment and seek advice on diarrhea management.

Patients with significant or recent gastrointestinal disorders with diarrhea as a major symptom, e.g., Crohn's disease, malabsorption or severe diarrhea of any etiology were excluded from the clinical trial. GIOTRIF is not recommended in this patient population.

Skin related adverse events

Grade 3 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions occurred in 6 (0.15%) of the 3865 patients who received GIOTRIF across clinical trials. In LUX-Lung 3, the overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 90%, and the incidence of Grade 3 cutaneous reactions was 16%. Palmar-plantar erythrodysaesthesia syndrome (PPE) was observed in 6.6% of patients. Grade 3 CTCAE PPE was reported in 1.3% of patients.

In general, rash manifests as a mild or moderate erythematous and acneiform rash, which may occur or worsen in areas exposed to sun. Bullous, blistering and exfoliative skin conditions have been reported including rare cases suggestive of Stevens-Johnson syndrome.

In vitro studies have shown that GIOTRIF has phototoxic potential and in rats afatinib accumulated in the retina and skin (see TOXICOLOGY).

Patients should be advised to avoid sun exposure or wear sufficient sun protection. Early intervention of dermatologic reactions can facilitate

continuous GIOTRIF treatment. Patients with prolonged or severe skin reactions require temporary interruption of therapy, dose reduction or discontinuation (see DOSAGE AND ADMINISTRATION), additional therapeutic intervention, and referral to a specialist with expertise in managing these dermatologic effects. GIOTRIF treatment should be discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

Interstitial Lung Disease (ILD)

ILD or ILD-like events (such as lung infiltration, pneumonitis, acute respiratory distress syndrome (ARDS), alveolitis allergic), including fatalities, were reported in patients receiving GIOTRIF for treatment of NSCLC. The incidence of drug-related ILD-like events was 1.3% in the pivotal study. ILD-like events were fatal in 0.4% of patients (see ADVERSE REACTIONS).

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnea, cough, fever) should be performed to exclude ILD. GIOTRIF should be interrupted pending investigation of these symptoms. If ILD is diagnosed, GIOTRIF should be permanently discontinued and appropriate treatment instituted as necessary.

Patients with a history of ILD have been excluded in clinical trials. GIOTRIF is not recommended for this patient subpopulation.

Hepatotoxicity

Hepatic failure, including fatalities, has been reported during treatment with GIOTRIF in less than 1% of patients. In patients receiving GIOTRIF 40mg, the frequencies of alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALKP) and total bilirubin Grade 2 were 7.2%, 4.6%, 6.4% and 1.4%, respectively. The values ≥ Grade 3 were 2.8%, 2.0%, 4.0% and 2.2% respectively.

Periodic liver function testing should be performed for all patients. GIOTRIF dose interruption may be necessary in patients who experience worsening of liver function (see DOSAGE AND ADMINISTRATION). In patients who develop severe hepatic impairment while taking GIOTRIF, treatment should be discontinued.

2.2 Interpretation and Guidance

Burden of Illness and Need

It is estimated that in 2012 there will be 25,600 new cases and 20,100 deaths associated with NSCLC in Canada with an incidence and mortality rate of 54/100,000 and 42/100,000 population, respectively. The 5 year survival across all stages of NSCLC is 15% and a majority of patients present with advanced stage disease. If left untreated, patients with metastatic NSCLC have a median survival after diagnosis of 4-5 months.

Palliative chemotherapy with a platinum based doublet has been the cornerstone of treatment for patients with advanced stage NSCLC and has resulted in a modest historical increase in overall survival (OS) and associated quality of life (QoL). Platinum doublet chemotherapy is accompanied

by significant toxicity and due to advanced age, poor performance status and/or co-morbidities many patients do not receive treatment in the first-line setting. Cisplatin-pemetrexed has become the preferred platinum-doublet for first-line treatment of those non-squamous patients who do not have an activating EGFR mutation due to superior outcomes and side effect profile compared to older drug regimens. Two EGFR tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, have been approved for first-line therapy for advanced EGFR mutation positive NSCLC due to improved progression free survival (PFS), response rates (ORR) and QoL compared to chemotherapy. These agents are now established as standard of care in this patient population. In jurisdictions that fund gefitinib, it is funded for first-line treatment. Erlotinib was approved in 2012 for first-line use but the manufacturer did not submit this indication for funding review. Erlotinib is currently funded in all provinces for second-line treatment only.

EGFR activating mutations exist in 12% of the non-Asian NSCLC population. Although the EGFR mutation positive population 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 not inconsequential. Also, in a subset of patients this rate can be as high as 60%. Afatinib has shown activity in rare mutations including those within exon 20 of kinase domain of EGFR, which are generally found to be resistant to erlotinib and gefitinib and are the mutations responsible for acquired resistance to these agents in a majority of cases. Up front EGFR mutation testing is required to determine the presence of the EGFR mutations and eligibility for first-line EGFR TKIs. In most jurisdictions this has been established due the use of gefitinib and erlotinib.

Effectiveness

Two randomized controlled trials, LUX-Lung 3 and LUX-lung 6, have demonstrated a statistically and clinically significant improvement in PFS and ORR in favour of afatinib versus standard platinum doublet chemotherapy for untreated, locally advanced or metastatic EGFR mutation positive NSCLC. The benefits between both trials were similar in magnitude. Both trials included patients with common EGFR mutations, deletion 19 and L858R, and rare mutations found within exons 18-21 of the kinase domain of EGFR.

The preliminary analysis for OS in both studies did not demonstrate a benefit with afatinib. This is likely due to the rate of cross over to an EGFR TKI following progression on chemotherapy which confounds the analysis (64.9% in LUX-lung 3, and 48.4% in LUX-lung 6 received an EGFR TKI post progression). This is similar to previous EGFR TKI trials that have yet to demonstrate an improved survival compared to chemotherapy. The median survival in these studies are much longer than historical controls supporting improved prognosis of advanced EGFR mutation positive NSCLC treated with an EGFR TKI.

During this review, data of afatinib activity in rare mutations in patients enrolled in LUX lung 2, 3 and 6 became available and was reported in an oral presentation at the 15th World Conference on Lung Cancer on October 28, 2013.[6] Response rates in exon 20 mutations and T790M mutation were low at 8% and 14% respectively; and median PFS was short, 2.7 and 2.9 months respectively. However, a disease stability rate of 65% was found in both groups. In rare mutations other than exon 20 insertions and T790M mutations ORR, PFS and OS reported were similar to those reported with the common mutations.

Quality of life was assessed in both phase III studies and all patient-reported symptoms and health-related QoL had seen either an improvement or no difference with afatinib compared to

chemotherapy. Both studies reported a clinically meaningful improvement in dyspnea and a delay in time to deterioration in cough and dyspnea with afatinib compared to cisplatin-based chemotherapy. LUX-lung 6 also reported an improvement in cough, pain and global health status with afatinib, and a delay in time to deterioration in pain and global health status. The difference in QoL seen between trials may reflect the comparator chemotherapy, as in LUX-lung 3 the comparator was cisplatin/pemetrexed which has superior outcomes compared to cisplatin/gemcitabine the comparator in LUX lung 6. Importantly, no difference in time to deterioration of global health status was observed for afatinib compared to cisplatin/pemetrexed in LUX lung 3. In both studies, study personnel, treating physicians and, patients were not blinded to treatment assignment which may have resulted in bias in QoL assessments by the patients.

The LUX-Lung 3 study was conducted worldwide; however approximately 70% of the study population was defined as East Asian. In addition, the LUX-Lung 6 study was conducted solely in Asia. It is possible that this population has a different disease course or responds differently to treatment than other populations, thus the results of both studies may be difficult to generalize to a Canadian population. However, previous EGFR TKI studies in Western populations have shown similar outcomes to those conducted primarily in Asia, supporting that the presence of an EGFR mutation is main the driver for outcomes with EGFR TKIs as opposed to clinical parameters, such as ethnicity.

Although the median PFS demonstrated by afatinib in the two Phase III clinical trials suggests an improvement compared to the currently available EGFR TKIs, gefitinib and erlotinib, this is an indirect treatment comparison across clinical trials. LUX-lung 3 did compare afatinib to cisplatin/pemetrexed which is currently the best comparator chemotherapy. A network multivariate analysis was submitted by the manufacturer comparing afatinib with other pharmacological interventions for first-line treatment of locally advanced or metastatic NSCLC which included gefitinib and erlotinib. There were limitations noted in the critical appraisal such as the network included studies of patients with only EFGR mutation positive NSCLC as well as data from studies that included both EGFR mutation positive and EGFR mutation negative patients, and did not report the data for subgroups separately. During this review, a network analysis was presented as a poster at the 15th World Conference on Lung Cancer on October 29, 2013, and included only patients with EGFR mutation positive NSCLC and found no difference in PFS and ORR between afatinib, gefitinib and erlotinib (trials included, OPTIMAL, EURTAC, LUX-lung 3, LUX-lung 6, IPASS, WJTOG, North East Japan).[7] Therefore, at present the benefit of one EGFR TKI over the other is uncertain. The CGP noted that the data of most interest from the LUX lung 7 clinical trial, which is comparing afatinib to gefitinib in treatment naïve advanced EGFR mutation positive NSCLC, is a comparison of toxicity and QoL between the two EGFR TKI's. Based on information received from the submitter, this study is an exploratory trial that is not powered as superiority or non-inferiority trial. The submitter indicated that there is no pre-defined hypothesis and no formal sample size calculation was performed (See section 6.4).

Safety

Afatinib had an expected toxicity profile of increased diarrhea, stomatitis and rash compared to chemotherapy and overall comparable grade 3 /4 adverse events to chemotherapy. Approximately half of the patients in LUX-lung 3 and a quarter in LUX-lung 6 required dose reductions due to toxicity. However the degree of toxicity appeared to be manageable as the rate of discontinuation was low and treatment related mortality was low (<1%). It is important to note that both trials had a starting dose of 40 mg, with the possibility to increase to 50 mg after the first cycle if tolerated; however only a small proportion of patients in each trial had this increase (6.1% in LUX-Lung 3 and 15.9% in LUX-Lung 6), and no data are presented on whether this dose was tolerable in these patients in the long term. Despite the adverse events noted with afatinib there was improvement

of clinically meaningful global health status compared to cisplatin/gemcitabine in LUX-lung 6 and no difference compared to cisplatin/pemetrexed in LUX-lung 3.

There is concern that there may be greater toxicity with afatinib compared to the first generation TKIs gefitinib and erlotinib. In IPASS, North east Japan, WJTOG clinical trials with gefitinib the rate of grade ≥3 rash ranged from 2 to 5.3%, in EURTAC with erlotinib the rate was 13% and with afatinib rates in LUX-lung 3 and 6 were 16% and 15% respectively. In the IPASS, North east Japan and WJTOG trial with gefitinib the rate of grade ≥3 diarrhea was 0.9 to 3.8 %, in EURTAC with erlotinib the rate was 5%. Although, LUX-lung 6 reported a similar rate of grade ≥3 diarrhea as EURTAC (5.4 and 5.9% respectively), in LUX-lung 3 the rate of grade ≥3 diarrhea was 14.4%. In the Lux-Lung 3 study all grades diarrhea, stomatitis and paronychia were reported in 95% vs.15.3%, 72% vs.15.3% and 57% vs 0% of patients receiving afatinib vs placebo, respectively, while in Lux-Lung 6 all grades diarrhea, stomatitis and paronychia were reported in 88% vs.10.6%, 52% vs. 5.3% and 33% vs 0% of patients receiving afatinib vs. placebo, respectively. Dose reductions appeared higher with afatinib with 52 % of patients requiring a dose modification due to toxicity in LUX-lung 3 and 28% in LUX-lung 6. Dose reductions in IPASS with gefitinib were 16% and EURTAC with erlotinib was 21%. However, the rate of discontinuation due to adverse events appears similar with afatinib compared to gefitinib and erlotinib with a discontinuation rate of 6% in IPASS with gefitinib, 13% in EURTAC with erlotinib and 6% and 8% with afatinib in LUX lung 6 and 3 respectively. The rates of discontinuation in the chemotherapy arm in these trials did not correlate with the rates of discontinuation of the EGFR TKIs suggesting that the rate of discontinuation did not reflect differences in patient populations, the investigators or protocol-mandated discontinuation (rate of discontinuation of chemotherapy in LUX-lung 3 was 12%, IPASS 14%, EURTAC 23% and LUX-lung 6 40%). Data will become available in the future regarding the relative toxicity of afatinib compared to gefitinib (LUX Lung 7) and erlotinib (LUX Lung 8).

Summary

With an improvement in PFS and QoL compared to chemotherapy it is felt to be of sufficient benefit to support use of afatinib, particularly as it is associated with modest treatment-related toxicity. Thus afatinib appears to be a superior alternative to standard chemotherapy as first-line systemic therapy in advanced or metastatic EGFR mutation positive NSCLC. Currently, there is a lack of data to recommend the use of one EGFR TKI over the other in the first-line setting for advanced NSCLC. Afatinib was compared to superior first-line chemotherapy and PFS may be improved compared to EGFR TKIs erlotinib and gefitinib; however the toxicity may be slightly worse. Therefore, afatinib should be considered as one of the options for the first-line treatment of advanced or metastatic EGFR mutation positive NSCLC in addition to gefitinib and erlotinib. The Panel tried to draw conclusions if afatinib would be the preferred treatment option over gefitinib and erlotinib in rare mutations as afatinib is the only EGFR TKI to be studied prospectively in this group of patients. However, recent data of afatinib efficacy in rare mutations particularly exon 20 insertions and T790M mutation were not as robust as expected and thus currently there is insufficient data to support the use of one EGFR TKI over the other in rare EGFR mutations.

In response to feedback received from stakeholders regarding the comparative efficacy of afatinib to gefitinib, the CGP considered the following from a clinical perspective, in the absence of a head-to-head trial:

- Now that Cisplatin/pemetrexed is funded in many provinces for first-line treatment for advanced NSCLC, one can argue that this is now the standard of care, and afatinib is the only EGFR TKI that has been compared to the "best" chemotherapy, and was clearly shown to be superior.

- At the moment, indirect comparison is all that is available; therefore it is not truly know if afatinib is superior to gefitinib. However, in patients that harbor common EGFR mutations the PFS with afatinib was ~4 months greater than the PFS reported for gefitinib which exclusively enrolled patients with common mutations (13 months versus 9 months). From a clinical perspective, it is not likely that afatinib would be considered less efficacious with respect to the primary outcome of all of these trials, which is PFS.
- Clinically, afatinib may have higher rates of diarrhea, stomatitis and rash compared to gefitinib as suggested by indirect trial comparisons. However, it is uncertain from a clinical perspective that these common side effects of EGFR TKIs differ much from erlotinib. The side effects of afatinib are also manageable with Imodium for diarrhea, clindamycin/ hydrocortisone creams and antibiotics for rash and also with dose reductions.
- The CGP supports that clinicians should have the option to prescribe afatinib. For the time being, individual clinicians will need to decide if this drug should replace gefitinib for these patients, based on their own interpretation of the data as there will be some physicians who will want to switch, and others who will not.
- With regards to the type of data expected from the LUX-Lung 7 trial, the CGP consider that the most important data that will be generated from the trial will be a direct comparison of toxicity and QoL data between afatinib and gefitinib. It is unlikely that this study will answer if either afatinib or gefitinib should be the treatment of choice for EGFR positive treatment naïve metastatic NSCLC patients.

- Lastly, the CGP noted that for the subset of patients harbouring rare mutations, current testing in Canada varies with regard to the mutations that are screened. As such patients with a rare EGFR mutation may not know that their tumours harbor a rare mutation. As afatinib is the only EGFR TKI that has been properly studied in this patient population (LUX-Lung 3 and 6) clinicians are likely to extrapolate this data to gefitinib and erlotinib and consider that the mutations, excluding exon 20 and T790M mutation, are sensitive to all EGFR TKI's. As such clinicians are likely to treat patients with a rare EGFR mutation with gefitinib or erlotinib, as well as afatinib, as a first-line therapy

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to afatinib over chemotherapy as first-line treatment of locally advanced or metastatic EGFR mutation positive NSCLC. This conclusion is based on two phase III randomized clinical trials, LUX-Lung 3 and LUX-Lung 6, which demonstrated an improvement of progression free survival, overall response rate and quality of life with afatinib compared to standard cisplatin based chemotherapy in previously untreated locally advanced or metastatic EGFR mutation positive NSCLC. With appropriate companion EGFR mutation testing, the panel concluded that afatinib is a new and reasonable option over chemotherapy for first-line systemic therapy for locally advanced or metastatic EGFR mutation positive NSCLC.

The Clinical Guidance Panel acknowledged that there are two EGFR TKIs, gefitinib and erlotinib, available for the first-line treatment of locally advanced or metastatic EGFR mutation positive NSCLC. 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 as there are no head to head clinical trials comparing these agents. The CGP noted that from a clinical perspective, is unlikely that afatinib would be considered less efficacious than gefitinib or erlotinib in terms of PFS and any potential differences in harms would be manageable. As such the CGP considered that clinicians should have the option to prescribe either EGFR TKI in the first line setting. Afatinib may be associated with increased toxicity leading to dose modification; however these are cross-trial comparisons, and at present there are no head-to-head data available to inform which EGFR TKI may be the superior agent in this setting. The results of pending trials may further clarify this.

The Clinical Guidance Panel also considered that:

- No overall survival advantage has been demonstrated with afatinib however, limited follow up and a high rate of crossover to EGFR TKI inhibitors following progression of chemotherapy in the two phase III trials are potential confounding factors that limit the assessment of afatinib's impact on overall survival. The Panel felt it would have been unethical to deny an EGFR TKI to patients with a known mutation after progressing from chemotherapy.
- The use of afatinib beyond first-line therapy including patients who had received a prior EGFR TKI was beyond the scope of this review and it would be inappropriate to draw conclusions in this patient population.
- The CGP noted that the most important data that will be generated from the LUX-Lung 7 trial will be direct comparative evidence regarding toxicities and QoL between afatinib and gefitinib. Although direct comparative efficacy data will also be made available from this trial, it may not be powered to detect statistically significant differences among the two arms.
- Although patients with rare mutation represent a small minority of the patient population, from a clinical perspective, it is likely that clinicians will extrapolate data from the LUX-Lung 3 and 6 trials evaluating afatinib, to gefitinib and erlotinib and consider that rare mutations are sensitive to all EGFR TKI inhibitors. As such, in clinical practice, patients with rare mutations are likely to be treated with gefitinib or erlotinib, as well as afatinib, as first line therapy.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lung Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Non-small-cell lung (NSCLC) remains the leading cause of cancer-related deaths globally for both men and women with the majority of patients presenting with non-curable disease.[8,9] It is estimated that in 2012 there will be 25,600 new cases and 20,100 deaths associated with NSCLC in Canada with an incidence and mortality rate of 54/100,000 and 42/100,000 population, respectively.[26] If left untreated, patients with advanced NSCLC have a median survival after diagnosis of 4-5 months.[10] The most important risk factor for developing lung cancer remains tobacco use, accounting for an estimated 86% of lung cancer cases in high-income countries like Canada.[27]

3.2 Accepted Clinical Practice

Palliative chemotherapy with a platinum based doublet has been the cornerstone of treatment for patients with advanced stage NSCLC and has resulted in a modest historical increase in overall survival (OS) and associated quality of life (QoL).[28,29] The introduction of third generation cytotoxic chemotherapeutic drugs such as vinorelbine, gemcitabine, pemetrexed, paclitaxel and docetaxel paired with platinum agents in the first-line setting has resulted in further small improvements, although the majority of patients still experience disease progression with a median time to progression of only four months, and a median survival of 8-10 months.[11-13] Platinum doublet chemotherapy is also accompanied by significant toxicity and due to advanced age, poor performance status and/or co-morbidities many patients do not receive treatment in the first-line setting.[30,31]

In 2004, two pivotal studies showed that the presence of somatic activating mutations in the kinase domain of the epidermal growth factor receptor (EGFR) of NSCLC tumours, particularly small in frame deletions in exon 19 (deletion 19) and L858R missense mutation in exon 21 (L858R) which accounts for 90% of the EGFR mutations, strongly correlated with increased responsiveness to EGFR tyrosine kinase inhibitors (TKIs).[14-16] First generation small molecule reversible EGFR TKIs, gefitinib and erlotinib are now standard first-line treatment for patients with advanced NSCLC whose tumours harbour activating EGFR mutations. The IPASS study evaluated gefitinib versus carboplatin/paclitaxel in chemotherapy naïve patients.[32] In the EGFR unselected population the study showed no benefit in OS, time to progression or response rates (ORR) compared to chemotherapy. However, in patients with tumours harbouring the common EGFR mutations, progression free survival (PFS) was significantly longer (HR 0.48, 95% CI 0.36-0.64, $p<0.001$) and associated with improvement of QoL. Subsequently, four additional randomized phase III studies of chemotherapy versus either gefitinib or erlotinib have reported a significant improvement in PFS with EGFR TKIs and shown improved tolerability and health related QoL compared with platinum-based doublet chemotherapy.[33-36] One of these trials included the EURTAC trial which was significant as it was conducted in a western European population. This study randomized EGFR mutation positive patients to a platinum based doublet (docetaxel/gemcitabine) chemotherapy regimen versus erlotinib.(ref-Rosell 2012 Lancet Oncol) Erlotinib had a PFS advantage of 9.7 versus 5.2 months (HR 0.37, 95% CI 0.25-0.54).[37] However, among these trials no difference in OS has been found, most likely because of the high proportion of crossover from chemotherapy to EGFR TKIs observed after study completion (65 - 95% crossover rates; EURTAC study design including crossover) and the strong response to EGFR TKIs in the salvage setting. Although the

median OS among patients in these trials ranged from 18.6 to 39 months, compared to chemotherapy trials of 8 to 10 months.[11-13,32-36] The aforementioned trials had used platinum doublet chemotherapy combinations with a taxane or gemcitabine as the second drug in the regimen. Pemetrexed has become a preferential drug for patients with non-squamous NSCLC due to randomized trials showing favourable responses and survival with better tolerability.[11,38,39]

3.3 Evidence-Based Considerations for a Funding Population

EGFR activating mutations are limited to non-squamous histology and mutually exclusive to other oncogenic driver mutations including Echinoderm microtubule associated protein like-4/anaplastic lymphoma kinase (ALK) gene rearrangements and KRAS.[40] The rate of EGFR mutations in the general NSCLC adenocarcinoma population is 12% and in a subset of patients this rate can be as high as 60%.[32,40] These mutations are more common in never smokers, east Asian ethnicity, and female.[40]

Afatinib is an irreversible ErbB-family blocker with ability to block signaling from EGFR (ErbB1), human epidermal growth factor receptor 2 (HER2/ErbB2), ErbB4, and all relevant ErbB family dimers.[1,2] Afatinib has shown preclinical activity against cancer cells harbouring activating EGFR mutations, including the common mutations (deletion 19 and L858R) but in addition mutations in exon 20 of the kinase domain of EGFR and HER2. This includes the gatekeeper T790M mutation that is generally found to be resistant to EGFR TKIs and is responsible for acquired resistance to erlotinib and gefitinib in 60% of cases.[17-20] LUX lung 2, the phase II study with afatinib in advanced EGFR mutation positive NSCLC included 129 patients that were treatment naïve or had progressed following chemotherapy.[21] ORR of afatinib by independent review was 61% with a median PFS of 10.1 months (95% Cl 8.1-13.8) and median OS of 24.8 months (95% CI 22.0–38·7). ORR in patients with the two common activating EGFR mutations (deletion 19 or L858R) was 66% and 39% in those with less common mutations. Most common grade 3/4 adverse events were diarrhea (22%) and acne/rash (28%). There were 4 cases of possible interstitial lung disease, of which one was fatal.

The clinical trial data published and reviewed subsequently in this clinical guidance report only supports this drug's use in untreated advanced NSCLC patients (defined as stage wet IIIB/IV AJCC 6th edition, stage IV AJCC 7th edition) that have tested positive for EGFR activating mutations.

3.4 Other Patient Populations in Whom the Drug May Be Used

Three additional populations have been identified in which afatinib may be used outside the submitted indication.

Afatinib may be used in patients who have progressed on erlotinib and/or gefitinib, particularly those with EGFR mutation positive disease. LUX-Lung 1, was a randomized, double-blind, multicentre, phase 2b/3 study of afatinib versus placebo in patients with stage IIIB/IV lung adenocarcinoma who had received at least one platinum-based chemotherapy regimen, and at least 12 weeks of previous erlotinib or gefitinib treatment.[41] EGFR mutation status was not required for entry into the study. The primary endpoint of OS was not met, although PFS, a secondary endpoint was significant favouring afatinib (HR 0.38, 95% CI 0.31-0.48, p <0.0001). In a prespecified subgroup analysis of EGFR mutation status, it appeared that EGFR mutated patients derived the greatest benefit from afatinib; PFS in EGFR mutation positive patients was 3.3 months [95% CI 0.31 -0.85] versus 1.0 month [0.95-1.2] (HR 0.51, 95% CI 0.31-0.85, p=0.009). By contrast no difference in PFS was seen between treatment groups in EGFR mutation negative patients.

Both erlotinib and gefitinib have been studied in the maintenance setting after first-line induction with platinum based chemotherapy. The SATURN study enrolled patients with unresectable NSCLC (all histologies) that had received four cycles of platinum-doublet chemotherapy without disease progression and were randomly assigned to erlotinib maintenance therapy or placebo until progression.[37] The primary endpoint of PFS was met in the intent-to-treat population (HR 0.71, 95% CI 0.62-0.82, p<0.0001), and an OS benefit with erlotinib was reported (HR 0.81, 95% Cl 0.71-0.95, p=0.0088). A prespecified subgroup analysis revealed erlotinib maintenance was active in both EGFR mutation positive patients (PFS, HR 0.10, 95% CI, 0.04-0.25, p<0.0001), and EGFR mutation negative patients (PFS, HR 0.78, 95% CI 0.63-0.96, p=0.0185; OS, HR 0.77, 95% CI 0.61-0.97, p=0.024). Survival had not been reached in the EGFR mutation positive patients, likely due to 67% of patients in the placebo arm crossed over to an EGFR TKI. A similar study conducted in China with gefitinib revealed a PFS advantage of gefitinib maintenance in EGFR mutation positive patients compared to placebo with no OS advantage.[42] Erlotinib is licensed in Canada as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after four cycles of standard platinum-based first-line chemotherapy. To date there is no level 1 evidence for maintenance therapy for afatinib.

Afatinib has potential activity in multiple cancers including those that have driver mutations/amplifications in EGFR and/or HER2 including squamous cell carcinoma of the head and neck, gliomablastoma multiforme, colorectal, prostate, exocrine pancreatic, biliary tract, esophagogastric, and breast carcinomas. To date there is no level 1 evidence for drug utilization outside of the NSCLC indication and thus should only be considered with the auspices of a clinical trial.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

A patient advocacy group, Lung Cancer Canada ("LCC"), provided input on afatinib (Giotrif) for the first line treatment of EGFR mutation positive, advanced non-small cell lung cancer ("NSCLC"), which is summarized below.

The LCC conducted one-to-one conversations with three (3) respondents with end-stage lung cancer who have previously received all available chemotherapy and have no further treatment options and who are currently receiving afatinib through the Health Canada Special Access Program. Input was also provided through personal experience of LCC with chemotherapy and afatinib, and published literature on chemotherapy and afatinib.

From a patient perspective, the availability of afatinib will help improve the quality of life of Canadians with NSCLC compared to first-line chemotherapy and improve the controlling of symptoms for patients with advanced lung cancer. Because afatinib is administered orally, respondents reported that the side effects were minimal, and the respondents were not required to undergo frequent visits to the hospital. 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.

Please see below for a summary of specific input received from the patient advocacy group.

Personal identifying information has been removed from the registered patient advocacy group section, to the Clinical Guidance Report.

4.1 Condition and Current Therapy Information

4.1.1 Experiences patients have with NSCLC

LCC submits that patients with advanced lung cancer have the highest symptom burden of all cancer patients. More than 90% of Canadians with advanced lung cancer have at least one severe symptom, such as severe cough, pain, shortness of breath and/or coughing up blood, and over 80% have all three 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.

LCC reported that in a published survey of Canadian patients with advanced lung cancer, two-thirds of patients feel their symptoms interfere with daily activities; and 27% of the respondents reported "frequent" or "constant" anxiety or worry being common. (*See Patel et al. Proc ASCO 2003; Zawisza et al. WCLC 2013*). Rates of depression in advanced lung cancer patients vary from 16-50%, consistently higher than other cancer sites (*See Aass et al. 1997, Hopwood et al 2000, Akechi et al 1998*). It is believed that they also have higher physical symptom burden and impairment in daily living than those with other cancers.

As part of the Canadian study, 41% of patients reported experiencing financial hardship, and 69% of respondents believed their illness imposed a significant hardship on those close to them.

4.1.2 Patients' Experiences with Current Therapy for NSCLC

LCC notes that most Canadians with advanced lung cancer receive chemotherapy for first-line treatment of NSCLC, irrespective of their EGFR mutation status. Generally, chemotherapy is associated with severe side effects including nausea, vomiting, hair loss, fatigue and the risk of fever and infection, and 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.

Due to the side-effects of the treatment, this poses a tremendous burden on patients and their caregivers, who must take time off from work to receive treatment, and then additional time off to manage chemotherapy toxicity, including frequent admission to hospital. The cost of travel is an additional burden, more so in rural communities. Hospital appointments are difficult to obtain and access to chemotherapy suites is limited in both urban areas, and more so in outlying areas. Also, some patients may be deemed unsuitable of chemotherapy, for reasons of age or other illnesses, further shortening their survival and ability to fight their advanced lung cancer.

4.1.3 Impact of NSCLC and Current Therapy on Caregivers

LCC acknowledges that caregivers play an important role in making decisions about treatment and care. LCC asserts that during the brief, intense and relentlessly progressive course of advanced lung cancer, caregivers report difficulties in juggling the competing demands of providing emotional and tangible support to patients while meeting the ongoing obligations of home, work, and family. The demands of providing transportation, scheduling and making hospital visits, arranging for home nursing and oxygen support, and managing family finances are physically and emotionally devastating for both cancer patients and their caregivers. Moreover, persistent psychological distress and role adjustment problems experienced by caregivers have been reported up to a year after patients have completed treatment for cancer, with levels of distress far higher than those found in healthy controls (*Source: http://www.cancer.gov*).

In addition to the above, LCC contends that many caregivers and all lung cancer patients must take time off – most people affected by lung cancer are of lower socioeconomic status, and many families are devastated by the loss of one or both earners to lung cancer as patient and caregiver. Intensive chemotherapy requires caregivers both to attend hospital and treatment sessions, as well as to support patients at home through nausea and vomiting, fever and other toxicities.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Afatinib

LCC submits that the availability of afatinib will help improve the quality of life of thousands of Canadians with NSCLC compared to first-line chemotherapy, with dramatic and rapid improvement in cough, fatigue, shortness of breath and pain, and overall quality of life. LCC states that it is also more convenient in terms of administration and has a more favourable side effect profile than intravenous chemotherapy, and therefore, patients would not require frequent visits to the hospital, time off work, reduce length of

chemotherapy administration and needles and the side effects of chemotherapy. As a result, LCC concludes that this would save time for patients with lung cancer, their families and caregivers, and even the healthcare system, relieving pressure on the overburdened hospital system and chemotherapy administration units.

LCC notes the main side effects of afatinib are rash and diarrhea, similar to the other EGFR TKIs. However, these side effects may be managed by creams, anti-diarrheal medication and even antibiotics, and can all be well controlled.

LCC notes that there are two (2) other approved treatments through Health Canada, gefitinib and erlotinib, which have also been shown to be superior to chemotherapy first-line in EGFR mutation positive advanced NSCLC patients. However, LCC considers that afatinib has similar response rates to the other EGFR TKIs and also improves progression-free survival with a similar hazard ratio, and significantly improves quality of life in nearly all domains compared to standard chemotherapy. LCC postulates that afatinib, an irreversible EGFR TKI, differs chemically from the earlier generation reversible EGFR TKIs (gefitinib, erlotinib), and has evidence of activity against markers of acquired EGFR TKI resistance (a secondary mutation in the EGFR TKI domain, T790M). LCC acknowledges that while the superiority of this EGFR TKI over the others remains unproven, Canadians with NSCLC should be provided with more active options for advanced lung cancer than the few that currently exist. Having multiple EGFR TKIs to choose from would promote greater competition in pricing, yield more options to choose from for patients and practitioners, and potentially promote further research into how to best use these agents to maximize quality of life and survival in lung cancer.

LCC conducted an interview with three (3) respondents with end-stage lung cancer who have previously received all available chemotherapy and have no further treatment options and are currently receiving afatinib through the Health Canada Special Access Program. The summary of the respondents' experience with afatinib are outlined below.

> **Patient Profile #1** Mr. [redacted], Age 38, Diagnosis in December 2008 with Stage IV NSCLC. Mr. [redacted] explains that a year after diagnosis he experienced metastatic cancer to the head. He underwent radiation and chemotherapy treatments. In December, 2011, Mr. [redacted] started afatinib through the Health Canada Special Access program. To date Mr. [redacted] is enjoying a better quality of life with very few side effects. "*This drug has given me more time to live my life longer and spend more time with my family*."
>
> **Patient Profile #2** Ms. [redacted], Age 57, Diagnosis in January 2012 with Stage IV NSCLC.
>
> Ms. [redacted] has been taking the drug afatinib since February 22, 2013. Ms. [redacted] notes the benefits as follows:
>
> - some shrinkage of the metastasized tumours,
> - afatinib comes in pill form and taken once a day and is user friendly.
>
> Most importantly, there is no need to go to a hospital to get the drug administered. This is a huge benefit in that she does not have to travel, and acknowledges the importance for other patients especially if they live far from the hospital and this of course, contributes to their independence.

Her side effects have been minimal. "*The diarrhea and dry skin are the side effects I have experienced and both have been extremely manageable. When one is fighting for their life with stage 4 cancers, these side effects are very acceptable and truly have not affected my overall quality of life.*"

"*Overall, Afatinib is another option as a cancer drug and therefore, offers hope and perhaps a longer life when battling stage 4 lung cancer. Time is of the essence when one is fighting terminal cancer. I am hopeful that you will consider all of the above and approve of Afatinib as soon as possible so that others and I may live another day with smiles and joy.*"

Patient Profile #3 Mr. [redacted], Age 55 and diagnosed 4 years ago with inoperable Stage III disease, progressed to Stage IV approximately 3 years ago, began afatinib in January, 2013.

Mr. [redacted] has reported positive results from the use of afatinib. His lung tumour has remained stable with minimal noticeable side effects. When he compares this oral pill to prior chemo treatment, Mr. [redacted] highlights that this drug is easier on his body and he no longer experiences nausea.
The adverse effects such as, rash, skin irritation and sun sensitivity are manageable.

It was reported that afatinib has given Mr. [redacted] hope and the ability to function as normally as possible on a daily basis.

4.3 Additional Information

LCC submits that lung cancer remains the deadliest cancer to affect Canadians, and receives the least support, not only in terms of research funding, but also in terms of government and social support. LCC believes that EGFR TKI therapy is revolutionary in the treatment of lung cancer – "it is a pill that causes dramatic shrinkage often within 7 days, major symptom improvement and quality of life, and better cancer control and outcomes than chemotherapy, all without needles and chemotherapy toxicity". In view of the above, LCC asserts that it is critical that Canadians with lung cancer have access to highly effective treatments like afatinib.

LCC request that pCODR and the provincial authorities recognize the importance of having more active treatments available for Canadians with lung cancer given the poor prognosis and survival rates. In addition, Canadians with a lung cancer diagnosis need access to systematic molecular testing within the health care system, and subsidized drug access. Many Canadians with lung cancer are from lower socioeconomic strata, and not able to afford major out of pocket expenses associated with many novel cancer therapies.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for afatinib (Giotrif) for advanced non-small cell lung cancer (NSCLC). The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on afatinib (Giotrif) for advanced non-small cell lung cancer was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, afatinib has enablers that include being an oral therapy that can be easily delivered in the community setting and EGFR testing being in place in many jurisdictions. Barriers include the potential for use of afatinib in the second-line treatment of NSCLC and for the treatment of other solid tumours, ahead of clinical trial data being available.

Please see below for more details.

5.1 Factors Related to Comparators

PAG noted that this submission is based on a trial where the comparator is cisplatin/pemetrexed, the standard of care in first-line treatment of advanced NSCLC. However, in jurisdictions that fund gefitinib, it is funded for first-line treatment. As such, PAG noted that gefitinib may be the more appropriate comparator since gefitinib is an oral drug for patients with EGFR mutation positive NSCLC and noted that comparative data of afatinib versus gefitinib is not yet available.

It was also noted that erlotinib was approved in 2012 for first-line use but the manufacturer did not submit this indication for funding review. Erlotinib is currently funded in all provinces for second-line treatment only.

5.2 Factors Related to Patient Population

PAG noted that the submitter's funding request is for first-line treatment of EGFR mutation positive non-small cell lung cancer but the proposed Health Canada indication does not limit to first-line treatment. PAG has concerns that afatinib may be requested for use in the second-line setting as an alternate or in the third-line setting after gefitinib/erlotinib.

PAG also noted that afatinib is currently undergoing clinical trials in other solid tumors such as breast, head and neck, and gliomas. PAG has concerns there may be requests for use in these other cancers prior to trial completion and availability of the data.

5.3 Factors Related to Accessibility

PAG noted that afatinib is another oral drug for NSCLC that can be delivered to patients more easily than intravenous therapy in both rural and urban settings. As such, PAG identified the oral route of administration, in which patients could easily use in the community, as an enabler.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these

jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

5.4 Factors Related to Dosing

PAG indicated that the one tablet once daily dosing is an enabler and is a very convenient dosing schedule for patients. However, PAG noted that there are three tablet strengths and the submitted price is the same per tablet, regardless of strength. PAG stressed the importance of pricing be per mg and indicated that the flat pricing for all tablet strengths is a barrier. PAG expressed concerns with wastage and increase in costs if dose reductions or escalations were required.

5.5 Factors Related to Implementation Costs

PAG noted that up front EGFR mutation testing is already established and this is an enabler for implementation.

5.6 Other Factors

None identified.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of single-agent therapy with afatinib compared to an appropriate comparator, in patients with previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations.

See Table 5 in Section 6.2.1 for outcomes of interest and appropriate comparators.

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- Critical appraisal of a network meta-analysis comparing afatinib with other pharmacological interventions for the first-line treatment of locally advanced or metastatic NSCLC

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 5. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCT	Patients with previously untreated locally advanced or metastatic NSCLC with EGFR mutations.	Afatinib 40 mg/d	Gefitinib monotherapy Erlotinib monotherapy Cisplatin+pemetrexed Cisplatin+gemcitabine	OS PFS Response rates (ORR, CR) **QOL** Adverse events Diarrhea Rash Pneumonitis
Notes: EGFR=epidermal growth factor receptor; **NSCLC**=non-small cell lung cancer; **ORR**=objective response rate; **OS**=overall survival; **PFS**=progression-free survival; **QOL**=quality of life; **RCT**=randomized controlled trial.				

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid;

The Cochrane Central Register of Controlled Trials (2014, Issue 1) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were afatinib, Giotrif, Gioltrif, and BIBW-2992.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The search is considered up to date as of February 5, 2014.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

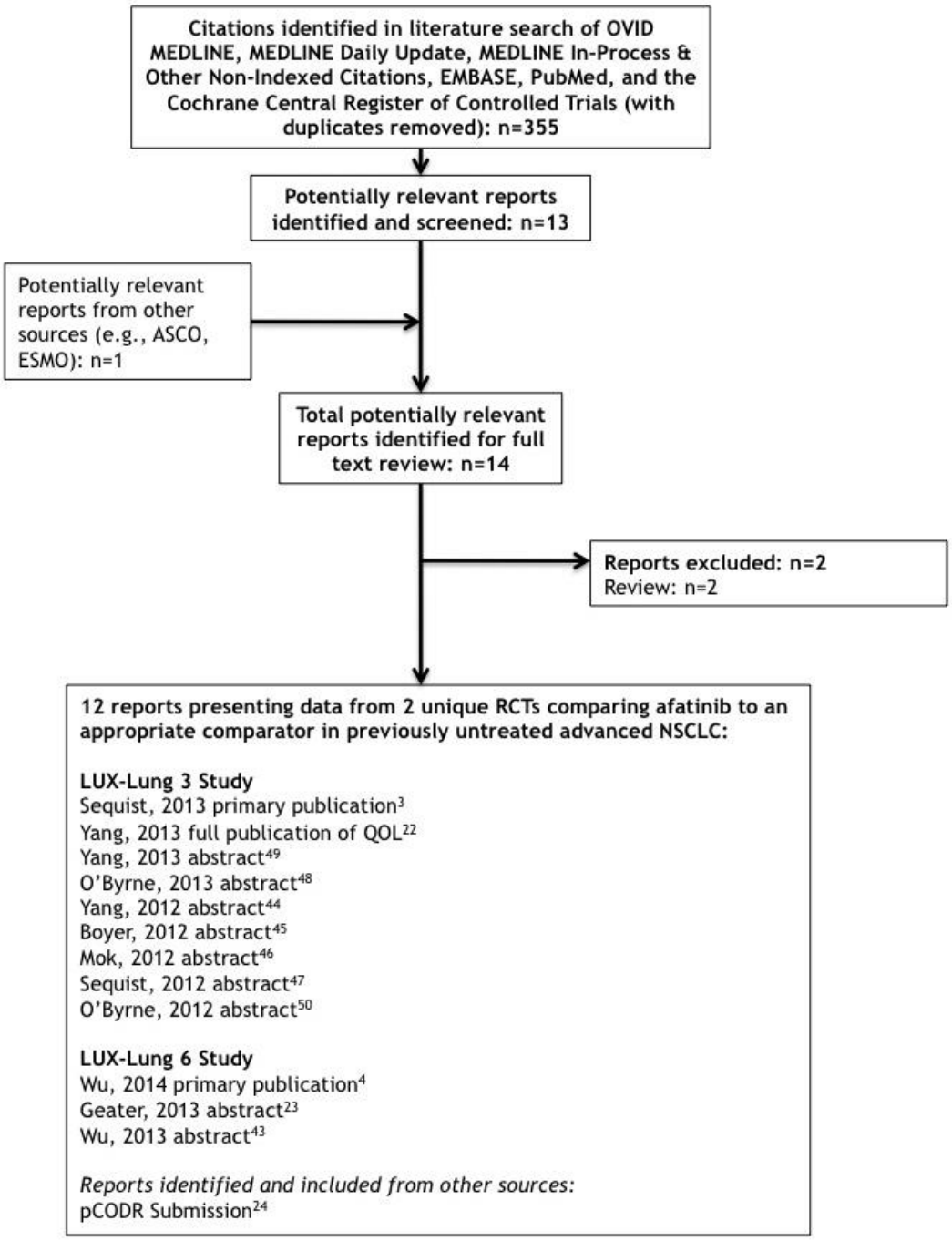
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 14 potentially relevant reports identified for full text review (Figure 1), 12 studies were included in the pCODR systematic review[3,4,22,23,43-50] and two studies were excluded because they were review articles.[51,52]

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of Studies.



Note: Additional data related to studies LUX-Lung 3 and LUX-Lung 6 were also obtained through requests to the Submitter by pCODR.[5,53]

6.3.2 Summary of Included Studies

Two randomized controlled trials were identified that met the eligibility criteria of this systematic review (see Tables 1 & 6).

6.3.2.1 Detailed Trial Characteristics

Table 6. Summary of Trial characteristics of the included studies of afatinib in patients with previously untreated locally advanced or metastatic NSCLC with EGFR mutations.

LUX-Lung 3 Study[3,5,22,44-50,54]			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
NCT00949650 LUX-Lung 3 Study 133 sites in 25 countries in Asia, Europe, Australia, and North and South America Patients enrolled from August 2009 through February 2011 Data cut-off: February 9, 2012* Randomized: n=345 Open-label phase 3 RCT Randomized in a 2:1 ratio (afatinib: cisplatin and pemetrexed) Randomization was stratified by: A) Type of EGFR mutation (L858R, exon 19 deletion, or other B) Race (Asian or non-Asian) Funded by: Boehringer Ingelheim Pharmaceuticals	Age ≥18 years Previously untreated, pathologically confirmed Stage IIIB (with cytologically proven pleural or pericardial effusion) or Stage IV adenocarcinoma of the lung Mixed histology allowed if it was predominantly adenocarcinoma Activating EGFR mutation detected by central laboratory analysis using a standardized allele-specific quantitative real-time PCR kit (Therascreen EGFR 29) ECOG PS 0 or 1 Measurable disease using RECIST Version 1.1 Adequate end-organ function Life expectancy of ≥3 months **Exclusion criteria:** Prior treatment with EGFR targeting small molecules or antibodies. Radiotherapy or surgery (other than biopsy) within 4 weeks prior to randomization. Active brain metastases.	**Intervention:** Afatinib 40 mg/d orally, every 21 days, until disease progression (investigator-assessed) Dose could be increased to 50 mg/d orally after the first cycle if the patient did not experience Grade 2 or higher drug-related adverse events. Dose could be decreased in 10 mg increments (to a minimum of 20 mg/d) to manage Grade 3 or higher or selected prolonged Grade 2 adverse events **Control:** Cisplatin 75 mg/m^2 iv + pemetrexed 500 mg/m^2 iv, once every 21 days, for a maximum of 6 cycles	**Primary:** Progression-free survival (independently assessed) **Secondary:** Overall survival Objective response (CR+PR) Disease control (CR+PR+SD) Duration of response QOL (patient-reported) Adverse events
LUX-Lung 6 Study[4,23,43,55]			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**

NCT01121393 LUX-Lung 6 Study Number of sites: 36 Conducted in Asia Dates of patient enrolment: NR Data cut-off: October 29, 2012 Randomized: n=364 Open-label phase 3 RCT Funded by: Boehringer Ingelheim Pharmaceuticals	Age ≥18 years Pathologically confirmed Stage IIIB or Stage IV adenocarcinoma of the lung EGFR mutation detected by central laboratory analysis ECOG PS 0 or 1 Measurable disease using RECIST Version 1.1 Life expectancy of ≥3 months **Exclusion criteria:** Prior chemotherapy for relapsed and/or metastatic NSCLC Prior treatment with EGFR-targeted agents Prior radiotherapy or surgery within 4 weeks prior to randomization Patients unable to cope with protocol Pregnant or breast-feeding	**Intervention:** Afatinib 40 mg/d orally, every 21 days, until disease progression (investigator-assessed) Dose could be increased to 50 mg/d orally after the first cycle if the patient did not experience Grade 2 or higher drug-related adverse events. Dose could be decreased in 10 mg increments (to a minimum of 20 mg/d) to manage Grade 3 or higher or selected prolonged Grade 2 adverse events **Control:** Gemcitabine 1000 mg/m^2 iv days 1+8 + cisplatin 75 mg/m^2 iv day 1, every 21 days for a maximum of 6 cycles.	**Primary:** Progression-free survival (independently assessed) **Secondary:** Overall survival Objective response (CR+PR) Disease control (CR+PR+SD) QOL (patient-reported) Adverse events
Notes: AEs = adverse events**; CR** = complete response; **ECOG** = Eastern Cooperative Oncology Group; **EGFR** = epidermal growth factor receptor; **iv** = intravenously; **NR**=not reported; **PR** = partial response; **PS** = performance status; **QOL** = quality of life; **RECIST** = Response Evaluation Criteria in Solid Tumours. *Information obtained from submitter at Checkpoint Meeting.[5]			

a) Trials

Two randomized controlled trials met the inclusion criteria for this systematic review, LUX-Lung 3[3] and LUX-Lung 6[4]. Characteristics of the trials' designs can be found in Table 6 and select quality-related characteristics can be found in Table 1. Both trials randomized patients with previously untreated locally advanced or metastatic NSCLC with EGFR mutations in a 2:1 ratio to receive treatment with afatinib or to therapy with a cisplatin-based combination therapy. In LUX-Lung 3[3], the control arm was cisplatin plus pemetrexed, while in LUX-Lung 6[4] the control was cisplatin plus gemcitabine. Additionally, while LUX-Lung 3 enrolled 345 patients from Asia, Europe, Australia, and North and South America, LUX-Lung 6 enrolled 364 patients only from Asia.

Both studies were described as being open-label.[3,4] However, in both studies those who assessed tumour response and data analysts were blinded to treatment allocation.[3,4]

Both trials were multicentre studies: the LUX-Lung 3 study[3] was conducted at 133 sites in Asia, Europe, Australia, and North and South America, while the LUX-Lung 6 study[4] was conducted at 36 sites in China, Thailand, and South Korea. Both studies were funded by Boehringer Ingelheim Pharmaceuticals.[54,55]

The method of randomization was not reported for the LUX-Lung 3 study. The submitter reported to pCODR that randomization for that study was centralized and appropriate and was in the ratio of 2:1 for afatinib: control.[5] The LUX-Lung 3 study stratified the randomization by type of EGFR mutation (exon 19 deletion, L858R, or other) and by race (Asian or non-Asian).[3]

Wu et al[4] reported that randomization was done centrally using a validated random-number generating system using a block size of three. Allocation was concealed by use of a computer and voice-based system to obtain randomization assignments.[4] The LUX-Lung 6 study stratified the randomization by the type of EGFR mutation (exon 19 deletion, L858R, or other).[4]

The primary outcome in both trials was progression-free survival.[3,4] In both studies, it was defined as the time from randomization to progression (as determined by central independent and blinded review using RECIST criteria) or death. Secondary outcomes for both studies included objective response (complete and partial responses), overall survival, quality of life, and adverse events.

The sample size requirement in the LUX-Lung 3 study and the LUX-Lung 6 study was 330 patients to provide 217 events (see Table 1).[3,4]

The LUX-Lung 3 study was not terminated early and the final analysis for progression-free survival, dated February 9, 2012[5], included all randomized patients as assigned.[3] Progression-free survival curves were analyzed using the methods of Kaplan-Meier with the use of a stratified log-rank test, using the same factors used to stratify randomization.[3] A Cox proportional hazards model was used to estimate the hazard ratio (HR) and 95% confidence intervals (95% CI).[3] Objective response rate was defined as the proportion of patients with a complete response or partial response. The analysis of safety included all patients who received at least one dose of trial medication. The final analysis for overall survival will be conducted after 209 deaths are observed.[3]

The LUX-Lung 6 study was not terminated early and the final analysis for progression-free survival, dated October 29, 2012, included all randomized patients as assigned.[4] Progression-free survival was analyzed using the same methods as the LUX-Lung 3 study: a stratified log-rank test, by EGFR mutation type; a Cox proportional hazards model to estimate the HR and 95% CI; and survival curves estimated using the methods of Kaplan-Meier.[4] Objective response rate was defined as the proportion of patients with a complete or partial response. The safety analysis included all patients who received at least one dose of study medication. The final analysis for overall survival is planned to occur after approximately 237 patient deaths; however, an interim analysis of overall survival was conducted at the data cut-off date.[4]

b) Populations

A total of 345 patients (afatinib, n=230; cisplatin-pemetrexed, n=115) were randomized in the LUX-Lung 3 trial[3] and 364 patients (afatinib, n=242; cisplatin-gemcitabine, n=122) were randomized in the LUX-Lung 6 trial.[4] The LUX-Lung 3 trial and the LUX-Lung 6 trial were balanced for a number of baseline patient characteristics (see Table 7). Of note, in the LUX-Lung 6 trial, a higher proportion of patients in the cisplatin-gemcitabine arm (33.6% of 122 patients) had an ECOG performance status of 0 at baseline than in the afatinib arm (19.8% of 242 patients).[4]

Table 7. Baseline Patient Characteristics in the included studies of afatinib in patients with previously untreated locally advanced or metastatic NSCLC with EGFR mutations.				
Characteristic	**LUX-Lung 3 Study[3]**		**LUX-Lung 6 Study[4]**	
	Afatinib	**Cis-Pem**	**Afatinib**	**Cis-Gem**
n	230	115	242	122
Age (years)				
Median	61.5	61.0	58	58
Range	28-86	31-83	49-65	49-62
Sex, n (%)				
Male	83 (36.1)	38 (33.0)	87 (36.0)	39 (32.0)
Female	147 (63.9)	77 (67.0)	155 (64.0)	83 (68.0)
Race, n (%)				
White	61 (26.5)	30 (26.1)	0	0
East Asian	165 (71.7)	83 (72.2)	242 (100)	122 (100)
South-East Asian	NR	NR	14 (5.8)	10 (8.2)
South Korean	NR	NR	11 (4.5)	2 (1.6)
Chinese	NR	NR	217 (89.7)	110 (90.2)
Other	4 (1.7)	2 (1.7)	0	0
Smoking status, n (%)				
Never	155 (67.4)	81 (70.4)	181 (74.8)	99 (81.1)
Former	70 (30.4)	32 (27.8)	NR	NR
Current	5 (2.2)	2 (1.7)	NR	NR
ECOG PS				
0	92 (40.0)	41 (35.7)	48 (19.8)	41 (33.6)
1	138 (60.0)	73 (63.5)	194 (80.2)	81 (66.4)
2	0	1 (0.9)	0	0
Adenocarcinoma stage[A]				
IIIB with pleural effusion	20 (8.7)	17 (14.8)	16 (6.6)	6 (4.9)
IV	210 (91.3)	98 (85.2)	226 (93.4)	116 (95.1)
EGFR mutation				
Exon 19 mutation	113 (49.1)	57 (49.6)	124 (51.2)	62 (50.8)
L858R	91 (39.6)	47 (40.9)	92 (38.0)	46 (37.7)
Other	26 (11.3)	11 (9.6)	26 (10.7)[B]	14 (11.5)[B]

Notes: Cis-Pem=cisplatin-pemetrexed; **Cis-Gem**=cisplatin-gemcitabine; **ECOG PS**=Eastern Cooperative Oncology Group performance status; **EGFR**=epidermal growth factor receptor.
[A]Stage by American Joint Committee on Cancer, sixth edition.
[B]The authors reported these patients as having uncommon EGFR mutations.[4]

c) Interventions

Details of the dose and administration of treatment and control arms for both trials can be found in Table 6. Afatinib was administered at the same dose and schedule in both trials. In the LUX-Lung 3 trial, afatinib was administered for a median of 11.0 months (16 cycles).[3] Mean overall compliance with afatinib per patient was 98%.[3] Dose reduction to less than 40 mg per day was required for 120 of 230 patients (52%), with 43 (19%) requiring more than one dose reduction.[3] In the LUX-Lung 6 study, the median duration of treatment with afatinib was 13.1 months.[4] Afatinib dose was increased to 50 mg for 38 patients (15.9%), was reduced to 30 mg for 67 patients (28.0%), or was reduced to 20 mg for 10 patients (4.2%) out of 239 patients who received treatment with afatinib.[4] A total of 31 patients received afatinib for 1-

5 cycles (days 1-105), 36 patients for 5-10 cycles (days 106-210), 33 patients for 10-15 cycles (days 211-315), 30 patients for 15-20 cycles (days 316-420), and 109 patients for 20 or more cycles (days 420+).[5]

In the LUX-Lung 3 trial, 115 patients were randomized to the control arm to receive combination chemotherapy with cisplatin and pemetrexed, the details of which can be found in Table 6. The median number of chemotherapy cycles was six: 83 patients (75%) received four or more cycles and 61 patients (55%) received the maximum of six cycles.[3] Dose reductions for adverse events occurred in 18 patients (16%) and treatment was delayed by 6 days or more in 41 patients (40%).[3]

In the LUX-Lung 6 trial, 122 patients were randomized to the control arm to receive combination chemotherapy with cisplatin and gemcitabine (see Table 6 for details). The median duration of chemotherapy was 2.9 months.[4] The median number of chemotherapy cycles was four.[4] A total of 12 patients (10.6%) received 1 cycle; 11 patients (9.7%) 2 cycles; eight patients (7.1%) 3 cycles; 31 patients (27.4%) 4 cycles; 11 patients (9.7%) 5 cycles; and 40 patients (35.4%) the maximum of 6 cycles.[5] Dose delays occurred in the following number of patients in each cycle: 18 patients (17.8%) in cycle 2; 26 patients (28.8%) in cycle 3; 29 patients (35.4%) in cycle 4; 17 patients (33.4%) in cycle 5; and 11 patients (27.5%) in cycle 6.[5]

d) Patient Disposition

In the LUX-Lung 3 trial, all 345 randomized patients were included in the final efficacy analysis.[3] Of 230 patients assigned to the afatinib arm, one patient did not receive treatment. A total of 164 patients discontinued afatinib (progression during treatment, n=133; adverse events, n=23; refused to continue, n=6; other, n=2). At the data cut-off, 152 patients (66.1%) had disease progression by independent assessment and 67 patients (29.1%) had died. Of the 115 patients assigned to the cisplatin-pemetrexed arm, four patients did not receive treatment. Of the remaining 111 patients, 60 patients completed the maximum 6 cycles, and 51 discontinued cisplatin-pemetrexed (progression during treatment, n=19; adverse events, n=17; refused to continue, n=11; other, n=4). At the data cut-off, 69 patients (60.0%) had disease progression by independent assessment and 31 patients (27.0%) had died.[3] No patients were lost to follow-up.[5] Following progression, patients could take any other anti-cancer medication. Table 8 provides information on subsequent interventions following discontinuation of study medication.

In the LUX-Lung 6 trial, all 364 randomized patients were included in the final efficacy analysis.[5] Of the 242 patients randomized to the afatinib arm, three did not receive treatment.[4] A total of 182 patients discontinued afatinib (progression during treatment, n=154; adverse events, n=21; refused to continue, n=6; lost to follow-up, n=1).[4] Of the 122 patients randomized to the cisplatin-gemcitabine arm, nine did not receive treatment.[4] Of the remaining 113 patients, 38 completed the maximum 6 cycles and 75 discontinued treatment (progression during treatment, n=20; adverse events, n=45; non-compliant with the protocol, n=3; refused to continue, n=7).[4] Of note, one patient in the afatinib arm and none in the cisplatin-gemcitabine arm was lost to follow-up.[4] Following progression, patients could take any other anti-cancer medication. No patients crossed-over from the cisplatin-gemcitabine arm to the afatinib arm.[5] Table 8 provides information on subsequent interventions following discontinuation of study medication.

Table 8. Subsequent anti-cancer therapies after discontinuation of study medication in LUX-Lung 3 and LUX-Lung 6.[A]

	LUX-Lung 3 Study[5]		LUX-Lung 6 Study[53]	
	Afatinib N (%)	**Cis-Pem N (%)**	**Afatinib N (%)**	**Cis-Gem N (%)**
Patients	230	115	242	122
Discontinued study treatment	164 (100)	111 (100)	185 (100)*	122 (100)*
Any new anti-cancer therapy	118 (72.0)	89 (80.2)	108 (58.4)*	74 (60.7)*
Systemic anti-cancer therapy	114 (69.5)	89 (80.2)	108 (58.4)*	74 (60.7)*
Chemotherapy (or chemo-based combination)	102 (62.2)	36 (32.4)	101 (54.6)*	26 (21.3)
Platinum-based	80 (48.8)	7 (6.3)	87 (47.0)	13 (10.7)
Single agent chemotherapy	39 (23.8)	29 (26.1)	28 (15.1)	18 (14.8)
Platinum-based + bevacizumab	15 (9.1)	0	2 (1.1)	0
Single agent + bevacizumab	4 (2.4)	1 (0.9)	1 (0.5)	0
Other chemotherapy combinations	3 (1.8)	3 (2.7)	4 (2.2)	1 (0.8)
EGFR TKI	39 (23.8)	72 (64.9)	26 (14.1)	59 (48.4)*
Erlotinib	24 (14.6)	39 (35.1)	17 (9.2)	21 (17.2)
Gefitinib	15 (9.1)	40 (36.0)	10 (5.4)	38 (31.1)
Afatinib	0	3 (2.7)	-	-
Other	5 (3.0)	4 (3.6)	5 (2.7)	8 (6.6)
EGFR TKI in combination	2 (1.2)	8 (7.2)	2 (1.1)	2 (1.6)
Erlotinib in combination	2 (1.2)	6 (5.4)	2 (1.1)	1 (0.8)
Gefitinib in combination	0	2 (1.8)	0	1 (0.8)
Radiotherapy	18 (11.0)	9 (8.1)	1 (0.5)	1 (0.8)

Notes: cis-gem=cisplatin-gemcitabine; **cis-pem**=cisplatin-pemetrexed; **EGFR**=epidermal growth factor receptor; **N**=number of patients; **TKI**=tyrosine kinase inhibitor.
[A]The majority of the information in this table was obtained through requests to the submitter from pCODR. Data labelled with an asterisk was obtained from a source in the public domain (see note below).
*Information reported in Wu et al, 2014.[4]

e) Limitations/Sources of Bias

Please see Table 1 for a summary of key quality-related characteristics of the two included studies.

LUX-Lung 3 Study[3] The randomization method and the methods used to conceal allocation during the randomization process were not reported in the full publication; however, the submitter reported that randomization was conducted centrally.[5] The methods used were appropriate.[5] Overall the study was well-conducted; however, the study suffered from the following limitations:

The study personnel, treating physicians, and patients were not blinded to treatment assignment. This could have affected the results, especially for patient-reported outcomes such as quality-of-life, in favour of whichever arm the assessor (either study personnel or, in the case of quality-of-life, even the patient) felt was likely to provide benefit. Importantly,

tumour response and progression-free survival (the primary outcome) were unbiased outcomes, as a blinded and independent committee conducted tumour assessments.

The study was conducted worldwide; however, approximately 70% of the study population was defined as East Asian. If this population has a different disease course or responds differently to treatment than other populations, the results of the study may be difficult to generalize to non-East Asian populations.

LUX-Lung 6 Study[4]

Overall the LUX-Lung 6 study was well-conducted; however, the study suffered from the following limitations:

A higher proportion of patients in the cisplatin-gemcitabine arm had a better ECOG performance status (0) at baseline (33.6% of 122 patients) than in the afatinib arm (19.8% of 242 patients). This difference in baseline performance status between the study arms had the potential to bias the results of the study; however, if that bias existed, it may have resulted in an underestimate of the difference in treatment effect of afatinib compared to cisplatin-gemcitabine.

The study personnel, treating physicians, and patients were not blinded to treatment assignment. This had the potential to bias the results, especially for patient-reported outcomes such as quality-of-life, in favour of whichever arm the assessor (either study personnel or, in the case of quality-of-life, even the patient) felt was likely to provide benefit. Importantly, tumour response and progression-free survival (the primary outcome) were unbiased outcomes, as a blinded and independent committee conducted tumour assessments.

The study was conducted solely in Asia. If this population has a different disease course or responds differently to treatment than other populations, the results of the study may be difficult to generalize to non-East Asian populations.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

See Table 2 for a summary of the key efficacy results for the two included studies.

Overall Survival

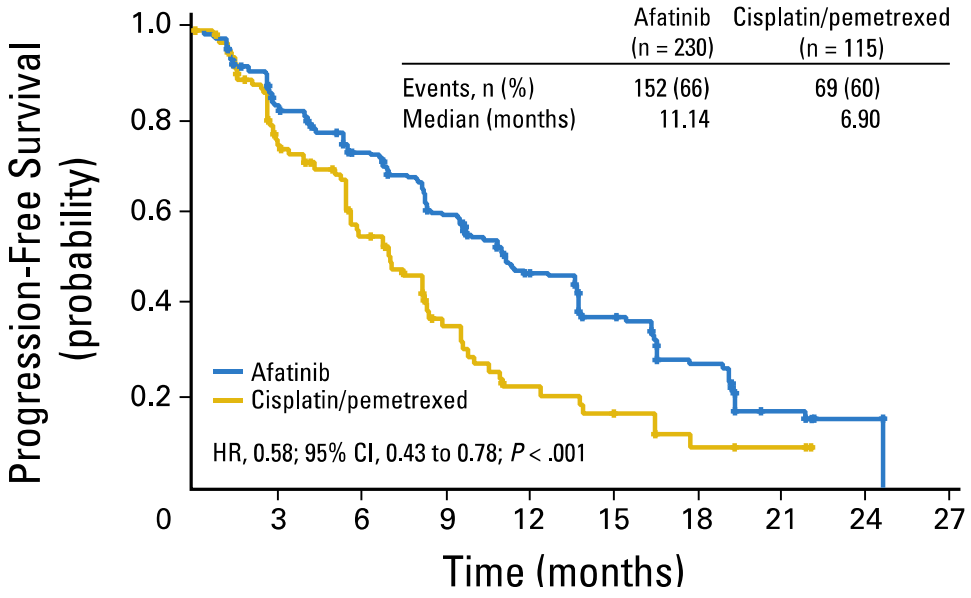
Both studies reported no statistically significant differences in overall survival for afatinib compared to the control arm (see Table 2). In the LUX-Lung 3 study, a total of 98 patients (28.4%) had died after a median follow-up of 16.4 months. The final overall survival is planned for when 209 deaths have occurred.[3] In the LUX-Lung 6 study, Wu et al[4] reported that a total of 155 patients (42.6%) had died; however, the length of follow-up was not reported. The authors reported no statistically significant difference in overall survival for the afatinib arm (median 22.1 months) compared to the cisplatin-gemcitabine arm (median 22.2 months; HR 0.95, 95% CI 0.68-1.33; p=0.76).[4] The final overall survival analysis is planned for when 237 deaths have occurred.[4]

Progression-Free Survival

Both studies reported statistically significant differences in independently-assessed progression-free survival in favour of the afatinib arm (see Table 2).

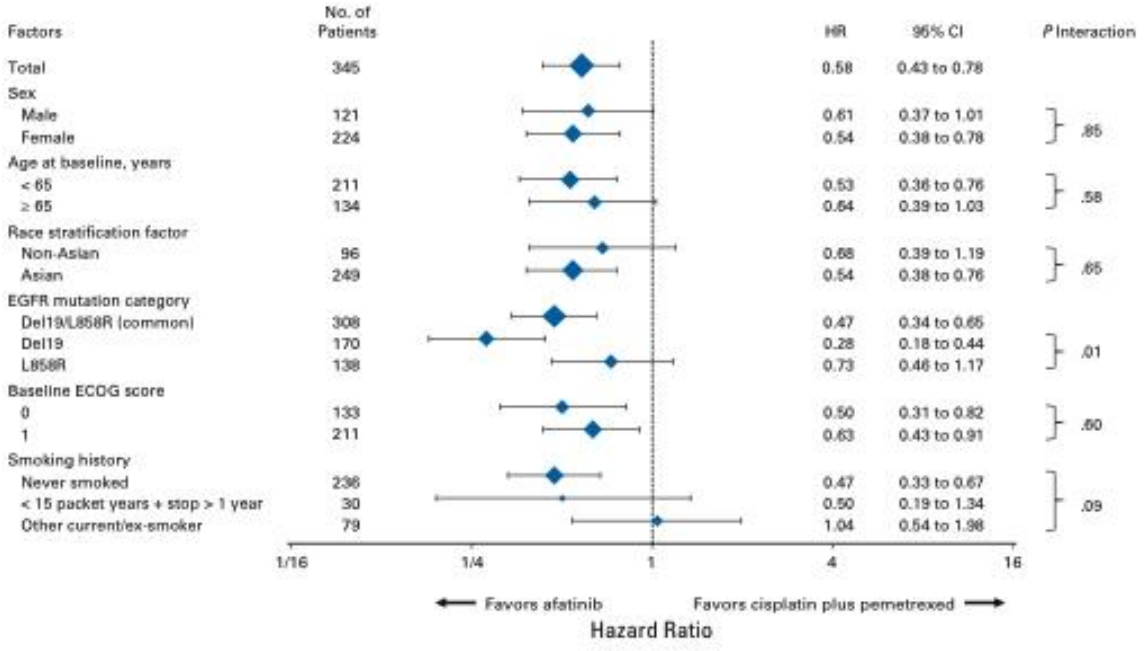
In the LUX-Lung 3 study, a total of 221 independently-assessed progression events or deaths occurred after a median follow-up of 16.4 months, with median progression-free survival of 11.1 months in the afatinib arm compared to 6.9 months in the cisplatin-pemetrexed arm (HR 0.58; 95% CI 0.43-0.78; p=0.001).[3] Figure 2 shows the Kaplan-Meier curves for independently-assessed progression-free survival. Investigator-assessed progression-free survival was similar (see Table 2). The results of pre-planned subgroup analyses of independently-assessed progression-free survival are shown in Figure 3. For the subgroups that did not show a statistically significant difference in progression-free survival between the afatinib arm and the cisplatin-pemetrexed arm (male sex, age ≥65 years, non-Asian race, L858R mutation, and smoking history), the subgroups were likely underpowered to detect a difference if one existed.[3]

Figure 2. Independently-assessed progression-free survival Kaplan-Meier curves from the LUX-Lung 3 study for afatinib compared to cisplatin-pemetrexed in patients with previously untreated locally advanced or metastatic NSCLC with EGFR mutations.[3]



Source: Sequist et al.[3]

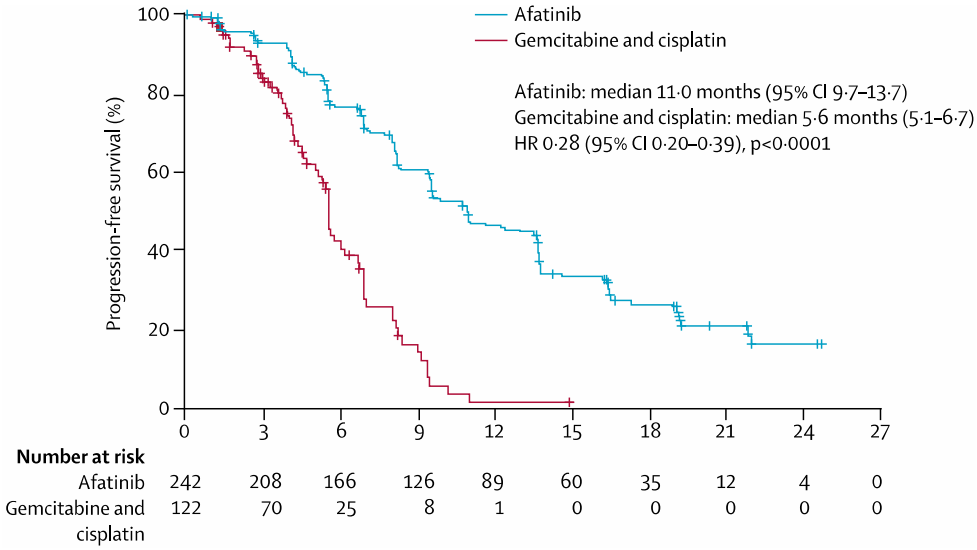
Figure 3. Subgroup analyses of independently-assessed progression-free survival from the LUX-Lung 3 study for afatinib compared to cisplatin-pemetrexed in patients with previously untreated locally advanced or metastatic NSCLC with EGFR mutations.[3]



Source: Sequist et al.[3]

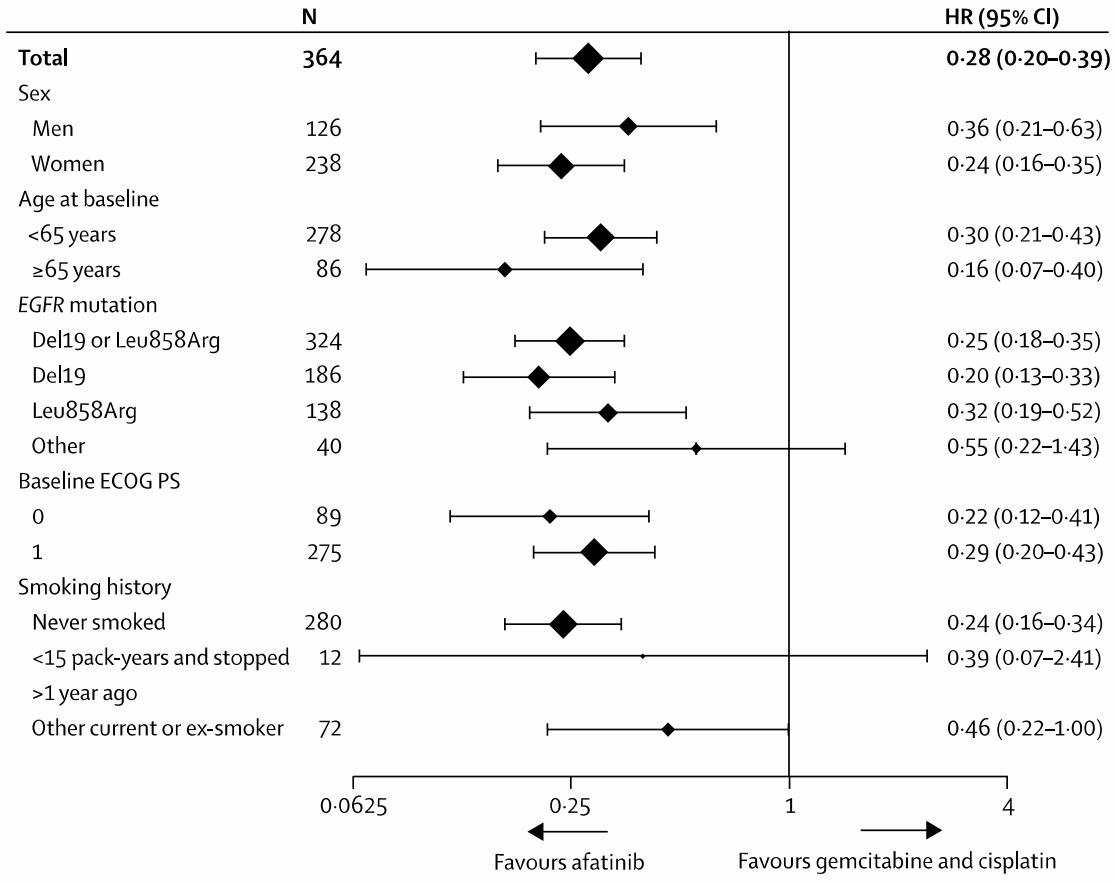
In the LUX-Lung 6 study, median independently-assessed progression-free survival was 11.0 months in the afatinib arm and 5.6 months in the cisplatin-gemcitabine arm (HR 0.28; 95% CI 0.20-0.39; p<0.0001).[4] The median length of follow-up was 16.6 months (interquartile range 4.7-19.4 months).[4] The number of events was not reported. Investigator-assessed progression-free survival was similar, with a slightly higher median in the afatinib arm (see Table 2).[4] Figure 4 shows the Kaplan-Meier curves for independently-assessed progression-free survival. Investigator-assessed progression-free survival was similar (see Table 2). The results of pre-planned subgroup analyses of independently-assessed progression-free survival are shown in Figure 5. For the subgroups that did not show a statistically significant difference in progression-free survival between the afatinib arm and the cisplatin-gemcitabine arm (Other EGFR mutation, smoking history—less than 15 pack-years and stopped more than one year ago, and smoking history—other current or ex-smoker), the subgroups were likely underpowered to detect a difference if one existed.[4]

Figure 4. Independently-assessed progression-free survival Kaplan-Meier curves from the LUX-Lung 6 study for afatinib compared to cisplatin-gemcitabine in patients with previously untreated locally advanced or metastatic NSCLC with EGFR mutations.[4]



Source: Wu et al.[4]

Figure 5. Subgroup analyses of independently-assessed progression-free survival from the LUX-Lung 6 study for afatinib compared to cisplatin-gemcitabine in patients with previously untreated locally advanced or metastatic NSCLC with EGFR mutations.[4]



Source: Wu et al.[4]

Tumour Response

Data on objective response can be found in Table 2. In the LUX-Lung 3 study, the objective response rate (by independent assessment) was 56% of 230 patients who received afatinib and 23% of 115 patients who received cisplatin-pemetrexed (p=0.001).[3] No data on complete response were reported in the full publication; however, the submitter reported that a complete response occurred in one patient (0.4%) in the afatinib arm and in no patients in the cisplatin-pemetrexed arm.[5]

In the LUX-Lung 6 study, the objective response rate (by independent assessment) was 66.9% of 242 patients who received afatinib compared to 23.0% of 122 patients who received cisplatin-gemcitabine (p<0.0001).[4] Three patients (1.2%) in the afatinib arm had a complete response while no patients in the cisplatin-gemcitabine arm experienced a complete response (Table 2).[4]

Quality of Life

Quality of life data were reported for the LUX-Lung 3 study in the primary publication by Sequist et al[3] and in a separate full publication by Yang et al.[22] Limited quality of life data for the LUX-Lung 6 study were reported in an abstract publication by Geater et al[23] and in the primary study publication by Wu et al.[4]

Methods

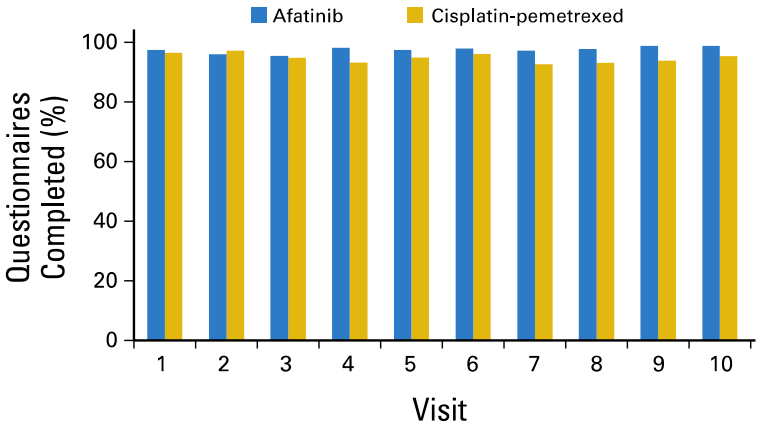
In the LUX-Lung 3 study, quality of life was assessed using self-administered questionnaires, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and a lung cancer-specific module (QLQ-LC13).[22] Questionnaires were completed at randomization and every 21 days until disease progression. The pre-specified quality of life outcomes of interest were cough (QLQ-LC13 question #1), dyspnea (composite of QLQ-LC13 questions #3-5), and pain (composite of QLQ-C30 questions #9 and #19).[22] The authors also included alternative measures for dyspnea (QLQ-C30 question #8) and pain (composite of QLQ-LC13 questions #10-12).[22] Raw scores for each item were transformed to a score from 0 to 100.[22] For symptom items, a high score represented a high or severe level of symptomatology. For function items, a high score represented a high or healthy level of functioning. Symptom improvement was defined as a 10-point or more decrease from baseline whereas a 10-point or more increase from baseline was considered symptom worsening. Patients with less than a 10-point change in score from baseline were considered stable.[22] The authors compared the distribution of patients who improved compared to not improved (stable or worse symptoms) using a multivariable logistic regression model that controlled for EGFR mutation type (Del 19, L858R, and other) and race (Asian and non-Asian). Time to deterioration in quality of life was measured in months, starting from the date of randomization, to the date of the first worsening of symptoms (a 10-point or more increase from baseline). Patients without symptom worsening were censored at the last available assessment.[22] Patients without documented symptom worsening who died were considered to have worsening symptoms at the time of death. The methods of Kaplan-Meier were used to obtain survival curves of time to deterioration and the afatinib arm was compared to the cisplatin-pemetrexed arm using a Cox proportional hazards regression model stratified by EGFR mutation type and race.[22] Changes in scores over time were analyzed by estimating the mean score over time (defined as the area under the estimated growth curve divided by the time to last assessment) with the treatment effect defined as the difference between the mean scores for the afatinib arm and the cisplatin-pemetrexed arm.[22] All randomly assigned patients with quality of life data were included in the quality of life analysis.

Quality of life in the LUX-Lung 6 study was reported in an abstract publication[23] and in the primary study publication.[4] Wu et al reported that the methods used to evaluate and analyze quality-of-life were identical to those used in the LUX-Lung 3 study.[4] This was confirmed by the submitter at the Checkpoint Meeting.[5]

Results

In the LUX-Lung 3 study, baseline questionnaires were completed by 97% of patients and the completion rate remained high prior to disease progression (see Figure 6).[22] The mean baseline scores for the three pre-specified quality of life outcomes (cough, dyspnea, and pain) were similar for the afatinib arm (cough, 35, standard deviation [SD] 26; dyspnea, 23, SD 19; pain 26, SD 24) and the cisplatin-pemetrexed arm (cough, 33, SD 25; dyspnea, 25, SD 24; pain, 24, SD 26).[22]

Figure 6. Compliance with EORTC QLQ-C30 and QLQ-LC13 questionnaires in the LUX-Lung 3 study.[22]

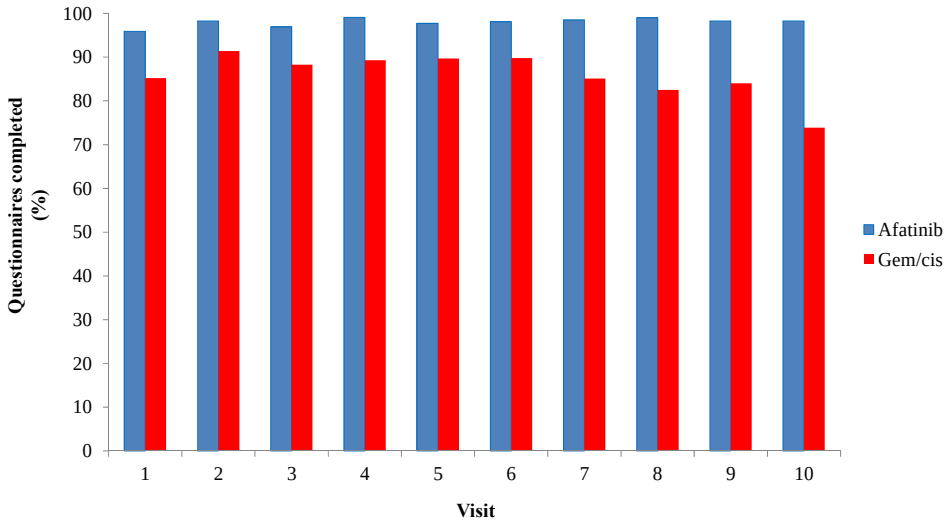


No. expected										
Afatinib	230	227	217	210	195	189	179	175	166	161
Cisplatin-pemetrexed	115	107	97	88	78	76	68	58	48	43

Source: Yang et al.[22]

In the LUX-Lung 6 study, baseline questionnaires were completed by approximately 85% of patients (see Figure 7).[4]

Figure 7. Compliance with EORTC QLQ-C30 and QLQ-LC13 questionnaires in the LUX-Lung 6 study.[4]



Number expected										
Afatinib	242	234	223	221	213	210	198	194	180	178
Gem/cis	122	105	94	84	68	59	47	40	25	23

Source: Wu et al.[4]

Proportion of Patients with Improvements in Symptoms

In the LUX-Lung 3 study a statistically significant higher proportion of patients in the afatinib arm experienced a clinically meaningful improvement in the composite dyspnea item compared to the cisplatin-pemetrexed arm (64% vs. 50%; p=0.010).[22] No statistically significant differences in the pre-specified cough or composite pain scores were demonstrated (Table 3).[22]

In the LUX-Lung 6 study, a higher proportion of patients in the afatinib arm had clinically meaningful improvements in cough (76% vs. 55%; p=0.0003), dyspnea (71% vs. 48%; p<0.0001), and pain (64% vs. 47%; p=0.003) compared to the cisplatin-gemcitabine arm (Table 3).[4,23] In addition, a higher proportion of patients in the afatinib arm experienced a clinically meaningful improvement in global health status (62.7% of 228 patients vs. 32.7% of 101 patients; p<0.0001) compared to the cisplatin-gemcitabine arm.[4]

Time to Deterioration of Symptoms

In the LUX-Lung 3 study, time to deterioration of cough and dyspnea were statistically significantly delayed for the afatinib arm compared to the cisplatin-pemetrexed arm (see Table 3), but no statistically significant difference was demonstrated for the composite pain score.[22] No statistically significant difference in the time to deterioration of global health status was observed for the afatinib arm (median 3.52 months) compared to the cisplatin-pemetrexed arm (median 3.75 months; HR 1.1013, 95% CI 0.751-1.368; p=0.9303).[53]

In the LUX-Lung 6 study, time to deterioration of cough, dyspnea, and pain were statistically significantly delayed in favour of afatinib compared to cisplatin-gemcitabine (see Table 3). Data for the median time to deterioration and the 95% CI's were not reported in the abstract publication; however, they were reported in the primary study publication by Wu et al.[4] A statistically significant difference in the time to deterioration in global health status was observed for the afatinib arm (median 8.84 months[53]) compared to the cisplatin-gemcitabine arm (median 2.79 months[53]; HR 0.560, 95% 0.41-0.77; p=0.0002).[4]

Mean Change in Score Over Time

In the LUX-Lung 3 study, statistically significant differences in mean symptom scores over time for cough and dyspnea in favour of the afatinib arm were also reported (see Table 3), but no statistically significant difference was demonstrated for the composite pain score.[22]

In the LUX-Lung 6 study, statistically significantly differences in mean symptom scores over time for dyspnea, cough, and pain favoured afatinib compared to cisplatin-gemcitabine (Table 3).[4] A statistically significant difference in the mean score over time for overall health status also favoured afatinib compared to the cisplatin-gemcitabine (mean treatment difference -8.78, 95% CI -11.19 to -6.36; p<0.0001).[4]

Harms Outcomes

No statistical comparisons of the rates of adverse events between the treatment and control arms were reported for either the LUX-Lung 3 or LUX-Lung 6 studies. In the LUX-Lung 3 study, 229 patients in the afatinib arm and 111 patients in the cisplatin-pemetrexed arm were included in the safety analysis.[3] In the LUX-Lung 6 study 239 patients in the afatinib arm and 113 patients in the cisplatin-gemcitabine arm were included in the safety analysis.[4] In the Lux-Lung 3 study all grades diarrhea, rash/acne, stomatitis and paronychia were reported in 95% vs.15.3%, 89.1% vs. 6.3%, 72% vs.15.3% and 57% vs 0% of patients receiving afatinib vs placebo, respectively, while in Lux-Lung 6 all grades diarrhea, rash/acne, stomatitis and paronychia were reported in 88% vs.10.6%, 80.8% vs. 8.8%, 52% vs. 5.3% and 33% vs 0% of patients receiving afatinib vs. placebo,

respectively. Table 9 shows the proportion of patients who experienced any grade treatment-related adverse events in 5% of more of patients in either of the study arms.

Table 9. Number of patients (percent) with All Grades treatment-related adverse events that occurred in 5% or more of patients in either arm of the included studies of afatinib in patients with previously untreated locally advanced or metastatic NSCLC with EGFR mutations.

All Grade Adverse Event	LUX-Lung 3 Study[3]		LUX-Lung 6 Study[4]	
	Afatinib, n=229 n (%)	Cis-Pem, n=111 n (%)	Afatinib, n=239 n (%)	Cis-Gem, n=113 n (%)
Any adverse event, n (%)	112 (49)	53 (48)	236 (98.7)	112 (99.1)
Laboratory or Hematologic				
Neutropenia, n (%)	2 (0.9)	35 (31.5)	5 (2.1)	61 (54.0)
Leukopenia, n (%)	4 (1.7)	21 (18.9)	8 (3.3)	58 (51.3)
Anemia, n (%)	7 (3.1)	31 (27.9)	13 (5.4)	31 (27.4)
Thrombocytopenia, n (%)	-	-	2 (0.8)	21 (18.6)
Hyponateremia	-	-	4 (1.7)	10 (8.8)
Haemoglobin concentration decreased, n (%)	-	-	4 (1.7)	20 (17.7)
Neutrophil count decreased, n (%)	-	-	2 (0.8)	29 (25.7)
White blood cell count decreased, n (%)	-	-	2 (0.8)	27 (23.9)
Platelet count decreased, n (%)	-	-	2 (0.8)	12 (10.6)
ALT concentration increase, n (%)	-	-	48 (20.1)	18 (15.9)
AST concentration increase, n (%)	-	-	36 (15.1)	12 (10.6)
Hypokalemia, n (%)	-	-	13 (5.4)	15 (13.3)
Diarrhea, n (%)	218 (95.2)	17 (15.3)	211 (88.3)	12 (10.6)
Rash/acne, n (%)	204 (89.1)	7 (6.3)	193 (80.8)	10 (8.8)
Stomatitis/mucositis, n (%)	165 (72.1)	17 (15.3)	124 (51.9)	6 (5.3)
Paronychia, n (%)	130 (56.8)	0	78 (32.6)	0
Dry skin, n (%)	67 (29.3)	2 (1.8)	-	-
Decreased appetite, n (%)	47 (20.5)	59 (53.2)	24 (10.0)	46 (40.7)
Prutitis, n (%)	43 (18.8)	1 (0.9)	26 (10.9)	0
Nausea, n (%)	41 (17.9)	73 (65.8)	18 (7.5)	85 (75.2)
Fatigue, n (%)	40 (17.5)	52 (46.8)	24 (10.0)	41 (36.3)

Vomiting, n (%)	39 (17.0)	47 (42.3)	23 (9.6)	91 (80.5)
Epistaxis, n (%)	30 (13.1)	1 (0.9)	30 (12.6)	1 (0.9)
Cheilitis, n (%)	28 (12.2	1 (0.9)	-	-
Constipation, n (%)	6 (2.6)	21 (18.9)	4 (1.7)	14 (12.4)
Notes: "-"=not reported; **Cis-Gem**=cisplatin+gemcitabine; **Cis-Pem**=cisplatin+pemetrexed; **n**=number of patients. **ALT**=alanine aminotransferase. **AST**=aspartate aminotransferase				

Grade 3 or 4 Adverse Events

Data on the incidence of Grade 3 or higher adverse events for the LUX-Lung 3 study and the LUX-Lung 6 study can be found in Table 4. In the LUX-Lung 3 study, the proportion of patients who experienced a grade 3 or higher adverse event was similar in the afatinib arm (49% of 229 patients) and the cisplatin-pemetrexed arm (48% of 111 patients).[3] In the LUX-Lung 6 study, the proportion of patients who experienced a grade 3 or higher adverse event was lower in the afatinib arm (36.0%) than in the cisplatin-gemcitabine arm (60.2%); of those events, one patient in each arm had a grade 5 event.[4]

In the LUX-Lung 3 study, the rates of grade 3 or higher neutropenia, leukopenia, anemia, and fatigue were higher in patients receiving cisplatin-pemetrexed than in those receiving afatinib (see Table 4). The rates of grade 3 or higher diarrhea (14.4% vs. 0%), rash or acne (16.2% vs. 0%), stomatitis or mucositis (8.7% vs. 0.9%), and paronychia (11.4% vs. 0%) were higher in the afatinib arm than in the cisplatin-pemetrexed arm, respectively.[3]

In the LUX-Lung 6 study, the rates of grade 3 or higher neutropenia, leukopenia, anemia thrombocytopenia, nausea, and vomiting were higher in patients receiving cisplatin-gemcitabine than in those receiving afatinib (Table 4).[4] The rates of grade 3 or higher diarrhea (5.4% vs. 0%), rash or acne (14.6% vs. 0%), and stomatitis (5.4% vs. 0%) were higher in the afatinib arm than in the cisplatin-gemcitabine arm, respectively (Table 4).[4]

Adverse Events Leading to Treatment Discontinuation

In the LUX-Lung 3 study, 8% of 229 patients in the afatinib arm and 12% of 111 patients in the cisplatin-pemetrexed arm discontinued therapy due to a treatment-related adverse event.[3]

In the LUX-Lung 6 study, 21 patients (8.8%) in the afatinib arm and 45 patients (39.8%) in the cisplatin-gemcitabine arm discontinued therapy due to an adverse event.[4]

Diarrhea

In the LUX-Lung 3 study, any grade of diarrhea occurred in 95.2% of 229 patients in the afatinib arm and in 15.3% of 111 patients in the cisplatin-pemetrexed arm.[3] Grade 3 or higher diarrhea also occurred in more patients in the afatinib arm than in the cisplatin-pemetrexed arm (14.4% vs. 0%).[3]

In the LUX-Lung 6 study, grade 3 or higher diarrhea occurred in 5.4% of 239 patients who received afatinib and in none of the 113 patients who received cisplatin-gemcitabine.[4] Diarrhea of any grade occurred in 88.3% of 239 patients who received afatinib and in 10.6% of patients who received cisplatin-gemcitabine.[4]

Rash

In the LUX-Lung 3 study, any grade of rash or acne occurred in 89.1% of patients in the afatinib arm and in 6.3% of patients in the cisplatin-pemetrexed arm.[3] Grade 3 or higher rash or acne also occurred in more patients in the afatinib arm than in the cisplatin-pemetrexed arm (16.2% vs. 0%).[3]

In the LUX-Lung 6 study, grade 3 or higher rash or acne occurred in 14.6% of patients in the afatinib arm and in none of 113 patients in the cisplatin-gemcitabine arm.[4] Rash of any grade occurred in 80.8% of 239 patients who received afatinib and in 8.8% of 113 patients who received cisplatin-gemcitabine.[4]

Pneumonitis

In the LUX-Lung 3 study, only 1 patient (0.4%) of 230 patients in the afatinib arm experienced pneumonitis compared to none of 115 patients in the cisplatin-pemetrexed arm.[5] No patients experienced a grade 3 or higher pneumonitis.[5]

In the LUX-Lung 6 study, one patient (0.4%) of 239 patients in the afatinib arm experienced a Grade 4 pneumonitis compared to none of 113 patients in the cisplatin-gemcitabine arm.[5]

Fatal Adverse Events

In the LUX-Lung 3 study, 14 of 229 patients (6.1%) in the afatinib arm had a fatal adverse event compared to three of 111 patients (2.7%) in the cisplatin-pemetrexed arm.[5] Four deaths in the afatinib arm were considered potentially treatment-related by the investigators (one grade 5 acute respiratory distress syndrome, and one grade 5 dyspnea, one sepsis, and one unknown).[5] No treatment-related fatal adverse events were reported in the cisplatin-pemetrexed arm.[5]

In the LUX-Lung 6 study, 15 of 239 patients (6.3%) in the afatinib arm had a fatal adverse event compared to five of 113 patients (4.4%) in the cisplatin-gemcitabine arm.[5] Of note, one patient in the afatinib arm and one patient in the cisplatin-gemcitabine arm had an investigator-classified drug-related death.[4] The patient with a drug-related death in the afatinib arm was classified as a "sudden death,"[4] which occurred while the patient was walking outside seven days after starting treatment with afatinib.[53] No autopsy was performed and no other adverse events were reported.[53] The patient with a drug-related death in the cisplatin-gemcitabine arm was classified as "cardiac failure."[4] The patient experienced cardiac arrest leading to death in hospital two days after discontinuation of chemotherapy due to life-threatening renal failure.[53]

6.4 Ongoing Trials

Only one ongoing randomized trial investigating the use of afatinib in patients with previously untreated advanced NSCLC with EGFR mutations met the eligibility criteria for this review: NCT01466660. Based on information received from the submitter, the LUX-Lung 7 study is not powered to be a superiority or non-inferiority trial and as such may or may not provide information as to whether afatinib improves PFS compared to gefitinib in this patient population. The submitter noted that there is no pre-defined hypothesis and sample size calculation was not performed. Details of this trial can be found in Table 10.

Table 10. Study NCT01466660: A randomized, open-label, phase IIb trial of afatinib versus gefitinib as first-line treatment of patients with EGFR mutation positive advanced adenocarcinoma of the lung.[56]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01466660 Active control, multicentre, open-label, randomized phase IIb trial. Start date: December 2011 Expected completion date: December 2014 Last verified in October 2013 – ongoing, but not recruiting patients. Estimated enrolment: 316 Sponsor: Boehringer Ingelheim Pharmaceuticals	Pathologically confirmed diagnosis of stage IIIB or IV adenocarcinoma of the lung. Documented activating EGFR mutation (Del19 and/or L858R). At least one measurable lesion according to RECIST version 1.1. ECOG PS 0 or 1 Age ≥18 years ***Excluded:*** Previous systemic chemotherapy for stage IIIB or IV NSCLC. Prior neo-adjuvant or adjuvant chemotherapy, chemo radiation, or radiotherapy within the 12-month period between the last treatment and disease progression. Active brain metastases.	**Afatinib arm** Afatinib once daily. Dose: NR. ***OR*** **Gefitinib arm** Gefitinib once daily. Dose: NR.	<u>Primary outcomes:</u> Progression-free survival Time to treatment failure Overall survival <u>Secondary outcomes:</u> Objective response rate Time to objective response Duration of objective response Duration of disease control Tumour shrinkage Quality of life
Notes: ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; NR=not reported; NSCLC=non-small cell lung cancer; PS=performance status; RECIST=Response Evaluation Criteria in Solid Tumours. Available from: http://clinicaltrials.gov/ct2/show/NCT01466660?term=afatinib&rank=33			

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of afatinib in the treatment of patients with previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations:

- Critical appraisal of a network meta-analysis comparing afatinib with other pharmacological interventions for the first-line treatment of locally advanced or metastatic NSCLC.[24]

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical Appraisal of a Network Meta-Analysis Comparing Afatinib with Other Pharmacological Interventions for the First-Line Treatment of Locally Advanced or Metastatic NSCLC.

7.1.1 Objective

To summarize and critically appraise the methods and findings of the manufacturer-submitted network meta-analysis comparing afatinib to available pharmacological interventions for the first-line treatment of locally advanced or metastatic NSCLC.

7.1.2 Findings

The manufacturer submitted a network meta-analysis with the objective of estimating the efficacy of afatinib indirectly compared to gefitinib and to erlotinib. Included in the network were all available pharmacological interventions for the first-line treatment of locally advanced or metastatic NSCLC. The network diagram included in the network meta-analysis provided by the manufacturer can be found in Figure 5 for progression-free survival and in Figure 6 for overall survival.

Figure 5. Network diagram for progression-free survival.

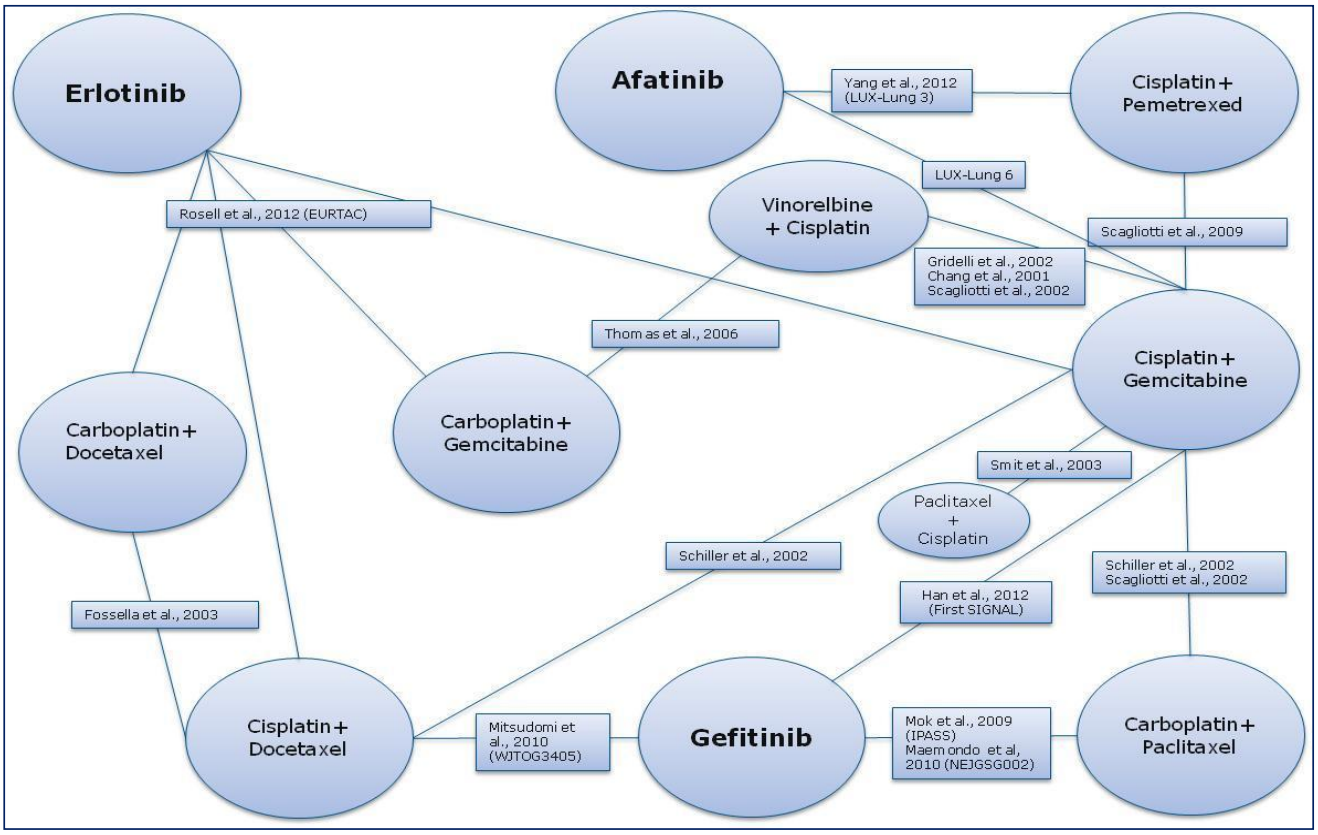
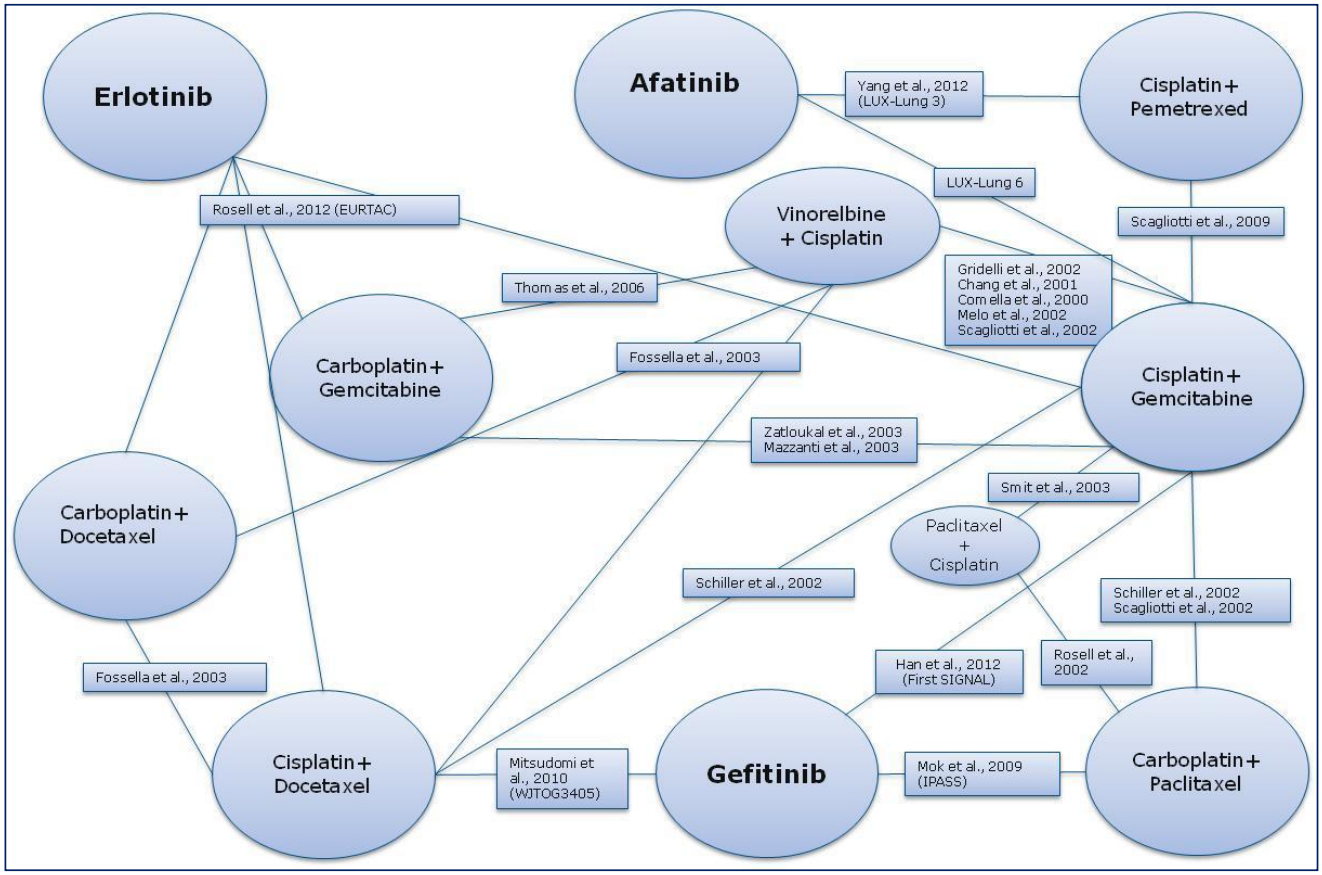


Figure 6. Network diagram for overall survival.



The main objective of the manufacturer-submitted network meta-analysis (NMA) was to estimate the comparative efficacy of afatinib relative to gefitinib or erlotinib in the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR mutations. The authors of the report indicated that the evidence was identified as part of a larger systematic review of all randomized controlled trials, systematic reviews, and meta-analyses published on NSCLC over the time period 2002 to 2012. The authors provided detailed literature search strategies, eligibility criteria, and a PRISMA flow diagram for the larger systematic review. From the evidence identified for that systematic review, the authors identified four randomized controlled trials that were conducted in patients with EGFR mutation-positive disease only, and a further four trials that provided subgroup data for patients with EGFR mutation-positive disease. In addition, the LUX-Lung 3 and the LUX-Lung 6 studies were included in the NMA as they are the only two randomized controlled trials that have investigated afatinib for the first-line treatment of EGFR mutation-positive locally advanced or metastatic NSCLC, although neither was identified in the larger systematic review.

In addition to the 10 trials that had data available for patients with EGFR mutation-positive disease, the NMA included a further 10 randomized controlled trials that did not separate data for patients with EGFR mutation-positive disease.

A total of 20 randomized trials were included in the network. A summary of the trial and patient characteristics was provided in a table format in the NMA report, which has been reproduced here

as Table 11. Of note, the authors did not provide an assessment of the quality of the individual trials. The individual progression-free survival and overall survival HR's and 95% confidence intervals (95% CI) can be found in Tables 12 and 13, respectively.

Table 11. Clinical trials included in the NMA provided by the manufacturer.

Study	Intervention	Comparator	Population	EGFR Mutation, n(%)		
				EXON 19 deletion	L858R	Other
Chang et al, 2001	Vinorelbine (20 mg/m^2) on day 1, 8, and 15 plus cisplatin (80 mg/m^2) on day 15	Gemcitabine (1000 mg/m^2) on day 1, 8, and 15 plus cisplatin (80 mg/m^2) on day 15	Chemo-naïve Stage IIIb or IV, ECOG PS≤2	NR	NR	NR
Comella et al, 2000	Cisplatin 100 mg/m^2 on day 1 and Gemcitabine 1000 mg/m^2 on day 1, 8, and 15 every 4 weeks	Cisplatin 120 mg/m^2 on day 1 and 29 (and then every 6 weeks) and vinorelbine 30 mg/m^2/week for 10 weeks	Chemo-naïve Stage IIIb or IV, ECOG PS≤1	NR	NR	NR
Fossella et al, 2003	Docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2 (both as 1h iv infusions on day 1, repeated every 3 weeks)	Docetaxel 75 mg/m^2 1h iv plus carboplatin iv AUC 6 mg/L (both on day 1, repeated every 3 weeks) Versus Vinorelbine 25 mg/m^2 as a 6- to 10-minute iv on days 1, 8, 15, and 22, plus cisplatin 100 mg/m^2 iv on day 1, repeated every 4 weeks	Chemo-naïve Stage IIIb or IV, Karnofsky PS≥70%	NR	NR	NR
Gridelli et al. 2002	Gemcitabine1,000 mg/m^2 plus vinorelbine 25 mg/m^2 on days 1 and 8. Additional therapy was at the discretion of the investigators. Cycles were given every 3 weeks and a total of 6 planned.	Gemcitabine 1,200 mg/m^2 on days 1 and 8 plus cisplatin 80 mg/m^2 on day 1 versus Vinorelbine 30 mg/m^2 on days 1 and 8 plus cisplatin 80 mg/m^2 on day 1. Cycles were given every 3 weeks and a total of 6 planned	Chemo-naïve Stage IIIb or IV, ECOG PS≤2	NR	NR	NR
Han et al, 2012 (First SIGNAL)	Gefinitib: 250 mg/day	Gemcitabine 1,250 mg/m^2 on days 1 and 8; cisplatin 80 mg/m^2 on day 1 every 3 weeks, for up to nine courses	Stage IIIB or IV lung adenocarcinoma, Eastern Cooperative Oncology Group performance status 0 to 2, and	NR	NR	NR

Study	Intervention	Comparator	Population	EGFR Mutation, n(%)		
				EXON 19 deletion	L858R	Other
			adequate organ function. EGFR-TK M+			
Maemondo et al, 2010 (NEJGSG002)	Gefitinib: 250 mg/day (3 week cycles)	Carboplatin: AUC 5/6/mg/mL/min Paclitaxel: 200 mg/m^2 (3 week cycles)	Advanced NSCLC harbouring sensitive EGFR mutations, the absence of the resistant EGFR mutation T790M	Gef: 50.9% Pac/Carb: 51.8%	Gef: 43.0% Pac/Carb: 42.1%	Gef: 6.1% Pac/Carb: 6.1%
Mazzanti et al, 2003	Gemcitabine/Carboplatin over a 21 day cycle (Gemcitabine 1200 mg/m^2 over 30 min on days 1 and 8); Carboplatin (AUC 5) given over 60 min on day 2)	Gemcitabine/Cisplatin over a 21 day cycle (Gemcitabine 1200 mg/m^2 over 30 min on days 1 and 8); Cisplatin 80 mg/m^2 over 45 min	Chemo-naïve Stage IIIb or IV, ECOG PS≤2	NR	NR	NR
Melo et al, 2002	Cisplatin 100 mg/m^2 day 1, vinorelbine 30 mg/m^2 day 1, 8, 15 q28d	Cisplatin 100 mg/m^2 day 1, gemcitabine 1000 mg/m^2 day 1, 8, 15 q28d Gemcitabine 1000 mg/m^2 day 1, 8, 15, cisplatin 100 mg/m^2 day 15 q28d	Locally advanced and metastatic NSCLC	NR	NR	NR
Mitsudomi et al, 2010 (WJTOG3405)	Gefinitb: 250 mg/day	Cisplatin: 80 mg/m^2 (1x) Docetaxel: 60mg/m^2 (1x) Every3 weeks for 6 cycles	Histologically or cytologically confirmed NSCLC, WHO performance status 0-1	Gef: 58.1% Doc/Cis: 43.0%	Gef: 41.9% Doc/Cis: 57%	
Mok et al, 2009 (IPASS)	Gefitinib: 250 mg/day	Carboplatin: AUC 5 or 6 (1x) Paclitaxel: 200 mg/m^2 (1x) Every 3 weeks for 6 cycles	Chemo-naïve stage IIIB or stage IV NSCLC, ECOG PS 0 or 2	NR	NR	NR
Rosell et al, 2002	Palitaxel 200 mg/m^2 (3-h iv infusion) followed by carboplatin at an AUC of	Paclitaxel 200 mg/m^2 (3-h iv infusion) followed by cisplatin at a dose of 80 mg/m^2, all	Chemo-naïve Stage IIIb or IV, ECOG PS≤2	NR	NR	NR

Study	Intervention	Comparator	Population	EGFR Mutation, n(%)		
				EXON 19 deletion	L858R	Other
	6, all repeated every 3 weeks	repeated every 3 weeks				
Rossell et al, 2012 (EURTAC)	Erlotinib: 150 mg/day until disease progression	Cisplatin: 75 mg/m^2 (1x) Docetaxel: 75 mg/m^2 (1x) Or Cisplatin: 75 mg/m^2 (1x) Gemcitabine: 1250 mg/m^2 (2x) Or Carboplatin: AUC 6 (1x) Docetaxel: 75 mg/m^2 (1x) Or Carboplatin: AUC 5 (1x) Gemcitabine: 1000 mg/m^2 (2x) For up to four 3-week cycles	Chemo-naïve stage IIIB (with pleural effusion) or stage IV NSCLC (based on the sixth TNM staging system), measurable or evaluable disease, presence of activating EGFR mutations (exon 19 deletion or L858R mutation in exon 21)	Erl: 66.3% Std Tx: 33.7%	Erl: 33.7% Std. Tx: 33.3%	Erl: 0% Std. Tx: 0%
Scagliotti et al, 2002	Gemcitabine 1,250 mg/m^2 days 1 and 8 plus cisplatin 75 mg/m^2 day 2 every 21 days	Paclitaxel 225 mg/m^2 (3-hour infusion) then carboplatin (AU the concentration-time curve of 6 mg/mL·min), both on day 1 every 21 days versus Vinorelbine 25 mg/m^2/wk for 12 weeks then every other week plus cisplatin 100 mg/m^2 day 1 every 28 days	Chemo-naïve Stage IV, ECOG PS≤2	NR	NR	NR
Scagliotti et al, 2009	Cisplatin: 75 mg/m^2 (1x) Pemetrexed: 500 mg/m^2 (1x) Repeated every 3 weeks	Cisplatin: 75 mg/m^2 (1x) Gemcitabine: 1,250 mg/m^2 (2x) Repeated every 3 weeks	Chemo-naïve stage IIIB or stage IV NSCLC, ECOG PS 0 or 1	NR	NR	NR
Schiller et al, 2002	Paclitaxel 135 mg/m^2 administered over 24h on day 1, followed by Cisplatin 75 mg/m^2 on day 2 (3-week cycles)	Gemcitabine 1000 mg/m^2 was administered on days 1, 8, and 15, and Cisplatin 100 mg/m^2 was administered on day 1 (4-week cycles)	Chemo-naïve patients with NSCLC stage IIIB/IV or recurrent disease	NR	NR	NR

Study	Intervention	Comparator	Population	EGFR Mutation, n(%)		
				EXON 19 deletion	L858R	Other
		Versus Docetaxel 75 mg/m^2 and Cisplatin 75 mg/m^2 on day 1 (3-week cycles) Versus Paclitaxel 225 mg/m^2 given over 3h on day 1, followed on the same day by Carboplatin (AUC 6.0), (3- week cycles)				
Smit et al, 2003	Paclitaxel 175 mg/m^2 on day 1 followed by Cisplatin 80 mg/m^2 on day 1 (3- week cycles)	Gemcitabine 1,250 mg/m^2 on days 1 and 8 and Cisplatin 80 mg/m^2 on day 1 after Gemcitabine (3- week cycles)	Chemo-naïve Stage IIIb or IV, ECOG PS≤2	NR	NR	NR
Thomas et al, 2006	Gemcitabine 1250mg/m^2 on days 1 and 8 plus Carboplatin (AUC 6) on day 1 (3-week cycles)	Vinorelbine 30 mg/m^2 weekly plus Cisplatin 80 mg/m^2 on day 1 (3- week cycles)	Chemo-naïve Stage IIIb or IB, WHO PS≤2	NR	NR	NR
Yang et al, 2012 (LUX-Lung 3) data on file	Afatinib daily 40 mg	Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2 q21 days up to 6 cycles	Stage IIIB/IV, PS 0-1, chemo-naïve	Afatinib: 49.1% Pem/Cis: 49.6%	Afatinib: 39.6% Pem/Cis: 40.9%	Afatinib: 11.3% Pem/Cis: 9.6%
LUX-Lung 6 data on file	Afatinib daily 40 mg	Gemcitabine 1000 mg/m^2 D1, 8 + Cisplatin 75 mg/m^2 q21 days up to 6 cycles	Stage IIIB/IV, PS 0-1, chemo-naïve	Afatinib: 51.2% Gem/Cis: 50.8%	Afatinib: 38.0% Gem/Cis: 37.7%	Afatinib: 10.7% Gem/Cis: 11.5%
Zatloukal et al, 2003	Gemcitabine 1200 mg/m^2 iv over 30 min on days 1 and 8 plus Cisplatin 80 mg/m^2 iv. Platinum analogues were administered at least 4h after Gemcitabine injection on day 1. Two weeks of treatment followed by a week of rest (3-week cycles)	Gemcitabine 1200 mg/m^2 iv over 30 min on days 1 and 8 plus carboplatin AUC=5 iv. Platinum analogues were administered at least 4h after gemcitabine injection on day 1. Two weeks of treatment followed by a week of rest (3-week cycles)	Chemo-naïve Stage IIIb or IV, Karnofsky PS≥70%	NR	NR	NR

Table 12. Progression-free survival data for the clinical trials included in the NMA submitted by the manufacturer.

Study	Treatments		Hazard Ratio	95% Confidence Interval	
				Lower	Upper
Chang et al, 2001	Gem/Cis	Vin/Cis	0.94	0.5	1.78
Gridelli et al, 2003	Gem/Cis	Vin/Cis	0.91	0.7	1.18
Han et al, 2012 (First SIGNAL)	Gefitinib	Gem/Cis	0.544	0.27	1.1
Maemondo et al, 2010 (NEJGSG002)	Gefitinib	Pac/Carb	0.3	0.22	0.41
Mitsudomi et al, 2010 (WJTOG3405)	Gefitinib	Doc/Cis	0.49	0.34	0.71
Mok et al, 2009 (IPASS)	Gefitinib	Pac/Carb	0.48	0.36	0.64
Rosell et al, 2012 (EURTAC)	Erlotinib	Doc/Cis	0.37	0.25	0.54
		Gem/Cis	0.37	0.25	0.54
		Doc/Carb	0.37	0.25	0.54
		Gem/Carb	0.37	0.25	0.54
Scagliotti et al, 2002	Gem/Cis	Vin/Cis	0.95	0.77	1.17
		Pac/Carb	1.05	0.85	1.29
Scagliotti et al, 2009	Pem/Cis	Gem/Cis	0.9	0.78	1.03
Schiller et al, 2002	Gem/Cis	Doc/Cis	0.87	0.73	1.04
		Pac/Cis	0.79	0.66	0.94
		Pac/Carb	0.84	0.7	0.99
Smit et al, 2003	Gem/Cis	Pac/Cis	0.89	0.65	1.22
Thomas et al, 2002	Gem/Carb	Vin/Cis	1.21	0.72	2.03
Yang et al, 2012 (LUX-Lung 3)	Afatinib	Pem/Cis	0.58 †	0.43	0.78
			0.49 ††	0.37	0.65
LUX-Lung 6, data on file	Afatinib	Gem/Cis	0.28 †	0.20	0.39
			0.26 ††	0.19	0.36

Notes: †=Independent assessment; ††=investigator assessment. Other than indicated for the LUX-Lung trials, it was not clear in the NMA report whether the data in this table based on investigator assessments or independent assessments of tumour progression.

Table 13. Overall survival data for the clinical trials included in the NMA submitted by the manufacturer.

Study	Treatments		Hazard Ratio	95% Confidence Interval	
				Lower	Upper
Chang et al, 2001	Gem/Cis	Vin/Cis	0.93	0.4	2.16
Comella et al, 2000	Gem/Cis	Vin/Cis	0.71	0.45	1.13
Fossella et al, 2003	Vin/Cis	Doc/Cis	1.183	0.989	1.416
	Vin/Cis	Doc/Carb	1.048	0.877	1.253
Gridelli et al, 2003	Gem/Cis	Vin/Cis	1.02	0.76	1.35
Han et al, 2012 (First SIGNAL)	Gefitinib	Gem/Cis	1.04	0.49	2.18
Mazzanti et al, 2003	Gem/Carb	Gem/Cis	1.09	0.75	1.59
Melo et al, 2002	Gem/Cis	Vin/Cis	0.71	0.41	1.22
Mitsudomi et al, 2010 (WJTOG3405)	Gefitinib	Doc/Cis	1.64	0.75	3.58
Mok et al, 2009 (IPASS)	Gefitinib	Pac/Carb	0.78	0.5	1.2
Rosell et al, 2002	Pac/Carb	Pac/Cis	1.22	1.03	1.43
Rosell et al, 2012 (EURTAC)	Erlotinib	Doc/Cis	1.04	0.65	1.68
		Gem/Cis	1.04	0.65	1.68
		Doc/Carb	1.04	0.65	1.68
		Gem/Carb	1.04	0.65	1.68
Scagliotti et al, 2002	Gem/Cis	Vin/Cis	0.87	0.69	1.09
		Pac/Carb	1.04	0.83	1.31
Scagliotti et al, 2009	Pem/Cis	Gem/Cis	0.84	0.71	0.99
Schiller et al, 2002	Gem/Cis	Doc/Cis	0.94	0.79	1.14
		Pac/Cis	0.92	0.76	1.1
		Pac/Carb	0.96	0.8	1.15
Thomas et al, 2002	Gem/Carb	Vin/Cis	0.89	0.53	1.49
Smit et al, 2003	Gem/Cis	Pac/Cis	0.9	0.65	1.25
Yang et al, 2012 (LUX-Lung 3), data on file	Afatinib	Pem/Cis	0.91	0.66	1.25
LUX-Lung 6, data on file	Afatinib	Gem/Cis	0.95	0.68	1.33
Zatloukal et al, 2003	Gem/Carb	Gem/Cis	0.98	0.69	1.39

The NMA used Bayesian methods to estimate the hazard ratios (HR) with 95% upper and lower credible intervals. The authors used both a fixed and a random effects model and reported results for both. Progression-free survival by investigator assessment and overall survival were the primary outcomes. A sensitivity analysis of progression-free survival was conducted using data from independently-assessed progression-free survival.

Table 14 provides the HR's and upper and lower credible intervals for the network meta-analysis of investigator-assessed progression-free survival (primary outcome) for each comparison of afatinib to other first-line treatments in locally advanced or metastatic NSCLC. Table 15 provides the HR's and upper and lower credible intervals for the network meta-analysis of independently-assessed progression-free survival (sensitivity analysis).

Table 14. Progression-free survival by investigator assessment as reported in the NMA submitted by the manufacturer.

Treatments	Fixed Effects			Random Effects		
	Hazard Ratio	lCr.Int	uCr.Int	Hazard Ratio	lCr.Int	uCr.Int
Afatinib vs. Gem/Cis	0.34	0.27	0.42	0.33	0.23	0.45
Afatinib vs. Vin/Cis	0.32	0.24	0.42	0.31	0.20	0.46
Afatinib vs. Pac/Carb	0.30	0.23	0.39	0.29	0.19	0.43
Afatinib vs. Pac/Cis	0.27	0.21	0.36	0.27	0.17	0.41
Afatinib vs. Gem/Carb	0.29	0.19	0.45	0.28	0.16	0.49
Afatinib vs. Doc/Cis	0.30	0.23	0.40	0.30	0.19	0.46
Afatinib vs. Pem/Cis	0.39	0.32	0.49	0.40	0.29	0.57
Afatinib vs. Gefitinib	0.73	0.54	0.98	0.70	0.43	1.10
Afatinib vs. Erlotinib	0.84	0.60	1.20	0.82	0.50	1.30
Afatinib vs. Doc/Carb	0.31	0.19	0.52	0.30	0.15	0.60
totresdev	25			19		
Sd	n.a.			0.13	0.01	0.31
DIC	-2.896			-3.779		
Data Points	20					

lCr.Int – lower credible interval, uCr.Int – upper credible interval; DIC – deviance information criterion; totresdev – total residual deviance; sd – between-study standard deviation; n.a. – non applicable

Table 15. Progression-free survival by independent assessment as reported in the NMA submitted by the manufacturer.

Treatments	Fixed Effects			Random Effects		
	Hazard Ratio	lCr.Int	uCr.Int	Hazard Ratio	lCr.Int	uCr.Int
Afatinib vs. Gem/Cis	0.38	0.30	0.48	0.36	0.25	0.52
Afatinib vs. Vin/Cis	0.36	0.27	0.48	0.35	0.21	0.53
Afatinib vs. Pac/Carb	0.34	0.26	0.45	0.32	0.20	0.49
Afatinib vs. Pac/Cis	0.31	0.23	0.41	0.30	0.18	0.47
Afatinib vs. Gem/Carb	0.33	0.22	0.51	0.31	0.17	0.57
Afatinib vs. Doc/Cis	0.35	0.26	0.46	0.34	0.21	0.53
Afatinib vs. Pem/Cis	0.45	0.36	0.56	0.46	0.32	0.66
Afatinib vs. Gefitinib	0.83	0.61	1.10	0.78	0.47	1.20

Afatinib vs. Erlotinib	0.95	0.67	1.40	0.91	0.53	1.50
Afatinib vs. Doc/Carb	0.35	0.21	0.59	0.34	0.16	0.68
totresdev	26			19		
sd	n.a.			0.14	0.02	0.34
DIC	-0.967			-2.859		
Data Points	20					

lCr.Int – lower credible interval, uCr.Int – upper credible interval; DIC – deviance information criterion; totresdev – total residual deviance; sd – between-study standard deviation; n.a. – non applicable

Table 16 provides the HR's and upper and lower credible intervals for the network meta-analysis of overall survival (primary outcome) for each comparison of afatinib to other first-line treatments in locally advanced or metastatic NSCLC.

Table 16. Overall survival as reported in the NMA submitted by the manufacturer.

Treatments	Fixed Effects			Random Effects		
	Hazard Ratio	lCr.Int	uCr.Int	Hazard Ratio	lCr.Int	uCr.Int
Afatinib vs. Gem/Cis	0.86	0.67	1.10	0.85	0.66	1.13
Afatinib vs. Vin/Cis	0.74	0.56	0.98	0.74	0.55	1.01
Afatinib vs. Pac/Carb	0.78	0.59	1.02	0.78	0.57	1.06
Afatinib vs. Pac/Cis	0.86	0.65	1.14	0.85	0.62	1.17
Afatinib vs. Gem/Carb	0.83	0.60	1.15	0.83	0.58	1.20
Afatinib vs. Doc/Cis	0.85	0.64	1.12	0.85	0.62	1.19
Afatinib vs. Doc/Carb	0.78	0.57	1.07	0.79	0.54	1.14
Afatinib vs. Pem/Cis	0.99	0.78	1.27	0.99	0.75	1.30
Afatinib vs. Gefitinib	0.84	0.55	1.30	0.83	0.54	1.34
Afatinib vs. Erlotinib	0.80	0.56	1.14	0.80	0.54	1.18
totresdev	19.00			18.40		
Sd	n.a.			0.05	0.00	0.16
DIC	-13.537			-11.565		
Data Points	26					

lCr.Int – lower credible interval, uCr.Int – upper credible interval; DIC – deviance information criterion; totresdev – total residual deviance; sd – between-study standard deviation; n.a. – non applicable

Adverse Events

Grade 3 or 4 adverse events of diarrhea, rash/acne and fatigue were also modelled in the network meta-analysis. However, due to the low numbers of adverse events in most of the treatment arms (sometimes zero), the model did not achieve convergence and produced very uncertain results that were not very informative.

Limitations

The quality of the manufacturer-submitted NMA was assessed according to the recommendations of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[57] Details and commentary with respect to the manufacturer-submitted NMA for each of the items identified by the ISPOR Task Force are provided in Table 17.

There are some limitations with the provided network meta-analysis. The network included studies of patients with only EGFR mutation-positive NSCLC as well as data from studies that had included patients with both EGFR mutation-positive and negative disease but did not report data for the subgroups separately. A primary assumption in meta-analysis is that included studies need to be sufficiently similar to yield meaningful results. In a network meta-analysis, if the trials differ with respect to certain study or patient characteristics, and those characteristics are modifiers of the treatment effect, then the estimate of the indirect comparison may be biased. It is not possible to estimate the direction of that bias given the number of comparisons in the network. There is uncertainty with respect to the estimated effect and the credible intervals. In addition, the definition of progression-free survival or tumour progression in each of the included studies may not have been the same. If progression-free survival or tumour progression were defined differently in some studies, the estimate of the indirect comparison may be biased.

Table 17. ISPOR checklist to evaluate a reported network meta-analysis and the scoring for the submitter's indirect treatment comparison report.[57]

ISPOR Checklist Item		Details and Comment
1.	Are the rationale for the study and the study objectives stated clearly?	Yes the rationale and objectives are clearly stated.
2	Does the methods section include the following: Description of eligibility criteria? Information sources? Study selection process? Data extraction (validity/quality assessment of individual studies?	The information sources, search strategy, and study selection criteria were clearly stated. No information was provided on the data extraction process, or on the validity/quality of the individual studies.
3	Are the outcome measures described?	Yes. Overall survival and progression-free survival.
4	Is there a description of methods for analysis/synthesis of evidence? Do the methods described include the following: Description of analyses methods/models? Handling of potential bias/inconsistency? Analysis framework?	Bayesian methods were used and described for the meta-analysis. Authors reported results using a fixed effects model and a random effects model and assessed model fit. No description of methods used to assess heterogeneity, homogeneity or consistency.
5.	Are sensitivity analyses presented?	Yes. Sensitivity analyses by independent assessment for progression-free survival, by using updated overall survival data for LUX-Lung 3 and LUX-Lung 6, and by using the independent assessment progression-free survival results for the common mutation population from the EURTAC trial.
6.	Do the results include a summary of the studies	Yes, a description of the studies with baseline

Table 17. ISPOR checklist to evaluate a reported network meta-analysis and the scoring for the submitter's indirect treatment comparison report.[57]		
ISPOR Checklist Item		**Details and Comment**
	included in the network meta-analysis? Individual study data? Network of studies?	patient characteristics, as well as study design is provided. A flow chart detailing the review process is given, along with figures describing the network of studies.
7.	Does the study describe an assessment of model fit? Are competing models being compared?	Yes. The authors describe an assessment of model fit using a fixed effects model and a random effects model.
8.	Are the results of the evidence synthesis presented clearly?	Yes. A table summarizing the hazard ratios for individual trials and the indirect comparison are provided. The results of the sensitivity analyses are presented in separate tables.
9.	Does the discussion include the following? Internal validity of analysis? External validity? Implications of results for target audience?	Yes. A description of the findings is included. Both internal and external validity of the results are discussed. The implications of results for the target audience are discussed.

The authors used investigator-assessed progression-free survival as the primary outcome for the NMA. Investigator assessments have the potential to be biased in favour of whichever treatment the investigator feels is superior. This could have led to biased estimates of progression-free survival in each of the included studies. By combining the results in a network meta-analysis, the estimate of the indirect comparisons may also be biased. Given the multitude of direct and indirect comparisons included in the network meta-analysis, it is not possible to estimate the direction or magnitude of the potential bias on the estimate of the indirect comparisons. In addition, the definition of progression-free survival in each of the included studies may not have been the same. If progression-free survival were defined differently across the included trials, the uncertainty around the estimates of the indirect comparisons would increase. This would affect both the investigator- and independently assessed progression-free survival estimates. There exists uncertainty around the estimates of effect reported in the network meta-analysis.

The authors reported the results of the NMA using both fixed and random effects models. Although the authors note that the fixed effects model fits the data better, the random effects model may be more appropriate as it takes into account heterogeneity across studies. For example, the identified studies included either EGFR mutation-positive and –negative disease, or just EGFR mutation-positive disease, with the identified studies also investigating differing treatments. It is likely that the differences in treatment effects observed in each study are not due simply to random chance (i.e., a fixed effects model), but instead due to the varying effects of the different treatments on the different patient groups, which would be better estimated using a random effects model.

7.1.3 Summary

The network meta-analysis provided by the manufacturer that investigated afatinib compared to any other pharmacological intervention reported that for patients with locally advanced or metastatic NSCLC, using a random effects model, the indirect comparison of afatinib to gefitinib for investigator-assessed progression-free survival demonstrated a HR of 0.70 with a 95% credible interval of 0.43 to 1.10.[24] Using independently assessed progression-free survival data, the HR

was 0.78 (95% credible interval 0.47 to 1.20). The indirect comparison of afatinib to erlotinib for investigator-assessed progression-free survival demonstrated a HR of 0.82, 95% credible interval 0.50 to 1.30. For independently assessed progression-free survival, the HR was 0.91, 95% credible interval 0.53 to 1.50. Grade 3/4 adverse events of diarrhea, rash/acne and fatigue were also modeled but due to the low number of events in treatment arms, the results of the analyses were highly uncertain and uninformative.

There is uncertainty with respect to the estimated HR's and credible intervals for the indirect comparisons due to several limitations of the NMA. The inclusion of studies that reported only combined data for EGFR mutation-positive and mutation-negative locally advanced or metastatic NSCLC with studies that included only patients with EGFR mutation-positive disease introduces a potential for bias in the estimates of the indirect comparisons. In addition, there is uncertainty in the HR's and credible intervals for the indirect comparisons for investigator-assessed progression-free survival as investigator assessments have the potential to be biased in favour of the treatment that the investigator feels is superior. It is not possible to estimate the magnitude or direction of that potential bias given the complexity of the network. Of note, the estimates of the HR's and credible intervals calculated based on the independent assessments of progression-free survival were similar to the estimates based on investigator assessments. Although the authors reported the results using both the fixed and random effects models, the random effects model may be more appropriate given the inclusion of studies with different patient groups (some had EGFR-positive patients, some had both EGFR-positive and negative patients). As the effect of any of the identified treatments may be different for EGFR mutation-positive disease compared to EGFR mutation-negative disease, there is likely to be more than one true treatment effect for each given treatment (e.g., one for EGFR mutation-positive patients and one for EGFR mutation-negative patients).

Of note, Lopes and Haaland reported, in abstract form at the 15th World Conference on Lung Cancer, the results of a network meta-analysis investigating the comparative effectiveness of gefitinib, erlotinib, afatinib, and chemotherapy in the first-line treatment of advanced NSCLC with EGFR mutations.[7] As this network meta-analysis has been published in abstract form only, insufficient information was reported in order to make any determinations regarding the study's potential limitations or risk of bias. What is notable is that the authors included randomized controlled trials that compared erlotinib, gefitinib, or afatinib to chemotherapy or to each other in the first-line treatment of advanced NSCLC. Studies were included only if the trial included only patients with EGFR activating mutations or if the study reported efficacy data separately for the subgroup of patients with EGFR activating mutations. Eight trials were included (OPTIMAL, EURTAC, LUX-Lung 3, LUX-Lung 6, IPASS, West Japan, North-east Japan, and First-SIGNAL). The pooled HR for progression-free survival for erlotinib vs. afatinib was 0.57 (95% CI, 0.26-1.23; 95% predictive interval, 0.21-1.55), and for afatinib vs. gefitinib was 1.02 (95% CI, 0.52-2.00; 95% predictive interval, 0.41-2.58).[7] The authors indicated that there was moderately high heterogeneity between studies (Q-statistic, p=0.003; I^2=72%).[7] For objective response rates, the pooled odds ratio for erlotinib vs. afatinib was 1.5 (95% CI, 0.7-3.3; 95% predictive interval, 0.6-3.7), and for afatinib vs. gefitinib was 1.3 (95% CI, 0.7-2.5; 95% predictive interval, 0.6-2.8), with moderate heterogeneity between studies (Q-statistic, p=0.198; I^2=32%).[7] No statistically significant differences were demonstrated for overall survival; however, no data were reported.[7]

8 ABOUT THIS DOCUMENT

This Final Clinical Guidance Report was prepared by the pCODR Lung Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on afatinib (Giotrif) for advanced non-small cell lung cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. Personal identifying information has been removed from the registered patient advocacy group section, to the Clinical Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Lung Clinical Guidance Panel is comprised of three medical oncologists .The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

1. Literature Search via OVID Platform.

Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, and Ovid MEDLINE (R) Daily Update.

1. Afatinib:.ti,ab,rn,nm,sh,hw,ot.
2. Gio?trif:.ti,ab,rn,nm,sh,hw,ot.
3. Tomtovok:.ti,ab,rn,nm,sh,hw,ot.
4. Tovok:.ti,ab,rn,nm,sh,hw,ot.
5. ((bibw adj 2992) or bibw2992).ti,ab,rn,nm,sh,hw,ot.
6. 439081-18-2.rn,nm.
7. Or/1-6
8. Limit 7 to English language

Human Filter

9. exp animals/
10. exp animal experimentation/
11. exp models animal/
12. exp animal experiment/
13. nonhuman/
14. exp vertebrate/
15. or/9-14
16. exp humans/
17. 15 not 16
18. 8 not 17

Ovid EMBASE

1. *afatinib/
2. (afatinib: or gio?trif: or tomtovok: or tovok: or (bibw adj 2992) or bibw2992).ti,ab.
3. 1 or 2
4. Limit 3 to English language

Human Filter

5. exp animals/
6. exp animal experimentation/
7. exp models animal/
8. exp animal experiment/
9. nonhuman/
10. exp vertebrate/
11. or/5-10
12. exp humans/
13. exp human experiment/
14. 12 or 13
15. 11 not 14
16. 4 not 15

2. Literature Search via PubMed

PubMed

1. afatinib* OR giotrif* OR gioltrif* OR tomtovok* OR tovok* OR bibw2992* OR bibw 2992
2. publisher[sb]
3. 1 AND 2

3. Literature Search via Cochrane Central Register of Controlled Trials (CENTRAL)

Search terms: afatinib* OR giotrif* OR gioltrif* OR tomtovok* OR tovok* OR bibw2992* OR bibw-2992* in Cochrane Central Register of Controlled Trials.

4. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: afatinib, giotrif, gioltrif, tomtovok, tovok, bibw-2992

Select International Agencies:

Food and Drug Administration (FDA):
www.fda.gov

European Medicines Agency (EMA):
www.ema.europa.eu

Search terms: afatinib, giotrif, gioltrif, tomtovok, tovok, bibw-2992

Conference Abstracts:

American Society of Clinical Oncology (ASCO)
via the *Journal of Clinical Oncology* search portal: http://jco.ascopubs.org/search

Search terms: afatinib, giotrif, gioltrif, tomtovok, tovok, bibw-2992

European Society for Medical Oncology (ESMO)
The abstracts for each of the ESMO annual conference are available here:
2013: 38th ESMO (European Cancer Congress 2013): *European Journal of Cancer* 2013;49(Suppl 2)
2012: 37th ESMO: *Annals of Oncology* 2012;23(Suppl 9)
2011: 36th ESMO (European Cancer Congress 2011): *European Journal of Cancer* 2011;47(Suppl 1)
2010: 35th ESMO: *Annals of Oncology* 2010;21(Suppl 8)

2009: 34th ESMO (European Cancer Congress 2009): *European Journal of Cancer* 2009;45(Suppl 1)

Search terms: afatinib, giotrif, gioltrif, tomtovok, tovok, bibw-2992

Note: Every two years, ESMO annual conference is held jointly with other European professional medical organizations. This joint conference is named the European Cancer Congress.

REFERENCES

1. Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene. 2008;27(34):4702-11.

2. Solca F, Dahl G, Zoephel A, Bader G, Sanderson M, Klein C, et al. Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. Journal of Pharmacology & Experimental Therapeutics. 2012;343(2):342-50.

3. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients With Metastatic Lung Adenocarcinoma With EGFR Mutations. Journal of Clinical Oncology. 2013;31(27):3327-34. [Epub ahead of print]. DOI: 10.1200/jco.2012.44.806.

4. Wu Y-L, Zhou C, Hu C-P, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncology. 2014;15(2):213-22. Supplementary appendices available at URL: http://www.thelancet.com/journals/lanonc/issue/current.

5. Boehringer Ingelheim Canada Ltd. response to checkpoint meeting questions [internal report]. Burlington (ON): Boehringer Ingelheim Canada Ltd.; 2013 Sep 30.

6. Yang JC, Sequist LV, Geater SL, Tsai C-M, Mok TS, Schuler M, et al. Activity of afatinib in uncommon epidermal growth factor receptor (EGFR) mutations: findings from three trials of afatinib in EGFR mutation-positive lung cancer. Journal of Thoracic Oncology. 2013;8(Suppl 2):S141; Abs O03.05.

7. Lopes G, Haaland B. Comparative effectiveness of gefitinib, erlotinib, afatinib and chemotherapy in the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) and epidermal growth factor receptor (EGFR) mutations. Journal of Thoracic Oncology. 2013;8(Suppl 2):S895-6; Abs P2.11-105.

8. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics.[Erratum appears in CA Cancer J Clin. 2011 Mar-Apr;61(2):134]. CA: a Cancer Journal for Clinicians. 2011;61(2):69-90.

9. Cancer Care Ontario. Cancer Fact: Lung cancer is the leading cause of cancer death among Ontario women [Internet]. Toronto: Cancer Care Ontario; 2012 Jan. [cited 2013 Sep 25]. Available from: https://http://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=122389.

10. Rapp E, Pater JL, Willan A, Cormier Y, Murray N, Evans WK, et al. Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer--report of a Canadian multicenter randomized trial. Journal of Clinical Oncology. 1988;6(4):633-41.

11. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. Journal of Clinical Oncology. 2008;26(21):3543-51.

12. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. New England Journal of Medicine. 2002;346(2):92-8.

13. Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. Journal of Clinical Oncology. 2003;21(16):3016-24.

14. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. New England Journal of Medicine. 2004;350(21):2129-39.

15. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004;304(5676):1497-500.

16. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nature Reviews Cancer. 2007;7(3):169-81.

17. Sos ML, Rode HB, Heynck S, Peifer M, Fischer F, Kluter S, et al. Chemogenomic profiling provides insights into the limited activity of irreversible EGFR Inhibitors in tumor cells expressing the T790M EGFR resistance mutation. Cancer Research. 2010;70(3):868-74.

18. Pao W, Miller VA, Politi KA, Riely GJ, Somwar R, Zakowski MF, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Medicine / Public Library of Science. 2005;2(3):e73.

19. Inukai M, Toyooka S, Ito S, Asano H, Ichihara S, Soh J, et al. Presence of epidermal growth factor receptor gene T790M mutation as a minor clone in non-small cell lung cancer. Cancer Research. 2006;66(16):7854-8.

20. Oxnard GR, Arcila ME, Sima CS, Riely GJ, Chmielecki J, Kris MG, et al. Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: distinct natural history of patients with tumors harboring the T790M mutation. Clinical Cancer Research. 2011;17(6):1616-22.

21. Yang JCH, Shih JY, Su WC, Hsia TC, Tsai CM, Ou SHI, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): A phase 2 trial. The Lancet Oncology. 2012;13(5):539-48.

22. Yang JC, Hirsh V, Schuler M, Yamamoto N, O'Byrne KJ, Mok TS, et al. Symptom Control and Quality of Life in LUX-Lung 3: A Phase III Study of Afatinib or Cisplatin/Pemetrexed in Patients With Advanced Lung Adenocarcinoma With EGFR Mutations. J Clin Oncol. 2013;31(27):3342-50. [Epub ahead of print]. DOI: 10.1200/jco.2012.46.1764.

23. Geater SL, Zhou C, Hu CP, Feng JF, Lu S, Huang Y, et al. LUX-Lung 6: Patient-reported outcomes (PROs) from a randomized open-label, phase III study in first-line advanced NSCLC patients (pts) harboring epidermal growth factor receptor (EGFR) mutations. Journal of Clinical Oncology. 2013;31(15 Suppl):Abstract 8061.

24. pan-Canadian Oncology Drug Review Manufacturer Submission: Giotrif (afatinib) for the first line treatment of EGFR mutation positive, advanced non-small cell lung cancer patients; Company: Boehringer Ingelheim (Canada) Ltd. Burlington (ON): Boehringer Ingelheim (Canada) Ltd.; 2013 Jun 7.

25. Pr Giotrif®. Afatinib tablets. 20, 30, and 40 mg afatinib (as afatinib dimaleate). Protein kinase inhibitor [product monograph]. Burlington (ON): Boehringer Ingelheim (Canada) Ltd.; 2013 Nov 2.

26. Canadian Cancer Society's Steering Committee. Canadian Cancer Statistics 2012. Toronto: Canadian Cancer Society; 2012.

27. Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M, the Comparative Risk Assessment collaborating group (Cancers). Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet. 2005;366(9499):1784-93.

28. NSCLC Meta-Analyses Collaborative Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. Journal of Clinical Oncology. 2008;26(28):4617-25.

29. Herbst RS, Lynch TJ, Sandler AB. Beyond doublet chemotherapy for advanced non-small-cell lung cancer: combination of targeted agents with first-line chemotherapy. Clinical Lung Cancer. 2009;10(1):20-7.

30. Herbst RS, Heymach JV, Lippman SM. Lung cancer. New England Journal of Medicine. 2008;359(13):1367-80.

31. Weiss J, Stinchcombe TE. Treatment of elderly patients with stage IV non-small-cell lung cancer. Expert Review of Anticancer Therapy. 2012;12(1):111-20.

32. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. New England Journal of Medicine. 2009;361(10):947-57.

33. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncology. 2010;11(2):121-8.

34. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. New England Journal of Medicine. 2010;362(25):2380-8.

35. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncology. 2011;12(8):735-42.

36. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncology. 2012;13(3):239-46.

37. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczesna A, Juhasz E, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncology. 2010;11(6):521-9.

38. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. Journal of Clinical Oncology. 2004;22(9):1589-97.

39. Scagliotti G, Hanna N, Fossella F, Sugarman K, Blatter J, Peterson P, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. Oncologist. 2009;14(3):253-63.

40. Shigematsu H, Gazdar AF. Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers. International Journal of Cancer. 2006;118(2):257-62.

41. Miller VA, Hirsh V, Cadranel J, Chen YM, Park K, Kim SW, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial.[Erratum appears in Lancet Oncol. 2012 May;13(5):e186]. Lancet Oncology. 2012;13(5):528-38.

42. Zhang L, Ma S, Song X, Han B, Cheng Y, Huang C, et al. Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised phase 3 trial. Lancet Oncology. 2012;13(5):466-75.

43. Wu YL, Zhou C, Hu CP, Feng JF, Lu S, Huang Y, et al. LUX-Lung 6: A randomized, open-label, phase III study of afatinib (A) versus gemcitabine/cisplatin (GC) as first-line treatment for Asian patients (pts) with EGFR mutation-positive (EGFR M+) advanced adenocarcinoma of the lung. Journal of Clinical Oncology. 2013;31(15 Suppl):Abstract 8016.

44. Yang JC-H, Schuler MH, Yamamoto N, O'Byrne KJ, Hirsh V, Mok T, et al. LUX-Lung 3: A randomized, open-label, phase III study of afatinib versus pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harboring EGFR-activating mutations. Journal of Clinical Oncology. 2012;30(18 Suppl):Abstract LBA7500.

45. Boyer M, Schuler M, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Lux-lung 3: A randomized, open-label, phase III study of afatinib versus pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harbouring EGFR-activating mutations. Journal of Thoracic Oncology. 2012;7(14 Suppl 3):S161, Abstract 033-O12.

46. Mok T, Schuler M, Yamamoto N, O'Byrne K, Hirsh V, Geater SL, et al. Lux-lung 3: Afatinib versus cisplatin and pemetrexed in asian patients with adenocarcinoma of the lung harbouring an epidermal growth factor receptor mutation. Journal of Thoracic Oncology. 2012;7(11 Suppl 5):S445, Abstract HO-003.

47. Sequist L, Schuler M, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Lux-lung 3: A randomized, open-label, phase III study of afatinib vs pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harboring egfr-activating mutations (subgroup analysis). Journal of Thoracic Oncology. 2012;7(15 Suppl 4):S203, Abstract 1.

48. O'Byrne KJ, Sequist LV, Schuler M, Yamamoto N, Hirsh V, Mok T, et al. LUX-Lung 3: Symptom and health-related quality of life results from a randomized phase III study in 1st-line advanced NSCLC patients harbouring EGFR mutations. Lung Cancer. 2013;79(7 Suppl 1):S11, Abstract 32.

49. Yang C-HJ, Sequist L, O'Byrne K, Schuler M, Mok T, Geater S, et al. Epidermal growth factor receptor (EGFR)-mediated adverse events (AEs) in patients (pts) with EGFR mutation positive (EGFR M+) non-small cell lung cancer treated with afatinib. European Journal of Cancer. 2013;49(Suppl 2):S190, Abstract 895.

50. O'Byrne K, Schuler M, Yamamoto N, Hirsh V, Mok T, Massey D, et al. Lux-lung 3: A randomized, open-label, phase iii study of afatinib vs. pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harboring egfr activating mutations. Journal of Thoracic Oncology. 2012;7(7):S102, Abstract O.02.

51. Passaro A, Gori B, de Marinis F. Afatinib as first-line treatment for patients with advanced non-small-cell lung cancer harboring EGFR mutations: focus on LUX-Lung 3 and LUX-Lung 6 phase III trials. Journal of Thoracic Disease. 2013;5(4):383-4.

52. LUX-Lung 3: A randomized, open-label, phase III study of afatinib vs pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harboring EGFR activating mutations (subgroup analysis). Clinical Advances in Hematology and Oncology. 2012;10(8 Suppl 11):4-6.

53. Boehringer Ingelheim Canada Ltd. response to additional information request [internal report]. Burlington (ON): Boehringer Ingelheim Canada Ltd.; 2013 Oct 16.

54. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT00949650, A randomized, open-label, phase III study of BIBW 2992 versus chemotherapy as first-

line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR activating mutation; 2009 Jul 29 [Last updated 2013 Jan 9; cited 2013 Aug 21]. Available from: http://clinicaltrials.gov/ct2/show/NCT00949650?term=nct00949650&rank=1.

55. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01121393, LUX-Lung 6: A randomized, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR activating mutation; 2010 Apr 21 [Last updated 2013 Aug 7; cited 2013 Aug 21]. Available from: http://clinicaltrials.gov/ct2/show/NCT01121393?term=nct01121393&rank=1.

56. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01466660, A randomized, open-label phase IIb trial of afatinib versus gefitinib as first-line treatment of patients with EGFR mutation positive advanced adenocarcinoma of the lung; 2011 Nov 4 [Last updated 2013 Oct 16; cited 2013 Oct 24]. Available from: http://clinicaltrials.gov/ct2/show/NCT01466660?term=nct01466660&rank=1.

57. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1. Value in Health. 2011;14(4):417-28.