Horizon Scanning in Oncology

Afatinib (Giotrif®) in combination therapy for patients with non-small cell lung cancer (NSCLC) who are refractory/resistant to erlotinib/gefitinib and afatinib monotherapy

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The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. A working version (unpublished) of V3.0 of the Model was used. Use of the HTA Core Model® does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

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1 Research questions

The EUnetHTA HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is afatinib?
A0022	Who manufactures afatinib?
A0007	What is the target population in this assessment?
A0020	For which indications has afatinib received marketing authorisation?
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C0005	What are the susceptible patient groups that are more likely to be harmed through the use of afatinib?
A0021	What is the reimbursement status of afatinib?

2 Drug description

Generic/Brand name/ATC code:

Europe: Afatinib/Giotrif®; USA: Gilotrif®/L01XE13

B0001: What is afatinib?

dual RTK inhibitor

Afatinib is a dual receptor tyrosine kinase (RTK) inhibitor [2]. It acts as a potent, selective and irreversible blocker of the ErbB family; this includes: epidermal-growth-factor-receptor (EGFR, ErbB1), HER2 (ErbB2), ErbB4 and specific EGFR mutations (e.g. alterations of L858R in exon 21 and deletions in exon 19) [3, 4]. The mechanism of action leads to the inhibition of tyrosine kinase auto phosphorylation, which in turn downregulates the ErbB signalling. The downregulation of this signalling pathway results in the inhibition of tumour growth [5].

once daily 40 mg orally

The recommended dose of afatinib is 40 mg orally once daily. Treatment should be continued until disease progression or until no longer tolerated by the patient [3, 5].

A0022: Who manufactures afatinib?

Boehringer Ingelheim International GmbH

3 Indication

A0007: What is the target population in this assessment?

for patients with NSCLC, refractory to erlotinib/ gefitinib & afatinib monotherapy

Afatinib (Giotrif®) in combination with paclitaxel is indicated for the treatment of erlotinib/gefitinib refractory/resistant non-small cell lung cancer (NSCLC) patients, who have progressed on afatinib monotherapy after initial benefit.

4 Current regulatory status

A0020: For which indications has afatinib received marketing authorisation?

approved by the EMA since 2013

Afatinib (Giotrif®) monotherapy was approved by the European Medicines Agency (EMA) for the treatment of TKI-naive adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations on 25 September 2013 [3]. In March 2016, the EMA approved afatinib for a new indication as follows: Afatinib (Giotrif®) monotherapy for the treatment of locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy [6].

The US Food and Drug Administration (FDA) approved afatinib (Gilotrif®) for the first-line treatment of NSCLC patients with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test (therascreen® EGFR RGQ PCR Kit) on 12 July 2013. The use of afatinib is limited to these two EGFR mutations; safety and efficacy have not been ascertained in NSCLC patients exhibiting other EGFR mutations [5].

approved by the FDA since 2013

5 Burden of disease

A0002: What is NSCLC?

Lung cancer or bronchogenic carcinomas are malignancies that arise in the airways or pulmonary parenchyma [7]. They can be classified as either small-cell lung cancer (SCLC) or NSCLC, which accounts for the majority of lung cancer patients (85%–90%) [8, 9]. There are three main types of NSCLC: squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma [10].

definition of disease

A0004: What is the natural course of NSCLC?

Generally, lung cancer is detected late in its natural history. A pulmonary nodule can grow and potentially metastasise before it causes any symptoms [11]. It can metastasise via the tissue, blood or lymph system [10]. Therefore, most patients with lung cancer have advanced disease at the time of diagnosis [11].

most patients have advanced diseases at initial presentation

Owing to the molecular pathogenesis of NSCLC, it is designated as a heterogeneous group of disease [7]. The factor that has the greatest impact on prognosis of NSCLC is the tumour node metastasis (TNM) staging system. It classifies tumours on the basis of primary tumour characteristics (T), the presence or absence of regional lymph node involvement (N), and the presence or absence of distant metastases (M). The final stage (staged from I to IV) is dependent on the particular combination of T, N, and M characteristics [12]. Of 100 newly diagnosed persons with lung cancer, 80 will be inoperable at presentation and about 20 will proceed to attempted resection [11].

heterogeneous group of diseases

A0006: What are the consequences of NSCLC for the society?

A0023: How many people belong to the target population?

About 12% of all malignant neoplasm cases in Austria are due to lung cancer. It is the most common cause of death as a result of cancer in males and second most common in females. In Austria, the incidence of lung cancer is 30.5 per 100,000 persons per year; in 2012, more than 4,500 persons were newly diagnosed, of whom one third already had remote metastasis [13]. Around 17% of lung cancer patients are alive at least 5 years after diagnosis [14]. The median age at diagnosis of lung cancer is 70 years; it is more frequently diagnosed in males than in females (incidence 2012: 40.9 vs 22.0) [13, 15].

incidence rate in Austria 30.5 per 100,000 persons/year

median age at diagnosis: 70 years

A0005: What are the symptoms and the burden of NSCLC?

most common symptoms: cough, dyspnoea, weight loss, chest pain & shortness of breath

Occasionally, lung cancer patients do not show any signs or symptoms [10]. Patients who are exhibiting symptoms are more likely to have chronic obstructive pulmonary diseases. In general, the most frequent symptoms of lung cancer imply cough, dyspnoea, weight loss, chest pain, haemoptysis, and shortness of breath [14, 16].

A0003: What are the known risk factors for NSCLC?

main risk factor: cigarette smoking

The predominant risk factor for developing lung cancer is cigarette smoking. It is estimated that smoking accounts for about 90% of all lung cancers [17]. The risk of a current smoker (one pack/day for 40 years) to develop lung cancer is around 20 times higher compared to someone who has never smoked [10]. Further, factors that may have an impact on the risk of lung cancer are: radiation therapy, environmental toxins (e.g. asbestos), pulmonary fibrosis, HIV infection, genetic factors, and alcohol [18].

A0024: How is NSCLC currently diagnosed according to published guidelines and in practice?

lung cancer screening via CT scans

A lung cancer screening is performed for high-risk current and former smokers using low-dose computerised tomography (CT) scans. If highly suspicious nodules are detected by CT scans, biopsy or surgical excision should be performed. For nodules with a low suspicion, further surveillance and the assessment of other patient factors are recommended. Dependent on the size and location of the tumour, additional mediastinal or distant diseases, patient characteristics and local expertise, the diagnostic strategy should be personalised for each patient. Further, evaluation and staging are required if the biopsy or surgical excision indicates a diagnosis of NSCLC [14, 19]. Pathologic evaluation is needed to classify the histological type (e.g. determine the extent of invasion) of lung cancer. Following molecular diagnostics, studies should be performed to evaluate whether particular gene alterations are present (i.e. EGFR mutations) [14, 20].

6 Current treatment

A0025: How is NSCLC currently managed according to published guidelines and in practice?

factors for therapeutic decisions

Certain factors have to be taken into account for the therapeutic decision:

- Stage of cancer (TNM)
- Type of NSCLC
- Mutation in certain genes (e.g. EGFR, anaplastic lymphoma kinase (ALK) gene)
- Health condition of the patient (Eastern Cooperative Oncology Group (ECOG) performance scale 0–4)[10]

stage I, II, and III treatment with a curative intent

Stage I, II, or III NSCLC is commonly treated with curative intent using surgery (provides the best chance of cure), chemotherapy, radiation therapy, or a combined modality approach [14, 21]. Systematic therapy is indicated for patients with stage IV (advanced disease) NSCLC or recurrence following initial definitive treatment [21]. Therapy options for advanced NSCLC without a driver mutation are:

no driver mutation: 1st line: 4–6 cycles of cytotoxic chemotherapy

- initial treatment of NSCLC: four to six cycles of cytotoxic chemotherapy with a platinum-based doublet (non-squamous tumour supplementation with bevacizumab).

2nd line immunotherapy or single-agent chemotherapy with a non-cross-resistant agent

- therapy after combination chemotherapy: immunotherapy with an anti-PD-1 antibody (e.g. nivolumab, pembrolizumab).
  - For patients who are not eligible for immunotherapy: single-agent chemotherapy with a non-cross-resistant agent is an alternative. Primary options for those who are receiving chemotherapy are pemetrexed (non-squamous tumours) and docetaxel [21, 22].

driver mutation:

Therapy options for advanced NSCLC with a driver mutation are:

1st line: targeted inhibitor

- initial treatment of NSCLC: targeted inhibitor: e.g. erlotinib, gefitinib, or afatinib (EGFR), crizotinib (ALK fusion oncogene or ROS1 translocations).

2nd line: targeted inhibitor

- therapy after initial chemotherapy: targeted therapy with a specific inhibitor.

single-agent chemotherapy & immunotherapy

- therapy after combination chemotherapy/treatment-specific inhibitor: single-agent chemotherapy as well as immunotherapy (e.g. nivolumab).

combination chemotherapy

- therapy after initial treatment with a targeted therapy: combination chemotherapy as in chemotherapy-naive patients [21, 22]. Another treatment option is osimertinib for patients with an activating mutation of EGRF who have progressed after erlotinib, afatinib or geftinib [14].

7 Evidence

literature search in 5 databases: 396 hits

A literature search was conducted on 18 April 2016 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were „Afatinib", „Giotrif", „Gilotrif", „bibw-2992", „non-small cell lung cancer" and „NSCLC". Also, the manufacturer was contacted, who submitted three additional references (two of which had already been identified by systematic literature search). Manual search identified 25 additional references (web documents and journal articles).

included:

Overall, 425 references were identified. Included in this report are:

1 phase III study

- 1 phase III study, assessing afatinib plus paclitaxel in NSCLC patients refractory to erlotinib, gefitinib, and afatinib monotherapy [23, 24].

1 phase II study

- 1 phase II study, assessing the clinical benefit of afatinib in patients with NSCLC who are resistant to erlotinib and/or gefitinib [25].

7.1 Clinical efficacy and safety – phase III studies

LUX-Lung 5: efficacy and safety of afa plus pac in 202 patients

The LUX-Lung 5 trial (a randomised, multicentre, open-label international phase III study) was conducted to assess the efficacy and safety of afatinib plus paclitaxel (40 mg/day; 80 mg/m^2/week) in patients with NSCLC, who had acquired resistance to erlotinib/gefitinib and had progressed on afatinib monotherapy after initial benefit [23, 24]. A total of 202 patients were randomly assigned in a 2:1 ratio to receive either afatinib plus paclitaxel (n = 134) or the investigator's choice of a single-agent chemotherapy (n = 68).

required 351 patients for 90% power were not reached

To assess the benefit of continued ErbB targeting beyond progression with afatinib, this trial consisted of a prior part (Part A), where patients were enrolled who had failed ≥ 1 line of chemotherapy and progressed following ≥ 12 weeks' clinical benefit on erlotinib/gefitinib. Every patient in Part A received single-agent afatinib (50 mg daily) to identify patients who derived clinical benefit from an ErbB blockade. However, participation in Part B was lower than expected as 351 patients (279 PFS events) would have been required to achieve 90% power at a two-sided 5% significance level for the log-rank test. In the end, only 202 patients were enrolled. As the calculated number of 351 eligible patients was not achieved, the protocol was changed following discussion with the Safety Monitoring Committee (DMC) on 18 January 2013: the time point for the primary analyses of progression-free survival (PFS) and overall survival (OS) was adapted accordingly, and the analyses were carried out as soon as the final randomised patients could be followed up for at least 6 months. Consequently, primary analysis was performed on 10 December 2013, after 163 PFS events had occurred.

median age of 60 years and ECOG performance status of 0–2

Enrolled patients had a median age of 60 years. The study population had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and had received ≥ 1 line of chemotherapy (including platinum and pemetrexed) and erlotinib/gefitinib after ≥ 12 weeks of treatment, and had to have obtained ≥ 12 weeks' clinical benefit on afatinib monotherapy with subsequent progression pursuant to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Testing of the EGFR mutation status was not obligatory. Detailed patient characteristics including inclusion and exclusion criteria can be found in Table 3.

primary outcome: PFS

The primary outcome of LUX-Lung 5 was PFS; secondary outcomes included OS and objective response (OR). Other evaluated study endpoints were health-related quality of life (QoL, assessed with EQ-5D, QLQ-C30, and QLQ-LC13) and safety. Adverse events were assessed in conformity with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0.

7.1.1 Clinical efficacy

D0001: What is the expected beneficial effect of afatinib on mortality?

The median OS was 12.2 (95% CI 10.2–14.9) months both in the afatinib-paclitaxel group and in the chemotherapy group (12.2 months, 95% CI 9.33–16.59). Compared with the control group, the hazard ratio (HR) of death was 1.00 (95% CI 0.70–1.43, p = 0.994) in the afatinib-paclitaxel arm. There were no differences in OS among the two treatment groups.

secondary endpoint: OS
no difference between the two groups

D0006: How does afatinib affect progression (or recurrence) of NSCLC?

The primary endpoint, PFS, was significantly improved (p = 0.003) in the afatinib-paclitaxel group compared to the chemotherapy group. Median PFS was 5.6 (95% CI 5.1–6.3) months in the afatinib-paclitaxel group and 2.8 (95% CI 1.7–3.9) months in the chemotherapy group. The HR for disease progression for afatinib-paclitaxel compared to chemotherapy was 0.60 (95% CI 0.43–0.85).

primary endpoint: PFS

median PFS gain:
2.8 months

D0005: How does afatinib affect symptoms and findings (severity, frequency) of NSCLC?

The objective response rates (ORR) were 32.1% (afatinib-paclitaxel) and 13.2% (chemotherapy); a complete response (CR) was achieved by one patient in the afatinib-paclitaxel group. Stable disease (SD) rates were 42.5% in the afatinib-paclitaxel group, and 32.4% in the chemotherapy group. The median durations of objective responses were 4.2 and 3.3 months in patients receiving afatinib-paclitaxel and in patients receiving chemotherapy respectively.

ORR
afa+pac: 32.1%
chemotherapy: 13.2%

D0011: What is the effect of afatinib on patients' body functions?

No evidence was found to answer this research question.

D0012: What is the effect of afatinib on generic health-related quality of life?

D0013: What is the effect of afatinib on disease-specific quality of life?

There was a difference regarding median time to deterioration for dyspnoea (2.5 vs 1.6 months, p = 0.158) and pain (2.8 vs 1.7 months, p = 0.154) between the afatinib-paclitaxel group and the chemotherapy group. Patients receiving chemotherapy had a longer median time to deterioration for cough (6.5 vs 5.4 months, p = 0.771) than patients who received afatinib-paclitaxel. Nevertheless, none of the differences was statistically significant. Furthermore, the global health status did not differ between the two study groups.

no statistically significant difference in QoL

Table 1: Efficacy results of the LUX-Lung 5 trial

Descriptive statistics and estimate variability	Treatment group	Afatinib-paclitaxel	Chemotherapy
	Number of subjects	134	68
	Median PFS, months	5.6 (5.1–6.3)	2.8 (1.7–3.9)
	Median OS, months	12.2 (10.2–14.9)	12.2 (9.33–16.59)
	ORR, % CR PR SD	32.1 0.7 31.3 42.5	13.2 0.0 13.2 32.4
	Median duration of objective response, months	4.2	3.3
Effect estimate per comparison	*Comparison groups*		*Afatinib-paclitaxel vs chemotherapy*
	PFS	HR	0.60
		95% CI	0.43–0.85
		Log-rank test p value	0.003
	OS	HR	1.00
		95% CI	0.70–1.43
		Log-rank test p value	0.994
	ORR	OR	3.41
		95% CI	1.41–6.79
		Logistic regression p value	0.005

Abbreviations: CI = confidence interval, CR = complete response, HR = hazard ratio, OR = odds ratio, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PR = partial response, SD = stable disease

7.1.2 Safety

C0008: **How safe is afatinib in relation to the comparator(s)?**

any grade AEs
afa+pac: 88.6%
chemotherapy: 70%

Adverse events (AEs) of any grade related to treatment were reported from 88.6% (afatinib-paclitaxel) and 70% (chemotherapy) of patients. The most frequent treatment-related AEs in the afatinib-paclitaxel group were diarrhoea (53.8%), alopecia (32.6%), asthenia (27.3%), decreased appetite (22.0%), and rash (20.5%).

grade 3–5 AEs
afa+pac: 48.5%
chemotherapy: 30.0%

Treatment-related grade 3–5 AEs could be observed in 48.5% of patients receiving afatinib-paclitaxel and in 30.0% of patients receiving chemotherapy. In the afatinib-paclitaxel group serious treatment-related AEs were more common (11.4%) than in the chemotherapy group (3.3%). Treatment-related peripheral neuropathy occurred in 9.1% and 8.3% of patients in the afatinib-paclitaxel group and in the chemotherapy group respectively. Treatment-related fatal pneumonia was experienced by one patient, which was attributed to paclitaxel. Permanent discontinuation due to AEs occurred in 18.9% (afatinib-paclitaxel) and 6.7% (chemotherapy) of patients. All treatment-related AEs can be found in Table 2.

C0002: Are the harms related to dosage or frequency of applying afatinib?

higher dose-reduction rate in the intervention group

One or two dose reductions of afatinib were necessary in 27.3% and 4.5% of patients respectively. Regarding paclitaxel, 23.5% of patients required one dose reduction, and in 35.6% of patients the dosage was reduced a second time. In the chemotherapy group, the dose-reduction rate as a result of AEs was 11.7% compared to 32.6% in the afatinib-paclitaxel group.

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of afatinib?

embryo-foetal toxicity

For pregnant women and patients who become pregnant while taking afatinib, there is a risk that it may cause foetal harm because of its mechanism of action. Afatinib has not been studied yet in patients with severe hepatic and renal impairment [5].

Table 2: Most frequent treatment-related adverse events[1]

Adverse event (according to CTCAE, version 3.0)	Afatinib-paclitaxel (n = 132)		Chemotherapy (n = 60)	
	Any grade n (%)	Grade 3–5 n (%)	Any grade n (%)	Grade 3–5 n (%)
Any	117 (88.6)	64 (48.5)	42 (70.0)	18 (30.0)
AEs leading to discontinuation	25 (18.9)	13 (9.8)	4 (6.7)	2 (3.3)
Occurring in > 10% of patients in any study group				
Diarrhoea	71 (53.8)	16 (12.1)	4 (6.7)	0 (0)
Alopecia	43 (32.6)	1 (0.8)	9 (15.0)	3 (5.0)
Asthenia	36 (27.3)	11 (8.3)	17 (28.3)	2 (3.3)
Decreased appetite	29 (22.0)	2 (1.5)	10 (16.7)	1 (1.7)
Fatigue	27 (20.5)	6 (4.5)	9 (15.0)	3 (5.0)
Rash	27 (20.5)	2 (1.5)	6 (10.0)	0 (0)
Neutropenia	24 (18.2)	15 (11.3)	8 (13.3)	5 (8.3)
Nausea	23 (17.4)	2 (1.5)	10 (16.7)	1 (1.7)
Paronychia	23 (17.4)	3 (3.2)	0 (0)	0 (0)
Vomiting	21 (15.9)	3 (2.3)	4 (6.7)	0 (0)
Anaemia	20 (15.2)	5 (3.8)	3 (5.0)	0 (0)
Leukopenia	20 (15.2)	6 (4.5)	7 (11.7)	3 (5.0)
Epistaxis	16 (12.1)	0 (0)	1 (1.7)	0 (0)
Stomatitis	13 (9.8)	2 (1.5)	2 (3.3)	0 (0)
Mucosal inflammation	12 (9.1)	1 (0.8)	0 (0)	0 (0)
Pruritus	10 (7.6)	0 (0)	3 (5.0)	1 (1.7)
Dry skin	6 (4.5)	0 (0)	0 (0)	0 (0)

Abbreviations: AEs = adverse events, CTCAE = Common Terminology Criteria for Adverse Events

[1] Ordered by rate of occurrence in the afatinib-paclitaxel group

7.2 Clinical efficacy and safety – further studies

LUX-Lung 4: efficacy of afatinib in NSCLC refractory to erlotinib/gefitinib

A multicentre, single-arm, open-label phase II trial [25] was conducted to assess the clinical benefit of afatinib in patients with NSCLC who are resistant to erlotinib and/or gefitinib (≥ 12 weeks of prior treatment). Included were 62 patients, 45 (72.6%) of whom had a positive EGFR mutation status in their primary tumour. The daily administered oral dose of afatinib was 50 mg. The primary endpoint was the objective response rate (ORR); secondary endpoints were overall survival (OS) and progression-free survival (PFS).

ORR (PR): 8.2% SD: 57.4%

ORR was 8.2%, of which five patients had a partial response (PR) and 35 (57.4%) patients had a stable disease (SD) for ≥ 6 weeks. The median PFS was 4.4 months (95% CI 2.8–4.6) after 72.1% of patients had a PFS event. 63.9% of patients had an OS event; median OS was 18.4 months. Most frequent treatment-related adverse events (AEs) were rash (91.9%) and diarrhoea (100%). Discontinuation due to treatment-related AEs occurred in 29% of patients. Dose reductions to a daily 40-mg dose were necessary in 69.4% of patients.

8 Estimated costs

A0021: What is the reimbursement status of afatinib?

estimated costs for one month: € 3,260 afa+pac

In Austria, afatinib is available as 20, 30, 40, and 50-mg film-coated tablets in packages of 28 pieces each. One package of 28 40-mg tablets is available for € 2,031.05 [26]. The recommended dose of afatinib is 40 mg orally once daily [5]. According to this dosage recommendation, the costs for a 30-day cycle would be € 2,176.13. Additional costs would incur due to the combination of afatinib with paclitaxel, which is administered at a dose of 80 mg/m^2 per week [23, 27]. Assuming a body surface of 1.70 m^2, total costs of about € 3,260 would incur for one month of combination therapy.

9 Ongoing research

2 phase IV, 4 phase III studies are ongoing, investigating afatinib in patients with NSCLC

In May 2016, a search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted. The following 6 ongoing phase III and IV trials are investigating afatinib in patients with NSCLC:

- NCT02438722: A randomised phase II/III trial of afatinib plus cetuximab versus afatinib alone in treatment-naive patients with advanced, EGFR mutation-positive non-small cell lung cancer (NSCLC). Estimated study completion date is February 2020.
- NCT01953913: An open label, multicentre single-arm trial to assess the safety of afatinib for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring EGFR mutation(s). Estimated study completion date is July 2018.
- NCT02695290: An open-label, single-arm phase IV study of afatinib in patients with stage IV or recurrent non-small cell lung cancer who have poor performance status and whose tumours have common epidermal growth factor receptor (EGFR) mutations, exon 19 deletions or exon 21 (L858R) substitution mutations. Estimated study completion date is October 2018.
- NCT02514174: A single-arm phase IV study of afatinib in elderly patients with stage IV or recurrent non-small cell lung cancer whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. Estimated study completion date is March 2018.
- NCT01523587: LUX-Lung 8: A randomised, open-label phase III trial of afatinib versus erlotinib in patients with advanced squamous cell carcinoma of the lung as second-line therapy following first-line platinum-based chemotherapy. Estimated study completion date is August 2016.
- NCT01121393: LUX-Lung 6: A randomised, 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. Estimated study completion date is December 2016.

numerous ongoing phase I and II trials in different indication and treatment lines

Various phase I and II studies are currently ongoing in different treatment lines in patients with NSCLC, either using afatinib monotherapy or combination treatment (e.g. NCT02364609, NCT01999985, NCT01542437, and NCT02625168). In addition, afatinib is also currently investigated for other indications, like squamous cell carcinoma of the head and neck, brain cancer, advanced oesophago-gastric cancer, and advanced refractory urothelial cancer.

10 Discussion

not approved by the EMA or the FDA

At the moment, afatinib in combination with paclitaxel for the treatment of erlotinib/gefitinib-refractory NSCLC patients who have progressed on afatinib after initial benefit is neither by the EMA nor by the FDA. However, afatinib received marketing authorisation in the US (July 2013) as well as in Europe (September 2013) for the treatment of EGFR TKI-naive adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations. Recently (March 2016), afatinib monotherapy was also approved by the EMA for the treatment of locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy [3, 5].

LUX-Lung 5: improvement in PFS (+ 2.8m) & ORR, but not in OS

A randomised, open-label phase III study, the LUX-Lung 5 trial [23], compared afatinib in combination with paclitaxel with single-agent chemotherapy in patients with NSCLC refractory/resistant to erlotinib/gefitinib after initial benefit of afatinib monotherapy in 202 patients. For patients treated with afatinib-paclitaxel, median PFS was significantly longer compared to the chemotherapy group (5.6 vs 2.8 months). Median OS did not differ between the two tested groups ($p = 0.994$). ORR was 32.1% in the afatinib-paclitaxel group versus 13.2% in the chemotherapy group.

treatment-related AEs any grade & grade 3–5 more common in the afatinib-paclitaxel group

In terms of safety, treatment-related AEs of any grade as well as of grade 3–5 were more common in the afatinib-paclitaxel group compared to the chemotherapy group. The most frequent AEs in the afatinib-paclitaxel arm were diarrhoea, alopecia, asthenia, decreased appetite, and rash. The discontinuation rate was higher in the afatinib-paclitaxel group compared to the chemotherapy group (18.9% vs 8.3%). No significant differences regarding QoL could be identified between the two study arms.

unbalanced EGFR status & number of prior post-progression therapies

The stratification of randomisation was based on the duration of benefit on previous gefitinib/afatinib treatment and sex. However, there is an imbalance in the number of post-progression therapies as well as in the EGFR status. Additionally, more patients in the intervention group had a better health status (ECOG 0: 35.1% vs 20.6%) as well as less lines of previous treatment (0 or 1 line: 34.3% vs 20.5%). The study was conducted in two parts: A and B. In Part B, which followed Part A, 202 patients with ≥ 12 weeks' clinical benefit on afatinib monotherapy with subsequent progression (according to RECIST) were eligible for the experimental part of the study. As only 14 patients in Part B had a confirmed EGFR mutation status (9 positive, 5 negative), it is not known whether the EGFR mutation status among the remaining 190 patients was balanced between the two arms.

identification of advantages/ disadvantages for a confirmed EGFR status

Documentation of the enrolled patients' EGFR mutation status was not obligatory. However, afatinib is currently approved in Europe as well as in the US for the first-line treatment of NSCLC patients with activating EGFR mutation. Therefore, prior testing via re-biopsy or liquid biopsy would be important to detect patients who are exhibiting an activating EGFR mutation. This could help to identify any advantages or disadvantages for patients with a positive/negative EGFR status receiving afatinib and paclitaxel as a late-line treatment.

limitations due to less power

A statistical limitation of the study is that 351 patients would have been necessary for the primary analysis to achieve 90% power at a two-sided 5% significance level for the log rank tests. As this patient number was not achieved, the time point for the primary analysis was changed, and only 202 patients

(57.5% of the required patient number) were enrolled in the study. This negatively influences the probability that a nominally statistically significant finding actually represents a true effect. Further, problems that occurred were an exaggerated estimate of the magnitude of the effect, and possibly increased the bias [28].

small sample size of subgroups

Another issue is that, due to the small sample size of various subgroups, it is not possible to make a clear statement about consistent PFS benefit across predefined subgroups. For instance, there is a trend of favouring chemotherapy in patients who have a smoking history of < 15 pack years and stopped > 1 year. Therefore, it would be important to investigate the PFS benefit of afatinib-paclitaxel in a higher patient number for different subgroups, in which uncommon and common mutations are also taken into account.

representation of the actual patient group

Generally, the median age at diagnosis of lung cancer is 70 years; further, lung cancer is commonly detected late in its natural history. Since patients were on average about 60 years old and had an ECOG score between 0 and 1 in 91% of cases, the study population conceivably did not reflect the patient group most affected by NSCLC in clinical practice.

possible evaluation-time & attrition bias

Furthermore, response assessment by a local investigator increases the potential of bias and measurement errors. If there are differences in evaluation times correspondent to treatment arms, evaluation-time bias can occur [29]. In addition, as the primary endpoint of the study was PFS, an attrition bias may be possible since it is difficult to determine a patient's progression time as soon as they are lost to follow-up [30].

overcoming resistance

However, another treatment option for the late-line therapy of NSCLC is the combination of afatinib with another inhibitor. For instance, the combination of afatinib with PI3K/Akt/mTOR inhibitors or SRC kinase inhibitors may be of interest in order to increase the efficacy of and protract resistance to monotherapies. The limitation of these combination therapies is often reduced tolerability because of dose-limiting toxicity [8, 31]. Therefore, another option, in particular for $EGFR^{T790M}$-positive patients, is a treatment with third-generation EGFR inhibitors (e.g. CO-1686, AP26113) [8].

treatment costs per month € 3,260

The costs per month for the treatment with afatinib-paclitaxel amount to € 3,260. Additional costs could incur due to obligatory testing of the EGFR mutation status if further trials were to identify a benefit for EGFR-positive patients.

modest PFS improvement & great extent of AEs

In conclusion, the treatment with afatinib-paclitaxel offers modest improvements in PFS (median gain 2.8 months) and no gain in OS at relatively high costs per month (€ 3,260) and a greater extent of AEs. Therefore, other afatinib-based combination therapies as well as third-generation inhibitors might be taken into consideration for the late-line treatment of NSCLC patients refractory to erlotinib/gefitinib and afatinib monotherapy. In addition, further trials are needed to evaluate the efficacy and safety for different subgroups who exhibit common/uncommon mutations, especially regarding the EGFR mutation status. Finally, the fact that the study was underpowered due to the small sample size (42.5% fewer patients than necessary) also has to be taken into account when considering the efficacy and safety results.

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12 Appendix

Table 3: Characteristics of the LUX-Lung 5 trial

Title: Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: phase III randomized LUX-Lung 5 trial [23, 24]			
Study identifier	NCT01085136, EudraCT number 2009-014563-39, LUX-Lung 5		
Design	Phase III, randomised, multicentre, open-label, international trial		
	Duration		Enrolment: April 2010 to May 2011 The study was conducted in two parts (A and B). In Part A, 1,154 patients were enrolled who had failed ≥ 1 line of chemotherapy and who had progressed ≥ 12 weeks after clinical benefit on erlotinib/gefitinib. Upon progression, patients with ≥ 12 weeks on afatinib were eligible for Part B. As the required patient number for Part B was not reached, the protocol was changed following discussion with the Safety Monitoring Committee on 18 January 2013. The time point for the primary analyses of PFS and OS was amended accordingly, and the analyses were carried out as soon as the final randomised patients could be followed up for at least 6 months. Consequently, primary analysis was performed on 10 December 2013.
Hypothesis	Superiority The study was designed to show a prolonged PFS (HR 0.67) in patients treated with afatinib plus paclitaxel compared to those who received the investigator's choice of single-agent chemotherapy. The planned sample size of the study was 351 patients to provide 90% power at a two-sided 5% significance level for the log-rank test. The required patient number was not reached (n = 202).		
Funding	Boehringer Ingelheim International GmbH		
Treatments groups	Intervention (n = 134)		Afatinib 40 mg/day, with dose reductions to 30 mg/day and 20 mg/day – oral Paclitaxel 80 mg/m² once weekly (7 weeks on/1 week off; 2 dose reductions were allowed) – intravenous
	Control (n = 68)		Investigator's choice of chemotherapy dosage was dependent on schedule (2 dose reductions were allowed) – intravenous/oral
Endpoints and definitions	Progression-free survival (primary outcome)	PFS	Day of randomisation to the day of progression according to RECIST, version 1.1
	Overall survival	OS	Time from the date of randomisation to the date of death
	Objective response rate	ORR	Best overall response of complete response or partial response as determined by RECIST 1.1 and as assessed by the investigator
Results and analysis			
Analysis description	**Primary analysis** Efficacy analyses were performed in the randomised set (all randomised patients irrespective of whether they were treated or not); no information on the included study population is available regarding safety and QoL analysis. PFS and OS were analysed by a stratified log-rank test. For HRs and CIs a stratified Cox proportional hazards model was used. A logistic regression was used to identify differences in the objective response rates (ORR; CR + PR).		
Analysis population	Inclusion		❖ Stage IIIB (wet) or IV NCSLC with measurable disease ❖ Failure of treatment with ≥ 1 line of chemotherapy (including platinum and pemetrexed) ❖ Erlotinib/gefitinib after ≥ 12 weeks of treatment ❖ ≥ 12 weeks' clinical benefit on afatinib monotherapy with subsequent progression according to RECIST, version 1.1 ❖ Age ≥ 18 years ❖ ECOG performance status of 0–2 ❖ Life expectancy of ≥ 12 weeks

Title: Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: phase III randomized LUX-Lung 5 trial [23, 24]

Study identifier	NCT01085136, EudraCT number 2009-014563-39, LUX-Lung 5			
Analysis population *(continuation)*	Exclusion	❁ Absence of clinical benefit from afatinib monotherapy ❁ Abnormal hepatic, renal or hematologic function ❁ Pregnancy and breastfeeding ❁ Peripheral polyneuropathy of > grade 2 ❁ Pre-existing or current interstitial lung disease ❁ Other malignancies diagnosed within the past five years (other than non-melanomatous skin cancer and in-situ cervical cancer) ❁ Clinically relevant cardiovascular abnormalities (uncontrolled hypertension, congestive heart failure – New York Heart Association functional classification of III, unstable angina, or poorly controlled arrhythmia) ❁ Myocardial infarction within 6 months prior to entering the trial ❁ Absolute neutrophil count at or less than 1,500/mm³ ❁ Platelet count at or less than 100,000/mm³ ❁ Bilirubin at or greater than 1.5 mg/dL (> 26 mol/L, SI unit equivalent) ❁ Patients with any serious active infection including known human immunodeficiency virus (HIV), active hepatitis B or active hepatitis C ❁ Known or suspected active drug or alcohol abuse ❁ Significant or recent acute gastrointestinal disorders (diarrhoea → major symptoms, e.g. Crohn's disease, mal-absorption, or CTCAE grade > 2 diarrhoea of any aetiology at baseline)		
	Characteristics		afatinib-paclitaxel	chemotherapy[2]
	Median age, years		60.0	60.5
	Gender: n (%)		♂ 69 (51.5) ♀65 (48.5)	♂ 34 (50.0) ♀ 34 (50.0)
	Baseline ECOG status, n (%)			
		0	47 (35.1)	14 (20.6)
		1	77 (57.5)	46 (67.6)
		2	10 (7.5)	8 (11.8)
	Smoking status, n (%)			
		Never smoked	71 (53.0)	37 (54.4)
		< 15 pack years, stopped > 1 year before diagnosis	14 (10.4)	10 (14.7)
		Current/other ex-smoker	49 (36.6)	21 (30.9)
	Tumour histology, n (%)			
		Adenocarcinoma	113 (84.3)	61 (89.7)
		Squamous	11 (8.2)	6 (8.8)
		Other	10 (7.5)	1 (1.5)
	Confirmed EGFR mutation status, n (%)			
		Positive	6 (4.5)	3 (4.4)
		Negative	2 (1.5)	3 (4.4)
	Prior EGFR TKI therapy, n (%)			
		Erlotinib	96 (71.6)	47 (69.1)
		Gefitinib	32 (23.9)	16 (23.5)
		Both	6 (4.5)	5 (7.4)
	Lines of prior chemotherapy, n (%)			
		0	5 (3.7)	2 (2.9)
		1	41 (30.6)	12 (17.6)
		2	39 (29.1)	28 (41.2)
		> 2	49 (36.6)	26 (38.2)

[2] Paclitaxel (35.0%), docetaxel (15.0%), pemetrexed (26.7%), vinorelbine (8.3%), gemcitabine (6.7%), carboplatin (1.7%), and non-protocol defined chemotherapy (6.7%)

Title: Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: phase III randomized LUX-Lung 5 trial [23, 24]			
Study identifier	NCT01085136, EudraCT number 2009-014563-39, LUX-Lung 5		
Analysis population *(continuation)*	Previous pemetrexed Yes No	 72 (53.7) 62 (46.3)	 39 (57.4) 29 (42.6)
	Previous taxane, n (%) Yes No	 67 (50.0) 67 (50.0)	 38 (55.9) 30 (44.1)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events, ECOG = Eastern Cooperative Oncology Group, EGFR = Epidermal Growth Factor Receptor, NSCLC = non-small cell lung cancer, RECIST = Response Evaluation Criteria in Solid Tumors, TKI = tyrosine kinase inhibitor

Table 4: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomized controlled trials) [32]

Criteria for judging risk of bias		**risk of bias**
Adequate generation of randomisation sequence		unclear
Adequate allocation concealment		unclear
Blinding	**Patient**	no
	Treating Physician	no
Selective outcome reporting unlikely		no
No other aspects which increase the risk of bias		no
Risk of bias – study level		high