Horizon Scanning in Oncology

Afatinib (Giotrif®) for the first-line treatment of EGFR TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s)

Ludwig Boltzmann Institut
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Ludwig Boltzmann Institut
Health Technology Assessment

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Author: Mag. Johanna Breuer
Project leader: Dr. med. Anna Nachtnebel, MSc
Internal review: Dr. med. Anna Nachtnebel, MSc
External review: Prof. Dr. med. Jürgen Wolf
Klinik I für Innere Medizin, Uniklinik Köln

CONTACT INFORMATION

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Nußdorferstr. 64, 6 Stock, A-1090 Vienna
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Responsible for Contents:

Ludwig Boltzmann Institut für Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

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1 Drug description

Generic/Brand name/ATC code:

Afatinib/Giotrif® (Europe), Gilotrif® (US)/L01XE13

Developer/Company:

Boehringer Ingelheim International GmbH

Description:

Afatinib is an orally bioavailable receptor tyrosine kinase inhibitor (TKI) with antineoplastic activity. Human epidermal growth factor receptors 1 (ErbB1; EGFR), 2 (ErbB2; HER2) and 4 (ErbB4; HER4) and certain EGFR mutants (including those caused by EGFR exon 19 deletion mutations or exon 21 (L858R) mutations) play a major role in tumour cell proliferation and tumour vascularisation and are overexpressed in many cancer cell types. Afatinib inhibits these receptors and therefore tumour growth by irreversible binding [1-4].

afatinib is a tyrosine kinase inhibitor of EGFR

The recommended dose of Giotrif® is 40 mg orally once daily until disease progression or unacceptable toxicity [5].

40 mg orally daily administered

2 Indication

Afatinib (Giotrif®) as monotherapy is indicated for the treatment of EGFR TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutations.

for EGFR TKI-naïve patients with advanced or metastatic NSCLC

3 Current regulatory status

In September 2013, the EMA granted marketing authorisation for Giotrif® 20 mg, 30 mg, 40 mg and 50 mg film-coated tablets

EMA licensed afatinib in September 2013

- intended for the treatment of EGFR TKI-naïve adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations [2].

The US Food and Drug Administration (FDA) approved afatinib (Gilotrif®) on 12 July 2013 for

FDA licensed afatinib in July 2013

- the first-line treatment of patients with metastatic NSCLC whose tumours have EGFR mutations [6].

4 Burden of disease

leading cause of death due to cancer in Austrian males

Lung cancer accounts for more than 11% of all malignant neoplasms in Austria and is the leading cause of death due to cancer in males. In 2010, about 2,700 men and 1,200 women were newly diagnosed with lung cancer in Austria and 3,650 people died [7]. The majority of lung cancer patients are diagnosed at an age ≥ 65 years and the median age at diagnosis for lung cancer is 70 years [8].

tobacco smoking as most important risk factor

The most important risk factor associated with lung cancer is tobacco smoking, accounting for about 90% of all lung cancers. Besides exposure to tobacco smoke, additional environmental factors and genetic predisposition affect the risk for lung cancer [9].

two types: SCLC and NSCLC

Lung cancer can be differentiated into two major classes, i.e. NSCLC and small cell lung cancer (SCLC). NSCLC accounts for more than 85% of all lung cancer cases and includes two major types:

- non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other cell types)
- squamous cell (epidermoid) carcinoma [10].

advanced or metastatic NSCLC complies with TNM stage IIIB and IV

Based on the tumour node metastasis (TNM) staging system which considers tumour size, location and invasion of the surrounding tissue, presence of metastasis in the lymph nodes or distant metastasis, four stages are distinguished. Locally advanced and metastasised NSCLC corresponds to TNM stage IIIB and IV [11].

assessment of mutational status

NSCLC can further be differentiated into EGFR mutational status positive or negative. Due to the development of targeted therapies, EGFR mutational status should also be assessed prior to therapy [10]. Some guidelines recommend routine testing for EGFR mutations only for non-squamous NSCLC (which comprises adenocarcinomas, the most frequent histo-pathological subtype) because EGFR mutations in squamous cell carcinomas are rather rare [10, 12, 13]. The two most common mutations are exon 19 deletions (50%) and L858R point mutations (40%) [14]. In addition to EGFR, other onco-genetic mutations have been identified, e.g. anaplastic lymphoma kinase (ALK) or rat sarcoma (RAS) mutations [15, 16].

5 Current treatment

surgery, radiation therapy, chemotherapy and targeted therapy

Modalities for the treatment of NSCLC which are generally used are surgery, radiation therapy, chemotherapy and targeted therapy. Depending on disease status, Eastern Cooperative Oncology Group (ECOG) performance status and prognostic factors, these treatments can be used either alone or in combination [12].

First-line therapy of advanced NSCLC depends on a number of factors, such as tumour stage, histo-pathological subtype and performance status. Current treatment options for the first-line therapy of patients with advanced or metastatic lung cancer are:

- double-agent chemotherapy regimen based on a platinum compound (cisplatin, carboplatin) in addition to one out of numerous other substances (paclitaxel, gemcitabine, vinorelbine or docetaxel and pemetrexed)

  double-agent platinum-based chemotherapy

- other chemotherapy regimens: due to the toxicity of platinum-based regimens, other drug combinations can be used (gemcitabine + docetaxel/paclitaxel/vinorelbine/pemtrexed, paclitaxel + vinorelbine)

  other combinations due to platinum toxicity

- single-agent chemotherapy as first-line treatment may be used for elderly patients

  single-agent chemotherapy

- targeted therapies: EGFR inhibitors (erlotinib, gefitinib), monoclonal antibodies (bevacizumab)

  targeted therapies

- a combined modality approach [10, 12, 15].

  combined approach

If patients are EGFR mutational status positive, EGFR-TK inhibitors (e.g. erlotinib, gefitinib) are increasingly used as standard first-line therapy, whereas patients with either unknown EGFR status or without EGFR mutation receive chemotherapy doublets, either alone or in combination with a monoclonal antibody (bevacizumab). If patients with driver mutations have initially been treated with chemotherapy, targeted therapy with a specific inhibitor is indicated after progression on the initial chemotherapy regimen either alone or in combination with chemotherapy [15, 16].

first and second-line treatment depending on mutations

6 Evidence

A literature search was conducted on the 23rd of September 2013 in 4 databases (Medline, Embase, CRD, Cochrane Central), resulting in 83 references. Search terms were "non-small cell lung cancer", "afatinib" or "Giotrif". Eligible for inclusion were phase III trials (full text, abstracts) and phase II studies published as full text but also other study designs such as results from compassionate-use programmes or meta-analyses. Also, the manufacturer was contacted for any further evidence and 9 studies were submitted. Of these, 7 had already been identified by the systematic literature search, resulting in 2 additional references. Overall, 85 references were identified.

literature search in 4 databases: 83 hits

manufacturer information

After applying the inclusion criteria, two phase III trials [3, 17] and one phase II trial [18] were included in this report.

included: 2 phase III, 1 phase II

6.1 Efficacy and safety – phase III studies

Table 1: Summary of efficacy of the LUX-Lung 3 trial

Study title LUX-Lung 3 trial: Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations [3] Symptom control and quality of life in LUX-Lung 3: A phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations [19]			
Source of information	Full texts [3, 19], FDA Document [20]		
Study identifier	ClinicalTrials.gov Identifier: NCT00949650, EudraCT Number: 2008-005615-18		
Design	Randomised, open-label, multicentre (133 centers in 25 countries) phase III study, 2:1 ratio		
	Duration	Enrolment: August 2009 – February 2011 Median follow-up: 16.4 months Cut-off dates for primary analysis: February 2012 (PFS), January 2013 (OS) [20] Cut-off date for final analyses: December 2013	
Hypothesis	Superiority		
Funding	Boehringer Ingelheim International GmbH		
Treatment groups	Intervention (n=230)	Afatinib 40 mg orally (once per day), until investigator-assessed progression	
	Control (n=115)	Cisplatin 75 mg/m² and pemetrexed 500 mg/m² intravenously (once every 21 days up to a maximum of six cycles) until investigator-assessed progression	
Endpoints and definitions	Progression-free survival (primary outcome)	PFS	Time from random assignment to progression or death as assessed by an independent review committee
	Objective response rate	ORR	The proportion of patients with best overall RECIST response of CR or PR, divided by the total number of patients randomly assigned to that arm
	Disease control rate	DCR	Proportion of patients with CR/PR+SD
	Duration of response	DOR	Time from the first documented response until disease progression or death from any cause
	Overall survival	OS	Time interval from date of randomisation to death from any cause
	Patient-reported outcomes	PROs	Measured with: • EORTC QLQ-C30 • EORTC QLQ-LC13 (lung cancer-specific module) PROs were assessed per standard published EORTC algorithms, including time to deterioration of symptoms calculated as the time from random assignment to the first 10-point worsening from the baseline score (considered clinically meaningful)
	Adverse events	AEs	Categorised and graded using NCI-CTCAE version 3.0
	Pharmacokinetics	–	Plasma concentrations analysed by validated high-performance liquid chromatography tandem mass spectrometry

Results and analysis				
Analysis description	ITT PFS was compared by a stratified log-rank test, Cox proportional hazard models and Kaplan-Meier estimates. Median follow-up time was calculated with the reverse Kaplan-Meier method. Descriptive statistics were used for all other secondary and exploratory analyses.			
Analysis population	Inclusion	✵ Treatment-naïve advanced lung adenocarcinoma ✵ Pathologically confirmed diagnosis of stage IIIB or stage IV adenocarcinoma of the lung ✵ Tumours harbour an activating mutation in EGFR ✵ Good performance status, defined as 0 or 1 on the ECOG scale ✵ Adequate end-organ function ✵ Measurable disease according to RECIST 1.1		
	Exclusion	✵ Prior chemotherapy for relapsed and/or metastatic NSCLC ✵ Neoadjuvant/adjuvant chemotherapy if at least 12 months has elapsed between the end of chemotherapy and randomisation ✵ Prior treatment with EGFR targeting small molecules or antibodies ✵ Radiotherapy or surgery (other than biopsy) within 4 weeks prior to randomisation ✵ Active brain metastases ✵ Any other current malignancy or malignancy diagnosed within the past five years ✵ Known pre-existing interstitial lung disease ✵ Significant or recent acute gastrointestinal disorders with diarrhoea as a major symptom ✵ History or presence of clinically relevant cardiovascular abnormalities		
	Characteristics	Age – median (range) (years): I 61.5 (28–86) vs C 61.0 (31–83) Male/female, n (%): I 83 (36.1)/147 (63.9) vs C 38 (33.0)/77 (67.0) Race, n (%): - White: I 61 (26.5) vs C 30 (26.1) - East Asian: I 165 (71.7) vs C 83 (72.2) - Other: I 4 (1.7) vs C 2 (1.7) Smoking status, n (%): - Never: I 155 (67.4) vs C 81 (70.4) - Former: I 70 (30.4) vs C 32 (27.8) - Current: I 5 (2.2) vs C 2 (1.7) ECOG – 0/1/2 (%): I 40/60/0 vs C 35.7/63.5/0.9 Adenocarcinoma stage, n (%): - IIIB with pleural effusion: I 20 (8.7) vs C 17 (14.8) - IV: I 210 (91.3) vs C 98 (85.2) EGFR mutation, n (%): - Exon 19 deletion: I 113 (49.1) vs C 57 (49.6) - L858R: I 91 (39.6) vs C 47 (40.9) - Other: I 26 (11.6) vs C 11 (9.6)		
Descriptive statistics and estimated variability			Afatinib	Cisplatin+pemetrexed
	Overall study population		**N=230**	**N=115**
	Median PFS – all patients, months		11.1	6.9
	95% CI		9.6–13.6	5.4–8.2

	ORR, % Complete Response Partial Response	56.1 0.4 55.7	23 0.0 22.6
	DCR, %	90	81
	Median DOR, months	11.1	5.5
	Median OS (95% CI), months Updated analysis [21]	16.6 (NR) 28.1 (24.6–33.0)	14.8 (NR) 28.2 (20.7–33.2)
	Median time to deterioration for cough/dyspnoea/pain, months	NE/10.3/4.2	8.0/2.9/3.1
	Subgroup analyses		
	Patients with common EGFR mutations Median PFS, months	N=204 13.6	N=104 6.9
	Patients with uncommon EGFR mutations Median PFS, months	N=26 2.8	N=11 9.9
Effect estimate per comparison	**Overall study population**		**Intervention vs Control**
	PFS – all patients	HR	0.58
		95% CI	0.43–0.78
		P value	0.001
	Median OS (updated analysis [21])	HR	1.12
		95% CI	0.73–1.73
		P value	0.6
	Time to deterioration of cough	HR	0.60
		95% CI	0.41–0.87
		P value	0.007
	Time to deterioration of dyspnoea	HR	0.68
		95% CI	0.50–0.93
		P value	0.015
	Time to deterioration of pain	HR	0.83
		95% CI	0.62–1.10
		P value	0.19
	Subgroup analyses PFS		
	PFS, patients with common EGFR mutations	HR	0.47
		95% CI	0.34–0.65
		P value	0.001
	PFS, patients with uncommon EGFR mutations	HR	1.89
		95% CI	0.84–4.28
		P value	NR
	Sex Male/Female	HR	0.61/0.54
		95% CI	0.37–1.01/0.38–0.78
		P value	0.85
	Age at baseline, years: <65/≥65	HR	0.53/0.64
		95% CI	0.36–0.76/0.39–1.03

		P value	0.58
	Race: Non-Asian/Asian	HR	0.68/0.54
		95% CI	0.39–1.19/0.38–0.76
		P value	0.65
	Baseline ECOG score: 0/1	HR	0.50/0.63
		95% CI	0.31–0.82/0.43–0.91
		P value	0.60
	Smoking history: Never smoked/<15 packet years+stop > 1 year/current or ex-smoker	HR	0.47/0.50/1.04
		95% CI	0.33–0.67/0.19–1.34/0.54–1.98
		P value	0.09

Abbreviations: AEs = adverse events, CI = confidence interval, CR = complete response, DCR = disease control rate, DOR = duration of response, ECOG = Eastern Cooperative Oncology Group, EGFR = epidermal growth factor receptor, EORTC-QLQ = European Organisation for Research and Treatment of Cancer – core quality-of-life questionnaire, HR = hazard ratio, ITT = intention to treat, N = number, NCI-CTCAE = National Cancer Institute – common terminology criteria for adverse events, NE = not evaluable, NR = not reported, NSCLC = non-small cell lung cancer, OS = overall survival, ORR = objective response rate, PFS = progression-free survival, PR = partial response, PROs = patient-reported outcomes, RECIST = response evaluation criteria in solid tumours, SD = stable disease

Table 2: Most frequent adverse events of the LUX-Lung 3 trial

NCT00949650				
Adverse event* (according to CTC version 3.0)	**Afatinib** (n=229)		**Cisplatin+pemetrexed** (n=111)	
	All Grades n (%)	Grade≥3 n (%)	All Grades n (%)	Grade≥3 n (%)
Diarrhoea	218 (95.2)	33 (14.4)	17 (15.3)	0 (0.0)
Rash/acne	204 (89.1)	37 (16.2)	7 (6.3)	0 (0.0)
Stomatitis/mucositis	165 (72.1)	20 (8.7)	17 (15.3)	1 (0.9)
Paronychia	130 (56.8)	26 (11.4)	0 (0.0)	0 (0.0)
Dry skin	67 (29.3)	1 (0.4)	2 (1.8)	0 (0.0)
Decreased appetite	47 (20.5)	7 (3.1)	59 (53.2)	3 (2.7)
Pruritus	43 (18.8)	1 (0.4)	1 (0.9)	0 (0.0)
Nausea	41 (17.9)	2 (0.9)	73 (65.8)	4 (3.6)
Fatigue	40 (17.5)	3 (1.3)	52 (46.8)	14 (12.6)
Vomiting	39 (17.0)	7 (3.1)	47 (42.3)	3 (2.7)
Epistaxis	30 (13.1)	0 (0.0)	1 (0.9)	1 (0.9)
Cheilitis	28 (12.2)	0 (0.0)	1 (0.9)	0 (0.0)
Anaemia	7 (3.1)	1 (0.4)	31 (27.9)	7 (6.3)
Constipation	6 (2.6)	0 (0.0)	21 (18.9)	0 (0.0)
Leukopenia	4 (1.7)	1 (0.4)	21 (18.9)	9 (8.1)
Neutropenia	2 (0.9)	1 (0.4)	35 (31.5)	20 (18.0)

Abbreviations: CTC = common toxicity criteria, n = number

* Events were included if reported in > 10% of patients in either treatment group and if there was ≥ 10% difference between the groups. Events are listed according to incidence in the afatinib group.

LUX-Lung 3 investigated efficacy and safety of afatinibin in 345 patients

The LUX-Lung 3 trial (a randomised, open-label, multicentre phase III study) aimed to assess the efficacy and safety of afatinib in patients with metastatic NSCLC whose tumours have EGFR mutations [3]. The trial compared first-line treatment with afatinib (n=230) to cisplatin plus pemetrexed (n=115). Patients in the intervention group received afatinib 40 mg orally (once per day), while patients in the control group received cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 intravenously (once every 21 days up to a maximum of six cycles).

median age of 61 years and ECOG performance status 0 or 1

The patients included had a median age of 61 years. The vast majority of the study population had never been smokers and had a good ECOG performance status (0 or 1). Since EGFR mutations are more common in women, never-smokers and Asians, this EGFR-enriched study population contained, as expected, mainly individuals with these characteristics.

median PFS was extended by 4.2 months in the afatinib group

secondary endpoints and subgroup analyses favoured patients treated with afatinib

For patients treated with afatinib, median PFS – the primary outcome – was extended by 4.2 months (11.1 vs. 6.9 months, HR 0.58, p=0.001) as determined by independent review. Secondary endpoints including objective response rate (56% with afatinib and 23% with cisplatin and pemetrexed) and duration of response (median duration of response for afatinib: 11.1 months compared with 5.5 months in the control group) favoured patients treated with afatinib. Subgroup analyses consistently favoured the afatinib group with the exception of the rather small (n=37) subgroup of patients with uncommon EGFR mutations (HR 1.89, CI 0.84–4.28, p=NR). Only preliminary results were reported for median OS in the publication but an updated analysis was found in the FDA licensing documents (28.1 vs. 28.2 months, HR=1.12, p=0.6) [21]. However, due to high post-progression crossover (62%–65%), results may be influenced by crossover.

afatinib delayed time to deterioration for cough and dyspnoea, but not for pain

Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer's quality-of-life questionnaire C30 (EORTC QLQ-C30) and a specific version for lung cancer patients (QLQ-LC13). Administration of afatinib resulted in a significantly delayed time to deterioration for cough and dyspnoea, but not for pain. It is important to note that a subgroup analysis in patients with EGFR common mutations demonstrated an increase in symptom improvement and control the higher the gains in PFS were [19].

haematological AEs more common with chemotherapy, skin-related AEs more common with afatinib

therapy discontinuation in 8% of patients with afatinib, 12 % with chemotherapy

Toxicity profiles rather differed between the two groups. While haematological AEs (e.g. anaemia, neutropenia) were more common with chemotherapy, skin-related AEs were more common with afatenib. Diarrhoea (95%), rash/acne (89%), stomatitis/mucositis (72%) and paronychia (57%) were the most frequent AEs with afatinib, whereas decreased appetite (53%), fatigue (47%), vomiting (42%) and neutropenia (31%) were the most commonly observed AEs in the control group. Occurrence of AEs grade ≥ 3 was comparable (afatinib: 49% vs chemotherapy: 48%). Therapy was discontinued because of treatment-related AEs in 8% of the patients receiving afatinib and in 12% of the patients receiving cisplatin plus pemetrexed. Dose reduction to less than 40 mg afatinib per day was required for 120 patients (52%) and 19% required more than one dose reduction.

Table 3: Summary of efficacy of the LUX-Lung 6 trial

Study title LUX-Lung 6: A randomized, open-label, phase III study of afatinib versus gemcitabine/cisplatin as first-line treatment for Asian patients with EGFR mutation-positive (EGFR M+) advanced adenocarcinoma of the lung [17] LUX-Lung 6: Patient-reported outcomes (PROs) from a randomized open-label, phase III study in first-line advanced NSCLC patients harboring EGFR mutations [22]			
Source of information	Based on abstracts and posters [17, 22]		
Study identifier	ClinicalTrials.gov Identifier: NCT01121393		
Design	randomised, open-label, multicentre (36 sites in 3 Asian countries) phase III study, 2:1 ratio		
	Duration	Enrolment: April 2010-November 2011 Median follow-up: NR Cut-off date for primary analysis: 29 October 2012	
Hypothesis	Superiority		
Funding	Boehringer Ingelheim International GmbH		
Treatment groups	Intervention (n=242)	Afatinib 40 mg orally (once per day), until progression or unacceptable AEs	
	Control (n=122)	Gemcitabine 1000 mg/m² (on day 1 and day 8) plus cisplatin 75 mg/m² intravenously (on day 1) of each 21-day cycle up to a maximum of six cycles	
Endpoints and definitions	Progression-free survival (primary outcome)	PFS	Time from random assignment to progression or death based on independent radiology review and determined by RECIST 1.1
	Objective response rate	ORR	The proportion of patients with best overall RECIST response of CR or PR, divided by the total number of patients randomly assigned to that arm
	Disease control rate	DCR	NR
	Duration of response	DOR	Time from the first documented response until disease progression or death from any cause
	Tumour shrinkage	–	NR
	Overall survival	OS	Time interval from date of randomisation to death from any cause
	Patient-reported outcomes	PROs	Measured with: • EQ-5D • EORTC QLQ-C30 • EORTC QLQ-LC13 (lung cancer-specific module) Measured at: randomisation and every 3 weeks until progression or new anticancer therapy Prespecified symptoms of interest were cough, dyspnoea and pain
	Safety and pharmacokinetics	–	Intensity and incidence of AEs were described using the NCI-CTCAE Version 3.0
Results and analysis			
Analysis description	ITT Stratified log-rank and Cox proportional hazard for PFS comparisons		
Analysis	Inclusion	• Pathologically confirmed diagnosis of stage IIIB (wet) or stage IV	

population		adenocarcinoma of the lung • EGFR mutation in the tumour sample • Measurable disease (RECIST 1.1) • No prior chemotherapy or EGFR-targeting drugs for advanced non-small cell lung cancer (NSCLC) • ECOG performance status 0 or 1 • Adequate organ function
	Exclusion	• Prior chemotherapy or EGFR-targeting drugs for advanced NSCLC • Asymptomatic brain metastases
	Characteristics	Age – median (range) (years): I 58 (29–79) vs C 58 (27–76) Male/female, n (%): I 87 (36)/155 (64) vs C 39 (32)/83 (68) Smoking status, n (%): - Never: I 181 (75) vs C 99 (81) - Former: I 44 (18) vs C 13 (11) - Current: I 17 (7) vs C 10 (8) ECOG – 0/1, n (%): I 48 (20)/194 (80) vs C 41 (34)/81 (66) Adenocarcinoma stage, n (%): - IIIB (wet): I 16 (7) vs C 6 (5) - IV: I 226 (93) vs C 116 (95) EGFR mutation, n (%): - Exon 19 deletion: I 124 (51) vs C 62 (51) - L858R: I 92 (38) vs C 46 (38) - Other: I 26 (11) vs C 14 (12)

Descriptive statistics and estimated variability	Treatment group	Afatinib	Gemcitabine+cisplatin
	Number of subjects	N=242	N=122
	Median PFS, months	11.0	5.6
	12-month PFS rate, %	47.0	2.0
	ORR, %	66.9	23.0
	DCR, %	92.6	76.2
	Median DOR, months, (95% CI)	9.7 (8.3–12.5)	4.3 (2.8–5.8)
	Median duration of disease control, months, (95% CI)	11.1 (9.7–13.8)	5.7 (5.5–6.9)
	Median OS, months	22.1	22.2
	Median time to deterioration, months/symptom improvement (≥10 points), % cough dyspnoea pain	NR/76 7.7/71 6.4/64	10.3/55 1.7/48 3.4/47
Effect estimate per comparison	*Comparison groups*		*Intervention vs Control*
	PFS	HR	0.28
		95% CI	0.20–0.39
		P value	p<0.0001
	ORR	OR	7.282
		95% CI	NR

		P value	p<0.0001
	DCR	OR	3.843
		95% CI	NR
		P value	p<0.0001
	OS	OR	0.95
		95% CI	NR
		P value	0.7593
	Time to deterioration of cough	HR	0.45
		95% CI	0.30–0.68
		P value	p=0.0001
	Time to deterioration of dyspnoea	HR	0.54
		95% CI	0.40–0.73
		P value	p<0.0001
	Time to deterioration of pain	HR	0.70
		95% CI	0.51–0.96
		P value	p=0.03
	Global health status	HR	0.56
		95% CI	0.41–0.77
		P value	NR
	Subgroup analyses PFS: Sex: Male/Female	HR	0.36/0.24
		95% CI	0.21–0.63/0.16–0.35
		P value	NR
	Age at baseline, years: <65/≥65	HR	0.30/0.16
		95% CI	0.21–0.43/0.07–0.40
		P value	NR
	EGFR mutation category: Exon 19 deletion or L858R (common)/exon 19 deletion/L858R/other (uncommon)	HR	0.25/0.20/0.32/0.55
		95% CI	0.18–0.35/0.13–0.33/0.19–0.52/0.22–1.43
		P value	NR
	Baseline ECOG score: 0/1	HR	0.22/0.29
		95% CI	0.12–0.41/0.20–0.43
		P value	NR
	Smoking history: Never smoked/<15 packet years+stop>1 year/current or ex-smoker	HR	0.24/0.39/0.46
		95% CI	0.16–0.34/0.07–2.41/0.22–1.00
		P value	NR

Abbrevations: AEs = adverse events, CI = confidence interval, DCR = disease control rate, DOR = duration of response, ECOG = Eastern Cooperative Oncology Group, EGFR = epidermal growth factor receptor, EORTC-QLQ = European Organisation for Research and Treatment of Cancer – core quality-of-life questionnaire, HR = hazard ratio, ITT = intention to treat, N = number, NCI-CTCAE = National Cancer Institute – common terminology criteria for adverse events, NR = not reported, NSCLC = non-small cell lung cancer, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PROs = patient-reported outcomes, RECIST = response evaluation criteria in solid tumours

Table 4: Safety summary of the LUX-Lung 6 trial

AEs, %	**Afatinib** (n=239)	**Gemcitabine+cisplatin** (n=113)
Drug-related AEs	98.7	99.1
Drug-related AEs Grade≥3	36.0	60.2
Drug-related AEs leading to dose reduction	32.2	26.5
Drug-related AEs leading to discontinuation	5.9	39.8
Drug-related serious AEs	5.4	7.0
Related AEs leading to death‡	0.4	0.9

Abbrevations: AEs = adverse events

Table 5: Most frequent adverse events of the LUX-Lung 6 trial

NCT01121393 (abstracts, poster)						
AEs* (according to CTC version 3.0)	**Afatinib** (n=239)			**Gemcitabine+cisplatin** (n=113)		
	All Grades, %	Grade 3, %	Grade 4, %	All Grades, %	Grade 3, %	Grade 4, %
Diarrhoea	88.3	5.4	0.0	10.6	0.0	0.0
Rash/acne	80.8	14.2	0.4	8.8	0.0	0.0
Stomatitis/mucositis	51.9	5.4	0.0	5.3	0.0	0.0
Paronychia	32.6	0.0	0.0	0.0	0.0	0.0
ALT increase	20.1	1.7	0.0	15.9	1.8	0.9
Vomiting	9.6	0.8	0.0	80.5	15.9	3.5
Nausea	7.5	0.0	0.0	75.2	7.1	0.9
Neutropenia	2.1	0.4	0.0	54.0	17.7	8.8
Leukopenia	3.3	0.4	0.0	51.3	13.3	1.8
Decreased appetite	10.0	1.3	0.0	40.7	1.8	0.0
Fatigue	10.0	0.4	0.0	36.3	0.9	0.0
Anaemia	5.4	0.4	0.0	27.4	7.1	1.8
Neutrophil count decreased	0.8	0.0	0.0	25.7	7.1	2.7
WBC decreased	0.8	0.0	0.0	23.9	6.2	0.0

Abbrevations: AEs = adverse events, ALT = alanine transaminase, CTC = common toxicity criteria, WBC = white blood cells

*most frequently reported drug-related AEs: >20%

LUX-Lung 6 investigated efficacy and safety of afatinib in 364 Asian patients

Results of the LUX-Lung 6 study have not been fully published yet, but preliminary results are published as posters and conference abstracts. This study (an open-label, randomised, multicentre phase III trial) investigated the efficacy and safety of afatinib for Asian patients with EGFR mutation-positive advanced NSCLC. A total of 364 patients were randomised to receive either afatinib (n=242) or gemcitabine plus cisplatin (n=122). A dose of 40 mg afatinib was administered orally, while gemcitabine 1000 mg/m^2 plus cisplatin 75 mg/m^2 was given intravenously. Patients had a median age of 58 years. NSCLC with EGFR mutation(s), first-line treatment and ECOG performance status 0 or 1 were criteria for inclusion.

median age of 58 years, ECOG performance status of 0 or 1

The primary endpoint in this trial was PFS, which was 11.0 months in the afatinib group compared to 5.6 months in the control group (HR 0.28, CI 0.20–0.39, p<0.0001). Gains in PFS for afatinib were consistent across all subgroup analyses with a less pronounced benefit for patients with uncommon EGFR mutations and smokers with < 15 pack years who had stopped smoking for more than 1 year, but again, these subgroups comprised only few patients. Objective response rates were 66.9% in the afatinib group and 23.0% in the control group. The disease control rate was 92.6% in patients receiving afatinib compared with 76.2% of patients receiving gemcitabine/cisplatin. Data on OS are immature but amount to 22.1 months in patients receiving afatinib and 22.2 months in the control group (OR 0.95, CI NR, p=0.7593).

PFS was extended by 5.4 months in the afatinib group

secondary endpoints and subgroup analyses favoured patients treated with afatinib

Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer's quality of life questionnaire C30 (EORTC QLQ-C30), a specific version for lung cancer patients (QLQ-LC13) and the EuroQol five-dimension questionnaire (EQ-5D). A higher proportion of afatinib-treated patients had symptom improvements in cough, dyspnoea and pain, and afatinib also significantly delayed time to deterioration for cough (HR 0.45, p=0.0001), dyspnoea (HR 0.54, p<0.0001) and pain (HR 0.70, p=0.03) compared with gemcitabine/cisplatin. Further, a significantly higher number of patients in the afatinib group had improvements in global health status/quality of life (63% vs. 33%, p<0.0001) compared with the control group. Also, improvements in functional scales were observed for the afatinib group (concerning physical, role, emotional, cognitive and social functioning).

assessment of quality of life

afatinib delayed time to deterioration for cough, dyspnoea and pain

patients treated with afatinib had higher improvement in global health status/quality of life

The most frequently reported AEs were diarrhoea (88.3%), rash/acne (80.8%) and stomatitis/mucositis (51.9%) with afatinib and vomiting (80.5%), nausea (75.2%) and neutropenia (54.0%) with gemcitabine/cisplatin. Drug-related AEs leading to dose reduction were observed in 32.2% in the afatinib group and in 26.5% in the control group, but discontinuation due to drug-related AEs was less frequent in the intervention group (5.9%) than in the gemcitabine/cisplatin group (39.8%). Drug-related serious AEs were 5.4% in the intervention group and 7.0% in the control group, while drug-related AEs leading to death occurred in 0.4% for afatinib and in 0.9% for gemcitabine/cisplatin.

AEs with afatinib: diarrhoea, skin-related AEs with chemotherapy: vomiting, nausea, neutropenia

therapy discontinuation in 5.9% of patients with afatinib, 39.8% with chemotherapy

6.2 Efficacy and safety – further studies

A phase II trial (LUX-Lung 2) [18] investigated the anti-tumour efficacy of afatinib in 129 patients. Patients whose disease progressed or relapsed after one chemotherapy regimen or chemotherapy-naïve patients with ECOG performance status of 0–2 were included in the study. 99 Patients were treated with 50 mg afatinib once a day and 30 patients with 40 mg afatinib once a day until disease progression, intolerable adverse events or withdrawal. The proportion of patients with a confirmed objective response (complete response or partial response) was the primary endpoint. 79 patients (69%) experienced an objective response (2 complete responses, 77 partial responses). Of 106 patients harbouring common EGFR mutations (exon 19 deletion or L858R), 70 patients (66%) had an objective response, while 9 (39%) of 23 patients with less common mutations experienced an objective response.

LUX-Lung 2 investigated efficacy of afatinib in 129 patients

treatment with 50 mg or 40 mg afatinib

objective response rate as primary endpoint

diarrhoea and rash/acne were most common AEs

treatment-related serious AEs occurred less common in patients with lower dose

Grade 3 events of diarrhoea and rash/acne (the most common AEs) were more common in patients receiving 50 mg of afatinib than in the other group receiving 40 mg afatinib. 22 (22%) of 99 patients had diarrhoea and 28 (28%) of 99 patients had rash/acne in the group receiving 50 mg afatinib, while 2 (7%) of 30 patients had diarrhoea and rash/acne in the group receiving 40 mg afatinib. Treatment-related serious AEs were less common in patients with 40 mg afatinib (2 of 30 patients vs. 14 of 99 patients) than in patients receiving a 50 mg dose.

7 Estimated costs

no cost estimates available

No cost estimates are yet available for Austria.

8 Ongoing research

4 ongoing phase III studies of afatinib in patients with NSCLC

At http://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ctr-search/ 4 phase III studies investigating afatinib in patients with NSCLC were found.

- NCT01121393: A randomised, open-label, phase III study to investigate the efficacy and safety of afatinib compared to standard first-line chemotherapy in patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR activating mutation. The estimated study completion date is May 2015.
- NCT01853826: An open-label trial to evaluate the safety and tolerability of afatinib in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring EGFR mutation(s) and have never been treated with an EGFR TKI. The estimated study completion date is July 2015.
- NCT01523587: A randomised, open-label phase III trial in patients with advanced squamous cell carcinoma of the lung requiring second-line treatment after receiving first-line platinum-based chemotherapy. The primary objective of this trial is to compare the efficacy of afatinib to erlotinib as second-line treatment in this group of patients. The estimated study completion date is November 2015.
- NCT01085136: A randomised, open-label, active-controlled, multicentre phase III study to determine the efficacy of afatinib given as an add-on to chemotherapy in patients with NSCLC stage IIIb or IV progressing after afatinib monotherapy compared to chemotherapy alone in this patient population. The estimated study completion is December 2015.

Several other phase I and phase II studies are currently conducted in different treatment lines (first-line, second-line) in patients with NSCLC either with afatinib alone or in combination with other agents. Further, a large number of trials were identified investigating the effects of afatinib for example on head and neck cancer, esophagogastric cancer, prostate cancer and malignant glioma.

afatinib also investigated in different treatment lines and indications

9 Commentary

In September 2013, the EMA granted marketing authorisation for afatinib (Giotrif®) for the treatment of EGFR TKI-naïve adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations [2]. Afatinib (Gilotrif®) was approved by the FDA in July 2013 for the first-line treatment of patients with NSCLC whose tumours have EGFR mutations [6].

approved by the EMA and the FDA

Two phase III studies (the LUX-Lung 3 and LUX-Lung 6 trial [3, 17, 19, 22]) examined the efficacy and safety of afatinib as first-line therapy of EGFR TKI-naïve patients with advanced or metastatic NSCLC with activating EGFR mutations. The results of the LUX-Lung 6 study are only available in abstract or poster form so far. The trials compared treatment of patients either with afatinib or a double-agent chemotherapy. For patients treated with afatinib, median PFS was extended by 4.2 months (11.1 vs 6.9 months, HR 0.58, p=0.001) [3] and 5.4 months respectively (11.0 vs 5.6 months, HR 0.28, p<0.0001) [17]. Secondary endpoints including objective response rate and duration of response favoured patients treated with afatinib. Quality of life was also assessed, showing a significantly delayed time to deterioration for cough and dyspnoea in the afatinib group [22] but conflicting results for pain [19]. Improvements in global health-related quality of life and in functional scales were observed for patients receiving afatinib compared with chemotherapy [22].

two phase III studies (LUX-Lung 3 and LUX-Lung 6 investigated afatinib compared with chemotherapy

median PFS was extended by 4.2 months and 5.4 months in patients with afatinib

improvements in quality of life were observed with afatinib

With afatinib the third EGFR TKI (besides erlotinib and gefitinib) is licensed for the first-line therapy of advanced NSCLC with EGFR mutations in Europe. The treatment paradigm has changed with the availability of these targeted therapies. Platinum-based double chemotherapy which has long been the standard treatment for the initial treatment of NSCLC is increasingly being replaced by EGFR TKIs. Even though the comparators used in the phase III studies therefore reflected common practice until recently, the head-to-head comparison of afatinib with erlotinib or gefitinib is of great interest (a phase IIb trial of afatinib versus gefitinib for the first-line treatment of EGFR mutation NSCLC is currently conducted and the estimated study completion date is December 2014 (NCT01466660). These comparative trials may also assist in eliciting whether emergence of secondary resistance is less common with the irreversible EGFR TKI afatinib than with the reversible inhibitors erlotinib and gefitinib [19]. Since aquired resistance eventually develops in all patients treated with a TKI [23] and afatinib has shown some activity in patients with resistance to erlotinib and gefitinib, futher clinical data for this setting will also help in better describing the role of afatinib for the treatment of NSCLC [24].

afatinib is the third TKI for advanced NSCLC with EGFR mutations

studies comparing afatinib, erlotinib and gefitinib directly are important

further studies are needed concerning acquired resistance in irreversible agent afatinib compared with reversible inhibitors

transferability of findings on Caucasian patients unclear

more detailed subgroup analyses for common/uncommon mutations

Phase III studies on EGFR TKIs have primarily been conducted in Asian patients [25, 26] and also the LUX-Lung 3 study comprised 72% of patients with Asian ethnicity [3], raising the question of transferability of the positive effects of afatinib to Caucasians. In addition, further clarification is needed in terms of efficacy of afatinib for certain subgroups of patients, primarily concerning common and uncommon EGFR mutations. Both phase III trials presented results for these two groups and yielded less favourable outcomes in PFS for those with uncommon mutations. However, PFS was still significantly higher in this subgroup than with chemotherapy. Further, data on quality of life indicate that better symptom improvement and control can be achieved the larger PFS gains are [27]. Since these subgroups comprised only few patients, investigations specifically targeting individuals with uncommon mutations are of interest to further describe patients with the potential to benefit the most from afatinib therapy.

distinct toxicity profiles in the afatinib and in the chemotherapy group, but data on long-term use is missing

duration of TKI therapy substantial

In terms of safety, AEs were common in the afatinib and in the chemotherapy groups, but distinct differences in the toxicity profiles exist. A dose reduction was required for more than 50% of the study participants with 19% of all patients requiring more than one dose reduction [3]. Drug-related serious AEs were 5.4% in the afatinib group and 7.0% in the control group [22]. Therapy was discontinued because of treatment-related AEs in 8% of the patients receiving afatinib and 12% of the patients receiving cisplatin plus pemetrexed [3]. Related AEs leading to death occurred in 0.4% for afatinib and in 0.9% for gemcitabine/cisplatin [22]. Despite this manageable side-effect profile, data on long-term use is missing. This is of particular importance because EGFR TKI first-line therapy and a combination with chemotherapy even after disease progression are options for the treatment of EGFR mutation-positive NSCLCs. Thus, the duration of TKI therapy may be a substantial factor.

treatment costs unknown, but influenced by testing for EGFR mutations

Finally, even though the costs for afatinib are not yet known, a potentially long-term treatment duration with this TKI, probably in combination with other drugs and repeated testing for EGFR mutations, will inevitably impact on treatment costs even though rather few patients will qualify for this therapy in Europe because the frequency of activating EGFR mutations in Caucasian patients ranges from 9% to 15% in contrast to up to 65% in Asians [13].

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