25 February 2016
EMA/CHMP/206630/2016
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Giotrif

International non-proprietary name: afatinib

Procedure No. EMEA/H/C/002280/II/0012

Marketing authorisation holder (MAH): Boehringer Ingelheim International GmbH

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BI	Boehringer Ingelheim
BSA	Body surface area
CI	Confidence interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical trial report
DCR	Disease control rate
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
ESMO	European Society for Medical Oncology
FF	Final formulation
GCP	Good Clinical Practice
HR	Hazard ratio
HRQoL	Health-related quality of life
ICH	International Conference on Harmonization
ILD	Interstitial lung disease
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NN	Non-complete response/non-progressive disease
NSCLC	Non-small cell lung cancer
ORR	Objective response rate

OS	Overall survival
PBRER	Periodic benefit-risk evaluation report
PD	Progressive disease
PFS	Progression-free survival
P-gp	Permeability glycoprotein
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAF	Safety analysis set
SCC	Squamous cell carcinoma
SD	Stable disease
SMQ	Standardised MedDRA query
SOC	System organ class
TF	Trial formulation
TKI	Tyrosine kinase inhibitor
TS	Treated set

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 7 July 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication for Giotrif to include patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy.

As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and RMP are updated in accordance.

Furthermore, minor editorial changes have been introduced throughout the PI.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. However, during the assessment by the CHMP of the significant benefit towards granting the additional year of marketing protection, the MAH withdrew its request.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	7 July 2015
Start of procedure	25 July 2015
CHMP Rapporteur's preliminary assessment report circulated on	18 September 2015
PRAC Rapporteur's preliminary assessment report circulated on	24 September 2015
PRAC RMP advice and assessment overview adopted by PRAC on	8 October 2015
CHMP Rapporteur's updated assessment report circulated on	15 October 2015
Request for supplementary information and extension of timetable adopted by the CHMP on	22 October 2015
MAH's responses submitted to the CHMP on	18 December 2015
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	26 January 2016
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	2 February 2016
PRAC RMP advice and assessment overview adopted by PRAC	11 February 2016
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	19 February 2016
CHMP opinion	25 February 2016

2. Scientific discussion

2.1. Introduction

Lung cancer has been among the most common cancers in the world for several decades. The 2012 worldwide estimates of cancer incidence and mortality by GLOBOCAN, indicate a total of 1.8 million new lung cancer cases and 1.6 million lung cancer related deaths, accounting for 13.0% of all cancer cases (except non-melanoma skin cancers) and 19.4% of all cancer deaths (except non-melanoma skin cancers). Furthermore, lung cancer incidence rates were two-fold higher in males compared to females (1,241,601 and 583,100, respectively). In 2013, the estimated number of lung cancer related deaths is 159,480 in the United States (Siegel et al 2013) and 269,610 in the European Union (Malvezzi et al 2013).

The two most prevalent sub-types of lung cancer are small cell lung cancer and non-small cell lung cancer (NSCLC). Approximately 85% of all lung cancers are NSCLC, which is frequently further subdivided into non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other

cell types) and squamous cell (epidermoid) carcinoma accounting for approximately 15% to 25% of all NSCLC (~230,000 to 380,000 cases)[1][2].

Adenocarcinoma (40% of lung cancers) is the most common type of lung cancer, and is also the most frequently occurring in non-smokers as reported in United States (US) data (American Cancer Society 2013).

Non-small cell lung cancer is associated with high mortality rates as >70% of the patients are diagnosed with locally advanced or metastatic disease (Molina et al 2008) [stages III and IV according to the American joint committee on cancer staging (AJCC)].

Tobacco use is the most important risk factor for lung cancer, with up to 80% of lung cancer patients reporting a history of tobacco use. Approximately 10% to 30% of non-SQ NSCLC occurs in patients with a never smoker history and a strong correlation with the presence of an activating epidermal growth factor receptor (EGFR) mutation or gene translocation. Squamous NSCLC almost universally occur in patients with a history of tobacco use and only rarely are tumours found, which contain an EGFR activating mutation[3]. Similarly, mutated ALK and ROS-1 appear rare and mutated KRAS has been reported in about 5% of squamous NSCLC, i.e. in a lower frequency than in adenocarcinoma (about 30%). Alterations in the PI3K/AKT/mTOR pathway appear common, up to close to 50%. TP53 is also frequently mutated[4][5][6][7].

In addition to the high mortality associated with NSCLC, a high proportion of patients experience severe morbidity as a result of local and metastatic spread of disease. Common morbidities include generalized weakness and fatigue, cough, and dyspnoea. Local spread of tumour can result in obstructive pneumonia, lobar collapse, haemoptysis, pain from chest wall and rib invasion, and pleural effusions, while distant spread to bone, brain, liver, and adrenals can lead to pain, neurologic sequelae, and laboratory abnormalities. Generalized effects of metastatic disease also include cachexia, thrombotic and embolic events, paraneoplastic conditions, and infections.

Historically, patients with locally advanced or metastatic NSCLC have been treated with standard chemotherapy and/or radiation, and while these treatments may provide modest survival benefits, they are rarely curative.

Refractory SQ NSCLC

Despite new treatments for NSCLC in the last 15 years, most of the available agents do not benefit patients with SQ NSCLC. Limited progress has been made in the treatment choices for these patients, especially in the second-line setting once their disease progresses after first-line platinum-based doublet chemotherapy. Recently, nivolumab, an anti-PD1 anti-body, has been approved for the treatment of patient with NSCLC with SQ cell histology, on the basis of a randomized trial conducted in 272 patients where nivolumab appeared to improve median OS of about 3.2 months when compared with docetaxel, given as second line treatment after first line platinum-combination chemotherapy.

[1] Brambilla E, Travis WD. Lung cancer. In: World Cancer Report, Stewart BW, Wild CP (Eds). World Health Organization, Lyon 2014.
[2] Schrump DS, Carter D, Kelsey CR, et al. Non-Small Cell Lung Cancer. Cancer: Principles and Practice of Oncology. 9th Edition. 2011. (Chapter 75).
[3] Cancer Genome Atlas Research Network. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012. Sep. 27;489(7417):519-25.
[4] Rekhtman N, Paik P et al Clarifying the spectrum of driver mutations in biomarker verified squamous carcinoma of the lung Clin Cancer Res: Feb 15 2012.
[5] Cumberbatch M, Tang X et al Identification of a Subset of Human Non–Small Cell Lung Cancer Patients with High PI3Kβ and Low PTEN Expression, More Prevalent in Squamous Cell Carcinoma Clin Cancer Res: Feb 1, 2014
[6] Cooper W, Lam D, et al Molecular biology of lung cancer J Thoracic D: Oct 2013
[7] Heist R, Sequist L, Engelman J, Genetic changes in squamous cell lung cancer: A review J Thoracic Onc: May 2012

About the product

Giotrif (afatinib) is an irreversible inhibitor of the ErbB family of receptor tyrosine kinases (TKI). It covalently binds to and blocks signalling from all homo- and heterodimers formed by the ErbB family members EGFR (ErbB1), HER 2 (ErbB2), ErbB3 and ErbB4. Aberrant ErbB signalling triggered by receptor mutations, and/or amplification, and/or receptor ligand overexpression contributes to the malignant phenotype.

Giotrif was first approved in the EU on 25 September 2013 for the following indication:

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 mutation(s).

The recommended dose is 40 mg once daily. Treatment should be continued until disease progression or until no longer tolerated by the patient.

The MAH applied to extend the indication as follows: treatment of locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy.

The proposed recommended dose is the same as the one already approved.

2.2. Non-clinical aspects

2.2.1. Introduction

The MAH submitted studies investigating the activity of afatinib in EGFR wild-type NSLC disease models. In addition, supplemental data on binding to secondary receptors are reported.

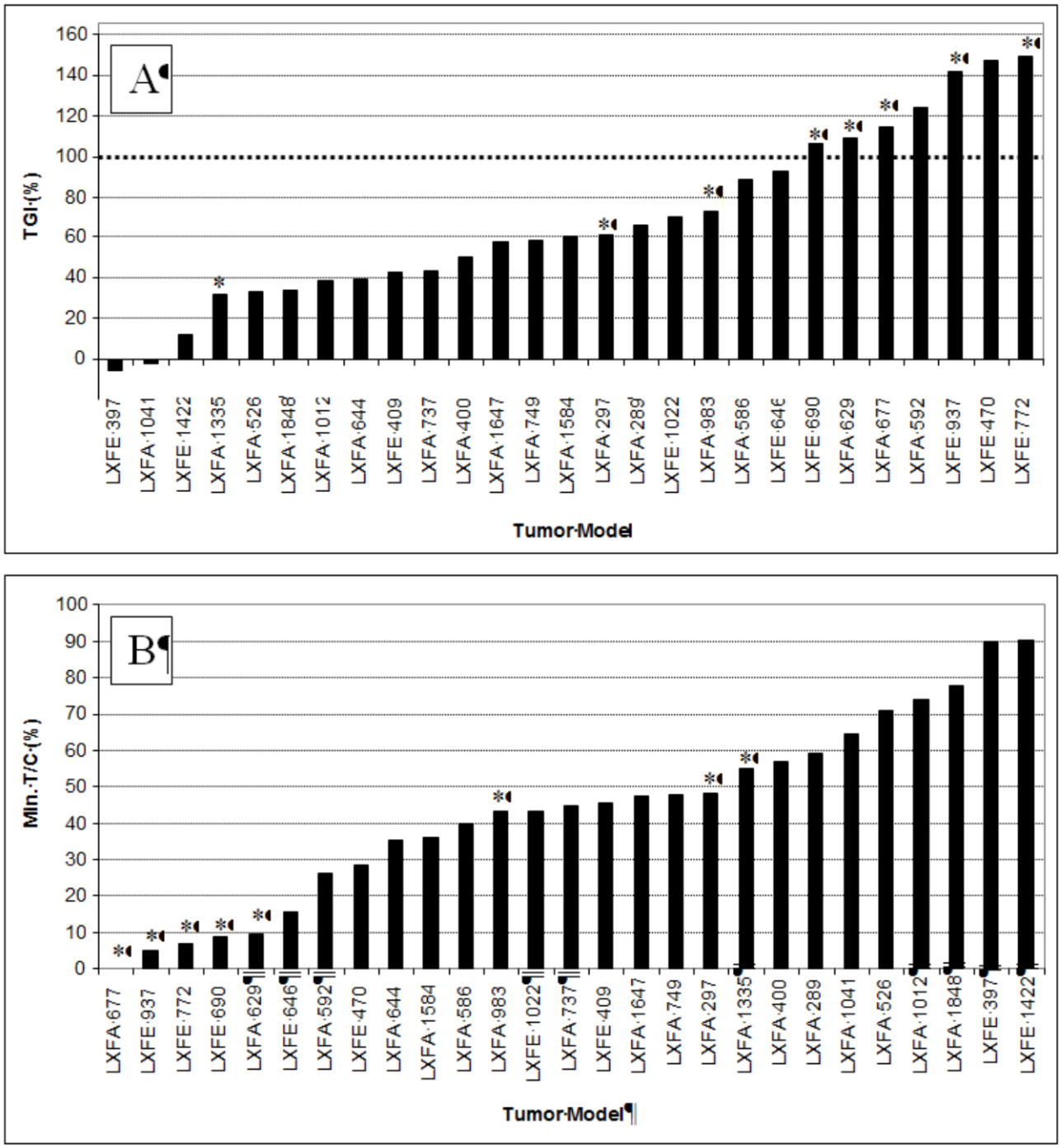
2.2.2. Pharmacology

Primary pharmacodynamic studies

The in vivo anti-tumour activity of afatinib as monotherapy was tested in 27 patient-derived non-small cell lung cancer xenografts expressing wild type EGFR (9/27 of squamous origin) passaged subcutaneously in female NMRI nude mice. Afatinib and its vehicle were administered orally (p.o.) once a day for 18 to 42 days (apart from dosing holidays), depending on tumour growth rates and efficacy. The dose volume for all treatments was 10 ml/kg, the dose of afatinib generally 12.5 mg/kg.

The range of sensitivity towards afatinib was wide and ranged from insensitive to very sensitive. Tumour regressions (TGI > 100%) were observed in 3/18 adenocarcinoma and 4/9 squamous carcinoma models (Figure 1).

Figure 1: Efficacy of BIBW 2992 in tumour xenograft-bearing mice



Overview over all tested tumour xenografts ordered according to increasing (A) TGI values (i.e. increasing sensitivity) or (B) increasing minimum T/C values (i.e. decreasing sensitivity). The statistical analysis was done on the last day of each experiment. Asterisks indicate statistical significance of BIBW 2992 -induced tumour growth inhibition relative to the vehicle control group.

Secondary pharmacodynamic studies

More in-depth functionality evaluations were performed for CCK4 [CCKA], MC4, α2- and β1-adrenergic receptors. No agonistic activity of BIBW 2992 was observed on any of the four receptors tested up to concentrations ranging from 10-100 µM (depending on the tested receptor). Compared with the clinical peak exposure, the highest respective test concentrations of BIBW 2992 were >189-, >189-, >63- and

>6300-fold higher. Furthermore, no antagonistic activity of BIBW 2992 was observed on the α2 adrenergic receptor up to the highest tested concentration of 10 µM. For CCK4 [CCKA], MC4, and β1-adrenergic receptors, the respective IC50 concentrations were determined (22 µM, 30 µM, and 47 µM). The values were thus >63-, 139-, 189- and 297- fold higher than the clinical peak exposure of afatinib (158 nM at 50 mg).

2.2.3. Ecotoxicity / environmental risk assessment

The PECsurface water for the already approved NSCLC indication was calculated using the default value for the market penetration (0.01) and the maximum daily dose of 50 mg afatinib is the same for the additional squamous NSCLC indication. The PEC/PNEC ratios calculated for the original approval is valid also in this case:

Compartment	PEC/PNEC ratio [-]	Trigger for Tier B
Surface water	0.156	1
Microorganisms	0.00055	0.1
Groundwater	0.00046	1

The screening for the potential for bioaccumulation/biomagnification as well as the screening for a risk for the terrestrial compartment in the approved ERA for afatinib also revealed no concern.

2.2.4. Discussion on non-clinical aspects

The submitted non-clinical data has no impact on the benefit-risk assessment and does not result in a need for changes to the product information.

Afatinib is approved for use in patients with tumours with sensitizing EGFR mutations. In the indication applied for, EGFR mutations are rare. The mouse xenograft data show that tumours with wild-type EGFR can be sensitive to afatinib, but also that sensitivity is highly variable. Data were available from only nine xenografts from patients with SQLC, but the analyses conducted are considered comprehensive and properly hypothesis driven and included ligand-receptor loop activation, EGFR mRNA expression, Erb-related gene amplification, however, without positive findings as regards potential predictive value.

2.2.5. Conclusion on the non-clinical aspects

There are no objections to the extension of indication in squamous NSCLC from a non-clinical point of view. The conducted xenograft studies are of obvious interest but the heterogeneity with respect to mutational patterns in SQLC, makes inconclusive findings highly likely. However, an outstanding clinical issue is related to the activity of afatinib in tumours negative by IHC for EGFR expression. The MAH is recommended to address this issue also from a non-clinical perspective.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of afatinib. Considering the above data, afatinib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

No new pharmacokinetic or specific dose – response studies have been conducted to support this extension of the indication.

2.4. Clinical efficacy

2.4.1. Main study

Study LUX-Lung 8 (1200.125): A randomized, 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

Methods

Study participants

First patient first visit was in March 2013, primary analysis of progression free survival (PFS) was conducted in September 2014, and the overall survival analysis March 2015.

Key inclusion criteria:

The study was planned to enrol patients with a diagnosis of advanced NSCLC squamous cell histology who have disease progression after completion of at least 4 cycles of platinum-based chemotherapy treatment in the first-line setting of advanced disease, and who are eligible to receive 2nd line therapy

- Squamous (or mixed) histology advanced stage NSCLC.
- At least 4 cycles of platinum based doublet.
- Including: Relapse within 6 months after adjuvant treatment.
- Discontinuation due to toxicity (but not PD) after at least 2 cycles
- Measurable disease
- ECOG 0 or 1
- Tumour tissue available
- Adequate organ function

Key exclusion criteria:

- Prior EGFR directed therapy.
- Active brain metastases

- Significant gastrointestinal disorder
- History or presence of significant cardiovascular disorders

Treatments

Patients received:

- Afatinib: 40 mg once daily in treatment courses of 28 days. The dose of afatinib was permitted to be escalated to 50 mg at the start of Course 2 in case of minimal toxicity (defined in the study protocol) until disease progression or unacceptable toxicity

- Erlotinib: 150 mg once daily in treatment courses of 28 days. Patients were to receive continuous daily treatment until the development of progressive disease or unacceptable adverse events.

Prior EGFR directed therapy was not accepted. The erlotinib dose was in accordance with the SmPC.

Objectives

The primary objective of the trial was to compare the efficacy of afatinib with erlotinib as second-line treatment in patients with squamous cell carcinoma of the lung, as measured by progression-free survival (PFS).

Outcomes/endpoints

Primary endpoint:

PFS, as determined by central independent review according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. One to 5 target lesions (not exceeding 2 lesions per organ) were to be identified at baseline. The central independent review was blinded for relevant data including investigators' selection of target lesions.

Imaging was performed at baseline, and weeks 8, 12, 16 and every 8 weeks thereafter.

Secondary endpoint:

- Overall survival (OS)

- Objective response (defined as complete response [CR], or partial response [PR]) according to RECIST version 1.1

- Disease control (defined as CR, PR, or stable disease [SD]) according to RECIST version 1.1

- Tumour shrinkage

- Health-related Quality of Life (EORTC QLQ-C30, QLQ-LC13 questionnaires and EQ-5D):

  - time to deterioration, defined as the time to a 10-point worsening from the baseline score. Patients who die before deteriorating will be analysed as having deteriorated at the time of death. Disease progression without scale deterioration will be censored at the time of the last scale measurement. Patients with no HRQoL assessments will be censored at day of randomisation.
  - change in cough, dyspnoea and pain scores assessed using a mixed effects growth curve model with the average profile over time for each endpoint described by a piecewise linear. The proportion of patients that are improved will be assessed. Improvement is defined as scores that improve by at least 10 points at any time during the study. All randomized patients will be included in the denominator.

- all single items and subscales (functional and symptom) from questionnaires
- usage of cough, dyspnoea, and pain medication
- incidence of cough and dyspnoea AEs

Biomarkers and pharmacogenomic analyses were considered investigational and required a separate consent.

Sample size

It was estimated that 372 PFS events would provide 90% power for the long-rank test, presuming a hazard ratio of 0.714 for afatinib relative to erlotinib (corresponding to median times of 14 vs. 10 weeks, respectively), with a two-sided α=0.05.

Randomisation

The randomisation was performed in a 1:1 ratio. Randomisation was stratified by the race of the patient (Eastern Asian vs. Non-Eastern Asian).

Blinding (masking)

This was an open-label trial, treated as blinded by the sponsor until the time of the primary PFS analysis database lock.

Statistical methods

The analysis of PFS considered all data collected until the cut-off date of 07 October 2013, i.e., the estimated date by which 372 PFS events had occurred. Three hundred seventy two was the protocol-specified number of PFS events required for the primary analysis. Overall survival was the key secondary endpoint. The primary analysis of OS will be conducted when 632 death events have occurred.

The alternative hypothesis of the primary analysis was that the progression-free survival time for patients treated with afatinib is different from that of patients who receive erlotinib. That is:

HA: $S_{afatinib}(t) \neq S_{erlotinib}(t)$, for $t>0$

The null hypothesis tested by this trial is:

H0: $S_{afatinib}(t) = S_{erlotinib}(t)$, for $t>0$

where S(t) is the probability that a patient passes time t without dying or experiencing disease progression. The subscripts represent the two treatment groups of either afatinib or erlotinib. The null hypothesis was tested at the two-sided 0.05 level.

Two analysis data sets were defined for this trial, the Randomised Set and the Treated Set.

Randomised Set (RS): all patients who were randomised, regardless of whether they received investigational treatment. The RS was used for disposition tables and listings, tables for demographic and other baseline characteristics, as well as for the primary evaluation of efficacy.

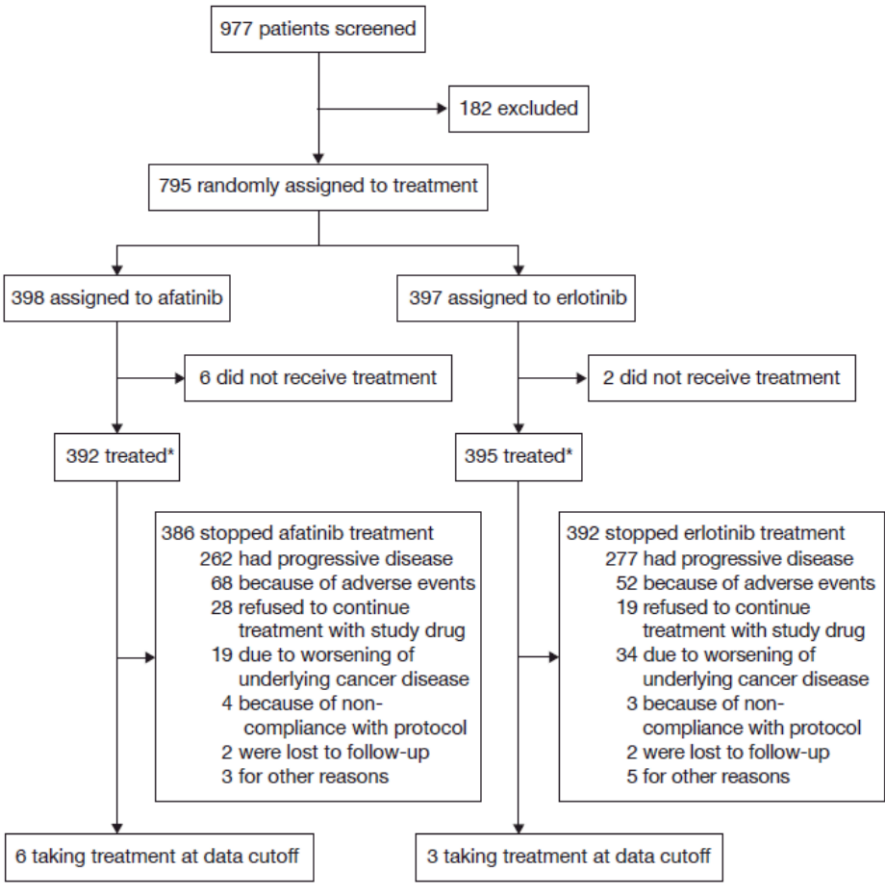
Treated Set (TS): all randomised patients who received at least one dose of investigational treatment (i.e., afatinib or erlotinib). Patients were allocated according to treatment actually rece3ived. The TS was used for the safety analysis.

The primary endpoint analysis was performed on the RS. A stratified log-rank test (2 sided, α = 0.05) was used to test for the effect of afatinib on PFS compared with erlotinib. The test was stratified by race (Eastern Asian vs. non-Eastern Asian).

A Cox proportional-hazards model, stratified by race, was used to estimate the hazard ratio and 95% confidence interval (CI) between the two treatment groups. Kaplan-Meier estimates and 95% CIs (using Greenwood's standard error estimate) were tabulated at 12-week time points and included a comparison of the treatment arms using a z-test (approximation of the normal distribution). Kaplan-Meier curves for the two treatment groups were also produced.

Results

Participant flow



Recruitment

At the time of the data cut-off, 835 patients were enrolled at 183 centres in 23 countries in Asia, Europe, North America, and South America and recruitment was ongoing.

Conduct of the study

The protocol was amended on 24 October 2012. The main change in the conduct of the trial was the inclusion of patients intended for four cycles of chemotherapy but who went off after 2 cycles due to toxicity (not PD) became eligible.

An interim "futility" analysis was performed after 130 patients of the first 176 patients randomised into

the trial had experienced PD or death. Objectives: (1) continue accrual until 800 patients had been randomised, as planned; (2) partially curtail accrual to the 500 patients required for the analysis of PFS; or (3) stop accrual for futility, safety, or extreme efficacy (Haybittle-Peto, p <0.0001).

The trial continued to full accrual. The MAH and the trial team remained blinded throughout this process and were notified only of the DMC's final recommendation, but not the analysis result.

Baseline data

Table 1: Baseline patient characteristics - study LUX-Lung 8

	Afatinib		Erlotinib		Total	
Total randomised (N[%])	398	(100.0)	397	(100.0)	795	(100.0)
Age [years]						
Median	65.0		64.0		64.0	
Range	36 - 84		35 - 88		35 - 88	
Age group (N[%])						
<65 years	189	(47.5)	210	(52.9)	399	(50.2)
>=65 years	209	(52.5)	187	(47.1)	396	(49.8)
Gender: (N[%])						
Male	335	(84.2)	331	(83.4)	666	(83.8)
Female	63	(15.8)	66	(16.6)	129	(16.2)
Baseline ECOG (N[%]) [1]						
0	126	(31.7)	134	(33.8)	260	(32.7)
1	269	(67.6)	262	(66.0)	531	(66.8)
Race for stratification (N[%])						
Eastern Asian	86	(21.6)	86	(21.7)	172	(21.6)
Non-eastern Asian	312	(78.4)	311	(78.3)	623	(78.4)
Race						
Amer.Ind./Alaska Nat	2	(0.5)	2	(0.5)	4	(0.5)
Asian	97	(24.4)	94	(23.7)	191	(24.0)
Black/African American	7	(1.8)	8	(2.0)	15	(1.9)
White	288	(72.4)	291	(73.3)	579	(72.8)
Smoking history (N[%])						
Never smoked	26	(6.5)	18	(4.5)	44	(5.5)
<15 pack years + stopped >1 year before diagnosis	11	(2.8)	12	(3.0)	23	(2.9)
Other current or ex-smokers	361	(90.7)	367	(92.4)	728	(91.6)
Current smokers	71	(17.8)	85	(21.4)	156	(19.6)

[1] 4 patients (0.5%) had baseline ECOG performance score of 2: afatinib 3 (0.8%), erlotinib 1 (0.3%). These 4 patients were protocol violations.

Table 2: Baseline disease characteristics - study LUX-Lung 8

	Afatinib		Erlotinib		Total	
Total randomised (N[%])	398	(100.0)	397	(100.0)	795	(100.0)
Clinical stage at screening (N[%]) [1]						
IIIB	48	(12.1)	48	(12.1)	96	(12.1)
IV	349	(87.7)	345	(86.9)	694	(87.3)
Histological classification (N[%]) [2]						
Squamous cell carcinoma	381	(95.7)	382	(96.2)	763	(96.0)
Mixed type (considered to be of squamous histology)	17	(4.3)	11	(2.8)	28	(3.5)
Baseline SD target lesions category - Independent (N[%])						
< Q1	78	(19.6)	76	(19.1)	154	(19.4)
Q1 - < Median	84	(21.1)	70	(17.6)	154	(19.4)
Median - < Q3	72	(18.1)	83	(20.9)	155	(19.5)
>= Q3	73	(18.3)	82	(20.7)	155	(19.5)
Prior chemotherapy regimens [3]						
Platinum-based doublet	397	(99.7)	397	(100.0)	794	(99.9)
Cisplatin-based	163	(41.0)	198	(49.9)	361	(45.4)
Carboplatin-based	249	(62.6)	229	(57.7)	478	(60.1)
Best response to 1st-line chemotherapy [4]						
CR/PR	186	(46.7)	185	(46.6)	371	(46.7)
SD	161	(40.5)	167	(42.1)	328	(41.3)
Unknown	47	(11.8)	42	(10.6)	89	(11.2)
Interval from last dose of chemotherapy [5]						
<16 weeks	206	(51.8)	230	(57.9)	436	(54.8)
>=16 weeks	192	(48.2)	167	(42.1)	359	(45.2)
Median (weeks)	15.3		13.3		14.3	
Range (weeks)	0.4-259.1		0.0-288.1		0.0-288.1	
Maintenance therapy						
Yes	25	(6.3)	20	(5.0)	45	(5.7)
No	373	(93.7)	377	(95.0)	750	(94.3)

[1] 5 patients (0.6%) were Stage IIIA at screening: afatinib 1 (0.3%), erlotinib 4 (1.0%). These 5 patients were protocol violations (Appendix 16.2.2, Listing 1).
[2] 4 patients (1.0%), all in the erlotinib group, had undifferentiated (considered to be of squamous histology).
[3] Patients could have received both cisplatin-based and carboplatin-based chemotherapy in the first line setting; thus, the total is >100%. 5 patients (0.6%) received oxaliplatin-based therapy: afatinib 3 (0.8%), erlotinib 2 (0.5%); 7 patients received nedaplatin-based therapy: afatinib 2 (0.5%), erlotinib 5 (1.3%); a total of 1 patient (0.3%) in the erlotinb group received lobaplatin-based therapy. 1 patient (0.3%) in the afatinib group received single-agent chemotherapy.
[4] 7 patients (0.9%) had PD as best response to first-line chemotherapy, as reported by the investigator: afatinib 4 (1.0%), erlotinib 3 (0.8%).
[5] From last dose of chemotherapy to signing ICF for this study.

Numbers analysed

Table 3: Timing and number of events for efficacy analyses- study LUX-Lung 8

Analysis (number of events)	Data cut-off	Patients randomised	Other endpoints analysed
Primary PFS analysis (414 PFS events)	07 Oct 2013	N=669	OS (interim analysis), ORR, DCR, tumour shrinkage, HRQoL
Primary OS analysis (632 OS events)	02 Mar 2015	N=795	Updated PFS, ORR, DCR, tumour shrinkage, HRQoL

Outcomes and estimation

Primary endpoint of PFS

Table 4: Primary analysis of progression free survival (cut-off date: Oct 2013) - study LUX-Lung 8

	Afatinib		Erlotinib	
Total randomised [N (%)]	335	(100.0)	334	(100.0)
Patients progressed or died [N (%)]	202	(60.3)	212	(63.5)
PFS time [months]				
Median (95% CI)	2.43	(1.91, 2.92)	1.94	(1.87, 2.17)
Afatinib vs. Erlotinib				
Hazard ratio[1]	0.822			
(95% CI)	(0.676, 0.998)			
p-value[2]	0.0427			

[1] Hazard ratio from Cox proportional hazards model stratified by Race.
[2] p-value from log-rank stratified by Race (two-sided).

Table 5: Updated analysis of progression free survival (cut-off date: Mar 2015) - study LUX-Lung 8

	Afatinib		Erlotinib	
Total randomised [N (%)]	398	(100.0)	397	(100.0)
Patients progressed or died [N (%)]	299	(75.1)	306	(77.1)
PFS time [months]				
Median (95% CI)	2.63	(2.00, 2.86)	1.94	(1.87, 2.10)
Afatinib vs. Erlotinib				
Hazard ratio[1]	0.814			
(95% CI)	(0.693, 0.956)			
p-value[2]	0.0103			

[1] Hazard ratio from Cox proportional hazards model stratified by Race.
[2] p-value from log-rank stratified by Race (two-sided).

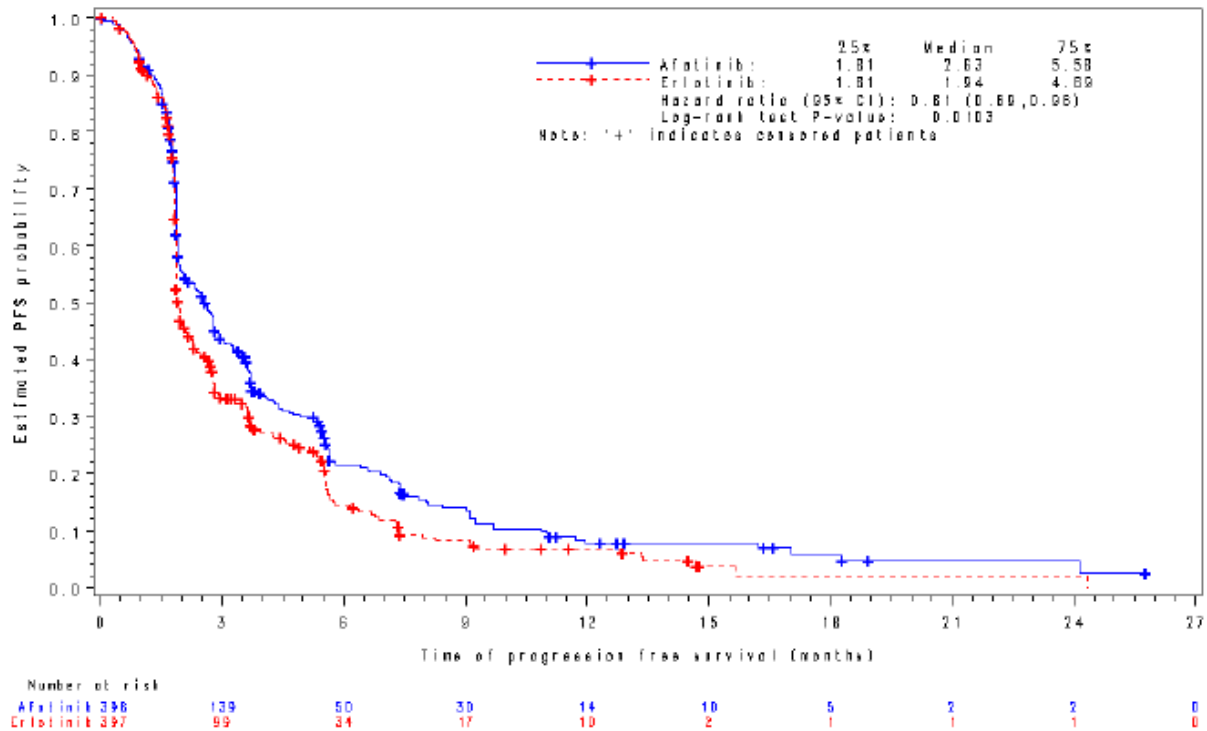


Figure 2: Probability of progression-free survival (cut-off date 02 March 2015) / randomised set- study LUX-Lung 8

The median PFS based on investigator assessment was 2.66 months in the afatinib group and 1.87 months in the erlotinib group (HR 0.786; p =0.0012).

The subgroup analysis of PFS is presented in the below figure.

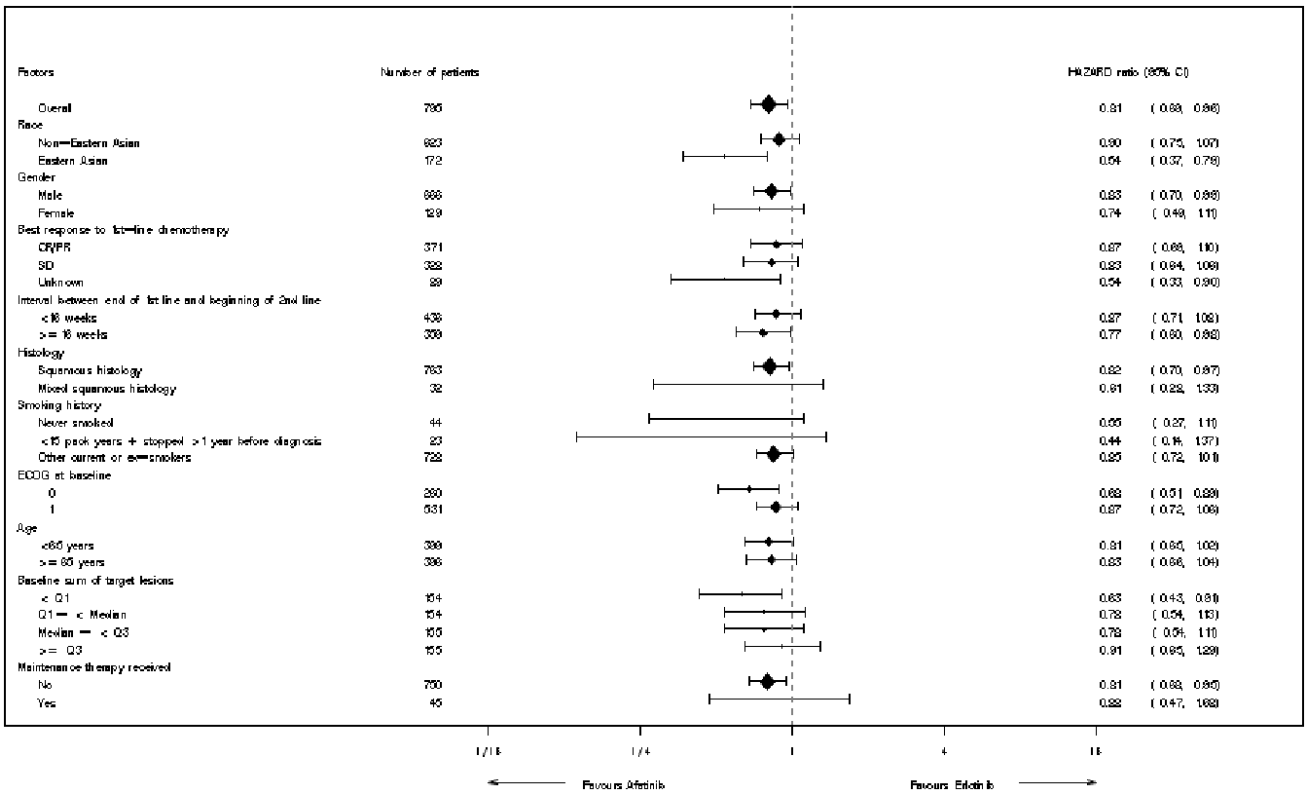


Figure 3: Forest plot of PFS (independent review) for all subgroups (cut-off date 02 March 2015) / randomised set- study LUX-Lung 8

Secondary endpoints:

Overall survival (OS)

Table 6: Overall survival / randomised set- study LUX-Lung 8

	GIOTRIF (N=398)	**Erlotinib (n=397)**	**Hazard Ratio/ Odds Ratio (95%CI) p-value**	**p-value**
OS				
Months (median)	7.92	6.77	HR 0.81	0.0077
95% CI	(7.19, 8.74)	(5.85, 7.79)	(0.69, 0.95)	
Alive at 12 months	36.4%	28.2%		
Alive at 18 months	22.0%	14.4%		

p-value based on stratified log-rank test.

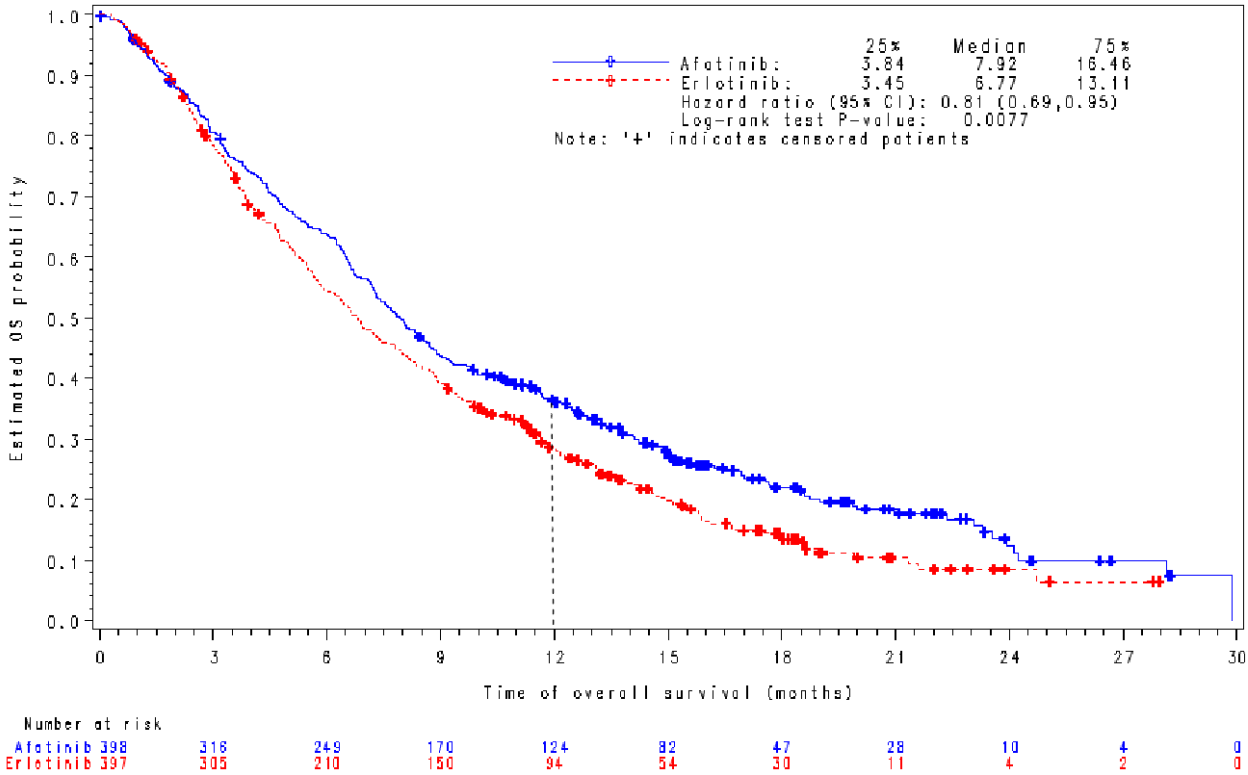


Figure 4: Kaplan-Meier curves of overall survival / randomised set- study LUX-Lung 8

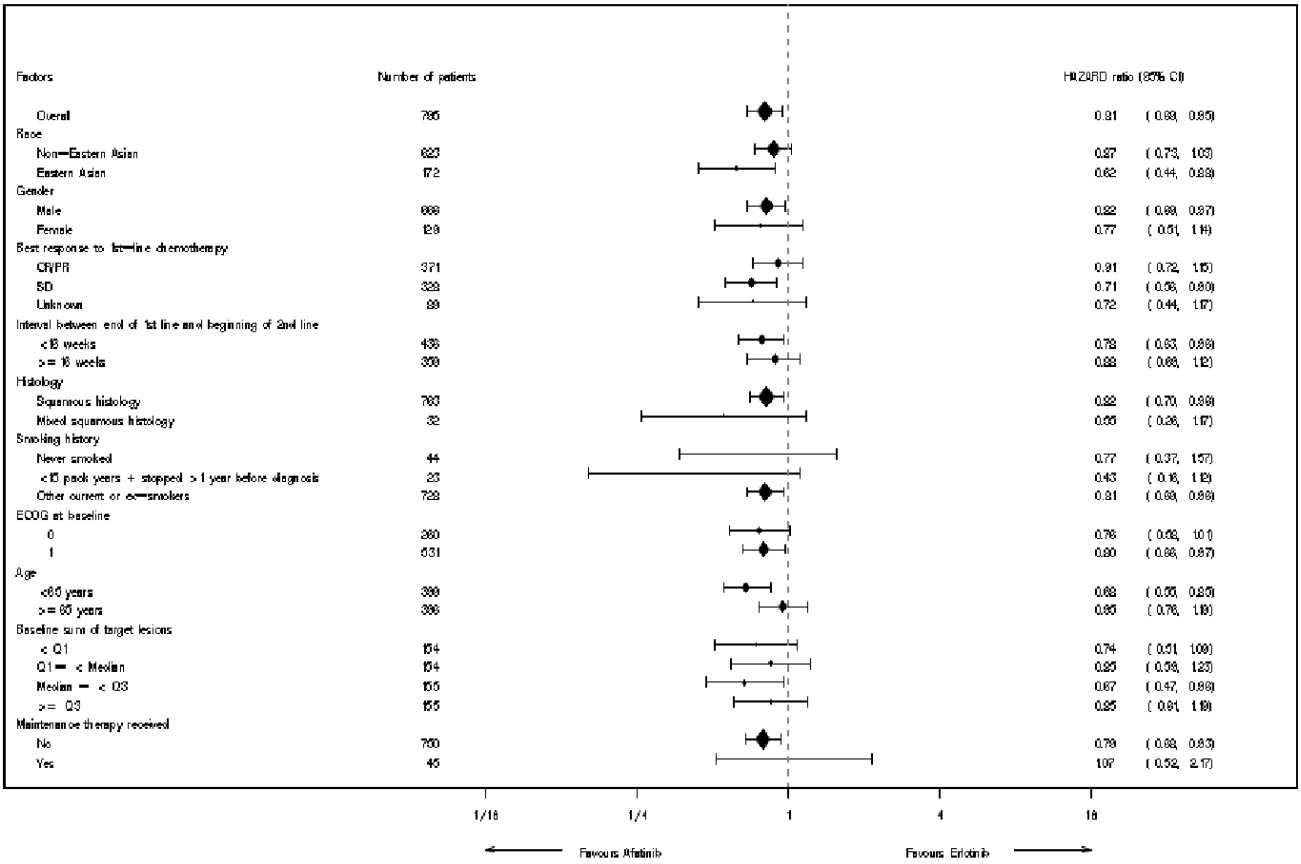


Figure 5: Forest plot of OS for all subgroups (cut-off date 02 March 2015) / randomised set- study LUX-Lung 8

OS data by age groups are summarised in the tables below.

Table 7: Summary of OS within age categories (<65 vs. >=65) - study LUX-Lung 8

	SAF-1 Afatinib			SAF-1 Erlotinib					
	Event/ Total	Median in Month	(95% CI)	Event/ Total	Median in Month	(95% CI)	HR	(95% CI)	Interaction p-value
Age									0.0498
<65 years	149/189	8.44	(7.23, 11.17)	178/210	6.14	(5.29, 7.29)	0.68	(0.55, 0.85)	
>=65 years	158/209	7.43	(6.44, 8.61)	147/187	7.69	(6.37, 8.84)	0.95	(0.76, 1.19)	

Table 8: Summary of OS within age categories (<70 vs. >=70) - study LUX-Lung 8

	SAF-1 Afatinib			SAF-1 Erlotinib					
	Event/ Total	Median in Month	(95% CI)	Event/ Total	Median in Month	(95% CI)	HR	(95% CI)	Interaction p-value
Age									0.0665
<70 years	213/273	8.31	(7.29, 9.99)	244/292	6.67	(5.65, 7.43)	0.73	(0.61, 0.88)	
>=70 years	94/125	7.20	(5.09, 8.51)	81/105	7.79	(5.62, 9.63)	1.01	(0.75, 1.37)	

Objective response rate (ORR)

Table 9: Best overall tumour response from independent review (regardless of confirmation) / randomised set- study LUX-Lung 8

	Afatinib		Erlotinib	
	N	(%)	N	(%)
Total randomised	398	(100.0)	397	(100.0)
Disease control	201	(50.5)	157	(39.5)
Objective response	22	(5.5)	11	(2.8)
Complete response	1	(0.3)	0	(0.0)
Partial response	21	(5.3)	11	(2.8)
Stable disease	124	(31.2)	103	(25.9)
Non-CR/non-PD[1]	55	(13.8)	43	(10.8)
Progressive disease	133	(33.4)	169	(42.6)
SD/NN for less than 42 days[2]	0	(0.0)	2	(0.5)
Not evaluable	64	(16.1)	71	(17.9)

Note Stable disease (SD) and Non-CR/non-PD must have minimum duration of 42 days from randomisation.
[1] NN identifies stable non-target disease in the absense of baseline target disease.
[2] CR/PR/SD/NN best response but less than 42 days from randomisation, followed by PD.

Table 10: Best overall tumour response from investigator assessment (regardless of confirmation) / randomised set- study LUX-Lung 8

	Afatinib		Erlotinib	
	N	(%)	N	(%)
Total randomised	398	(100.0)	397	(100.0)
Disease control	203	(51.0)	156	(39.3)
Objective response	43	(10.8)	16	(4.0)
Complete response	2	(0.5)	1	(0.3)
Partial response	41	(10.3)	15	(3.8)
Stable disease	160	(40.2)	140	(35.3)
Non-CR/non-PD[1]	0	(0.0)	0	(0.0)
Progressive disease	140	(35.2)	185	(46.6)
SD/NN for less than 42 days[2]	1	(0.3)	6	(1.5)
Not evaluable	55	(13.8)	56	(14.1)

Note Stable disease (SD) and Non-CR/non-PD must have minimum duration of 42 days from randomisation.
[1] NN identifies stable non-target disease in the absense of baseline target disease.
[2] CR/PR/SD/NN best response but less than 42 days from randomisation, followed by PD.

Duration of response (DOR)

Table 11: Time to and duration of objective response from independent review (regardless of confirmation), randomised set- study LUX-Lung 8

	Afatinib		Erlotinib	
	N	(%)	N	(%)
Total randomised	398	(100.0)	397	(100.0)
Patient with objective response	22	(5.5)	11	(2.8)
Time to objective response				
By Week 8 (Day 2 - 71)	14	(3.5)	7	(1.8)
By Week 12 (Day 72 - 99)	4	(1.0)	4	(1.0)
By Week 16 (Day 100 - 141)	1	(0.3)	0	(0.0)
> Week 16 (>Day 141)	3	(0.8)	0	(0.0)
Duration of objective response [Month]				
25th percentile (95% CI)	3.71	(1.22, 5.55)	2.79	(0.20, 3.71)
Median (95% CI)	7.29	(3.71, 16.49)	3.71	(2.60, 10.15)
75th percentile (95% CI)	14.39	(7.29, NA)	3.75	(2.86, 10.15)

Patient Reported Outcome

Table 12 Symptom outcomes for GIOTRIF vs. erlotinib in trial LUX-Lung 8 (EORTC QLQ-C30 & QLQ-LC13)

	Cough	Dyspnoea	Pain	Global Health Status / QoL
% of patients improved[a]	43% vs. 35%; p=0.0294	51% vs. 44%; p=0.0605	40% vs. 39%; p=0.7752	36% vs. 28%; p=0.0406
Delay of time to deterioration (months)[a,b]	4.5 vs. 3.7 HR 0.89; p=0.2562	2.6 vs. 1.9 HR 0.79; p=0.0078	2.5 vs. 2.4 HR 0.99; p=0.8690	2.7 vs. 2.6 HR 0.93; p=0.4394

[a] values presented for GIOTRIF vs. erlotinib, p-value based on logistic regression
[b] p-value for time to deterioration based on stratified log-rank test

Data on EQ-5D were not submitted.

Ancillary analyses

Disease progression after 1st line chemotherapy

According to the study protocol, patients were eligible if PD was diagnosed after at least 4 cycles of chemotherapy. Different platinum doublets were used. The cycle time varies between regimens, 3 – 4 weeks. A 28 days cut-off after last administration was used to mark the end of 1st line therapy as chemotherapy is administered in 3-4 week cycles and thus this window is considered as on treatment for the last received chemotherapy. The MAH reviewed the timing of progression on or after platinum-based chemotherapy (see table below).

Table 13: Cumulative incidence of disease progression (PD) relative to the end of 1st line chemotherapy- study LUX-Lung 8

		Frequency (n)	Percent (%)	Cumulative Frequency (n)	Cumulative Percent (%)
PD on 1st line chemotherapy	PD before 1st line chemotherapy last administration	29	3.70	29	3.70
	PD within 2 weeks of 1st line chemotherapy last administration	84	10.71	113	14.41
	PD 2-4 weeks after 1st line chemotherapy last administration	118	15.05	231	29.46
PD after 1st line chemotherapy	PD 4-12 weeks after 1st line chemotherapy last administration	197	25.13	428	54.59
	PD 12-24 weeks after 1st line chemotherapy last administration	196	25.00	624	79.59
	PD > 24 weeks after 1st line chemotherapy last administration	160	20.41	784	100.00
Frequency Missing = 11 (3 protocol violations with no PD and 8 with missing dates)					

Next line therapy

The most commonly administered next-line therapy was docetaxel. Overall there were no relevant differences between study arms.

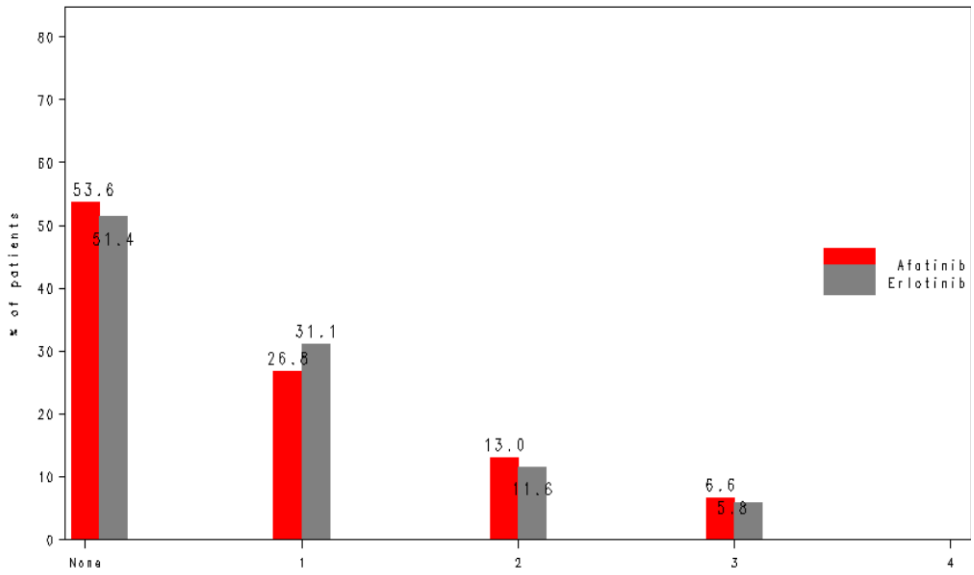


Figure 6: Number of subsequent lines of anti-cancer treatment after permanent discontinuation of study drug- study LUX-Lung 8

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14: Summary of Efficacy for trial LUX-Lung 8

Title: <title>				
Study identifier	1200-0125			
Design	Randomised, open label			
Hypothesis	Superiority			
Treatments groups	Experimental		Afatinib, 40 mg once daily until PD or intolerance	
	Control		Erlotinib, 150 mg once daily until PD or intolerance	
Endpoints and definitions	Primary endpoint	PFS		
	Secondary endpoint	OS	<free text>	
	Secondary endpoint	ORR	<free text>	
Database lock	Oct. 2013 (primary PFS analysis), March 2015 (OS, updated PFS analysis)			
Results and Analysis				
PFS (Oct. 2013) Independent review	Event rate		202/335 (60%)	212/334 (64%)
	Median, m. (95%CI)		2.4 (1.9; 2.9)	1.9 (1.9; 2.2)
	HR (95%)		0.82 (0.68; 1.00)	
	P-value		0.043	
PFS (March 2015) Independent review	Event rate		299/398 (75%)	306/397 (77%)
	Median, m. (95%CI)		2.6 (2.0; 2.9)	1.9 (1.9; 2.1)
	HR (95%)		0.81 (0.69; 0.96)	
	P-value		0.01	
PFS (March 2015) Investigator	Event rate		350/398 (88%)	355/397 (89%)
	Median, m. (95%CI)		2.7 (2.0; 3.3)	1.9 (1.9; 2.0)
	HR (95%)		0.79 (0.68; 0.91)	
	P-value		0.001	
OS (March 2015)	Event rate		307/398 (77%)	325/397 (82%)
	Median, m. (95%CI)		7.9 (7.2; 8.7)	6.8 (5.9; 7.8)
	HR (95%)		0.81 (0.69; 0.95)	
	P-value		0.008	
ORR independent review	RECIST 1.1		5.5%	2.8%
	P-value		0.055	
ORR investigator	RECIST 1.1		11%	4%
	P-value		0.005	

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

In line with the pivotal study protocol, a dose escalation to a maximum of 50 mg/day may be considered in patients who tolerate a 40 mg/day starting dose (i.e. absence of diarrhoea, skin rash, stomatitis, and other adverse reactions with CTCAE Grade > 1) in the first 28 days of treatment. The 50 mg dose of afatinib was tested in a prior study in first generation TKI refractory patients with the aim to overcome EGFR mutation T790M related resistance. Otherwise 40 mg once daily has been the selected dose in other confirmatory studies. A starting dose of 40 mg with optional increase to 50 mg is considered reasonable

In support of the proposed indication for the treatment of "patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy" the MAH has conducted a randomised, erlotinib controlled study. Of note, the study was conducted open label.

At time of initiation of the trial in 2013, docetaxel would have been the typical reference therapy, but erlotinib was also licensed for the treatment of patients with NSCLC after failure of at least one prior chemotherapy regimen. Recently, a change of importance took place due to the restriction of the indication to switch maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease after first-line chemotherapy.

The restriction was due to the negative outcome of the **IUNO** trial. In this study, early (end of chemotherapy) vs. late erlotinib (at PD) was investigated in patients with NSCLC and at least stable disease after 4 cycles of chemotherapy. Patients with EGFR mutation positive NSCLC were excluded, but patients with both squamous (38%) and non-squamous tumours were eligible.

PFS during the first "blinded" stage, erlotinib vs. no treatment, showed a HR of 0.94 (unstratified) and 0.87 (stratified). In patients with squamous NSCLC (SQLC) the PFS HR was 0.80 (95% CI 0.61; 1.04).

Overall survival (primary endpoint) in this comparison of early vs late erlotinib was negative (stratified analysis HR 1.07, unstratified HR 1.02). This was the case also for patients with SQLC: HR 1.0. This is expected due to planned cross-over and low activity as measured by PFS also in SQLC.

Differences between LUX-Lung 8 and IUNO, in addition to enrolment or not of non-squamous NSCLC, are also related to the inclusion only of patients with progressive disease (PD) in LUX-Lung 8.

Erlotinib is also indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Licensure of erlotinib in this indication was based on the placebo-controlled study BR.21. In patients with SQLC, the OS HR was 0.67 (95% CI 0.5; 0.9). The HR was similar in patients treated with one or two prior chemotherapy regimens.

The outcome of IUNO has casted some doubt on the activity of erlotinib in patients with wild type EGFR NSCLC. The outcome in patients with mutation positive SQLC in BR.21 is not reported separately, but the percentage of EGFR mutation positive was 5% in patients with non-adenocarcinoma NSCLC. Later studies with modern technologies have confirmed the low frequency of EGFR mutation positive SQLC. In 2012, the Cancer Genome Atlas reported EGFR mutation positive to be "rare" in SQLC[8]. There were no cases in 178 samples of del 19 or L858R (the most common alterations in adenocarcinoma), but there were two, in adenocarcinoma NSCLC uncommon mutations being sensitive to erlotinib. Rekhtman et al. screened 95 biomarker-verified SQLCs and found no case of EGFR mutation positive[9]. Altogether, the incidence of EGFR mutation positive in SQLC is too low to explain the positive outcome in patients with SQLC in study BR.21.

Based on these findings, it is still considered appropriate to view erlotinib as an active comparator in LUX-Lung 8, even though PFS in patients with SQLC in the maintenance study IUNO did not reach statistical significance.

As the indication for erlotinib as late line treatment of NSCLC (SQLC and non-SQLC) is restricted to EGFR expressing tumours, data in support of the activity afatinib were requested. In LUX-LUNG 8, however, there were only 60 samples available for EGFR expression analysis. As the estimated proportion of EGFR negative tumours by IHC in patients with SQLC, is about 5%[10], the sample size did not allow conclusions as regards activity in this subgroup. Thus there is no clinical evidence in support

[8] The Cancer Genome Atlas Research Network. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012 September 27; 489(7417): 519–525.
[9] Rekhtman et al. Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous carcinoma of lung: lack of EGFR/ KRAS and presence of PIK3CA/AKT1 mutations. Clin Cancer Res. 2012 February 15; 18(4): 1167–1176.
[10] Portrazza EPAR

of activity of afatinib in this subgroup, even though the panErb inhibitory character at least opens for the possibility, in contrast to EGFR targeting MoAbs and erlotinib.

Altogether and in a superiority study there are no objections to the selected reference regimen; erlotinib is sufficiently likely to be active in terms of OS in patients with SCC in the target population of this study.

The conduct of the study as open label is justified by the MAH by differences in the expected toxicity profiles, afatinib being more prone to induce e.g. diarrhoea. Qualitatively, however, the safety profiles are similar and in order to reduce possible bias in the reporting of safety and PRO data it would have been preferable at least to initiate the study as double blind and to unblind assigned treatment when dose reduction was considered.

The primary endpoint was PFS, but mature OS data have been submitted in support. The planned primary PFS analysis showed only statistically borderline results (p=0.04). OS data, however, are considered statistically more robust, p=0.008 based on mature event rates, >75% of the events in the long run.

During the review of the application, the wording of the indication encompassing patients progressing on platinum-based chemotherapy was questioned. The MAH provided further information regarding inclusion of patients with disease progression on or after 1st line chemotherapy within the study LUX-Lung 8 which provided reassurance regarding the targeted patient population.

Efficacy data and additional analyses

The HRs for PFS and OS are very similar, meaning that the absolute OS benefit is larger than the PFS benefit. This is not unexpected in NSCLC at hazard ratios not far from 1. Furthermore, there are no signs of imbalances in next-line therapies. The independent and investigator derived HRs for PFS are also very similar despite the higher censoring rates in the independent review.

None of the OS subgroup analyses raise specific concerns. As for most molecules studied in SQLC, no difference in OS between treatment arms was observed in older patients however the activity of erlotinib in older patients with SQLC in study BR.21 has not been reported. As a consequence, information regarding the OS data in older patients has been reported in section 5.1 of the SmPC.

Three PRO instruments (including EQ5D) were used however no primary hypothesis was defined and multiplicity issues were not addressed. In addition, the study was conducted open label. General claims, such as improved physical, role, cognitive and emotional functioning were therefore not accepted and actually found implausible due to the small difference in anti-tumour activity and added adverse reactions. However, a table reporting disease related symptoms (cough, dyspnoea and pain) was accepted for inclusion in the SmPC.

Exploratory, e.g. genetic biomarker analyses, were to be conducted, but have not been reported yet. The As EGFR by IHC has been reported to be of interest for cetuximab activity, at least these data would be of putative value as the survival benefit in the whole study population is modest. The MAH is recommended to conduct genetic biomarker analyses.

2.4.3. Conclusions on the clinical efficacy

Sufficiently methodologically robust study data support the conclusion that a modest survival benefit has been shown in comparison with the licensed medicinal product erlotinib.

2.5. Clinical safety

Introduction

The safety profile of afatinib in the treatment of NSCLC is relatively well characterised based on previously assessed confirmatory NSCLC trials, first-line and after failure on first generation TKIs. The assessment is focused on the results from the LUX-Lung 8 study.

Patient exposure

By convention Adverse Events included events up to 28 days after end of treatment. About 35% of patients in both study arms initiated next-line therapy during this period of time. The cut-off for AE reporting was March 2015.

The duration of therapy was slightly longer in the afatinib arm: mean 121 vs. 97 days, median 65 vs. 58 days.

Table 15: Exposure to study medication by dose level / treated set- study LUX-Lung 8

	Afatinib		Erlotinib	
	N	(%)	N	(%)
Total treated	392	(100.0)	395	(100.0)
Treatment time on 50mg (days)[1]				
N	39	(9.9)		
Mean	106.2			
SD	145.22			
Min	4			
Median	56.0			
Max	588			
Treatment time on 40mg/150mg (days)				
N	392	(100.0)	395	(100.0)
Mean	89.1		85.4	
SD	108.39		89.54	
Min	2		4	
Median	56.0		56.0	
Max	840		619	
Treatment time on 30mg/100mg (days)				
N	96	(24.5)	56	(14.2)
Mean	67.3		79.4	
SD	90.34		93.50	
Min	2		4	
Median	37.0		37.5	
Max	536		395	
Treatment time on 20mg/50mg (days)				
N	18	(4.6)	6	(1.5)
Mean	101.0		30.3	
SD	135.19		29.32	
Min	3		3	
Median	68.0		27.5	
Max	580		85	

Total treatment time includes off-treatment pauses, which are assigned to dose level before going off-treatment.
Dose levels for Afatinib are 50mg, 40mg, 30mg, 20mg and for Erlotinib are 150mg, 100mg, 50mg.
[1]For Afatinib patients with dose escalation.

Adverse events

Table 16: Summary of adverse events / treated set- study LUX-Lung 8

	Afatinib		Erlotinib	
	N	(%)	N	(%)
Number of patients	392	(100.0)	395	(100.0)
Patients with any AE	390	(99.5)	385	(97.5)
Patients with investigator defined drug-related AEs	366	(93.4)	321	(81.3)
Patients with AEs leading to dose reduction of trial drug	104	(26.5)	56	(14.2)
Patients with AEs leading to discontinuation of trial drug	79	(20.2)	67	(17.0)
Discontinued due to PD	24	(6.1)	32	(8.1)
Discontinued due to other AE	55	(14.0)	35	(8.9)
Patients with serious AEs	173	(44.1)	174	(44.1)
Fatal	77	(19.6)	71	(18.0)
Imm life-threatening	13	(3.3)	11	(2.8)
Disability/incap.	3	(0.8)	0	(0.0)
Req.hospitalisation	143	(36.5)	158	(40.0)
Prol.hospitalisation	30	(7.7)	16	(4.1)
Congenital anomaly	0	(0.0)	0	(0.0)
Other	7	(1.8)	9	(2.3)
Patients with highest CTC grade				
Grade 1	61	(15.6)	48	(12.2)
Grade 2	105	(26.8)	110	(27.8)
Grade 3	124	(31.6)	138	(34.9)
Grade 4	23	(5.9)	18	(4.6)
Grade 5	77	(19.6)	71	(18.0)

A patient may be counted in more than 1 seriousness criterion.
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 17.1

Table 17: ADRs with an incidence >10 % by treatment, highest CTCAE grade, grouped categories and MedDRA preferred term / treated set- study LUX-Lung 8

	afatinib (40 mg/day) N=392			**erlotinib** N=395		
NCI-CTC Grade	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
Infections and infestations						
Paronychia[1]	11.0	0.5	0	5.1	0.3	0
Metabolism and nutrition disorders						
Decreased appetite	24.7	3.1	0	26.1	2.0	0
Gastrointestinal disorders						
Diarrhoea	74.7	9.9	0.8	41.3	3.0	0.3
Stomatitis[2]	30.1	4.1	0	10.6	0.5	0
Nausea	20.7	1.5	0	16.2	1.0	0.3
Skin and subcutaneous tissue disorders						
Rash[3]	60.7	5.4	0	56.7	8.1	0
Dermatitis acneiform[4]	14.0	1.3	0	18.0	2.5	0

[*] Reporting the frequency of patients with all causality AEs
[1] Includes Paronychia, Nail infection, Nail bed infection
[2] Includes Stomatitis, Aphthous stomatitis, Mucosal inflammation, Mouth ulceration, Oral mucosa erosion, Mucosal erosion, Mucosal ulceration
[3] Includes group of rash preferred terms
[4] Includes Acne, Acne pustular, Dermatitis acneiform

Adverse events of special interest

Diarrhoea

Diarrhoea was more frequently reported in the afatinib group (see table above). Time to onset was typically <4 weeks. Altogether 16 patients (4%) in the afatinib group and 6 (1.5%) in the erlotinib group discontinued due to diarrhoea.

The diarrhoea substudy enrolled only 36 + 27 patients. The reported duration of grade 3 diarrhoea was 3 days in the afatinib group.

Rash

Rather similar between groups (table above). Time to onset was typically < 4 w. Dose reductions due to rash were reported in 6% (afatinib) and 9% (erlotinib) and discontinuations in 2.6% and 2%, respectively.

Renal impairment events

Table 18: Frequency [N (%)] of patients with renal failure, clinical consequences, outcome and time of onset by treatment, treated set- study LUX-Lung 8

	Afatinib		Erlotinib		hazard ratio (95% C.I.) significance level[3]
	N	(%)	N	(%)	
Total treated	392	(100.0)	395	(100.0)	
Time at risk(days)[1]					
Mean	139.7		120.6		
SD	129.56		96.91		
Patients with renal failure	27	(6.9)	10	(2.5)	2.60 (1.26, 5.38) p=0.0074
95% confidence interval [%]		(4.6, 9.9)		(1.2, 4.6)	
Drug-related renal failure	12	(3.1)	3	(0.8)	
Serious renal failure	15	(3.8)	5	(1.3)	
Outcome of renal failure					
Recovered	19	(4.8)	7	(1.8)	
Not yet recovered	1	(0.3)	1	(0.3)	
Sequelae	0	(0.0)	0	(0.0)	
Fatal	2	(0.5)	1	(0.3)	
Unknown	5	(1.3)	1	(0.3)	
Clinical consequences					
Dose reduced	1	(0.3)	1	(0.3)	
Discontinued	2	(0.5)	2	(0.5)	
Therapy required	17	(4.3)	7	(1.8)	
Highest CTC Grade					
Grade 1	9	(2.3)	3	(0.8)	
Grade 2	5	(1.3)	3	(0.8)	
Grade 3	8	(2.0)	3	(0.8)	
Grade 4	3	(0.8)	0	(0.0)	

[1] - Time at risk = Days until (1) the onset of the AE of interest, (2) date of death, or (3) total treatment time+ 28 day washout.
[2] - Number of patients with initial onset within the interval (cumulative K-M estimate of AE onset by interval end)
[3] - Hazard ratio of initial adverse event of interest from Cox proportional hazards model with treatment fitted as only factor; p-value from log-rank test (two-sided).

An increase in renal events was observed in the afatinib arm (table above). Fatal events were reported in 2 (afatinib) and 1 (erlotinib) patients.

Table 19: Patients with renal failure by treatment, primary system organ class and preferred term – treated set: on–treatment analysis - study LUX-Lung 8

System organ class/ Preferred term	Actual TRT at onset of AE	Age/ Gender	Start day@	Stop day@	Dura-tion	CTC Grade	Drug rel.	Action taken	The-rapy	Outcome	Other sign.	Serious
Renal and urinary disorders/												
Acute prerenal failure	Post-Treatment	58/M	85	85	1	5	No	Cont	No	Fatal	No	Fatal/Req hsp
Renal failure	Afatinib 40	73/M	56	114	59	4	Yes	Disc	Yes	Rcver	No	Req hsp
	Post-Treatment	64/F	32	38	7	2	No	Cont	Yes	Rcver	No	No
	Post-Treatment	65/M	119	121§	3§	1	Yes	Cont	Yes	Unk	No	No
	Post-Treatment	70/M	25	47§	23§	2	No	Cont	Yes	Unk	No	No
	Afatinib 40	79/M	8	10	3	3	No	Cont	Yes	Rcver	No	Req hsp
Renal failure acute	Afatinib 40	57/M	22	27	6	4	Yes	Cont	Yes	Rcver	No	Req hsp
	Afatinib 40	63/F	23	26	4	3	Yes	Decr	Yes	Rcver	No	Req hsp
	Post-Treatment	74/M	57	76§	20§	3	No	Cont	Yes	Unk	No	Prol hsp
	Afatinib 40	73/M	63	71	9	3	No	Cont	Yes	Rcver	No	Req hsp
	Afatinib 40	66/M	33	36	4	3	Yes	Cont	Yes	Rcver	No	Req hsp
	Post-Treatment	62/M	22	28§	7§	3	No	Cont	Yes	Unk	No	No
	Post-Treatment	58/M	58	70	13	2	No	Cont	Yes	Rcver	No	Req hsp
	Post-Treatment	54/M	21	32§	12§	2	No	Cont	Yes	Nrec&	No	Other
	Afatinib 40	73/M	19	27	9	1	No	Cont	Yes	Rcver	No	Req hsp
	Post-Treatment	71/M	26	26	1	5	Yes	Cont	Yes	Fatal	No	Fatal/Req hsp
Renal impairment	Post-Treatment	71/M	47	53	7	4	Yes	Disc	Yes	Rcver	No	Req hsp

Of note, among afatinib treated patients, the renal event occurred post treatment in 10 patients and was classified as drug-related in 3 cases. On therapy there were 7 events and 4 were reported as drug-related. One fatal, day 26 post treatment event was reported as drug related.

Stomatitis

The adverse events of stomatitis were more commonly reported in the afatinib arm, 30% vs. 11% in the erlotinib arm. In three individuals the event was classified as SAE. Dose reductions were reported in 3% in the afatinib arm vs. none, discontinuation 1% in the afatinib arm vs. none.

Hepatic impairment events

Table 20: Frequency [N (%)] of patients with hepatic impairment, clinical consequences, outcome and time of onset by treatment, treated set- study LUX-Lung 8

	Afatinib		Erlotinib		hazard ratio (95% C.I.) significance level[3]
	N	(%)	N	(%)	
Total treated	392	(100.0)	395	(100.0)	
Time at risk(days)[1]					
Mean	140.1		116.0		
SD	126.10		97.34		
Patients with hepatic impairment	22	(5.6)	34	(8.6)	0.58 (0.34, 1.00) p=0.0458
95% confidence interval [%]		(3.6, 8.4)		(6.0, 11.8)	
Drug-related hepatic impairment	9	(2.3)	9	(2.3)	
Serious hepatic impairment	0	(0.0)	6	(1.5)	
Outcome of hepatic impairment					
Recovered	7	(1.8)	16	(4.1)	
Not yet recovered	11	(2.8)	13	(3.3)	
Sequelae	0	(0.0)	0	(0.0)	
Fatal	0	(0.0)	1	(0.3)	
Unknown	4	(1.0)	4	(1.0)	
Clinical consequences					
Dose reduced	2	(0.5)	0	(0.0)	
Discontinued	1	(0.3)	3	(0.8)	
Therapy required	7	(1.8)	8	(2.0)	
Highest CTC Grade					
Grade 1	3	(0.8)	12	(3.0)	
Grade 2	11	(2.8)	13	(3.3)	
Grade 3	7	(1.8)	7	(1.8)	
Grade 4	1	(0.3)	1	(0.3)	

[1] - Time at risk = Days until (1) the onset of the AE of interest, (2) date of death, or (3) total treatment time+ 28 day washout.
[2] - Number of patients with initial onset within the interval (cumulative K-M estimate of AE onset by interval end)
[3] - Hazard ratio of initial adverse event of interest from Cox proportional hazards model with treatment fitted as only factor; p-value from log-rank test (two-sided).

These events were more commonly reported in the erlotinib arm, but events considered drug-related were reported in similar frequencies. Dose reductions and discontinuations were infrequent, <1% in both study arms. There was one fatal event in the erlotinib arm.

Grade 3 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations were observed in 1.6% (LUX-Lung 8) of patients with normal baseline liver tests treated with 40 mg/day. There were no Grade 3 ALT/AST elevations in patients with abnormal baseline liver tests in LUX-Lung 8.

Heart failure (HF)

HF is of potential interest due to HER2 inhibition (afatinib). Of note patients were excluded if there was a "History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3, unstable angina or poorly controlled arrhythmia as determined by the, investigator, myocardial infarction within 6 months prior to randomization."

Table 21: Frequency [N (%)] of patients with heart failure, clinical consequences, outcome and time of onset by treatment, treated set- study LUX-Lung 8

	Afatinib		Erlotinib		hazard ratio (95% C.I.) significance level[3]
	N	(%)	N	(%)	
Total treated	392	(100.0)	395	(100.0)	
Time at risk(days)[1]					
Mean	142.6		121.1		
SD	125.46		96.98		
Patients with heart failure	6	(1.5)	8	(2.0)	0.66 (0.23, 1.92) p=0.4459
95% confidence interval [%]		(0.6, 3.3)		(0.9, 4.0)	
Drug-related heart failure	0	(0.0)	0	(0.0)	
Serious heart failure	4	(1.0)	6	(1.5)	
Outcome of heart failure					
Recovered	2	(0.5)	1	(0.3)	
Not yet recovered	1	(0.3)	1	(0.3)	
Sequelae	0	(0.0)	0	(0.0)	
Fatal	2	(0.5)	4	(1.0)	
Unknown	1	(0.3)	2	(0.5)	
Clinical consequences					
Dose reduced	0	(0.0)	0	(0.0)	
Discontinued	0	(0.0)	1	(0.3)	
Therapy required	3	(0.8)	6	(1.5)	
Highest CTC Grade					
Grade 1	1	(0.3)	1	(0.3)	
Grade 2	2	(0.5)	2	(0.5)	
Grade 3	0	(0.0)	1	(0.3)	
Grade 4	1	(0.3)	0	(0.0)	

[1] - Time at risk = Days until (1) the onset of the AE of interest, (2) date of death, or (3) total treatment time+ 28 day washout.
[2] - Number of patients with initial onset within the interval (cumulative K-M estimate of AE onset by interval end)
[3] - Hazard ratio of initial adverse event of interest from Cox proportional hazards model with treatment fitted

In this selected group of patients there was no difference between treatment arms and the event rate was rather low (2%) taking into account the target population, even though selected.

Interstitial lung disease (ILD)

Table 22: Frequency [N (%)] of patients with ILD, clinical consequences, outcome and time of onset by treatment, treated set- study LUX-Lung 8

	Afatinib		Erlotinib		hazard ratio (95% C.I.) significance level[3]
	N	(%)	N	(%)	
Total treated	392	(100.0)	395	(100.0)	
Time at risk(days)[1]					
Mean	142.4		121.2		
SD	128.24		96.91		
Patients with ILD	11	(2.8)	8	(2.0)	1.26 (0.51, 3.14) p=0.6195
95% confidence interval [%]		(1.4, 5.0)		(0.9, 4.0)	
Drug-related ILD	5	(1.3)	4	(1.0)	
Serious ILD	7	(1.8)	5	(1.3)	
Outcome of ILD					
Recovered	2	(0.5)	2	(0.5)	
Not yet recovered	2	(0.5)	2	(0.5)	
Sequelae	0	(0.0)	0	(0.0)	
Fatal	3	(0.8)	3	(0.8)	
Unknown	4	(1.0)	1	(0.3)	
Clinical consequences					
Dose reduced	0	(0.0)	0	(0.0)	
Discontinued	3	(0.8)	3	(0.8)	
Therapy required	11	(2.8)	7	(1.8)	
Highest CTC Grade					
Grade 1	1	(0.3)	3	(0.8)	
Grade 2	2	(0.5)	0	(0.0)	
Grade 3	3	(0.8)	2	(0.5)	
Grade 4	2	(0.5)	0	(0.0)	

1] - Time at risk = Days until (1) the onset of the AE of interest, (2) date of death, or (3) total treatment time+ 28 day washout.
2] - Number of patients with initial onset within the interval (cumulative K-M estimate of AE onset by interval end)
3] - Hazard ratio of initial adverse event of interest from Cox proportional hazards model with treatment fitted as only factor; p-value from log-rank test (two-sided)

The overall incidence (about 2%) is rather similar in the study arms and the event was considered drug related in about 1%. Treatment was discontinued in 3+3 individuals.

In the pooled safety data of all patients treated with afatinib monotherapy, the frequency of ILD-like adverse reactions were reported in 0.7% of treated patients.

Pancreatitis

Pancreatitis has been classified as an important potential risk. There were no cases of pancreatitis identified in the afatinib group. In the erlotinib group, 1 patient experienced a serious post-treatment event of pancreatitis that was considered not related to erlotinib and resolved after 12 days.

Serious adverse event / deaths / other significant events

Table 23: SAEs occurring with >1% incidence by treatment, highest CTCAE grade, grouped categories, and MedDRA preferred term / treated set- study LUX-Lung 8

	Afatinib						Erlotinib					
	All grades		Grade 3		Grade 4		All grades		Grade 3		Grade 4	
User-defined AE category	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total treated	392	(100.0)	392	(100.0)	392	(100.0)	395	(100.0)	395	(100.0)	395	(100.0)
Total with serious adverse events	173	(44.1)	57	(14.5)	19	(4.8)	174	(44.1)	66	(16.7)	15	(3.8)
Pneumonia	26	(6.6)	7	(1.8)	2	(0.5)	16	(4.1)	8	(2.0)	3	(0.8)
Malignant neoplasm progression	23	(5.9)			3	(0.8)	16	(4.1)				
Diarrhoea	18	(4.6)	12	(3.1)	3	(0.8)	7	(1.8)	4	(1.0)		
Dehydration	12	(3.1)	6	(1.5)	4	(1.0)	4	(1.0)	3	(0.8)		
Dyspnoea	12	(3.1)	4	(1.0)	3	(0.8)	30	(7.6)	11	(2.8)	3	(0.8)
General physical health deterioration	11	(2.8)	4	(1.0)	1	(0.3)	6	(1.5)	4	(1.0)		
Pulmonary embolism	10	(2.6)	4	(1.0)			5	(1.3)	1	(0.3)	2	(0.5)
Renal failure acute	9	(2.3)	4	(1.0)	1	(0.3)	1	(0.3)	1	(0.3)		
Sepsis	9	(2.3)	1	(0.3)	3	(0.8)	2	(0.5)			1	(0.3)
Fatigue+	7	(1.8)	5	(1.3)			5	(1.3)	3	(0.8)	2	(0.5)
Abdominal pain	5	(1.3)	3	(0.8)	1	(0.3)	5	(1.3)	3	(0.8)	1	(0.3)
Anaemia	5	(1.3)	3	(0.8)	1	(0.3)	2	(0.5)	1	(0.3)		
Chronic obstructive pulmonary disease	5	(1.3)	3	(0.8)			4	(1.0)	1	(0.3)	1	(0.3)
Haemoptysis	5	(1.3)	2	(0.5)			10	(2.5)	2	(0.5)	1	(0.3)
Atrial fibrillation	4	(1.0)	3	(0.8)			2	(0.5)				
Convulsion	4	(1.0)	1	(0.3)	1	(0.3)	1	(0.3)			1	(0.3)
Death	4	(1.0)					2	(0.5)				
Interstitial lung disease	4	(1.0)	1	(0.3)	1	(0.3)	1	(0.3)				
Vomiting	4	(1.0)	2	(0.5)			5	(1.3)	3	(0.8)	1	(0.3)
Pleural effusion	3	(0.8)			1	(0.3)	6	(1.5)	4	(1.0)		
Pyrexia	3	(0.8)	2	(0.5)			4	(1.0)				
Bronchitis	2	(0.5)					6	(1.5)	6	(1.5)		
Dizziness	2	(0.5)	2	(0.5)			4	(1.0)	1	(0.3)		
Lung infection	2	(0.5)	1	(0.3)			5	(1.3)	2	(0.5)	1	(0.3)
Metastases to central nervous system	2	(0.5)			1	(0.3)	6	(1.5)	2	(0.5)	1	(0.3)
Respiratory failure	2	(0.5)	1	(0.3)			12	(3.0)	1	(0.3)	3	(0.8)
Hypercalcaemia	1	(0.3)			1	(0.3)	6	(1.5)	2	(0.5)	2	(0.5)
Chest pain							6	(1.5)	4	(1.0)		
Myocardial infarction							4	(1.0)	1	(0.3)		

Note: Grade 5 (fatal) AEs are presented in Table 15.3.2.2: 6 and Section 12.3.1
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 17.1
+ Preferred terms included in these groups are listed in Table 15.3.2.2: 9

Table 24: Fatal AEs by treatment, highest CTCAE grade, primary SOC, and MedDRA preferred term / treated set- study LUX-Lung 8

System Organ Class/ Preferred term	Afatinib Grade 5 N	(%)	Erlotinib Grade 5 N	(%)
Nervous system disorders	2	(0.5)	3	(0.8)
Cerebrovascular accident	1	(0.3)	1	(0.3)
Convulsion	1	(0.3)		
Altered state of consciousness			1	(0.3)
Haemorrhage intracranial			1	(0.3)
Cardiac disorders	2	(0.5)	8	(2.0)
Cardiac arrest	1	(0.3)	1	(0.3)
Cardiopulmonary failure	1	(0.3)	1	(0.3)
Cardiac failure			1	(0.3)
Cardiac tamponade			1	(0.3)
Cardio-respiratory arrest			1	(0.3)
Myocardial infarction			3	(0.8)
Vascular disorders			1	(0.3)
Haemorrhage			1	(0.3)
Respiratory, thoracic and mediastinal disorders	18	(4.6)	26	(6.6)
Pulmonary embolism	4	(1.0)		
Dyspnoea	3	(0.8)	10	(2.5)
Haemoptysis	2	(0.5)		
Interstitial lung disease	2	(0.5)	1	(0.3)
Pulmonary haemorrhage	2	(0.5)		
Acute respiratory distress syndrome	1	(0.3)	1	(0.3)
Hypoxia	1	(0.3)	1	(0.3)
Pulmonary oedema	1	(0.3)	1	(0.3)
Respiratory disorder	1	(0.3)		
Respiratory distress	1	(0.3)	1	(0.3)
Respiratory failure	1	(0.3)	8	(2.0)
Acute pulmonary oedema			1	(0.3)
Chronic obstructive pulmonary disease			1	(0.3)
Gastrointestinal disorders			1	(0.3)
Intestinal obstruction			1	(0.3)
Hepatobiliary disorders			1	(0.3)
Hepatic function abnormal			1	(0.3)
Renal and urinary disorders	2	(0.5)	1	(0.3)
Acute prerenal failure	1	(0.3)		
Renal failure acute	1	(0.3)		
Renal failure			1	(0.3)
General disorders and administration site conditions	13	(3.3)	5	(1.3)
General physical health deterioration	5	(1.3)		
Death	4	(1.0)	2	(0.5)
Asthenia	1	(0.3)		
Condition aggravated	1	(0.3)		
Multi-organ failure	1	(0.3)	1	(0.3)
Sudden death	1	(0.3)	1	(0.3)
Discomfort			1	(0.3)

Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 17.1

Table 25: Drug-related fatal AEs by treatment, highest CTCAE grade, primary SOC, and MedDRA preferred term (treated set) - study LUX-Lung 8

System Organ Class/ Preferred term	Afatinib Grade 5 N	(%)	Erlotinib Grade 5 N	(%)
Total treated	392	(100.0)	395	(100.0)
Total with related adverse events leading to death	6	(1.5)	5	(1.3)
Infections and infestations	1	(0.3)	2	(0.5)
Pneumonia	1	(0.3)	1	(0.3)
Peritonitis			1	(0.3)
Respiratory, thoracic and mediastinal disorders	3	(0.8)	2	(0.5)
Interstitial lung disease	2	(0.5)	1	(0.3)
Respiratory failure	1	(0.3)		
Pneumonitis			1	(0.3)
Gastrointestinal disorders			1	(0.3)
Intestinal obstruction			1	(0.3)
Renal and urinary disorders	1	(0.3)		
Renal failure acute	1	(0.3)		
General disorders and administration site conditions	1	(0.3)		
General physical health deterioration	1	(0.3)		

Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 17.1

Laboratory findings

Individual cases of grade 3 neutropenia and thrombocytopenia were reported in both treatment groups.

Safety in special populations

Gender

Table 26: Adverse events occurring with >10 % incidence in the afatinib arm within gender (male) by treatment, treated set- study LUX-Lung 8

	Afatinib								Erlotinib							
	All grades		Grade 3		Grade 4		Grade 5		All grades		Grade 3		Grade 4		Grade 5	
User-defined AE category	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total treated	331	(100.0)	331	(100.0)	331	(100.0)	331	(100.0)	330	(100.0)	330	(100.0)	330	(100.0)	330	(100.0)
Total with adverse events	329	(99.4)	94	(28.4)	19	(5.7)	69	(20.8)	321	(97.3)	114	(34.5)	16	(4.8)	59	(17.9)
Diarrhoea	239	(72.2)	30	(9.1)	2	(0.6)	0	(0.0)	130	(39.4)	10	(3.0)	1	(0.3)	0	(0.0)
Rash/Acne+	229	(69.2)	23	(6.9)	0	(0.0)	0	(0.0)	232	(70.3)	39	(11.8)	0	(0.0)	0	(0.0)
Rash+	201	(60.7)	18	(5.4)	0	(0.0)	0	(0.0)	191	(57.9)	30	(9.1)	0	(0.0)	0	(0.0)
Acne+	44	(13.3)	5	(1.5)	0	(0.0)	0	(0.0)	56	(17.0)	9	(2.7)	0	(0.0)	0	(0.0)
Fatigue+	107	(32.3)	13	(3.9)	1	(0.3)	1	(0.3)	96	(29.1)	19	(5.8)	2	(0.6)	0	(0.0)
Stomatitis+	97	(29.3)	13	(3.9)	0	(0.0)	0	(0.0)	29	(8.8)	2	(0.6)	0	(0.0)	0	(0.0)
Decreased appetite	80	(24.2)	11	(3.3)	0	(0.0)	0	(0.0)	82	(24.8)	6	(1.8)	0	(0.0)	0	(0.0)
Nausea	64	(19.3)	6	(1.8)	0	(0.0)	0	(0.0)	44	(13.3)	4	(1.2)	1	(0.3)	0	(0.0)
Dyspnoea	61	(18.4)	11	(3.3)	1	(0.3)	3	(0.9)	80	(24.2)	14	(4.2)	3	(0.9)	8	(2.4)
Cough	55	(16.6)	2	(0.6)	0	(0.0)	0	(0.0)	60	(18.2)	1	(0.3)	0	(0.0)	0	(0.0)
Haemoptysis	43	(13.0)	2	(0.6)	0	(0.0)	2	(0.6)	42	(12.7)	2	(0.6)	1	(0.3)	0	(0.0)
Vomiting	39	(11.8)	3	(0.9)	0	(0.0)	0	(0.0)	35	(10.6)	3	(0.9)	1	(0.3)	0	(0.0)
Paronychia+	36	(10.9)	1	(0.3)	0	(0.0)	0	(0.0)	17	(5.2)	1	(0.3)	0	(0.0)	0	(0.0)
Weight decreased	35	(10.6)	2	(0.6)	0	(0.0)	0	(0.0)	46	(13.9)	1	(0.3)	0	(0.0)	0	(0.0)
Constipation	34	(10.3)	0	(0.0)	0	(0.0)	0	(0.0)	37	(11.2)	1	(0.3)	0	(0.0)	0	(0.0)
Pruritus	34	(10.3)	1	(0.3)	0	(0.0)	0	(0.0)	46	(13.9)	0	(0.0)	0	(0.0)	0	(0.0)

Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 17.1

Table 27: Adverse events occurring with >10 % incidence in the afatinib arm within gender (female) by treatment, treated set- study LUX-Lung 8

	Afatinib								Erlotinib							
	All grades		Grade 3		Grade 4		Grade 5		All grades		Grade 3		Grade 4		Grade 5	
User-defined AE category	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total treated	61	(100.0)	61	(100.0)	61	(100.0)	61	(100.0)	65	(100.0)	65	(100.0)	65	(100.0)	65	(100.0)
Total with adverse events	61	(100.0)	30	(49.2)	4	(6.6)	8	(13.1)	64	(98.5)	24	(36.9)	2	(3.1)	12	(18.5)
Diarrhoea	54	(88.5)	9	(14.8)	1	(1.6)	0	(0.0)	33	(50.8)	2	(3.1)	0	(0.0)	0	(0.0)
Rash/Acne+	44	(72.1)	3	(4.9)	0	(0.0)	0	(0.0)	44	(67.7)	3	(4.6)	0	(0.0)	0	(0.0)
Rash+	37	(60.7)	3	(4.9)	0	(0.0)	0	(0.0)	33	(50.8)	2	(3.1)	0	(0.0)	0	(0.0)
Acne+	11	(18.0)	0	(0.0)	0	(0.0)	0	(0.0)	15	(23.1)	1	(1.5)	0	(0.0)	0	(0.0)
Fatigue+	25	(41.0)	6	(9.8)	0	(0.0)	0	(0.0)	23	(35.4)	4	(6.2)	1	(1.5)	0	(0.0)
Stomatitis+	21	(34.4)	3	(4.9)	0	(0.0)	0	(0.0)	13	(20.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dyspnoea	18	(29.5)	1	(1.6)	2	(3.3)	0	(0.0)	14	(21.5)	4	(6.2)	1	(1.5)	2	(3.1)
Decreased appetite	17	(27.9)	1	(1.6)	0	(0.0)	0	(0.0)	21	(32.3)	2	(3.1)	0	(0.0)	0	(0.0)
Nausea	17	(27.9)	0	(0.0)	0	(0.0)	0	(0.0)	20	(30.8)	0	(0.0)	0	(0.0)	0	(0.0)
Hypokalaemia	13	(21.3)	5	(8.2)	0	(0.0)	0	(0.0)	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	12	(19.7)	0	(0.0)	0	(0.0)	0	(0.0)	5	(7.7)	1	(1.5)	0	(0.0)	0	(0.0)
Urinary tract infection	11	(18.0)	1	(1.6)	0	(0.0)	0	(0.0)	3	(4.6)	0	(0.0)	0	(0.0)	0	(0.0)
Cough	10	(16.4)	0	(0.0)	0	(0.0)	0	(0.0)	9	(13.8)	1	(1.5)	0	(0.0)	0	(0.0)
Dry skin	10	(16.4)	0	(0.0)	0	(0.0)	0	(0.0)	11	(16.9)	0	(0.0)	0	(0.0)	0	(0.0)
Anaemia	9	(14.8)	0	(0.0)	0	(0.0)	0	(0.0)	7	(10.8)	2	(3.1)	0	(0.0)	0	(0.0)
Constipation	9	(14.8)	0	(0.0)	0	(0.0)	0	(0.0)	6	(9.2)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal pain upper	8	(13.1)	0	(0.0)	0	(0.0)	0	(0.0)	3	(4.6)	0	(0.0)	0	(0.0)	0	(0.0)
Back pain	7	(11.5)	3	(4.9)	0	(0.0)	0	(0.0)	6	(9.2)	0	(0.0)	0	(0.0)	0	(0.0)
Dehydration	7	(11.5)	2	(3.3)	0	(0.0)	0	(0.0)	1	(1.5)	1	(1.5)	0	(0.0)	0	(0.0)
Paronychia+	7	(11.5)	1	(1.6)	0	(0.0)	0	(0.0)	3	(4.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia	7	(11.5)	1	(1.6)	1	(1.6)	1	(1.6)	4	(6.2)	1	(1.5)	1	(1.5)	1	(1.5)

Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 17.1

In both study arms, diarrhoea and stomatitis were more commonly reported in females.

Age

Table 28: Adverse events occurring with >10 % incidence in the afatinib arm within age categories (≥65) by treatment, treated set- study LUX-Lung 8

	Afatinib								Erlotinib							
	All grades		Grade 3		Grade 4		Grade 5		All grades		Grade 3		Grade 4		Grade 5	
User-defined AE category	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total treated	207	(100.0)	207	(100.0)	207	(100.0)	207	(100.0)	186	(100.0)	186	(100.0)	186	(100.0)	186	(100.0)
Total with adverse events	206	(99.5)	57	(27.5)	14	(6.8)	47	(22.7)	181	(97.3)	69	(37.1)	4	(2.2)	32	(17.2)
Diarrhoea	166	(80.2)	24	(11.6)	2	(1.0)	0	(0.0)	91	(48.9)	4	(2.2)	1	(0.5)	0	(0.0)
Rash/Acne+	144	(69.6)	11	(5.3)	0	(0.0)	0	(0.0)	140	(75.3)	24	(12.9)	0	(0.0)	0	(0.0)
Rash+	126	(60.9)	8	(3.9)	0	(0.0)	0	(0.0)	113	(60.8)	19	(10.2)	0	(0.0)	0	(0.0)
Acne+	26	(12.6)	3	(1.4)	0	(0.0)	0	(0.0)	39	(21.0)	5	(2.7)	0	(0.0)	0	(0.0)
Fatigue+	73	(35.3)	11	(5.3)	0	(0.0)	1	(0.5)	66	(35.5)	15	(8.1)	2	(1.1)	0	(0.0)
Stomatitis+	64	(30.9)	12	(5.8)	0	(0.0)	0	(0.0)	26	(14.0)	1	(0.5)	0	(0.0)	0	(0.0)
Decreased appetite	54	(26.1)	5	(2.4)	0	(0.0)	0	(0.0)	55	(29.6)	2	(1.1)	0	(0.0)	0	(0.0)
Dyspnoea	46	(22.2)	8	(3.9)	2	(1.0)	3	(1.4)	50	(26.9)	10	(5.4)	2	(1.1)	4	(2.2)
Nausea	43	(20.8)	1	(0.5)	0	(0.0)	0	(0.0)	39	(21.0)	3	(1.6)	1	(0.5)	0	(0.0)
Vomiting	32	(15.5)	1	(0.5)	0	(0.0)	0	(0.0)	22	(11.8)	3	(1.6)	1	(0.5)	0	(0.0)
Cough	31	(15.0)	1	(0.5)	0	(0.0)	0	(0.0)	37	(19.9)	1	(0.5)	0	(0.0)	0	(0.0)
Weight decreased	25	(12.1)	1	(0.5)	0	(0.0)	0	(0.0)	24	(12.9)	1	(0.5)	0	(0.0)	0	(0.0)
Constipation	24	(11.6)	0	(0.0)	0	(0.0)	0	(0.0)	24	(12.9)	0	(0.0)	0	(0.0)	0	(0.0)
Paronychia+	24	(11.6)	1	(0.5)	0	(0.0)	0	(0.0)	14	(7.5)	1	(0.5)	0	(0.0)	0	(0.0)
Haemoptysis	22	(10.6)	0	(0.0)	0	(0.0)	0	(0.0)	20	(10.8)	1	(0.5)	0	(0.0)	0	(0.0)
Pruritus	22	(10.6)	1	(0.5)	0	(0.0)	0	(0.0)	31	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)

Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 17.1

Table 29: Adverse events occurring with >10% incidence in the afatinib arm within age categories (<65) by treatment, treated set- study LUX-Lung 8

	Afatinib								Erlotinib							
	All grades		Grade 3		Grade 4		Grade 5		All grades		Grade 3		Grade 4		Grade 5	
User-defined AE category	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total treated	185	(100.0)	185	(100.0)	185	(100.0)	185	(100.0)	209	(100.0)	209	(100.0)	209	(100.0)	209	(100.0)
Total with adverse events	184	(99.5)	67	(36.2)	9	(4.9)	30	(16.2)	204	(97.6)	69	(33.0)	14	(6.7)	39	(18.7)
Rash/Acne+	129	(69.7)	15	(8.1)	0	(0.0)	0	(0.0)	136	(65.1)	18	(8.6)	0	(0.0)	0	(0.0)
Rash+	112	(60.5)	13	(7.0)	0	(0.0)	0	(0.0)	111	(53.1)	13	(6.2)	0	(0.0)	0	(0.0)
Acne+	29	(15.7)	2	(1.1)	0	(0.0)	0	(0.0)	32	(15.3)	5	(2.4)	0	(0.0)	0	(0.0)
Diarrhoea	127	(68.6)	15	(8.1)	1	(0.5)	0	(0.0)	72	(34.4)	8	(3.8)	0	(0.0)	0	(0.0)
Fatigue+	59	(31.9)	8	(4.3)	1	(0.5)	0	(0.0)	53	(25.4)	8	(3.8)	1	(0.5)	0	(0.0)
Stomatitis+	54	(29.2)	4	(2.2)	0	(0.0)	0	(0.0)	16	(7.7)	1	(0.5)	0	(0.0)	0	(0.0)
Decreased appetite	43	(23.2)	7	(3.8)	0	(0.0)	0	(0.0)	48	(23.0)	6	(2.9)	0	(0.0)	0	(0.0)
Nausea	38	(20.5)	5	(2.7)	0	(0.0)	0	(0.0)	25	(12.0)	1	(0.5)	0	(0.0)	0	(0.0)
Cough	34	(18.4)	1	(0.5)	0	(0.0)	0	(0.0)	32	(15.3)	1	(0.5)	0	(0.0)	0	(0.0)
Dyspnoea	33	(17.8)	4	(2.2)	1	(0.5)	0	(0.0)	44	(21.1)	8	(3.8)	2	(1.0)	6	(2.9)
Haemoptysis	27	(14.6)	2	(1.1)	0	(0.0)	2	(1.1)	29	(13.9)	1	(0.5)	1	(0.5)	0	(0.0)
Dry skin	20	(10.8)	0	(0.0)	0	(0.0)	0	(0.0)	19	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	20	(10.8)	2	(1.1)	0	(0.0)	0	(0.0)	17	(8.1)	1	(0.5)	0	(0.0)	0	(0.0)
Constipation	19	(10.3)	0	(0.0)	0	(0.0)	0	(0.0)	19	(9.1)	1	(0.5)	0	(0.0)	0	(0.0)
Paronychia+	19	(10.3)	1	(0.5)	0	(0.0)	0	(0.0)	6	(2.9)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	19	(10.3)	2	(1.1)	0	(0.0)	0	(0.0)	18	(8.6)	1	(0.5)	0	(0.0)	0	(0.0)

Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 17.1

Renal AEs were higher among older Afatinib treated patients, with drug related events observed in less than 5% in either age group. More than half of the renal impairment AEs in afatinib treated patients were defined by the investigator as not drug related. Review of drug-related renal SAEs due to diarrhoea showed age did not impact the frequency of renal AEs.

Only 2 patients ≥70 years of age out of 122 (1.6%) developed diarrhoea related renal failure (or renal SAEs) indicating that diarrhoea induced pre-renal insufficiency is manageable in elderly patients.

GI adverse reactions did not show significant differences in the two age groups. Diarrhoea was more frequently reported in elderly patients in both study arms.

Renal impairment

Afatinib-treated patients with moderately impaired renal function at baseline (creatinine clearance 30 to <60 mL/minute) had a higher overall incidence of AEs as compared to patients with normal renal function (creatinine clearance ≥90 mL/minute) or mildly impaired renal function (creatinine clearance 60 to <90 mL/minute). Patients with moderately impaired renal function also reported a higher incidence of diarrhoea and stomatitis, had a higher incidence of Grade 3 AEs and had a higher incidence of AEs leading to treatment discontinuation. In the erlotinib group, there were no consistent trends were noted when examining AEs by renal function subgroup.

Discontinuation due to adverse events

Table 30: AEs leading to treatment discontinuation occurring with >1% incidence by treatment, highest CTCAE grade, grouped categories, and MedDRA preferred term (treated set) - study LUX-Lung 8

	Afatinib						Erlotinib					
	All grades		Grade 3		Grade 4		All grades		Grade 3		Grade 4	
User-defined AE category	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total treated	392	(100.0)	392	(100.0)	392	(100.0)	395	(100.0)	395	(100.0)	395	(100.0)
Total with adverse events leading to treatment discontinuation	79	(20.2)	33	(8.4)	16	(4.1)	67	(17.0)	35	(8.9)	9	(2.3)
Diarrhoea	16	(4.1)	9	(2.3)			6	(1.5)	4	(1.0)		
Rash/Acne+	10	(2.6)	5	(1.3)			8	(2.0)	4	(1.0)		
Rash+	9	(2.3)	4	(1.0)			5	(1.3)	3	(0.8)		
Malignant neoplasm progression	7	(1.8)	2	(0.5)	3	(0.8)	3	(0.8)			2	(0.5)
Pneumonia	6	(1.5)	2	(0.5)	3	(0.8)	1	(0.3)				
Dyspnoea	5	(1.3)	3	(0.8)			6	(1.5)	4	(1.0)		
Stomatitis+	4	(1.0)	1	(0.3)								
Fatigue+	3	(0.8)			1	(0.3)	4	(1.0)	4	(1.0)		

Note: Grade 5 (fatal) AEs are presented in Table 15.3.2.2: 4 and Section 12.3.1
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 17.1
+ Preferred terms included in these groups are listed in Table 15.3.2.2: 9

Table 31: Cumulative incidence of permanent discontinuation due to AE by treatment, treated set - study LUX-Lung 8

	Afatinib		Erlotinib	
	N	(%)	N	(%)
Total treated	392	(100.0)	395	(100.0)
Permanent discontinuation due to AE	79	(20.2)	67	(17.0)
<= 1 month	24	(6.1)	25	(6.3)
>1 to <= 2 months	21	(11.5)	19	(11.1)
>2 to <= 4 months	19	(16.3)	12	(14.2)
>4 to <= 6 months	7	(18.1)	6	(15.7)
>6 to <= 9 months	4	(19.1)	3	(16.5)
>9 to <= 12 months	4	(20.2)	0	(16.5)
>12 to <= 15 months			1	(16.7)
>15 to <= 18 months			0	(16.7)
>18 to <= 21 months			1	(17.0)

Altogether 11% vs. 5% of AEs leading to discontinuation were considered drug related by the investigator in the afatinib and erlotinib arms respectively, the difference largely attributable to diarrhoea and stomatitis.

Adverse events leading to dose reduction

	Afatinib								Erlotinib							
	All grades		Grade 3		Grade 4		Grade 5		All grades		Grade 3		Grade 4		Grade 5	
User-defined AE category	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total treated	392	(100.0)	392	(100.0)	392	(100.0)	392	(100.0)	395	(100.0)	395	(100.0)	395	(100.0)	395	(100.0)
Total with adverse events leading to dose reduction	104	(26.5)	60	(15.3)	2	(0.5)			56	(14.2)	37	(9.4)				
Diarrhoea	58	(14.8)	22	(5.6)	2	(0.5)			14	(3.5)	5	(1.3)				
Rash/Acne+	23	(5.9)	15	(3.8)					37	(9.4)	28	(7.1)				
Rash+	17	(4.3)	11	(2.8)					24	(6.1)	19	(4.8)				
Acne+	6	(1.5)	4	(1.0)					14	(3.5)	9	(2.3)				
Stomatitis+	12	(3.1)	11	(2.8)												
Fatigue+	5	(1.3)	4	(1.0)					3	(0.8)	2	(0.5)				

Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 17.1

Diarrhoea was the leading cause of dose reduction in the afatinib arm whilst rash dominated in the erlotinib arm.

2.5.1. Discussion on clinical safety

Afatinib is currently approved in more than 60 countries and the overall cumulative patient exposure to marketed Giotrif is estimated to be 5086 patient-years from July 2013 to March 2015.

In general, the safety pattern in the post-marketing experience has been consistent with that observed in the clinical trials. The majority of the AEs are related to EGFR inhibition (e.g. diarrhoea, rash) and the underlying disease. Characteristics of key risks such as ILD and cardiac disorders have been consistent with clinical trial data.

The adverse event profile of afatinib in LUX Lung 8 is very similar to what has been reported in prior first-line studies. Actually no new safety concerns have been identified. The major benefit from a safety evaluation perspective was the head to head comparison with erlotinib, being a reversible EGFR TK inhibitor. The only major differences are related to diarrhoea, mucositis and paronychia, probably due to the pan ErbB mechanism of action of afatinib. Irrespective of the type of event, most of the new/worsening of events were reported during the first 2 cycles.

The most frequently reported SAEs (≥ 3%) in the afatinib treatment group were pneumonia (6.6%), malignant neoplasm progression (5.9%), diarrhoea (4.6%), dehydration (3.1%), and dyspnoea (3.1%).

In the erlotinib group, the most frequently reported SAEs (≥ 3%) were dyspnoea (7.6%), pneumonia (4.1%), malignant neoplasm progression (4.1%), and respiratory failure (3.0%).

SAEs considered related were more frequently reported in the afatinib arm, 12 vs. 6%. Differences in diarrhoea and dehydration made up for most of this difference.

In relation to the reported fatal events, it is difficult to determine causality: underlying disease, co-morbidity, treatment, or an interaction between treatment and disease.

Total AEs leading to death were similar between treatment arms. An apparent increase is seen for infectious events and general disorders in the afatinib arm and in the control, respiratory and cardiovascular. Also “drug related” events leading to death appear similar without informative patterns.

Further to the CHMP request, the applicant provided data to support the claim that dose reduction would lead to AE grade reduction which was considered acceptable.

About 35% of patients initiated next-line therapy during the 28 days after end of treatment, however, this has not confounded the incidence of AEs.

2.5.2. Conclusions on clinical safety

No new safety concern has been identified on the basis of the data submitted in support of this application. Available safety data are sufficient to support a risk-benefit assessment in patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP):

The PRAC considered that the RMP 5.0 (dated 14 December 2015) is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Table 32: Summary of safety concerns

Important identified risks	Diarrhoea (incl. dehydration and renal impairment secondary to diarrhoea) Severe skin reactions ILD Keratitis Hepatic impairment Pancreatitis
Important potential risks	Decreased LVEF/heart failure Developmental toxicity Gastrointestinal perforation Hypersensitivity reactions Poor survival following off-label use in combination with vinorelbine in breast cancer Use in combination with chemotherapy
Missing information	Paediatric patients (<18 years) Patients with severe renal impairment Patients with severe hepatic impairment Patients with cardiac impairment Chemotherapy pre-treated patients with EGFR M +NSCLC (additional characterisation)

Pharmacovigilance plan

Table 33: Ongoing and planned studies in the PhV development plan

Study / activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Study 1200.217 Additional safety and efficacy data of afatinib 40mg qd in chemotherapy pre-treated patients with EGFR M +NSCLC (category 3)	Further characterise safety and efficacy of afatinib 40 mg qd in patients pre-treated with chemotherapy	Chemotherapy pre-treated patients with EGFR M +NSCLC (additional characterisation)	Ongoing	Q4 2017

Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	***Routine risk minimisation measures***	***Additional risk minimisation measures***
Important identified risk		
Diarrhoea (incl. dehydration and renal impairment secondary to diarrhoea)	*Labelling in SmPC Sections 4.2, 4.4, and 4.8. Prescription only medicine.*	*None*
Severe skin reactions	*Labelling in SmPC Sections 4.2, 4.4, and 4.8. Prescription only medicine.*	*None*
Interstitial lung disease	*Labelling in SmPC Sections 4.2, 4.4, and 4.8. Prescription only medicine.*	*None*
Keratitis	*Labelling in SmPC Sections 4.4 and 4.8. Prescription only medicine.*	*None*
Hepatic impairment	*Labelling in SmPC Section 4.4. Prescription only medicine.*	*None*
Pancreatitis	*Labelling in SmPC Section 4.8. Prescription only medicine.*	*None*
Important potential risk		
Decreased LVEF/heart failure	*Labelling in SmPC Section 4.4. Prescription only medicine.*	*None*
Developmental toxicity	*Labelling in SmPC Section 4.6 Prescription only medicine..*	*None*
Gastrointestinal perforation	*Prescription only medicine.*	*None*
Hypersensitivity reactions	*Labelling in SmPC Section 4.3. Prescription only medicine.*	*None*
Poor survival following off-label use in combination with vinorelbine in breast cancer	*Prescription only medicine.*	*None*
Use in combination with chemotherapy	*Prescription only medicine.*	*None*

Missing information		
Paediatric patients (<18 years)	*Labelling in SmPC Section 4.2. Prescription only medicine.*	*None*
Patients with severe renal impairment	*Labelling in SmPC Section 4.2. Prescription only medicine.*	*None*
Patients with severe hepatic impairment	*Labelling in SmPC Sections 4.2. Prescription only medicine.*	*None*
Patients with cardiac impairment	*Labelling in SmPC Section 4.4. Prescription only medicine.*	*None*
Chemotherapy pre-treated patients with EGFR M +NSCLC (additional characterisation)	*Prescription only medicine.*	*None*

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A full user consultation with target patient groups on the package leaflet was not performed and it has been found acceptable for the following reasons: changes made to the package leaflet were not considered significant and were not affecting its readability.

3. Benefit-Risk Balance

Benefits

Beneficial effects

A survival benefit of 1.1 months (6.8 vs. 7.9 m HR=0.81 [95% CI 0.69; 0.95], p=0.008) has been shown over erlotinib. Whilst modest, the data are mature and considered sufficiently robust.

PFS was the primary endpoint and at the primary analysis, the p-value was borderline statistically significant p= 0.043. At time of the updated PFS analysis, the p-value for the independent review analysis was 0.01 and the HR=0.8 (95% CI, 0.69; 0.96). The absolute benefit in terms of difference in medians was small (1.9 vs. 2.4 m.).

With respect to PRO data, it is accepted that descriptive information related to symptom control are included in section 5.1 of the SmPC despite deficiencies in the planning of the study.

Uncertainty in the knowledge about the beneficial effects

The MAH has reported extensive data derived from analyses using the Foundation One Next generation sequencing platform and human explants mouse xenografts. No biomarkers, however, have been identified of predictive value. This is perhaps not surprising due to the extreme heterogeneity in SQCL as regards putative driving and passenger mutations. Thus available data do not at this stage allow the identification of patients likely to derive more benefit from the treatment with afatinib and the

applicant is recommended to further investigate genetic biomarkers of efficacy.

No OS benefit over erlotinib has been shown in patients above 65 (70) years of age and the activity of erlotinib in older patients with SQLC is unknown (Tarceva EPAR).

Even though there is a potential for anti-tumour activity of this panErb inhibitor in patients with SQLC with EGFR negative tumours by IHC, the efficacy of afatinib has not been established.

Risks

Unfavourable effects

The most frequently reported grade 3 ADRs in the pivotal trial were diarrhoea (9.9%), rash (5.4%), stomatitis (4.1%) and decreased appetite (3.1%).

A benefit from the perspective of the assessment of safety is the comparison of this pan ErbB inhibitor with erlotinib an ErbB1 (EGFR-TK) inhibitor. This comparison reveals a clear increase in diarrhoea, mucositis and paronychia at rather similar levels of rash/acne.

The safety profile as documented in prior studies remains essentially unaltered.

Altogether 9% vs. 4% (afatinib vs. erlotinib) of AEs leading to discontinuation were considered drug related by the investigator, the difference largely attributable to diarrhoea and stomatitis. Overall 18 vs. 14% discontinued due to AEs. Taking number of patients at risk, there was no difference between study arms.

Dose reductions were undertaken in about 24 and 12% of patients treated with afatinib and erlotinib, respectively.

It has been clearly shown that dose reductions lead to reduction of stomatitis and diarrhoea.

Diarrhoea is the main concerns from a tolerability perspective and dehydration and pre-renal renal events have been reported, but at a rather low level also in patients above 70 years of age.

Uncertainty in the knowledge about the unfavourable effects

Missing data as regards patients with non-trivial heart disorders remains a potential concern due to inhibition of HER2/ErbB2.

Effects Table

Table 34: Effects Table for Giotrif in squamous NSCLC (data cut-off: Oct. 2013 [primary PFS analysis], March 2015 [OS, updated PFS analysis])

Effect	Experimental arm	Control arm	HR	P-value	Comment
Favourable effects					
Survival Months	Median 7.9	Median 6.8	0.8	0.008	Reliable Modest
PFS Primary analysis (IRC)	Median 2.4	Median 1.9	0.8	0.04	Borderline Very modest
PFS Update (IRC)	Median 2.6	Median 1.9	0.8	0.01	Supportive of OS
ORR RECIST 1.1	5.5%	2.8%		0.055	Low activity Minor difference
Duration of therapy Median m.	2	2			In order to contextualise: OS

Mean m.	4	3			benefit, 1 months
Unfavourable effects					
Total AE, excl. PD leading to: Discontinuation % Dose reduction %	 18 27	 14 14	No difference taking number of patients at risk into account		
Related AE Discontinuation	 9%	 4%			
SAE % Pneumonia %b Dyspnoea % Dehydration %	44 6.6 3.1 3.1	44 4.1 7.6	Similar		
Diarrhoea Grade all % Grade 3/4 % Dose reduction % Discontinuation %	 74.7 10.7 15 4.1	 41.3 3.3 3.5 1.5	Relevant difference. Dose reduction reduces grade.		
Rash/Acne Grade all Grade 3/4 Dose reduction % Discontinuation %	 69.6 6.6 5.9 2.6	 69.9 10.6 9.4 2.0	Slightly favourable for afatinib		
Stomatitis Grade all Grade 3/4 Dose reduction % Discontinuation %	 30.1 4.1 3.1 1	 10.6 0.5 0 0	Relevant difference. Dose reduction reduces grade.		

Benefit-Risk Balance

Benefit-risk balance

Mature and reliable survival data have been provided and the safety profile of afatinib, taking prior confirmatory studies into account, is considered sufficiently well documented for a benefit – risk assessment. Overall, the benefit-risk balance is considered positive in view of the survival advantage and acceptable toxicity profile.

Discussion on the Benefit-Risk Balance

The benefit-risk balance of Giotrif in the treatment of locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy is considered positive. The MAH is recommended to further investigate the activity/efficacy of afatinib according to biomarkers (in particular EGFR status).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy for Giotrif.

As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and RMP are updated in accordance.

Furthermore, minor editorial changes have been introduced throughout the PI.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indications to include patients with locally advanced or metastatic Non-small cell lung cancer (NSCLC) of squamous histology progressing on or after platinum-based chemotherapy.

Summary

Please refer to the published Assessment Report Giotrif H-2280-II-12-AR.