AFATINIB*

B A C K G R O U N D E R

1. **What is afatinib?**
2. **How does afatinib work?**
3. **Data overview: the LUX-Lung clinical trial programme**
4. **Tolerability**

1. WHAT IS AFATINIB?

Afatinib is an irreversible ErbB Family blocker approved in more than 80 markets. It is indicated for the treatment of patients with distinct types of epidermal growth factor receptor *EGFR* mutation-positive (*EFGR* M+) locally advanced or metastatic non-small cell lung cancer (NSCLC), and for the treatment of patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy. It is an oral, once-daily, targeted therapy.[1]

2. HOW DOES AFATINIB WORK?

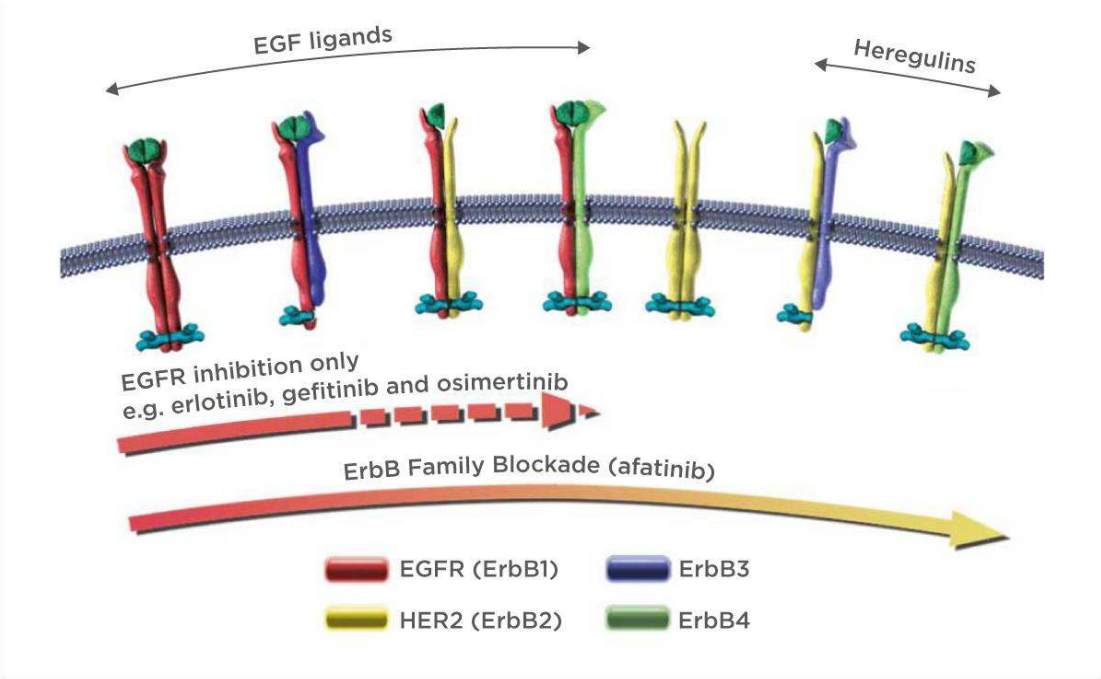
Afatinib selectively, potently and irreversibly binds to and blocks EGFR (ErbB1), HER2 (ErbB2) and ErbB4. In doing so, afatinib blocks downstream signalling from all homo- and heterodimers formed by ErbB Family members.[2,3,4] This family of receptors is often mutated in lung cancer and is involved in fundamental processes such as cell proliferation, survival, invasion, and differentiation.[5,6]

The irreversible binding of afatinib is unlike reversible compounds, as it aims to provide sustained, selective and complete blockade of ErbB Family members. Afatinib's mechanism of action prevents tumour cell growth and spread across a broad range of cancers, compared with other treatments that offer single, reversible receptor blocking (Figure 1).[2,3,4]

*Afatinib is approved in more than 80 markets including the EU, Japan, Taiwan, and Canada under the brand name GIOTRIF®, in the US under the brand name GILOTRIF® and in India under the brand name Xovoltib®; for the full list please see here. European Union Summary of Product Characteristics.

This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK). Afatinib is subject to country-specific regulations and the approved product label may vary from country to country. Information on this website is derived from the approved European Summary of Product Characteristics. Please refer to your local product label for full details.

Figure 1. Afatinib, an irreversible ErbB Family blocker.



3. DATA OVERVIEW: THE LUX-LUNG CLINICAL TRIAL PROGRAMME

The LUX-Lung clinical trial programme comprises eight studies investigating afatinib in a number of patient populations with advanced NSCLC. A brief overview of the trials is provided in **Table 1.**

It includes two pivotal Phase III studies, LUX-Lung 3[7,8] and LUX-Lung 6[9,10].

LUX-Lung 7 was the first global head-to-head trial comparing second- with first-generation EGFR-targeting agents (afatinib and gefitinib, respectively) in 1st-line EGFR M+ NSCLC.[11] LUX-Lung 8 directly compared the efficacy of two EGFR targeting compounds, afatinib vs erlotinib, in patients with advanced squamous cell carcinoma (SqCC) of the lung.[12]

Table 1. An overview of the LUX-Lung trial programme for afatinib in NSCLC.

LUX-Lung trial	Methods overview	Endpoints overview
LUX-Lung 1[13] CT.gov identifier: NCT00656136	Phase IIb/III Randomised, double-blind Afatinib plus BSC vs placebo plus BSC Patients with NSCLC failing erlotinib or gefitinib	**Primary**: OS **Secondary**: PFS, ORR
LUX-Lung 2[14] CT.gov identifier: NCT00525148	Phase II Open-label trial Continuous once-daily, oral treatment with afatinib Patients with Stage IIIB or IV lung adenocarcinoma with an *EGFR*-activating mutation	**Primary**: ORR (CR or PR) **Secondary**: PFS, OS
LUX-Lung 3[7,8] CT.gov identifier: NCT00949650	Phase III Randomised, open-label Afatinib vs chemotherapy as first-line treatment Patients with Stage IIIB or IV lung adenocarcinoma with an *EGFR*-activating mutation	**Primary**: PFS, assessed by independent review **Secondary**: ORR, percentage with DC, OS, ECOG PS change since baseline, DCR, HRQoL, pharmacokinetics
LUX-Lung 4[15] CT.gov identifier: NCT00711594	Phase I/II Open-label trial Continuous, once-daily, oral treatment with afatinib Phase I: patients with advanced NSCLC Phase II: patients with NSCLC failing erlotinib or gefitinib	**Phase I, primary**: incidence of DLT, incidence and intensity of AEs **Phase I, secondary**: pharmacokinetics, summary of *EGFR* mutations **Phase II, primary**: ORR **Phase II, secondary**: DCR, time and duration of OR, duration of disease control, PFS, OS, trough plasma concentrations, summary of *EGFR* mutations
LUX-Lung 5[16] CT.gov identifier: NCT01085136	Phase III Randomised trial Afatinib plus weekly paclitaxel vs investigator's choice of chemotherapy following afatinib monotherapy Patients with NSCLC failing previous erlotinib or gefitinib treatment	**Primary**: PFS **Secondary**: OS, ORR, HRQoL
LUX-Lung 6[9,10] CT.gov identifier: NCT01121393	Phase III Randomised, open-label Afatinib vs chemotherapy as first-line treatment Patients with Stage IIIB or IV lung adenocarcinoma with an *EGFR*-activating mutation	**Primary**: PFS **Secondary**: OS, ORR, DCR, time to and duration of OR, duration of disease control, ECOG PS change since baseline, HRQoL, pharmacokinetics

LUX-Lung 7[11,17] CT.gov identifier: NCT01466660	Phase IIb Randomised, open-label Afatinib vs gefitinib as first-line treatment Patients with *EGFR* mutations (del19/L858R) and advanced adenocarcinoma of the lung	**Primary**: PFS by independent review, TTF, OS **Secondary**: ORR, time to response, duration of response, duration of disease control, tumour shrinkage, HRQoL
LUX-Lung 8[12] CT.gov identifier: NCT01523587	Phase III Randomised, open-label Afatinib vs erlotinib as second-line therapy following first-line platinum-based chemotherapy Patients with advanced SqCC of the lung	**Primary:** PFS **Secondary:** OS, OR, DCR, tumour shrinkage, HRQoL

AE, adverse event; BSC, best supportive care; CR, complete response; DC, disease control; DCR, disease control rate; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life; NSCLC, non-small cell lung cancer; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SqCC, squamous cell carcinoma; TTF, time to treatment failure.

Afatinib's efficacy and safety profile

The LUX-Lung 3 and LUX-Lung 6 trials both met their primary endpoint of progression-free survival, as afatinib significantly delayed tumour growth vs standard chemotherapy in patients with *EGFR* M+ NSCLC.[7–10]

In a prespecified subgroup analysis, LUX-Lung 3 and LUX-Lung 6 independently demonstrated that afatinib is the first treatment to show an overall survival benefit for patients with the most common type of *EGFR* mutation (del19). These patients lived a median of more than 1 year longer if they started treatment with afatinib rather than standard chemotherapy.[18]

Post-hoc analysis of clinical outcomes in a combined data set from LUX-Lung 3 and LUX-Lung 6 trials showed that afatinib delayed the onset and progression of brain metastases in patients with *EGFR* M+ NSCLC.[19] Together, these data could help inform treatment decisions for patients with *EGFR* M+ NSCLC. Brief overviews of the LUX-Lung programme results are shown below.

LUX-Lung 3[7,8] (afatinib vs pemetrexed/cisplatin)	LUX-Lung 6[9,10] (afatinib vs gemcitabine/cisplatin)
PFS[8,9] (primary endpoint)	
• 11.1 vs 6.9 months for all patients with *EGFR* mutations by independent review (p=0.001) • 13.6 vs 6.9 months for patients with the most common mutations (del19 and L858R; ~89% of all patients) by independent review (p=0.001)	• 11.1 vs 5.6 months for all patients with *EGFR* mutations by independent review (p<0.0001) • Based on investigator review, patients lived for well over a year before their tumour started to grow again, vs just under half a year for those on standard chemotherapy (PFS of 13.7 vs 5.6 months, p<0.0001)
• The delay in tumour growth compared well in both trials, substantiating the efficacy of afatinib and the robustness of the data	
OS[18] (secondary endpoint)	
• Statistically significant improvement in OS, in patients with common mutations (del19/L858R), with afatinib compared with chemotherapy (median 27.3 vs 24.4 months, p=0.037) in the post-hoc analysis combining LUX-Lung 3 and LUX-Lung 6	
• More than 1 year OS benefit (median 33.3 vs 21.1 months, p=0.0015) with afatinib in patients with the del19 mutation compared with chemotherapy in the prespecified subgroup analysis of LUX-Lung 3	• More than 1 year OS benefit (median 31.4 vs 18.4 months, p=0.023) with afatinib in patients with the del19 mutation compared with chemotherapy in the prespecified subgroup analysis of LUX-Lung 6
• In the overall patient population for each individual study, there was no significant OS benefit of afatinib compared with chemotherapy (28.2 vs 28.2 months for LUX-Lung 3 and 23.1 vs 23.5 months for LUX-Lung 6)	
ORR[8,9] (tumour shrinkage, secondary endpoint)	
• Higher ORR was observed in patients taking afatinib (56%) compared with those receiving chemotherapy (23%), as assessed by independent review (p=0.001)	• A greater proportion of patients receiving afatinib (66.9%) had an ORR compared with patients in the gemcitabine/cisplatin chemotherapy (23%) arm, as assessed by independent review (p<0.0001)
• Tumour shrinkage translated into improvements in disease-related symptoms	
Disease-related symptoms[7,10] (secondary endpoint)	
• In LUX-Lung 3 and LUX-Lung 6, more patients taking afatinib experienced improvement of symptoms such as dyspnoea, cough and chest pain. Afatinib treatment also delayed the onset of these symptoms	
HRQoL[7,10] (measured by patient questionnaires, secondary endpoint)	
• Patients taking afatinib in LUX-Lung 3 and LUX-Lung 6 were reported to have a significantly better HRQoL than those on chemotherapy (LUX-Lung 3, p=0.015; LUX-Lung 6, p<0.0001)	

LUX-Lung 3[7,8] (afatinib vs pemetrexed/cisplatin)	LUX-Lung 6[9,10] (afatinib vs gemcitabine/cisplatin)
Grade ≥3 AEs[8,9]	
• The most common drug-related AEs observed in the afatinib treatment arm were diarrhoea, rash and paronychia • The most common drug-related AEs observed in the chemotherapy arm were nausea/vomiting, decreased appetite and fatigue • There was a low discontinuation rate associated with treatment-related AEs in the trial (8% discontinuation rate for afatinib; 12% for chemotherapy) • In the afatinib arm, only diarrhoea (1.3%) and paronychia (0.9%) resulted in treatment discontinuation	• The most common drug-related AEs associated with afatinib were diarrhoea, rash/acne and stomatitis/mucositis • The most common AEs associated with chemotherapy were neutropenia, vomiting and leucopenia • The discontinuation rate due to AEs was 6% of patients in the afatinib arm and 40% of patients in the chemotherapy arm

AE, adverse event; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; HRQoL, health-related quality of life.

LUX-Lung 5[16] (afatinib + paclitaxel vs investigators' choice of chemotherapy)
PFS (primary endpoint)
• 5.6 vs 2.8 months (statistically significant, p=0.003)
OS (secondary endpoint)
• OS was similar in both arms (12.2 vs 12.2 months, p=0.994)
ORR (secondary endpoint)
• 32.1% of patients taking afatinib experienced tumour shrinkage compared with 13.2% in the chemotherapy arm (p=0.005) • Tumour shrinkage translated into improvements in disease-related symptoms
AEs
• The most common drug-related AEs observed in the afatinib treatment arm were diarrhoea (53.8%), alopecia (32.6%) asthenia (27.3%), decreased appetite (22.0%) and rash (20.5%)

AE, adverse event; OS, overall survival; ORR, objective response rate; PFS, progression-free survival.

LUX-Lung 7[11,17] (afatinib vs gefitinib)
PFS (primary endpoint)
• 11.0 vs 10.9 months (statistically significant, p=0.017 by independent review)
TTF
• 13.7 vs 11.5 months (p=0.007)
OS
• Primary OS analysis: 27.9 vs 25.0 months (p=0.33) • Mature OS analysis: 27.9 vs 24.5 months (p=0.258)
ORR (secondary endpoint)
• 70% vs 56% (p=0.008)
AEs
• AE profile was similar in both groups, with drug-related AEs leading to discontinuations occurring in 6.3% of patients in both treatment groups. The most common drug-related Grade 3 AEs were diarrhoea (11.9%), rash/acne (9.4%), fatigue (5.6%) and stomatitis (4.4%) in the afatinib group, while in the gefitinib group increased ALT (7.5%) and rash/acne (3.1%) were common

AE, adverse event; ALT, alanine aminotransferase; ORR, objective response rate; PFS, progression-free survival; TTF, time to treatment failure.

LUX-Lung 8[12] (afatinib vs erlotinib)
PFS (primary endpoint)
• 2.4 vs 1.9 months (statistically significant, p=0.043 by independent review)
ORR (secondary endpoint)
• 6.0% vs 3.0% (p=0.055)
DCR (secondary endpoint)
• 51.0% vs 40.0% (statistically significant, p=0.0020)
HRQoL (secondary endpoint)
• More patients had improved overall HRQoL with afatinib than with erlotinib (36% vs 28%, p=0.041)
OS (secondary endpoint)
• OS was significantly greater in the afatinib group than in the erlotinib group (median 7.9 vs 6.8 months, p=0.0077)
AEs
• AE profiles were similar in each group. Grade ≥3 AEs were comparable in both groups (224 [57%] afatinib vs 227 [57%] erlotinib). There were higher incidences of treatment-related Grade 3 diarrhoea with afatinib (10% vs 2%) and Grade 3 stomatitis with afatinib (4% vs 0%), while Grade 3 rash or acne was higher with erlotinib (6% vs 10%)

AE, adverse event; DCR, disease control rate; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

4. TOLERABILITY

The side effects of afatinib are predictable, generally manageable and reversible. In studies to date, drug-related adverse events (AEs) were largely related to the gastrointestinal tract (diarrhoea) and skin disorders (rash), which is in line with EGFR tyrosine kinase inhibition.[6–25] For further details, please refer to the AEs section in each of the above studies (LUX-Lung 3, 6, 7 and 8) and the Summary of Product Characteristics.[1]

More information on the dosing of afatinib can be found here and also in the Summary of Product Characteristics.[1]

REFERENCES

1. GIOTRIF Summary of Product Characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002280/WC500152392.pdf (Accessed:Feb 2017).

2. Reid A, Vidal L, Shaw H, do Bono J. Dual inhibition of ErbB1 (EGFR/HER1) and ErbB2 (HER2/neu). Eur J Cancer 2007;43(3):481–89.

3. Solca F, Dahl G, Zoephel A, et al. Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. J Pharmacol Exp Ther 2012;343(2):342–50.

4. Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene 2008;27(34):4702–11.

5 Hynes NE, MacDonald G. ErbB receptors and signalling pathways in cancer. Curr Opin Cell Biol 2009;21(2):177–84.

6. Breuleux M. Role of heregulin in human cancer. Cell Mol Life Sci 2007;64(18):2358–77.

7. Yang J, Hirsh V, Schuler M, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with epidermal growth factor receptor mutations. J Clin Oncol 2013;31(27)3342–50.

8. Sequist L, Yang J, Yamamoto N, et al. Phase III Study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with epidermal growth factor receptor mutations. J Clin Oncol 2013;31(27)3327–34.

9. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014;15(2):213–22.

10. Geater, SL, MD. LUX-Lung 6: Patient reported outcomes (PROs) from a randomized open-label, Phase III study in 1st-line advanced NSCLC patients (pts.) harbouring epidermal growth factor receptor (EGFR) mutations. American Society of Clinical Oncology, Chicago, 1 June 2013. (Abstract and poster 8061).

11. Park K, Tan E-H, O'Byrne K et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol 2016;17(5):577–89.

12. Soria JC, Felip E, Cobo M, et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. Lancet Oncol 2015;16(8):897–907.

13. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;13(5):528–38.

14. Yang JC, MD, Shih Y-J, Su C-W, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. Lancet Oncol 2012;13(5):539–48.

15. Katakami N, Atagi S, Goto K, et al. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. J Clin Oncol 2013;31(27):3335–41.

16. Schuler M, Chih-Hsin Yang J, et al. Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: phase III randomized LUX-Lung 5 trial. Ann Oncol 2016;27(3):417–23.

17. Paz-Ares L, Tan E-H, O'Byrne K, et al. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Ann Oncol 2017;28(2):270–77..

18. Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015;16(2):141–51.

19. Schuler M, Wu, Y-L, Hirsh V, et al. First line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. J Thorac Oncol 2016;11(3):380–90.

20. Plummer R, Vidal L, Li L, et al. Phase I study of BIBW2992, an oral irreversible dual EGFR/HER2 inhibitor, showing activity in tumours with mutated EGFR. Eur J Cancer Suppl 2006;4(12):173–4 (Abstract 573).

21. Agus DB, Terlizzi E, Stopfer P, et al. A Phase I dose escalation study of BIBW 2992, an irreversible dual EGFR/HER2 receptor tyrosine kinase inhibitor, in a continuous schedule in patients with advanced solid tumors. J Clin Oncol 2006;24(18, Suppl.): Abstract 2074.

22. Mom CH, Eskens FA, Gietema JA, et al. Phase 1 study with BIBW 2992, an irreversible dual tyrosine kinase inhibitor of epidermal growth factor receptor 1 (EGFR) and 2 (HER2) in a 2 week on 2 week off schedule. J Clin Oncol 2006;24(18, Suppl.): Abstract 3025.

23. Shaw H, Plummer R, Vidal l, et al. phase I dose escalation study of BIBW 2992, an irreversible dual EGFR/HER2 receptor tyrosine kinase inhibitor, in patients with advanced solid tumours. J Clin Oncol 2006;24(18, Suppl.): Abstract 3027.

24. Eskens FA, Mom CH, Planting AS, et al. A phase I dose escalation study of BIBW 2992, an irreversible dual inhibitor of epidermal growth factor receptor 1 (EGFR) and 2 (HER2) tyrosine kinase in a 2-week on, 2-week off schedule in patients with advanced solid tumours. Br J Cancer 2008;98(1):80–5.

25. Marshall J, Hwang J, Eskens FA, et al. A Phase I, open-label, dose escalation study of afatinib, in a 3-week-on/1-week-off schedule in patients with advanced solid tumors. Invest New Drugs 2013;31(2):399–408.