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GIOTRIF® (AFATINIB*)

BACKGROUNDER

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1. WHAT IS GIOTRIF® (AFATINIB*)?

Afatinib* is an irreversible ErbB Family Blocker approved in over 50 countries worldwide including the EU, US and Japan. It is indicated for the treatment of patients with distinct types of Epidermal Growth Factor Receptor (EGFR) mutation-positive locally advanced or metastatic non-small cell lung cancer (NSCLC), a specific type of lung cancer. It is an oral, once daily targeted therapy.

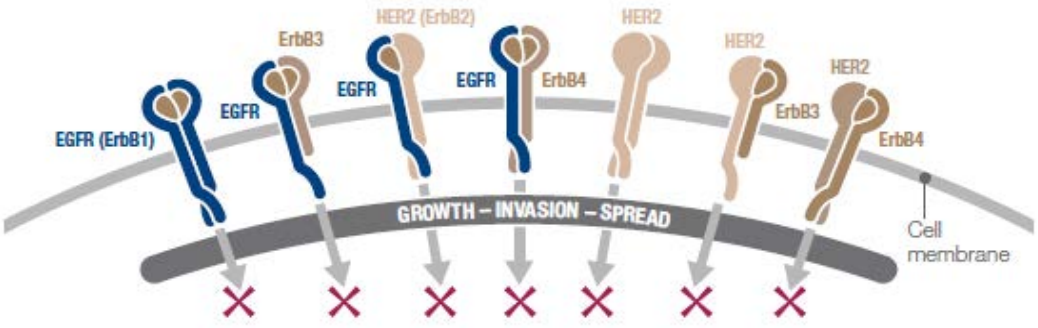
2. HOW DOES GIOTRIF® (AFATINIB*) WORK?

The ErbB Family of receptors consists of four related enzymes called tyrosine kinases: EGFR (ErbB1), HER2 (ErbB2), ErbB3 and ErbB4.[1] These receptors are often dysregulated, i.e. over expressed (too many are produced) or mutated in many cancers (including lung, breast, head and neck, and colorectal cancers), and are involved in fundamental processes which allow tumour cells to grow and multiply.[2]

Afatinib* irreversibly blocks EGFR (ErbB1) as well as other members of the ErbB Family, (ErbB3 is blocked indirectly via transphosphorylation), that are known to play a critical role in the growth and spread of the most widespread cancers and cancers associated with high mortality (death).

The irreversible binding of afatinib* is unlike other compounds which are reversible in that it aims to provide a sustained, selective and complete ErbB Family Blockade. Afatinib's* mechanism of action could potentially lead to a greater overall effect on the tumour, preventing tumour cell growth and spread across a broad range of cancers, compared to other treatments which offer single, reversible, receptor blocking.[3,4]

Targeting Signal Transduction



The signalling of ErbB3 is blocked indirectly through blocking of transphosphorylation
Source: Hynes NE, et al. Nat Rev Cancer 2005;5:341-54.

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3. DATA OVERVIEW

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.

- Two pivotal Phase III studies, LUX-Lung 3[5,6] and LUX-Lung 6[7,8] represent the largest and most robust clinical trial programme in EGFR mutation-positive NSCLC to date.
- LUX-Lung 5[9] is the first prospective trial looking at the advantage of continuing treatment with afatinib*, in combination with chemotherapy in NSCLC, after the tumour started to grow on afatinib* alone (treatment beyond progression).
- LUX-Lung 7 is a head-to-head trial directly comparing the efficacy and safety of afatinib* and gefitinib (another EGFR-directed treatment) as first-line treatments in patients with EGFR mutation-positive adenocarcinoma of the lung.
- LUX-Lung 8 is the first prospective, head-to-head trial directly comparing the efficacy and safety of two EGFR-directed treatments, afatinib* and erlotinib, in patients with advanced squamous cell carcinoma (SCC) of the lung.[10]

In addition to NSCLC, afatinib* is being investigated in another disease area, head and neck cancer. The LUX-Head & Neck clinical trial programme is investigating afatinib* in different settings of head and neck squamous cell cancer (HNSCC).

- LUX-Head & Neck 1 and 3 evaluate the efficacy and safety of afatinib* in patients with recurrent and/or metastatic HNSCC versus methotrexate (a chemotherapy) following first-line chemotherapy.[11]
- LUX-Head & Neck 2 and 4 trials are investigating the activity of afatinib* as an adjuvant therapy in patients with locally advanced disease, who have received definitive chemo-radiotherapy.

Efficacy and Safety Profile

LUX-Lung 3 and **LUX-Lung 6** are multicentre, randomised, open-label, Phase III trials of afatinib* versus chemotherapy (pemetrexed/cisplatin and gemcitabine/cisplatin respectively) as first-line treatment for patients with EGFR-mutation positive advanced and metastatic NSCLC.[5,6,7,8]

Both trials met their primary endpoint of progression-free survival, as afatinib* significantly delayed tumour growth when compared to standard chemotherapy in patients with EGFR mutation-positive NSCLC.[5,6,7,8]

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In a pre-specified 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 (exon 19 deletion/del19). These patients lived a median of more than one year longer if they started treatment with afatinib* rather than standard chemotherapy.[12]

A combined exploratory analysis of the LUX-Lung 3 and LUX-Lung 6 trials demonstrated that afatinib* offered an overall survival benefit to the subgroup of patients whose tumours harbour common EGFR mutations (del19/L858R), who lived for a median of three months longer when compared with standard chemotherapy.[12]

LUX-Lung 3[5,6] (afatinib* vs pemetrexed/cisplatin)	**LUX-Lung 6**[7,8] (afatinib* vs gemcitabine/cisplatin)
Progression-Free Survival[6,8] (PFS: length of time before a tumour starts to progress, primary endpoint)	
• **11.1 months vs 6.9 months** for all patients with EGFR mutations by independent review (p=0.001) • **13.6 months vs 6.9 months** for patients with **the most common mutations** (~89% of all patients, del19 and L858R) by independent review (p=0.001)	• **11.0 months 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, versus just under half a year for those on standard chemotherapy **(PFS of 13.7 months vs 5.6 months, p<0.0001)** • In addition, **47% of afatinib*-treated patients were alive and progression-free after 1 year of treatment compared to only 2% on chemotherapy**
• The delay in tumour growth compared well in both trials, substantiating the efficacy of afatinib* and the robustness of the data	
Overall Survival (OS: length of time a patient lives for, secondary endpoint)[12]	
• **More than one year overall survival benefit** (median 33.3 vs 21.1 months, p=0.0015) in patients with the **del19** mutation compared to chemotherapy in the pre-specified subgroup analysis of LUX-Lung 3	• **More than one year overall survival benefit** (median 31.4 vs 18.4 months, p=0.0229) in patients with the **del19** mutation compared to chemotherapy in the pre-specified subgroup analysis of LUX-Lung 6
• Statistically significant improvement in **overall survival, in patients with common mutations (del19/L858R)**, with afatinib* compared to chemotherapy (**median 27.3 vs 24.4 months, p=0.037**) in the post-hoc analysis combining LUX-Lung 3 and LUX-Lung 6	
• In the overall patient population for each individual study, there was no significant overall survival benefit of afatinib* compared with chemotherapy (28.1 vs 28.2 months for LUX-Lung 3 and 23.1 vs 23.5 months for LUX-Lung 6)	

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Objective Response[6,7] (Tumour shrinkage, secondary endpoint)

- **One in two patients (56%) taking afatinib* experienced tumour shrinkage compared to one in four (23%) in the chemotherapy arm**, by independent review (p<0.001)
- **In 67% of patients taking afatinib* the tumour shrunk significantly in size compared to 23% in the chemotherapy arm,** by independent review (p<0.0001)
- Tumour shrinkage translated into improvements in disease-related symptoms

Disease Related Symptoms[5,8] (Secondary endpoint)

- In LUX-Lung 3 and LUX-Lung 6, more patients taking afatinib* **experienced improvement of symptoms such as dyspnoea (shortness of breath), cough and chest pain** compared to chemotherapy. Afatinib* treatment also delayed the onset of these symptoms compared to chemotherapy

Quality of Life (Measured by patient questionnaires, secondary endpoint)[5,8]

- Afatinib* patients in LUX-Lung 3 and LUX-Lung 6 reported to have **a significantly better quality of life** than those on chemotherapy (LUX-Lung 3, p=0.015; LUX-Lung 6, p<0.0001)

Grade ≥3 Adverse Events (AEs)[6,7]

- The most common drug-related AEs observed in the afatinib* treatment arm were diarrhoea, rash and paronychia (infection of the skin next to the nail)
- 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**)
- **1% of patients in the afatinib* arm discontinued treatment due to diarrhoea**
- The most common drug-related AEs associated with afatinib* were diarrhoea, rash/acne and stomatitis/mucositis (inflammation of mouth and throat)
- The most common AEs associated with chemotherapy were neutropenia (an abnormally low level of neutrophils, a type of white blood cell), vomiting and leukopenia (a decrease in the number of white blood cells)
- The discontinuation rate due to AEs was **6% of patients on the afatinib* arm** and **40% of patients on the chemotherapy arm**
- **Only 2% of patients in the afatinib* arm discontinued due to rash/acne and none for diarrhoea**

LUX-Lung 5 is a randomised, open label Phase III trial comparing afatinib* with chemotherapy versus chemotherapy alone in patients with late-stage lung cancer after failure of several treatments, including chemotherapy, erlotinib or gefitinib, and afatinib* alone (treatment beyond progression).[9]

Those patients who continued afatinib* treatment, with the addition of chemotherapy, after progressing on afatinib* alone, had a further delay in tumour growth compared to the group who stopped afatinib* treatment, and received chemotherapy only (tumour growth was delayed by 5.6 months and 2.8 months respectively). This corresponded to a 40% reduction in risk of disease progression for the afatinib* plus chemotherapy arm compared to the chemotherapy only arm.[9]

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LUX-Lung 5[9] (Part B: afatinib* + paclitaxel vs investigators choice of single agent chemotherapy)
Progression-Free Survival (PFS: length of time before tumour starts to progress, primary endpoint)
• **5.6 months vs 2.8 months (statistically significant, p=0.003)**
Objective Response (Tumour shrinkage, secondary endpoint)
• Almost **a third of patients (32.1%)** taking afatinib* experienced tumour shrinkage compared to **13.2%** in the chemotherapy arm (p=0.005)
• Tumour shrinkage translated into improvements in disease-related symptoms
Overall survival (OS: length of time patients live for, secondary endpoint)
• OS was **12.2 months vs 12.2 months** on both arms
Adverse Events (AEs)
• The most common drug-related AEs observed in the afatinib* plus paclitaxel treatment arm were diarrhoea, fatigue, rash/acne and alopecia (hair loss) • The most common drug-related AEs on the investigator´s choice single agent chemotherapy (80% of patients treated either with paclitaxel, docetaxel or pemetrexed) were fatigue, nausea, decreased appetite and alopecia

LUX-Lung 8 is the first prospective, head-to-head trial comparing two EGFR-directed treatments, afatinib* and erlotinib, in patients with advanced SCC of the lung, progressing after treatment with first-line chemotherapy.[10]

Results demonstrated superior progression-free survival for afatinib* compared to erlotinib; reducing the risk of disease progression by 19%, and a significant improvement in overall survival with afatinib* compared to erlotinib.[10,13]

LUX-Lung 8[10,13] (afatinib* vs erlotinib)
Progression-Free Survival (PFS: length of time before tumour starts to progress, primary endpoint) [13]
• **2.6 months vs 1.9 months (statistically significant, p=0.010)**
Overall Survival (OS: length of time a patient lives for, secondary endpoint)[13]
• Statistically significant improvement in **overall survival** in patients treated with afatinib* compared to erlotinib (**7.9 months vs 6.9 months**), corresponding to a 19% reduction in the risk of death **(statistically significant, p=0.008)**
Objective Response Rate (ORR – percentage of patients who achieved a partial or complete response to therapy, secondary endpoint)
• **5.5% vs 2.8% (numerical difference)**

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Disease Control Rate (DCR – the percentage of patients who achieved complete response, partial response and stable disease, secondary endpoint)

- **50.5% vs 39.5% (statistically significant, p=0.002)**

Quality of Life (Measured by patient questionnaires, secondary endpoint)

- An improved control of cancer-related symptoms was seen in patients treated with afatinib*: a higher proportion of patients treated with afatinib* reported improvement in cough (43.4% vs 35.2%, p=0.029), shortness of breath (51.3% vs 44.1%, p=0.061) and overall well-being/quality of life (35.7% vs 28.3%, p=0.041) compared with erlotinib[13]

Adverse Events (AEs)

- The rate of severe adverse events (≥grade 3) was similar between afatinib* and erlotinib treatment arms (57.1% vs 57.5%). A higher incidence of severe diarrhoea and stomatitis (mouth sores) was observed with afatinib* compared to erlotinib (grade 3/4 diarrhoea: 9.9/0.5% vs 2.3/0.3%, grade 3 stomatitis: 4.1% vs 0.0%), while a higher incidence of severe rash/acne was reported with erlotinib compared to afatinib* (grade 3 rash/acne: 10.4% vs 5.9%)[13]

Results from **LUX-Head & Neck 1** showed that afatinib* significantly delayed tumour growth versus chemotherapy in patients with recurrent and/or metastatic head and neck squamous cell cancer following failure of first-line chemotherapy.[11]

Patients taking afatinib* experienced a significant delay in tumour growth of 2.6 months versus 1.7 months with chemotherapy which translated into a 20% reduction in risk of disease progression.[11]

LUX-Head & Neck 1[11]
(afatinib* vs methotrexate – a chemotherapy)

Progression-Free Survival (PFS: length of time before tumour starts to progress, primary endpoint)

- **2.6 months vs 1.7 months (statistically significant, p=0.030)**

Objective Response (Tumour shrinkage, secondary endpoint)

- Tumour shrinkage was observed in **34.8%** of patients in the afatinib* arm compared to **22.3%** of patients in the chemotherapy arm

Objective Response Rate (ORR – percentage of patients who achieved a partial or complete response to therapy, secondary endpoint)

- **10.2% vs 5.6% (numerical difference)**

Disease Control Rate (DCR – the percentage of patients who achieved complete response, partial response and stable disease, secondary endpoint)

- **49.1% vs 38.5% (statistically significant, p=0.035)**

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Disease Related Symptoms (secondary endpoint)

- In quality-of-life questionnaires, patients taking afatinib* reported significantly less pain and a delay in time to worsening of symptoms including pain, swallowing and global health status (overall health and quality of life), when compared to chemotherapy

Overall survival (OS: length of time patients live for, secondary endpoint)

- No significant difference between afatinib* and chemotherapy was observed (median 6.8 vs 6.2 months)

Adverse Events (AEs)

- The most frequent drug-related severe adverse events (≥ grade 3) were rash/acne (9.7%) and diarrhoea (9.4%) with afatinib*, and leukopenia (15.6%) and stomatitis (8.1%) with chemotherapy. The most common side effects in patients treated with afatinib* compared to chemotherapy were rash/acne (74.4% vs 8.1%), diarrhoea (72.2% vs 11.9%) and paronychia (nail infection) (14.4% vs. 0%), and with chemotherapy compared to afatinib* were stomatitis (43.1% vs 39.1%), fatigue (31.9% vs 24.7%) and nausea (22.5% vs 20.0%). There were fewer drug-related dose reductions and discontinuations for patients taking afatinib* compared to chemotherapy.

Tolerability

Overall, the side effects of afatinib* were predictable, generally manageable and reversible. In studies to date, drug-related adverse events were largely related to the gastrointestinal tract (diarrhoea) and skin disorders (rash), which is in line with EGFR tyrosine-kinase inhibition.[5-19] For further details, please refer to the adverse events section in each of the above studies (LUX-Lung 3, 5, 6, 8 and LUX-Head and Neck 1).

4. CLINICAL POTENTIAL

The irreversible binding properties of afatinib* and its selective and irreversible ErbB Family Blockade, may potentially provide benefits and broaden potential indications in many cancers. Phase III trials in HNSCC indications and investigations in other tumour types are ongoing.

The results from LUX-Lung 3 and LUX-Lung 6 showcase the positive data of afatinib* compared to standard of care chemotherapy. The consistent results substantiate the efficacy and safety profile of afatinib*, and reinforce confidence in the data.[5,6,7,8]

More recent study results have supported the clinical potential of afatinib*. LUX-Lung 8 directly compared the efficacy and safety of two EGFR-directed treatments in patients with advanced SCC of the lung and demonstrated superior progression-free survival and overall survival of afatinib* compared to erlotinib.[10,13]

The study programme evaluating afatinib* in these indications and beyond will provide more clinical data in order to further establish the efficacy and safety profile of this compound demonstrated in earlier studies.

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5. GIOTRIF® (AFATINIB*) APPROVAL AND REIMBURSEMENT STATUS

Afatinib* is approved for use in the **EU** and the following countries:

Australia	**Argentina**	**Canada**	**Chile**
Costa Rica	**Cuba**	**Ecuador**	**El Salvador**
India	**Israel**	**Japan**	**Korea**
Kuwait	**Malaysia**	**Mexico**	**New Zealand**
Nicaragua	**Paraguay**	**Peru**	**Philippines**
Russia	**Serbia**	**Singapore**	**Switzerland**
Thailand	**Taiwan**	**Uruguay**	**USA**
Venezuela			

Afatinib* is reimbursed in major EU markets, e.g. France, Germany, Italy, Spain, the UK and further European as well as some non-European countries including Japan, Canada, Taiwan and South Korea.

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