GIOTRIF® (AFATINIB*)

BACKGROUNDER

1. What is GIOTRIF® (afatinib*)?
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1. WHAT IS GIOTRIF®* (AFATINIB*)?

Afatinib* (GIOTRIF®) is an irreversible ErbB Family Blocker approved in over 40 countries worldwide including the EU, US, Japan, Taiwan, Canada and Mexico. 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.

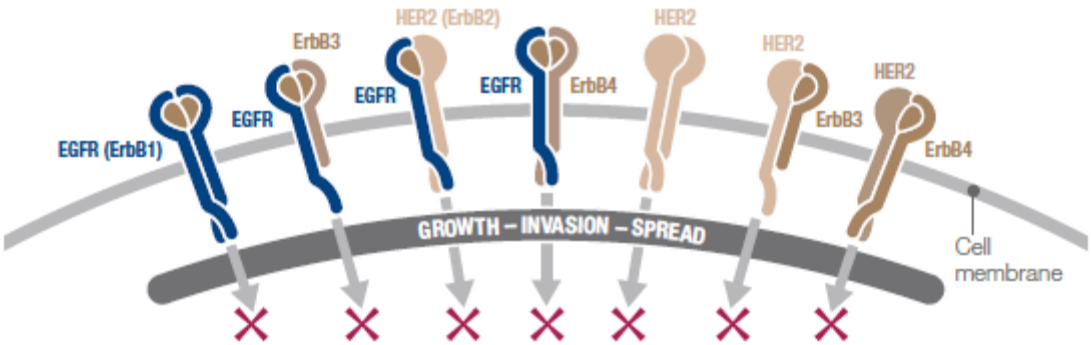
2. HOW DOES GIOTRIF® (AFATINIB*) WORK?

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 over expressed (i.e. 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 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* unique 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]

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

The LUX-Lung clinical trial programme is investigating afatinib* in a number of patient populations with advanced NSCLC. There are currently eight studies in the LUX-Lung clinical trial programme, including investigating the use of afatinib* in patients who have EGFR mutations and those with recurrent disease.

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.

A further study, LUX-Lung 5[9], is the first prospective trial looking at the advantage of continuing treatment with afatinib, in combination with chemotherapy, after the tumour started to grow on afatinib alone (treatment beyond progression).

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 advanced and metastatic NSCLC with an EGFR mutation.[5,6,7,8]

LUX-Lung 3[5,6] (Afatinib* vs pemetrexed/cisplatin)	**LUX-Lung 6**[7,8] (Afatinib* vs gemcitabine/cisplatin)
Progression-Free Survival[6,8] (PFS – time patient is alive without their tumour starting to grow)	
• **11.1 months vs. 6.9 months** for all patients with EGFR mutations by independent review • **13.6 months vs. 6.9 months** for patients with **the most common mutations** (~90% of all patients, del19 and L858R) by independent review	• **11.0 months vs. 5.6 months** for all patients with EGFR mutations by independent review • 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)** • In addition, **47% of afatinib-treated patients are alive and progression-free after 1 year of treatment compared to only 2% on chemotherapy**
• The delay in tumour growth compares well in both trials, substantiating the efficacy of afatinib and the robustness of the data	
Objective Response[6,7] (Tumour Shrinkage)	
• **One in two patients (56%) taking afatinib experienced tumour shrinkage compared to one in four (23%) in the chemotherapy arm**, by independent review	• **In 67% of patients taking afatinib the tumour shrunk significantly in size compared to 23% in the chemotherapy arm,** by independent review
• Tumour shrinkage translated into improvements in disease-related symptoms	

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Disease Related Symptoms[5,8]

- More patients across both studies taking afatinib **experienced improvement of symptoms such as dyspnoea (shortness of breath), cough and chest pain**. Afatinib treatment also delayed the onset of these symptoms

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

- Afatinib patients in LUX-Lung 3 and LUX-Lung 6 reported to have **a significantly better quality of life** (for example, at work and during household activities) than those on chemotherapy

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% discontinued due to rash/acne and none for diarrhoea**

Overall survival (OS)[10]

- 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**) in the post-hoc analysis combining LUX-Lung 3 and LUX-Lung 6.
- One year overall survival benefit (median 33.3 vs. 21.1 months) in patients with the del19 mutation compared to chemotherapy
- More than one year overall survival benefit (median 31.4 vs. 18.4 months) in patients with the del19 mutation compared to chemotherapy
- *In the overall patient population, there was no significant overall survival benefit of afatinib compared with chemotherapy (28.16 vs. 28.22 months for LUX-Lung 3 and 23.1 vs. 23.5 months for LUX-Lung 6)*

Overall survival data presented at ASCO in 2014: Overall survival results from a post-hoc analysis[10] combining the data of of the LUX-Lung 3 and LUX-Lung 6 studies demonstrated that afatinib significantly prolonged survival of lung cancer patients with common EGFR mutations (del19/L585R) compared with standard chemotherapy by a median of 3 months (27.3 to 24.3 months), significantly reducing the risk of death by 19%. The most pronounced reduction in risk of death by 41%, was noted for patients with the most frequent type of EGFR mutation (deletion in exon 19 of the EGFR gene; del19).

Data on prespecified subgroups from the individual trials LUX-Lung 3 and LUX-Lung 6 showed for afatinib a prolongation of survival in lung cancer patients with the most common type of EGFR mutation (del19) compared with standard chemotherapy by a

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median of more than 12 months in both the trials (LUX-Lung 3; 33.3 months compared to 21.1 months, LUX-Lung 6; 31.4 months compared to 18.4 months).

The conclusions of this analysis further substantiate earlier published results on delay in tumour growth (progression-free survival), better control of lung cancer symptoms and adverse events associated with afatinib in comparison with standard chemotherapy.

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).

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.

LUX-Lung 5[9] (afatinib* vs pemetrexed/cisplatin)
Progression-Free Survival (PFS – time patient is alive without their tumour starting to grow)
• **5.6 months vs. 2.8 months**
Objective Response (Tumour Shrinkage)
• **Almost a third of patient patients (32.1%) taking afatinib experienced tumour shrinkage compared to 13.2% in the chemotherapy arm**
• Tumour shrinkage translated into improvements in disease-related symptoms
Overall survival (OS)
• OS was similar in both arms **12.2 vs 12.2 months**
Adverse Events (AEs)
• The most common drug-related AEs observed in the afatinib* treatment arm were diarrhoea, alopecia (hair loss) asthenia (a condition in which the body lacks or has lost strength either as a whole or in any of its parts

Tolerability

The side effects of afatinib* are 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.[5-16]

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5. CLINICAL POTENTIAL

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

The positive results from the Phase III LUX-Lung trials showcase the growing evidence of the superiority of afatinib* over standard of care chemotherapy. The consistent results substantiate the robust efficacy and safety profile of afatinib*, and reinforce confidence in the data.

The study programme evaluating afatinib* in a number of indications will provide more clinical data to further establish the benefits of this compound demonstrated in earlier studies.

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