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GIOTRIF® (AFATINIB*)

BACKGROUNDER

1. WHAT IS GIOTRIF® (AFATINIB*)?

Tyrosine kinase inhibitors (TKIs) are a type of targeted treatment that work inside cancer cells and block signals needed for tumours to grow. Afatinib*, a second-generation TKI, is the first approved irreversible ErbB Family Blocker. It is an oral, once-daily targeted therapy.

Afatinib is approved in more than 70 countries for the first-line treatment of patients with EGFR mutation-positive non-small cell lung cancer (NSCLC) (under the brand names: GIOTRIF® / GILOTRIF® / XOVOLTIB®).

Afatinib is also approved in Europe, US and other markets for the treatment of patients with advanced squamous cell carcinoma (SqCC) of the lung whose disease has progressed (on or) after treatment with platinum-based chemotherapy (under the brand names: GIOTRIF® / GILOTRIF® / XOVOLTIB®).

2. HOW DOES 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 preventing transphosphorylation), that are known to play a critical role in the growth and spread of the most common cancers and those associated with high mortality.

The irreversible binding of afatinib, unlike other compounds which are reversible in that, aims to provide a sustained, selective and complete ErbB Family Blockade. Afatinib's mechanism of action potentially leads 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

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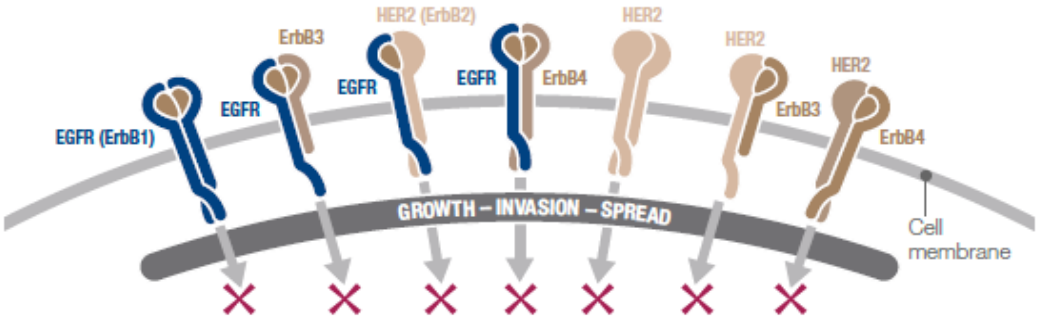
LET'S WORK
ONCOLOGY FROM BOEHRINGER INGELHEIM

Boehringer Ingelheim



The signalling of ErbB3 is blocked indirectly through blocking of transphosphorylation

3. LUX-LUNG CLINICAL TRIAL PROGRAMME

Afatinib has been extensively studied in the LUX-Lung programme – the largest collection of clinical trials of any EGFR TKI, with over 3760 patients in eight studies conducted across the world. The comprehensive programme includes two pivotal studies in the first-line setting (LUX-Lung 3 and 6) as well as two head-to-head studies of afatinib versus first-generation EGFR TKIs (LUX-Lung 7 and 8). The LUX-Lung programme has involved lung cancer specialists across over 680 sites in 40 countries around the world, reflecting the strong partnership between Boehringer Ingelheim and the lung cancer specialist community.

4. AFATINIB FOR THE FIRST-LINE TREATMENT OF EGFR MUTATION-POSITIVE NSCLC

Afatinib has demonstrated significant benefits compared to chemotherapy in the LUX-Lung 3 and 6 trials, as well as compared to first-generation TKI, gefitinib, in the LUX-Lung 7 trial. Adverse events (AEs) for afatinib in these trials were as expected with EGFR inhibition and were manageable.[5,6,7,8]

LUX-Lung 3 [NCT00949650] and LUX-Lung 6 [NCT01121393] 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. Both trials met their primary endpoint of progression-free survival (PFS), as afatinib significantly delayed tumour growth when compared to standard chemotherapy in patients with EGFR mutation-positive NSCLC.[5,7]

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Consistent across both the LUX-Lung 3 and LUX-Lung 6 trials, afatinib, compared to standard chemotherapy, demonstrated:[5,6,7]

- ✓ Significant delay in tumour growth
- ✓ Significant overall survival (OS) benefit
- ✓ Significant tumour shrinkage
- ✓ Significantly better quality of life
- ✓ Clinically meaningful symptom improvement
- ✓ AEs which were as expected with EGFR inhibition, and were predictable and manageable

LUX-Lung 7 [NCT01466660] is the first global, head-to-head trial comparing second- and first-generation EGFR-directed therapies (afatinib and gefitinib respectively) for patients with EGFR mutation-positive NSCLC who received no prior treatment. The Phase IIb trial included 319 patients with advanced stage NSCLC harbouring common EGFR mutations (del19 or L858R). The trial's co-primary endpoints were PFS by independent review, time to treatment failure and OS; and the secondary endpoints included objective tumour response rate (ORR; a clinically meaningful decrease in tumour size), disease control rate, tumour shrinkage, patient-reported outcomes and safety.[8]

In the LUX-Lung 7 trial afatinib, compared to gefitinib, significantly improved:[8]

- ✓ PFS; afatinib reduced the risk of lung cancer progression by 27% compared to gefitinib; the improvement in PFS became more pronounced over time. After two years of treatment, more than twice as many patients on afatinib were alive and progression free than those on gefitinib (after 18 months; 27% vs 15% and after 24 months; 18% vs 8%)
- ✓ Time to treatment failure; patients on afatinib had a significantly longer time on treatment, and risk of treatment failure was reduced by 27% versus gefitinib
- ✓ ORR; significantly more patients had an objective tumour response (ORR; a clinically meaningful decrease in tumour size) with afatinib when compared to gefitinib (70% vs 56%), with a median duration of response of 10.1 months and 8.4 months, respectively

Both afatinib and gefitinib demonstrated similar improvements in patient-reported outcome measures in the LUX-Lung 7 trial with no significant differences in health-related quality of life with afatinib compared to gefitinib treatment. Treatment with both afatinib and gefitinib was generally tolerable, leading to an equal rate of treatment-related discontinuation in both arms (6%). AEs observed in the trial were consistent with the known safety profiles of both treatments.[8]

Dose modification of afatinib was available for patients who met set criteria in order to better manage AEs. As gefitinib is only available in one dose formulation, no dose reduction was foreseen.[8]

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Data for the co-primary endpoint of OS are not yet mature and will be presented in the future.

5. AFATINIB FOR THE TREATMENT OF SQCC OF THE LUNG

LUX-Lung 8 [NCT01523587] is a head-to-head trial in patients with SqCC of the lung whose tumours progressed (on or) after first-line chemotherapy. In the trial, afatinib, compared to erlotinib, demonstrated:[9]

- ✓ Significant delay in progression of lung cancer (PFS, primary endpoint), reducing the risk of cancer progression by 19%
- ✓ Significant improvement in OS (key secondary endpoint), reducing the risk of death by 19%
- ✓ Significantly improved disease control rate
- ✓ An improvement in quality of life and control of cancer symptoms

The rate of severe AEs was similar between the two treatment arms with differences observed in the incidence of certain side effects.[9]

6. AFATINIB TREATMENT BEYOND PROGRESSION

LUX-Lung 5 [NCT01085136] is the first prospective trial looking at the advantage of continuing treatment with afatinib in combination with chemotherapy in NSCLC, after the tumour has started to grow during treatment with 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.[10]

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