AFATINIB*

BACKGROUNDER

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 (EGFR 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.
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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 and LUX-Lung 6.

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

<table>
<thead>
<tr>
<th>LUX-Lung trial</th>
<th>Methods overview</th>
<th>Endpoints overview</th>
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</table>
| LUX-Lung 1<sup>13</sup>  
CT.gov identifier: NCT00656136 | Phase Ib/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<sup>14</sup>  
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<sup>7,8</sup>  
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<sup>15</sup>  
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<sup>16</sup>  
CT.gov identifier: NCT01085136 | Phase III  
Randomised trial  
Afatinitib plus weekly paclitaxel vs investigator's choice of chemotherapy following afatinib monotherapy  
Patients with NSCLC failing previous erlotinib or gefitinib | Primary: PFS  
Secondary: OS, ORR, HRQoL |
| LUX-Lung 6<sup>9,10</sup>  
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 |

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**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.
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).

<table>
<thead>
<tr>
<th><strong>LUX-Lung 3</strong>&lt;sup&gt;7,8&lt;/sup&gt; (afatinib vs pemetrexed/cisplatin)</th>
<th><strong>LUX-Lung 6</strong>&lt;sup&gt;9,10&lt;/sup&gt; (afatinib vs gemcitabine/cisplatin)</th>
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<tbody>
<tr>
<td><strong>PFS</strong>&lt;sup&gt;8,9&lt;/sup&gt; (primary endpoint)</td>
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<tr>
<td>• 11.1 vs 6.9 months for all patients with <em>EGFR</em> mutations by independent review (p=0.001)</td>
<td>• 11.1 vs 5.6 months for all patients with <em>EGFR</em> mutations by independent review (p&lt;0.0001)</td>
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<tr>
<td>• 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)</td>
<td>• 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&lt;0.0001)</td>
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<td>• The delay in tumour growth compared well in both trials, substantiating the efficacy of afatinib and the robustness of the data</td>
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<tr>
<td><strong>OS</strong>&lt;sup&gt;18&lt;/sup&gt; (secondary endpoint)</td>
<td><strong>OS</strong>&lt;sup&gt;18&lt;/sup&gt; (secondary endpoint)</td>
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<tr>
<td>• 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</td>
<td>• 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</td>
</tr>
<tr>
<td>• 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</td>
<td>• 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)</td>
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<tr>
<td><strong>ORR</strong>&lt;sup&gt;8,9&lt;/sup&gt; (tumour shrinkage, secondary endpoint)</td>
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</tr>
<tr>
<td>• Higher ORR was observed in patients taking afatinib (56%) compared with those receiving chemotherapy (23%), as assessed by independent review (p=0.001)</td>
<td>• 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&lt;0.0001)</td>
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<tr>
<td>• Tumour shrinkage translated into improvements in disease-related symptoms</td>
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<tr>
<td><strong>Disease-related symptoms</strong>&lt;sup&gt;7,10&lt;/sup&gt; (secondary endpoint)</td>
<td><strong>Disease-related symptoms</strong>&lt;sup&gt;7,10&lt;/sup&gt; (secondary endpoint)</td>
</tr>
<tr>
<td>• 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</td>
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<tr>
<td><strong>HRQoL</strong>&lt;sup&gt;7,10&lt;/sup&gt; (measured by patient questionnaires, secondary endpoint)</td>
<td><strong>HRQoL</strong>&lt;sup&gt;7,10&lt;/sup&gt; (measured by patient questionnaires, secondary endpoint)</td>
</tr>
<tr>
<td>• 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&lt;0.0001)</td>
<td></td>
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</tbody>
</table>
## LUX-Lung 3\textsuperscript{7,8}
(afatinib vs pemetrexed/cisplatin)

- 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.

## LUX-Lung 6\textsuperscript{9,10}
(afatinib vs gemcitabine/cisplatin)

- 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.

## LUX-Lung 5\textsuperscript{16}
(afatinib + paclitaxel vs investigators’ choice of chemotherapy)

<table>
<thead>
<tr>
<th>PFS (primary endpoint)</th>
<th>OS (secondary endpoint)</th>
<th>ORR (secondary endpoint)</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6 vs 2.8 months (statistically significant, p=0.003)</td>
<td>OS was similar in both arms (12.2 vs 12.2 months, p=0.994)</td>
<td>32.1% of patients taking afatinib experienced tumour shrinkage compared with 13.2% in the chemotherapy arm (p=0.005)</td>
<td>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%)</td>
</tr>
</tbody>
</table>

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

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LUX-Lung 7\textsuperscript{11,17}
(aatifinib vs gefitinib)

<table>
<thead>
<tr>
<th>PFS (primary endpoint)</th>
<th>11.0 vs 10.9 months (statistically significant, p=0.017 by independent review)</th>
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<tbody>
<tr>
<td>TTF</td>
<td>13.7 vs 11.5 months (p=0.007)</td>
</tr>
<tr>
<td>OS</td>
<td>Primary OS analysis: 27.9 vs 25.0 months (p=0.33)</td>
</tr>
<tr>
<td></td>
<td>Mature OS analysis: 27.9 vs 24.5 months (p=0.258)</td>
</tr>
<tr>
<td>ORR (secondary endpoint)</td>
<td>70% vs 56% (p=0.008)</td>
</tr>
<tr>
<td>AEs</td>
<td>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</td>
</tr>
</tbody>
</table>

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

LUX-Lung 8\textsuperscript{12}
(aatifinib vs erlotinib)

<table>
<thead>
<tr>
<th>PFS (primary endpoint)</th>
<th>2.4 vs 1.9 months (statistically significant, p=0.043 by independent review)</th>
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<tbody>
<tr>
<td>ORR (secondary endpoint)</td>
<td>6.0% vs 3.0% (p=0.055)</td>
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<tr>
<td>DCR (secondary endpoint)</td>
<td>51.0% vs 40.0% (statistically significant, p=0.0020)</td>
</tr>
<tr>
<td>HRQoL (secondary endpoint)</td>
<td>More patients had improved overall HRQoL with afatinib than with erlotinib (36% vs 28%, p=0.041)</td>
</tr>
<tr>
<td>OS (secondary endpoint)</td>
<td>OS was significantly greater in the afatinib group than in the erlotinib group (median 7.9 vs 6.8 months, p=0.0077)</td>
</tr>
<tr>
<td>AEs</td>
<td>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%)</td>
</tr>
</tbody>
</table>

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

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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


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).


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