Afatinib in patients with \textit{EGFR} mutation-positive NSCLC harboring uncommon mutations: overview of clinical data

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In patients with adenocarcinoma, the most common type of NSCLC, somatic mutations of EGFR have been reported in:

- ~50% of Asian patients\(^1\),
- 10–15% of Caucasian patients\(^1\), and
- ~26% of Latin American patients\(^2\)

The most frequent EGFR mutations in these populations are the common Del19 and/or L858R mutations\(^3\)

- Exon 19 deletion (Del19) ~45–62%\(^3\)
- Exon 21 L858R insertion (L858R) ~33–40%\(^3\)

~10–15% of tumors harbor uncommon EGFR mutations, comprising mutations in exons 18–21\(^4\)
The current standard of care for first-line treatment of patients with \( \text{EGFR}^{m+} \) NSCLC is an EGFR TKI:\(^5\)
- Reversible first-generation EGFR TKIs: erlotinib\(^6\) and gefitinib\(^7\)
- Irreversible second-generation ErbB family blocker: afatinib\(^8\)
  - In LUX-Lung 7, afatinib demonstrated significantly improved PFS and ORR versus gefitinib in patients with NSCLC harboring common \( \text{EGFR} \) mutations\(^9\)

Other EGFR TKIs are also being assessed as first-line treatment options for patients with Del19/L858R \( \text{EGFR}^{m+} \) NSCLC in Phase III trials:
- Irreversible second-generation ErbB family blocker: dacomitinib (ARCHER 1050\(^{10}\))
- Irreversible third-generation EGFR/T790M inhibitor: osimertinib (FLAURA\(^{11}\))
  - Mature OS data from FLAURA are still not available

\( \text{EGFR}^{m+} \), \( \text{EGFR} \) mutation-positive; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor
Despite the expanse of research into the optimal first-line EGFR TKI for patients with NSCLC and common EGFR mutations, and more recently, the optimal treatment sequence,\textsuperscript{12} there remains a paucity of clinical data on the sensitivity of these EGFR TKIs to uncommon EGFR mutations.
Afatinib reduced cell proliferation and inhibited EGFR phosphorylation at similar concentrations in L858M/L861Q- and L858R-mutant cells

First- and third-generation EGFR TKIs exhibited a decreased capacity to reduce cell proliferation and prevent EGFR phosphorylation in L858M/L861Q cells, compared with L858R-mutant cells

Afatinib has shown similar *in vitro* activity against L861Q and S768I mutations as it has against L858R

- \( \text{IC}_{50} \) values were consistently low across all three cell lines with afatinib\(^\text{13}\)
- \( \text{IC}_{50} \) values were higher and more variable across the cell lines with erlotinib and osimertinib\(^\text{13}\)

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Erlotinib</th>
<th>Osimertinib</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>L858R</td>
<td>L861Q</td>
<td>S768I</td>
</tr>
<tr>
<td></td>
<td>0.2 nM</td>
<td>0.5 nM</td>
<td>0.7 nM</td>
</tr>
</tbody>
</table>

Afatinib reduced cell proliferation and inhibited EGFR phosphorylation at similar concentrations in L858M/L861Q- and L858R-mutant cells\(^\text{14}\)

First- and third-generation EGFR TKIs exhibited a decreased capacity to reduce cell proliferation and prevent EGFR phosphorylation in L858M/L861Q cells, compared with L858R-mutant cells\(^\text{14}\)

\( \text{IC}_{50} \), half maximal inhibitory concentration
Clinical data

Here, we review clinical data for afatinib in $EGFR_m$+ NSCLC harboring uncommon $EGFR$ mutations, including data from the clinical trial and real-world clinical practice settings.

Post-hoc analysis of LUX-Lung 2, 3 and 6$^{15}$

- 75 of 600 patients (13%) treated with afatinib in the three trials had tumors harboring uncommon $EGFR$ mutations.
- Patients were grouped according to mutation status:
  - **Group 1** Point mutations or duplications in exons 18–21, alone or in combination with each other
  - **Group 2** $De$ $novo$ T790M mutation in exon 20, alone or in combination with other mutations
  - **Group 3** Exon 20 insertions
Clinical data (cont’d)

Efficacy outcomes (N=75)

<table>
<thead>
<tr>
<th>Group</th>
<th>Median PFS (95% CI), months</th>
<th>Median OS (95% CI), months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n=38)</td>
<td>10.7 (5.6–14.7)</td>
<td>19.4 (16.4–26.9)</td>
</tr>
<tr>
<td>Group 2 (n=14)</td>
<td>2.9 (1.2–8.3)</td>
<td>14.9 (8.1–24.9)</td>
</tr>
<tr>
<td>Group 3 (n=23)</td>
<td>2.7 (1.8–4.2)</td>
<td>9.2 (4.1–14.2)</td>
</tr>
</tbody>
</table>

ORR* by mutation type in Group 1:
- S768I (n=8): 100%
- G719X (n=18): 78%
- L861Q (n=16): 56%

ORR: 71%, ORR: 14%, ORR: 9%
Based on data from the post-hoc analysis of LUX-Lung 2, 3 and 6, the label for afatinib was expanded by the U.S. Food and Drug Administration to include first-line treatment of patients with metastatic NSCLC whose tumors have non-resistant \textit{EGFR} mutations, including \textbf{L861Q}, \textbf{G719X} and \textbf{S768I}, as detected by an FDA-approved test.

Other labels already include non-resistant uncommon \textit{EGFR} mutations; for example, since 2013, approval by the European Medicines Agency has included NSCLC with activating \textit{EGFR} mutations.
Clinical data (cont’d)

**Ongoing Phase IIIb open-label, single-arm study: interim analysis**

Patients (N=479) received afatinib 40 mg (orally, once daily) until investigator-assessed tumor progression or lack of tolerability

<table>
<thead>
<tr>
<th>Phase IIIb</th>
<th>Patients</th>
<th>Primary endpoint</th>
<th>Other endpoints</th>
<th>ClinicalTrials.gov</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open label, single arm, multicenter</td>
<td>Advanced <em>EGFR</em>+ NSCLC not previously treated with an <em>EGFR</em> TKI; ECOG PS 0–2; Patients with asymptomatic brain metastases† were eligible</td>
<td>Safety assessment; number of SAEs</td>
<td>TTSP,‡ PFS, TRAEs</td>
<td>NCT01953913</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group Performance Status; SAEs, serious adverse events; TRAEs, treatment-related adverse events; TTSP, time to symptomatic progression

*Data from larger Asian patient populations will be evaluated in further analyses of this trial

†For at least 4 weeks on stable doses of medication

‡TTSP = Time from first administration of afatinib to the date of first documented clinically significant symptomatic progression that required a change in or stopping of anti-cancer treatment, according to the investigator’s assessment. Clinical symptomatic progression was assessed by the investigator
Clinical data (cont’d)

<table>
<thead>
<tr>
<th>Mutation type</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>EGFR</em>m+</td>
<td>479 (100)</td>
</tr>
<tr>
<td>Uncommon <em>EGFR</em> mutations§</td>
<td>55 (11)</td>
</tr>
<tr>
<td>T790M</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Exon 20 insertions and T790M</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Exon 20 insertions</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Exon 18–21 point mutations/duplications</td>
<td>35 (7)</td>
</tr>
</tbody>
</table>

§Patients with uncommon *EGFR* mutations only (not including patients with tumors harboring both common and uncommon *EGFR* mutations)
Clinical data (cont’d)

PFS in patients with tumors harboring point mutations or duplications in exons 18–21
(equivalent to **Group 1** in LUX-Lung 2, 3 and 6 post-hoc analysis)

![Estimated survival probability (PFS) graph]

- **Afatinib 40 mg**
  - 25th: 5.52
  - Median: 9.49
  - 75th: NE

<table>
<thead>
<tr>
<th>Time since start of treatment (months)</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at risk:</td>
<td>35</td>
<td>28</td>
<td>25</td>
<td>15</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Afatinib 40 mg</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

NE, not evaluable
Clinical data (cont’d)

Time to symptomatic progression (TTSP) in patients with tumors harboring point mutations or
duplications in exons 18–21 (equivalent to Group 1 in LUX-Lung 2, 3 and 6 post-hoc analysis)

![Graph showing TTSP](image)

- **Afatinib 40 mg**
  - 25th: 5.68
  - Median: NE
  - 75th: NE

**Number at risk:**
- Afatinib 40 mg: 35 31 26 19 14 11 8 7 7 6 5 5 5 1 0 0
Clinical data (cont’d)

Retrospective real-world analysis\textsuperscript{18,19}

- 165 patients with recurrent/metastatic NSCLC were treated with first-line afatinib at a single institute in South Korea\textsuperscript{18}

**EGFR mutation type\textsuperscript{18}**

- Del19 (n=114; 69%)
- L858R (n=37; 22%)
- Uncommon (n=14; 8%)
  - G719X (n=3)
  - G719X + S768I (n=1)
  - Del19 + L747_P753>Q (n=1)
  - Exon 20 insertion (n=1)
  - L861Q (n=3)
  - L858R + H870R (n=1)
  - Del19 + T790M (n=1)
  - L858R + T790M (n=3)
## Clinical data (cont’d)

<table>
<thead>
<tr>
<th>EGFR mutation type</th>
<th>Median PFS, months (^{19})</th>
<th>ORR (^{18*})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon, excluding T790M (n=10)</td>
<td>Not reached</td>
<td>80%</td>
</tr>
<tr>
<td>Uncommon, including T790M (n=4)</td>
<td>4.7</td>
<td>25%</td>
</tr>
<tr>
<td>Common, Del19 (n=114)</td>
<td>19.1</td>
<td></td>
</tr>
<tr>
<td>Common, L858R (n=37)</td>
<td>15.8</td>
<td></td>
</tr>
</tbody>
</table>

*ORR: partial response + complete response

\(^{18*}\) The ORR was calculated using the last observation carried forward method.
Summary

• Afatinib has pre-clinical and clinical activity in patients with NSCLC harboring certain uncommon *EGFR* mutations.

• ORR, PFS and OS outcomes from a post-hoc analysis of LUX-Lung 2, 3 and 6 showed that afatinib was more active in patients with tumors harboring point mutations or duplications in exons 18–21, compared with *de novo* T790M mutations or exon 20 insertions\(^\text{15}\).

• The activity of afatinib against certain uncommon *EGFR* mutations is being substantiated by studies outside of the randomized controlled trial setting, including in the real-world clinical setting, demonstrating high ORR and long PFS\(^\text{17–19}\).
References

7. U.S. FDA 2015. Iressa. Highlights of prescribing information
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