Afatinib in patients with *EGFR* mutation-positive NSCLC harbouring uncommon mutations: overview of clinical data

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Presented at the European Lung Cancer Congress (ELCC), Geneva, Switzerland, 11–14 April 2018
In patients with adenocarcinoma, the most common type of NSCLC, somatic mutations of $EGFR$ have been reported in:

$\sim50\%$ of Asian patients and $10–15\%$ of Caucasian patients\(^1\)

The most frequent $EGFR$ mutations in these populations are the common mutations Del19 and/or L858R\(^2\)

$\sim10–15\%$ of tumours harbour uncommon $EGFR$ mutations, comprising mutations in exons 18–21\(^3\)
Background (cont’d)

- The current standard of care for patients with \textit{EGFRm+} NSCLC is treatment with an EGFR TKI: \cite{4}
  - Reversible first-generation EGFR TKIs: erlotinib\textsuperscript{5} and gefitinib\textsuperscript{6}
  - Irreversible second-generation ErbB family blocker: afatinib\textsuperscript{7}
    - In LUX-Lung 7, afatinib demonstrated significantly improved PFS and ORR versus gefitinib in patients with NSCLC harbouring common \textit{EGFR} mutations\textsuperscript{8}
- Other EGFR TKIs are also being assessed as first-line treatment options for patients with Del19/L858R \textit{EGFRm+} NSCLC, in Phase III trials:
  - Irreversible second-generation ErbB family blocker: dacomitinib (ARCHER 1050\textsuperscript{9})
  - Irreversible third-generation EGFR/T790M inhibitor: osimertinib (FLAURA\textsuperscript{10})
    - Mature OS data from both trials are awaited

\textit{EGFRm+}, \textit{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{11} there remains a paucity of clinical data on the sensitivity of these EGFR TKIs to uncommon *EGFR* mutations.
Background (cont’d)

**Pre-clinical activity against uncommon EGFR mutations**

- Afatinib has shown similar *in vitro* activity against L861Q and S768I as it has against L858R
  - IC$_{50}$ values were consistently low across all three cell lines with afatinib$^{12}$
- IC$_{50}$ values were higher and were more variable across the cell lines with erlotinib and osimertinib treatment$^{12}$

### Table: Pre-clinical activity against uncommon EGFR mutations

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Erlotinib</th>
<th>Osimertinib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L858R</td>
<td>L861Q</td>
<td>S768I</td>
</tr>
<tr>
<td></td>
<td>0.2nM</td>
<td>0.5nM</td>
<td>0.7nM</td>
</tr>
<tr>
<td>L861Q</td>
<td>0.7nM</td>
<td>4.5nM</td>
<td>92nM</td>
</tr>
<tr>
<td>S768I</td>
<td>146nM</td>
<td>49nM</td>
<td>9nM</td>
</tr>
<tr>
<td>L858R</td>
<td>9nM</td>
<td>2.5nM</td>
<td>49nM</td>
</tr>
</tbody>
</table>

- Afatinib reduced cell proliferation and inhibited EGFR phosphorylation at similar concentrations in L858M/L861Q-and L858R-mutant cells$^{13}$
  - 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$^{13}$

IC$_{50}$, half maximal inhibitory concentration
Clinical data

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

Post-hoc analysis of LUX-Lung 2, 3 and 6

- 75 of 600 patients (13%) treated with afatinib in the three trials had tumours harbouring 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 in exon 20, alone or in combination with other mutations
  - **Group 3**  Exon 20 insertions
Clinical data (cont’d)

Post-hoc analysis of LUX-Lung 2, 3 and 6

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>

CI, confidence interval

*ORR: partial response + complete response
U.S. label expansion: first-line afatinib for patients with metastatic NSCLC harbouring non-resistant \textit{EGFR} mutations\textsuperscript{6}

Based on data from the post-hoc analysis of LUX-Lung 2, 3 and 6\textsuperscript{14}, 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 tumours have non-resistant \textit{EGFR} mutations, including \textbf{L861Q}, \textbf{G719X} and \textbf{S768I}, as detected by an FDA-approved test\textsuperscript{7}

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\textsuperscript{15}
Clinical data

Ongoing Phase IIIb open-label, single-arm study: interim analysis*16

Patients (N=479) received afatinib 40 mg (orally, once daily) until investigator-assessed tumour 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, multicentre</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 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)

Ongoing Phase IIIb open-label, single-arm study: interim analysis*16

<table>
<thead>
<tr>
<th>Mutation type</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFRm+</td>
<td>479 (100.0)</td>
</tr>
<tr>
<td>Uncommon EGFR 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 tumours harbouring both common and uncommon EGFR mutations)
Clinical data (cont’d)

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

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

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Number at risk:
- Afatinib 40 mg: 35, 28, 25, 15, 12, 8, 7, 6, 6, 6, 5, 3, 3, 0, 0, 0

NE, not evaluable
Clinical data (cont’d)

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

Number at risk:
Afatinib 40 mg          35 31 26 19 14 11 8 7 7 6 5 5 5 1 0 0

Months since start of treatment

Estimated survival probability (TTSP)

Afatinib 40 mg          25th  Median  75th
5.68  NE       NE
Clinical data (cont’d)

Retrospective real-world analysis\textsuperscript{17}

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

\textit{EGFR} mutation type

- 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[^18]</th>
<th>ORR[^17]*</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>p=0.01</td>
</tr>
<tr>
<td>Common, L858R (n=37)</td>
<td>15.1</td>
<td>-</td>
</tr>
</tbody>
</table>

[^18]: Months
[^17]: ORR: partial response + complete response
Summary

• Afatinib has shown pre-clinical and clinical activity in patients with NSCLC harbouring certain uncommon EGFR mutations

• ORR, PFS and OS outcomes from a post-hoc analysis of LUX-Lung 2, 3 and 6 suggested that afatinib was more active in patients with tumours harbouring point mutations or duplications in exons 18–21, compared with de novo T790M or exon 20 insertions \textsuperscript{14}

• The activity of afatinib against certain uncommon EGFR mutations is being substantiated by studies outside of the randomised controlled trial setting, including in the real-world clinical setting, demonstrating high ORR and long PFS \textsuperscript{16–18}
References

5. U.S. FDA 2004. Tarceva. highlights of prescribing information
7. U.S. FDA 2018. Gilotrif. highlights of prescribing information
Acknowledgements

Development of this poster was supported by Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version.

Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Laura Winton, of GeoMed, an Ashfield company, part of UDG Healthcare plc, during the development of this poster.

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