Efficacy of EGFR TKIs in Patients With NSCLC With Uncommon EGFR Mutations

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Faculty Disclosure

- Honoraria: AstraZeneca; Boehringer Ingelheim; Chugai Pharma; Kyowa Hakko Kirin; Lilly; Ono Pharmaceutical; Pfizer; Roche; Taiho Pharmaceutical
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EGFR Mutations in NSCLC

Mitsudomi et al., Cancer Science, 2007
Common or Uncommon/Non-classical (N=1,632)

Complex uncommon/non-classical, **without** Del19 and L858R: 2%

Uncommon/non-classical mutation **with** Del19/L858R: 6%

**Single, uncommon/non-classical mutations or insertion: 8%**

<table>
<thead>
<tr>
<th>Exon</th>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon 21</td>
<td>single</td>
<td>1%</td>
</tr>
<tr>
<td>Exon 20</td>
<td>single</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>insertions</td>
<td>3%</td>
</tr>
<tr>
<td>Exon 19</td>
<td>single</td>
<td>0.4%</td>
</tr>
<tr>
<td>Exon 18</td>
<td>single</td>
<td>3%</td>
</tr>
</tbody>
</table>

- **Del19** (n=354)
  - 42%

- **Ex21 L858R** (n=356)
  - 42%
In Vitro Activity of First-, Second-, and Third-Generation TKIs Against Uncommon EGFR Mutations

• Irreversible second- and third-generation TKIs overcome resistance induced by uncommon secondary mutations

In Vitro Activity of First-, Second-, and Third-Generation TKIs Against Uncommon \textit{EGFR} Mutations

- In separate assays, first- and third-generation TKIs demonstrated reduced activity against cell lines harbouring uncommon mutations, whereas the response to afatinib was similar across cell lines.

TKI = tyrosine kinase inhibitor; IC\textsubscript{50} = 50\% inhibitory concentration.

**EGFR Exon 18 Mutations in Lung Cancer: Molecular Predictors of Augmented Sensitivity to Afatinib as Compared with First- or Third-Generation TKIs**

- Among 1,402 *EGFR* mutations, Del19, L858R, and Ins20 were detected in 40%, 47%, and 4%, respectively. Exon 18 mutations, including G719X, E709X, and Del18, were present in 3.2%.

- Patients with lung cancers harbouring G719X exhibited higher response rate to afatinib (80%) than to 1G TKIs (35%–56%).

Kobayashi Y et al. CCR 2015.
Case Report: Afatinib in a TKI-Pretreated Patient With EGFR L858M/L861Q (in cis)

- 62-year-old Caucasian female with extensive involvement of a poorly differentiated adenocarcinoma
- Worsening disease with 4 months of erlotinib and 4 months of chemotherapy
- Radiographic response 2 months after initiation of afatinib
- Remained on afatinib, with Grade 1 diarrhoea as her only side effect, for 10 months and continues treatment
Clinical Data in TKI-Pretreated Patients: Radiographic Responses After Suboptimal Response to Other EGFR-TKIs

Cell-free DNA tumor response. Cell-free DNA analysis of total somatic alteration burden detected over five time points and the EGFR variant-specific results over time reflect responses to changes in matched therapy. TP53, tumor protein p53

Clinical Data in TKI-Pretreated Patients: Best Response in Patients With LMD Harbouring Uncommon Mutations

- 3/11 patients with leptomeningeal carcinoma treated with afatinib harboured an uncommon Exon 18 mutation (L719X)

- Median CSF concentration in all 11 patients was 2.88 nM (afatinib’s IC\textsubscript{50} for EGFR being 0.5 nM). PFS and OS in patients harbouring a G719X mutation were 5.6 months (2.0-10.0) and 7.0 months (5.6 ongoing to 13.0)

| Concentration of Afatinib in Plasma and CSF, Penetration Rate, and Efficacy in Patients With \textit{EGFR} Mutation-Positive NSCLC With LMD |
|---|---|---|---|---|
| | Plasma | CSF | Best Response | PFS (Days) | OS (Days) |
| 1 | 146.9 | NE | PR | 309 | 396 |
| 2 | 192.0 | 6.0 | PD | 61 | 212 |
| 3 | 767.6 | 0.8 | PR | 171\textsuperscript{a} | 171\textsuperscript{b} |

\textsuperscript{a}Treatment continued after data cutoff; \textsuperscript{b}Censored at data cutoff (patient still alive).

LMD = leptomeningeal disease; CSF = cerebrospinal fluid; PFS = progression-free survival; OS = overall survival; NE = Not evaluated; PR = partial response; PD = progressive disease.

Clinical Data in TKI-Pretreated Patients: Time to Treatment Failure With Afatinib

- 66 uncommon mutations were reported (18.4% of all known EGFR mutations in the compassionate-use programme)
  - Majority of patients (67%) received afatinib as third- or fourth-line treatment, with median treatment duration of 3.6 months
- No significant difference between median TTF for patients with uncommon/non-classical mutations (3.6 months) compared with those with Del19 (4.6 months) or L858R (5.8 months) mutations

**Distribution of the 60 Rare EGFR Mutations (N=60)**

- Complex mutations incl. T790M, 29 (48%)
- Complex mutations, 9 (15%)
- Exon 18 substitution, 1, 2%
- Exon 19 insertion/deletion, 2, 3%
- Exon 19 substitution, 4, 7%
- Exon 20 insertion, 3, 5%
- T790M, 1, 2%
- Exon 21 substitution, 4, 7%

**TTF = time to treatment failure.**

First-line Clinical Data: Retrospective Analysis of PFS in 57 Patients Treated With Afatinib or First-Generation TKIs

- In all mutation groups analysed, the afatinib group exhibited longer median PFS compared with first-generation TKIs
  - Entire uncommon mutations cohort, except exon 20 insertions: 11.0 mo vs 3.6 mo
  - G719X, S768I, or L861Q: 18.3 mo vs 2.6 mo
  - Uncommon mutations with Del19 or L858R: 11.0 mo vs 8.2 mo
    - Del19+ 18G721D; Del19+ 19L732P; Del19+ 20L792P; Del19+ 20S768I + 20V774M; Del19+ 21L858R + 21K860I; 21L858R + 18E709X; 21L858R + 20S768I; 21L858R + 20V786E; 21L858R + 20T790M; 21L858R + 20 insertion; 21L858R + 21L833VI; 21L858R + 21K860I; 21L858R + 18G719X +20 insertion
  - Uncommon mutation alone or in combination with other uncommon mutations: 18.3 mo vs 2.8 mo

CI = confidence interval. *exon 20 insertions (except A763_Y764 insFQEA).

First-line Clinical Data: Prospective Efficacy Assessments in the LUX-Lung Programme

- Of 600 patients given afatinib in LUX-Lung 2/3/6, 75 (12%) patients had uncommon EGFR mutations\(^1\)
- The LUX-Lung programme provides the largest series of prospective efficacy data in uncommon mutations\(^1-4\)

### LUX-Lung 2
**Phase 2**
\((N=129)^5\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Afatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line of treatment</td>
<td>First- and second-line (after chemotherapy)</td>
</tr>
<tr>
<td>Mutation test</td>
<td>Direct sequ. (central)</td>
</tr>
<tr>
<td>Common mutations</td>
<td>Del19=52</td>
</tr>
<tr>
<td></td>
<td>L858R=54</td>
</tr>
<tr>
<td>Uncommon mutations; treated with afatinib(^4)</td>
<td>N=23</td>
</tr>
<tr>
<td></td>
<td>N=23</td>
</tr>
</tbody>
</table>

### LUX-Lung 3
**Phase 3**
\((N=345)^6\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Afatinib vs Cis/Pem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line of treatment</td>
<td>First-line</td>
</tr>
<tr>
<td>Mutation test</td>
<td>EGFR29(^a) (central)</td>
</tr>
<tr>
<td>Common mutations</td>
<td>Del19=170</td>
</tr>
<tr>
<td></td>
<td>L858R=138</td>
</tr>
<tr>
<td>Uncommon mutations; treated with afatinib(^4)</td>
<td>N=37</td>
</tr>
<tr>
<td></td>
<td>N=26</td>
</tr>
</tbody>
</table>

### LUX-Lung 6
**Phase 3**
\((N=364)^4\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Afatinib vs Cis/Gem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line of treatment</td>
<td>First-line</td>
</tr>
<tr>
<td>Mutation test</td>
<td>EGFR29(^a) (central)</td>
</tr>
<tr>
<td>Common mutations</td>
<td>Del19=186</td>
</tr>
<tr>
<td></td>
<td>L858R=138</td>
</tr>
<tr>
<td>Uncommon mutations; treated with afatinib(^4)</td>
<td>N=40</td>
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<tr>
<td></td>
<td>N=26</td>
</tr>
</tbody>
</table>


LUX-Lung 2, 3, and 6: Tumour Shrinkage by Independent Review (n=67\textsuperscript{a})

- 3 patients in group 1 achieved complete response
  - 1 each with G719X, K739_1744dup6, and L858R+Q709G/V

\textsuperscript{a}8 patients were not included because of insufficient data.
\textsuperscript{b}T790M alone.

# LUX-Lung 2, 3, and 6: Response Rate, PFS, and OS by Independent Review

<table>
<thead>
<tr>
<th></th>
<th>T790M (n=14)</th>
<th>Exon 20 ins (n=23)</th>
<th>Mut/Dup Exon 18-21 (n=38)</th>
<th>G719X (n=18)</th>
<th>L861Q (n=16)</th>
<th>S768I (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rate (%)</strong></td>
<td>14.3</td>
<td>8.7</td>
<td>71.1</td>
<td>77.8</td>
<td>56.3</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>PFS (mo)</strong></td>
<td>2.9</td>
<td>2.7</td>
<td>10.7</td>
<td>13.8</td>
<td>8.2</td>
<td>14.7</td>
</tr>
<tr>
<td><strong>OS (mo)</strong></td>
<td>14.9</td>
<td>9.2</td>
<td>19.4</td>
<td>26.9</td>
<td>17.1</td>
<td>NE</td>
</tr>
</tbody>
</table>
Summary

• Afatinib has shown preclinical and clinical activity in TKI-naive and TKI-pretreated patients with NSCLC harbouring uncommon EGFR mutations.

• Activity of afatinib against uncommon EGFR mutations in patients with LMD was also reported.

• Afatinib was especially active in NSCLC tumours harbouring point mutations or duplications in exons 18-21 (e.g., G719X, S768I, L861Q K739_1744dup6, and L858R+Q709G/V).

• Anecdotal data from erlotinib/gefitinib trials show variable and mainly limited responses to these EGFR TKIs in patients with NSCLC harbouring uncommon mutations.

• These data could help inform clinical decisions for patients with NSCLC harbouring uncommon EGFR mutations.
Yokohama, when sunny, and in later fall...

We are HERE

Just 3 train stops, or 30 min. walk!

Ocean liner Hikawa maru, Yamashita Park