Impact of afatinib dosing on safety and effectiveness in patients with \textit{EGFR} mutation-positive advanced NSCLC in a real-world setting (RealGiDo)

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Background

- Randomised controlled trials (RCTs) are a trusted standard for assessing safety and efficacy, but may not always reflect real-world experience
  - RCTs generally involve select groups of patients and are set in well-defined, controlled clinical conditions
- In the real-world, patients may be less compliant, and have poorer prognostic factors and/or more co-morbidities
- Further, routine medical practice may differ from that specified in clinical trial protocols
- In the LUX-Lung clinical trials involving patients with EGFR mutation-positive (EGFRm+) NSCLC, the incidence and severity of adverse events was reduced by the use of tolerability-guided dose adjustments, without compromising efficacy\(^1,2\)
- We report findings from the RealGiDo study, which evaluated the impact of afatinib dose adjustment on efficacy and safety in a real-world setting
Methods

Study design and patients

• Non-interventional, observational study

• Conducted at 29 sites across 13 countries worldwide (Austria, Canada, France, Germany, Italy, Japan, South Korea, Mexico, Poland, Singapore, Spain, Taiwan, and United States; NCT02751879)
  – A maximum of 15 patients were enrolled per site

• Retrospective review of medical records from consecutive patients with EGFRm+ (Del19/L858R) tyrosine kinase inhibitor (TKI)-naïve advanced NSCLC who were treated first-line with afatinib within the approved label
  – Patients provided written informed consent where required
  – Patients were excluded if they had been treated in a clinical trial
  – To avoid early censoring and enable collection of mature data, inclusion was restricted to patients with treatment initiation ≥6 months prior to enrollment
  – However, patients who discontinued afatinib before completing 6 months of treatment (e.g. due to toxicity or progressive disease) were included to prevent selection bias
Methods (cont…)

Primary endpoints

Safety
Percentage of patients with ADRs* by severity

Effectiveness
TTF† with afatinib
TTP with afatinib

Secondary endpoints

Percentage of patients receiving a modified starting dose of afatinib
Reasons for modifying the starting dose

*ADR, adverse drug reaction; graded using Common Terminology Criteria for Adverse Events, version 4.0.
†TTF, time to treatment failure; synonymous with time on treatment
TTP, time to progression
Results

• 228 patients were included
• Baseline characteristics were consistent with the pivotal, global, Phase III LUX-Lung 3 trial, with the exception of:
  – More Del19 patients (78% vs 49%)
  – Fewer Asian patients (44% vs 72%)
  – 12% had Eastern Cooperative Oncology Group (ECOG) performance status 2/3 (vs none in LUX-Lung 3)
Results (cont…)

Patient demographics and disease characteristics

<table>
<thead>
<tr>
<th>N (%)</th>
<th>RealGiDo</th>
<th>LUX-Lung 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any starting dose (n=228)</td>
<td>Starting dose ≤30 mg (n=71)</td>
</tr>
<tr>
<td>Female</td>
<td>138 (60.5)</td>
<td>48 (67.6)</td>
</tr>
<tr>
<td>Median age, yr (range)</td>
<td>67.0 (32–90)</td>
<td>69.0 (35–85)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>96 (42.1)</td>
<td>37 (52.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>100 (43.9)</td>
<td>26 (36.6)</td>
</tr>
<tr>
<td>Stage IV disease</td>
<td>216 (94.7)</td>
<td>66 (93.0)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>90 (39.5)</td>
<td>25 (35.2)</td>
</tr>
<tr>
<td>1</td>
<td>102 (44.7)</td>
<td>31 (43.7)</td>
</tr>
<tr>
<td>2/3</td>
<td>27 (11.9)</td>
<td>8 (11.3)</td>
</tr>
</tbody>
</table>

EGFR mutation

<table>
<thead>
<tr>
<th></th>
<th>Del19</th>
<th>L858R</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>178 (78.1)</td>
<td>49 (21.5)</td>
</tr>
<tr>
<td></td>
<td>59 (83.1)</td>
<td>12 (16.9)</td>
</tr>
<tr>
<td></td>
<td>117 (75.5)</td>
<td>37 (23.9)</td>
</tr>
<tr>
<td></td>
<td>112 (48.7)</td>
<td>91 (39.6)</td>
</tr>
</tbody>
</table>
Results (cont…)

- 31% of patients received an afatinib starting dose of <40 mg/day; 20% of these patients had dose increases during the study
- The main reason for dose modification was ADRs
- 78% of patients in RealGiDo had a dose modification
- Among patients who received a starting dose of afatinib 40 mg/day and had a dose modification within the first 6 months (n=90), data were consistent with LUX-Lung 3:
  - Most dose reductions occurred within the first 6 months of treatment (86% in RealGiDo and LUX-Lung 3)
  - The rate of dose reductions was numerically higher in RealGiDo (67% RealGiDo vs 53% LUX-Lung 3)
Results (cont…)

Afatinib starting dose in RealGiDo:
- 50 mg: 0.9%
- 40 mg: 0.9%
- 30 mg: 30.3%
- 20 mg: 68.0%
- Other: 6.8%

Reason given for a modified starting dose:
- Previous experience with EGFR TKIs: 15.0%
- Institutional standard: 31.5%
- Investigators decision: 41.1%
- Patient characteristics: 6.8%
- Other: 5.4%
Results (cont…)

Proportion of patients who started on afatinib 40 mg and had a dose reduction within the first 6 months (overall and by patient subgroup): RealGiDo compared with LUX-Lung 3

Patients with dose reductions at any time
Patients with dose reductions within first 6 months

Characteristics of patients with dose reductions

- Male patients
- Female patients
- <65 years
- ≥65 years
- <50 kg
- ≥50 kg
- Caucasian
- Japanese
- Asian
- ECOG PS 0
- ECOG PS 1
- ECOG PS 2
- ECOG PS 3
- Del19
- L858R

Patients with dose reductions (%)

- LUX-Lung 3
- RealGiDo
## Safety: comparison to LUX-Lung 3

<table>
<thead>
<tr>
<th></th>
<th>RealGiDo Any starting dose</th>
<th>RealGiDo Starting dose 40 mg</th>
<th>LUX-Lung 3 Starting dose 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>228 (100)</td>
<td>155 (100)</td>
<td>229 (100)</td>
</tr>
<tr>
<td>Drug-related adverse event (DRAE)</td>
<td>215 (94.3)</td>
<td>146 (94.2)</td>
<td>229 (100)</td>
</tr>
<tr>
<td>DRAEs grade ≥3</td>
<td>56 (24.6)</td>
<td>44 (28.4)</td>
<td>112 (48.9)</td>
</tr>
<tr>
<td>DRAEs leading to discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to rash</td>
<td>2 (0.9)</td>
<td>2 (1.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Discontinuation due to diarrhea</td>
<td>8 (3.5)</td>
<td>5 (3.2)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Drug-related serious AE</td>
<td>15 (6.6)</td>
<td>8 (5.2)</td>
<td>32 (14.0)</td>
</tr>
<tr>
<td>Most frequent drug-related ADRs/AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash/acne</td>
<td>143 (62.7)</td>
<td>95 (61.3)</td>
<td>204 (89.1)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>171 (75.0)</td>
<td>120 (77.4)</td>
<td>219 (95.2)</td>
</tr>
<tr>
<td>Paronychia/nail effect</td>
<td>111 (48.7)</td>
<td>73 (47.1)</td>
<td>130 (56.8)</td>
</tr>
<tr>
<td>Stomatitis/mucositis</td>
<td>78 (34.2)</td>
<td>58 (37.4)</td>
<td>165 (72.1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (0.9)</td>
<td>1 (0.7)</td>
<td>39 (17.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (3.1)</td>
<td>6 (3.9)</td>
<td>40 (17.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (3.5)</td>
<td>3 (1.9)</td>
<td>41 (17.9)</td>
</tr>
<tr>
<td>Dry skin/pruritus</td>
<td>60 (26.3)</td>
<td>32 (20.7)</td>
<td>67 (29.3)</td>
</tr>
</tbody>
</table>
Safety: comparison to LUX-Lung 3 (cont…)

- No new safety signals were identified in RealGiDo
- Among the 90 patients who received a starting dose of afatinib 40 mg/day and had a dose modification within the first 6 months:
  - 72 (98.6%) experienced an ADR of any grade prior to dose modification, compared with 52 (71.2%) after dose modification
  - Dose reductions also led to decreases in severity of ADRs
Effectiveness

ADRs in patients receiving afatinib 40 mg/day who had a dose reduction within 6 months (n=90)

ADRs by starting dose

- Pre-dose modification
  - Grade 4: 11.0%
  - Grade 3: 57.5%
  - Grade 2: 37.0%
  - Grade 1: 12.3%
- Post-dose modification
  - Grade 4: 1.4%
  - Grade 3: 27.4%
  - Grade 2: 12.3%
  - Grade 1: 20.6%

- Started on ≥40 mg (n=157)
  - Grade 4: 3.2%
  - Grade 3: 24.8%
  - Grade 2: 44.6%
  - Grade 1: 21.0%
- Started on ≤30 mg (n=71)
  - Grade 4: 16.9%
  - Grade 3: 57.8%
  - Grade 2: 21.1%
  - Grade 1: 21.1%
Effectiveness (cont…)

![Graph showing time to treatment failure](image)

<table>
<thead>
<tr>
<th>Group</th>
<th>Median TTF (months), 95% CI</th>
<th>Estimated 12 / 18 month rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥40 mg in first 6 months (n=66)</td>
<td>19.5 (13.4–NR)</td>
<td>70% / 53%</td>
</tr>
<tr>
<td>Reduced to &lt;40 mg within first 6 months (n=91)</td>
<td>17.7 (14.5–21.5)</td>
<td>74% / 50%</td>
</tr>
<tr>
<td>Started on ≤30 mg (n=71)</td>
<td>19.4 (12.9–NR)</td>
<td>66% / 53%</td>
</tr>
</tbody>
</table>

p=0.5431
Effectiveness (cont…)

Time to progression

- ≥40 mg in first 6 months (n=66)
- Reduced to <40 mg within first 6 months (n=91)
- Started on ≤30 mg (n=71)

<table>
<thead>
<tr>
<th></th>
<th>≥40 mg in first 6 months (n=66)</th>
<th>Reduced to &lt;40 mg within first 6 months (n=91)</th>
<th>Started on ≤30 mg (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TTP (months), 95% CI</td>
<td>29.0 (17.9–NR)</td>
<td>20.0 (14.7–23.0)</td>
<td>25.9 (17.3–NR)</td>
</tr>
<tr>
<td>Total population</td>
<td>20.8 (19.1–25.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated 12 / 18 month rate</td>
<td>79% / 65%</td>
<td>84% / 60%</td>
<td>86% / 64%</td>
</tr>
</tbody>
</table>
Key findings and conclusions

• Dose adjustments with afatinib in real-world practice reduced the frequency and intensity of ADRs without impacting effectiveness.

• As seen in the LUX-Lung trials, the effectiveness of afatinib (as shown by overall median TTF and TTP of 18.7 and 20.8 months, respectively) was consistent regardless of whether patients had a dose reduction or a modified starting dose.

• These results show that outcomes can be optimised by tailoring afatinib dose based on individual patient characteristics and ADRs.
References


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