Prevalence of *EGFR* T790M mutation in NSCLC patients after afatinib failure, and subsequent response to osimertinib

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Targeted treatment with first- or second-generation EGFR TKIs has become the standard first-line treatment for patients with advanced EGFRm+ NSCLC. First-generation reversible TKIs include Gefitinib and Erlotinib. Second-generation irreversible ErbB family blocker is Afatinib. All have improved PFS and ORR versus chemotherapy in Phase III studies. Afatinib improved OS versus chemotherapy in Del19+ patients in Phase III studies. Afatinib improved PFS, ORR, and TTF versus gefitinib in a Phase IIb study. Disease progression usually occurs after 9–14 months of treatment.
The ‘gatekeeper’ EGFR T790M mutation is the most common mechanism of acquired resistance to erlotinib and gefitinib, with prevalence rates of 49–69%\textsuperscript{10–12}.

Available data suggest that development of the EFGR T790M mutation may also be the predominant mechanism of resistance to afatinib\textsuperscript{12,13}.

- In the Phase I/II AURA study, 68% of patients with acquired resistance to afatinib had the EGFR T790M mutation\textsuperscript{12}.
- In a Taiwanese analysis, 48% of patients with acquired resistance to afatinib had the EGFR T790M mutation\textsuperscript{13}.

However, further data on resistance mechanisms to afatinib are needed, particularly in Caucasian patients who receive first-line afatinib.
Background (cont’d)

- Osimertinib is an irreversible EGFR TKI that is selective for both EGFR-activating and T790M-resistance mutations\textsuperscript{14}
  - In a Phase III study, osimertinib significantly improved PFS and ORR versus chemotherapy in patients with $EGFR$ T790M-positive advanced NSCLC who had progressed after first-line treatment with a first- or second-generation TKI\textsuperscript{14}
  - Most patients in this study had received erlotinib and gefitinib as first-line treatment, with only 20/279 (7\%) patients receiving osimertinib after first-line afatinib\textsuperscript{14}
- However, emerging data indicate that clinical outcomes in patients who receive osimertinib following afatinib are favorable
  - In a retrospective analysis of patients treated in LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7, median duration of treatment with osimertinib was 20.2 months (95\% CI: 12.8–31.5) in patients who had previously received afatinib\textsuperscript{15}

\textit{CI}, confidence interval
Response to osimertinib and chemotherapy after a first- or second-generation TKI in a Phase III study\textsuperscript{14} (\textit{EGFR} T790M-positive advanced NSCLC)

<table>
<thead>
<tr>
<th></th>
<th>Osimertinib (n=279)</th>
<th>Platinum-pemetrexed (n=140)</th>
<th>HR (95% CI); p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS, months</strong></td>
<td>Median 10.1 (8.3–12.3)</td>
<td>Median 4.4 (4.2–5.6)</td>
<td>0.30 (0.23–0.41); &lt;0.001</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>71 (65–76)</td>
<td>31 (24–40)</td>
<td>5.39 (3.47–8.48); &lt;0.001</td>
</tr>
<tr>
<td><strong>DCR, %</strong></td>
<td>93 (90–96)</td>
<td>74 (66–81)</td>
<td>4.76 (2.64–8.84); &lt;0.001</td>
</tr>
</tbody>
</table>

DCR, disease control rate; HR, hazard ratio; OR, odds ratio
Objectives

• To identify the prevalence of the *EGFR* T790M mutation in patients who progressed after treatment with afatinib
• To assess the response to osimertinib after afatinib in patients with the *EGFR* T790M mutation
Methods

• Single-center, retrospective analysis of patients with EGFRm+ stage IV adenocarcinoma of the lung
• Included all patients who progressed between April 2015 and April 2017 after initially achieving ≥3 months’ disease control with afatinib at the Department of Respiratory and Critical Care Medicine and the Ludwig Boltzmann Institute of COPD and Respiratory Epidemiology, Otto Wagner Hospital, Vienna, Austria
• Tumor responses were assessed by centralized radiological review according to RECIST v1.1

CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease
Baseline characteristics

- 48 patients were included in this analysis; median age was 65 years (range: 34–89)
- 11 (23%) patients had received first-generation EGFR TKIs prior to afatinib
Baseline characteristics (cont’d)

Baseline characteristics for the overall cohort

Gender
- 65% female
- 35% male

Race
- Caucasian (92%)
- Asian (8%)

Smoking status
- Never smokers (79%)
- Current smokers (2%)
- Ex-smokers (19%)

Brain metastases
- No brain metastases (83%)
- Brain metastases (17%)

EGFR mutation status
- Del19 (58%)
- L858R (25%)
- Other EGFR mutation (17%)

Treatment line
- First-line afatinib (75%)
- Second-line afatinib (19%)
- Third-line afatinib (6%)

Brain metastases (17%)
No brain metastases (83%)
Prevalence of acquired T790M mutation

- 27/48 (56%) patients who progressed with afatinib tested positive for the EGFR T790M mutation

  Positive 27 (56%)  Negative 21 (44%)

- Additional tissue re-biopsy was carried out in 34 patients to confirm liquid biopsy findings
  – Test results were aligned in 31/34 patients, giving a concordance rate of 91% between the two tests

- Baseline characteristics of the 27 patients who acquired the EGFR T790M mutation were comparable to those of the overall cohort
  – 67%, 22%, and 11% of patients received afatinib in the first, second, and third lines, respectively
  – 8 (30%) patients had received first-generation EGFR TKIs prior to afatinib
Efficacy

Response to afatinib
• ORR was 90% (43/48) in all patients treated with afatinib and 93% (25/27) in patients who acquired an \textit{EGFR} T790M mutation
  – ORRs were higher than in previous studies, as this analysis only included patients who had achieved ≥3 months’ disease control with afatinib before progression\textsuperscript{5,6,8}
Efficacy (cont’d)

- Duration of response (CR, PR, or SD) did not appear to correlate with the emergence of the \textit{EGFR} T790M mutation, the type of \textit{EGFR} mutation at baseline, or any other defined parameter.

<table>
<thead>
<tr>
<th>Duration of response (CR, PR, or SD)</th>
<th>All patients (N=48)</th>
<th>Acquired T790M (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months (95% CI)</td>
<td>12.5 (9–14)</td>
<td>13 (9–17)</td>
</tr>
<tr>
<td>≥6 months, n (%)</td>
<td>42 (88)</td>
<td>25 (93)</td>
</tr>
<tr>
<td>≥12 months, n (%)</td>
<td>25 (52)</td>
<td>16 (59)</td>
</tr>
<tr>
<td>≥18 months, n (%)</td>
<td>10 (21)</td>
<td>7 (26)</td>
</tr>
<tr>
<td>≥24 months, n (%)</td>
<td>4 (8)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>
Efficacy (cont’d)

Response to osimertinib

• ORR with osimertinib was 81% among the 27 patients who had disease progression and developed the *EGFR T790M* mutation after initially achieving ≥3 months’ disease control with afatinib.

NE, not evaluable; PD, progressive disease
Efficacy (cont’d)

- Data for duration of response to osimertinib are immature
- At the time of analysis, osimertinib treatment was ongoing in 11 (41%) patients

Median time on sequential treatment with afatinib and osimertinib was 25.0 months (95% CI: 20–33 months)
Key findings and conclusions

Prevalence of acquired T790M mutation
• In this single-center, real-world analysis, the EGFR T790M mutation was present in 56% of patients who progressed after initially achieving ≥3 months’ disease control with afatinib
  – This is consistent with prevalence rates of 48–68% in previous analyses of patients with acquired resistance to afatinib, and 49–69% among patients who progressed on first-generation EGFR TKI treatment10–13
• Emergence of the EGFR T790M mutation did not appear to correlate with baseline characteristics
• For patients receiving afatinib in the second or third line, it is not known when the EGFR T790M mutation emerged, as testing took place after failure on afatinib therapy

Response to afatinib and osimertinib
• Rates of response to afatinib were high (ORR 90%), although this analysis only included patients who had achieved ≥3 months’ disease control with afatinib
• Osimertinib elicited a high ORR (81%) in afatinib-pretreated patients who acquired the EGFR T790M mutation, with 22% of patients having a CR
References


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Data were previously presented: Hochmair, et al. OGP 2017, poster #P55.

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