Competing CNS or systemic progression analysis for *EGFR* mutation-positive NSCLC patients on afatinib in LUX-Lung 3, 6, and 7

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Background

- Central nervous system metastases are a known complication of advanced EGFR mutation-positive NSCLC

\[\sim 25-40\% \text{ of patients with NSCLC develop brain metastases}^{1,2}\]

This rises to \[\sim 40-60\% \text{ in patients with } EGFR \text{ mutations}^{3,4}\]

- The efficacy and optimal integration of EGFR TKIs in the treatment concept of brain metastases is less defined; therefore, LUX-Lung trials investigating the ErbB-family blocker afatinib allowed enrolment of patients with asymptomatic brain metastases

**LUX-Lung 3 and 6**
- Randomized Phase III studies; first-line afatinib versus platinum-based chemotherapy

**LUX-Lung 7**
- Randomized Phase IIb study; first-line afatinib versus gefitinib; common EGFR mutations

TKI, tyrosine kinase inhibitor
Background (cont’d)

- In all three studies, the magnitude of PFS improvement with afatinib versus chemotherapy or gefitinib in patients with brain metastases was similar to that observed in patients without brain metastases
  - HR = 0.54, 0.47, and 0.76 in patients with brain metastases, versus 0.48, 0.22, and 0.74 in patients without brain metastases, in LUX-Lung 3, 6, and 7, respectively\(^4,5\)

HR, hazard ratio; PFS, progression-free survival
Background (cont’d)

- In a combined analysis of patients in LUX-Lung 3 and 6, PFS was significantly improved with afatinib versus chemotherapy in patients with asymptomatic brain metastases (Figure 1)\(^4\)

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**Figure 1\(^\dagger\)**

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>8.21</td>
<td>5.39</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.50 (0.27–0.95)</td>
<td></td>
</tr>
<tr>
<td>(p) value</td>
<td>0.0297</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
<th>30</th>
<th>33</th>
<th>36</th>
<th>39</th>
<th>42</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afatinib</td>
<td>48</td>
<td>39</td>
<td>25</td>
<td>19</td>
<td>17</td>
<td>13</td>
<td>11</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>33</td>
<td>16</td>
<td>5</td>
<td>3</td>
<td>1</td>
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<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^\dagger\)Adapted from Schuler. J Thorac Oncol 2016 (ref. 4) under the terms of the Creative Commons Attribution License (CC BY)
Real-world data

- In a single-center retrospective analysis in Korea (n=165), ORR for afatinib monotherapy was 76%, with 21% CR. PFS data were not significantly different between patients receiving afatinib monotherapy, or afatinib plus surgery or WBRT.

**Figure 2‡**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib in pts w/o BM</td>
<td>NR</td>
</tr>
<tr>
<td>Afatinib monotherapy in pts with BM</td>
<td>15.7</td>
</tr>
<tr>
<td>Afatinib + gamma knife surgery</td>
<td>15.6</td>
</tr>
<tr>
<td>Afatinib + whole-brain radiotherapy</td>
<td>11.5</td>
</tr>
</tbody>
</table>

BM, brain metastases; CR, complete response; ORR, overall response rate; WBRT, whole-brain radiotherapy

‡Adapted from Kim Y. et al. J Thorac Oncol 2017;12:S2209 [presented at WCLC] (ref. 6) with permission
Real-world data (cont’d)

- In another retrospective review, ORR was similar for patients receiving afatinib monotherapy (82%; n=11) and patients receiving afatinib in combination with WBRT (88%; n=17); TTF and OS were numerically higher for patients on afatinib monotherapy.\(^7\)

OS, overall survival; TTF, time to treatment failure
Objective

• To investigate whether afatinib can prevent CNS progression or metastasis, we performed competing risk analyses for the progression and metastasis pattern in the CNS or non-CNS region in patients with and without brain metastases in LUX-Lung 3, 6, and 7
Methods

- Competing risk analyses were performed in patients with stage IIIB/IV *EGFR* mutation-positive NSCLC who received afatinib 40 mg/day in LUX-Lung 3, 6, and 7.
- Analyses were performed separately for patients with baseline brain metastases and without baseline brain metastases.
- Risk of CNS progression versus non-CNS progression or death was calculated based on the cumulative frequency of the event of interest versus the competing risk event.
Results

Patients with baseline brain metastases (Figure 3):

• 48 patients with baseline brain metastases received afatinib in LUX-Lung 3 and 6
• Median follow-up was 10.3 months
• Cumulative incidence of CNS progression was 39.9% lower than that of non-CNS progression (31.3% versus 52.1%)
• Best CNS response in patients with baseline brain metastases classified as target lesion (n=5): 2 CRs, 1 PR, and 2 SDs
  – PR/CR was achieved by visits 1–2

PD, progressive disease; PR, partial response; SD, stable disease
Results (cont’d)

Figure 3

<table>
<thead>
<tr>
<th>Cumulative incidence</th>
<th>CNS progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 6 months, %</td>
<td>15.5</td>
</tr>
<tr>
<td>At 12 months, %</td>
<td>24.5</td>
</tr>
<tr>
<td>At 24 months, %</td>
<td>34.4</td>
</tr>
</tbody>
</table>

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Results (cont’d)

Patients without baseline brain metastases (Figure 4):

- 485 patients without baseline brain metastases received afatinib in LUX-Lung 3, 6, and 7
- Median follow-up was 13.0 months
- Risk of de novo CNS progression was very low (6.4%) compared with non-CNS progression (78.4%)
Results (cont’d)

Cumulative incidence

<table>
<thead>
<tr>
<th>CNS progression</th>
<th>Cumulative incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 6 months, %</td>
<td>1.3</td>
</tr>
<tr>
<td>At 12 months, %</td>
<td>2.6</td>
</tr>
<tr>
<td>At 24 months, %</td>
<td>5.3</td>
</tr>
</tbody>
</table>

Figure 4

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Conclusions

• These results add to the existing evidence supporting afatinib use in patients with \textit{EGFR} mutation-positive NSCLC and CNS metastases

• Taken together, these results show that afatinib delays the onset/progression of brain metastases
Summary

- Previous findings from the LUX-Lung trials and real-world practice show that afatinib has clinical activity against brain metastases in \( \text{EGFR} \) mutation-positive NSCLC.
- Cumulative incidence of CNS progression was lower than that of non-CNS progression in patients with \( \text{EGFR} \) mutation-positive NSCLC and baseline brain metastases treated with afatinib in LUX-Lung 3 and 6.
- Risk of \textit{de novo} CNS progression in patients with \( \text{EGFR} \) mutation-positive NSCLC treated with afatinib was very low in LUX-Lung 3, 6, and 7.
References

1. Owen S, Souhami L. Front Oncol 2014;4:248
8. Girard N. Future Oncol 2018;14:1117–32

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Data were previously presented: Yang J, et al. ELCC 2018; poster #143PD

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