Competing central nervous system or systemic progression analysis for patients with EGFR mutation-positive NSCLC receiving afatinib in LUX-Lung 3, 6, and 7

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Background

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

- 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

\[ \text{~25–40% of patients with NSCLC develop brain metastases}^{1,2} \quad \text{This rises to} \quad \text{~40–60% in patients with EGFR mutations}^{3,4} \]

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

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

TKI, tyrosine kinase inhibitor
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\(^4,5\)
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).
Real-world data

- In a single-centre 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).  

![Figure 2](image.png)

**Figure 2**

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Median PFS, mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>No brain metastases</td>
<td>NR</td>
</tr>
<tr>
<td>Non-irradiated brain metastases</td>
<td>15.7</td>
</tr>
<tr>
<td>GKS</td>
<td>15.6</td>
</tr>
<tr>
<td>WBRT</td>
<td>11.5</td>
</tr>
</tbody>
</table>

CR, complete response; GKS, gamma knife surgery; ORR, overall response rate; WBRT, whole-brain radiotherapy

*Adapted from Kim Y. et al. J Thorac Oncol 2017;12:S2209 [presented at WCLC] 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 was numerically higher for patients with 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
- 31.3% had CNS progression versus 52.1% with non-CNS progression
- 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>

PD, progressive disease; PR, partial response; SD, stable disease

*Adapted from Girard N. Future Oncol. (2018) with permission of Future Medicine Ltd.
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)

Figure 4*

Cumulative incidence

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Cumulative incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0.1</td>
</tr>
<tr>
<td>12</td>
<td>0.4</td>
</tr>
<tr>
<td>18</td>
<td>0.6</td>
</tr>
<tr>
<td>24</td>
<td>0.8</td>
</tr>
<tr>
<td>30</td>
<td>0.9</td>
</tr>
<tr>
<td>36</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Non CNS PD

CNS PD

Cumulative incidence

CNS progression

At 6 months, % 1.3
At 12 months, % 2.6
At 24 months, % 5.3

*Adapted from Girard N. Future Oncol. (2018) with permission of Future Medicine Ltd
Conclusions

• These results add to the existing evidence supporting afatinib use in patients with *EGFR* mutation-positive NSCLC and CNS metastases
• Taken together, these results suggest afatinib delays the onset/progression of brain metastases
Summary

• Previous findings from the LUX-Lung trials and real-world practice show afatinib has clinical activity against brain metastases in EGFR mutation-positive NSCLC.
• Cumulative incidence of CNS progression was lower than that of non-CNS progression in patients with EGFR mutation-positive NSCLC and baseline brain metastases treated with afatinib in LUX-Lung 3 and 6.
• Risk of de novo CNS progression in patients with 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
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