Improving outcomes for NSCLC patients with brain metastases

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**Afatinib**

**Indications:**

In Switzerland, afatinib is approved as monotherapy for patients with non-small cell lung cancer (Stage IIIb/IV) with activating mutations of *EGFR* (exon 19 deletions or exon 21 L858R substitutions), not previously treated with EGFR TKIs. It is also indicated for the treatment of patients with locally advanced or metastatic squamous cell cancer of the lung whose carcinoma progressed during or after platinum-based chemotherapy and for whom immunotherapy is not suitable.

**Posology:**

The recommended dose is 40 mg once daily, orally. Maximum daily dose in squamous cell carcinoma of the lung is 50 mg, orally. Not recommended in patients with an eGFR <15 mL/min, in patients requiring dialysis and in severe hepatic failure.
Disclosures

• Corporate-sponsored research for Boehringer Ingelheim, BMS and Novartis

• Has been a consultant for AstraZeneca, Boehringer Ingelheim, BMS, Celgene, Lilly, Novartis and Roche

• Has received honoraria from Alexion, Boehringer Ingelheim, BMS, Celgene, Lilly and Novartis
Introduction

• The brain is a common site of metastasis in NSCLC, affecting 21–64% of patients

• Patients with NSCLC defined by specific oncogenic drivers (e.g. EGFR and ALK) have a particularly high prevalence of BMs at primary diagnosis and at progression
  – ~24% at diagnosis
  – ~30–70% at progression

• Intracranial responses and growth delay of CNS metastases with EGFR TKI treatment have been reported

• Intracranially active TKI may defer the need for brain irradiation, which is associated with substantial morbidity

ALK, anaplastic lymphoma kinase; BM, brain metastasis; CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

Prospective data for first-generation EGFR TKIs in patients with BMs are limited

<table>
<thead>
<tr>
<th>Phase II study with either erlotinib or gefitinib&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Phase II CTONG-0803 study of erlotinib as second-line treatment&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• N=28</td>
<td>• N=48 with asymptomatic brain metastasis after first-line CT&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Systemic PR=83%; SD=11%; mPFS 6.6 months; mOS 15.9 months</td>
<td>• Intracranial mPFS 10.1 months; overall mPFS 9.7 months</td>
</tr>
<tr>
<td>• No significant differences</td>
<td>• Eight patients with EGFR&lt;sub&gt;m&lt;/sub&gt;+ disease</td>
</tr>
<tr>
<td>• No information was provided on intracranial activity</td>
<td>– No intracranial efficacy was reported</td>
</tr>
</tbody>
</table>

CT, chemotherapy; EGFR<sub>m</sub>, epidermal growth factor receptor mutation; mPFS, median progression-free survival; mOS, median overall survival; PR, partial response; SD, stable disease.

Prospective data for CSF-permeant TKI: AZD3759 – the BLOOM study

**BLOOM study design overview**
Phase I study to assess the safety, tolerability, pharmacokinetics and preliminary antitumour efficacy of AZD3759 or osimertinib in patients with EGFRm+ advanced NSCLC

**Dose escalation**
- AZD3759
  - Cohort 1: 50 mg BID
  - Cohort 2: 100 mg BID
  - Cohort 3: 200 mg BID
  - Cohort 4: 300 mg BID
  - Cohort 5: 500 mg BID

**Dose expansion cohorts**
- LM
  - Cohort 1: T790M unselected LM (n=21)
  - Cohort 2: T790M + LM (n=20)
  - AZD3759
    - 200 or 300 mg BID*
  - BM

**Osimertinib**
- 160 mg QD
- TKI-pretreated LM
- Cohort 1: T790M unselected LM (n=21)
- Cohort 2: T790M + LM (n=20)

- 20 TKI-naïve patients with advanced EGFRm+ NSCLC were enrolled (16 with BM and four with LM)
- 15 (83%) of 18 patients with measurable BM at baseline had confirmed objective response (14 PRs and one CR)
- Median best percentage change of intracranial lesions was –54% (investigator assessed)

*Both AZD3759 200 and 300 mg BID were explored to evaluate long-term tolerability and efficacy; †Requires stable extracranial disease if EGFR TKI pretreated; ‡Confirmed response. BID, twice daily; CR, complete response; CSF, cerebrospinal fluid; LM, leptomeningeal metastasis; QD, once daily.

Prospective data for second-generation TKI: LUX-Lung 3/6: PFS in patients with BM and common *EGFRT*mutations

<table>
<thead>
<tr>
<th>Combined LUX-Lung 3/6</th>
<th>Afatinib (n=48)</th>
<th>CT (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months</td>
<td>8.2</td>
<td>5.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.50 (0.27–0.95)</td>
<td>p = 0.03</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio.
Prospective data for second-generation TKI: LUX-Lung 3/6: competing risk for progression in patients with baseline BM

**Table 1:**

<table>
<thead>
<tr>
<th>LUX-Lung 3/6/7&lt;sup&gt;1&lt;/sup&gt;</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS PD</td>
<td>15</td>
<td>31.3</td>
</tr>
<tr>
<td>Censored</td>
<td>8</td>
<td>16.7</td>
</tr>
<tr>
<td>Non-CNS PD or death</td>
<td>25</td>
<td>52.1</td>
</tr>
</tbody>
</table>

**Risk for CNS progression (LUX-Lung 3/6, common mutation)<sup>2</sup>**

<table>
<thead>
<tr>
<th></th>
<th>With baseline BM</th>
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<tbody>
<tr>
<td>6 months</td>
<td>15.5%</td>
</tr>
<tr>
<td>12 months</td>
<td>24.5%</td>
</tr>
<tr>
<td>24 months</td>
<td>34.4%</td>
</tr>
</tbody>
</table>

PD, progressive disease.
Prospective data for second-generation TKI: LUX-Lung 3/6/7: competing risk for progression in patients without baseline BM

<table>
<thead>
<tr>
<th>LUX-Lung 3/6/7¹</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS PD</td>
<td>31</td>
<td>6.4</td>
</tr>
<tr>
<td>Censored</td>
<td>74</td>
<td>15.3</td>
</tr>
<tr>
<td>Non-CNS PD or death</td>
<td>380</td>
<td>78.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk for CNS progression (LUX-Lung 3/6, common mutation)²</th>
<th>Without baseline BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>1.3%</td>
</tr>
<tr>
<td>12 months</td>
<td>2.6%</td>
</tr>
<tr>
<td>24 months</td>
<td>5.3%</td>
</tr>
</tbody>
</table>

Prospective data for second-generation TKI: dacomitinib

- A phase II study of dacomitinib in patients with progressive BM was terminated because of slow enrollment

- In the Phase III ARCHER 1050 trial, dacomitinib demonstrated superior benefit over gefitinib (mPFS 14.7 vs 9.2 months; p<0.0001), but patients with CNS metastases were excluded
Prospective data for third-generation TKI: FLAURA – competing risk analysis (CNS full analysis set)

FLAURA data cut-off was 12 June 2017. *Conditional on the patient not experiencing a competing risk at that time. Competing risks were defined as non-CNS progression and death by any cause in the absence of non-CNS or CNS progression.

Real-world experience: Korean patients with BM receiving first-line afatinib

- A retrospective population-based study in 165 adult patients receiving first-line afatinib at the Samsung Medical Center in South Korea

**Brain tumour response to afatinib**

<table>
<thead>
<tr>
<th>BM without irradiation</th>
<th>39</th>
</tr>
</thead>
<tbody>
<tr>
<td>No follow-up brain MRI</td>
<td>10</td>
</tr>
<tr>
<td>Nonirradiated BM with follow-up MRI data</td>
<td>29 (100)</td>
</tr>
<tr>
<td>Disappeared</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Significantly decreased</td>
<td>16 (55.2)</td>
</tr>
<tr>
<td>No significant change</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>Progression</td>
<td>2 (6.9)</td>
</tr>
</tbody>
</table>

Response rate to BM with afatinib: 22 (75.9)

GKS, gamma-knife surgery; WBRT, whole brain radiation therapy.
Real-world experience: Taiwanese patients with BM treated with afatinib WBRT

- 28 lung adenocarcinoma patients with BM
- CNS imaging examinations every 3–6 months after beginning treatment; brain MRI or CT scan was also performed for follow-up CNS evaluation after a patient completed WBRT or exhibited metastatic brain symptoms


14.5 months (afatinib + WBRT) vs 18.5 months (afatinib monotherapy), p=0.381

18.6 months (afatinib + WBRT) vs not recorded (afatinib monotherapy), p=0.299

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Summary

• The first-generation, reversible EGFR TKIs erlotinib and gefitinib have limited intracranial activity in patients with NSCLC\(^1,2\)

• A novel CSF-permeant, reversible EGFR TKI (AZD3759) is in early clinical development\(^3\)

• The third-generation EGFR TKI osimertinib clearly has activity in patients with BM or LMD
  – Osimertinib delayed onset and progression of BM in prospective clinical trials independent of treatment line (FLAURA, AURA-3)\(^4-6\)
  – Risk for CNS progression at 1 year was 8% for patients with baseline BM (first-line)\(^5\)
  – Intracranial CR rate of 41% and ORR of 66%\(^5\)
  – PFS was improved with osimertinib versus first-generation TKI or patient-based CT in patients with BM, with a similar magnitude as that observed in patients without BM (HR=0.47 and 0.46, respectively, in FLAURA; HR=0.32 and 0.40, respectively, in AURA-3)\(^4,6\)

Summary (continued)

• The second-generation EGFR TKI afatinib has a strong body of evidence showing efficacy in patients with EGFRm+ NSCLC with BM
  - First-line afatinib delayed onset and progression of BM in prospective clinical trials. Risk for CNS progression at 1 year was 2.6% for patients without BM and 24.5% for patients with baseline BM¹,²
  - Intracranial CR rate of 21% and ORR of 76%¹
  - PFS was improved with afatinib versus CT or gefitinib in patients with BM, with the magnitude being similar to that observed in patients without BM (HR=0.54, 0.47, and 0.76 in LUX-Lung 3, 6 and 7, respectively)³,⁴
  - Patients with LMD showed improvement in performance status and neurological/cognitive function⁵–⁹
  - Real-world data showing treatment time of ~15 months confirm the efficacy of afatinib¹⁰,¹¹