Clinical Considerations in *EGFR* Mutation-Positive NSCLC: the Challenge of Preventing and Managing Brain Metastases

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Disclosures

• Has been a consultant or advisor to Boehringer Ingelheim, Bristol-Myers Squibb, Guardant Health, Merck Sharp & Dohme, Pfizer, Roche

• Has received trial funding from Novartis, Pfizer, Roche
Introduction

• The brain is a common site of metastasis in NSCLC, affecting 18%-64% of patients1

• Patients with NSCLC defined by specific oncogenic drivers (eg, EGFR and ALK) have a particularly high prevalence of BM at primary diagnosis and progression2,3
  – ≈24% at diagnosis
  – ≈30%-70% at progression

• Intracranial responses and growth delay of CNS metastases with EGFR TKI treatment have been reported4

• Intracranially active TKI may defer the need for brain irradiation, which is associated with substantial morbidity5

ALK = anaplastic lymphoma kinase; BM = brain metastases; 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 BM Are Limited

<table>
<thead>
<tr>
<th>Phase 2 Study With Either Erlotinib or Gefitinib&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Phase 2 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>
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<tr>
<td>• No significant differences</td>
<td>• Eight patients with $EGFR_{m}^{+}$ disease</td>
</tr>
<tr>
<td>• No information was provided on intracranial activity</td>
<td>- No intracranial efficacy was reported</td>
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CT = chemotherapy; $EGFR_{m}$ = 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 1 study to assess the safety, tolerability, pharmacokinetics, and preliminary antitumour efficacy of AZD3759 or osimertinib in patients with EGFRm+ advanced NSCLC

<table>
<thead>
<tr>
<th>Dose Escalation</th>
<th>Dose Expansion Cohorts</th>
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<tbody>
<tr>
<td>AZD3759</td>
<td></td>
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<tr>
<td>5 mg BID</td>
<td></td>
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<tr>
<td>10 mg BID</td>
<td></td>
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<tr>
<td>20 mg BID</td>
<td></td>
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<tr>
<td>30 mg BID</td>
<td></td>
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<tr>
<td>200 mg BID</td>
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<tr>
<td>300 mg BID</td>
<td></td>
</tr>
<tr>
<td>500 mg BID</td>
<td></td>
</tr>
<tr>
<td>100 mg BID</td>
<td></td>
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</tbody>
</table>

- **Osimertinib** 160 mg QD
- **TKI-pretreated LM**

- **Cohort 1:** T790M unselected LM (n=21)
- **Cohort 2:** T790M + LM (n=20)

- **20 TKI-naive patients with advanced EGFRm+ NSCLC were enrolled (16 with BM and 4 with LM)**
- **83% (15/18) patients with measurable CNS target lesions at baseline had confirmed objective response (14 PRs and one CR)**

\[\text{AZD3759} 200 \text{ mg BI}D\]
\[\text{AZD3759} 300 \text{ mg BI}D\]

\[\text{Osimertinib} 160 \text{ mg QD}\]

\[\text{BM} = \text{BM cohort}\]
\[\text{LM} = \text{LM cohort}\]

\[\text{Patient changes in CNS target lesions with time}\]

\[\text{Percent change of BM target lesion size with time}\]

\[\text{Discontinued patients}\]
\[\text{Continuing patients at data cut-off}\]

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*Both AZD3759 200 and 300 mg BID were explored to evaluate long-term tolerability and efficacy; \(^{\text{a}}\)Requires stable extracranial disease if EGFR TKI pretreated; \(^{\text{b}}\)Confirmed response. BID = twice daily; CR = complete response; CSF = cerebrospinal fluid; LM = leptomeningeal metastasis; QD = once daily.

Prospective Data for Second-Generation TKI: Dacomitinib

- A phase 2 study of dacomitinib in patients with progressive BM was terminated because of slow enrolment\(^1\)
- In the phase 3 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\(^2,3\)

**Satisfaction factors**
- Race (includes Asian vs non-Asian)
- \(EGFR\) mutation type (exon 19 vs 21)

**Primary end point**
- PFS by blinded independent review
  - \(\geq 256\) PFS events
  - PFS HR \(\leq 0.667\) (50%↑)
  - 90% power
  - 1-sided \(\alpha=0.025\)
  - mPFS: 14.3 vs 9.5 mo

**Secondary end points**
- PFS (investigator assessed), ORR, DOR, TTF, OS, safety, PROs

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DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PO = by mouth; PRO = patient-reported outcome; R = randomisation; TTF = time to treatment failure.

FLAURA: PFS by Investigator Review in Patients With CNS Metastases at Study Entry

With CNS Metastases (n=116)

- CNS progression events occurred in 17 (6%) and 42 (15%) patients receiving osimertinib or 1st-gen TKI, respectively.

Data cut-off: 12 June 2017.
AURA3: Competing Risk Analysis—Full Analysis Set

The probability of experiencing a CNS progression event was lower for osimertinib than for chemotherapy at both 3 and 6 months\(^a\)

### Probability

<table>
<thead>
<tr>
<th></th>
<th>Osimertinib 80 mg (n=75)</th>
<th>Chemotherapy (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS Conditional Probability</td>
<td>2.7 (0.8-9.6)</td>
<td>8.2 (2.3-28.7)</td>
</tr>
<tr>
<td>At 3 mo, % (95% CI)</td>
<td>11.5 (5.9-22.4)</td>
<td>28.2 (16.6-48.0)</td>
</tr>
<tr>
<td>At 6 mo, % (95% CI)</td>
<td>22.2 (9.7-46.3)</td>
<td>36.5 (19.5-59.1)</td>
</tr>
</tbody>
</table>

\(^a\)Conditional on the patient not experiencing a competing risk at that time. Types of event, osimertinib/chemotherapy; CNS progression, 15% (n=11)/24% (n=10); Non-CNS progression, 25% (n=19)/37% (n=15); Death, 11% (n=8)/10% (n=4); Censored, 49% (n=37)/29% (n=12).

Prospective Data for Second-Generation TKI: LUX-Lung 3/6—PFS in Patients With BM and Common EGFRm

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>
<thead>
<tr>
<th>LUX-Lung 3/6¹</th>
<th>n</th>
<th>%</th>
<th>Risk for CNS Progression (LUX-Lung 3/6, Common Mutation)²</th>
<th>With Baseline BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS PD</td>
<td>15</td>
<td>31.3</td>
<td>6 mo</td>
<td>15.5%</td>
</tr>
<tr>
<td>Censored</td>
<td>8</td>
<td>16.7</td>
<td>12 mo</td>
<td>24.5%</td>
</tr>
<tr>
<td>Non-CNS PD or death</td>
<td>25</td>
<td>52.1</td>
<td>24 mo</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:**

<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>

**Risk for CNS Progression (LUX-Lung 3/6/7, Common Mutation)²**

- Without Baseline BM
  - 6 mo: 1.3%
  - 12 mo: 2.6%
  - 24 mo: 5.3%

**Graph:**

- Cumulative Incidence
- Months

Real-World Experience in Korea in Patients With BM Receiving First-Line Afatinib

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

Brain Tumour Response to Afatinib

<table>
<thead>
<tr>
<th>Description</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM without irradiation</td>
<td>39</td>
</tr>
<tr>
<td>No follow-up brain MRI</td>
<td>10</td>
</tr>
<tr>
<td>Non-irradiated 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>
<tr>
<td>Response rate to BM with afatinib</td>
<td>22 (75.9%)</td>
</tr>
</tbody>
</table>

GKS = gamma knife surgery; WBRT = whole brain radiotherapy
Real-World Experience With Afatinib: Phase 3b Study

- Phase 3b open-label study of afatinib in a broad Asian* population (N=479) of EGFR TKI-naive patients
- 92 (19.2%) patients had BM at baseline

This study provides additional evidence for the efficacy of afatinib in patients with BM

*China, India, Taiwan, Hong Kong, Singapore.
PFS = progression-free survival; TTSP = time to symptomatic progression.
Real-World Experience With Afatinib: Case Study #1

May 2018, ADC stage IV (bone, lung mets) Del 19 positive

MRI: unique brain metastasis with oedema

No neurologic symptoms

Afatinib 40 mg QD started on May 2018

Systemic & CNS PR after 3 months on afatinib
No radiotherapy or corticosteroids applied

MRI May 2018

MRI July 2018
Real-World Experience With Afatinib: Case Study #2

Stage IV Lung ADC, EGFR Ex20 (S768I) and Ex18 (G719X)

Afatinib 40 mg QD
CR (Jan 2014)

1st oligo-PD: node
SBRT and afatinib continuation (Sept 2014)

2nd oligo-PD: CNS
SBRT and afatinib continuation (June 2015)

Multifocal-PD: CNS
WBRT and 2nd line (Dec 2015)

Treatment time on afatinib and local strategies = 24 months
Summary

- The first-generation, reversible EGFR TKIs erlotinib and gefitinib have limited intracranial activity in patients with NSCLC\textsuperscript{1,2}
- A novel CSF-permeant, reversible EGFR TKI (AZD3759) is in early clinical development\textsuperscript{3}
- The third-generation EGFR TKI osimertinib clearly has activity in patients with BM
  - Osimertinib delayed onset and progression of BM independent of treatment line (FLAURA, AURA3)\textsuperscript{4-6}
  - Intracranial ORR of 66%\textsuperscript{5}
- The second-generation TKI afatinib has a strong body of evidence showing efficacy against and delayed onset of cerebral manifestations
  - First-line afatinib delayed onset and progression of BM (LUX-Lung trials)\textsuperscript{7-10}
  - Real-world data showing treatment time of \(\approx\)15 months, with an intracranial ORR of 76%, confirm the efficacy of afatinib\textsuperscript{11,12}