Osimertinib Activity in Patients With Leptomeningeal Disease From Non-Small Cell Lung Cancer: Updated Results From the BLOOM Study

Abstract 9002

Leptomeningeal Metastases

**INCIDENCE**
- In patients with NSCLC\(^1,2\): 3% to 5%
- In patients with EGFRm NSCLC\(^3\): 9%

**PROGNOSIS**
- Median OS from diagnosis\(^1,4\): 4.5 months to 11.0 months
- Cause of death\(^2\):
  - 28% LM progression
  - 31% LM + systemic progression
  - 41% systemic progression

**First and second-generation EGFR-TKIs have limited BBB penetration\(^5,6,7\)**

**Osimertinib has demonstrated systemic activity in patients with EGFRm NSCLC and brain metastases\(^8,9\)**

**PROGNOSIS**
- Median OS from diagnosis\(^1,4\): 4.5 months to 11.0 months
- Cause of death\(^2\):
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  - 31% LM + systemic progression
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BBB, blood brain barrier; CNS, central nervous system; EGFRm, epidermal growth factor receptor mutation positive; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; LM, leptomeningeal metastasis; NSCLC, non-small cell lung cancer; OS, overall survival


CNS Exposure of Osimertinib: Preclinical Rationale

- Osimertinib induced sustained tumor regression in an EGFRm PC9 mouse brain metastasis model.
- Human PK and mouse PKPD model suggests doses of 80 mg and 160 mg could be active in human CNS disease.
- PET imaging showed marked exposure of osimertinib in NHP and mouse model, in contrast to rociletinib and gefitinib.

<table>
<thead>
<tr>
<th>Brain exposure in NHP</th>
<th>Brain to blood ratio AUC_{0-90 min} *</th>
</tr>
</thead>
<tbody>
<tr>
<td>([^{11}C])osimertinib (n = 3)</td>
<td>2.6 ± 1.4</td>
</tr>
<tr>
<td>([^{11}C])rociletinib (n = 2)</td>
<td>0.025</td>
</tr>
<tr>
<td>([^{11}C])gefitinib (n = 2)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

*corrected for radioactivity in cerebral blood.

AUC, area under curve; CNS, central nervous system; PD, pharmacodynamics; PET, positive emission tomography; PK, pharmacokinetics; NHP, non-human primate.

BLOOM Study Design Overview

Phase I study to assess the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of AZD3759 or osimertinib in patients with EGFRm advanced NSCLC.

<table>
<thead>
<tr>
<th>AZD3759</th>
<th>Dose Escalation</th>
<th>Dose Expansion Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 50 mg bid</td>
<td>Cohort 2 200 mg bid</td>
<td>Leptomeningeal metastasis</td>
</tr>
<tr>
<td>Cohort 3 300 mg bid</td>
<td>Cohort 4 500 mg bid</td>
<td>• EGFR-TKI naïve or pre-treated†</td>
</tr>
<tr>
<td>Cohort 5 200 mg or 300 mg bid*</td>
<td></td>
<td>Brain metastasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• EGFR-TKI naïve</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Osimertinib 160 mg qd</th>
<th>Dose Expansion Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR-TKI pre-treated patients with NSCLC and LM</td>
<td>Cohort 1: EGFRm NSCLC and LM</td>
</tr>
<tr>
<td></td>
<td>Stable extracranial disease, N = 21 (current report)</td>
</tr>
<tr>
<td></td>
<td>Cohort 2: T790M positive‡ NSCLC and LM</td>
</tr>
<tr>
<td></td>
<td>No restriction on stable extracranial disease, N = 20 (accrual ongoing)</td>
</tr>
</tbody>
</table>

*Both AZD3759 200 mg and 300 mg bid were explored to evaluate long-term tolerability and efficacy; †Requires stable extracranial disease if EGFR TKI pre-treated; ‡T790M status is based on testing of an extracranial tumor or plasma sample.


**BLOOM Study Design: Osimertinib LM Cohort 1**

**Study objectives, cohort 1—EGFRm NSCLC and LM:**
To assess the safety and tolerability of osimertinib in patients with LM

First patient dosed: April 14, 2015

**Osimertinib LM cohort 1**

Advanced or metastatic EGFRm NSCLC and confirmed diagnosis of LM by positive CSF cytology

Key inclusion criteria:

- Primary tumor with EGFR L858R or exon 19 deletion
- Prior EGFR-TKI treatment
- ECOG PS 0–2
- Stable extracranial disease
- At least one LM lesion by MRI scan

**Assessments**

- Adverse events*
- Efficacy assessment:
  - OS
  - Brain MRI and extracranial MRI or CT scan*†
  - CSF cytology
  - Neurological exam*
  - CNS symptoms*
- PK in CSF
- Quantification of EGFRm DNA in CSF

Data cut-off: March 10, 2016

*As assessed by study investigator; †modified RECIST for CNS disease; RECIST 1.1 for extracranial disease; CT/MRI, CSF cytology and neurological exam frequency every 6 weeks; 1 cycle = 21 days of continuous dosing.

CSF, cerebrospinal fluid; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group Performance Status; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria In Solid Tumors


Patient Demographics: Osimertinib LM Cohort 1

- All 21 patients were Asian with adenocarcinoma histology
- Two patients had T790M detected in CSF at study entry; 6 patients had T790M detected in plasma
- Duration of treatment: 1 to 49 weeks ongoing
- Twenty-one patients dosed; 15 patients are ongoing treatment
  - Safety analysis: n = 21
  - Efficacy analysis n = 21*

<table>
<thead>
<tr>
<th>Characteristic, n</th>
<th>N = 21</th>
</tr>
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<tbody>
<tr>
<td>Gender: Male / female</td>
<td>6 / 15</td>
</tr>
<tr>
<td>Age: Median (range), years</td>
<td>59.0 (44-75)</td>
</tr>
<tr>
<td>Smoking status: Current / former / never</td>
<td>1 / 5 / 15</td>
</tr>
<tr>
<td>ECOG PS: 0 / 1 / 2</td>
<td>1 / 11 / 9</td>
</tr>
<tr>
<td>Neurological assessment at baseline: Normal / abnormal</td>
<td>11 / 10</td>
</tr>
<tr>
<td>Prior lines of systemic therapy: Median (range)</td>
<td>3.0 (1-8)</td>
</tr>
<tr>
<td>Prior whole brain radiotherapy</td>
<td>11</td>
</tr>
<tr>
<td>Prior EGFR-TKIs†: Gefitinib / erlotinib / dacomitinib / HM61713 (BI 1482694)</td>
<td>16 / 3 / 1 / 1</td>
</tr>
<tr>
<td>Prior systemic response to EGFR-TKI: Partial response / stable disease / progressive disease</td>
<td>14 / 6 / 1</td>
</tr>
<tr>
<td>Tumor tissue EGFRm mutation status (local test)‡: Ex19Del / L858R</td>
<td>9 / 13</td>
</tr>
</tbody>
</table>

*Efficacy analysis set included all dosed patients; †One patient received two lines of therapy: gefitinib and HM61713; ‡One patient had both Ex19Del and L858R detected at baseline. Ex19del, exon 19 deletion

Summary of Adverse Events

- Twenty patients experienced ≥1 AE
- Grade ≥3 AEs were observed in 9 (43%) patients
  - Drug-related grade ≥3 AEs were observed in 3 (14%) patients
- Serious AEs occurred in 3 (14%) patients, none of which were drug-related
- AEs leading to dose interruption and dose reduction were observed in 2 (10%) patients due to skin pruritus and neutropenia, respectively
  - No drug-related AEs led to dose discontinuation
- One patient died due to aspiration pneumonia not related to drug

Population: safety analysis, n = 21. As assessed by the study investigator. Patients could experience multiple events with different grades; table shows the highest grade AE experienced by each patient.

### Drug-related AEs by preferred term, n (%)

<table>
<thead>
<tr>
<th>Drug-related AEs by preferred term, n (%)</th>
<th>CTCAE grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Rash (grouped terms)</td>
<td>6 (29)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>6 (29)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

*Only AEs with frequency >10% were listed; One drug-related Grade 3 neutropenia not listed.

Efficacy assessments were conducted on 21 patients

- Seven patients had confirmed* radiological improvement
- Two patients had confirmed* CSF cytology clearance; no tumor cells were detected in two consecutive CSF samples
- Five patients had confirmed* improved neurological function

### Best MRI Imaging

<table>
<thead>
<tr>
<th>Intracranial Response</th>
<th>Confirmed*</th>
<th>Unconfirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responding</td>
<td>7 (33%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (43%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Early withdrawal</td>
<td>2 (10%)</td>
<td></td>
</tr>
</tbody>
</table>

Population: efficacy, n = 21.*Response confirmation was done at least 4 weeks after the initial response; †Response assessed by neurological examination

### Best Confirmed Neurological Status†

<table>
<thead>
<tr>
<th>Neurological Status at Baseline</th>
<th>NORMAL (N=11)</th>
<th>ABNORMAL (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>No change</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Worsened</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Early withdrawal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unconfirmed</td>
<td></td>
<td></td>
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</tbody>
</table>

Changes in EGFRm DNA Copy Number in CSF With Osimertinib Treatment

- Droplet digital PCR was used to detect EGFRm DNA copy number; data were available for 9 patients*
- All patients had EGFR-TKI sensitizing mutations detected in screening CSF; 2 patients had T790M
- Among them, 6 patients had a >50% decrease in EGFRm DNA copies up to C9D1; 5 had sustained decrease
  - 4 out of 6 improved neurological function
  - 4 out of 6 LM-MRI responded; 2 out of 6 LM-MRI stable disease
  - 2 out of 6 CSF clearance

*Note: Patients with at least 12 weeks of assessment are included—9 out of 21 patients reached 12 week assessment and had CSF samples available for EGFRm DNA detection.
†Patients with T790M mutations detected in screening CSF; ‡No sample was available from this patient on C11D1.

Time on Treatment

Fifteen patients were ongoing treatment at time of data cut-off (March 10, 2016), seven of whom had been on treatment for >9 months.

*Patient died due to aspiration pneumonia. Arrows represent observations at the time of data cut-off.
Two patients experienced AEs leading to dose reduction: one patient had skin pruritus and one patient had neutropenia.

Case Study: 63 Year Old Korean Male Patient

Diagnosed with advanced NSCLC (L858R) in June, 2013 with most recent disease progression in March, 2015

- Prior therapy included:
  - Gefitinib (March, 2013 to May, 2015)
  - WBRT (April, 2013 to May, 2013)

Osimertinib 160 mg qd started May 20, 2015

- LM response ongoing from week 6
- Stable extracranial disease since week 6; partial response since week 12
- Normal neurological function since baseline
- Continuous response for >9 months by data cut-off

WBRT; whole brain radiotherapy

Conclusions

• Preclinical data indicate that osimertinib crosses the BBB
• Osimertinib shows encouraging preliminary safety, tolerability, and activity in pretreated patients with EGFRm advanced NSCLC and LM
  – The AE profile is as expected and manageable
  – Neurological function improved from baseline in 5 patients
  – Radiological improvements in LM were seen in 7 patients
  – Clearance of tumor cells from the CSF occurred in 2 patients at 2 consecutive visits
  – Time on treatment suggests durable clinical benefit with 15 patients remaining on treatment, 7 of whom have been on treatment for >9 months
• Further evaluation of osimertinib in this setting is warranted
• The BLOOM study is ongoing and a cohort enrolling patients with T790M positive NSCLC and LM is open; T790M status is based on testing of an extracranial tumor or plasma sample