EGFR TKIs in Brain Metastases: which best therapeutic course?

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Great advances have been made in lung cancer therapy

Stratification for **EGFR**, **ALK**, and histology

- **EGFR Mut+**
  - EGFR TKI
- **ALK+**
  - ALK TKI
- **EGFR WT/ALK−**
  - PD-L1+
  - Platinum doublet + bevacizumab
  - OR
  - Platinum + pemetrexed ± bevacizumab
- **EGFR WT/ALK−**
  - squamous
  - Platinum-based doublet
- **ROS1+**
- **BRAF+**

**WT**, wild type.
EGFR, the most frequent targetable alteration

- Full WT 15%
- KRAS 29%
- Unknown 35%
- BRAF 2%
- HER2 1%
- PIK3CA 2%
- ALK 5%

F.Barlesi et al, lancet 2016
# Front-line EGFR mutant NSCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>TKI</th>
<th>Chemo</th>
<th>Mutation</th>
<th>mPFS (TKI vs Chemo), p</th>
<th>PFS HR (95%CI)</th>
<th>ORR% (TKI vs Chemo)</th>
<th>≥G3 TKI tox (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS</td>
<td>Gefitinib</td>
<td>Carbo-Taxol</td>
<td>All</td>
<td>9.5 vs 6.3; p&lt;0.001</td>
<td>0.48 (0.36-0.64)</td>
<td>71 vs 47</td>
<td>33</td>
</tr>
<tr>
<td>NEJ002</td>
<td>Gefitinib</td>
<td>Carbo-Taxol</td>
<td>L858R, Del19</td>
<td>10.8 vs 5.4; p&lt;0.001</td>
<td>0.30 (0.22-0.41)</td>
<td>74 vs 31</td>
<td>41</td>
</tr>
<tr>
<td>WJTOG 3405</td>
<td>Gefitinib</td>
<td>Cis-Doce</td>
<td>L858R, Del19</td>
<td>9.2 vs 6.3; p&lt;0.001</td>
<td>0.49 (0.34-0.71)</td>
<td>62 vs 32</td>
<td>NR</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>Erlotinib</td>
<td>Carbo-Gem</td>
<td>L858R, Del19</td>
<td>13.1 vs 4.6; p&lt;0.001</td>
<td>0.16 (0.10-0.26)</td>
<td>83 vs 36</td>
<td>17</td>
</tr>
<tr>
<td>EURTAC</td>
<td>Erlotinib</td>
<td>Cis/Carbo-Doce/Gem</td>
<td>L858R, Del19</td>
<td>9.7 vs 5.2; p&lt;0.001</td>
<td>0.37 (0.25-0.54)</td>
<td>58 vs 15</td>
<td>46</td>
</tr>
<tr>
<td>LUX-3</td>
<td>Afatinib</td>
<td>Cis-Pem</td>
<td>L858R, Del19</td>
<td>13.6 vs 6.9; p&lt;0.0001</td>
<td>0.47 (0.34-0.65)</td>
<td>56 vs 23</td>
<td>49</td>
</tr>
<tr>
<td>LUX-6</td>
<td>Afatinib</td>
<td>Cis-Gem</td>
<td>L858R, Del19</td>
<td>11.0 vs 5.6; p&lt;0.0001</td>
<td>0.28 (0.20-0.39)</td>
<td>67 vs 23</td>
<td>36</td>
</tr>
</tbody>
</table>

Mok NEJM (2009); Mitsudomi Lancet Oncol (2010); Maemondo NEJM (2010); Zhou Lancet Oncol (2011); Rossell Lancet Oncol (2012); Sequist JCO (2013); Wu Lancet Oncol (2014); NR, not reported
**EGFR-TKIs based on EGFR sensitive and resistant mutations: Never ended story**

**EGFRm+**
(Del19, Exon 21)

First generation
TKI (10 months)
Gefitinib, erlotinib

Second generation
TKI (14-16 months)
Afatinib, dacomatinib

50% T790M exon20

Osimertinib for T790M
(10 months)

Chemo (5 months)

Chemo (5 months)

Osimertinib for T790M
(10 months)

Chemo (5 months)

Chemo (5 months)

mOS: 25-30 months
CNS metastases – EGFRm+
(brain metastases and leptomeningeal metastases)

**INCIDENCE of CNS metastases**
- In patients with EGFRm+ NSCLC\(^1\): 44% (including BM and LM)

**PROGNOSIS**
- **BM**
  - Median OS\(^1,2\): 16-18 months
  - Cause of death\(^1\): 11% CNS, 35% CNS + systemic, 54% systemic
- **LM**
  - Median OS\(^3,4\): 4.5-11.0 months
  - Cause of death\(^5\): 28% LM, 31% LM + systemic, 41% systemic

Most of these studies included small sample sizes, retrospective analyses, and case reports with inadequate power to exclude clinically relevant differences in efficacy.

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The cumulative incidence of post-diagnosis BM increased over time:
- 34.2% at 1 year,
- 38.4% at 2 years
- 46.7% at 3 years

presence of BM, clinicopathologic data, and tumor genotype retrospectively compiled and analyzed from a cohort of 381 patients

Deepa Rangachari et al, lung cancer 2015
Higher risk of recurrence of brain metastasis according to EGFRm

EGFR-mutant tumor had a significantly higher risk of recurrence of brain metastasis (hazard ratio=4.49, 95% CI: 1.20–16.80, p=0.026)
Blood-brain barrier

- For successful treatment of brain metastases, a drug must first be able to cross the BBB

- BBB penetration is influenced by factors such as
  - drug's affinity for the ATP-binding cassette efflux transporters,
  - permeability glycoprotein (P-gp)
  - breast cancer-resistance protein (BCRP)
  - molecular weight of the drug

- Chemotherapy agents and large monoclonal antibodies are generally unable to cross the BBB
Lower rates of BM progression in EGFR+ NSCLC pts initially treated with EGFR-TKI compared with upfront chemotherapy

Patients without prior CNS involvement

Erlotinib or gefitinib

Stephanie Heon et al, CCR 2012
### Select trials with EGFR-TKI therapy (1\textsuperscript{st} ou 2\textsuperscript{nd} generation) in NSCLC-BM

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Patient</th>
<th>RR in Brain</th>
<th>OS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>17</td>
<td>EGFR M+</td>
<td>82%</td>
<td>NS</td>
<td>Porta et al. (7)</td>
</tr>
<tr>
<td>Gefitinib or 28</td>
<td>EGFRM+</td>
<td>83%</td>
<td>15.9 months</td>
<td>Park et al. (8)</td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td>9</td>
<td>EGFRM+</td>
<td>89%</td>
<td>NS</td>
<td>Li (19)</td>
</tr>
<tr>
<td>Gefitinib or 23</td>
<td>Non Smoker Asian</td>
<td>74%</td>
<td>18.8 months</td>
<td>Kim et al. (20)</td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>40</td>
<td>Non-selective</td>
<td>86%</td>
<td>11.8 months</td>
<td>Welsh et al. (21)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>41</td>
<td>EGFRM+</td>
<td>88%</td>
<td>21.9 months</td>
<td>Iuchi et al. (22)</td>
</tr>
<tr>
<td>Afatinib</td>
<td>32</td>
<td>EGFRM+, TKI-treatment history</td>
<td>35%</td>
<td>9.8 months</td>
<td>Hoffknecht et al. (23)</td>
</tr>
</tbody>
</table>

But benefit short in time...

Current EGFR TKIs cannot effectively treat CNS and LM at the approved doses

<table>
<thead>
<tr>
<th></th>
<th>CSF concentration</th>
<th>CSF penetration rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>3.7 +/- 1.9 ng/ml</td>
<td>1.13 +/- 0.36%</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>28.7 +/- 16.8 ng/ml</td>
<td>2.77 +/- 0.45%</td>
</tr>
</tbody>
</table>

Kpuu, CSF (ratio of cerebral spinal fluid concentration/free plasma concentration)

Kpuu,brain is well established as a good predictor of BBB permeability, with values greater than 0.3 indicative of good diffusion across the BBB.
Erlotinib was deemed more effective than gefitinib in preventing intracranial lesions and prolonging survival

Retrospective analysis
Single institution

Jumpei Kashima et al, Med Oncol 2016
EGFR TKI Pulse administration?

Up to 10-fold increases of approved doses of gefitinib or erlotinib transiently reach the predicted efficacious concentration in CSF and demonstrate modest palliative effect.
Pulse administration: modest palliative effect
- But patients could not tolerate long term treatment due to serious adverse effects
- In addition, the response duration very short
EGFR TKIs plus WBRT demonstrated no survival benefit than TKIs alone in NSCLC patients with EGFR mutation and brain metastases

- 230 patients were retrospectively collected
- Chinese population

- Addition of WBRT to EGFR TKIs did not appear to have survival benefit superior to that of EGFR TKIs alone in with EGFR-mutant NSCLC with BM.

- WBRT also did not bring additional benefit to chemotherapy in patients with BM and EGFR of wild-type or unknown status.

Study Design (NCT01724801)

Phase III Trial Comparing WBI and Chemotherapy with Icotinib

- Advanced NSCLC with BM
- EGFR mutation & EGFR TKIs naive
- Brain metastatic sites ≥ 3
- 18-75 years
- Life expectancy ≥ 12 weeks
- ECOG PS score 0-1

R: 1 : 1

Icotinib arm 125mg tid

WBI ARM 30GY/3GY/10F ± Chemo

Icotinib+ chemo

WBI+ icotinib/chemo

Icotinib 125mg tid

PD

survival follow-up

Primary endpoint:
Intracranial progression-free survival (iPFS)

Secondary endpoints:
Progression–free survival (PFS)
Intracranial Objective response rate (iORR);
Overall survival (OS)
Safety and tolerability

PL03.05: WBI vs. Icotinib in EGFR mutant NSCLCs with brain M (CTONG 1201) by Yi-long Wu

Yan JJ et al, Lancet Respir Med 2017
Intracranial RR and overall RR

Intracranial ORR

- Icotinib: 40.9% (Δ26.2%, P < 0.001)
- WBI±Chemo: 67.1% (84.7%)

Intracranial DCR

- Icotinib: 11.1% (Δ17.6%, P=0.014)
- WBI±Chemo: 54.8% (78.8%)

Overall ORR

- Icotinib: 55.0% (Δ43.9%, P < 0.001)
- WBI±Chemo: 78.8% (84.7%)

Overall DCR

- Icotinib: 1.8% (Δ24.0%, P=0.001)
- WBI±Chemo: 54.8% (78.8%)

Yan JJ et al, Lancet Respir Med 2017
Primary endpoint: iPFS

PL03.05: WBI vs. Icotinib in EGFR mutant NSCLCs with brain M (CTONG 1201) by Yi-long Wu

Yan JJ et al, Lancet Respir Med 2017
Secondary endpoint: PFS

**Factors**

<table>
<thead>
<tr>
<th>N</th>
<th>PFS</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>64</td>
<td>0.69 (0.40~1.17)</td>
</tr>
<tr>
<td>Female</td>
<td>94</td>
<td>0.31 (0.19~0.50)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60 years</td>
<td>97</td>
<td>0.41 (0.26~0.63)</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>61</td>
<td>0.52 (0.30~0.91)</td>
</tr>
<tr>
<td><strong>ECOG Performance Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>20</td>
<td>0.35 (0.13~0.93)</td>
</tr>
<tr>
<td>1</td>
<td>137</td>
<td>0.48 (0.33~0.70)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>112</td>
<td>0.42 (0.27~0.69)</td>
</tr>
<tr>
<td>Yes</td>
<td>46</td>
<td>0.49 (0.26~0.88)</td>
</tr>
<tr>
<td><strong>EGFR mutation status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>exon 19 mutation</td>
<td>93</td>
<td>0.36 (0.22~0.57)</td>
</tr>
<tr>
<td>exon 21 (L858R) mutation</td>
<td>57</td>
<td>0.52 (0.29~0.94)</td>
</tr>
<tr>
<td>Uncommon mutation</td>
<td>8</td>
<td>2.12 (0.46~9.71)</td>
</tr>
<tr>
<td><strong>The Brain metastases Symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>132</td>
<td>0.44 (0.30~0.64)</td>
</tr>
<tr>
<td>Yes</td>
<td>26</td>
<td>0.52 (0.23~1.18)</td>
</tr>
<tr>
<td><strong>Treatment line</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-line</td>
<td>145</td>
<td>0.45 (0.31~0.64)</td>
</tr>
<tr>
<td>Second-line</td>
<td>13</td>
<td>0.23 (0.04~1.45)</td>
</tr>
</tbody>
</table>

**NO. at Risk**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBI</td>
<td>73</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>Icotinib</td>
<td>85</td>
<td>61</td>
<td>22</td>
</tr>
</tbody>
</table>

**Progression-Free Survival (%)**

- WBI: 55.0% reduction in 6 months, 19.0% in 12 months
- Icotinib: 22.0% reduction in 6 months, 9.0% in 12 months

**Hazard ratio (95% CI):**

- WBI vs Icotinib: 0.44 (0.31~0.63)

- **5 months:**
  - WBI: 55.0%
  - Icotinib: 22.0%
  - Delta: 33%

- **12 months:**
  - WBI: 19.0%
  - Icotinib: 9.0%
  - Delta: 10%

- **Yan JJ et al, Lancet Respir Med 2017**
# Ongoing phase III studies of upfront EGFR TKI vs. WBRT in BM from EGFR-mutated NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparator</th>
<th>Primary endpoint</th>
<th>Secondary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02714010</td>
<td>Erlotinib, Gefitinib or Icotinib</td>
<td>iPFS</td>
<td>OS, ORR, cognitive QoL, toxicity</td>
</tr>
<tr>
<td>NCT02338011</td>
<td>Gefitinib</td>
<td>iPFS, sPFS</td>
<td>OS, QoL, mental status</td>
</tr>
</tbody>
</table>

**Study**: NCT02714010 - EGFR-TKI Concurrent With/Without WBRT in Brain Metastasis From NSCLC

**Comparator**: Erlotinib, Gefitinib or Icotinib

**Primary endpoint**: iPFS

**Secondary endpoints**: OS, ORR, cognitive QoL, toxicity

**Study**: NCT02338011 - Compare the effect and safety of gefitinib alone with gefitinib plus concomitant WBRT

**Comparator**: Gefitinib

**Primary endpoint**: iPFS, sPFS

**Secondary endpoints**: OS, QoL, mental status
Brain Metastases in TKI–Naive EGFR NSCLC: A Retrospective Multi-Institutional Analysis

SRS followed by EGFR-TKI resulted in the longest OS

prospective, multi-institutional randomized trial of SRS followed by EGFR-TKI versus EGFR-TKI followed by SRS at intracranial progression is urgently needed

William J. Magnuson et al, JCO 2017
Novel agents are an area of need:
Osimertinib is selective for EGFR sensitising mutations (L858R and exon19del) and T790M mutations
Osimertinib a new standard – EGFR+

1\textsuperscript{st} line vs EGFR-TKI and 2\textsuperscript{nd} line vs chemoT (T790M+)

At resistance (EGFR- T790M+)

First line EGFRm+

EGFR T790M+
AURA3 trial (Osimertinib vs ChemoT)

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>Median PFS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30 (0.22, 0.41)</td>
<td>10.1 (8.3, 12.3)</td>
</tr>
</tbody>
</table>

OSIMERTINIB FIRST LINE VS GEFTINIB OR ERLOTINIB

FLAURA TRIAL

342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)

T.Mok et al, NEJM 2017
AZD9291 (osimertinib) is distributed to mouse brain to a greater extent than gefitinib, CO-1686, or afatinib

AZD9291 and gefitinib p.o.

AZD9291 25 mg/kg and gefitinib 6.25 mg/kg mouse brain and plasma concentrations

AZD9291, gefitinib, CO-1686, and afatinib p.o. plasma and brain C_{max}

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>AZD9291</th>
<th>Gefitinib</th>
<th>CO-1686</th>
<th>Afatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>25</td>
<td>6.25</td>
<td>100</td>
<td>7.5</td>
</tr>
<tr>
<td>Plasma C_{max} (µM)</td>
<td>0.82</td>
<td>0.82</td>
<td>3.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Brain C_{max} (µM)</td>
<td>2.8</td>
<td>0.17</td>
<td>BLQ</td>
<td>BLQ</td>
</tr>
<tr>
<td>Brain/plasma ratio</td>
<td>3.4</td>
<td>0.21</td>
<td>NC</td>
<td>NC</td>
</tr>
</tbody>
</table>

BLQ, below limit of quantification (CO-1686 0.25 µM, afatinib 0.05 µM); C_{max}, maximum concentration; NC, not calculated; p.o., orally. Doses are equivalent to clinical doses or reported previously for preclinical studies.

Osimertinib shown to have a good Kpuu,brain value (0.39) compared with other currently available TKIs and rociletinib, suggesting it has the potential to achieve good brain exposure

Anti-tumour efficacy of AZD9291 (osimertinib) and gefitinib (bioluminescence) in PC9 mouse brain mets model

- **AZD9291** (osimertinib) is efficacious in the PC9 (EGFRm+) mouse brain mets model
  - AZD9291 at 25 mg/kg in mouse approximates 80 mg once daily clinical exposure
  - **Gefitinib** at 6.25 mg/kg in mouse approximates 250 mg once daily clinical exposure

[\textsuperscript{11}C]AZD9291 (osimertinib) showed marked exposure in the cynomolgus monkey brain in contrast to other EGFR-TKIs.

**[\textsuperscript{11}C]AZD9291**

**[\textsuperscript{11}C]AZD9291** Head/neck

Radioactivity (kBq/cc)

Abdomen

Radioactivity (kBq/cc)

**Radiolabeled imaging**

<table>
<thead>
<tr>
<th></th>
<th>Brain to blood ratio</th>
<th>AUC_{0–90 min}</th>
</tr>
</thead>
<tbody>
<tr>
<td>[\textsuperscript{11}C]AZD9291</td>
<td>2.6 ± 1.4*</td>
<td></td>
</tr>
<tr>
<td>[\textsuperscript{11}C]CO-1686</td>
<td>0.025†</td>
<td></td>
</tr>
</tbody>
</table>

**[\textsuperscript{11}C]CO-1686**

Brain metastases – Case Study 1

- **Sixty-three-year-old Korean female diagnosed with advanced NSCLC (exon 19 deletion) in December 2010**


- AZD9291 40 mg daily started 7 August 2013 in T790M+ expansion cohort, best response PR, with non-CR/non-PD reported in NTLs (including evidence of shrinkage in brain mets) from 18 August 2013 and is still ongoing at 40 mg (11 months NTL response)

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MRI, magnetic resonance imaging; NTL, non-target lesion
Brain metastases – Case Study 2

Sixty-year-old Taiwanese female diagnosed with advanced NSCLC (L858R) in January 2011


- AZD9291 80 mg daily started 2 September 2013 in expansion cohort, best response PR. A single brain met target lesion decreased from 13 mm at baseline to 12 mm at Week 6, 8 mm at Week 12–18 (38% shrinkage). NTLs including brain mets had non-CR/non-PD reported for 4 months between 8 October 2013 to 2 January 2014, but progressed in the brain met NTLs on 13 February 2014

Brain MRI
A) Baseline on 9 August 2013. B) 8 October 2013

NE, not evaluable
Pooled analysis of two Phase II studies (AURA extension and AURA2), CNS target lesions show shrinkage from baseline

- Median best percentage change from baseline in CNS target lesion size was -53% (range: -100% – +80%)

n=50 Patients with ≥1 measurable CNS lesion

The CNS ORR was 54% (95% CI 39, 68)
CNS overall response rate was encouraging

- Confirmed complete response rate was 12%
- 82% of patients responded by time of first assessment (within 6 weeks)
- CNS DCR was 92%
- CNS responses were observed regardless of prior brain radiation

### Patients evaluable for CNS response (n=50)

<table>
<thead>
<tr>
<th></th>
<th>Complete response, n (%)</th>
<th>Partial response, n (%)</th>
<th>Stable disease ≥6 weeks, n (%)</th>
<th>Progressive disease, n (%)</th>
<th>Not evaluable, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CNS ORR</strong>, %</td>
<td>6 (12)</td>
<td>21 (42)</td>
<td>19 (38)</td>
<td>3 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>CNS DCR</strong>, %</td>
<td>92 (95% CI 81, 98)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CNS response based on prior brain RT status*

<table>
<thead>
<tr>
<th>Prior RT ≤6 months before first dose, n</th>
<th>CNS ORR, %</th>
<th>Complete response / partial response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 / 50</td>
<td>32% (95% CI 13, 57)</td>
<td>11 / 21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No prior RT or RT &gt;6 months before first dose, n</th>
<th>CNS ORR, %</th>
<th>Complete response / partial response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 / 50</td>
<td>68% (95% CI 48, 83)</td>
<td>13 / 55</td>
</tr>
</tbody>
</table>

Population: evaluable for response
Scans were performed at baseline and every 6 weeks thereafter until RECIST disease progression
RT, radiation therapy

DCR is calculated from the percentage of patients with a best overall CNS response of complete response, partial response, or stable disease at ≥6 weeks, prior to CNS progression
No objective response includes stable disease, non-evaluable and disease progression
*Responses required confirmation after 4 weeks
Clinically meaningful efficacy in the CNS

- At 9 months, 75% (95% CI 53, 88) of patients were estimated to remain in CNS response without progression or death

<table>
<thead>
<tr>
<th>CNS PFS by BICR</th>
<th>Total (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up for CNS PFS*</td>
<td>11.2 months</td>
</tr>
<tr>
<td>CNS progression or death#</td>
<td>19 / 50</td>
</tr>
<tr>
<td>Maturity</td>
<td>38%</td>
</tr>
<tr>
<td>Median CNS PFS#, months</td>
<td>NC (95% CI 7, NC)</td>
</tr>
<tr>
<td>Progression-free</td>
<td></td>
</tr>
<tr>
<td>at 6 months§</td>
<td>72% (95% CI 57, 83)</td>
</tr>
<tr>
<td>at 12 months§</td>
<td>56% (95% CI 40, 70)</td>
</tr>
</tbody>
</table>
AURA3 study design

Progression following 1\textsuperscript{st} line, T790M+

Key eligibility criteria

- ≥18 years (≥20 years in Japan)
- Locally advanced or metastatic NSCLC
- Evidence of disease progression following first-line EGFR-TKI therapy
- Documented EGFRm and central confirmation of tumour EGFR T790M mutation from a tissue biopsy taken after disease progression on first-line EGFR-TKI treatment
- WHO performance status of 0 or 1
- No more than one prior line of treatment for advanced NSCLC
- No prior neo-adjuvant or adjuvant chemotherapy treatment within 6 months prior to starting first EGFR-TKI treatment
- Stable* asymptomatic CNS metastases allowed

Endpoints

Primary:
- PFS by investigator assessment (RECISTv1.1)

Secondary and exploratory:
- Overall survival
- Objective response rate
- Duration of response
- Disease control rate
- Tumour shrinkage
- BICR-assessed PFS
- Patient reported outcomes
- Safety and tolerability

Optional crossover
Protocol amendment allowed patients on chemotherapy to begin post-BICR confirmed progression open-label osimertinib treatment

Endpoints

Primary:
- PFS by investigator assessment (RECISTv1.1)

Secondary and exploratory:
- Overall survival
- Objective response rate
- Duration of response
- Disease control rate
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- BICR-assessed PFS
- Patient reported outcomes
- Safety and tolerability

Optional crossover
Protocol amendment allowed patients on chemotherapy to begin post-BICR confirmed progression open-label osimertinib treatment
### PFS benefit with osimertinib observed across all subgroups in AURA3

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall (n=419)</strong></td>
<td></td>
</tr>
<tr>
<td>Cox proportional hazards</td>
<td>0.37 (0.29, 0.48)</td>
</tr>
<tr>
<td>Log rank (primary)</td>
<td>0.30 (0.23, 0.41)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Asian (n=274)</td>
<td>0.32 (0.24, 0.44)</td>
</tr>
<tr>
<td>Non-Asian (n=145)</td>
<td>0.48 (0.32, 0.75)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male (n=150)</td>
<td>0.43 (0.28, 0.65)</td>
</tr>
<tr>
<td>Female (n=269)</td>
<td>0.34 (0.25, 0.47)</td>
</tr>
<tr>
<td><strong>Age at screening</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;65 (n=242)</td>
<td>0.38 (0.28, 0.54)</td>
</tr>
<tr>
<td>≥65 (n=177)</td>
<td>0.34 (0.23, 0.50)</td>
</tr>
<tr>
<td><strong>EGFR-TKI sensitising mutation status prior to start of study</strong></td>
<td></td>
</tr>
<tr>
<td>Exon 19 deletion (n=279)</td>
<td>0.34 (0.24, 0.46)</td>
</tr>
<tr>
<td>L858R (n=128)</td>
<td>0.46 (0.30, 0.71)</td>
</tr>
<tr>
<td><strong>Duration of prior EGFR-TKI</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;6 months (n=24)</td>
<td>NC</td>
</tr>
<tr>
<td>≥6 months (n=395)</td>
<td>0.39 (0.30, 0.51)</td>
</tr>
<tr>
<td><strong>CNS metastases</strong></td>
<td></td>
</tr>
<tr>
<td>Yes (n=144)</td>
<td>0.32 (0.21, 0.49)</td>
</tr>
<tr>
<td>No (n=275)</td>
<td>0.40 (0.29, 0.55)</td>
</tr>
<tr>
<td><strong>Smoking history</strong></td>
<td></td>
</tr>
<tr>
<td>Ever (n=136)</td>
<td>0.40 (0.27, 0.62)</td>
</tr>
<tr>
<td>Never (n=283)</td>
<td>0.36 (0.26, 0.49)</td>
</tr>
</tbody>
</table>

Population: intent-to-treat

HR <1 implies a lower risk of progression on osimertinib 80 mg. Cox proportional hazards model includes randomised treatment, the subgroup covariate of interest, and the treatment by subgroup interaction. Size of circle is proportional to the number of events. Overall population analysis was performed using a Cox proportional hazards model and the primary analysis (U and V statistics) from stratified log-rank test. If there were <20 events in a subgroup then the analysis was not performed; NC, non-calculable.
## CNS overall response

**Evaluable for response set**

<table>
<thead>
<tr>
<th></th>
<th>Osimertinib 80 mg</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CNS ORR (95% CI)</strong></td>
<td>70% (51, 85)</td>
<td>31% (11, 59)</td>
</tr>
<tr>
<td><strong>Odds ratio (95% CI)</strong></td>
<td>5.13 (1.44, 20.64); p=0.015</td>
<td></td>
</tr>
<tr>
<td><strong>Median time to response, weeks</strong></td>
<td>6.1</td>
<td>6.1</td>
</tr>
<tr>
<td><strong>Median DoR, months (95% CI)</strong></td>
<td>8.9 (4.3, NC)</td>
<td>5.7 (NC, NC)</td>
</tr>
<tr>
<td><strong>DCR (95% CI)</strong></td>
<td>93% (78, 99)</td>
<td>63% (35, 85)</td>
</tr>
</tbody>
</table>

- CNS ORR in patients who had brain RT within 6 months of randomization vs no prior brain RT or RT ≥6 months before randomization (full analysis set) were:
  - Osimertinib: 64% (9/14) (95% CI 35, 87) and 34% (21/61) (95% CI 23, 48)
  - Chemotherapy: 22% (2/9) (95% CI 2, 60) and 16% (5/32) (95% CI 5, 33)

---

Populations: CNS evaluable for response set: patients with ≥1 measureable CNS metastases on baseline brain scan by BICR. CNS full analysis set: patients with ≥1 measureable and/or non-measurable CNS metastases on baseline brain scan by BICR

Data cut-off: April 15, 2016. CR, complete response; DoR, duration of response; NE, not evaluable; NC, not calculable; ORR, objective response rate; PD, progressive disease; PR, partial response; RT, radiotherapy; SD, stable disease; *response did not require confirmation
Tumor response in CNS

Evaluable for response set

- Median baseline CNS target lesion size:
  - 16.3 mm (range 10–60 mm)
- Median best percentage change from baseline in CNS target lesion size:
  - -43% (range -100% to +20%)

- Median baseline CNS target lesion size:
  - 16.2 mm (range 11–56 mm)
- Median best percentage change from baseline in CNS target lesion size:
  - -16% (range -100% to +20%)

Population: CNS evaluable for response set: patients with ≥1 measurable CNS metastases on baseline brain scan by BICR

Data cut-off: April 15, 2016. *1 patient was not evaluable due to no evaluable follow-up assessments. #Best % change in CNS target lesions for 3 patients with stable disease could not be imputed as the patients did not meet any of the three imputation criteria, 2 patients were not evaluable due to death (n=1) and study withdrawal due to progressive disease (n=1)
CNS PFS in AURA3

CNS full analysis set

Population: CNS full analysis set: patients with ≥1 measureable and/or non-measurable CNS metastases on baseline brain scan by BICR
Data cut-off: April 15, 2016
*Censored patients only; #Only includes progression events that occurred within 19 weeks of the last evaluable assessment; §Estimated by Kaplan-Meier technique,

<table>
<thead>
<tr>
<th>Median CNS PFS, months</th>
<th>n</th>
<th>CNS PFS</th>
<th>HR (95%, CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib 80mg</td>
<td>75</td>
<td>11.7</td>
<td>0.32 (0.15-0.69); p=0.004</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>41</td>
<td>4.2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median CNS PFS, months</th>
<th>n</th>
<th>CNS PFS</th>
<th>HR (95%, CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib 80mg</td>
<td>93</td>
<td>8.5</td>
<td>0.32 (0.21-0.49); p&lt;0.001</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>51</td>
<td>4.2</td>
<td></td>
</tr>
</tbody>
</table>

Overall population

<table>
<thead>
<tr>
<th>Median PFS, months</th>
<th>CNS metastases : Yes</th>
<th>CNS metastases : No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>PFS</td>
</tr>
<tr>
<td>Osimertinib 80mg</td>
<td>93</td>
<td>8.5</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>51</td>
<td>4.2</td>
</tr>
</tbody>
</table>
Probability of experiencing a CNS progression event lower for osimertinib

Full analysis set

<table>
<thead>
<tr>
<th>Type of event, n %</th>
<th>Osimertinib 80mg n=75</th>
<th>Chemotherapy n=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS progression</td>
<td>11 (15)</td>
<td>10 (24)</td>
</tr>
<tr>
<td>Non-CNS progression</td>
<td>19 (25)</td>
<td>15 (37)</td>
</tr>
<tr>
<td>Death</td>
<td>8 (11)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Censored</td>
<td>37 (49)</td>
<td>12 (29)</td>
</tr>
</tbody>
</table>

CNS conditional probability
- At 3 months, % (95% CI): **2.7 (0.8, 9.6)** 8.2 (2.3, 28.7)
- At 6 months, % (95% CI): **11.5 (5.9, 22.4)** 28.2 (16.6, 48.0)

- The probability of experiencing a CNS progression event (conditional on the patient not experiencing a competing risk at that time) was lower for osimertinib than for chemotherapy at both 3 and 6 months

- There is **clear separation of the cumulative incidence curves** in favour of osimertinib, for both CNS and non-CNS progression, for the duration of the follow-up period

Population: CNS full analysis set: patients with ≥1 measurable and/or non-measurable CNS metastases on baseline brain scan by BICR

Data cut-off: April 15, 2016
A competing risk analysis with CNS progression, non-CNS progression and death as competing events was conducted.

For each patient, the first event of CNS progression, non-CNS progression or death was counted.

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (N=151)</th>
<th>Alectinib (N=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with events, n (%)</td>
<td>68 (45)</td>
<td>18 (12)</td>
</tr>
</tbody>
</table>

Cause-specific HR
(95% CI)
P-value (log-rank test)

0.16
(0.10–0.28)
P<0.0001

Crizotinib 12 month CIR: 41.4% (95% CI, 33.2–49.4)
Alectinib 12 month CIR: 9.4% (95% CI, 5.4–14.7)
1st line EGFR+ CNS efficacy in FLAURA

- CNS progression in patient with CNS met at presentation:
  - Osimertinib: 10/53 (18.9%)
  - SoC: 27/63 (42.7%)

- CNS progression in patients without CNS met at presentation:
  - Osimertinib: 5 patients
  - SoC: 17 patients

With CNS metastases (n=116)

Hazard Ratio 0.47 (95% CI 0.30, 0.74)

Median PFS, months (95% CI)
- Osimertinib: 15.2 (12.1, 24.4)
- SoC: 9.6 (7.0, 12.4)

T.Mok, ESMO 2017
So what does this mean?

▲ *Osimertinib is highly active in the brain*
   - Rapid, durable responses
   - Active against LM disease

▲ *Osimertinib is protective against CNS metastases*
   - Without compromising PFS
   - An early switch to osimertinib on PD: preferred
   - Questions « treatment beyond PD » on 1st line TKI and role of CNS RT?
New drug...AZD3759

- AZD3759 is an oral, CNS penetrable, reversible inhibitor of EGFR activating mutations, designed to achieve high free-drug exposure in brain, CSF and plasma.

- AZD3759 shows profound anti-tumor efficacy in pre-clinical BM and LM models\(^6,7\), and promising anti-tumor activity in TKI relapsed patients with CNS metastases in dose escalation cohorts of BLOOKM study.
First and second generation EGFR-TKIs modestly penetrate Blood Brain Barrier (BBB)

AZD3759 outstanding BBB characteristics

AZD3759 is not a substrate
- of PGP
- or BCRP efflux transporters

Median $K_{puu,\text{brain}} = 0.86$

$K_{puu,\text{CSF}}$ (cerebral spinal fluid [CSF] concentration/free plasma concentration)

Significantly prolonged animal survival in PC-9 BM model, compared with gefitinib, erlotinib, icotinib

Kim DW, et al. ASCO 2015
BLOOM study design overview

Phase I study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumor efficacy of AZD3759 or osimertinib in patients with EGFRm advanced NSCLC

---

**Dose escalation**

- AZD3759
- Cohort 1: 50 mg BID
- Cohort 2: 200 mg BID
- Cohort 3: 300 mg BID
- Cohort 4: 500 mg BID
- Cohort 5: 200 or 300 mg BID

**Dose expansion cohorts**

- Leptomeningeal metastasis
  - TKI naïve (n = 4) or pre-treated* (n = 18)
- Brain metastasis
  - TKI naïve (n = 16)

---

**Osimertinib**

- 160 mg QD
- TKI pre-treated LM

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

---

*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; BID, twice daily; QD, once daily

This presentation only covers AZD3759 TKI naïve BM (n = 16) and LM (n = 4) cohorts
Promising intracranial anti-tumor efficacy

- 15 out of 18 (83%) patients with measurable BM lesions at baseline had confirmed objective response, 14 PRs and 1 CR.
- Median best % change of intracranial target lesions was -54% (ranging -100% to 0)
- 16 patients were still on AZD3759 treatment at data cut-off on December 12th, 2016.
Promising extracranial anti-tumor efficacy

Best % change of extracranial target lesions

% change of extracranial target lesion size with time

- 13 out of 18 (72%) patients with extracranial lesions had confirmed objective response 11 PRs and 2 CRs (these two patients had non-target lesions at baseline).
- Median best % change of extracranial target lesions was -50% (ranging -74% to -20%)
- 12 patients were still responding at data cut-off on December 12th, 2016

Patients with extracranial target lesions at baseline and at least one RECIST assessment were included. *: confirmed response
BLOOM study design overview

Phase I study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumor efficacy of AZD3759 or osimertinib in patients with EGFRm advanced NSCLC

AZD3759

Cohort 1
100 mg BID

Cohort 2
200 mg BID

Cohort 3
300 mg BID

Cohort 4
500 mg BID

Cohort 5
500 mg BID

Dose expansion cohorts

Leptomeningeal metastasis
- TKI naïve (n = 4) or pre-treated* (n = 18)

Brain metastasis
- TKI naïve (n = 16)

200 or 300 mg BID*

Osimertinib
160 mg QD

TKI pre-treated LM

Cohort 1: T790M unselected LM (n = 21)

Cohort 2: T790M+ LM (n = 20)

*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; BID, twice daily; QD, once daily

This presentation only covers AZD3759 TKI naïve BM (n = 16) and LM (n = 4) cohorts
BLOOM study: duration of exposure (T790M unselected cohort, n=21)

- Median duration of exposure: 12.4 months (range: 0–22 months)
- 5 patients (24%): dose reduction
- 4 patients (19%): dose reduction due to an AE

ae, discontinued treatment due to an AE; D, died; dc, discontinued treatment; dcD, discontinued and died; QD, once daily.

James Chih-Hsin Yang et al, ASCO 2017
**BLOOM study: osimertinib activity across LM assessments**

Overall LM response by investigator assessment in the evaluable for LM response analysis set (*T790M unselected cohort, n=21*)

<table>
<thead>
<tr>
<th>LM response*, % (95% CI)</th>
<th>T790M unselected cohort (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best LM response, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Complete response*</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Responding*</td>
<td>8 (38%)</td>
</tr>
<tr>
<td>Stable disease (≥ 6 weeks)</td>
<td>9 (43%)</td>
</tr>
<tr>
<td>Progression</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>2 (10%)</td>
</tr>
</tbody>
</table>

Median duration of response

18.9 months
(range: 5.6–19.3 months; 95% CI 11.1, NC)

*Response for LM is defined as at least one confirmed response of Complete Response or Responding (as defined by investigator’s assessment), requires confirmation after 4 weeks.

LM, leptomeningeal metastases.

James Chih-Hsin Yang et al, ASCO 2017
BLOOM study: dynamic changes in EGFR-mutant DNA copy number in T790M unselected cohort \((\text{mutant DNA copies/mL; } n=15)\)

From screening to Cycle 2 Day 1, mean decrease in EGFR-mutant DNA copy: 39% in 15/21
CNS responses in pts with leptomeningeal metastases at baseline (AURA 3: Progression following 1st line, T790M+)

Full analysis set

- Patients with leptomeningeal metastases (LM) were not excluded from the trial
- Retrospective independent radiological review based on RANO-LM\(^1\) identified LM in 7/116 patients with CNS metastases at baseline in the osimertinib arm
- **4 out of 7 patients had a LM response**
  - 2 patients had a complete LM response
  - 2 patients had a partial LM response
- In patients with an LM response, clinical activity was also seen in the CNS and systemically

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Prior brain radiotherapy</th>
<th>Best objective response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LANO RANO-LM score</td>
</tr>
<tr>
<td>Osimertinib 80 mg</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>CR</td>
</tr>
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<td>No</td>
<td>PR</td>
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<td>No</td>
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<td>No</td>
<td>SD</td>
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<tr>
<td></td>
<td>Yes</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>SD</td>
</tr>
</tbody>
</table>

Data cut-off: April 15, 2016
Population: CNS full analysis set: patients with ≥1 measurable and/or non-measurable CNS metastases on baseline brain scan by BICR
In conclusion

- In EGFRm NSCLC, brain increasingly become a sanctuary site where the BBB may offer protection from pharmacological agents

- Poor penetration rates of 1st /2nd generation EGFR-TKIs across the BBB

- Role of systemic chemotherapy is controversial

- 3rd EGFR TKI like osimertinib is particularly promising in BM or LM population:
  - Osimertinib approved by the FDA/EMA for treatment of patients with NSCLC harboring a T790M mutation
  - Moving in 1st line … FLAURA trial

- AZD3759 outstanding BBB characteristics

- Further evaluation of in larger clinical studies is required alone and in combination with brain irradiation
Optimal sequence for EGFR mutation?

First generation TKI (10 months)
- Gefitinib, erlotinib

Osimertinib for T790M (10 months)

Chemo (5 months)

Second generation TKI (14-16 months)
- Afatinib, dacomitinib

Osimertinib for T790M (10 months)

Chemo (5 months)

A place for radiotherapy?

Osimertinib (19 months)

Chemo (5 months)
THANK YOU!

Acknowledgments
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Benjamin BESSE
Thierry Le Chevalier

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