TREATMENT OF EGFR TKI RESISTANT PATIENTS WITH T790M

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ESMO Advanced course Seoul (2016.10.28)
Molecular mechanisms of acquired resistance in lung cancer to EGFR TKIs

2. Plotrowska z et al Cancer Discov 2015;5;713-722
Heterogeneity even in T790M mutant tumors

- Pre-existing EGFR
- Evolution
- Drug tolerant
- Other

46% with > 1 resistance mechanism after 1st line EGFR TKI

T790M + SCNA + SNV 5%
T790M + SNV 7%
T790M + SCNA 34%
T790M only 54%

1. Piotrowska z et al Cancer Discov 2015;5;713-722
Before 2015, there was no specific treatment options for patients with EGFR T790M NSCLC who have received prior EGFR TKI therapy

- IMPRESS trial did not show any survival advantage receiving platinum doublet chemotherapy following progression on gefitinib

![Graph showing PFS (primary endpoint; ITT)]

**Mok TSK, et al. Lancet Oncol 2015**
History of EGFR and EGFR TKIs


EGFR isolated
EGFR TKI developed
Gefitinib FDA approved
T790M mutation
I-PASS
OPTIMAL EURTAC
AZD9291 CO1686

Phase I Gefitinib
EGFR Mutation Isolated Erlotinib FDA approved
FIRST signal NEJ002
LUX-LUNG 3 and 6
Resistance Development

How does T790M cause resistance to EGFR-TKIs?

Prevention of EGFR-TKI binding

Increased ATP-binding affinity

T790M arises from a mutation; substitution of threonine for methionine in the mutant causes steric hindrance, which reduces early generation EGFR-TKI binding.\(^1\)

T790M increases the binding affinity of EGFR for ATP, resulting in reduced potency of EGFR-TKIs.\(^2\)

### Development of 3rd Generation EGFR TKI to overcome T790M mutation

- Targeting both activating EGFR mutations and T790M but sparing wild type EGFR, leading to less toxicity on skin or GI tract

<table>
<thead>
<tr>
<th>Agents</th>
<th>Binding mode</th>
<th>$\text{EGFR}^{L858R} \text{IC}_{50}$ (nM)</th>
<th>$\text{EGFR}^{L858R/T790M} \text{IC}_{50}$ (nM)</th>
<th>$\text{EGFR WT} \text{IC}_{50}$ (nM)</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>WZ 4002</td>
<td></td>
<td>2</td>
<td>8</td>
<td>Not inhibited</td>
<td>Pyrimidine</td>
</tr>
<tr>
<td>CO-1686</td>
<td>Irreversible</td>
<td>6</td>
<td>&lt; 1</td>
<td>&gt; 2000</td>
<td>Pyrimidine</td>
</tr>
<tr>
<td>(Rociletinib)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZD9291</td>
<td>Irreversible</td>
<td>6.6</td>
<td>2.5</td>
<td>1684</td>
<td>Pyrimidine</td>
</tr>
<tr>
<td>(Osimertinib)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BI 1482694</td>
<td>Irreversible</td>
<td>14.6</td>
<td>2.9</td>
<td>101</td>
<td>Pyrimidine</td>
</tr>
<tr>
<td>(Olmutinib)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASP8273</td>
<td>Irreversible</td>
<td>8-33</td>
<td>26</td>
<td>230</td>
<td>Pyrimidine</td>
</tr>
<tr>
<td>EGF816</td>
<td>Covalent inhibitor</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Efficacy of 3rd generation EGFR TKIs

- AZD9291 and Rociletinib have been granted breakthrough therapy designation by FDA in 2014 based on robust activity

AZD9291 in T790M positive (n=63/411)

<table>
<thead>
<tr>
<th>RR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>66/71%</td>
<td>9.7/11.0M</td>
</tr>
</tbody>
</table>

Rociletinib in T790M positive (n=46)

<table>
<thead>
<tr>
<th>RR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>59%</td>
<td>8.0M</td>
</tr>
</tbody>
</table>
Efficacy of 3\textsuperscript{rd} generation EGFR TKIs

BI 148264 (Olmutinib) in T790M positive (n=76)

PR (n=43)
Confirmed PR (n=32)
SD (n=20)
NE (n=3)
PD (n=3)

RR 62%
(cPR46%)
PFS 9.6M

Park et al ELCC 2016,
Efficacy and side effects of 3rd generation EGFR TKIs

<table>
<thead>
<tr>
<th>Agents</th>
<th>ORR</th>
<th>PFS</th>
<th>G3/ 4Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD9291 (Osimertinib)</td>
<td>71%</td>
<td>11.0m</td>
<td>ILD (2%)</td>
</tr>
<tr>
<td>CO-1686 (Rociletinib)</td>
<td>59%</td>
<td>13.1m</td>
<td>Hyperglycemia (17%) QTc (2.5%)</td>
</tr>
<tr>
<td>BI 1482694 (Olmutinib)</td>
<td>62%</td>
<td>9.6m</td>
<td>Palmar-Plantar erythrodysesthesia (3%) Skin rash (5%) ALT/AST (3%)</td>
</tr>
</tbody>
</table>

- Unfortunately, further development of rociletinib (by Clovis) and BI1482694 (by Boehringer Ingelheim) has been suspended.
- AZD 9291 is the only 3rd generation TKI approved by FDA.
AZD9291 binds irreversibly to EGFR kinase at the **cysteine-797 residue** in the ATP-binding site.

AZD9291 has a distinct chemical structure from other EGFR-TKIs e.g. rociletinib and WZ4002:

- Distinct monoanilinopyrimidine structure from other EGFR-TKIs *
- Electrophilic functionality resides on the pyrimidine C-2 substituent ring
- The pyrimidine 4-substituent is C-linked and heterocyclic
- The pyrimidine 5-position is devoid of substitution

AZD9291 chemical structure

*anilinoquinazolines

with permission from AACR
EGFR and 1st generation TKIs
T790M mutation
The efficacy of AZD 9291 \textit{in vivo} xenograft models

Cross DA et al. Cancer Discovery 2014;4:1046-1061
Patients with T790M-positive aNSCLC whose disease has progressed following either one prior therapy with an EGFR-TKI or following treatment with both EGFR-TKI and other anticancer therapy.

Rolling six design

AURA Phase II

- Escalation
  - Cohort 1 (20 mg)
    - Positive
  - Cohort 2 (40 mg)
    - Positive
  - Cohort 3 (80 mg, n=63)
    - Positive
    - Negative
  - Cohort 4 (160 mg)
    - Positive
    - Negative
  - Cohort 5 (240 mg)
    - Positive

AURA2 Ph II

- Expansion
  - Central T790M mutation testing* of biopsy sample collected following confirmed disease progression
  - T790M positive
  - T790M negative

- AURA Phase II Extension (n=201)
  - Osimertinib 80 mg QD
  - Negative
  - First-line
  - Biopsy
  - Tablet
  - Cytology

AURA Ph I/II AURA2 Ph II

Patients with confirmed EGFRm locally advanced or metastatic NSCLC who have progressed following prior therapy with an approved EGFR-TKI.

- Not eligible for enrollment

AURA Ph I data cut-off 4 January, 2016; AURA pooled Ph II data cut-off 1 November, 2015.

*The EGFR T790M mutation status of the patient’s tumour was prospectively determined by the designated central laboratory using the cobas™ EGFR Mutation Test (Roche Molecular Systems) by biopsy taken after confirmation of disease progression on the most recent treatment regimen. Data from cohorts in grayed out boxes are not included in the analyses reported here.
Dose escalation / expansion (Aura Phase I) and extension (Aura Extension) study design

**Primary objective** – assessment of the safety, tolerability and efficacy (ORR) of AZD9291 in patients with acquired resistance to EGFR-TKIs

**Escalation**
- Not preselected by T790M status

**Expansion**
- Enrolment by local testing followed by central laboratory confirmation (cobas™ EGFR Mutation Test) of T790M status or by central laboratory testing alone

<table>
<thead>
<tr>
<th>Cohort</th>
<th>dosage</th>
<th>T790M status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>20 mg</td>
<td>Positive</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>40 mg</td>
<td>Positive</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>80 mg</td>
<td>Positive</td>
</tr>
<tr>
<td>Cohort 4</td>
<td>160 mg</td>
<td>Positive</td>
</tr>
<tr>
<td>Cohort 5</td>
<td>240 mg</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**Rolling six design**

- T790M cohorts

**Phase II extension:** AZD9291 80 mg once daily in patients with T790M positive NSCLC who have progressed on EGFR-TKI

*Paired biopsy cohort patients with T790M positive tumours; safety and efficacy data only reported here

#Prior therapy not permissible in this cohort

##Not selected by mutation status, US only

§T790M positive from cytology specimen, Japan only

ORR, objective response rate

Pasi et al  ASCO 2015
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Escalation N=31</th>
<th>Expansion N=222</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male/Female</td>
<td>11/20 (35/65)</td>
<td>86/136 (39/61)</td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td>61 (39–81)</td>
<td>60 (28–88)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian/Asian/Other/Missing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/22/1/0 (26/71/3/0)</td>
<td>82/134/5/1 (37/60/2/0.5)</td>
<td></td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adeno/Squamous/Other/Missing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29/1/1/0 (94/3/3/0)</td>
<td>213/2/5/2 (96/1/2/1)</td>
<td></td>
</tr>
<tr>
<td>T790M status,* n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive/Negative/Unknown</td>
<td>Central testing not required for escalation</td>
<td>138/62/22 (62/28/10)</td>
</tr>
<tr>
<td>Prior regimens of systemic therapy, median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (1–12)</td>
<td>3 (1–12)</td>
<td></td>
</tr>
<tr>
<td>Prior EGFR-TKIs, median (range)#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regimen, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td>1 (1–4)</td>
<td>2 (1–5)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>22 (71)</td>
<td>128 (58)</td>
</tr>
<tr>
<td>Afatinib</td>
<td>15 (48)</td>
<td>128 (58)</td>
</tr>
<tr>
<td>1 (3)</td>
<td>51 (23)</td>
<td></td>
</tr>
<tr>
<td>Immediate prior EGFR-TKI, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/No/Missing</td>
<td>14/17/0 (45/55/0)</td>
<td>137/84/1 (62/38/0.5)</td>
</tr>
<tr>
<td>EGFR-TKI-sensitising mutation, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex19del/L858R/Other/None/Unknown</td>
<td>Central testing not required for escalation</td>
<td>112/65/10/13/22 (50/29/5/6/10)</td>
</tr>
</tbody>
</table>

*Central testing not required for escalation

Pasi et al  ASCO 2015
# All causality adverse events, all grade

<table>
<thead>
<tr>
<th>AE by preferred term occurring in at least 10% of patients overall</th>
<th>20 mg N=21</th>
<th>40 mg N=58</th>
<th>80 mg N=90</th>
<th>160 mg N=63</th>
<th>240 mg N=21</th>
<th>Total N=253</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>5 (24)</td>
<td>24 (41)</td>
<td>30 (33)</td>
<td>43 (68)</td>
<td>16 (76)</td>
<td>118 (47)</td>
</tr>
<tr>
<td>Rash (grouped term)</td>
<td>5 (24)</td>
<td>13 (22)</td>
<td>29 (32)</td>
<td>40 (63)</td>
<td>15 (71)</td>
<td>102 (40)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (14)</td>
<td>10 (17)</td>
<td>16 (18)</td>
<td>19 (30)</td>
<td>7 (33)</td>
<td>55 (22)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7 (33)</td>
<td>11 (19)</td>
<td>14 (16)</td>
<td>16 (25)</td>
<td>6 (29)</td>
<td>54 (21)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (14)</td>
<td>10 (17)</td>
<td>16 (18)</td>
<td>19 (30)</td>
<td>7 (33)</td>
<td>55 (22)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (19)</td>
<td>15 (26)</td>
<td>9 (10)</td>
<td>11 (17)</td>
<td>5 (24)</td>
<td>44 (17)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>2 (10)</td>
<td>5 (9)</td>
<td>11 (12)</td>
<td>18 (29)</td>
<td>6 (29)</td>
<td>42 (17)</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (14)</td>
<td>9 (16)</td>
<td>12 (13)</td>
<td>13 (21)</td>
<td>0</td>
<td>37 (15)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1 (5)</td>
<td>5 (9)</td>
<td>9 (10)</td>
<td>13 (21)</td>
<td>3 (14)</td>
<td>31 (12)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (14)</td>
<td>4 (7)</td>
<td>9 (10)</td>
<td>7 (11)</td>
<td>6 (29)</td>
<td>29 (11)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0</td>
<td>6 (10)</td>
<td>11 (12)</td>
<td>9 (14)</td>
<td>2 (10)</td>
<td>28 (11)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>0</td>
<td>1 (2)</td>
<td>3 (3)</td>
<td>2 (3)</td>
<td>0</td>
<td>6 (2)</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>0</td>
<td>2 (3)</td>
<td>4 (4)</td>
<td>4 (6)</td>
<td>1 (5)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Pneumonitis-like event*</td>
<td>0</td>
<td>0</td>
<td>2 (2)</td>
<td>4 (6)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Overall Response Rate

In the overall population:
- confirmed ORR was 51% (123/239; 95% CI 45%, 58%)
- DCR (CR+PR+SD) was 84% (95% CI 79%, 88%)

**ORR 51%**

**T790M + ORR 61% (70% at 80mg)**

**T790M - ORR 21%**
Progression free survival

A) T790M+ (95% CI)

B) T790M- (95% CI)

T790M + PFS 9.6M

T790M - PFS 2.8M

Pasi et al, ASCO 2015
Phase I Objective Response Rate (ORR) in patients with centrally confirmed T790M positive tumours, by Investigator assessment

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>160 mg</th>
<th>240 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (175)</td>
<td>10</td>
<td>32</td>
<td>61</td>
<td>59</td>
<td>13</td>
<td>175</td>
</tr>
<tr>
<td>Confirmed ORR (95% CI)</td>
<td>50% (19, 81)</td>
<td>62% (44, 79)</td>
<td>70% (54, 81)</td>
<td>56% (42, 69)</td>
<td>54% (25, 81)</td>
<td>62% (54, 69)</td>
</tr>
</tbody>
</table>

DCR (CR+PR+SD) in patients with centrally confirmed T790M positive tumours was 95% (166 /175; 95% CI 90, 98)
Duration of response (DoR) and Progression-free Survival (PFS) in AURA Phase I (80 mg dose)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>AURA Phase I 80 mg pre-treated T790M mutation positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N* (maturity)</td>
</tr>
<tr>
<td><strong>DoR (months)</strong></td>
<td>BICR</td>
</tr>
<tr>
<td></td>
<td>Investigator</td>
</tr>
<tr>
<td><strong>PFS (months)</strong></td>
<td>BICR</td>
</tr>
<tr>
<td></td>
<td>Investigator</td>
</tr>
</tbody>
</table>

Based on efficacy and adverse events, 80mg was defined as RPII dose

* For DoR n=number of responders who have subsequently progressed or died, N=number of patients with a confirmed objective response in the evaluable for response analysis set;
  For PFS n=number of PFS events, N=number of patients in full analysis set.
Data cut-off 1 May 2015
Update results of AURA I/II analysis at 80mg: Study Designs

AURA Ph I/II

Patients with T790M-positive aNSCLC whose disease has progressed following either one prior therapy with an EGFR-TKI or following treatment with both EGFR-TKI and other anticancer therapy

Rolling six design

Escalation

Expansion

Cohort 1 20 mg
Cohort 2 40 mg
Cohort 3 80 mg n=63
Cohort 4 160 mg
Cohort 5 240 mg

Positive
Positive
Positive
Positive
Positive

Central T790M mutation testing* of biopsy sample collected following confirmed disease progression

AURA2 Ph II

Patients with confirmed EGFRm locally advanced or metastatic NSCLC who have progressed following prior therapy with an approved EGFR-TKI

AURA Phase II Extension (n=201)
Osimertinib 80 mg QD

T790M positive

AURA (n=210)
Osimertinib 80 mg QD

T790M negative

Not eligible for enrollment

Pooled Phase II

AURA Ph I data cut-off 4 January, 2016; AURA pooled Ph II data cut-off 1 November, 2015.

*The EGFR T790M mutation status of the patient’s tumour was prospectively determined by the designated central laboratory using the cobas™ EGFR Mutation Test (Roche Molecular Systems) by biopsy taken after confirmation of disease progression on the most recent treatment regimen.

Data from cohorts in grayed out boxes are not included in the analyses reported here.

Yang et al ELCC 2016
Baseline Demographics

**AURA Ph I**
- 63 patients received osimertinib 80 mg QD
  - 61 patients in the evaluable for response set
- Data cut-off: 4 January 2016
- Total median treatment duration: 13.2 months
- 22 (35%) patients are still receiving study treatment

**AURA pooled Ph II**
- 411 patients received osimertinib 80 mg QD
  - 397 patients in the evaluable for response set*
- Data cut-off: 1 November 2015
- Total median treatment duration: 13.0 months (AURA extension: 13.2; AURA2: 13.0)
- 228 (56%) patients are still receiving study treatment:
  - 106 (53%) ongoing in AURA extension
  - 122 (58%) ongoing in AURA2

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>AURA Ph I (80 mg) N=63</th>
<th>AURA pooled Ph II (80 mg) N=411</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, Male / Female</td>
<td>38 / 62</td>
<td>32 / 68</td>
</tr>
<tr>
<td>Age, median (range); years</td>
<td>60 (40–81)</td>
<td>63 (35–89)</td>
</tr>
<tr>
<td>Race, Caucasian / Asian / Other† / Not reported</td>
<td>35 / 59 / 2 / 5</td>
<td>36 / 60 / 3 / 1</td>
</tr>
<tr>
<td>EGFR mutation type by central test, T790M / Ex19del / L858R / Other</td>
<td>100 / 65 / 27 / 3</td>
<td>99‡ / 68 / 29 / 4</td>
</tr>
<tr>
<td>Smoking status, never / current / former</td>
<td>67 / 2 / 32</td>
<td>72 / 2 / 27</td>
</tr>
</tbody>
</table>

AURA Ph I data cut-off 4 January 2016 (characteristics data taken from 1 May 2015 DCO); AURA pooled Ph II data cut-off 1 November 2015
*14 patients excluded due to no measurable disease at baseline by Blinded Independent Central Review;
†including Black or African American, Native Hawaiian or other Pacific Islanders;
‡AURA2: Two patients were initially screen failures, but were rescreened and entered the study; T790M positive status was identified at the initial screening visit but was not transferred during the rescreening process, AURA ext: Three patients with EGFR T790M not detected (negative) and one patient not centrally tested entered the study; these were consequently considered important protocol deviations.

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Yang et al ELCC 2016
Tumor Responses to osimertinib

AURA Ph I

AURA pooled Ph II

<table>
<thead>
<tr>
<th>Best percentage change from baseline in target lesion size (%)</th>
<th>Complete response</th>
<th>Partial response</th>
<th>Stable disease</th>
<th>Progressive disease</th>
<th>Not evaluable</th>
</tr>
</thead>
<tbody>
<tr>
<td>AURA Ph I (80 mg) N=61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed ORR</td>
<td>71% (95% CI 57, 82)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease control rate†</td>
<td>93% (95% CI 84, 98)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best objective response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable disease ≥6 weeks</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
<td></td>
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</tr>
<tr>
<td>Not evaluable</td>
<td></td>
<td></td>
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<tr>
<td>AURA pooled Ph II (80 mg) N=397</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Confirmed ORR</td>
<td>66% (95% CI 61, 71)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Disease control rate†</td>
<td>91% (95% CI 88, 94)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Best objective response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>256</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Stable disease ≥6 weeks</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Progressive disease</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AURA Ph I data cut-off 4 January 2016; population: evaluable for response set; assessment: investigator assessed; AURA pooled Ph II data cut-off 1 November 2015; population: evaluable for response set; assessment: BICR

*Represents imputed values: if it is known that the patient has died, has new lesions or progression of non-target lesions, has withdrawn due to disease progression, and has no evaluable target lesion (before or at progression) assessments, best change will be imputed as 20%;
†Complete response, partial response, stable disease ≥6 weeks

Yang et al ELCC 2016
Progression free survival with osimertinib

AURA Ph I (80 mg)
N=63

Median PFS*, months (95% CI) 9.7 (8.3, 13.6)

Remaining alive and progression-free, † % (95% CI)
12 months 41 (29, 53)
18 months 29 (18, 41)
24 months 17 (8, 30)

AURA pooled Ph II (80 mg)
N=411

Median PFS*, months (95% CI) 11.0 (9.6, 12.4)

Remaining alive and progression-free, † % (95% CI)
12 months 48 (42, 53)
18 months NC
24 months NC

AURA Ph I data cut-off 4 January 2016; population: safety analysis set; assessment: investigator assessed;
AURA pooled Ph II data cut-off 1 November 2015; population: full analysis set; assessment: BICR
Progression events that do not occur within 14 weeks of the last evaluable assessment (of first dose) are censored; Tick marks on the Kaplan-Meier plot denote censored observations

*Progression-free survival is the time from date of first dosing until the date of objective disease progression or death; †Calculated using the Kaplan-Meier technique
Causally-related adverse events: AURA Phase I

AURA Ph I data cut-off 4 January 2016; population: safety analysis set

*Total median treatment duration 13.0 months; †2 unknown; ‡1 unknown; #As of June 1, 2015, of more than 1200 patients across all studies dosed with AZD9291, ILD grouped term events were reported in approximately 2.9% of patients (35 events): nine Grade 1, six Grade 2, 18 Grade ≥3, two currently ungraded. A total of four patients are reported to have died due to ILD (Grade 5).

### Causally-related AEs occurring in ≥15% of patients overall, n (%)

| Causally-related AEs occurring in ≥15% of patients overall, n (%) | AURA Ph I (80 mg) N=63* |
|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade ≥3 | Any grade |
| Rash (grouped terms) | 21 (33) | 2 (3) | 0 | 23 (37) |
| Diarrhoea | 16 (25) | 3 (5) | 1 (2) | 22 (35)† |
| Paronychia (grouped terms) | 11 (18) | 6 (10) | 1 (2) | 18 (29) |
| Dry skin (grouped terms) | 11 (18) | 3 (5) | 0 | 14 (22) |
| Fatigue | 9 (14) | 0 | 0 | 10 (16)‡ |

<table>
<thead>
<tr>
<th>Select AEs</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ILD (grouped terms)#</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>
## Causally-related adverse events: AURA Pooled II

AURA pooled Ph II data cut-off 1 November 2015; population: full analysis set
*Total median treatment duration 13.2 months; †As of June 1, 2015, of more than 1200 patients across all studies dosed with AZD9291, ILD grouped term events were reported in approximately 2.9% of patients (35 events): nine Grade 1, six Grade 2, 18 Grade ≥3, two currently ungraded. A total of four patients are reported to have died due to ILD (Grade 5)

### Causally-related AEs occurring in ≥15% of patients overall, n (%)

<table>
<thead>
<tr>
<th></th>
<th>AURA pooled Ph II (80 mg) N=411*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
</tr>
<tr>
<td>Rash (grouped terms)</td>
<td>146 (36)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>138 (34)</td>
</tr>
<tr>
<td>Dry skin (grouped terms)</td>
<td>116 (28)</td>
</tr>
<tr>
<td>Paronychia (grouped terms)</td>
<td>88 (21)</td>
</tr>
</tbody>
</table>

### Select AEs

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade ≥3</th>
<th>Any grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILD (grouped terms)†</td>
<td>4 (1)</td>
<td>0</td>
<td>8 (2)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>7 (2)</td>
<td>3 (&lt;1)</td>
<td>4 (1)</td>
<td>14 (3)</td>
</tr>
</tbody>
</table>

Yang et al ELCC 2016
CNS metastases remain unmet medical needs in EGFRm NSCLC
AZD9291 is distributed to mouse brain to a greater extent than gefitinib, rociletinib, or afatinib.

Given the high incidence of CNS metastasis in EGFRm NSCLC especially EGFR TKI resistant, these patients have unmet medical needs.

**AZD9291 and gefitinib p.o.**

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

**AZD9291, gefitinib, rociletinib, and afatinib p.o. plasma and brain C_max**

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>AZD9291</th>
<th>Gefitinib</th>
<th>Rociletinib</th>
<th>Afatinib</th>
</tr>
</thead>
<tbody>
<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 (rociletinib 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.
$[^{11}\text{C}]\text{AZD9291}$ is distributed to cynomolgus monkey brain

$[^{11}\text{C}]\text{AZD9291}$

Head/neck

Abdomen

$[^{11}\text{C}]\text{Rociletinib}$

Brain to blood ratio $\text{AUC}_{0-90 \text{ min}}$

$[^{11}\text{C}]\text{AZD9291}$  
2.6 ± 1.4$^*$

$[^{11}\text{C}]\text{Rociletinib}$  
0.025$^†$

$n=3$; $n=2$

Summation images acquired 5 min up to 2 h after intravenous microdose (<3 µg) injection.
Osimertinib shows significant brain exposure and tumor shrinkage in *in vivo* brain metastases models.

Intra-carotid artery injection of tumor cells

Mouse brain tumor formation

Confirmation of tumor formation and target expression

Mouse PC9 tumor growth inhibition with AZD9291, rociletinib, and control


PC9 cells had EGFR exon 19 deletion activating mutation

H&E, hematoxylin and eosin; pEGFR, phosphorylated EGFR; qd, once daily

Billard et al WCLC 2016
AZD9291 activity in CNS metastasis

- AZD9291 showed tumor regression in patients with brain metastasis and leptomeningeal disease
- AZD9291 is being investigated in pts with CNS metastases in phase I study (BLOOM)
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. BID, twice daily; QD, once daily

BLOOM study design overview

Phase I study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity 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

Osimertinib

160 mg QD

EGFR-TKI pre-treated patients with NSCLC and LM

Cohort 1: EGFRm NSCLC and LM
Stable extracranial disease, N=21 (current report)

Cohort 2: T790M positive† NSCLC and LM
No restriction on stable extracranial disease, N=20 (accrual ongoing)

Presented by: James Chih-Hsin Yang

EGFR-TKI naïve or pre-treated

Leptomeningeal metastasis

Brain metastasis

NCT02228369
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

Osimertinib activity across LM assessments

Data cut-off: March 10, 2016. Population: efficacy, n=21.*Response confirmation was done at least 4 weeks after the initial response; †Response assessed by neurological examination

<table>
<thead>
<tr>
<th>Best MRI imaging intracranial response, n (%)</th>
<th>Investigator assessment (N=21)</th>
<th>Confirmed*</th>
<th>Unconfirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responding</td>
<td></td>
<td>7 (33)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Stable disease</td>
<td></td>
<td>9 (43)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>2 (10)</td>
<td></td>
</tr>
</tbody>
</table>

Presented by: James Chih-Hsin Yang

Preserved at: ASCO ANNUAL MEETING '16

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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–May 2015)
  - whole brain radiotherapy (April 2013–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

Presented by: James Chih-Hsin Yang
Confirmatory phase III Study (AURA3) is ongoing

Key Eligibility:
- Nonsquamous NSCLC
- Advanced or metastatic
- EGFR mutation (+) T790M (+)
- Prior EGFR TKI
- ECOG PS 0-1

Pemetrexed 500mg/m²
Cisplatin 80mg/m²
- total 4 cycles

AZD 9291 80mg po daily

Treat until PD

Primary endpoint: progression-free survival

- Press release: AURA3 study met the primary end-point (18 July 2016)
- The results will be presented at 2016 WCLC meeting
Heterogeneity even in T790M mutant tumors

- ctDNA analysis using CAPP-Seq in 41 pts treated with 1/2\textsuperscript{nd} generation EGFR TKI demonstrated additional putative resistance mechanisms
- Co-occurrence of T790M with other resistance is considerably greater

1. Piotrowska z et al Cancer Discov 2015;5;713-722
Resistance to EGFR-TKIs can occur through a number of mechanisms. Combinations of molecularly targeted agents may offer clinical benefit by addressing or delaying resistance.

The TATTON multi-arm, open-label, Phase Ib study (NCT02143466) evaluates osimertinib-based combinations in patients with EGFRm advanced NSCLC.

- Osimertinib + durvalumab (anti-PD-L1 mAb)
- Osimertinib + selumetinib (MEK1/2 inhibitor)
- Osimertinib + savolitinib (MET inhibitor)

Pt with progression on EGFR TKI

Further development of osimertinib + durvalumab arm has been suspended due to high incidence of interstitial lung disease (38%, 13/34)

Ahn et al. ELCC 2016
What’s next?

- F/65, Never-smoker, Exon 19 deletion
- NSCLC (ADC, T2bN1M1a) with lung to lung metastasis
- GC # 4 (2009.8.-2010.1), gefitinib # 38 (2010,4-2013.4)
- Second biopsy : T790M mutation
- AZD9291 (2013.10.8-2016.4.14)
Gefitinib Exon 19

AZD 9291 T790M

What’s next?

Dr. Ohe will discuss at next session
Evolution of resistance mechanisms
Heterogeneity still remains big challenges

1st or 2nd EGFR TKI

EGFR activating mutation

T790M+

AZD9291

T790M+ plus C797S

T790M+ plus unknown resistance

T790M-

No response

T790M -

Increased Heterogeneity

Jane et al WCLC 2015
Conclusion and Future Directions

- Although 1 and 2\textsuperscript{nd} generation EGFR TKIs improved clinical outcomes in EGFR mutant NSCLC, development of resistance is inevitable.
- T790M mutation is the most common resistant mechanism accounting for 50-60%.
- 3\textsuperscript{rd} generation EGFR TKI showed robust response rate, longer PFS with less side effect and should be considered standard treatment.
- Given the heterogeneity even in T790M mutant, repeat biopsy (including ctDNA) with NGS is essential to understand the resistant mechanism.
- To overcome resistance to 3\textsuperscript{rd} generation EGFR TKI, further novel treatment strategies will be needed.
Thank you for your attention