Expert Review in Lung Cancer:

New Evidence to Optimize Management of EGFR-Mutant NSCLC in Front-Line and Beyond

Reference Slides
Key Milestones in EGFR-Targeted Therapy Development

- 2004: Erlotinib approved for second line therapy*
- 2005: EGFR T790M resistance mutation reported
- 2006: Identification of EGFR mutations in patients responsive to gefitinib
- 2007: Gefitinib approved for EGFR-mutant NSCLC
- 2008: Gefitinib approved for first-line EGFR-mutant advanced NSCLC
- 2009: Erlotinib approved for maintenance therapy*
- 2010: Erlotinib approved for first-line EGFR-mutant advanced NSCLC
- 2011: Activity of third generation EGFR TKIs against EGFR T790M while sparing wildtype EGFR reported
- 2012: Afatinib approved for first-line EGFR-mutant advanced NSCLC
- 2013: Osimertinib approved for resistant (T790M+) NSCLC
- 2014: Gefitinib approved for first-line EGFR-mutant advanced NSCLC
- 2015: 

*nonselected patients

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor

Evolution of NSCLC: Subtyping From Histology to Molecular Based

First Treatment Decision Point in Advanced NSCLC: Histology and Mutation Testing

Histology
- Squamous
- Nonsquamous

Mutation testing
- EGFR
- ALK
- ROS1
- BRAF
- HER2
- RET

Type of Mutation
- EGFR TKI sensitive
  - G719X
  - Exon 19 deletion/insertion
  - L858R L861Q
- EGFR TKI resistant
  - Exon 20 T790M insertion

EGFR TKI Selection
Consider patient
- Performance status
- Age
- Comorbidity
- Preference
- Communication
First and Second Generation EGFR TKIs

First generation (reversible)
- Gefitinib (HER1)
- Erlotinib (HER1)

Second generation (irreversible)
- Afatinib (HER1, HER2, HER4)
- Dacomitinib (HER1, HER2, HER4)
Clinical Efficacy of First Generation EGFR-TKIs vs Chemotherapy As First-Line Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pop.</th>
<th>Experimental Drug</th>
<th>EGFR Mut +, N</th>
<th>ORR, % TKI vs Chemo</th>
<th>PFS TKI vs Chemo, Months (HR, 95% CI)</th>
<th>OS TKI vs Chemo, Months (HR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS(^1,2)</td>
<td>Asia</td>
<td>Gefitinib</td>
<td>261</td>
<td>71.2 vs 47.3</td>
<td>9.5 vs 6.3 (0.48 (0.36, 0.64))</td>
<td>21.6 vs 21.9 (1.00 (0.76, 1.33))</td>
</tr>
<tr>
<td>First-SIGNAL(^3)</td>
<td>Asia</td>
<td>Gefinitib</td>
<td>42</td>
<td>84.6 vs 37.5</td>
<td>8.0 vs 6.3 (0.54 (0.27, 1.10))</td>
<td>27.2 vs 25.6 (1.04 (0.50, 2.18))</td>
</tr>
<tr>
<td>WJTOG 3405(^4,5)</td>
<td>Asia</td>
<td>Gefitinib</td>
<td>172</td>
<td>62.1 vs 32.2</td>
<td>9.6 vs 6.6 (0.56 (0.41, 0.77))</td>
<td>34.8 vs 37.3 (1.25 (0.88, 1.78))</td>
</tr>
<tr>
<td>NEJGSG002(^6,7)</td>
<td>Asia</td>
<td>Gefitinib</td>
<td>224</td>
<td>73.7 vs 30.7</td>
<td>10.8 vs 5.4 (0.30 (0.22, 0.41))</td>
<td>27.7 vs 26.6 (0.89 (0.63, 1.24))</td>
</tr>
<tr>
<td>OPTIMAL(^8,9)</td>
<td>Asia</td>
<td>Erlotinib</td>
<td>154</td>
<td>83 vs 36</td>
<td>13.1 vs 4.6 (0.16 (0.10, 0.26))</td>
<td>22.8 vs 27.2 (1.19 (0.83, 1.71))</td>
</tr>
<tr>
<td>EURTAC(^10,11)</td>
<td>Europe</td>
<td>Erlotinib</td>
<td>173</td>
<td>58.1 vs 14.9</td>
<td>9.7 vs 5.2 (0.37 (0.25, 0.54))</td>
<td>22.9 vs 19.6 (0.92 (0.63, 1.35))</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival
LUX-Lung 3 and 6 Phase III Trials

Stage IIIB (wet)/IV lung adenocarcinoma, with EGFR mutation in tumor (central lab testing; Therascreen® EGFR29a RGQ PCR)

Randomization 2:1
Stratified by EGFR mutation (Del19/L858R/other)

LUX-Lung 31
(n = 345)

Cisplatin + Pemetrexed
75 mg/m² + 500 mg/m²
IV q21d, up to 6 cycles

Afatinib
40 mg/db

LUX-Lung 62
(n = 364; Asian patients)

Gemcitabine + Cisplatin
1000 mg/m² D1, D8 + 75 mg/m²
IV q21d, up to 6 cycles

Primary endpoint: PFS (RECIST 1.1, independent review)c
Secondary endpoints: ORR, DCR, DOR, tumor shrinkage, OS, PRO, safety

a EGFR29:19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A, and G719C (or G719X), S768I.
b Dose escalated to 50 mg if limited AE observed in cycle 1. Dose reduced by 10 mg decrements in case of related grade 3 or prolonged grade 2 AE.
c Tumor assessments: q6wk until week 48 and q12wk thereafter until progression/start of new therapy.
d EQ-5D, EORTC QLQ-C30 and QLQ-LC13 at randomization and q3wk until progression or new anticancer therapy.

AE, adverse event; EORTC, European Organisation for Research and Treatment of Cancer; DCR, disease control rate; DOR, duration of response; ORR, overall response rate; OS, overall survival; PCR, polymerase chain reaction; PRO, patient-reported outcomes; RESIST, Response Evaluation Criteria in Solid Tumors
LUX-Lung 3 and 6: OS

LUX-Lung 3 and 6: OS
Combined Analysis According to Mutation Status

**EGFR Deletion Exon 19**

- **Afatinib (n=236)**
  - Median, months: 31.7 (28.1–35.1)
  - 95% CI: 20.7 (16.3–25.6)
  - HR (95% CI): 0.59 (0.45–0.77)
  - pvalue: 0.0001

- **Chemotherapy (n=119)**

**EGFR Exon 21 (L858R)**

- **Afatinib (n=183)**
  - Median, months: 22.1 (19.6–25.4)
  - 95% CI: 26.9 (23.2–31.7)
  - HR (95% CI): 1.25 (0.92–1.71)
  - pvalue: 0.16

- **Chemotherapy (n=93)**

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Afatinib Activity in *EGFR*-Mutated Lung Cancer—“Uncommon Mutations”

A combined *post hoc* analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6

![PFS Graph](image)

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (months); (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>10.7 (5.6–14.7)</td>
</tr>
<tr>
<td>Group 2</td>
<td>2.9 (1.2–8.3)</td>
</tr>
<tr>
<td>Group 3</td>
<td>2.7 (1.8–4.2)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>8.2 (5.2–10.8)</td>
</tr>
</tbody>
</table>

Group 1 = point mutations or duplications in exons 18-21  
Group 2 = *de novo* Thr790Met mutations  
Group 3 = exon 20 insertions

Common Toxicities With First and Second Generation TKIs

- Importance of patients education about potential side effects, preventive measures, early recognition and management (supportive care, dose reduction)

Impact of Dose Adjustment on the Safety and Efficacy of Afatinib and LUX-Lung 3 and LUX-Lung 6

• *Post hoc* analyses were performed to assess the influence of afatinib dose reduction on AEs, pharmacokinetics and PFS in the LUX-Lung 3 and LUX-Lung 6 trials
• Dose reductions occurred in 122 of 229 (53%) and 67 of 239 (28%) afatinib-treated patients in LUX-Lung 3 and 6, respectively; most reduction occurred within the first 6 months of treatment

**Key treatment-related AEs in patients with dose reductions**

PFS in Patients With or Without Dose Reduction of Afatinib in the First 6 Months of Treatment

Afatinib Plasma Levels in Patients Who Dose Reduced to 30 mg or Who Remained on 40 mg: Combined Analyses of LUX-Lung 3 and LUX-Lung 6

Boxes represent the median and interquartile range; the whiskers represent the 10th and 90th percentiles and the dots show data points outside percentiles. For patients who dose reduced to afatinib 30 mg before day 43 (n = 59), only 22 had valid trough concentrations for afatinib 40 mg at day 22 (the rest had either no pharmacokinetics sampling at this time (n = 15), were already receiving afatinib 30 mg at day 22 (n = 14) or were excluded from the analyses due to invalid sampling (n = 8).

First or Second Generation TKI? LUX-Lung 7 Randomized Phase IIb Study

- Stage IIIb/IV adenocarcinoma of the lung
- EGFR mutation (Del19 and/or L858R) in the tumor tissue*
- No prior treatment for advanced/metastatic disease
- ECOG PS 0/1

Primary endpoints:
- PFS (independent)
- TTF
- OS

Secondary endpoints:
- ORR
- Time to response
- Duration of response
- Duration of disease control
- Tumor shrinkage
- HRQoL
- Safety

**Treatment beyond progression allowed if deemed beneficial by investigator**

**RECIST assessment performed at weeks 4, 8 and every 8 weeks thereafter until week 64, and every 12 weeks thereafter**

*Central or local test
†Dose modification to 50 mg, 30 mg, 20 mg permitted in line with prescribing information
ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; PS, performance status; TTF, time to treatment failure
Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n = 160)</th>
<th>Gefitinib (n = 159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>63 (30-86)</td>
<td>63 (32-89)</td>
</tr>
<tr>
<td>Gender, %</td>
<td>Female/male</td>
<td>57/43</td>
</tr>
<tr>
<td>Race, %</td>
<td>Asian</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Non-Asian</td>
<td>41</td>
</tr>
<tr>
<td>Brain metastases*, %</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td>Never smoker</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Light exsmoker</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Current/other exsmoker</td>
<td>21</td>
</tr>
<tr>
<td>Baseline ECOG, %</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>68</td>
</tr>
<tr>
<td>NSCLC stage, %</td>
<td>IIIB</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>95</td>
</tr>
<tr>
<td>EGFR mutation, %</td>
<td>Del19</td>
<td>58</td>
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<tr>
<td></td>
<td>L858R</td>
<td>42</td>
</tr>
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</table>

LUX-Lung 7: PFS*, TTF, and ORR* (*independent review)

**PFS**

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P value</th>
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<tr>
<td>0.73 (0.57-0.95)</td>
<td>.0165</td>
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</table>

**TTF**

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P value</th>
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</thead>
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<tr>
<td>0.73 (0.58-0.92)</td>
<td>.010073</td>
</tr>
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</table>

**ORR**

<table>
<thead>
<tr>
<th>P value</th>
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<tbody>
<tr>
<td>.008</td>
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</table>

### PFS by Independent Review

#### Subgroup Analyses

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Afatinib Median (95% CI)</th>
<th>Gefitinib Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>PInteraction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR mutation</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Leu858Arg</td>
<td>10.9 (8.1-12.9)</td>
<td>10.8 (7.2-12.8)</td>
<td>0.71 (0.48-1.06)</td>
<td>0.809</td>
</tr>
<tr>
<td>Del19</td>
<td>12.7 (10.6-14.7)</td>
<td>11.0 (9.1-12.7)</td>
<td>0.76 (0.55-1.06)</td>
<td></td>
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<tr>
<td><strong>Brain metastases</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Absent</td>
<td>12.7 (10.9-13.3)</td>
<td>10.9 (9.1-12.7)</td>
<td>0.74 (0.56-0.98)</td>
<td>0.93</td>
</tr>
<tr>
<td>Present</td>
<td>7.2 (3.7-17.0)</td>
<td>7.4 (5.4-12.8)</td>
<td>0.76 (0.41-1.44)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline ECOG PS</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>11.0 (10.6-17.4)</td>
<td>12.8 (10.8-14.7)</td>
<td>0.89 (0.54-1.47)</td>
<td>0.43</td>
</tr>
<tr>
<td>1</td>
<td>11.0 (9.0-13.2)</td>
<td>10.5 (8.0-11.0)</td>
<td>0.71 (0.52-0.95)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>10.9 (7.3-12.9)</td>
<td>10.8 (7.3-12.8)</td>
<td>0.88 (0.59-1.31)</td>
<td>0.39</td>
</tr>
<tr>
<td>Women</td>
<td>12.8 (10.8-14.7)</td>
<td>10.9 (9.0-12.2)</td>
<td>0.65 (0.47-0.91)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>11.0 (9.2-17.0)</td>
<td>9.2 (7.3-11.0)</td>
<td>0.68 (0.48-0.97)</td>
<td>0.309</td>
</tr>
<tr>
<td>≥65</td>
<td>11.0 (9.2-12.9)</td>
<td>11.4 (10.8-12.9)</td>
<td>0.85 (0.59-1.22)</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnic origin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Asian</td>
<td>12.7 (10.8-14.7)</td>
<td>10.6 (7.4-12.7)</td>
<td>0.72 (0.49-1.06)</td>
<td>0.88</td>
</tr>
<tr>
<td>Asian</td>
<td>11.0 (9.1-12.9)</td>
<td>11.0 (9.1-12.8)</td>
<td>0.76 (0.54-1.06)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>11.0 (9.2-12.9)</td>
<td>11.0 (9.1-12.8)</td>
<td>0.80 (0.58-1.10)</td>
<td>0.083</td>
</tr>
<tr>
<td>Light ex-smoker*</td>
<td>9.2 (7.2-10.9)</td>
<td>10.9 (7.2-13.3)</td>
<td>1.09 (0.56-2.14)</td>
<td></td>
</tr>
<tr>
<td>Other current or ex-smokers</td>
<td>17.0 (10.7-20.1)</td>
<td>9.1 (3.5-12.7)</td>
<td>0.48 (0.27-0.85)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>11.0 (10.6-12.9)</td>
<td>10.9 (9.1-11.5)</td>
<td>0.73 (0.57-0.95)</td>
<td></td>
</tr>
</tbody>
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Efficacy in Patients With Del19 Mutation

Efficacy in Patients With L858R Mutation

### LUX-Lung 7: Safety

#### Drug-Related AEs (>10%)

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n = 160)</th>
<th>Gefitinib (n = 159)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
<td>≥Grade 3</td>
</tr>
<tr>
<td>Total</td>
<td>106 (66%)</td>
<td>124 (78%)</td>
</tr>
<tr>
<td></td>
<td>50 (31%)</td>
<td>29 (18%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>124 (78%)</td>
<td>95 (60%)</td>
</tr>
<tr>
<td></td>
<td>20 (13%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Rash or acne</td>
<td>127 (79%)</td>
<td>124 (78%)</td>
</tr>
<tr>
<td></td>
<td>15 (9%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>96 (60%)</td>
<td>38 (24%)</td>
</tr>
<tr>
<td></td>
<td>7 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Paronychia</td>
<td>86 (54%)</td>
<td>26 (16%)</td>
</tr>
<tr>
<td></td>
<td>3 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>52 (33%)</td>
<td>59 (37%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>37 (23%)</td>
<td>36 (23%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 (15%)</td>
<td>23 (14%)</td>
</tr>
<tr>
<td></td>
<td>9 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25 (16%)</td>
<td>19 (12%)</td>
</tr>
<tr>
<td></td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (15%)</td>
<td>22 (14%)</td>
</tr>
<tr>
<td></td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>17 (11%)</td>
<td>24 (15%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (11%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>ALT/AST increased</td>
<td>16 (10%)</td>
<td>25 (16%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>14 (9%)</td>
</tr>
</tbody>
</table>

- Afatinib and gefitinib had equally low rates (6%) of treatment discontinuation due to adverse events

ALT, alanine aminotransferase; AST, aspartate aminotransferase

LUX-Lung 7: Summary and Conclusion

• Afatinib significantly improved PFS of patients with EGFR+ NSCLC relative to gefitinib. Results are consistent across subgroups (HR 0.73, 95% CI 0.57-0.95, P value: .0165)
• Afatinib was associated with a significant improvement in response rate and TTF
• The improvement in efficacy was observed in both Del19 and L858R populations
• Overall survival data are immature (current HR 0.87, 95% CI 0.66-1.15)
• Adverse events in both groups were consistent with previous experience, and were manageable leading to equally low rates of treatment discontinuation
• LUX-Lung 7 confirms the benefit of irreversible ErbB blockade with afatinib over reversible EGFR inhibition with gefitinib in the treatment of EGFR+ NSCLC

Development of Acquired Resistance to EGFR TKIs

TKI-naïve EGFR-mutant tumor

1st or 2nd generation EGFR TKIs: Erlotinib, Gefitinib, Afatinib
PFS ~12 months
Response rate ~70%

T790M+

T790M-

Unknown

3rd generation EGFR mutant–specific TKIs:
AZD9291, Rociletinib
PFS ~9-13 months
Response rate ~60%

T790M+ C797S+

T790M+ C797S-

3rd generation EGFR mutant–specific TKIs:
AZD9291, Rociletinib
PFS ~2.8-5.6 months
Response rate 21%-29%

T790M- C797S+

T790M- C797S-
Mechanisms of Acquired Resistance

Resistance Mutations

- **MET amplification**: 3%
- **Small cell + MET**: 1%
- **Small cell + T790M**: 2%
- **MET + T790M**: 3%
- **HER2**: 8%
- **HER2 + T790M**: 4%
- **Unknown**: 18%
- **T790M**: 60%

Overcoming *T790M*-Mediated Resistance: Third Generation EGFR-TKIs

- Third generation EGFR TKIs are irreversible inhibitors with much higher activities against mutant EGFR
- Targeting both activating EGFR mutations and T790M but sparing wildtype EGFR
- Have favorable safety profile
  - Osimertinib (AZD9291): Approved
  - Rociletinib (CO-1686): May 6, 2016, development of the drug and enrollment in all ongoing trials was terminated after US Food and Drug Administration’s Oncologic Drug Advisory Committee (ODAC) rejected rociletinib accelerated approval due to benefit/risk concerns
  - BI 1482694 (HM61713)
  - EGF816
  - ASP8273
    - In development
AURA Trial: Overall Study Schema

Phase I expansion

Enrollment by local testing followed by central laboratory confirmation§ of T790M status or by central laboratory testing alone

Phase II extension

Enrollment by central laboratory confirmation§ of T790M status

AURA Trial: Osimertinib in Patients With $EGFR^{T790M+}$ and $EGFR^{T790M-}$

RR: 61% $EGFR^{T790M+}$

RR: 21% $EGFR^{T790M-}$

Osimertinib in Pretreated Patients With $EGFR^{T790M+}$

Updated AURA Phase I and pooled Phase II Results: Efficacy

| Osimertinib (80 mg) | AURA Phase I *  
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>N = 61</td>
<td></td>
</tr>
<tr>
<td>Confirmed ORR, %</td>
<td>71</td>
<td>66</td>
</tr>
<tr>
<td>Disease control rate, %</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td>Median DOR, months</td>
<td>9.6</td>
<td>12.5</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>9.7</td>
<td>11.0</td>
</tr>
</tbody>
</table>

|                     | AURA Pooled Phase II**  
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 397</td>
<td></td>
</tr>
</tbody>
</table>

*investigators assessment; **blinded independent central review (BICR)

## Updated AURA Phase I and pooled Phase II results: Safety

<table>
<thead>
<tr>
<th>AURA Pooled Phase II Treatment-Related AEs Occurring in ≥15% of Patients Overall, n (%)</th>
<th>Any Grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash, n(%)</td>
<td>167 (41)</td>
<td>3(&lt;1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>157 (38)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>125 (30)</td>
<td>0</td>
</tr>
<tr>
<td>Paronychia</td>
<td>118 (29)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1(&lt;1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Activity of BI 1482694 (HM61713) in T790M+ NSCLC

- The most common drug-related AEs; mild-to-moderate diarrhea, nausea, rash, and pruritis

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Evaluable Patients (N = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>43 (62)</td>
</tr>
<tr>
<td>Confirmed objective response</td>
<td>32 (46)</td>
</tr>
<tr>
<td>Disease control</td>
<td>63 (91)</td>
</tr>
<tr>
<td>Progression disease</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

EGFR T790M–Negative Resistance

EGFR TKI Continuation (ASPIRATION)

- Slow, indolent, asymptomatic progression

Patients ≥18 years with stage IV, *EGFR* mut+ NSCLC

Erlotinib

PD by RECIST 1.1

Erlotinib

PD by physician assessment

PFS 1

PFS 2

PFS2, second progression-free survival (time from randomization to second progression)

EGFR TKI Continuation (ASPIRATION)

Survival Probability

PFS Time, Months

1.0
0.8
0.6
0.4
0.2
0.0
11.0 months
14.1 months

PFS1
PFS2

Patients
• Age ≥18 years (≥20 years in Japan)
• WHO PS 0-1
• Histologically confirmed stage IIIb/IV EGFR mut+ advanced NSCLC
• Chemotherapy-naïve
• Achieved CR/PR ≥4 months or SD >6 months with first-line gefitinib
• Disease progression (RECIST) <4 weeks prior to study randomization

Endpoints
Primary
• PFS
Secondary
• OS
• ORR
• Disease control rate
• Safety and tolerability
• HRQoL

Exploratory
• Biomarkers (incl T790M EGFR mutation)

Cisplatin 75 mg/m² + Pemetrexed 500 mg/m² (≤6 cycles) + Gefitinib 250 mg
Cisplatin 75 mg/m² IV + Pemetrexed 500 mg/m² IV (≤6 cycles) + Placebo 250 mg

1:1 randomization

---

a Progressive disease based on radiologic evaluation (modified Jackman’s criteria) and RECIST v 1.1. Tumor assessments were performed ≤4 weeks before the start of treatment (baseline), and every 6 weeks (±7 days) after randomization until progressive disease;
b Randomization did not include stratification factors; analyses were adjusted for 2 covariates; age (<64 years vs ≥65 years) and prior response to gefitinib (SD vs PR+CR)
c Will be reported separately

d ORAL17.08.
IMPRESS: *T790M* ctDNA Biomarker Analysis

**Objectives**
- To evaluate detection rate of the *T790M* resistance mutation following first-line gefitinib failure (upon entry into IMPRESS)
- To study the IMPRESS primary outcome according to *T790M* patient subgroups

**T790M subtype: ctDNA detection by BEAMing**
- For patients with plasma samples available for biomarkers analysis, there was a slight imbalance between treatment arms with the number of patients with *T790M* positive-/negative mutation status
  - *T790M* mutation status unknown in 14 patients

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib, % (n/N)</th>
<th>Placebo, % (n/N)</th>
<th>Total, % (n/N)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>T790M</em>+</td>
<td>61.8 (81/131)</td>
<td>46.9 (61/130)</td>
<td>54.4 (142/261)</td>
</tr>
<tr>
<td><em>T790M</em>-</td>
<td>35.1 (46/131)</td>
<td>45.4 (59/130)</td>
<td>40.2 (105/261)</td>
</tr>
</tbody>
</table>

\(^a\)Includes unknowns
*T790M* ctDNA status assessed at baseline
BEAMing digital PCR assay (Sysmex®) conducted at a central laboratory (positive defined as ≥0.02% mutant DNA fraction)
BEAMing analysis is limited only to exon 19 del, *L858R*, and *T790M* – did not test for uncommon EGFR sensitizing mutations ctDNA, circulating free tumor-derived DNA

IMPRESS: PFS According to \textit{T790M} Mutation Status

- For patients with \textbf{plasma-positive for \textit{T790M}} at the time of RECIST progression, gefitinib should not be continued when platinum doublet chemotherapy is used as second-line therapy in combination with doublet chemotherapy may offer clinical benefit.

- For patients with \textbf{plasma-negative for \textit{T790M}} at the time of RECIST progression, gefitinib in combination with doublet chemotherapy may offer clinical benefit.

First-Line Third Generation TKI: Phase I

Summary of Updated Efficacy of AURA First-Line
(Phase I expansion cohorts, investigator assessed)

<table>
<thead>
<tr>
<th>Osimertinib</th>
<th>80 mg N = 30</th>
<th>160 mg N = 30</th>
<th>Total N = 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, %</td>
<td>67</td>
<td>87</td>
<td>77</td>
</tr>
<tr>
<td>Median DOR, months</td>
<td>Not yet reached</td>
<td>16.7</td>
<td>Not yet reached</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>Not yet reached</td>
<td>19.3</td>
<td>19.3</td>
</tr>
<tr>
<td>Progression free at 18 months, %</td>
<td>57</td>
<td>53</td>
<td>55</td>
</tr>
</tbody>
</table>

*5 patients were EGFR T790M positive

Most common all grade AEs: Diarrhea, stomatitis, and paronychia
- No ≥grade 3 toxicity in 80 mg arm
- Dose reduction due to AEs required in 2/30 (10%) patients at 80 mg and 14/30 (47%) patients at 160 mg

FLAURA Trial: Randomized Phase III Study
Osimertinib vs Gefitinib or Erlotinib

Enrollment by local* or central# EGFR mutation testing of biopsy sample

Stratified by:
- Asian / non-Asian
- Ex19del / L858R

RECIST 1.1 assessment every 6 weeks until objective progressive disease

Patients randomized to standard of care may receive AZD9291 after progression §

Primary objective: efficacy by PFS

AZD9291 (80 mg PO qd)

EGFR-TKI standard of care##:
- gefitinib (250 mg PO qd) or erlotinib (150 mg PO qd)

*With central laboratory assessment performed for sensitivity
#cobas™ EGFR Mutation Test
##Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation
§Patients randomized to the standard-of-care treatment arm may receive open-label treatment with AZD9291 on central confirmation of both objective disease progression and T790M-positive tumor

Liquid Biopsy ctDNA

- Tumor cells release small fragments of cell-free DNA into circulation by multiple mechanisms
- Cancer-associated genetic alterations such as point mutations, copy number variations, chromosomal rearrangements, and methylation patterns can be detected in circulating cell-free DNA
- Tumor cell derived DNA is only ≤0.5% of total cell-free DNA

# Liquid Biopsy Versus Tissue Biopsy

<table>
<thead>
<tr>
<th>Tumor Biopsy</th>
<th>Liquid Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive and expensive</td>
<td>Noninvasive and less expensive</td>
</tr>
<tr>
<td>Specific to localized tumor site</td>
<td>Less dependent on original tumor site since tumor from both primary and metastatic sites release DNA into the bloodstream</td>
</tr>
<tr>
<td>Assessment of tumor heterogeneity limited to section of biopsy analyzed</td>
<td>Can capture tumor heterogeneity</td>
</tr>
<tr>
<td>A limited amount of tissue may be obtained for immunohistochemical and genomic analysis</td>
<td>A few copies of mutant ctDNA are sufficient for analysis</td>
</tr>
<tr>
<td>Difficult to biopsy some organs</td>
<td>Easy to collect sample from blood</td>
</tr>
<tr>
<td>Not viable if primary tumor has been resected or if the tumor cannot be easily visualized via imaging studies</td>
<td>Allows for serial evaluation in absence of detectable primary tumor or metastases</td>
</tr>
<tr>
<td>Serial biopsies are difficult to tolerate</td>
<td>Patient can tolerate serial blood draws for evaluation; may lead to greater compliance</td>
</tr>
</tbody>
</table>

Potential Applications of Liquid Biopsy

Mok T. 16th World Conference on Lung Cancer; September 6-9, 2015: Denver, Colorado. Discussion.
Technologies for Tissue Samples are Potentially Applicable to Plasma ctDNA

<table>
<thead>
<tr>
<th>Technologies</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARMS-PCR (Amplification Refractory Mutation System)</td>
<td>1%</td>
</tr>
<tr>
<td>Clamping PCR</td>
<td>0.1% - 1%</td>
</tr>
<tr>
<td>castPCR (Competitive Allele-Specific TaqMan PCR)</td>
<td>0.1% - 1%</td>
</tr>
<tr>
<td>ICE COLD-PCR (Improved &amp; Complete Enrichment CO-amplification at Lower Denaturation temperature)</td>
<td>0.1% - 1%</td>
</tr>
<tr>
<td>BEAMing Digital PCR (Beads, Emulsions, Amplification and Magnetics)</td>
<td>0.01%</td>
</tr>
<tr>
<td>Droplet Digital PCR</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>NGS (Next-Generation Sequencing)</td>
<td>1% - 5%</td>
</tr>
</tbody>
</table>

AURA Phase I: Plasma Genotyping for Predicting Benefit From Osimertinib in Patients With Advanced NSCLC

Central plasma genotyping was performed using BEAMing

**Sensitivity/Specificity of Plasma Genotyping**

- Sensitivity was 82% - 86% for sensitizing mutations and 70% for *T790M*
- False positive rate was 3% - 4% for sensitizing mutations but higher (31%) for *T790M*, perhaps due to heterogeneous presence of a resistance mutation missed in the reference tumor biopsy
- Sensitivity for *T790M* was highly associated with detection of a sensitizing mutation in cfDNA

AURA Phase I: High ORR in Patients With Tumor or Plasma Positive T790M

Data cut-off: 1 May 2015

AURA Phase I: PFS by Tumor and Plasma T790M Status

- Tumor T790M–positive predicts for a prolonged median PFS of 9.7 months, longer than seen in tumor T790M–negative cases ($P < .001$)

- Plasma T790M–positive status also predicts a prolonged PFS of 9.7 months; however, this is not significantly longer than seen in plasma T790M–negative cases ($P = .188$)

- Plasma T790M–negative outcomes may be better than expected due to the occurrence of T790M plasma-false-negatives

Data cut-off: 1 May 2015. Multiple doses included

Tissue-Based Paradigm for Use of Plasma Genotyping

• These data support consideration of a paradigm where plasma genotyping is used as a screening test for \textit{T790M}, prior to performing an \textit{EGFR} resistance biopsy.

FFPE, formalin-fixed paraffin-embedded

Histology and molecular testing are key treatment decision points in patients with advanced NSCLC.

First generation EGFR inhibitors (erlotinib, gefitinib), and second generation inhibitor (afatinib) are established first-line EGFR-targeted therapies.

Afatinib is more potent panHER TKI and demonstrated:
- Overall survival benefit in EGFR exon 19–mutated lung cancers
- Activity in “uncommon mutations” except EGFR exon 20 insertions and T790M
- Significantly superior efficacy over gefitinib

Patient education, preventive measures, and early recognition, and management of adverse events is extremely important.

When toxicity is an issue, afatinib dose can be reduced without loss of efficacy.

Early first-line results with third generation EGFR TKI osimertinib are promising.
The most common mechanism of resistance to EGFR TKIs is the acquisition of the EGFR T790M point mutation (~60% of patients).

Plasma genotyping may replace conventional tissue biopsy in the near future as a screening test for T790M after progression on first-line EGFR targeted therapy.

The third generation TKI osimertinib is the only approved T790M-targeted agent and updated results confirmed high efficacy (ORR 66% and PFS 11 months) and favorable toxicity profile.

Several other third generation TKIs are under development.

Management of T790M-negative resistance remain challenging; patients may benefit from continuation of EGFR TKI beyond progression + chemotherapy.

Next generation sequencing technology is emerging and will replace current genomic analysis technologies.