Maximising Clinical Benefit from TKIs in the Treatment of Advanced NSCLC

2017 WCLC- PACIFICO Yokohama Convention Center

16 October, 2017

BI symposium
Meeting Welcome and Introductions

2017 WCLC- PACIFICCO Yokohama Convention Center

Tetsuya Mitsudomi, MD, PhD
Kindai University Faculty of Medicine
Osaka-Sayama, Japan
Faculty Disclosure

• Honoraria and Advisory boards: AstraZeneca, Boehringer Ingelheim, Chugai, Pfizer, MSD, and Ono

• Grant support: Boehringer Ingelheim, Chugai, Pfizer, and Ono.
# Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:45 – 12:50</td>
<td>Meeting Welcome and Introductions</td>
<td>Tetsuya Mitsudomi (Japan)</td>
</tr>
<tr>
<td>12:50 – 13:10</td>
<td>Emerging Algorithm for Optimal Sequencing of EGFR TKIs in EGFR Mutation-Positive NSCLC</td>
<td>Keunchil Park (S. Korea)</td>
</tr>
<tr>
<td>13:10 – 13:30</td>
<td>Efficacy of EGFR TKIs in NSCLC Patients with Uncommon EGFR Mutations</td>
<td>Terufumi Kato (Japan)</td>
</tr>
<tr>
<td>13:50 – 14:10</td>
<td>Panel Discussion Carrying the Data into the Clinic: TKI Sequencing Decisions for EGFR Mutation-Positive NSCLC Patients</td>
<td>All Faculty Moderator: Tetsuya Mitsudomi</td>
</tr>
<tr>
<td>14:10 – 14:15</td>
<td>Meeting Close</td>
<td>Tetsuya Mitsudomi</td>
</tr>
</tbody>
</table>
Faculty

Chair: Tetsuya Mitsudomi, MD, PhD
Kindai University Faculty of Medicine
Osaka-Sayama, Japan

Keunchil Park, MD, PhD
Samsung Medical Center, Sungkyunkwan University School of Medicine
Seoul, Korea

Terufumi Kato, MD
Kanagawa Cardiovascular and Respiratory Center
Tokyo, Japan

Barbara Melosky, MD, FRCPC
University of British Columbia, British Columbia Cancer Agency
Vancouver, BC
Emerging Algorithm for Optimal Sequencing of EGFR TKIs in EGFR Mutation–Positive NSCLC

2017 WCLC- PACIFICO Yokohama Convention Center
Keunchil Park, MD, PhD
Samsung Medical Center,
Sungkyunkwan University School of Medicine
Faculty Disclosure

• Consulting or Advisory Role: Astellas Pharma; AstraZeneca; Boehringer Ingelheim; Clovis Oncology; Hanmi; Kyowa Hakko Kirin; Lilly; Novartis; Ono Pharmaceutical; Roche

• Speakers' Bureau: Boehringer Ingelheim

• Research Funding: AstraZeneca
Key Factors in First-line EGFR TKI Selection

Sequence makes survival

Not all TKIs are equal

Drug-drug interactions

Efficacy

Adverse event profile

Not all TKIs are equal

Efficacy

Adverse event profile

Drug-drug interactions

Sequence makes survival
Key Factors in First-line EGFR TKI Selection

Sequence makes survival

Not all TKIs are equal

Drug-drug interactions

Efficacy

Adverse event profile
The Family of EGFR TKIs

**1st-generation TKI**
- **Erlotinib Gefitinib**
  - EGFR inhibition
  - Activity range:
    - Reversible binding to wild-type and mutant EGFR
    - Inactive on T790M mutant

**2nd-generation TKI**
- **Afatinib Dacomitinib**
  - ErbB Family blockade
  - Activity range:
    - Irreversible covalent binding to EGFR, ErbB2 and ErbB4 to inhibit all ErbB Family signalling
    - Broader activity to overcome EGFR TKI-resistant mutations

**3rd-generation TKI**
- **Osimertinib**
  - EGFR mutant–specific inhibitor
  - Activity range:
    - Specificity for *EGFR* T790M mutant; EGFR wild-type sparing
    - Irreversible covalent binding to mutant EGFR

**Activity range**
- **Intrinsic mutant EGFR**
- **ErbB heterodimers (eg, Her2: ErbB3)**
- **Acquired T790M EGFR**

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Activity of First-, Second-, and Third-Generation EGFR TKIs Against *EGFR* Mutations

- **IC<sub>50</sub>** = half-maximal inhibitory concentration.
Key Factors in First-line EGFR TKI Selection

- Sequence makes survival
- Not all TKIs are equal
- Drug-drug interactions
- Adverse event profile
- Efficacy
First- and Second-Generation EGFR TKIs Are Standard for First-line Treatment of NSCLC With Common *EGFR* Mutations

- Better PFS vs platinum-based chemotherapy

---

<table>
<thead>
<tr>
<th>Treatment</th>
<th>EURTAC</th>
<th>ENSURE</th>
<th>OPTIMAL</th>
<th>WJTOG</th>
<th>NJE002</th>
<th>IPASS</th>
<th>LL3</th>
<th>LL6</th>
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<tbody>
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<td>11</td>
<td>13.1</td>
<td>9.2</td>
<td>10.8</td>
<td>9.7(^a)</td>
<td>13.6</td>
<td>11</td>
<td>5.2</td>
</tr>
<tr>
<td>Gefitinib(^a)</td>
<td>5.2</td>
<td>5.5</td>
<td>4.6</td>
<td>[VALUE]</td>
<td>[VALUE]</td>
<td>5.4</td>
<td>[VALUE](^a)</td>
<td>6.9</td>
</tr>
<tr>
<td>Afatinib</td>
<td>5.6</td>
<td>5.6</td>
<td>4.6</td>
<td>[VALUE]</td>
<td>[VALUE]</td>
<td>5.4</td>
<td>[VALUE](^a)</td>
<td>6.9</td>
</tr>
<tr>
<td>Platinum-based</td>
<td>5.6</td>
<td>5.6</td>
<td>4.6</td>
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<td>[VALUE]</td>
<td>5.4</td>
<td>[VALUE](^a)</td>
<td>6.9</td>
</tr>
</tbody>
</table>

\(^a\)PFS not reported for common mutations only.

NSCLC = non-small cell lung cancer.

First- and Second-Generation EGFR TKIs Are Not Equal: Response Rate and PFS in LUX-Lung 7

LUX-Lung 7: Afatinib vs Gefitinib

- **Response Rate (%):**
  - **ITT:** Afatinib 73%, Gefitinib 56%
  - **Del19:** Afatinib 75%, Gefitinib 66%
  - **L858R:** Afatinib 69%, Gefitinib 42%

- **PFS (%):**
  - Median, mo: Afatinib 11.0, Gefitinib 10.9
  - HR (95% CI): 0.73 (0.57-0.95)
  - P value: 0.017

First- and Second-Generation EGFR TKIs Are Not Equal: PFS in ARCHER 1050

ARCHER 1050: Dacomitinib vs Gefitinib (excluding CNS metastases)

**PFS in ARCHER 1050**

**ARCHER 1050: Dacomitinib vs Gefitinib (excluding CNS metastases)**

**Mok et al. ASCO 2017. Abstract LBA9007.**

CNS = central nervous system; ITT = intent-to-treat; CI, confidence interval.

Mok et al. ASCO 2017. Abstract LBA9007.
First and Third-Generation EGFR TKIs Are Not Equal: PFS in FLAURA

FLAURA: Osimertinib vs Gefitinib or Erlotinib

**Primary Endpoint: PFS (by Investigator Assessment)**

<table>
<thead>
<tr>
<th>Time from randomisation (months)</th>
<th>Osimertinib</th>
<th>Gefitinib or Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>279</td>
<td>277</td>
</tr>
<tr>
<td>3</td>
<td>262</td>
<td>239</td>
</tr>
<tr>
<td>6</td>
<td>233</td>
<td>197</td>
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<tr>
<td>9</td>
<td>210</td>
<td>152</td>
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<tr>
<td>12</td>
<td>178</td>
<td>107</td>
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<tr>
<td>15</td>
<td>139</td>
<td>78</td>
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<tr>
<td>18</td>
<td>71</td>
<td>37</td>
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<td>21</td>
<td>26</td>
<td>10</td>
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<tr>
<td>24</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Median PFS, months (95% CI):
  - Osimertinib: 18.9 (15.2-21.4)
  - Gefitinib or Erlotinib: 10.2 (9.6-11.1)

- HR (95% CI): 0.46 (0.37-0.57)
- *P* value: *P*<0.0001

**Note:** Tick marks indicate censored data. For statistical significance, *P*<0.0015, determined by O’Brien planning approach, was required.

OS = overall survival; SoC = standard of care; NS = not significant; DCO = data cut-off.

Key Factors in First-line EGFR TKI Selection

- Sequence makes survival
- Not all TKIs are equal
- Drug-drug interactions
- Efficacy
- Adverse event profile

Not all TKIs are equal.
## Safety

### Second- or Third-Generation TKIs vs First-Generation TKIs

<table>
<thead>
<tr>
<th></th>
<th>LUX-Lung 71,2</th>
<th>ARCHER 10503</th>
<th>FLAURA4</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Afatinib (n=160)</td>
<td>Gefitinib (n=159)</td>
<td>Dacomitinib (n=227)</td>
</tr>
<tr>
<td>Treatment discontinuation rate</td>
<td>6.3%</td>
<td>6.3%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Most common grade ≥3 AEs</td>
<td>Diarrhoea: 12%</td>
<td>Liver enzyme elevation: 9%</td>
<td>Acne: 14%</td>
</tr>
<tr>
<td></td>
<td>Rash/acne: 9%</td>
<td>Rash/acne: 3%</td>
<td>Paronychia: 8%</td>
</tr>
</tbody>
</table>

Dose Reduction of Afatinib Reduced Drug-Related AEs Without Compromising Efficacy


PFS = progression-free survival; HR = hazard ratio; CI = confidence interval.
Key Factors in First-line EGFR TKI Selection

- Sequence makes survival
- Not all TKIs are equal
- Drug-drug interactions
- Efficacy
- Adverse event profile

Not all TKIs are equal

Drug-drug interactions

Sequence makes survival

Adverse event profile

Efficacy
### Enzymes Involved in the Metabolism of Oral EGFR TKIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolised by CYP Enzymes</th>
<th>May Inhibit</th>
<th>May Induce</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3A4</strong></td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3A5</strong></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2D6</strong></td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1A1</strong></td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1A2</strong></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1B1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2C8</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2C9</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Gefitinib
- Metabolised by CYP Enzymes: ++, ++, ++, +, -
- May Inhibit: CYP2C19 (w), CYP2D6 (w), UGT1A9, BRCP
- May Induce: CYP1A2

#### Erlotinib
- Metabolised by CYP Enzymes: ++, ++, +, +, ++, +, +, +
- May Inhibit: CYP3A4 (m), CYP2C8 (m), CYP1A1 (s), UGT1A1 (s)
- May Induce: CYP1A1

#### Afatinib
- Metabolised by CYP Enzymes: -, -, -, -, -, -, -, -
- May Inhibit: -
- May Induce: -

#### Dacomitinib
- Metabolised by CYP Enzymes: +, ++
- May Inhibit: -
- May Induce: CYP2D6 (s)

#### Osimertinib
- Metabolised by CYP Enzymes: ++, +++
- May Inhibit: -
- May Induce: BCRP

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DDI = drug-drug interaction; CYP = cytochrome P450 enzyme; BCRP = breast cancer resistance protein; UGT = UDPglycosyltransferase.

Key Factors in First-line EGFR TKI Selection

Sequence makes survival

Drug-drug interactions

Not all TKIs are equal

Efficacy

Adverse event profile
OS with Afatinib in **EGFR-Mutant NSCLC**

**Common Mutations (del19/L858R) (n=307)**

Only 6 patients in the afatinib arm were treated with osimertinib because of lack of availability (trial recruitment was from August 2009 to February 2011).

NSCLC = non–small cell lung cancer.

Molecular Mechanisms of Acquired Resistance to First-/Second-Generation EGFR TKIs

- 155 EGFR mutant NSCLC, acquired resistance after TKI
- Molecular analyses on re-biopsy specimen

![Pie chart showing molecular mechanisms:]
- T790M (60%)
- HER2 (8%)
- HER2 T790M (4%)
- Unknown (18%)
- MET amplification (3%)
- Small cell + MET (1%)
- Small cell (1%)
- Small cell + T790M (2%)
- MET + T790M (3%)
- HER2 (8%)
- Unknown (18%)
- MET amplification (3%)
- Small cell + MET (1%)
- Small cell (1%)
- Small cell + T790M (2%)
- MET + T790M (3%)
OS in Patients Treated With Third-Generation TKIs Subsequently in LUX-Lung 7

20%/17% who discontinued afatinib/gefitinib received third-generation TKIs (osimertinib, olmutinib, rociletinib)

<table>
<thead>
<tr>
<th>Months</th>
<th>Estimated OS probability</th>
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<tr>
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<td>Afatinib (n=30)</td>
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<tr>
<td>0</td>
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</tr>
<tr>
<td>3</td>
<td>0.9</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td>9</td>
<td>0.8</td>
</tr>
<tr>
<td>12</td>
<td>0.7</td>
</tr>
<tr>
<td>15</td>
<td>0.6</td>
</tr>
<tr>
<td>18</td>
<td>0.6</td>
</tr>
<tr>
<td>21</td>
<td>0.6</td>
</tr>
<tr>
<td>24</td>
<td>0.6</td>
</tr>
<tr>
<td>27</td>
<td>0.6</td>
</tr>
<tr>
<td>30</td>
<td>0.6</td>
</tr>
<tr>
<td>33</td>
<td>0.6</td>
</tr>
<tr>
<td>36</td>
<td>0.6</td>
</tr>
<tr>
<td>39</td>
<td>0.6</td>
</tr>
<tr>
<td>42</td>
<td>0.6</td>
</tr>
<tr>
<td>45</td>
<td>0.6</td>
</tr>
<tr>
<td>48</td>
<td>0.6</td>
</tr>
<tr>
<td>51</td>
<td>0.6</td>
</tr>
<tr>
<td>54</td>
<td>0.6</td>
</tr>
<tr>
<td>57</td>
<td>0.6</td>
</tr>
</tbody>
</table>

No. at risk:
- Afatinib: 30 30 30 30 30 29 29 29 28 28 26 21 17 14 8 1 0
- Gefitinib: 26 26 25 25 25 24 23 23 22 22 22 20 17 10 4 1 0

Median, mo: AF 48.3, GE NE

HR (95% CI): 0.49 (0.20-1.19), P=0.107

Corral et al. ELCC 2017. Abstract 93PD.
Treatment Sequences in EGFR-Mutant NSCLC After First-line EGFR TKI

1st-/2nd-generation TKI

- T790M +
  - Osimertinib
  - Chemotherapy
  - Except if molecular target

- T790M -
  - Chemotherapy
  - Other MET/HER2 inhibitor
  - 1st-/2nd-generation TKI

Osimertinib

- Chemotherapy
  - Except if molecular target

NEED MATURE OS AND TREATMENT SEQUENCES FROM AURA3 and FLAURA (med PFS = 18.9 months)
Key Factors in First-line EGFR TKI Selection

- Sequence makes survival
- Not all TKIs are equal
- Drug-drug interactions
- Efficacy
- Adverse event profile

Not all TKIs are equal implies different efficacy profiles. Drug-drug interactions can affect the overall survival. Sequence is crucial for survival. Adverse event profiles vary among different TKIs.
For more information about other BI events and collaborations, please visit [www.inOncology.com](http://www.inOncology.com)
Efficacy of EGFR TKIs in Patients With NSCLC With Uncommon EGFR Mutations

2017 WCLC- PACIFICOC Yokohama Convention Center
Terufumi Kato, MD
Kanagawa Cancer Center, Yokohama, Japan
Faculty Disclosure

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• Consulting or Advisory Role: AstraZeneca; Nippon Boehringer Ingelheim; Ono Pharmaceutical

• Research Funding: Abbvie; Astellas Pharma; AstraZeneca; Bristol-Myers Squibb; Chugai Pharma; Daiichi Sankyo; Kyowa Hakko Kirin; Lilly; Merck Sharp & Dohme; Nippon Boehringer Ingelheim; PAREXEL; Pfizer; Quintiles; Shionogi Pharma; Taiho Pharmaceutical; Takeda; Yakult Honsha
EGFR Mutations in NSCLC

Mitsudomi et al., Cancer Science, 2007
Common or Uncommon/Non-classical (N=1,632)

- **Single, uncommon/non-classical mutations or insertion:** 8%
  - Exon 21 single: 1%
  - Exon 20 single: 1%
  - Exon 20 insertions: 3%
  - Exon 19 single: 0.4%
  - Exon 18 single: 3%

Complex uncommon/non-classical, **without** Del19 and L858R: 2%

Uncommon/non-classical mutation **with** Del19/L858R: 6%

<table>
<thead>
<tr>
<th>Exon</th>
<th>Type</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Ex19</td>
<td>single</td>
<td>0.4%</td>
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<tr>
<td>Ex20</td>
<td>single</td>
<td>1%</td>
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<tr>
<td>Ex20</td>
<td>insertions</td>
<td>3%</td>
</tr>
<tr>
<td>Ex21</td>
<td>single</td>
<td>1%</td>
</tr>
<tr>
<td>Ex21</td>
<td>L858R</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Del19</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>Ex21 L858R</td>
<td>42%</td>
</tr>
</tbody>
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In Vitro Activity of First-, Second-, and Third-Generation TKIs Against Uncommon EGFR Mutations

- Irreversible second- and third-generation TKIs overcome resistance induced by uncommon secondary mutations

In Vitro Activity of First-, Second-, and Third-Generation TKIs Against Uncommon EGFR Mutations

- In separate assays, first- and third-generation TKIs demonstrated reduced activity against cell lines harbouring uncommon mutations, whereas the response to afatinib was similar across cell lines.


TKI = tyrosine kinase inhibitor; IC50 = 50% inhibitory concentration.

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**L858M/L861Q**

<table>
<thead>
<tr>
<th>Cell viability (%)</th>
<th>µM</th>
</tr>
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<tbody>
<tr>
<td>Afatinib</td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td></td>
</tr>
<tr>
<td>Osimertinib</td>
<td></td>
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</tbody>
</table>

**L861Q and S768I**

<table>
<thead>
<tr>
<th>IC50 ratio relative to L858R</th>
<th>µM</th>
</tr>
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<tbody>
<tr>
<td>Erlotinib</td>
<td></td>
</tr>
<tr>
<td>Afatinib</td>
<td></td>
</tr>
<tr>
<td>Osimertinib</td>
<td></td>
</tr>
</tbody>
</table>
**EGFR Exon 18 Mutations in Lung Cancer: Molecular Predictors of Augmented Sensitivity to Afatinib as Compared with First- or Third-Generation TKIs**

- Among 1,402 EGFR mutations, Del19, L858R, and Ins20 were detected in 40%, 47%, and 4%, respectively. Exon 18 mutations, including G719X, E709X, and Del18, were present in 3.2%.
- Patients with lung cancers harbouring G719X exhibited higher response rate to afatinib (80%) than to 1G TKIs (35%–56%).

### IC\textsubscript{50}s of EGFR-TKIs in Transfected Ba/F3 Cells (nmol/L)

<table>
<thead>
<tr>
<th>IC\textsubscript{50}</th>
<th>Gefitinib</th>
<th>Erlotinib</th>
<th>Afatinib</th>
<th>Dacomitinib</th>
<th>AZD9291</th>
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<tbody>
<tr>
<td>Del 18</td>
<td>10^{-4}</td>
<td>10^{-3}</td>
<td>10^{-2}</td>
<td>10^{-1}</td>
<td>10^{0}</td>
</tr>
<tr>
<td>E709K</td>
<td>448</td>
<td>167</td>
<td>167</td>
<td>166</td>
<td>93</td>
</tr>
<tr>
<td>Del 19</td>
<td>882</td>
<td>884</td>
<td>2,717</td>
<td>29,16</td>
<td>3,078</td>
</tr>
<tr>
<td>WT</td>
<td>7</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>G719A</td>
<td>713</td>
<td>&gt;10,000</td>
<td>&gt;10,000</td>
<td>&gt;10,000</td>
<td>&gt;10,000</td>
</tr>
</tbody>
</table>

### Exon 18

- Del 19: 40% (n=563)
- Ins 20: 4% (n=63)
- Others: 5% (n=71)
- L858R: 47% (n=660)

Kobayashi Y et al. CCR 2015.
Case Report: Afatinib in a TKI-Pretreated Patient With EGFR L858M/L861Q (in cis)

- 62-year-old Caucasian female with extensive involvement of a poorly differentiated adenocarcinoma
- Worsening disease with 4 months of erlotinib and 4 months of chemotherapy
- Radiographic response 2 months after initiation of afatinib
- Remained on afatinib, with Grade 1 diarrhoea as her only side effect, for 10 months and continues treatment
Clinical Data in TKI-Pretreated Patients: Radiographic Responses After Suboptimal Response to Other EGFR-TKIs

Patient With ex19del, T790M, and G724S

Cell-free DNA tumor response. Cell-free DNA analysis of total somatic alteration burden detected over five time points and the EGFR variant-specific results over time reflect responses to changes in matched therapy. TP53, tumor protein p53

Clinical Data in TKI-Pretreated Patients: Best Response in Patients With LMD Harbouring Uncommon Mutations

- 3/11 patients with leptomeningeal carcinoma treated with afatinib harboured an uncommon Exon 18 mutation (L719X).

- Median CSF concentration in all 11 patients was 2.88 nM (afatinib’s IC$_{50}$ for EGFR being 0.5 nM). PFS and OS in patients harbouring a G719X mutation were 5.6 months (2.0-10.0) and 7.0 months (5.6 ongoing to 13.0).

Concentration of Afatinib in Plasma and CSF, Penetration Rate, and Efficacy in Patients With EGFR Mutation-Positive NSCLC With LMD

<table>
<thead>
<tr>
<th>Concentration (nM)</th>
<th>Plasma</th>
<th>CSF</th>
<th>Best Response</th>
<th>PFS (Days)</th>
<th>OS (Days)</th>
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<tbody>
<tr>
<td>1</td>
<td>146.9</td>
<td>NE</td>
<td>PR</td>
<td>309</td>
<td>396</td>
</tr>
<tr>
<td>2</td>
<td>192.0</td>
<td>6.0</td>
<td>PD</td>
<td>61</td>
<td>212</td>
</tr>
<tr>
<td>3</td>
<td>767.6</td>
<td>0.8</td>
<td>PR</td>
<td>171$^a$</td>
<td>171$^b$</td>
</tr>
</tbody>
</table>

*Treatment continued after data cutoff; $^b$Censored at data cutoff (patient still alive).

LMD = leptomeningeal disease; CSF = cerebrospinal fluid; PFS = progression-free survival; OS = overall survival; NE = Not evaluated; PR = partial response; PD = progressive disease.

Clinical Data in TKI-Pretreated Patients: Time to Treatment Failure With Afatinib

- 66 uncommon mutations were reported (18.4% of all known \textit{EGFR} mutations in the compassionate-use programme)
  - Majority of patients (67%) received afatinib as third- or fourth-line treatment, with median treatment duration of 3.6 months
- No significant difference between median TTF for patients with uncommon/non-classical mutations (3.6 months) compared with those with Del19 (4.6 months) or L858R (5.8 months) mutations

\textbf{Distribution of the 60 Rare \textit{EGFR} Mutations (N=60)}

- Exon 18 substitution, 1, 2%
- Exon 19 insertion/deletion, 2, 3%
- Exon 19 substitution, 4, 7%
- Exon 20 insertion, 3, 5%
- T790M, 1, 2%
- Exon 21 substitution, 4, 7%
- Complex mutations incl. T790M, 29, 48%
- Complex mutations, 9, 15%

\textbf{TTF = time to treatment failure.}

First-line Clinical Data: Retrospective Analysis of PFS in 57 Patients Treated With Afatinib or First-Generation TKIs

- In all mutation groups analysed, the afatinib group exhibited longer median PFS compared with first-generation TKIs
  - Entire uncommon mutations cohort, except exon 20 insertions: 11.0 mo vs 3.6 mo
  - G719X, S768I, or L861Q: 18.3 mo vs 2.6 mo
  - Uncommon mutations with Del19 or L858R: 11.0 mo vs 8.2 mo
    - Del19 + 18G721D; Del19 + 19L732P; Del19 + 20L792P; Del19 + 20S768I + 20V774M; Del19 + 21L858R + 21K860I; 21L858R + 18E709X; 21L858R + 20S768I; 21L858R + 20V786E; 21L858R + 20T790M; 21L858R + 20 insertion; 21L858R + 21L833VI; 21L858R + 21K860I; 21L858R + 18G719X +20 insertion
  - Uncommon mutation alone or in combination with other uncommon mutations: 18.3 mo vs 2.8 mo

CI = confidence interval. *exon 20 insertions (except A763_Y764 insFQEA).

First-line Clinical Data: Prospective Efficacy Assessments in the LUX-Lung Programme

- Of 600 patients given afatinib in LUX-Lung 2/3/6, 75 (12%) patients had uncommon EGFR mutations\(^1\)
- The LUX-Lung programme provides the largest series of prospective efficacy data in uncommon mutations\(^1-4\).

---

**LUX-Lung 2**
- **Phase 2**
  - (N=129)\(^5\)
  - Treatment: Afatinib
  - Line of treatment: First- and second-line (after chemotherapy)
  - Mutation test: Direct sequ. (central)
  - Common mutations: Del19=52, L858R=54
  - Uncommon mutations: N=23

**LUX-Lung 3**
- **Phase 3**
  - (N=345)\(^6\)
  - Treatment: Afatinib vs Cis/Pem
  - Line of treatment: First-line
  - Mutation test: EGFR29\(^a\) (central)
  - Common mutations: Del19=170, L858R=138
  - Uncommon mutations: N=37

**LUX-Lung 6**
- **Phase 3**
  - (N=364)\(^4\)
  - Treatment: Afatinib vs Cis/Gem
  - Line of treatment: First-line
  - Mutation test: EGFR29\(^a\) (central)
  - Common mutations: Del19=186, L858R=138
  - Uncommon mutations: N=40

---


LUX-Lung 2, 3, and 6: Tumour Shrinkage by Independent Review (n=67) 

- 3 patients in group 1 achieved complete response
  - 1 each with G719X, K739_1744dup6, and L858R+Q709G/V

8 patients were not included because of insufficient data.

LUX-Lung 2, 3, and 6: Response Rate, PFS, and OS by Independent Review

<table>
<thead>
<tr>
<th></th>
<th>T790M (n=14)</th>
<th>Exon 20 ins (n=23)</th>
<th>Mut/Dup Exon 18-21 (n=38)</th>
<th>G719X (n=18)</th>
<th>L861Q (n=16)</th>
<th>S768I (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate (%)</td>
<td>14.3</td>
<td>8.7</td>
<td>71.1</td>
<td>77.8</td>
<td>56.3</td>
<td>100.0</td>
</tr>
<tr>
<td>PFS (mo)</td>
<td>2.9</td>
<td>2.7</td>
<td>10.7</td>
<td>13.8</td>
<td>8.2</td>
<td>14.7</td>
</tr>
<tr>
<td>OS (mo)</td>
<td>14.9</td>
<td>9.2</td>
<td>19.4</td>
<td>26.9</td>
<td>17.1</td>
<td>NE</td>
</tr>
</tbody>
</table>
Summary

• Afatinib has shown preclinical and clinical activity in TKI-naive and TKI-pretreated patients with NSCLC harbouring uncommon EGFR mutations

• Activity of afatinib against uncommon EGFR mutations in patients with LMD was also reported

• Afatinib was especially active in NSCLC tumours harbouring point mutations or duplications in exons 18-21 (eg, G719X, S768I, L861Q K739_1744dup6, and L858R+Q709G/V)

• Anecdotal data from erlotinib/gefitinib trials show variable and mainly limited responses to these EGFR TKIs in patients with NSCLC harbouring uncommon mutations

• These data could help inform clinical decisions for patients with NSCLC harbouring uncommon EGFR mutations
Yokohama, when sunny, and in later fall...

Just 3 train stops, or 30 min. walk!

Ocean liner Hikawa maru, Yamashita Park

We are HERE
For more information about other BI events and collaborations, please visit www.inOncology.com
Considerations for Choosing TKIs for Squamous NSCLC in the Era of Immunotherapy: Which Patients Could Benefit?

2017 WCLC- PACIFICO Yokohama Convention Center

Barbara Melosky
University of British Columbia,
British Columbia Cancer Agency

BI Symposium
Faculty Disclosure

- Honoraria: Boehringer Ingelheim, Merck, Eli Lilly, Bristol-Myers Squibb, Novartis, Pfizer, AstraZeneca
Squamous Cell Carcinoma (SqCC) of the Lung

- Squamous histology represents approximately 20–40% of NSCLC\textsuperscript{1,2}
- SqCC of the lung remains a disease with high unmet need
- SqCC of the lung is associated with poor prognosis\textsuperscript{3}
- Targetable oncogenic alterations are few
- Additional therapeutic options are needed

OS = overall survival; NSCLC = non-small cell lung cancer.
Current Treatment Recommendations for Metastatic SqCC of the Lung

- **Never or former light smoker (<15 pack/year)**
- **Molecular test (ALK/EGFR)**
  - Molecular test negative
  - Molecular test positive
- **Targeted therapy**

### Stage IV SqCC

#### I) Age
- <70 years and PS 0–1
  - 4–6 cycles: Cisplatin – gemcitabine (I, A)
  - Cisplatin – docetaxel (I, A)
  - Cisplatin – vinorelbine (I, A)
  - Carboplatin – paclitaxel (I, A)
  - Carboplatin – nab-paclitaxel (I, B)
  - Cisplatin – gemcitabine – necitumumab (if EGFR expression by IHC) (I, B; MCBS 1)

#### II) PS
- <70 years and PS 2 or >70 years and PS 0–2
  - 4–6 cycles: Carboplatin-based doublets (II, B)
  - Single-agent chemotherapy (gemcitabine, vinorelbine or docetaxel) (I, A)

- **BSC (II, B)**
- **PS 3–4**

- **Disease progression**
- **BSC**

### PS 0–2

#### Nivolumab (I, A; MCBS 5)
- Pembrolizumab if PD-L1 >1%
  - (I, A; MCBS 3 if PD-L1 >1%; MSBC 5 if PD-L1 >50%)
- Docetaxel (I, B)
- Ramucirumab – docetaxel (I, B; MCBS 2)
- Erlotinib (II, C)
- Afatinib (I, C; MCBS 1)

### BSC (II, B)

- Docetaxel (I, B)
- Ramucirumab – docetaxel (I, B; MCBS 2)
- Erlotinib (II, C)
- Afatinib (I, C; MCBS 1)

---

*ESMO guidelines do not recommend maintenance therapy in the treatment of squamous cell carcinoma NSCLC. ¹ BSC = Best Standard of Care; EGFR = epidermal growth factor receptor; MCBS = Magnitude of Clinical Benefit Scale; NSCLC = non-small cell lung cancer; PD-L = programmed death-ligand; PS = Performance Status; SqCC = squamous cell carcinoma.

Overview of Recent Key Phase III ≥ Second-line Treatment Studies in Patients With SqCC of the Lung

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Median PFS (mo)</th>
<th>HR for PFS</th>
<th>Median OS (mo)</th>
<th>HR for OS</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVEL¹</td>
<td>Ramucirumab + doce vs doce (n=1253)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Squamous (n=328)</td>
<td>4.5 vs 3.0</td>
<td>0.76*</td>
<td>10.5 vs 9.1</td>
<td>0.86*</td>
<td>22.9 vs 13.6*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.2 vs 2.7</td>
<td>0.76*</td>
<td>9.5 vs 8.2</td>
<td>0.88</td>
<td>26.8 vs 10.5*</td>
</tr>
<tr>
<td>CheckMate-017²</td>
<td>Nivolumab vs doce</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All squamous (n=272)</td>
<td>3.5 vs 2.8</td>
<td>0.62*</td>
<td>9.2 vs 6.0</td>
<td>0.59*</td>
<td>20.0 vs 9.0*</td>
</tr>
<tr>
<td>KEYNOTE-010³</td>
<td>Pembrolizumab vs doce</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PD-L1 PS ≥50% (n=442) Squamous (n=222)</td>
<td>2 mg: 5.0 vs 4.1</td>
<td>2 mg: 0.59*</td>
<td>14.9 vs 8.2</td>
<td>0.54*</td>
<td>30.0 vs 8.0*</td>
</tr>
<tr>
<td></td>
<td>10 mg: 5.2 vs 4.1</td>
<td>10 mg: 0.59*</td>
<td>17.3 vs 8.2</td>
<td>0.50*</td>
<td>29.0 vs 8.0*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NR for squamous</td>
<td>0.86</td>
<td>NR for squamous</td>
<td>0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LUX-Lung 8⁴</td>
<td>Afatinib vs erlotinib (n=795)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All squamous</td>
<td>2.6 vs 1.9</td>
<td>0.81*</td>
<td>7.9 vs 6.8</td>
<td>0.81*</td>
<td>6.0 vs 2.8*</td>
</tr>
<tr>
<td>OAK⁵</td>
<td>Atezolizumab vs doce (n=850)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Squamous (n=222)</td>
<td>2.8 vs 4.0</td>
<td>0.95</td>
<td>13.8 vs 9.6</td>
<td>0.73*</td>
<td>14 vs 13</td>
</tr>
<tr>
<td></td>
<td>NR for squamous</td>
<td>NR for squamous</td>
<td>NR for squamous</td>
<td>0.73*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05.

doce = docetaxel; EMEA = European Medicines Agency; FDA = US Food and Drug Administration; HR = hazard ratio; mo = months; NR = not reported; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PS = proportion score; SqCC = squamous cell carcinoma.

ESMO Guidelines: Second-line Recommendations

Nivolumab (I, A; MCBS 5)
Pembrolizumab if PD-L1 >1%
(I, A; MCBS 3 if PD-L1 >1%; MSBC 5 if PD-L1 >50%)
Docetaxel (I, B)
Ramucirumab – docetaxel (I, B; MCBS 2)
Erlotinib (II, C)
Afatinib (I, C; MCBS 1)

MCBS = Magnitude of Clinical Benefit Scale; PD-L = programmed death-ligand.
SqCC of the Lung: Genetically Complex Malignancy

- High burden of somatic mutations/genomic alterations

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Somatic Mutation Prevalence (Number Mutations per Megabase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocytic astrocytoma</td>
<td>-</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>-</td>
</tr>
<tr>
<td>AML</td>
<td>-</td>
</tr>
<tr>
<td>Thyroid</td>
<td>-</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>-</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>-</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>-</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>-</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>-</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>-</td>
</tr>
<tr>
<td>Lung adenocarcinoma</td>
<td>-</td>
</tr>
<tr>
<td>Lung squamous cell cancer</td>
<td>-</td>
</tr>
<tr>
<td>Melanoma</td>
<td>-</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>-</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>-</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>-</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>-</td>
</tr>
<tr>
<td>Myeloma</td>
<td>-</td>
</tr>
<tr>
<td>CML</td>
<td>-</td>
</tr>
<tr>
<td>ALL</td>
<td>-</td>
</tr>
<tr>
<td>Kidney chromophobe</td>
<td>-</td>
</tr>
<tr>
<td>Lung small cell cancer</td>
<td>-</td>
</tr>
<tr>
<td>Brain cancer</td>
<td>-</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>-</td>
</tr>
<tr>
<td>Oral cavity cancer</td>
<td>-</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>-</td>
</tr>
<tr>
<td>Rectum cancer</td>
<td>-</td>
</tr>
<tr>
<td>Cervix cancer</td>
<td>-</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>-</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>-</td>
</tr>
<tr>
<td>Lung adenocarcinoma</td>
<td>-</td>
</tr>
<tr>
<td>Lung squamous cell cancer</td>
<td>-</td>
</tr>
</tbody>
</table>

- Overexpression/derangements of EGFR,\(^2,3\) HER2,\(^4,5\) HER4,\(^6\) and/or dysregulation of their downstream pathways implicated in the pathogenesis of SqCC of the lung

ErbB Pathway is Frequently Dysregulated in SqCC of the Lung

- EGFR overexpression, gene amplification and aberrations of other ErbB receptors have all been implicated in the pathobiology of SqCC\(^1,2\)

- These findings likely account for the benefits these patients derive from erlotinib\(^{11−13}\) and other EGFR-directed therapies in different treatment settings,\(^{14−16}\) despite the low frequency of EGFR-activating mutations\(^{17}\)

<table>
<thead>
<tr>
<th>ErbB Receptor</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR overexpression(^2−5)</td>
<td>26−86</td>
</tr>
<tr>
<td>EGFR amplification(^2,5)</td>
<td>15−27</td>
</tr>
<tr>
<td>EGFRvIII mutation(^6)</td>
<td>5</td>
</tr>
<tr>
<td>EGFR kinase domain mutation(^7)</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>ERBB2 mutation/amplification(^2)</td>
<td>5</td>
</tr>
<tr>
<td>ERBB3 mutation(^8)</td>
<td>1</td>
</tr>
<tr>
<td>ERBB3 overexpression(^9)</td>
<td>10</td>
</tr>
<tr>
<td>ERBB4(^10)</td>
<td>8</td>
</tr>
</tbody>
</table>

**Frequency of known genetic drivers in SqCC\(^{17}\)**

- EGFRvIII
- PI3KCA
- EGFRT
- DDR2
- FGFR1 Amp
- Unknown

Amp = amplification; EGFR = epidermal growth factor receptor; FGFR = fibroblast growth factor receptor; SqCC = squamous cell carcinoma.

Afatinib is the First Irreversible ErbB Family Blocker

- Afatinib covalently binds and irreversibly blocks EGFR, HER2, and ErbB4
- Targeting the whole ErbB Family enhances the effect on important signaling pathways

LUX-Lung 8: Study Design

- Advanced SqCC NSCLC (Stage IIIB/IV)
- PD after ≥4 cycles of a first-line platinum doublet
- ECOG PS 0 or 1
- No prior anti-EGFR therapy
- No active brain metastases

Randomisation 1:1 (N=795)

Afatinib (n=398)
40 mg qd

Erlotinib (n=397)
150 mg qd

Treatment until disease progression or unacceptable AEs

- Stratification: East Asian vs non-East Asian
- Tumour tissue collected for correlative science
- Radiographic tumour assessment at baseline; Weeks 8, 12, 16; every 8 weeks thereafter
- Primary endpoint: PFS; key secondary endpoint: OS

AE = adverse event; EGFR = epidermal growth factor receptor; ECOG PS = Eastern Cooperative Oncology Group performance status; NSCLC = non-small cell lung cancer; OS = overall survival; PD = disease progression; PFS = progression-free survival; qd = once daily; SqCC = squamous cell carcinoma.

LUX-Lung 8: Significant Improvement in PFS and OS With Afatinib Compared With Erlotinib

Updated PFS analysis by Independent Review (n=795)

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Time (months)</th>
<th>Afatinib 40 mg QD (n=398)</th>
<th>Erlotinib 150 mg QD (n=397)</th>
</tr>
</thead>
<tbody>
<tr>
<td>398</td>
<td>0</td>
<td>1.00</td>
<td>0.94</td>
</tr>
<tr>
<td>139</td>
<td>3</td>
<td>0.79</td>
<td>0.72</td>
</tr>
<tr>
<td>50</td>
<td>6</td>
<td>0.60</td>
<td>0.49</td>
</tr>
<tr>
<td>30</td>
<td>9</td>
<td>0.48</td>
<td>0.35</td>
</tr>
<tr>
<td>14</td>
<td>12</td>
<td>0.40</td>
<td>0.27</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>0.35</td>
<td>0.21</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>0.28</td>
<td>0.15</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>0.22</td>
<td>0.10</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>0.19</td>
<td>0.08</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>0.16</td>
<td>0.06</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients progressed or died, n (%) Afatinib 40 mg QD (n=398) = 299 (75.1); Erlotinib 150 mg QD (n=397) = 306 (77.1)

Median PFS (months) Afatinib 40 mg QD (n=398) = 2.6; Erlotinib 150 mg QD (n=397) = 1.9

HR 0.81; 95% CI: 0.69–0.96; P = 0.0103

Primary analysis of OS (key secondary endpoint) (n=795)

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Time (months)</th>
<th>Afatinib 40 mg QD (n=398)</th>
<th>Erlotinib 150 mg QD (n=397)</th>
</tr>
</thead>
<tbody>
<tr>
<td>398</td>
<td>0</td>
<td>1.00</td>
<td>0.94</td>
</tr>
<tr>
<td>316</td>
<td>3</td>
<td>0.79</td>
<td>0.72</td>
</tr>
<tr>
<td>249</td>
<td>6</td>
<td>0.60</td>
<td>0.49</td>
</tr>
<tr>
<td>170</td>
<td>9</td>
<td>0.48</td>
<td>0.35</td>
</tr>
<tr>
<td>124</td>
<td>12</td>
<td>0.40</td>
<td>0.27</td>
</tr>
<tr>
<td>82</td>
<td>15</td>
<td>0.35</td>
<td>0.21</td>
</tr>
<tr>
<td>47</td>
<td>18</td>
<td>0.28</td>
<td>0.15</td>
</tr>
<tr>
<td>28</td>
<td>21</td>
<td>0.22</td>
<td>0.10</td>
</tr>
<tr>
<td>10</td>
<td>24</td>
<td>0.19</td>
<td>0.08</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>0.16</td>
<td>0.06</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients died, n (%) Afatinib 40 mg QD (n=398) = 307 (77.1); Erlotinib 150 mg QD (n=397) = 325 (81.9)

Median OS (months) Afatinib 40 mg QD (n=398) = 7.9; Erlotinib 150 mg QD (n=397) = 6.8

HR 0.81; 95% CI: 0.69–0.95; P = 0.0077

Cl = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; QD = once daily.

Post-hoc Analysis of LUX-Lung 8 Patients Deriving Long-term Benefit\textsuperscript{1}

Post-hoc analysis identified 21 patients who received \( \geq 12 \) months of afatinib treatment

– Median treatment duration was 17.6 months (range: 12.3–27.6 months)

\textsuperscript{1} Yang J et al. ELCC 2017. Poster #102P.
Post-hoc Analysis of LUX-Lung 8 Patients Deriving Long-term Benefit

OS and PFS in Patients Deriving Long-term Benefit

- Median OS was 21.1 months (range: 12.9–31.6 months)
- Median PFS was 16.6 months (range: 2.8–25.8 months)

Median OS was 21.1 months (range: 12.9–31.6 months)
Median PFS was 16.6 months (range: 2.8–25.8 months)

Afatinib OS, 7.9 mo
Treatment Response* and OS in Patients Deriving Long-term Benefit

- Median OS was 21.1 months (range: 12.9–31.6 months)
- Median PFS (independent central review) was 16.6 months (range: 2.8–25.8 months)

*Stable disease unless noted otherwise (patient 2 was classified as non-evaluable); †Patients were ordered and numbered by treatment duration, with patient 1 being on treatment longest; ‡First observed response at time of tumour measurement; §Last observed response at time of tumour measurement; ¶Treatment ongoing until death; ‖Received ≥1 line of chemotherapy after afatinib; CR = complete response; PR = partial response.

Yang J et al. ELCC 2017. Poster #102P.
Genomic Aberrations in Patients Deriving Long-term Benefit

• ErbB family mutations were more frequent in LTRs than in the overall afatinib-treated population

All afatinib-treated patients (n=132*)

- ErbB2, 6.8%
- ErbB3, 4.6%
- ErbB4, 2.3%
- EGFR, 6.8%
- ErbB WT, 81.1%

LTRs (n=10*)

- ErbB2, 0%
- ErbB3, 10.0%
- ErbB4, 10.0%
- EGFR, 20.0%
- ErbB WT, 50.0%

*Next-generation sequencing was undertaken in 10/21 LTRs and 132/398 afatinib-treated patients overall; WT = wild-type.

Yang J et al. ELCC 2017. Poster #102P.
Experience With Afatinib for SqCC of the Lung: Case Report From LUX-Lung 8

Baseline characteristics
• 59-year-old white male
• ECOG PS: 1
• Stage IV
• Primary site: left upper lobe
• Number of metastases: 2; no brain metastases
• Smoking status: ex smoker (41 pack-years)

Treatments
• First-line: carboplatin/paclitaxel (Aug 2012 to Oct 2012; best response: CR); no maintenance therapy
• Second-line: afatinib within LUX-Lung 8
Experience With Afatinib for SqCC of the Lung: Case Report From LUX-Lung 8

Outcomes with second-line afatinib

- **Treatment duration:** 19.6 months (Mar 2013 to Nov 2014)
  - Afatinib dosage: 40 mg for 28 days; 50 mg for 18.7 months

- **PFS:** 17.1 months
- **OS:** 23.1 months

Biomarker analysis

- **Mutation:** *HER2* E395K

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Case study.

BM = bone metastasis; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CR = complete response; DC = discontinued; ECOG PS = Eastern Cooperative Oncology Group performance status; OS = overall survival; PD = disease progression; PFS = progression-free survival; SqCC = squamous cell carcinoma.
See You at the Poster!

- P3.01 – Advanced NSCLC (ID 621)
  09:30 am – 04:00 pm | 10/18/2017 | Location: Exhibit Hall (Hall B + C)
  Type: Poster Session with Presenters Present | Track: Advanced NSCLC

  - P3.01-043 – Impact of ErbB Mutations on Clinical Outcomes in Afatinib- or Erlotinib-Treated Patients with SCC of the Lung
Summary and Conclusions

- LUX-Lung 8¹
  - Afatinib significantly improved PFS vs erlotinib: 2.6 vs 1.9 months (HR 0.81; \( P=0.0427 \))
  - Afatinib significantly improved OS vs erlotinib: 7.9 vs 6.8 months (HR 0.81, \( P=0.0077 \))

- Survival rates at 12 and 18 months favored afatinib
  - 12 months (afatinib vs erlotinib): 36% vs 28% (\( P=0.016 \))
  - 18 months: 22% vs 14% (\( P=0.013 \))

- In patients on afatinib for ≥ 12 months, a median survival benefit of nearly 2 years was seen
  - ErbB family mutations were more frequent in this group³

Summary and Conclusions

In treatment of SqCC, afatinib should be considered:

- As a treatment option in patients who have failed previous treatment with chemotherapy and immunotherapy
- In the second-line setting in patients who are not eligible for immune checkpoint inhibitors

HR = hazard ratio; OS = overall survival; PFS = progression-free survival; SqCC = squamous cell carcinoma.

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Panel Discussion
Carrying the Data into the Clinic: TKI Sequencing Decisions for *EGFR* Mutation-Positive NSCLC Patients

2017 WCLC- PACIFICO Yokohama Convention Center

All Faculty
Moderator: T. Mitsudomi

BI Symposium
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