First-line treatment of EGFR mutated NSCLC
Resistance, TKI sequencing

Tetsuya Mitsudomi, MD
Thoracic Surgery, Kindai University Faculty of Medicine
Disclosure information Tetsuya Mitsudomi

- **Personal financial interests - Consulting and advisory services, speaking or writing engagements, public presentations:**
  - AstraZeneca, Pfizer, Ono Pharmaceutical, Taiho, Boehringer Ingelheim, Chugai/Roche, Bristol Myers Squibb, Novartis, Eli Lilly

- **Institutional financial interests - Financial support for clinical trials or contracted research:**
  - Boehringer Ingelheim, Pfizer, Chugai, Taiho, Ono Pharmaceutical

- **Non-financial interests - Senior leadership roles:**
  - President, Japanese Lung Cancer Society Board of directors, Japanese Society of Medical Oncology Council member, Japanese Association of Chest Surgery

- **Non-financial interests - non-remunerated activities:**
  - Steering committee of the trial (Chugai) co-PI of the global trial (AstraZeneca) IDMC of the global trial (Novartis)
EGFR mutation and TKI sensitivity

EGFR mutation and TKI sensitivity

Oncogene addiction

EGFR

EGFR mutation

dependence on EGFR pathway

ligand independent

phosphorylation

cell proliferation

survival

EGFR-TKI treatment

TKI

apoptosis

Mitsudomi et al., Lancet Oncol., 2010

Memondo et al., New Engl J Med., 2010

Gefitinib

Chemotherapy

Gefitinib

Chemotherapy

Gefitinib (n=86)

Cisplatin and docetaxel (n=86)

6.3 months (5.8-7.8)

Median (95% CI) progression-free survival

p=0.0001

0

10

20

30

40

50

60

70

80

90

100

Months since Randomization

0

2

4

6

8

10

12

14

16

18

20

22

24

26

28

30

32

34

36
PFS and OS in the phase III trials comparing EGFR-TKI with platinum-doublet chemotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>gefitinib</th>
<th>erlotinib</th>
<th>afatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEJ002</td>
<td>10.8</td>
<td>13.7</td>
<td>11.0</td>
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<tr>
<td>WJTOG3405</td>
<td>27.7</td>
<td>22.8</td>
<td>26.7</td>
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<tr>
<td>OPTIMAL</td>
<td>26.6</td>
<td>27.2</td>
<td>22.9</td>
</tr>
<tr>
<td>EURTAC</td>
<td>26.0</td>
<td>19.6</td>
<td>26.5</td>
</tr>
<tr>
<td>ENSURE</td>
<td>5.4</td>
<td>5.1</td>
<td>5.5</td>
</tr>
<tr>
<td>Lux Lung 3</td>
<td>9.6</td>
<td>4.6</td>
<td>6.9</td>
</tr>
<tr>
<td>Lux Lung 6</td>
<td>6.6</td>
<td>10.4</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>35.5</td>
<td>10.0</td>
<td>22.8</td>
</tr>
<tr>
<td></td>
<td>38.8</td>
<td>22.9</td>
<td>22.9</td>
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<td></td>
<td>35.5</td>
<td>19.6</td>
<td>28.2</td>
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<td>28.2</td>
<td>26.7</td>
<td>28.2</td>
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<td></td>
<td>23.1</td>
<td>11.1</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>23.5</td>
<td>11.0</td>
<td>23.5</td>
</tr>
</tbody>
</table>

Months
Not all EGFR mutations in lung cancer are created equal: Perspectives for individualized treatment strategy

Kobayashi, Y. and Mitsudomi, T., Cancer Science 2016

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>G719X</td>
<td>3.1%</td>
</tr>
<tr>
<td>L858R</td>
<td>39.8%</td>
</tr>
<tr>
<td>L861Q</td>
<td>0.9%</td>
</tr>
<tr>
<td>L861Q</td>
<td>0.9%</td>
</tr>
<tr>
<td>Del18</td>
<td>0.3%</td>
</tr>
<tr>
<td>Del19</td>
<td>44.8%</td>
</tr>
<tr>
<td>E709X</td>
<td>0.3%</td>
</tr>
<tr>
<td>Ins19</td>
<td>5%</td>
</tr>
<tr>
<td>Ins20</td>
<td>5.8%</td>
</tr>
<tr>
<td>S768I</td>
<td>1.1%</td>
</tr>
<tr>
<td>Del18</td>
<td>0%</td>
</tr>
<tr>
<td>Del19</td>
<td>47%</td>
</tr>
<tr>
<td>S768I</td>
<td>41%</td>
</tr>
<tr>
<td>L858R</td>
<td>41%</td>
</tr>
<tr>
<td>L861Q</td>
<td>1%</td>
</tr>
<tr>
<td>E709X</td>
<td>1%</td>
</tr>
<tr>
<td>Ins19</td>
<td>1%</td>
</tr>
<tr>
<td>Ins20</td>
<td>6%</td>
</tr>
<tr>
<td>L861Q</td>
<td>3%</td>
</tr>
</tbody>
</table>

Diagram showing the distribution of EGFR mutations.
EGFR-TKIs

1st generation
gefitinib

erlotinib

dacomitinib

2nd generation
afatinib

3rd generation
osimertinib

quinazoline
acrylamide
pyrimidine
A method of high-throughput functional evaluation of EGFR gene variants of unknown significance in cancer

Shinji Kohsaka,1,5 Masaaki Nagano,2,3,7 Yoshihide Ueno,2 Yoshiyuki Suehara,4 Takuo Hayashii,5 Naoko Shimada,6 Kazuhisa Takahashi,6 Kenji Suzuki,7 Kazuya Takamochi,7 Fumiyuki Takahashi,6 Hiroyuki Mano2,8


Table:

<table>
<thead>
<tr>
<th>Gefitinib / Erlotinib / Osimertinib</th>
<th>Afatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitive</td>
<td>IC50 &lt; 100 nM</td>
</tr>
<tr>
<td>Partially sensitive</td>
<td>100 nM ≤ IC50 ≤ 500 nM</td>
</tr>
<tr>
<td>Resistant</td>
<td>IC50 &gt; 500 nM</td>
</tr>
</tbody>
</table>

Diagram:

Exon 2-15 Exon 18 Exon 19 Exon 20 Exon 21 Exon 28
A method of high-throughput functional evaluation of EGFR gene variants of unknown significance in cancer

Shinji Kohsaka, Masaaki Nagano, Toshihide Ueno, Yoshiyuki Suehara, Takuo Hayashi, Naoko Shimada, Kazuhisa Takahashi, Kenji Suzuki, Kazuya Takamochi, Fumiyuki Takahashi, Hiroyuki Mano

<table>
<thead>
<tr>
<th>Gefitinib / Erlotinib / Osimertinib</th>
<th>Afatinib</th>
<th>Rociletinib</th>
<th>Cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitive</strong></td>
<td>IC&lt;sub&gt;90&lt;/sub&gt; &lt; 100 nM</td>
<td>IC&lt;sub&gt;90&lt;/sub&gt; &lt; 5 nM</td>
<td>IC&lt;sub&gt;90&lt;/sub&gt; &lt; 100 nM</td>
</tr>
<tr>
<td>Partially sensitive</td>
<td>100 nM ≤ IC&lt;sub&gt;90&lt;/sub&gt; ≤ 500 nM</td>
<td>5 nM ≤ IC&lt;sub&gt;90&lt;/sub&gt; ≤ 10 nM</td>
<td>100 nM ≤ IC&lt;sub&gt;90&lt;/sub&gt; ≤ 1 µM</td>
</tr>
<tr>
<td>Resistant</td>
<td>IC&lt;sub&gt;90&lt;/sub&gt; &gt; 500 nM</td>
<td>IC&lt;sub&gt;90&lt;/sub&gt; &gt; 50 nM</td>
<td>IC&lt;sub&gt;90&lt;/sub&gt; &gt; 1 µM</td>
</tr>
</tbody>
</table>

Exon 2-15 Exon 18 Exon 19 Exon 20 Exon 21 Exon 28
Cobas test covers only a subset of various mutations
### Activity of afatinib in specific uncommon EGFR mutations in LL2,3,6

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>ORR, n (%)</th>
<th>PFS (months), median (95% CI)</th>
<th>OS (months), median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G719X (n=18)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G719X (n=8)</td>
<td>14 (78)</td>
<td>13.8 (6.8–NE)</td>
<td>26.9 (16.4–NE)</td>
</tr>
<tr>
<td>G719X+T790M (n=1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G719X+S768I (n=5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G719X+L861Q (n=3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G719X+T790M+L858R (n=1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>L861Q (n=16)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L861Q (n=12)</td>
<td>9 (56)</td>
<td>8.2 (4.5–16.6)</td>
<td>16.9 (15.3–22.0)</td>
</tr>
<tr>
<td>L861Q+G719X (n=3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L861Q+Del19 (n=1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>S768I (n=8)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S768I (n=1)</td>
<td>8 (100)</td>
<td>14.7 (2.6–NE)</td>
<td>NE (3.4–NE)</td>
</tr>
<tr>
<td>S768I + G719X (n=5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S768I +L858R (n=2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: A patient may be presented in more than one category

Yang et al., WCLC 2013
An open-label, multicenter, phase II single arm trial of osimertinib in non-small cell lung cancer patients with uncommon EGFR mutation (KCSG-LU15-09)

Jang Ho Cho¹, Jong-Mu Sun¹, Se-Hoon Lee¹, Jin Seok Ahn¹, Keunchil Park¹, Keon Uk Park², Eun Joo Kang³, Yoon Hee Choi⁴, Ki Hwan Kim⁵, Ho Jung An⁶, Hyun Woo Lee⁷, Myung-Ju Ahn¹

Percent Change in Tumor Burden of the Target Lesion (N=35)

- Median best percentage change from baseline in target lesion size: -35% (range -79% to 44%)

Data cut-off: April 30, 2018. 1 patient was withdrew consent. 1 patient with Exon 20 insertion was excluded

ORR=18/35
Concomitant mutation was significantly associated with shorter PFS and OS in EGFR mu+ NSCLC treated with EGFR-TKI.
Acquired resistance
54F adenocarcinoma (cT2N2M1a)
EGFR exon 19 deletion
Mechanisms of acquired resistance against EGFR-TKIs

- EGFR-TKI sensitivity
  - apoptosis
  - ATP

Acquired resistance
- Secondary mutation of the target gene
  - TKI
  - ATP
  - survival

Bypass pathway activation
- TKI
- survival

Histologic transformation
- SCLC
- EMT

References:
- Kobayashi et al., NEJM 2005
- Pao et al., PLoS Med 2005
- Engelman et al., Science 2007
- Bean et al., PNAS 2007
- Sequist et al., Sci Transl Med, 2011
The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP

Kai-Hong Yun*, Kristen E. Mengwasser†, Angela V. Tomss*, Michele S. Wool*, Heidi Greulich††, Kwok-Kin Wong††, Matthew Meyerson†††, and Michael J. Eckt***

©2009–2007 | PNAS | February 12, 2008 | vol. 105 | no. 6

Departments of Biological Chemistry and Molecular Pharmacology and Pathology, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115; Departments of Cancer Biology and Medical Oncology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115; Department of Medicine, Brigham and Women’s Hospital, Boston, MA 02115; and The Broad Institute of Harvard and Massachusetts Institute of Technology, 320 Charles Street, Cambridge, MA 02141

Inhibitor dissociation constants (K\(_d\)) for gefitinib and Michaelis-Menten constants for ATP (K\(_m\)[ATP])

The ratio K\(_d\) / K\(_m\)[ATP] provides a relative estimate of inhibitor potency.
Acquired resistance to the EGFR-TKI

**RESULTS: ACQUIRED RESISTANCE MECHANISMS WITH COMPARATOR EGFR-TKI (n=129)**

First line gefitinib/erlotinib In Flaura trial

The most common acquired resistance mechanisms were EGFR T790M, MET amplification and HER2 amplification.

Acquired T790M: 47%
Other EGFR mutations*: 1%

HER2 amplification: 2%

PIK3CA mutations: 3%†

PIK3CA

mTOR

AKT

p53

BIM

BCL2

Acquired T790M + C797S + L718Q: 1%; †PIK3CA + T790M (n=1), PIK3CA + T790M + C797S (n=1), and PIK3CA (n=1)

MET amplification: 4%

CCDC6-RET: 2%

BRAF D594N: 1%
KHAS G12C: 1%
NFAS G12D: 1%

PI3K

MEK

ERK

Proliferation

Ramalingam ESMO 2018

*Resistance mechanism reported may overlap with another; †Acquired T790M + C797S + L718Q: 1%; †PIK3CA + T790M (n=1), PIK3CA + T790M + C797S (n=1), and PIK3CA (n=1)
Resistance mechanisms in 119 lesions present in 15 autopsied patients who acquired resistance after EGFR-TKI therapy

In 8/15 patients, resistance mechanisms were heterogeneous

Comparison of IC50 values of the 1\textsuperscript{st}, 2\textsuperscript{nd}, and 3\textsuperscript{rd} generation EGFR-Tkis in vitro

Del19=PC9, WT NCIH2073, Del19+T790M, PC9/VanR, Data from Cross et al., Cancer Discov., 2014
Randomised Phase III study of osimertinib vs platinum /pemetrexed for EGFR T790M+ advanced NSCLC (AURA3)
Mok et al., NEJM, 2016

Key eligibility criteria:
- 18 years (20 years in Japan)
- Locally advanced or metastatic NSCLC
- Evidence of disease progression following first-line EGFR-TKI therapy
- Documented EGFR T790M mutation from a tissue biopsy taken after disease progression on first-line EGFR-TKI treatment
- WHO performance status of 0 or 1
- No more than one prior line of treatment for advanced NSCLC
- No prior non-adjunct or adjacent chemotherapy treatment within 6 months prior to starting first EGFR/TKI treatment

Endpoints:
- Primary: Osimertinib vs platinum/pemetrexed
- Secondary and exploratory:
  - Overall survival
  - Objective response rate
  - Duration of response
  - Disease control rate
  - Tumor shrinkage
  - BCR-3 assessed PFS
  - Patient-reported outcomes
  - Safety and tolerability

PFS by investigator assessment

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Median PFS (months [95% CI])</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>10.1 (8.3, 12.3)</td>
<td>0.30 (0.23, 0.41)</td>
</tr>
<tr>
<td>Platinum-pemetrexed</td>
<td>4.4 (4.2, 5.6)</td>
<td>p=0.001</td>
</tr>
</tbody>
</table>

- Analysis of PFS by BCR was consistent with the investigator-based analysis. HR 0.28 (95% CI 0.20, 0.36), p<0.001; median PFS 11.0 vs 4.2 months.
Osimertinib has good penetration of the blood-brain barrier and showed high efficacy in patients with CNS disease I in AURA/AURA2.

Table: 

<table>
<thead>
<tr>
<th>Radiotracer</th>
<th>Label</th>
<th>No.</th>
<th>Brain to Blood Ratio (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[11C] osimertinib</td>
<td>(n=3)</td>
<td>2.6 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>[11C] rociletinib</td>
<td>(n=2)</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>[11C] gefitinib</td>
<td>(n=2)</td>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>

[11C]EGFR-TKI distribution in Cynomolgus monkey brain

CNS response to osimertinib in patients with T790M+ advanced NSCLC: pooled data from two Phase II trials

Goss G et al., WCLC 2017, MA 16.11
AE ≥ G3 in AURA 3 compared with pooled analysis from 13 gefitinib trials (N=457), 5 erlotinib trials (N=513) and 3 afatinib trials (N=498)

Takeda et al., Lung Cancer, 2015
Rebiopsy for patients with NSCLC after EGFR-TKI failure
Kawamura et al., Cancer Sci., 2016

- EGFR_{Mut+} NSCLC: PD after EGFR-TKI (n = 139)
  - Eligible for third generation EGFR-TKI (n = 120; 86%)
    - Rebiopsy (n = 75) 62.5%
  - Pathological diagnosis (n = 71; 95%)
  - EGFR mutation analysis (n = 61) 50.8%
    - T790M+ (n = 20; 33%)

Ineligible for trial—
- poor PS: n = 10;
- comorbidity: n = 7;
- elderly: n = 2

Ineligible for rebiopsy—
- inaccessible tumor sites: n = 19 (18 brain metastases and 1 lung lesion <20 mm);
- physician decision: n = 10; patient refusal: n = 6; unknown: n = 10
Liquid biopsy

Issues to be considered in plasma cfDNA diagnosis of T790M

- Total plasma DNA may be dependent on tumor burden/tumor necrosis
- Trade-off between sensitivity and specificity...usually low sensitivity and high specificity
- EGFR mutant allele is often amplified T790M is present in only some of the mutated alleles

Contamination of normal cells is unavoidable
- Preferential excretion of tumor derived DNA into plasma compared with normal DNA

Resistance mechanisms may be heterogeneous depending on the tumor regions
Methods for detecting EGFR mutations, relative performance and applications Tan et al., JTO, 2016

<table>
<thead>
<tr>
<th>Technique</th>
<th>Sensitivity (% Mutant DNA)</th>
<th>Mutations Identified</th>
<th>Detection of Co-mutations</th>
<th>Potential Applications</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct sequencing</td>
<td>10%-25%</td>
<td>Known and new</td>
<td>No</td>
<td>Tissue</td>
<td>Multiple studies</td>
</tr>
<tr>
<td>Pyrosequencing</td>
<td>5%-10%</td>
<td>Known only</td>
<td>No</td>
<td>Tissue</td>
<td>Young et al., 2013</td>
</tr>
<tr>
<td>Multiplex PCR (Snapshot)</td>
<td>5%</td>
<td>Known only</td>
<td>Yes (hotspots)</td>
<td>Tissue</td>
<td>Dias-Santagata et al., 2010</td>
</tr>
<tr>
<td>cobas</td>
<td>3%-5%</td>
<td>Known only</td>
<td>No</td>
<td>Tissue</td>
<td>Lopez-Rios et al., 2013</td>
</tr>
<tr>
<td>WAVE-surveyor</td>
<td>2%</td>
<td>Known only</td>
<td>No</td>
<td>Plasma</td>
<td>Janne et al., 2006</td>
</tr>
<tr>
<td>Mass spectrometry based</td>
<td>1%-10%</td>
<td>Unknown</td>
<td>Yes (hotspots)</td>
<td>Plasma</td>
<td>Arclia et al., 2011</td>
</tr>
<tr>
<td>High-depth NGS (at least 200x depth)</td>
<td>1%-10% depending on error rates and sequencing depth</td>
<td>Known and new</td>
<td>Yes</td>
<td>Tissue Plasma</td>
<td>Uchida et al., 2015</td>
</tr>
<tr>
<td>Therascreen</td>
<td>1%-5%</td>
<td>Known only</td>
<td>No</td>
<td>Tissue</td>
<td>Lopez-Rios et al., 2013</td>
</tr>
<tr>
<td>Scorpions ARMS</td>
<td>1%</td>
<td>Known only</td>
<td>No</td>
<td>Tissue</td>
<td>Chiu et al., 2014</td>
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<tr>
<td>Locked nucleic acid clamp</td>
<td>1%</td>
<td>Known only</td>
<td>No</td>
<td>Plasma</td>
<td>Costa et al., 2014</td>
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<tr>
<td>TAm-Seq</td>
<td>2%</td>
<td>Known and new</td>
<td>Yes</td>
<td>Tissue</td>
<td>Forshaw et al., 2012</td>
</tr>
<tr>
<td>BEAMing</td>
<td>&lt;0.1%</td>
<td>Known only</td>
<td>No</td>
<td>Plasma</td>
<td>Taniguchi et al., 2011</td>
</tr>
<tr>
<td>Digital droplet PCR</td>
<td>&lt;0.1%</td>
<td>Known only</td>
<td>No</td>
<td>Plasma</td>
<td>Watanabe et al., 2015</td>
</tr>
<tr>
<td>CAPP-Seq</td>
<td>~0.02%</td>
<td>Known and new</td>
<td>Yes</td>
<td>Plasma</td>
<td>Newman et al., 2014</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor gene; PCR, polymerase chain reaction; NGS, next-generation sequencing; ARMS, amplification refractory mutation system; CAPP, cancer personalized profiling by deep sequencing.
Acquired resistance mechanisms post-osimertinib (n=73)

Summary
- Acquired EGFR mutations: 21%
- MET amp*: 19%
- Cell cycle gene alterations: 12%
- HER2 amp*: 5%
- PIK3CA amp* / mutation: 5%
- Oncogenic fusion: 4%
- BRAF V600E: 3%

*Amplification events may be underrepresented in plasma analyses
amp, amplification
Activities of erlotinib, afatinib, and osimertinib against T790M, C797S, and T790M/C797S

Dr. Yosuke Togashi, unpublished observation

<table>
<thead>
<tr>
<th>Relative IC50</th>
<th>erlotinib</th>
<th>afatinib</th>
<th>osimertinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>L858R</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>L858R/T790M</td>
<td>2442.7</td>
<td>77.7</td>
<td>0.7</td>
</tr>
<tr>
<td>L858R/C797S</td>
<td>1.1</td>
<td>11.1</td>
<td>474.5</td>
</tr>
<tr>
<td>L858R/T790M/C797S</td>
<td>2307.3</td>
<td>4367.3</td>
<td>549.9</td>
</tr>
</tbody>
</table>
In search for better 1L treatment

- **Newer TKI**
  - 2G afatinib       Lux-Lung 7
  - dacomitinib       ARCHER 1050
  - 3G osimertinib    Flaura

- **Combination**
  - EGFR-TKI + chemotherapy   NEJ 009
  - EGFR-TKI + bevacizumab    NEJ026

- EGFR-TKI + small molecules
2G-EGFR TKI may prolongs OS

Lux Lung 7

10.9 11.0

HR 0.74, P=0.0178

24.5 27.9

HR 0.86, P=0.2580

Paz-Ares ESMO 2016

ARCHER 1050

9.2 14.7

HR 0.59, P<0.0001

26.8 34.1

HR 0.76, P=0.0438

Mok et al., ASCO 2018
**FLAURA DOUBLE-BLIND STUDY DESIGN**

**Patients with locally advanced or metastatic NSCLC**
- Key inclusion criteria
  - ≥18 years
  - WHO performance status 0 / 1
  - Exon 19 deletion / L858R (enrolment by local or central EGFR testing)
  - No prior systemic anti-cancer / EGFR-TKI therapy
  - Stable CNS metastases allowed

**Endpoints**
- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

**Stratification by mutation status** (Exon 19 deletion / L858R and race (Asian / non-Asian))

**Randomised 1:1**
- Osimertinib (80 mg p.o. qd) (n=279)
- EGFR-TKI SoC:
  - Gefitinib (250 mg p.o. qd) or Erlotinib (150 mg p.o. qd) (n=277)

**RECIST 1.1 assessment every 6 weeks** until objective progressive disease
- Crossover was allowed for patients in the SoC arm, who could receive open-label osimertinib upon central confirmation of progression and 1790M positivity
FLAURA STUDY (Osimertinib in untreated EGFR-mutated NSCLC)

For statistical significance at this interim analysis of overall survival, a P < 0.0015 was required. DCO2 data will be available in 2019.
Comparison between different EGFR-TKIs

- **WJOG5108L**
  - Gefitinib: 8.3 months
  - Erlotinib: 10.0 months
  - HR: 1.093

- **Lux-Lung 7**
  - Gefitinib: 10.9 months
  - Afatinib: 11.0 months
  - HR: 0.73
  - Brain mets: ~15%

- **ARCHER 1050**
  - Gefitinib: 9.2 months
  - Dacomitinib: 14.7 months
  - HR: 0.59
  - Brain mets: 0%

- **Flaura**
  - Gefitinib: 10.2 months
  - Erlotinib: 18.9 months
  - HR: 0.46
  - Brain mets: ~20%

**References:**
- Urata JCO 2016
- Park Lancet Oncol 2016
- Wu et al, Lancet Oncol 2017
- Soria NEJM 2017
RESULTS: CANDIDATE ACQUIRED RESISTANCE MECHANISMS WITH OSIMERTINIB (n=91)*

- No evidence of acquired EGFR T790M
- The most common resistance mechanisms were MET amplification and EGFR C797S mutation
- Other mechanisms included HER2 amplification, PIK3CA and RAS mutations

*Resistance mechanism reported may overlap with another; *Two patients had de novo T790M mutations at baseline of whom one acquired C797S at progression

L858R 0.3%
Del19 9.2%
In search for better 1L treatment

- Newer TKI
  - 2G afatinib
  - 2G dacomitinib
  - 3G osimertinib

- Combination
  - EGFR-TKI + chemotherapy
  - EGFR-TKI + bevacizumab

- EGFR-TKI + small molecules
### Recent trials of the first line treatment for EGFR+ patients

Nakamura ASCO 2018, Yamamoto ASCO 2018, Soria NEJM 2017, Mok ASCO 2018, Paz-Ares ESMO 2016,

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Survival (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEJ009</strong></td>
<td>gefitinib</td>
<td>11.2 HR 0.494</td>
</tr>
<tr>
<td></td>
<td>gefitinib + carboplatin + pemetrexed</td>
<td>20.9 HR 0.695</td>
</tr>
<tr>
<td><strong>JO25567</strong></td>
<td>erlotinib</td>
<td>9.8 HR 0.52</td>
</tr>
<tr>
<td></td>
<td>erlotinib + bevacizumab</td>
<td>16.4 HR 0.81, NS</td>
</tr>
<tr>
<td><strong>FLAURA</strong></td>
<td>gefitinib/erlotinib</td>
<td>10.2 HR 0.46</td>
</tr>
<tr>
<td></td>
<td>osimertinib</td>
<td>18.9 HR 0.63</td>
</tr>
<tr>
<td><strong>ARCHER 1050</strong></td>
<td>gefitinib</td>
<td>9.2 HR 0.59</td>
</tr>
<tr>
<td></td>
<td>dacomitinib</td>
<td>14.7 HR 0.760</td>
</tr>
<tr>
<td><strong>Lux-Lung 7</strong></td>
<td>gefitinib</td>
<td>10.9 HR 0.74</td>
</tr>
<tr>
<td></td>
<td>afatinib</td>
<td>11.2 HR 0.86, NS</td>
</tr>
</tbody>
</table>
Erlotinib+Bevacizumab vs. Erlotinib

JO25567, Yamamoto et al., ASCO 2018
NEJ026, Furuya et al., ASCO 2018

### Table 1: Survival Analysis

<table>
<thead>
<tr>
<th></th>
<th>EB</th>
<th>E</th>
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</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>16.4</td>
<td>9.8</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.52 (0.35-0.76)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.0005</td>
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</table>

### Table 2: Survival Analysis

<table>
<thead>
<tr>
<th></th>
<th>EB</th>
<th>E</th>
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</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>47.0</td>
<td>47.4</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.81 (0.53-1.23)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.3267</td>
<td></td>
</tr>
</tbody>
</table>

### Graphs:
- **Graph 1:** Erlotinib+Bevacizumab vs. Erlotinib (Median 16.4 vs. 9.8, HR 0.52, P = 0.0005)
- **Graph 2:** Erlotinib+Bevacizumab vs. Erlotinib (Median 47.0 vs. 47.4, HR 0.81, P = 0.3267)
- **Graph 3:** Erlotinib+Bevacizumab vs. Erlotinib (Median 16.9 vs. 13.3, HR 0.605, P = 0.01573)
EGFR陽性肺癌に対する
ゲフィチニブ＋カルボプラチン＋ペメトレキセドと
ゲフィチニブ単剤治療との第III相試験

NEJ009

Non-squamous NSCLC
Previously untreated
stage IIIIB, IV, recurrence
PS 0-1
Positive EGFR mutation

Induction Phase
Gefitinib (daily)
Carboplatin +
Pemetrexed
(4-6 cycles, q21d)

Maintenance Phase
Gefitinib (daily)
Pemetrexed

Stratified by sex, stage,
type of EGFR mutation, and smoking history

*Recommended by the protocol

PFS

Gefitinib+Cb+Pem → Gefitinib+Pem

PFS2

Gefitinib → Cb+Pem → Pem

OS
Hazard ratios of OS by EGFR mutational status in 3 Phase III trials comparing ICI with docetaxel

KEYNOTE-010
pembrolizumab

CheckMate 057
nivolumab

Oak
atezolizumab
IMpower 150

PFS in key biomarker populations

<table>
<thead>
<tr>
<th>Population</th>
<th>n (%)*</th>
<th>Median PFS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT (including EGFR/ALK mutant +)</td>
<td>600 (100%)</td>
<td>8.3 8.8</td>
</tr>
<tr>
<td>EGFR/ALK mutant + only</td>
<td>108 (14%)</td>
<td>9.7 6.1</td>
</tr>
<tr>
<td>ITT-WT</td>
<td>692 (87%)</td>
<td>8.3 6.8</td>
</tr>
</tbody>
</table>

Reck et al., ESMO-IO 2017
Socinski et al., ASCO 2018

国内未承認情報を含む
Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of EGFR/ALK+ Patients

Presented By Mark Socinski at 2018 ASCO Annual Meeting
Best sequence

- **Osimertinib**
  - If T790M predictable
  - Trials planned

- **Dacomitinib/afatinib**
  - Only ~50% can receive osi

- **CBDCA+PAC+BEV+Atez 30+**
  - Only ~7%
  - If T790M predictable

- **CBDCA+PAC+BEV+Atez**
  - (DOC+)BEV+Atez ?

- **CBDCA+PEM+Osimertinib -> PEM+Osi**
  - (DOC+)BEV+Atez ?
Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†
Stage IV lung carcinoma with EGFR-activating mutation

PS 6-2 [I, A]
PS 3-4 for all following options [II, A]

Gefitinib [I, A]
Erlotinib [I, A]
+/- bevacizumab [II, B; MCBS 3]*
Afatinib [I, A]
Dacomitinib [I, A]*
Osimertinib [I, A; MCBS 4]
Gefitinib/cisplatin/pemetrexed [I, B]*

Disease progression

Oligoprogression

Local treatment (surgery or RT) and continue targeted systemic treatment [IV, C]

Systemic progression

Exon 20 T790M mutation testing: Re-biopsy or cfDNA plasma testing, with re-biopsy if plasma test is negative [II, A]

Exon 20 T790M mutation positive

Osimertinib [I, A; MCBS 4]

Systemic progression

Exon 20 T790M mutation negative or re-biopsy indicated but not feasible

Platinum-based ChT [I, A] (see Figure 3) Carboplatin/paclitaxel/bevacizumab/atezolizumab [II, A]*
Stage IV lung carcinoma with EGFR-activating mutation

A strongly recommended
B generally recommended
1L treatment and sequencing of EGFR-TKI

- Recent positive clinical trials provided with several options of sequenced treatment of EGFR mutant lung cancer
- When compared with gefitinib/erlotinib, osimertinib showed the best HR for PFS and OS as the first line treatment.
- Toxicity profiles favor osi over 2G.
- 2G followed by osi may result in long TDTKI (time to discontinuation of TKI). However, other half of the patients cannot enjoy osi treatment.
- Possible OS advantage of Cb/Pem/gefitinib over gefitinib (NEJ009) may be due to high rate (~100%) of chemotherapy usage that could cope with various co-driver mutations.
- Impower 150 showed that atezolizumab/Cb/Pac/Bev significantly prolonged PFS and OS even for EGFR/ALK 2L cohort, compared with Cb/Pac/Bev.