Strategic Approaches

Sequence or intercalation of use of targeted agents and Chemotherapy
Definition of progression under TKI

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China
Strategic Approaches

• Sequence or intercalation of use of targeted agents and Chemotherapy

• Definition of progression under TKI
Treatment Paradigm with Immunotherapy for advanced NSCLC in 2016

<table>
<thead>
<tr>
<th></th>
<th>EGER/ALK/ROS1/…</th>
<th>PD-L1+ (≥50%)</th>
<th>PD-L1-Non-SCC</th>
<th>PD-L1-SCC</th>
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<tbody>
<tr>
<td><strong>1st line</strong></td>
<td>TKIs</td>
<td>Pembro</td>
<td>Cb/Pac/Bev</td>
<td>Chemo D</td>
</tr>
<tr>
<td><strong>1st line</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Maintenance</strong></td>
<td></td>
<td></td>
<td>Bev or Pem</td>
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<tr>
<td><strong>2nd line</strong></td>
<td>AZD9291 for T790M M+</td>
<td>Chemo D</td>
<td>Atezo</td>
<td>Atezo</td>
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<tr>
<td></td>
<td>2nd ALK TKI</td>
<td></td>
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<tr>
<td></td>
<td>Alectinib for brain M</td>
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<td></td>
<td>Chemo D</td>
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<tr>
<td><strong>3rd line</strong></td>
<td>Chemo S</td>
<td>Chemo S</td>
<td>Chemo S</td>
<td>Chemo S</td>
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</table>
# Studies of EGFR TKIs in EGFR Act Mut+ NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>EGFR TKI</th>
<th>n</th>
<th>Line</th>
<th>HR</th>
<th>mPFS (M)</th>
<th>mOS (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS</td>
<td>Gefitinib</td>
<td>132</td>
<td>First</td>
<td>0.48</td>
<td>9.5</td>
<td>21.6</td>
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<td>WJTOG 3405</td>
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<td>0.49</td>
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<td>NEJSG 002</td>
<td>Gefitinib</td>
<td>114</td>
<td>First</td>
<td>0.36</td>
<td>10.8</td>
<td>27.7</td>
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<td>OPTIMAL</td>
<td>Erlotinib</td>
<td>82</td>
<td>First</td>
<td>0.16</td>
<td>13.1</td>
<td>30.4</td>
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<td>EURTAC</td>
<td>Erlotinib</td>
<td>87</td>
<td>First</td>
<td>0.37</td>
<td>9.7</td>
<td>19.3</td>
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<td>ENSURE</td>
<td>Erlotinib</td>
<td>110</td>
<td>First</td>
<td>0.34</td>
<td>11.0</td>
<td>26.3</td>
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<tr>
<td>LUN-3</td>
<td>Afatinib</td>
<td>230</td>
<td>First</td>
<td>0.58</td>
<td>11.1</td>
<td>28.2</td>
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<tr>
<td>LUN-6</td>
<td>Afatinib</td>
<td>242</td>
<td>First</td>
<td>0.28</td>
<td>11.0</td>
<td>23.1</td>
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<tr>
<td>CONVINCE</td>
<td>Icotinib</td>
<td>148</td>
<td>First</td>
<td>0.67</td>
<td>9.9</td>
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</table>
Advanced NSCLC: EGFR mutation treatment strategy

Could we improve the efficacy for 1st line EGFR TKIs treatment?

First line EGFR TKIs

Combination with others
--- chemo
- -- Concurrent or Intercalated

BSC
OPTIMAL: most benefits from TKI and chemotherapy

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Events</th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received chemo only*</td>
<td>21 17 (81)</td>
<td>11.70</td>
<td>7.29–22.87</td>
</tr>
<tr>
<td>Received EGFR TKI only‡</td>
<td>33 22 (67)</td>
<td>20.67</td>
<td>16.62–28.32</td>
</tr>
<tr>
<td>Received EGFR TKI and chemo §</td>
<td>94 50 (53)</td>
<td>30.39</td>
<td>25.99–NR</td>
</tr>
</tbody>
</table>

Zhou, et al. ASCO 2012, abstr 7520
Combination with platinum doublet
4 failures

<table>
<thead>
<tr>
<th>Trial</th>
<th>Chemo Regimen</th>
<th>RR (%)</th>
<th>TTP (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTACT 1</td>
<td>GEM/CIS</td>
<td>47.2</td>
<td>6</td>
<td>10.9</td>
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<td></td>
<td>GEM/CIS/G250</td>
<td>51.2</td>
<td>5.8</td>
<td>9.9</td>
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<tr>
<td></td>
<td>GEM/CIS/G500</td>
<td>50.3</td>
<td>5.5</td>
<td>9.9</td>
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<tr>
<td>INTACT 2</td>
<td>CAR/PAC</td>
<td>28.7</td>
<td>5</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td>CAR/PAC/G250</td>
<td>30.4</td>
<td>5.3</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td>CAR/PAC/G500</td>
<td>30</td>
<td>4.6</td>
<td>8.7</td>
</tr>
<tr>
<td>TALENT</td>
<td>GEM/CIS</td>
<td>28.2</td>
<td>5.6</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td>GEM/CIS/E150</td>
<td>30</td>
<td>5.4</td>
<td>9.9</td>
</tr>
<tr>
<td>TRIBUTE</td>
<td>CAR/PAC</td>
<td>19.3</td>
<td>4.9</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td>CAR/PAC/E150</td>
<td>21.5</td>
<td>5.1</td>
<td>10.8</td>
</tr>
</tbody>
</table>

Randomized phase II study of concurrent versus sequential alternating gefitinib and chemotherapy in EGFR mutant patients

Stage IV NS NSCLC
Activating EGFR mutations
No prior systemic therapy
N=80

Concurrent (C group)
Gefitinib 250 mg daily
Carboplatin+Pemetrexed (d1, q21d) 6cycles

Concurrent Gefitinib
Pemetrexed (q21d)

Sequential (S group)
Gefitinib (d1-28)
Carboplatin+Pemetrexed (d29,51) 3cycles

Sequential Gefitinib and Pemetrexed alternate

Stratify: sex, clinical stage of NSCLC (IIIB, IV, or postoperative relapse).

The primary objective: PFS

Secondary end points: OS, ORR, toxicity profile

Sugawara et al An Oncol 2015
### NEJ005: Result

#### PFS

<table>
<thead>
<tr>
<th></th>
<th>Concurrent</th>
<th>Sequential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>32 (78.0%)</td>
<td>31 (79.5%)</td>
</tr>
<tr>
<td>m PFS (m)</td>
<td>18.3 (9.7–21.9)</td>
<td>15.3 (11.3–17.4)</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P=0.20, HR 0.80

#### OS

<table>
<thead>
<tr>
<th></th>
<th>Concurrent</th>
<th>Sequential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>16 (39.0%)</td>
<td>24 (61.5%)</td>
</tr>
<tr>
<td>m OS (m)</td>
<td>41.9</td>
<td>30.7</td>
</tr>
<tr>
<td>95% CI</td>
<td>(35.1–NR)</td>
<td>(23.2–40.5)</td>
</tr>
</tbody>
</table>

P=0.042, HR 0.55

Better OS was observed in the concurrent regimen group.

Sugawara et al. *An Oncol* 2015
JMIT: Gefitinib With and Without Pemetrexed in 1st line EGFR mutant patients

Inclusion Criteria:
- Adult patients ≥18 years (≥20 years in Japan and Taiwan)
- Confirmed advanced (Stage IV) or recurrent NS NSCLC
- Activating EGFR mutations
- ECOG PS ≤1
- No prior systemic chemotherapy, immunotherapy, or biological therapy

Randomize

N=191
2:1

Oral gefitinib 250 mg QD + pemetrexed 500 mg/m² IV on Day 1 every 3-week cycle (n=126)
Standard folic acid and Vitamin B₁₂ supplementation

Oral gefitinib 250 mg QD (n=65)

Until disease progression, unacceptable toxicity, or another permitted reason for study discontinuation

Primary Endpoint: PFS

Key Secondary Endpoints: Overall survival (OS), Overall response, Disease control rate (DCR), Duration of response (DoR), Quality of life (QoL), Safety

Enrollment period: February 2012 – August 2013
Data cut-off date: 22 April 2015

Cheng Y JCO 2016

Cheng Y JCO 2016
Prolonged PFS in first-line gefitinib+pemetrexed vs. gefitinib for East Asian patients with EGFR mutation-positive NS NSCLC
1st line treatment

FASTACT-II (CTONG0902)

THE LANCET Oncology 2013

Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-II): a randomised, double-blind trial

FASTACT-II (MO22201; CTONG0902) study design

<table>
<thead>
<tr>
<th>Screening</th>
<th>Study treatment</th>
<th>Maintenance phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously untreated stage IIIB/IV NSCLC, PS 0/1 (n=451)</td>
<td>Gemcitabine 1,250mg/m² (d1, 8) + carboplatin AUC=5 or cisplatin 75mg/m² (d1) + erlotinib 150mg/day (d15–28); q4wks x 6 cycles GC-erlotinib (n=226)</td>
<td>Erlotinib 150mg/day</td>
</tr>
<tr>
<td>R</td>
<td></td>
<td>PD</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine 1,250mg/m² (d1, 8) + carboplatin AUC=5 or cisplatin 75mg/m² (d1) + placebo (d15–28); q4wks x 6 cycles GC-placebo (n=225)</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD</td>
</tr>
<tr>
<td></td>
<td>Erlotinib 150mg/day</td>
<td>PD</td>
</tr>
</tbody>
</table>

Primary endpoint: Progression-free survival (PFS)

Secondary endpoints: subgroup analyses, overall survival (OS) in all patients and subgroups, objective response rate (ORR), duration of response, time to disease progression (TTP), non-progression rate (NPR) at 16 weeks, safety, quality of life (QoL)
Combination of EGFR-TKIs and Chemotherapy as First-Line Therapy for Advanced NSCLC: A Meta-Analysis

Pu-Yun OuYang¹,²,³, Zhen Su¹,²,³, Yan-Ping Mao¹,², Wuguo Deng¹, Fang-Yun Xie¹,²

¹ State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China. ² Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China.

A

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
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</thead>
<tbody>
<tr>
<td>CALGB 30406(2012)</td>
<td>-0.2107</td>
<td>0.1793</td>
<td>9.4%</td>
<td>0.81 [0.57, 1.15]</td>
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<tr>
<td>FASTACT(2009)</td>
<td>-0.7472</td>
<td>0.1844</td>
<td>9.2%</td>
<td>0.47 [0.33, 0.68]</td>
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<tr>
<td>FASTACT-II(2013)</td>
<td>-0.563</td>
<td>0.098</td>
<td>13.8%</td>
<td>0.57 [0.47, 0.69]</td>
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<tr>
<td>Hirsch et al.(2011)</td>
<td>-0.0305</td>
<td>0.2202</td>
<td>7.7%</td>
<td>0.97 [0.63, 1.49]</td>
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<tr>
<td>INTACT 1(2004)</td>
<td>-0.0513</td>
<td>0.0877</td>
<td>14.4%</td>
<td>0.95 [0.80, 1.13]</td>
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<tr>
<td>INTACT 2 (2004)</td>
<td>-0.1508</td>
<td>0.0386</td>
<td>14.6%</td>
<td>0.86 [0.73, 1.01]</td>
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<tr>
<td>TALENT(2007)</td>
<td>-0.0202</td>
<td>0.0666</td>
<td>15.5%</td>
<td>0.98 [0.86, 1.12]</td>
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<tr>
<td>TRIBUTE(2005)</td>
<td>-0.0651</td>
<td>0.0705</td>
<td>15.3%</td>
<td>0.94 [0.82, 1.08]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.81 [0.69, 0.95]

Heterogeneity: Tau² = 0.04; Chi² = 35.17, df = 7 (P < 0.0001); I² = 80%

Test for overall effect: Z = 2.53 (P = 0.010)

B

<table>
<thead>
<tr>
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<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
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<tbody>
<tr>
<td>CALGB 30406(2012)</td>
<td>0.1044</td>
<td>0.2069</td>
<td>3.4%</td>
<td>1.11 [0.74, 1.67]</td>
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<td>FASTACT(2009)</td>
<td>0.0862</td>
<td>0.2259</td>
<td>2.9%</td>
<td>1.09 [0.70, 1.60]</td>
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<tr>
<td>FASTACT-II(2013)</td>
<td>-0.2282</td>
<td>0.1113</td>
<td>11.8%</td>
<td>0.80 [0.64, 0.99]</td>
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<tr>
<td>Hirsch et al.(2011)</td>
<td>0.27</td>
<td>0.2778</td>
<td>1.9%</td>
<td>1.31 [0.76, 2.26]</td>
</tr>
<tr>
<td>INTACT 1(2004)</td>
<td>0.0583</td>
<td>0.095</td>
<td>16.2%</td>
<td>1.06 [0.88, 1.28]</td>
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<tr>
<td>INTACT 2 (2004)</td>
<td>0.01</td>
<td>0.094</td>
<td>16.5%</td>
<td>1.01 [0.84, 1.21]</td>
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<tr>
<td>TALENT(2007)</td>
<td>0.0583</td>
<td>0.0835</td>
<td>20.9%</td>
<td>1.06 [0.96, 1.25]</td>
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<tr>
<td>TRIBUTE(2005)</td>
<td>-0.005</td>
<td>0.0744</td>
<td>25.4%</td>
<td>1.00 [0.86, 1.15]</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 1.01 [0.93, 1.08]

Heterogeneity: Chi² = 6.40, df = 7 (P = 0.49); I² = 0%

Test for overall effect: Z = 0.16 (P = 0.87)
Which is the best?

<table>
<thead>
<tr>
<th></th>
<th>Concurrent JMIT</th>
<th>Concurrent NEJ005</th>
<th>Intercalated FASTACT-2 EGFR mutation</th>
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<tbody>
<tr>
<td>N</td>
<td>126</td>
<td>41</td>
<td>49</td>
</tr>
<tr>
<td>PFS</td>
<td>15.8m</td>
<td>18.3m</td>
<td>16.8m</td>
</tr>
<tr>
<td>OS</td>
<td>NR</td>
<td>41.9m</td>
<td>31.4m</td>
</tr>
<tr>
<td>ORR</td>
<td>80.20%</td>
<td>87.8%</td>
<td>84%</td>
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</tbody>
</table>

Limiting to sample size, and phase 2 or subgroup analysis
Advanced NSCLC: EGFR mutation treatment strategy

Could we improve the efficacy for 1\textsuperscript{st} line EGFR TKIs treatment?

First line EGFR TKIs

Combination with others

--- Anti-angiogenesis
Erlotinib + bevacizumab vs Erlotinib in 1st line treatment for advanced EGFR mutant NSCLC

Study design

Chemotherapy-naïve
Stage IIIB/IV or postoperative recurrence
Non-squamous NSCLC
Activating EGFR mutations*
  - Exon 19 deletion
  - Exon 21 L858R
Age ≥20 years
PS 0–1
No brain metastasis

* T790M excluded

Stratification factors:
  - sex, smoking status,
  - clinical stage,
  - EGFR mutation type

Primary endpoint:
  - PFS (RECIST v1.1, independent review)
Secondary endpoints:
  - OS, tumor response, QoL, safety
Exploratory endpoint:
  - biomarker assessment

EB combination
  Erlotinib 150mg qd + bevacizumab 15mg/kg q3w (n = 75)

E monotherapy
  Erlotinib 150mg qd (n = 75)

Presented by: Terufumi Kato

Presented By Terufumi Kato at 2014 ASCO Annual Meeting
### A+T vs T (J025567): RR and DCR

<table>
<thead>
<tr>
<th></th>
<th>EB (n=75)</th>
<th>E (n=77)</th>
<th>P*</th>
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<tbody>
<tr>
<td>CR (%)</td>
<td>4</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>PR (%)</td>
<td>65</td>
<td>62</td>
<td>-</td>
</tr>
<tr>
<td>SD (%)</td>
<td>29</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>PD (%)</td>
<td>0</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>NE (%)</td>
<td>1</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>69</td>
<td>64</td>
<td>0.4951</td>
</tr>
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</table>

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<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DCR (%)</td>
<td>99</td>
<td>88</td>
<td>0.0177</td>
</tr>
</tbody>
</table>

A+T vs T (JO25567) : Primary Endpoint: PFS

- **A+T (n=75)**
  - mPFS = 16.0M
- **T (n=77)**
  - mPFS = 9.7M

HR = 0.54 (95% CI: 0.36-0.79)
P = 0.0015

Advanced NSCLC: EGFR mutation treatment strategy

First line EGFR TKIs → Treated Resistant → chemo → BSC → Death

Clinical Model

Molecular Model
Acquired Resistant: Clinical Perspectives

• How do we define progressive disease?
• EGFR-TKI continuation in combination with or sequential chemotherapy
• When should we switch from monotherapy to combination?
How do we define progressive disease?

• RECIST & JACKMAN criteria

• China criteria
Defining resistance by RECIST may lead to premature termination of TKI
Clinical modes of EGFR tyrosine kinase inhibitor failure and subsequent management in advanced non-small cell lung cancer

120 trials Pts, training set
107 non-trial Pts validating set

Based on Clinical factors:
- Tumor burden
- Target lesions
- non-target lesions
- EGFR TKI exposure time
- Symptom

**EGFR TKI failure in NSCLC**

- **Dramatic progression**
  - Disease control ≥3 months
  - Compared with previous assessment, rapid increment of tumour burden
  - Symptom deterioration

- **Gradual progression**
  - Disease control ≥6 months
  - Compared with previous assessment, minor increment of tumour burden
  - Symptom benefit

- **Local progression**
  - Disease control ≥3 months
  - Solitary extracranial progression or intracranial progression
  - Symptom benefit

- **Chemotherapy**

- **Continuation of EGFR-TKIs**

- **Continuation of EGFR-TKIs plus local intervention**

---

*Modified from Yang et al. Lung Cancer 2013;79:33–39*
Continuation of afatinib beyond progression: Results of a randomized, open-label, phase III trial of afatinib plus paclitaxel (P) versus investigator’s choice chemotherapy (CT) in patients (pts) with metastatic non-small cell lung cancer (NSCLC) progressed on erlotinib/gefitinib (E/G) and afatinib—LUX-Lung 5 (LL5)

- **Key results**

  - **PFS**
    - PFS event, n (%): Afatinib + paclitaxel (n=134) 105 (78.4) vs Investigator choice (n=68) 54 (79.4)
    - Median PFS (mo): 5.6 vs 2.8
    - HR (95% CI): 0.60 (0.43, 0.85) with p=0.0031

- **OS**
  - OS event, n (%): Afatinib + paclitaxel (n=134) 100 (74.6) vs Investigator choice (n=68) 46 (67.6)
  - Median OS (mo): 12.2 vs 12.2
  - HR (95% CI): 1.00 (0.70, 1.43) with p=0.99

- **Conclusion**
  - PFS (and ORR) were significantly improved with continued afatinib combined with paclitaxel vs CT alone in heavily pretreated patients with acquired resistance to erlotinib/gefitinib and progression after afatinib monotherapy.
ASPIRATION- erlotinib beyond progression in EGFR+

- Continuing erlotinib beyond RECIST PD is feasible and could delay subsequent treatment including chemotherapy
- Single arm study, requires randomised validation
EGFR TKI failure in NSCLC

- **Dramatic progression**
  - Disease control ≥3 months
  - Compared with previous assessment, rapid increment of tumour burden
  - Symptom deterioration

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- **Local progression**
  - Disease control ≥3 months
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- **Chemotherapy**

- **Continuation of EGFR-TKIs**

- **Continuation of EGFR-TKIs plus local intervention**

- **Symptom**

- **Switch Chemo**
Iressa Mutation Positive Multicenter Treatment Beyond Progression Study (IMPRESS; NCT01544179)

**IMPRESS trial**
- continue with TKI AND add chemotherapy?

**Patients**
- Stage IIIb / IV NSCLC
- EGFR mutation-positive
- Chemotherapy-naïve
- CR / PR ≥4 months, or SD >6 months with first-line gefitinib
- Disease progression <4 weeks prior to study randomisation

**Endpoints**
- **Primary**
  - Progression-free survival
- **Secondary**
  - Overall survival
  - Objective response rate
  - Disease control rate
  - Safety and tolerability
  - QoL
- **Exploratory**
  - Biomarkers

1:1 randomisation
- Cisplatin + Pemetrexed (≤6 cycles) + Gefitinib 250 mg
- Cisplatin + Pemetrexed + Placebo 250 mg

**Randomisation (1:1)**
- Cisplatin 75 mg/m² IV + Pemetrexed 500 mg/m² IV + Gefitinib 250 mg oral QD
- Cisplatin 75 mg/m² IV + Pemetrexed 500 mg/m² IV + Placebo 250 mg oral QD
- ≤6 cycles

**Time from progressive disease to randomization**
- ≤4 weeks

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Jackman et al 2010
IMPRESS trial - primary endpoint

**Graph:**
- Plot showing the probability of progression-free survival (PFS) over time for two groups: Gefitinib (n=133) and Placebo (n=132).
- Trend lines for both groups are shown.
- The x-axis represents the time of randomisation (months) ranging from 0 to 14.
- The y-axis represents the probability of PFS ranging from 0.0 to 1.0.

**Table:*

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib (n=133)</th>
<th>Placebo (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>5.4</td>
<td>5.4</td>
</tr>
<tr>
<td>Number of events, n (%)</td>
<td>98 (73.7)</td>
<td>107 (81.1)</td>
</tr>
</tbody>
</table>

**HR** (95% CI) = 0.86 (0.65, 1.13); p=0.273

*Patients at risk:*
- Gefitinib: 133, 110, 88, 40, 25, 12, 6, 0
- Placebo: 132, 100, 85, 39, 17, 5, 4, 0

26-30 September 2014, Madrid, Spain
Advanced NSCLC: EGFR mutation treatment strategy

First line EGFR TKIs → Treated Resistant → chemo → BSC → Death

Clinical Model
Molecular Model
Mechanisms of Resistance to EGFR kinase inhibitors in EGFR mutant NSCLC

Randomised Phase III study of osimertinib vs platinum-pemetrexed for EGFR T790M-positive advanced NSCLC (AURA3)

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AURA3 study design

Key eligibility criteria

- ≥18 years (≥20 years in Japan)
- Locally advanced or metastatic NSCLC
- Evidence of disease progression following first-line EGFR-TKI therapy
- Documented EGFRm and central confirmation of tumour EGFR T790M mutation from a tissue biopsy taken after disease progression on first-line EGFR-TKI treatment
- WHO performance status of 0 or 1
- No more than one prior line of treatment for advanced NSCLC
- No prior neo-adjuvant or adjuvant chemotherapy treatment within 6 months prior to starting first EGFR-TKI treatment
- Stable* asymptomatic CNS metastases allowed
- Patients were stratified at randomisation based on ethnicity (Asian/Non-Asian)
- RECISTv1.1 assessments performed every 6 weeks until objective disease progression; patients could receive study treatment beyond RECISTv1.1 defined progression as long as they experienced clinical benefit
- With 221 events of progression or death, the study would have 80% power to reject the null hypothesis of no significant difference in duration of PFS between the two treatment groups, assuming a treatment effect HR of 0.67 at 5% two-sided significance

Endpoints

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

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

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

Osimertinib (n=279)
- 80 mg orally QD

Platinum-pemetrexed (n=140)
- Pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² Q3W for up to 6 cycles + optional maintenance pemetrexed

*Defined as not requiring corticosteroids for 4 weeks prior to study treatment; For patients whose disease had not progressed after 4 cycles of platinum-pemetrexed

HR, hazard ratio; Q3W, every 3 weeks; R, randomisation; RECIST, Response Evaluation Criteria In Solid Tumors; WHO, World Health Organization

Mok, Wu et al. NELM 2016
AURA3 primary endpoint: PFS by investigator assessment

- Analysis of PFS by BICR was consistent with the investigator-based analysis: HR 0.28 (95% CI 0.20, 0.38), p<0.001; median PFS 11.0 vs 4.2 months.

Population: intent-to-treat
Progression-free survival defined as time from randomisation until date of objective disease progression or death. Progression included deaths in the absence of RECIST progression.
Tick marks indicate censored data; CI, confidence interval

Mok, Wu et al. NELM 2016
Overcome resistance to EGFR TKIs with MET alternation

Partial responses were observed in all molecular subgroups, particularly in patients with high cMET amplification-status tumors.

Wu, et al ASCO 2016 9020
In summary:

Taking home message

• Strategy of EGFR TKI combination with others is not established yet.

• EGFR TKIs resistance could be treated based on clinical model --- Gradual, local and dramatic progression.

• Molecular resistance to EGFR TKIs include T790M, CMET aberrance and others

• Osimertinib has been SoC of T790M positive patients who failure to EGFR TKIs.

• CMET inhibitor is developing.
Thank You