STRATEGIES TO IMPROVE OUTCOME IN EGFR MUTANT NSCLC

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DISCLOSURES

Honorarium/ advisory board: Astra-Zeneca, BMS, Boehringer Ingelheim, Lilly, Merck, Novartis, Pfizer, Roche, Taiho
STRATEGIES TO IMPROVE OUTCOME IN EGFR MUTANT NSCLC

- Identify EGFR+ population
  - Who to test?
  - Improving the test
- Special populations
  - Uncommon mutations
  - CNS/leptomeningeal disease
- 1L Combination therapy
  - Anti-angiogenesis
  - Chemotherapy
- Treatment at progression
  - Oligometastatic disease
  - Continuation beyond progression
  - T790M-ve
  - Combination therapy
- 3G EGFR TKI
  - 1st line therapy
- Immunotherapy
  - 1L combination
  - Treatment at progression
STRATEGIES TO IMPROVE OUTCOME IN EGFR MUTANT NSCLC

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- Identifying EGFR+ population
  - Anti-angiogenesis
  - Chemotherapy

- Special populations
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  - CNS/leptomeningeal disease

- Uncommon mutations
  - Combination therapy
  - Immunotherapy

- T790M-ve
  - 3rd generation EGFR TKI
  - Combination therapy

- Continuation beyond progression
- Treatment at progression

- Combination therapy
- 1L combination
- Treatment at progression
Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology

Section I: When Should Molecular Testing of Lung Cancers Be Performed?

Question 1: Which Patients Should Be Tested for EGFR Mutations and ALK Rearrangements?

1.1a: Recommendation: EGFR molecular testing should be used to select patients for EGFR-targeted TKI therapy, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.

1.1b: Recommendation: ALK molecular testing should be used to select patients for ALK-targeted TKI therapy, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.

1.2: Recommendation: In the setting of lung cancer resection specimens, EGFR and ALK testing is recommended for adenocarcinomas and mixed lung cancers with an adenocarcinoma component, regardless of histologic grade. In the setting of fully excised lung cancer specimens, EGFR and ALK testing is not recommended in lung cancers that lack any adenocarcinoma component, such as pure squamous cell carcinomas, pure small cell carcinomas, or large cell carcinomas lacking any immunohistochemistry (IHC) evidence of adenocarcinoma differentiation.

1.3: Recommendation: In the setting of more limited lung cancer specimens (biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, EGFR and ALK testing may be performed in cases showing squamous or small cell histology but clinical criteria (e.g., young age, lack of smoking history) may be useful in selecting a subset of these samples for testing.
IGNITE STUDY

**EGFR mt in 14% Asia-Pac non-ADC**

### EGFR mutation frequency

<table>
<thead>
<tr>
<th></th>
<th>Tissue / cytology samples</th>
<th>Plasma samples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADC</td>
<td>non-ADC</td>
</tr>
<tr>
<td>Overall</td>
<td>952/2249 (42.3%)</td>
<td>89/927 (9.6%)</td>
</tr>
<tr>
<td>AsiaPac</td>
<td>862/1749 (49.3%)</td>
<td>75/525 (14.1%)</td>
</tr>
<tr>
<td>Russia</td>
<td>90/500 (18.0%)</td>
<td>15/402 (3.7%)</td>
</tr>
</tbody>
</table>

- Immunohistochemistry analyses showed that:
  - 43.9% (351/799) of TTF-1-positive patient samples were *EGFR* mutation-positive
  - 9.8% (25/256) of TTF-1-negative patient samples were *EGFR* mutation-positive

TTF-1, thyroid transcription factor 1

15-18 April 2015, Geneva, Switzerland
EGFR testing not as often as imagined...

<table>
<thead>
<tr>
<th>Country (n Cases Diagnosed with NSCLC)</th>
<th>Proportion Tested for EGFR Mutations % (95% CI)</th>
<th>Proportion of Men/Woman, Smokers and Nonsmokers, and Histological Subtypes that were Tested for EGFR Mutations</th>
<th>Sex</th>
<th>Smoking Status</th>
<th>ADC/Other Morphological Subtypes/Only SCC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (22,193)</td>
<td>31.8 (31.2–32.5)</td>
<td></td>
<td>26.9/40.2</td>
<td>47.0/57.4</td>
<td>50.4/12.5/12.5</td>
</tr>
<tr>
<td>China (12,086*)</td>
<td>18.3 (17.6–19.0)</td>
<td></td>
<td>15.2/25.3</td>
<td>N.D.</td>
<td>30.3/8.0/9.4</td>
</tr>
<tr>
<td>Hong Kong (795)</td>
<td>42.0 (38.6–45.5)</td>
<td></td>
<td>36.2/52.3</td>
<td>34.1/52.1</td>
<td>55.4/9.0/6.4</td>
</tr>
<tr>
<td>Japan (2379)</td>
<td>64.8 (62.9–66.7)</td>
<td></td>
<td>63.6/67.0</td>
<td>68.8/68.3</td>
<td>69.2/55.0/50.3</td>
</tr>
<tr>
<td>Korea (3794)</td>
<td>33.5 (32.0–35.0)</td>
<td></td>
<td>26.1/38.1</td>
<td>27.1/42.9</td>
<td>62.7/9.8/8.3</td>
</tr>
<tr>
<td>Taiwan (2890)</td>
<td>54.3 (52.5–56.1)</td>
<td></td>
<td>47.1/64.3</td>
<td>37.0/56.8</td>
<td>69.3/15.5/8.5</td>
</tr>
<tr>
<td>Thailand (249*)</td>
<td>57.8 (51.6–63.8)</td>
<td></td>
<td>51.6/69.3</td>
<td>49.5/84.7</td>
<td>83.6/7.1/6.9</td>
</tr>
</tbody>
</table>

Yatabe JTO 2015
Don’t forget to test for EGFR MT in Asian male smokers

Pack-years and frequency of *EGFR* mutation

Shi JTO 2014
## Improving EGFR testing

<table>
<thead>
<tr>
<th>Method</th>
<th>Mutations detected</th>
<th>Lower detection limit of mt allele</th>
<th>Relative cost</th>
<th>Relative TAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanger</td>
<td>All within sequenced regions</td>
<td>20%</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Allele specific real time PCR</td>
<td>Limited to a specific mutation</td>
<td>1%</td>
<td>Low</td>
<td>Fast</td>
</tr>
<tr>
<td>Allele specific ddPCR</td>
<td></td>
<td>0.1%</td>
<td>Low</td>
<td>Fast</td>
</tr>
<tr>
<td>NGS</td>
<td>All within sequenced regions</td>
<td>0.1%</td>
<td>High</td>
<td>Slow</td>
</tr>
</tbody>
</table>

Improvements in mutation-specific diagnostic kits are needed to detect rare but targetable mutations.
68 year old woman, never smoker.

P/W cord compression.

Spinal instrumentation, palliative RT

EGFR WT (allele specific PCR)

ALK/ ROS1 (FISH): negative
NGS identified actionable genomic alterations in 65% of tumors from NS/light smokers without targetable genomic alterations by earlier non-NGS testing

Drilon CCR 2015
STRATEGIES TO IMPROVE OUTCOME IN EGFR MUTANT NSCLC

- Identify EGFR+ population
- Who to test?
- Improving the test

Special populations
- Uncommon mutations
- CNS/leptomeningeal disease

Anti-angiogenesis
- Chemotherapy

Cerebrospinal fluid
- Chemotherapy

1st line therapy
- 2nd line therapy
- 3rd line therapy
- 4th line therapy

Treatment at progression
- T790M+ve
- Combination therapy
- Continuation beyond progression
- Combination beyond progression
- 1L combination
Outcomes in patients with uncommon mutations treated with afatinib

- *EGFR* mutations other than Del19 and L858R
- COSMIC database May 2016

<table>
<thead>
<tr>
<th>Category</th>
<th>Present survey</th>
<th>COSMIC (n = 16138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del19</td>
<td>44.8</td>
<td>27.4</td>
</tr>
<tr>
<td>L858R</td>
<td>39.8</td>
<td>52.7</td>
</tr>
<tr>
<td>Ins20</td>
<td>5.8</td>
<td>2.0</td>
</tr>
<tr>
<td>G719X</td>
<td>3.1</td>
<td>2.8</td>
</tr>
<tr>
<td>S768I</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>L861Q</td>
<td>0.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Ins19</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>E709X</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Del18</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Others</td>
<td>3.3</td>
<td>5.0</td>
</tr>
<tr>
<td>T790M</td>
<td>Excluded</td>
<td>6.6</td>
</tr>
<tr>
<td>Total (%)</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*EGFR* epidermal growth factor receptor.
## ORR to EGFR-TKI in NSCLC with uncommon mt

<table>
<thead>
<tr>
<th>Mutation</th>
<th>ORR (%)</th>
<th>1st generation</th>
<th>Afatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>delE709_T710insD</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E709A/H/K+complex</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G719X/A/S/C</td>
<td>32</td>
<td></td>
<td>77.8</td>
</tr>
<tr>
<td>G719X/A/S/C+complex</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ins19</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ins20</td>
<td>17</td>
<td></td>
<td>8.7</td>
</tr>
<tr>
<td>S768I</td>
<td>42</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>S768I+G719X/G724S/V769L/V774M</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L861Q</td>
<td>39</td>
<td></td>
<td>56</td>
</tr>
<tr>
<td>L861Q+G719X</td>
<td>92</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pooled analysis</th>
<th>ORR (%)</th>
<th>DOR (months)</th>
<th>DCR (%)</th>
<th>PFS (mths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 point mutations and duplications, or both, in e18–21</td>
<td>71.1</td>
<td>11.1</td>
<td>84.2</td>
<td>10.7</td>
</tr>
<tr>
<td>Group 2 de-novo T790M</td>
<td>14.3</td>
<td>8.2</td>
<td>64.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Group 3 exon 20 insertions</td>
<td>8.7</td>
<td>7.1</td>
<td>65.2</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Yang Lancet
**UNCOMMON MUTATIONS: SELECTING THE APPROPRIATE EGFR TKI**

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>Erlotinib</th>
<th>Afatinib</th>
<th>Dacomitinib</th>
<th>Neratinib</th>
<th>Osimertinib</th>
<th>Rociletinib</th>
<th>Olmutinib (B1482694)</th>
<th>Nazartinib (EGF816)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ins20 (others)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
Leptomeningeal disease

- EGFR mutant NSCLC: 9%
- Prognosis: 4-12 months
- 1st and 2nd generation EGFR TKI: limited CNS activity
- Osimertinib 160mg: CNS activity
- BLOOM study

PET imaging showed marked exposure of osimertinib in NHP and mouse model, in contrast to rociletinib and gefitinib

PET images showing uptake of different tracers in the brain.

**BLOOM study design overview**

Phase I study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of AZD3759 or osimertinib in patients with EGFRm advanced NSCLC.

- **Dose escalation**
  - AZD3759
    - Cohort 1: 50mg BID
    - Cohort 2: 100mg BID
    - Cohort 3: 150mg BID
    - Cohort 4: 200mg BID
    - Cohort 5: 250mg BID

- **Dose expansion cohorts**
  - Leptomeningeal metastasis
    - EGFR-TKI naïve or pre-treated
  - Brain metastasis
    - EGFR-TKI naïve

**Osimertinib 160mg QD**

- EGFR-TKI pre-treated patients with NSCLC and LM

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

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

Kuiper Lung Cancer 2015, Ahn ECCO 2015, Yang ASCO 2016
Efficacy assessments were conducted on 21 patients

- Seven patients had confirmed radiological improvement
- Two patients had confirmed CSF cytology clearance; no tumor cells were detected in two consecutive CSF samples
- Five patients had confirmed improved neurological function

### Best MRI imaging

<table>
<thead>
<tr>
<th></th>
<th>Confirmed</th>
<th>Unconfirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intracranial response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responding</td>
<td>7 (33)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (43)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Early withdrawal</td>
<td>2 (10)</td>
<td></td>
</tr>
</tbody>
</table>

Population: efficacy, n=21. Response confirmation was done at least 4 weeks after the initial response. Response assessed by neurological examination.

**Presented by:** James Chih-Hsin Yang
STRATEGIES TO IMPROVE OUTCOME IN EGFR MUTANT NSCLC

1L Combination therapy

- Anti-angiogenesis
- Chemotherapy

Who to test?

Improving the test

Uncommon mutations

CNS/leptomeningeal disease

1L Combination therapy

- Oligometastatic disease
- Combination therapy
- T790M ve
- Immunotherapy

1st line therapy

Continuation beyond progression

1L combination

Treatment at progression
1L EGFR TKI + ANTI-ANGIOGENESIS

- EGFR signal activation increases VEGF production
- Oncogenic properties of EGFR might be mediated by stimulation of tumor angiogenesis through upregulation of potent angiogenesis growth factors.

1L EGFR TKI + ANTI-ANGIOGENESIS

Okayama Lung Cancer Study Group Trial 1001: gefitinib + bevacizumab

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>2</td>
<td>4.7</td>
</tr>
<tr>
<td>Partial response</td>
<td>29</td>
<td>69.0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>10</td>
<td>23.8</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>1</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>Response rate (95% CI)</strong></td>
<td>31</td>
<td>73.8 (58.0–86.1)</td>
</tr>
<tr>
<td><strong>Disease control rate (95% CI)</strong></td>
<td>41</td>
<td>97.6 (87.4–99.9)</td>
</tr>
</tbody>
</table>

EU approval of bevacizumab in combination with erlotinib for 1L EGFR M+ NSCLC granted June 2016

JO25567: 1L erlotinib+ bevacizumab vs erlotinib in EGFR+ advanced NSCLC

<table>
<thead>
<tr>
<th>Best response</th>
<th>Erlotinib + bev (n=75)</th>
<th>Erlotinib (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>PR</td>
<td>65%</td>
<td>62%</td>
</tr>
<tr>
<td>SD</td>
<td>29%</td>
<td>25%</td>
</tr>
<tr>
<td>ORR</td>
<td>69%</td>
<td>63%</td>
</tr>
</tbody>
</table>

Ichihara JTO 2015, Seto Lancet Oncol 2014
**BELIEF: 1L ERLOTINIB + BEVACIZUMAB IN ADVANCED NSCLC HARBORING ACTIVATING EGFR MT**

- Open-label phase II study
  - Primary endpoints: PFS

Chemo-naïve IIIB-IV nonsquamous NSCLC EGFR mutations (del 19, L858R), brain mets allowed

**Erlotinib 150 mg QD + Bevacizumab 15 mg/kg q3w**

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>T790M+</th>
<th>T790M-</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>6.4%</td>
<td>8.1%</td>
<td>5.6%</td>
</tr>
<tr>
<td>PR</td>
<td>69.7%</td>
<td>62.2%</td>
<td>73.6%</td>
</tr>
<tr>
<td>SD</td>
<td>16.5%</td>
<td>24.3%</td>
<td>12.5%</td>
</tr>
<tr>
<td>PD</td>
<td>2.8%</td>
<td>0%</td>
<td>4.2%</td>
</tr>
<tr>
<td>NE</td>
<td>4.6%</td>
<td>5.4%</td>
<td>4.2%</td>
</tr>
<tr>
<td>DOR (months)</td>
<td>14.8 (12-NE)</td>
<td>NE (14.7-NE)</td>
<td>12 (8.2-23.3)</td>
</tr>
</tbody>
</table>

**Treat until disease progression or unacceptable toxicity**

Stahel ECC 2015
BELIEF: 1L ERLOTINIB + BEVACIZUMAB IN ADVANCED NSCLC HARBORING ACTivating EGFR MT

<table>
<thead>
<tr>
<th></th>
<th>Events/N</th>
<th>Median PFS, months (95%CI)</th>
<th>12-month PFS, % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>57/109</td>
<td>13.8 (10.3, 21.3)</td>
<td>56.7 (46.0, 66.0)</td>
</tr>
<tr>
<td>T790M+</td>
<td>15/37</td>
<td>16.0 (13.1, NE)</td>
<td>72.4 (53.4, 84.7)</td>
</tr>
<tr>
<td>T790M-</td>
<td>42/72</td>
<td>10.5 (9.2, 16.2)</td>
<td>49.4 (36.6, 61.0)</td>
</tr>
</tbody>
</table>

T790M 34%

Stahel ECC 2015
1L erlotinib +/- bevacizumab: ongoing trials

1. BEVERLY (n=200) EudraCT number, 2015-002235-17:

- Control arm
  - Erlotinib 150 mg orally once daily

- Experimental arm
  - Erlotinib 150 mg orally once daily
  - Bevacizumab 15 mg/kg, i.v., every 3 weeks

Stratification:
- PS (0-1 versus 2)
- Type of mutation (exon19 del versus 21 L858R mut versus others)

2. Academic and Community Cancer Research United: Randomized phase II trial (NCT01532089)
1L Chemotherapy+ TKI

- Gefitinib + pemetrexed vs gefitinib: Randomized, open-label phase II study
- Primary endpoints: PFS
- Secondary endpoints: TTP, OS, tumor response, DOR, safety

Pts with treatment naive, non-squamous NSCLC and activating EGFR mutations, (N = 191)

Gefitinib 250 mg QD + Pemetrexed 500 mg/m² q3w (n = 126)

Gefitinib 250 mg QD (n = 65)

Treat until disease progression or unacceptable toxicity

China, Japan, Korea, and Taiwan

Pts with treatment naive, non-squamous NSCLC and activating EGFR mutations, (N = 191)

Stratified by gender, stage, smoking history, EGFR mt type (e19 v L858R)

Cheng JCO 2016
1L gefitinib + pemetrexed vs gefitinib

**Progression-Free Survival (probability)**

**Time (months)**

**Median PFS, months (95% CI)**
- P+G: 15.8 (12.6 to 18.3)
- Gefitinib: 10.9 (9.7 to 13.9)
- HR: 0.68 (0.48 to 0.96)
- Adjusted P: One-sided, .014; two-sided, .029

Cheng JCO 2016
Pts with treatment naive, non-squamous NSCLC and activating EGFR mutations, \( (N = 191) \)

- 1L gefitinib + carboplatin/pemetrexed: 2 schedules
- Randomized, open-label phase II study
- Primary endpoints: PFS
- Secondary endpoints: OS, tumor response, safety

Stratified by gender, stage
NEJ005/TCOG0902: 1L gefitinib + carboplatin/pemetrexed

Ongoing Phase III study: NEJ009
Combination Carboplatin/ pemetrexed + gefitinib v gefitinib in EGFR+ advanced NSCLC (UMIN000006340)

Sugawara Ann Oncol 2015
STRATEGIES TO IMPROVE OUTCOME IN EGFR MUTANT NSCLC

Who to test?

- Uncommon mutations
- CNS/leptomeningeal disease
- Anti-angiogenesis
- Chemotherapy

Treatment at progression

- Oligometastatic disease
- Continuation beyond progression
- T790M
- Combination therapy

1L combination therapy

1L combination therapy

Treatment at progression

1L combination therapy
TREATMENT OF OLIGOMETASTASIS
SUGGESTED CRITERIA FOR CONSIDERING LOCAL ABLATIVE THERAPY OF OLIGOPROGRESSIVE DISEASE AND TREATMENT WITH A TKI BEYOND PROGRESSION

1. ALK positive or EGFR-mutant metastatic NSCLC
2. Relevant TKI (e.g., crizotinib or erlotinib) is well tolerated
3. Oligoprogressive disease on TKI therapy, defined as:
   CNS progression without leptomeningeal disease amenable to WBRT, SRS, or surgical resection.
   Progression in ≤ 4 extra-CNS sites amenable to SBRT, XRT, or surgical resection.

Weickhardt et al. J Thorac Oncol 2012
Local Ablative Therapy for oligoprogressive disease confers additional 6m disease control

(A) PFS of all patients treated with LAT and continuation of TKI therapy

(B) CNS only as site of first progression

(C) eCNS as site of first progression

Total N = 65
ALK+ = 38
EGFR MT = 27

Weickhardt et al. J Thorac Oncol 2012
CONTINUATION BEYOND PROGRESSION

ASPIRATION
ASPIRATION

PFS1 = time from 1st study dose to first RECIST 1.1-defined PD or death
PFS2 = time from 1st study dose to off-erlotinib PD in the subset of patients who continued erlotinib therapy beyond RECIST 1.1 PD

Park JAMA Oncol 2015
ASPIRATION

Selection bias
Slow or minimal PD, PD only to bone, asymptomatic PD, stable primary tumor, better PS, good radiologic response, and long disease-control duration. Doesn’t account for types of PD. Non randomised.

PFS1=11.0
PFS2=14.1

Park JAMA Oncol 2015
COMBINATION THERAPY AT TIME OF PROGRESSION

Chemotherapy +1G EGFR: IMPRESS study
EGFR MoAb + EGFR TKI
**Study design**

*Enrollment period: March 2012–December 2013*

**Patients**
- Age ≥18 years (≥20 years in Japan)
- WHO PS 0-1
- Histologically confirmed stage IIIIB / IV *EGFR* mutation-positive 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 randomisation

**Endpoints**
- **Primary**
  - Progression-free survival
- **Secondary**
  - Overall survival
  - Objective response rate
  - Disease control rate
  - Safety and tolerability
  - Health-related quality of life
- **Exploratory**
  - Biomarkers

**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**

---

*a* Progressive disease based on radiological evaluation (modified Jackman’s criteria) and RECIST version 1.1. Tumour assessments were performed ≤4 weeks before the start of treatment (baseline), and every 6 weeks (±7 days) after randomisation until progressive disease; *b* Randomisation did not include stratification factors; analyses were adjusted for two covariates: age (<65 versus ≥65 years) and prior response to gefitinib (SD versus PR+CR); *c* Will be reported separately; *d* Analyses not yet completed and will be reported separately.

CR, complete response; PR, partial response; PS, performance status; SD, stable disease; WHO; World Health Organization; *Jackman et al 2010*
PFS (PRIMARY ENDPOINT; ITT)

<table>
<thead>
<tr>
<th>Time of randomisation (months)</th>
<th>Gefitinib (n=133)</th>
<th>Placebo (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>133</td>
<td>132</td>
</tr>
<tr>
<td>2</td>
<td>110</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients at risk:
- Gefitinib 133
- Placebo 132

Median PFS, months:
- Gefitinib: 5.4
- Placebo: 5.4

Number of events, n (%):
- Gefitinib: 98 (73.7)
- Placebo: 107 (81.1)

HR\(^a\) (95% CI) = 0.86 (0.65, 1.13); \(p=0.273\)

Gefitinib (n=133) Placebo (n=132)

Primary cox analysis with covariates: A HR <1 implies a lower risk of progression with gefitinib

Mok ESMO 2014
ACQUIRED RESISTANCE: SIGNIFICANT % ARE T790M-VE

- T790M (55%)
- HER2 (12%)
- MET (5%)
- PIK3CA (5%)
- MAPK1 (3%)
- BRAF (1%)

↑E: KDM5, FGFR2, FGFR1, AXL, ROR1, or Notch-1
↑A: NFKB, Wnt-tankyrase-β-catenin, JAK2, or VEGFR
↑R: ADAM17
↓R: DAPK or NF1
↓E: IGF binding proteins
EMT/SCLC transformation
Gain of stem-cell like properties
Tumor stromal factors
COMBINATION THERAPY

EGFR-dependent progression
- T790M
- Cetuximab
- EGFR

Bypass mechanisms
- Her family
- Met
- EGFR
- T790M
- CO-1686
- AZD9291

EMT
- AXL
- Inhibitor

SCLC transformation
- Axl
- Inhibitor

Immune escape
- PDL1
- PD1

Immune checkpoint inhibitors

Small molecule inhibitor/TKI
- Antibody

Resistance

Gibbons Cancer Discovery 2014
Dual Targeting in EGFR TKI-resistant EGFR Mt+ NSCLC

Afatinib/Cetuximab

Afatinib/nimotuzumab

---

**Afatinib/Cetuximab**

- \(N=126\)
- ORR: Overall 29%
- T790M+ve 32%
- T790M-ve 25%

**Afatinib/nimotuzumab**

- \(N=44\)
- ORR: Overall 23%
- T790M+ve 18%
- T790M-ve 33%

---

**Figure 2.** Waterfall plot showing maximum percentage change from baseline in size of tumors in patients who received the concurrent regimen of afatinib and cetuximab. Data available for 112 patients. Tumor tissue from 2 patients was confirmative as to T790M status. LLD, sum of the longest diameter.

### Dual Targeting with Afatinib/Cetuximab in EGFR TKI–Resistant EGFR M+ NSCLC

<table>
<thead>
<tr>
<th></th>
<th>All grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Total patients treated</td>
<td>126 (100)</td>
<td>126 (100)</td>
<td>126 (100)</td>
</tr>
<tr>
<td>Total patients with related adverse events</td>
<td>125 (99)</td>
<td>56 (44)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Rash&lt;sup&gt;a&lt;/sup&gt;</td>
<td>114 (90)</td>
<td>25 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>89 (71)</td>
<td>8 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nail effects&lt;sup&gt;a&lt;/sup&gt;</td>
<td>72 (57)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stomatitis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>71 (56)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>50 (39)</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Headache</td>
<td>46 (37)</td>
<td>4 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ocular effects&lt;sup&gt;a&lt;/sup&gt;</td>
<td>38 (30)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>37 (29)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>33 (26)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>29 (23)</td>
<td>3 (2)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Use limited by toxicity and the efficacy of third-generation EGFR TKI.

MET TKI+ EGFR TKI

Tepotinib + gefitinib: phase Ib

Figure 4. Relative change in sum of longest diameter of target lesions from baseline over time (safety population)*

- c-Met status and polysomy result
- c-Met = 2+ Polyosomy status = Positive
- c-Met = 3+ Polyosomy status = Negative
- Progressive disease Polyosomy status = Missing

Baseline

INC280+ gefitinib: phase II

Acquired resistance: exon 19 del, T790M+, MET IHC+2

Soo ESMO Asia 2015, Yu ASCO 2016

INC280+ EGF816: phase I/II

Baseline

2 cycles EGF816/INC280
STRATEGIES TO IMPROVE OUTCOME IN EGFR MUTANT NSCLC

- Who to test?
- Improving the test
- Common mutations
- CNS/leptomeningeal disease
- Anti-angiogenesis
- Chemotherapy
- Oligometastatic disease
- Continuation beyond progression
- T790M-ve
- Combination therapy

3G EGFR TKI

1st line therapy

1L combination

Treatment at progression
3G EGFR TKI in the 1\textsuperscript{st} line

Greater pre-clinical efficacy

**PC9 (EGFR exon 19 deletion)**

- Vehicle only BID
- Gefitinib 6.25 mg/kg QD
- AZD9291 5 mg/kg QD
- AZD9291 25 mg/kg QD

**H3255 (EGFR L858R)**

- Vehicle only BID
- Gefitinib 6.25 mg/kg QD
- AZD9291 5 mg/kg QD
- Afatinib 7.5 mg/kg QD

Longer time to resistance

- *In vitro in EGFRm+ (exon 19 deletion) PC9 cells, resistance to AZD9291 took significantly longer to emerge compared with other TKIs\textsuperscript{1}*
  - Resistance to 10 nM AZD9291 took on average 43 days longer to develop than with 0.8 nM afatinib, 30 nM WZ4002, or 20 nM gefitinib

Initial concentration was equal to the proliferative IC\textsubscript{50} previously determined for each inhibitor: gefitinib 10 nM, afatinib 0.8 nM, WZ4002 30 nM, AZD9291 10 nM

n = number of separate resistant populations; error bars are standard error of the mean

Planchard ELCC 2016
Activity of 3G TKIs in 1L

<table>
<thead>
<tr>
<th>ORR</th>
<th>PFS</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>77%</td>
<td>19.3m</td>
<td>22.1m</td>
</tr>
</tbody>
</table>

Best percentage change from baseline in target lesion size (%)

- 1st line 80 mg
- 1st line 160 mg

Probability of PFS survival

Number of patients at risk:

- 1st line 80 mg
- 1st line 160 mg

Ramalingam ELCC 2016
Optimal sequencing of EGFR TKIs

1G/2G EGFR TKI
Progression T790M- 
Platinum doublet
Death

9-11m
5-6m

1G/2G EGFR TKI
Progression T790M+
Platinum doublet 
Death

19+m

1st line studies:
FLAURA (Osimertinib)
SOLAR (ASP8273)

3G EGFR TKI
Progression 
Platinum doublet 
Death

18-20m

19+m
STRATEGIES TO IMPROVE OUTCOME IN EGFR MUTANT NSCLC

Who to test?
Improving the test
Uncommon mutations
CSF/leptomeningeal disease
Anti-angiogenesis
Chemotherapy
CNS/leptomeningeal disease
Treatment at progression
Oligometastatic disease
Continuation beyond progression
T790M-ve
Combination therapy
1L combination
Treatment at progression
Immunotherapy
1L combination
Treatment at progression
RELATIONSHIP BETWEEN EGFR MUTATIONS AND THE PD-1/PD-L1 AXIS

NSCLC harboring EGFR mutations is associated with PD-L1 expression

EGFR signaling induced by EGFR mutations activated PD-L1 expression and induced immune escape

PD-L1 was significantly higher in EGFR mutation-positive cell lines

Table 2. Multivariate analysis of the relation between PD-L1 expression in tumor specimens and other patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Coefficient (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1 versus III</td>
<td>2.0 (1.8 to 2.2)</td>
<td>0.846</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤66 versus &gt;66</td>
<td>5.3 (2.9 to 6.4)</td>
<td>0.581</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female versus male</td>
<td>1.6 (0.2 to 5.9)</td>
<td>0.511</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker versus never</td>
<td>-18.6 (6.4 to 27.3)</td>
<td>0.026</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adeno carcinoma versus SCC</td>
<td>25.1 (25.0 to 49.3)</td>
<td>0.016</td>
</tr>
<tr>
<td>EGFR status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutant versus wild type</td>
<td>25.4 (2.9 to 47.9)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

SCC, squamous cell carcinoma.

Akbay Cancer Discovery 2013, Azuma Ann Oncol 2014
1st line EGFR TKI + checkpoint inhibitor

Phase I Gefitinib + durvalumab

Dose escalation

Cohort A: Gefitinib + durvalumab
3mg/kg Q2W

If ≤1 DLT

Cohort A: Gefitinib + durvalumab
10mg/kg Q2W

Dose expansion

Arm 1: Gefitinib + durvalumab
10mg/kg Q2W

Arm 2: Gefitinib 4w then Gefitinib + durvalumab
10mg/kg Q2W

Recommended dose

<table>
<thead>
<tr>
<th></th>
<th>Arm 1, n=9</th>
<th>Arm 2, n=10</th>
<th>Overall, n=19</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>78</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>SD ≥24w</td>
<td>0</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

Advanced NSCLC
no std therapy available
PS 0-1
Dose escalation: ≤4 lines
Dose expansion: EGFR+, TKI naïve

Gibbons ELCC 2016
# Gefitinib + durvalumab

<table>
<thead>
<tr>
<th>Event</th>
<th>Arm 1, %</th>
<th>Arm 2, %</th>
<th>Overall, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment related AE</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Treatment related AE G3-4</td>
<td>40</td>
<td>70</td>
<td>55</td>
</tr>
<tr>
<td>Treatment related AE leading to discontinuation</td>
<td>0</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>All cause G3-4 AE</td>
<td>50</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>ALT</td>
<td>30</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>AST</td>
<td>0</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Bone pain</td>
<td>10</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Dry skin</td>
<td>10</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>10</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>
Immune checkpoint + EGFR TKI

TATTON: osimertinib + durvalumab arm

**Part A: Dose escalation**
Patients who progressed after previous EGFR-TKI therapy; prior anti-PD-L1 or anti-PD-1 treatment excluded

**Part B: Dose expansion**
Patients with EGFR-TKI treatment-naïve disease

- **Primary objective**: safety and tolerability
- **Treatment location**: Asia and USA
- **Key inclusion criteria**: EGFRm NSCLC, adequate performance status and organ function
- **Key exclusion criteria**: History of ILD or radiation pneumonitis which required steroid treatment, live vaccine or immunosuppressants within 1 month
- **Data cutoff**: 13 November 2015

*Part B combination dose chosen based on preliminary signal of clinical efficacy and an acceptable safety and tolerability profile

Ahn M-J, et al. ELCC 2016; Abstract 136O
## TATTON: Response rate and duration of response

<table>
<thead>
<tr>
<th>Part</th>
<th>Osimertinib 80 mg QD / durvalumab 3 mg/kg Q2W (n=10)</th>
<th>Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (n=13)</th>
<th>Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed responses, n (%; 95% CI)</td>
<td>4 (40%; 12, 74)</td>
<td>5 (39%; 14, 68)</td>
<td>7 (70%; 35, 93)</td>
</tr>
<tr>
<td>Patients with T790M positive NSCLC</td>
<td>6/9 (67%; 30, 93)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients with T790M negative NSCLC</td>
<td>3/14 (21%; 5, 51)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Population: evaluable for response set; data cutoff: 13 Nov 2015

Ahn M-J, et al. ELCC 2016; Abstract 136O

![Graph showing duration of response](image)
TATTON: Time to onset and frequency of ILD

- Time to ILD onset in TATTON (n=13):
  - Mean 80 days
  - Median 69 days

### Part A

<table>
<thead>
<tr>
<th>Dose 1: Osimertinib</th>
<th>6/23 (26%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose 2: Osimertinib</td>
<td>2/10 (20%)</td>
</tr>
<tr>
<td>Part B: Osimertinib</td>
<td>4/13 (31%)</td>
</tr>
<tr>
<td>Part A and Part B</td>
<td>13/34 (38%; 95% CI 18, 52)</td>
</tr>
</tbody>
</table>

### Entire osimertinib clinical programme (Phase I and II)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib monotherapy</td>
<td>35/1207 (2.9%)</td>
</tr>
<tr>
<td>Durvalumab monotherapy</td>
<td>23/1149 (2.0%)</td>
</tr>
</tbody>
</table>

*One patient reported ILD following 13 Nov 2015 data cutoff

†5 events were Grade 3/4 and there were no fatalities; most cases were managed using steroids

Population: safety analysis set; data cutoff: 13 Nov 2015
Synergistic tumor cell killing effects were not observed with combination EGFR-TKIs and anti-PD-1 Ab in co-culture system.
In pretreated setting: EGFR MT and ALK rearrangements have poorer outcomes with PD1/PDL1 inhibitors

### Antitumor Activity by EGFR and KRAS Status

<table>
<thead>
<tr>
<th></th>
<th>Study</th>
<th>TPS ≥50%</th>
<th>TPS 1-49%</th>
<th>TPS &lt;1%</th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>ORR, %</td>
<td>ORR, %</td>
<td>ORR, %</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>144</td>
<td>38.2</td>
<td>11.9</td>
<td>10.0</td>
<td>20.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(32.4-46.7)</td>
<td>(7.6-17.4)</td>
<td>(4.4-18.6)</td>
<td>(16.9-23.8)</td>
</tr>
<tr>
<td>EGFR wild type</td>
<td>113</td>
<td>39.8</td>
<td>12.2</td>
<td>12.7</td>
<td>21.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(30.7-49.5)</td>
<td>(7.5-18.4)</td>
<td>(5.6-23.5)</td>
<td>(17.8-25.6)</td>
</tr>
<tr>
<td>EGFR mutant</td>
<td>20</td>
<td>20.0</td>
<td>8.7</td>
<td>0.0</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5.7-43.7)</td>
<td>(1.1-28.0)</td>
<td>(0.0-23.2)</td>
<td>(2.9-16.2)</td>
</tr>
<tr>
<td>KRAS wild type</td>
<td>51</td>
<td>29.4</td>
<td>12.9</td>
<td>7.5</td>
<td>16.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(17.5-43.8)</td>
<td>(6.6-22.0)</td>
<td>(1.6-20.4)</td>
<td>(11.9-21.7)</td>
</tr>
<tr>
<td>KRAS mutant</td>
<td>26</td>
<td>30.8</td>
<td>0.0</td>
<td>18.2</td>
<td>17.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(14.3-51.8)</td>
<td>(0.0-14.2)</td>
<td>(2.3-51.8)</td>
<td>(10.0-28.8)</td>
</tr>
</tbody>
</table>

*Includes patients for whom a PD-L1 TPS could not be assigned (n = 141). Data are not shown for patients with wildtype EGFR (n = 78) or ALK (n = 220) status.

---

**EGFR** | Study | OS | Reference
---|-------|----|--------
MT | KN001* | 6.5 months | Hui, ASCO 2016
WT | 13.2 months | | 
MT | KN010 | 0.88 (0.45-1.7) | Herbst, Lancet 2016
WT | 0.66 (0.55-0.8) | | 
MT | CM057 | 1.18 (0.69-2) | Borghaei, NEJM 2015
WT | 0.66 (0.51-0.86) | | 
MT | OAK | 1.24 | Barlesi, ESMO 2016
WT | 0.69 | | 
MT | POPLAR | 0.99 | Smith, ASCO 2016 #9028
WT | 0.70 | | 

*TPS >1%

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**Gainor CCR 2016**

---

**Gainor CCR 2016**
Tumors harboring druggable oncogenic drivers are more likely to have low TMB.

Frequency of LC patients with selected variants between TMB-high vs. TMB-low cohorts

TMB (mutations/Mb) was assessed as the number of somatic, coding, base substitution and indel alterations per Mb of genome.
CONCLUSIONS

- Sensitive platforms can identify tumors harboring EGFR mutations
- 1st line combination therapy holds great promise but require confirmatory randomised studies
- Multiple treatment options exists for patients with acquired resistance but require confirmatory studies
- New generation EGFR TKIs are highly promising
- Role of immune checkpoint inhibitor- more research needs to be done
THANK YOU FOR YOUR ATTENTION