PROGRESSION AFTER THIRD GENERATION TKI

What next?

National Cancer Center Hospital
Yuichiro Ohe, MD
<table>
<thead>
<tr>
<th>Name of lead presenter</th>
<th>Yuichiro Ohe</th>
<th>Institution or company/position</th>
<th>Deputy-director National Cancer Center Hospital</th>
</tr>
</thead>
<tbody>
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<td>If yes, please specify the name of company and/or organization, your status.</td>
<td>National Cancer Center Hospital</td>
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<td>employee of company and/or profit-making organization</td>
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<td>fees of testimony, judgment, comment, etc.</td>
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<td>representative of organization for clinical study receiving research expenses from company</td>
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Metastatic Non-small-cell Lung Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up

- First-line treatment with an EGFR TKI (erlotinib, gefitinib or afatinib) is the standard of care for tumours bearing an activating (sensitising) EGFR mutation [I, A].

- Patients with EGFR mutation and PS 3-4 may also be offered an EGFR TKI [II, A].

- If information on an EGFR-sensitising mutation becomes available during first-line platinum-based chemotherapy, continue chemotherapy for up to four cycles and offer the EGFR TKI as maintenance treatment in patients achieving disease control, or as second-line treatment at the time of progression [I, A].

- In patients who progress after an EGFR TKI, rebiopsy is strongly encouraged to look for EGFR T790M mutation, relevant for therapeutic strategy. An alternative to tissue rebiopsy is represented by liquid biopsy [III, A].

- Osimertinib is recommended in patients who have developed the EGFR T790M resistance mutation after EGFR TKI treatment [III, A].

- When a rebiopsy is not feasible, or when the EGFR T790M mutation is not detected in patients who progress after an EGFR TKI, the standard of care is platinum-based doublet chemotherapy. No data support the concurrent use of EGFR TKI and platinum-based doublet chemotherapy [I, A].
Possible Treatment of *EGFR*-mutation Positive NSCLC after 3rd Generation EGFR-TKI

- Platinum-based doublets with/without bevacizumab
- Docetaxel with/without ramucirumab
- Immune check point inhibitors
- Others
Platinum-based Doublets for *EGFR*-mutation Positive NSCLC

**IPASS: ORR**

- **Odds Ratio (95% CI) = 2.59 (1.25, 2.01), p=0.0001**
- **Odds Ratio (95% CI) = 2.75 (1.65, 4.60), p=0.0001**
- **Odds Ratio (95% CI) = 0.04 (0.01, 0.27), p=0.0013**

**NEJ002**

- **ORR: 25.4%**

**IMPRESS**

- **CDDP+PEM alone**
  - **ORR: 34%**
  - **mPFS: 5.4 months**
Platinum-based Doublets for EGFR-mutation Positive NSCLC

Study profile

391 Lung adenocarcinoma patients with examined for EGFR mutation status who were admitted to the National Cancer Center Hospital from May 2007 through January 2014

257 EGFR-mutation
- 51 first-line CT, 17 combination of TKI and CT
- 3 transferred, 2 CRT, 2 RT, 2 BSC, 1 surgery

179 received EGFR-TKIs
- 14 continued TKI
- 8 transferred

157 acquired resistance to TKIs
- 47 BSC, 30 other EGFR-TKIs,
- 18 single agent CT, 5 lost of follow up

57 received second-line platinum-doublet CT

134 EGFR WT
- 22 single agent CT
- 2 investigational agents

110 received first-line platinum-doublet CT

Overall survival

Median: 41.7 vs 16.8 m

log rank p<0.001
HR 0.38, 95%CI 0.22-0.62
Platinum-based Doublets for \textit{EGFR}-mutation Positive NSCLC

\textbf{PFS from platinum-doublet CT}

- Red: EGFR M+ n=57
- Blue: EGFR WT n=110

Median: 5.9 vs 5.4 m

\textbf{Survival from platinum-doublet CT}

- Red: EGFR M+ n=57
- Blue: EGFR WT n=110

Median: 21.3 vs 15.4 m
Japanese Clinical Practice of The Treatment of EGFR-mutation Positive NSCLC

Characteristics and overall survival of EGFR mutation-positive non-small cell lung cancer treated with EGFR tyrosine kinase inhibitors: a retrospective analysis for 1660 Japanese patients

- EGFR-mutation positive NSCLC
- The treatment were started between Jan 2008 and Dec 2012
- 17 hospitals (Cancer Center: 3, University Hospital: 5, General Hospital: 9)
- Exclude patients treated with IND
- As of Dec 2014, Alive: 380 (23%); Dead: 965 (58%); Lost follow-up: 312 (19%); Total 1657
Japanese Clinical Practice of The Treatment of EGFR-mutation Positive NSCLC

Initial Treatment
- EGFR-TKI: 1060
- Platinum-based: 509
- Others: 88

EGFR-TKI ± α: 61.47%
Platinum doublet ± Bev.: 8.15%
Other Chemo ± Bev.: 8.07%
Other: 0.07%
Non-treatment: 22.24%
Japanese Clinical Practice of The Treatment of EGFR-mutation Positive NSCLC

<table>
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<tr>
<th>Rank</th>
<th>First-line</th>
<th>Second-line</th>
<th>Third-line</th>
<th>Patients</th>
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<tr>
<td>1</td>
<td>Gefitinib ± α</td>
<td>Gefitinib ± α</td>
<td>Gefitinib ± α</td>
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<tr>
<td>2</td>
<td>Gefitinib ± α</td>
<td>Other EGFR-TKI ± α</td>
<td>Gefitinib ± α</td>
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<td>3</td>
<td>Pt doublet ± BV</td>
<td>Gefitinib ± α</td>
<td>Other CTx ± BV</td>
<td>96</td>
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<tr>
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<td>Gefitinib ± α</td>
<td>Gefitinib ± α</td>
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<td>Gefitinib ± α</td>
<td>Pt doublet ± BV</td>
<td>Other CTx ± BV</td>
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<td>Gefitinib ± α</td>
<td>Other EGFR-TKI ± α</td>
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<td>7</td>
<td>Gefitinib ± α</td>
<td>Pt doublet ± BV</td>
<td>Pt doublet ± BV</td>
<td>68</td>
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<td>8</td>
<td>Pt doublet ± BV</td>
<td>Other EGFR-TKI ± α</td>
<td>Other CTx ± BV</td>
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<td>9</td>
<td>Pt doublet ± BV</td>
<td>Other EGFR-TKI ± α</td>
<td>Other EGFR-TKI ± α</td>
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<td>10</td>
<td>Gefitinib ± α</td>
<td>Other EGFR-TKI ± α</td>
<td>Pt doublet ± BV</td>
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Treatment frequency

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<th>0</th>
<th>1</th>
<th>2</th>
<th>≥3</th>
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<tbody>
<tr>
<td>EGFR-TKI</td>
<td>54 (3.3%)</td>
<td>956 (57.7%)</td>
<td>453 (27.3%)</td>
<td>194 (11.7%)</td>
</tr>
<tr>
<td>Gefitinib ± α</td>
<td>269 (16.2%)</td>
<td>1221 (73.7%)</td>
<td>138 (8.3%)</td>
<td>29 (1.8%)</td>
</tr>
<tr>
<td>Other EGFR-TKI ± α</td>
<td>922 (55.6%)</td>
<td>589 (35.5%)</td>
<td>114 (6.9%)</td>
<td>32 (2.0%)</td>
</tr>
<tr>
<td>Platinum doublet ± BV</td>
<td>825 (49.8%)</td>
<td>701 (42.3%)</td>
<td>113 (6.8)</td>
<td>18 (1.1%)</td>
</tr>
<tr>
<td>Other chemotherapy ± BV</td>
<td>1024 (61.8%)</td>
<td>378 (22.8%)</td>
<td>148 (8.9%)</td>
<td>107 (6.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>1630 (98.4%)</td>
<td>26 (1.6%)</td>
<td>1 (0.1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

31.7%
Japanese Clinical Practice of The Treatment of EGFR-mutation Positive NSCLC

OS categorized by 1st + 2nd line treatment

- EGFR-TKI = a\(^+\) only: 367, 100.0%, 67.7%, 47.5%, 35.3%, 29.3%, 24.9%
- EGFR-TKI = a\(^+\) → EGFR-TKI = a\(^-\): 223, 100.0%, 90.9%, 59.5%, 30.1%, 25.6%, 15.3%
- EGFR-TKI = a\(^-\) → Chemotherapy: 336, 100.0%, 90.4%, 64.1%, 41.7%, 24.5%, 15.5%
- Chemotherapy only: 33, 100.0%, 53.8%, 46.6%, 42.8%, 28.8%, 21.4%
- Chemotherapy → EGFR-TKI: a\(^+\): 437, 100.0%, 87.3%, 63.6%, 43.3%, 32.9%, 23.6%
- Chemotherapy → Chemotherapy: 55, 100.0%, 83.1%, 69.4%, 44.8%, 22.5%, 20.4%

Median OS (m)
(95% CI)
- 21.57 (10.13, 22.90)
- 26.30 (25.47, 32.63)
- 31.40 (27.57, 34.03)
- 18.30 (5.17, 43.87)
- 30.70 (28.70, 35.23)
- 31.50 (25.50, 39.23)

(a\(^+\) denotes agent non-platinum agents, e.g. Bev)
Docetaxel Plus Ramucirumab for *EGFR*-mutation Positive NSCLC

**REVEL**

---

**Lancet 384: 665, 2014**
Docetaxel Plus Ramucirumab for EGFR-mutation Positive NSCLC

Study Design

Primary Population (No prior TKI)
- Platinum combination

Explanatory Population (Prior TKI)
- Platinum combination → TKI
  - TKI → Platinum combination

Randomize 1:1
- A: RAM (10 mg/kg) + DOC (60 mg/m²)
- B: PL + DOC (60 mg/m²)

- Double-blind study
- For the primary population, randomization was stratified by ECOG PS (0 vs. 1), gender (female vs male), and prior maintenance therapy (yes vs no); for the explanatory population, randomization was not stratified
- Enrollment: 16 months; Follow-up: 4 months; Treatment cycle: 21 days

Patient Disposition

- Entered (N = 228)
  - Not enrolled (n = 31)
  - Enrolled (N = 197)
  - Randomized Primary Population (n = 162)

Randomized Exploratory Population (N = 35)

- RAM + DOC (N = 18)
  - Patients treated (n = 18)
    - On treatment (n = 2)
    - Reasons for discontinuation (n = 16)
      - Progressive disease 6
      - Adverse event 10
- PL + DOC (N = 17)
  - Patients treated (n = 17)
    - On treatment (n = 0)
    - Reasons for discontinuation (n = 17)
      - Progressive disease 10
      - Adverse event 6
      - Subject decision 1

DOC, docetaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; PL, placebo; RAM, ramucirumab; TKI, tyrosine kinase inhibitor

Docetaxel Plus Ramucirumab for \textit{EGFR}-mutation Positive NSCLC

\textbf{All patients in REVEL}

<table>
<thead>
<tr>
<th></th>
<th>Median (95% CI)</th>
<th>Censoring rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab plus docetaxel</td>
<td>4.5 months (4.2–5.4)</td>
<td>11.1%</td>
</tr>
<tr>
<td>Placebo plus docetaxel</td>
<td>3.0 months (2.8–3.9)</td>
<td>6.7%</td>
</tr>
<tr>
<td>Ramucirumab vs placebo</td>
<td>Stratified HR 0.76 (95% CI 0.68–0.86); $p&lt;0.0001$</td>
<td></td>
</tr>
</tbody>
</table>

\textbf{EGFR}-mutation positive patients in JVCG

\begin{tabular}{|l|c|c|}
\hline
Variable & \textbf{RAM+DOC} & \textbf{PL+DOC} \\
\hline
Median (95\% CI) PFS & 5.7 months (3.1, 9.9) & 4.4 months (2.9, 9.9) \\
HR (95\% CI)* & 0.68 (0.31, 1.48) & \\
Censored, n (%) & 5 (27.8) & 2 (11.8) \\
\hline
\end{tabular}

*\textit{RAM+DOC vs PL+DOC}  
CI, confidence interval; DOC, docetaxel; HR, hazard ratio; PFS, progression-free survival; PL, placebo; RAM, ramucirumab
Platinum-based Chemotherapy and Pemetrexed or Docetaxel May Prolong Survival of EGFR-mutation Positive NSCLC

Data from NEJ002
Anti-PD-1 Antibody for *EGFR*-mutation Positive NSCLC

**CheckMate057**

**A. Overall Survival**

- Overall Survival (% of patients)
- Months: 0, 3, 6, 9, 12, 15, 18, 21, 24, 27
- Survival rates for Nivolumab and Docetaxel
- Hazard ratio for death: 0.73 (96% CI, 0.59–0.89) P=0.002

**B. Subgroup Analysis**

- **EGFR mutation status**
  - Positive: 82 patients, 1.18 (0.69–2.00)
  - Not detected: 340 patients, 0.66 (0.51–0.86)
  - Not reported: 160 patients, 0.74 (0.51–1.06)

- **KRAS mutation status**
  - Positive: 62 patients, 0.52 (0.29–0.95)
  - Not detected: 123 patients, 0.98 (0.66–1.48)
  - Not reported: 397 patients, 0.74 (0.58–0.94)

**N Engl J Med 373: 1627, 2015**
Anti-PD-1 Antibody for *EGFR*-mutation Positive NSCLC

**KEYNOTE 010**

![Graph showing overall survival and hazard ratio for different treatments](image)

Anti-PD-L1 Antibody for \textit{EGFR}-mutation Positive NSCLC

\textbf{OAK}

\begin{center}
\textbf{OVERALL SURVIVAL, ITT (N = 850)}
\end{center}

\begin{itemize}
  \item [\textbf{HR, 0.73 \textsuperscript{*}}]
  \item [\textit{95% CI, 0.62, 0.87}]
  \item [\textit{P = 0.0003}]
  \item [\textit{Minimum follow up = 19 months}]
\end{itemize}

\begin{itemize}
  \item \textbf{Median 9.6 mo (95\% CI, 8.6, 11.2)}
  \item \textbf{Median 13.8 mo (95\% CI, 11.8, 15.7)}
\end{itemize}

\begin{itemize}
  \item \textbf{Atezolizumab}
  \item \textbf{Docetaxel}
\end{itemize}

\begin{itemize}
  \item \textbf{EGFR mutant} 85 (10\%)
  \item \textbf{EGFR wildtype} 628 (74\%)
\end{itemize}

\begin{itemize}
  \item \textbf{ITT} 850 (100\%)
\end{itemize}

\begin{itemize}
  \item [\textit{In favor of atezolizumab}]
  \item [\textit{Hazard Ratio}] 2
  \item [\textit{In favor of docetaxel}]
\end{itemize}

\*Stratified HR for ITT. Unstratified HR for subgroups. OS, overall survival.
## Anti-PD-1/PD-L1 Antibody for EGFR-mutation Positive NSCLC

<table>
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<tr>
<th>Study</th>
<th>PD-L1 status</th>
<th>Total patients</th>
<th>OS HR for all patients</th>
<th>OS HR for EGFR-mutation positive patients</th>
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<td>CheckMate 057</td>
<td>All</td>
<td>582</td>
<td>0.73 (0.59-0.89)</td>
<td>1.18 (0.69-2.00)</td>
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<tr>
<td>KEYNOTE 010</td>
<td>TPS(\geq)1%</td>
<td>1034</td>
<td>0.67 (0.56-0.80)</td>
<td>0.88 (0.45-1.7)</td>
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<tr>
<td>OAK</td>
<td>All</td>
<td>850</td>
<td>0.73 (0.62-0.87)</td>
<td>1.24</td>
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Possible Treatment Sequence After Progression of 3rd Generation EGFR-TKI

1. **Re-biopsy**
   - Liquid biopsy

2. **Exon 20 T790M mutation +**
   - Osimertinib [III, A]

3. **Platinum-based doublets with/without bevacizumab**

4. **Exon 20 T790M mutation -**
   - Platinum-based chemotherapy

5. **Platinum-based chemotherapy with/without ramucirumab**

6. **Immune checkpoint inhibitors**
   - Nivolumab, pembrolizumab, atezolizumab
# Resistance Mechanism of 3rd Generation EGFR-TKIs

<table>
<thead>
<tr>
<th>Change of target</th>
<th>EGFR mutation</th>
<th>EGFR loss/amplification</th>
<th>Alternative signal</th>
<th>Downstream</th>
<th>Morphological change</th>
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<tr>
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<td>C797S (all)</td>
<td>L718Q, L844V (Rocil, WZ(^2))</td>
<td>T790M loss (Osim)</td>
<td>HER2 amplification (Osim(^6))</td>
<td>EMT (Rosi(\bar{\text{l}})(^5))</td>
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<td>EGFR amplification (Rosi(\bar{\text{l}})(^1))</td>
<td>MET amplification (Osim(^6, 7))</td>
<td>SCLC (Rosi(\bar{\text{l}})(^1))</td>
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<td>IGF1R activation (WZ(^8))</td>
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<td></td>
<td>1/15(^6)</td>
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</table>


Osim: osimertinib, Rocil: rociletinib, WZ: WZ4002
High MET amplification level as a resistance mechanism to osimertinib (AZD9291) in a patient that symptomatically responded to crizotinib treatment post-osimertinib progression

Sai-Hong Ignatius Ou\textsuperscript{a,\textdagger}, Nikita Agarwal\textsuperscript{b}, Siraj M. Ali\textsuperscript{b}

\textsuperscript{a} Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA 92868, USA
\textsuperscript{b} Foundation Medicine, Inc., Cambridge, MA 02141, USA

73-year never-smoker Asian female
Stage IV adenocarcinoma
Exon 19 del

Erlotinib 14months
CBDCA+PEM x 2
CBDCA+GEM x 2
Afatinib 10 months
↓
Osimertinib

High level of MET amplification of 30 copies was observed after osimertinib.

Fig. 2. CT scan of the lung mass post-osimertinib and pre-crizotinib and post-crizotinib.
A rational approach to the design of two compound series derived from 1 and 2, supported by computer-aided drug design.

Kinase inhibitory activities (single point) of the most potent new compounds in a triple-mutant EGFR enzyme assay.
Overcoming EGFR(T790M) and EGFR(C797S) resistance with mutant-selective allosteric inhibitors

Yong Jia, Cai-Hong Yun, Eunyoung Park, Dalia Ercan, Mari Manuia, Jose Juarez, Chunxiao Xu, Kevin Rhee, Ting Chen, Haikuo Zhang, Sangeetha Palakurthi, Jaebong Jang, Gerald Lelais, Michael DiDomato, Badry Bursulaia, Pierre-Yves Michelys, Robert Epple, Thomas H. Marsillje, Matthew McNeill, Wenshao Lu, Jennifer Harris, Steven Bender, Kwok-Kin Wong, Pasi A. Jänne & Michael J. Eck

Overcoming EGFR(T790M) and EGFR(C797S) resistance with mutant-selective allosteric inhibitors

Yong Jia1, Cai-Hong Yun2,a, Eunyoung Park2,b, Dalia Ercan4, Mari Manuia3, Jose Juarez3, Chunxiao Xu4, Kevin Rheee1, Ting Chen2, Haikuo Zhang2, Sangeetha Palakurthi2, Jaebong Jang1,c, Gerald Lalais1, Michael DiDonato1, Badry Bursulaya1, Pierre-Yves Michelys1, Robert Eppe1, Thomas H. Marsilje2, Matthew McNeill2, Wenshao Lu1, Jennifer Harris1, Steven Bender1, Kwok-Kin Wong1,2, Pasie A. Jänne1,2,3 & Michael J. Eck2,3
Conclusions

- 3rd generation EGFR-TKI is a standard treatment for T790M EGFR-mutation positive NSCLC.

- Platinum-based chemotherapy should be used after progression of 3rd generation EGFR-TKI.

- Docetaxel with/without ramucirumab and immune check point inhibitors are also treatment options.

- Development of C797S is most common mechanism of 3rd generation EGFR-TKI resistance.

- New agents overcome C797S resistant mutation are under the development.