**11-011**

**Preliminary results of: Observational study of treatment of epidermal growth factor receptor activating mutation positive (EGFRm+) advanced or recurrent non-small-cell lung cancer (NSCLC), after radiological progression to the first-line therapy with EGFR tyrosine kinase inhibitors (EGFR-TKI).**

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**Background**

- Although NSCLC with activating EGFR mutation is generally sensitive to EGFR-TKI, such as gefitinib or erlotinib, it eventually gets acquired resistance.
- In the prospective trials of first-line EGFR-TKI, the progression-free survival generally ranges in 5-14 months. On the other hand, the overall survival is approximately 3 years, thus the prognosis of those patients is favorable after radiological "PD".
- The clinical course after radiological (RECIST-based) "progressive disease" (PD) judgment is highly variable, and some patients are reported to do well with continuation of TKI beyond PD, or with or without local therapy. Those reports are anecdotal, and based on limited selected patients.
- There is a concern for "disease flares" after discontinuation of EGFR-TKI.

**Study design and purpose**

- Multicentre, cooperative, prospective cohort study.
- To survey actual treatment pattern after PD judgment according to RECIST criteria as well as the clinical course after discontinuation of the treatment in patients with EGFRm+ advanced or recurrent NSCLC who receive first-line therapy with EGFR-tyrosine kinase inhibitor (EGFR-TKI).

**Study endpoints**

- **Primary**
  - Time from RECIST-based radiological PD to clinical PD, in patients who were continuously received EGFR-TKI beyond "RECIST-PO".
- **Secondary**
  - Proportion of patients who continued to receive EGFR-TKI beyond "RECIST-PO", with or without concomitant therapy.
  - Proportion of patients in which "disease flares" developed after discontinuation of treatment with EGFR-TKI.
  - Organ at the time of judgment as RECIST-based PD.
  - Overall duration of treatment with EGFR-TKI.
  - Survival time after discontinuation of EGFR-TKI.
  - Survival time after RECIST-based PD to EGFR-TKI was judged.
  - Survival time after clinical PD to EGFR-TKI was judged.
  - Overall duration of treatment with EGFR-TKI.
  - Reason of discontinuation of EGFR-TKI therapy.
  - Overall survival.

**Definition of specific terms**

- **Clinical PD** (disease progression) – Symptomatic progression
- **Declining of PD** due to progression
- **Threat to major organ(s)** – Unequivocal multi-organ progression
- **Death** – Death or exacerbation of disease which necessitated hospitalization and made it impossible to go on to the next treatment, within 30 days after discontinuation of EGFR-TKI.
- **Worsening after start of the post-therapy is excluded.**
- **Clinical deterioration not related to the exacerbation of NSCLC, such as infection and thrombophlebitis, is also excluded.**

**Study subjects**

- **Inclusion criteria**
  - Advanced or post-operational recurrent non-small-cell lung cancer
  - Diagnosed as having tumor harboring EGFR mutation
  - Histologically verified EGFR gene mutation
  - 
  - (A) Deletion of exon 19 (irrespective of the subtype)
  - (B) Insertion (Exon 20_719ins)
  - (C) Other rare mutations (Exon 18_705ins, etc.)
  - 
  - (A) Exon 19 deletion mutation
  - (B) T790M
  - (C) Treatment with EGFR-TKI (Gefitinib or Erlotinib) was started from January 1, 2009 until December 31, 2013 as the initial anti-cancer therapy
- **Exclusion criteria**
  - Prior treatment with cytotoxic chemotherapy
  - Concomitant malignancy

**Patient accrual status as of Sep.30/2013**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients (n = 450)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TKI agent</td>
<td>Gefitinib/Erlotinib</td>
<td>417/33</td>
</tr>
<tr>
<td>Registration for clinical studies No./No.</td>
<td>24/426</td>
<td>5.3/94.7</td>
</tr>
<tr>
<td>Gender: Male/Female</td>
<td>139/111</td>
<td>30.9/69.1</td>
</tr>
<tr>
<td>Age: 20-49/50-69/PD</td>
<td>157/275/36</td>
<td>34.9/57.1/8.0</td>
</tr>
<tr>
<td>EGFR mutation: Ex19Del/Ex21L858R/Other</td>
<td>223/210/17</td>
<td>49.6/46.7/3.8</td>
</tr>
<tr>
<td>Smoking history: Never/Current/Past</td>
<td>298/34/16/2</td>
<td>66.2/27.5/6.3</td>
</tr>
</tbody>
</table>

**Reasons for discontinuation**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST-PO w/o/w/o Clinical PD</td>
<td>115</td>
</tr>
<tr>
<td>Clinical PD w/o/w/o AE</td>
<td>77</td>
</tr>
<tr>
<td>AE or patient’s pref.</td>
<td>38</td>
</tr>
<tr>
<td>Others</td>
<td>16</td>
</tr>
<tr>
<td>Treatment on-going</td>
<td>38</td>
</tr>
</tbody>
</table>

**Efficacy of EGFR-TKI**

<table>
<thead>
<tr>
<th>Best response</th>
<th>No. of patients (n = 284)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>5</td>
<td>1.8</td>
</tr>
<tr>
<td>PR</td>
<td>182</td>
<td>64.1</td>
</tr>
<tr>
<td>SD</td>
<td>59</td>
<td>20.8</td>
</tr>
<tr>
<td>PD</td>
<td>9</td>
<td>3.2</td>
</tr>
<tr>
<td>NE</td>
<td>22</td>
<td>7.7</td>
</tr>
<tr>
<td>Not reported</td>
<td>7</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**Median time to RECIST-PO (Progression-free survival): 297 days**

**Conclusion**

**Purpose**

- To clarify the living status of patients who discontinued EGFR-TKI beyond PD, with or without concomitant therapy.
- To survey the clinical course after discontinuation of EGFR-TKI.
- To clarify the overall survival after discontinuation of EGFR-TKI.

**Results**

<table>
<thead>
<tr>
<th>Living status</th>
<th>Alive</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>97</td>
<td>161</td>
</tr>
<tr>
<td>Due to NSCLC</td>
<td>148</td>
<td></td>
</tr>
<tr>
<td>Treatment-related death (Intestinal lung disease)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Due to other causes</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>Median overall survival</th>
<th>8080days</th>
</tr>
</thead>
</table>

**EGFR-TKI beyond RECIST-PO**

- **Total No. of patients who received EGFR-TKI “Beyond PD”** (N=246)
  - Median time from RECIST-PO to Clinical PD
  - 96 days
- **Patients with termination of EGFR-TKI** (N=246)
  - EGFR-TKI continued beyond RECIST-PO (without Clinical PD)
  - 32
- **Time from RECIST-PO to Clinical PD**
  - 1-30days 10 31-90days 8 91-120days 14
- **Patients with continued administration of EGFR-TKI** (N=38)
  - Without RECIST-PO 28
  - With RECIST-PO and Clinical PD 1
  - With RECIST-PO, no Clinical PD 9
  - Time from RECIST-PO to Clinical PD 49-573 days

**First post-TRK systemic therapy**

- **No systemic therapy given** 64
- **Deterioration of PS** 33
- **Death** 12
- **Patient refusal** 10
- **Lost to follow-up/other(s)** 11
- **Not reported** 18

**Systemic therapy given** 157

- **Cisplatin-based combination** 64
- **Carboplatin-based combination** 38
- **Single-agent cytotoxic agent** 27
- **Another EGFR-TKI** 45
- **Others/unknown** 3

**Conclusions**

- **Pattern of care for the patients who got radiological PD after first-line EGFR-TKI therapy was surveyed.**
- *Disease flare* rate after discontinuation of EGFR-TKI appears to be lower than previously reported.
- *Some patients showed a prolonged (>90days) administration of EGFR-TKI beyond radiological PD, without clinical deterioration.
- Identification of the patient subgroup who benefit from extended use of EGFR-TKI “Beyond PD” warrants further investigation.