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# 上皮性増殖因子受容体変異陽性（EGFRm+）肺癌に対するチロシンキナーゼ阻害剤での初回治療の観察研究

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Comprehensive Support Project

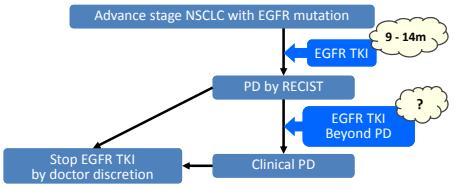
## Background

- 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 9-14 months. On the other hand, the overall survival are 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, with or without local therapy. Those reports are anecdotal, and based only on selected patients.
- There is a concern for “disease flare” 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).

## Treatment outline




## Study endpoints

- **Primary**
  - Time from RECIST-based radiological PD to clinical PD, in patients who were continuously received EGFR-TKI beyond “RECIST-PD”.
- **Secondary**
  - Proportion of patients who continued to receive EGFR-TKI beyond “RECIST- PD”, with or without concomitant therapy.
  - Proportion of patients in which “disease flare” 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 PS due to progression
  - Threat to major organ(s)
  - Unequivocal multi-organ progression
- **Disease flare**
  - Death or exacerbation of disease which necessitated hospitalization and made it impossible to go on to the next treatment, within 1month 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
    - Definition of EGFR gene mutation positive (mutation of sensitive gene)
      - (A) Deletion of Exon19 (irrespective of the subtype)
      - (B) Exon 21 L858R
      - (C) Other rare mutations (Exon 18 G791X, etc.)
    - EGFR gene mutation excluded from this study:
      - (A) Exon 20 insertion mutation
      - (B) T790M
  - Treatment with EGFR-TKI (Gefitinib or Erlotinib) was started from January 1, 2009 until December 31, 2011 as the initial anti-cancer therapy
- **Exclusion criteria**
  - Prior treatment with cytotoxic chemotherapy
  - Concomitant malignancy

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### 発表者・研究責任者の利益相反開示事項

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## Results

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

- Participating Institutions, which registered at least 1 patient: 25 (planned participation: 34)
- Registered patients: 450 (planned registry: 500 - 800)
- Initial CRF received: 284

### Patient characteristics

| Characteristics | No. of patients (n=450) | % |
|---|---|---|
| TKI agent Gefitinib/Erlotinib | 417/33 | 92.7/7.3 |
| Registration for clinical studies Yes/No | 24/426 | 5.3/94.7 |
| Gender Male/Female | 139/311 | 30.9/69.1 |
| Age 20-49/50-69/70- | 157/257/36 | 34.9/57.1/8.0 |
| ECOG PS 0/1/2/3-4/unknown | 150/190/67/42/1 | 33.3/42.2/14.9/9.3/0.2 |
| EGFR mutation Ex19Del/Ex21 L858R/Other | 223/210/17 | 49.6/46.7/3.8 |
| Smoking history Never/Current/Past/unknown | 298/34/116/2 | 66.2/7.6/25.8/0.4 |

### EGFR-TKI beyond RECIST-PD

| | |
|---|---|
| **Total No. of patients who received EGFR-TKI “beyond PD”** | **41** |
| Median time from RECIST-PD to Clinical PD | 96 days |
| **Patients with termination of EGFR-TKI** | **(N=246)** |
| EGFR-TKI continued beyond RECIST-PD (without Clinical PD) | 32 |
| Time from RECIST-PD to Clinical PD | 7-403 days |
| 1-30days | 10 |
| 31-90days | 8 |
| 91-days | 14 |
| **Patients with continued administration of EGFR-TKI** | **(N=38)** |
| Without RECIST-PD | 28 |
| With RECIST-PD and Clinical PD | 1 |
| With RECIST-PD, no Clinical PD | 9 |
| Time from RECIST-PD to Clinical PD | 49-573 days |

### Reasons for discontinuation

| Reason | Total |
|---|---|
| RECIST-PD w/ or w/o Clinical PD | 115 |
| Clinical PD w/ or w/o AE | 77 |
| AE or patient’s pref. | 38 |
| Others | 16 |
| Treatment on-going | 38 |

### Efficacy of EGFR-TKI

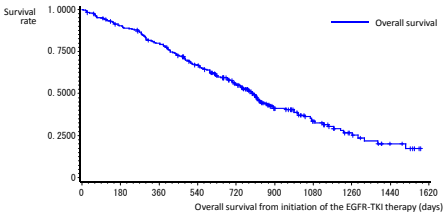
| Best response | No. of patients (n = 284) | % |
|---|---|---|
| CR | 5 | 1.8 |
| PR | 182 | 64.1 |
| SD | 59 | 20.8 |
| PD | 9 | 3.2 |
| NE | 22 | 7.7 |
| Not reported | 7 | 2.5 |

**Median time to RECIST-PD (Progression-free survival): 297 days**
**Disease flare after discontinuation: 6 (2.4%)**

### Living status

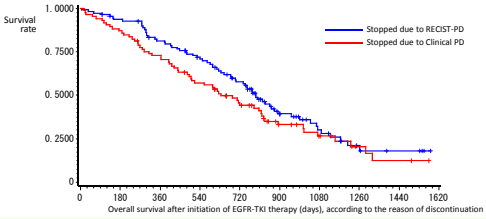
| | |
|---|---|
| Alive | 97 |
| Dead | 161 |
| Due to NSCLC | 148 |
| Treatment-related death (interstitial lung disease) | 2 |
| Due to other causes | 3 |
| Lost to follow-up | 24 |
| Not reported | 2 |
| **Median overall survival** | **800days** |

### Overall survival




### Overall survival according to the reason of TKI discontinuation

| Reason for Discontinuation | No. of patients | Median survival (days) |
|---|---|---|
| RECIST-PD | 110 | 794 |
| Clinical PD* (*including those on TKI, with RECIST-PD) | 85 | 636 |




### First post-TKI systemic therapy

| No systemic therapy given | 84 |
|---|---|
| Deterioration of PS | 33 |
| Death | 12 |
| Patient refusal | 10 |
| Lost to follow-up/ others | 11 |
| Not reported | 18 |

| Systemic therapy given | 157 |
|---|---|
| Cisplatin-based combination | 44 |
| 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 received prolonged (>90days) administration of EGFR-TKI beyond radiological PD, without clinical deterioration.
- Identification of the patient subgroup who benefit from extended use od EGFR-TKI “beyond PD” warrants further investigation.