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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Comprehensive Support Project

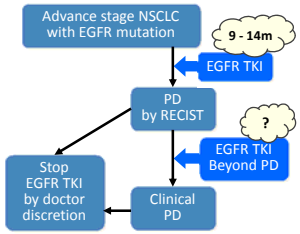
Background

- 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

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

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

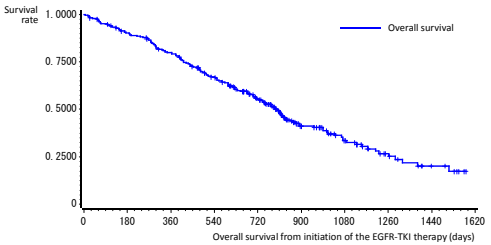
Best response	No. of patients (n = 284)	%
CR	5	1.8
PR	182	64.1
SD	59	20.8
PD	9	3.2
NE	22	7.7
Not reported	7	2.5

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

Living status

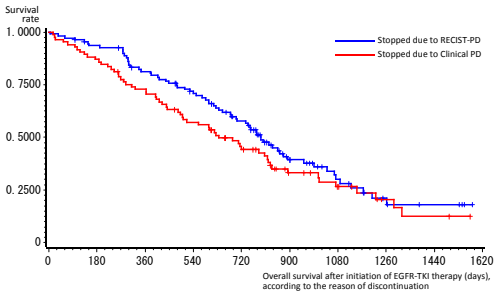
Alive	97
Dead	161
Due to NSCLC	148
Treatment-related death (interstitial lung disease)	2
Due to other causes	3
Lost to follow-up	24
Not reported	2
Median overall survival	**800days**

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



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

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.

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