1290-P

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

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Comprehensive Support Project

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Background

- Although NSCLC with activating EGFR mutation is generally sensitive to EGFR-TKI, such as gefitinib or erlotinib, acquired resistance is eventually seen.
- In the prospective trials of first-line EGFR-TKI, the progression-free survival generally ranges from 9-14 months. On the other hand, the overall survival 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

- Multicenter 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 continuously received an 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 judging it 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**
  - Survival time after clinical PD to EGFR-TKI
  - Reason for discontinuation of EGFR-TKI therapy.
  - **Overall survival.**

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

Definition of specific terms

- **Clinical PD (disease progression)**
  - Symptomatic progression
  - Decline 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.
  - Exacerbation after the start of the post-therapy is excluded.
  - Clinical deterioration not related to the exacerbation of NSCLC, such as infection and thrombophlebitis, is also excluded.

Results

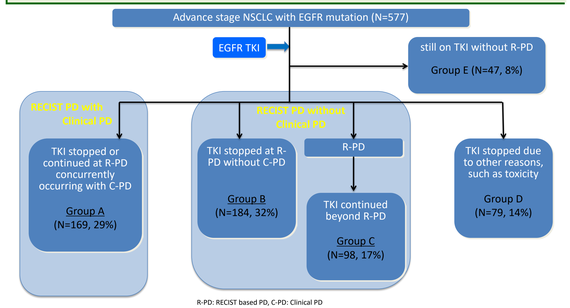
Patient accrual status as of Sep.9/2014

- Participating Institutions, which registered at least 1 patient: 31
- Registered patients: 580
- Initial CRF received: 577

Patient characteristics

Characteristics	No. of patients (n = 580)	%
TKI agent Gefitinib/Erlotinib	531/49	91.6/8.4
Registration for clinical studies Yes/No	31/549	5.3/94.7
Gender Male/Female	178/402	30.7/69.3
Age median(min-max)	69(27-93)	
ECOG PS 0/1/2/3-4/unknown	191/246/84/56/3	32.9/42.4/14.5/9.7/0.5
EGFR mutation Ex19Del/Ex21 L858R/Other	282/274/24	48.6/47.2/4.2
Smoking history Never/Current/Past/unknown	384/42/152/2	66.2/7.2/26.2/0.4

Treatment outline



34.8% (98/282) of the patients without clinical deterioration at R-PD were continued on TKI

Response Ratio

	No. of patients (n = 577)	%
CR/PR/SD/PD/NE	11/386/113/33/34	2/67/20/6/6

Time from RECIST-based radiological PD to clinical PD

Group	No. of patients	Median time from R-PD to C-PD (range)
Group C	98	150 (37-799) days
More than 6 months	40 patients	40.8%
More than 1 year	15 patients	15.3%

Progression free survival

	Median survival (days)	95%CI (days)
RECIST PD free survival	299	268-322
Clinical PD free survival	483	428-554

The cases that were discontinued without PD, were censored cases

Post-TKI systemic therapy

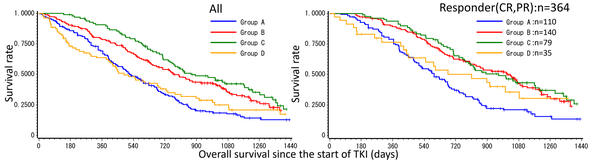
	No. of Patients
No systemic therapy given	**149**
Deterioration of PS	93
Death	36
Patient refusal	20
Not determined	**77**
Lost to follow-up/ others	32
Not reported	45
Systemic therapy given	**351**

Re-administration of EGFR-TKI in later line n=530

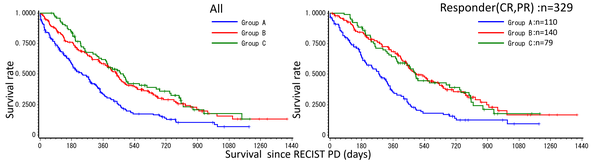
Group	No. of patients	%	Median re-administration period (days; range)
Group A	78	46.2%	104 (1-524)
Group B	89	48.4%	74 (1-1344)
Group C	34	34.7%	43 (6-1013)
Group D	35	44.3%	154 (1-1039)

Survival of each group

Group	No. of patients	Median survival from the start of EGFR-TKI (days; range)
Group A	169	509 (5-1987+)
Group B	184	704 (32-1935+)
Group C	98	813 (140-1989+)
Group D	79	440 (20-1710)



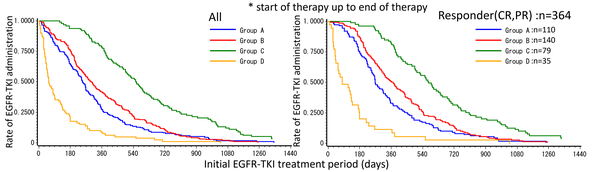
Group	No. of patients	Median survival from RECIST PD (days; range)
Group A	169	196 (1-1921+)
Group B	184	372 (5-1600+)
Group C	98	390 (63-1901+)



Initial* EGFR-TKI treatment period of each group

Group	No. of patients	Median days (Range)
Group A	169	249 (3-1550)
Group B	184	298 (7-1536)
Group C	98	555 (119-1661)
Group D	79	56 (2-1038)

* start of therapy up to end of therapy



Conclusions

- Pattern of care for the patients who got radiological PD after first-line EGFR-TKI therapy was surveyed.
- About one-third of the patients without clinical deterioration at R-PD were continued on TKI.
  Median time to clinical deterioration (Clinical PD) or discontinuation of TKI was 150 days.
  40% of them continued to receive TKI and were clinically stable for 6 months or more after radiological PD.
- Among clinically stable patients with R-PD, survival of those with continued TKI was no worse than that with its discontinuation.
- Re-administration of EGFR-TKI were carried out in 45% of the cases.

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