8071 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

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.**

(We present the data in bold)

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.

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

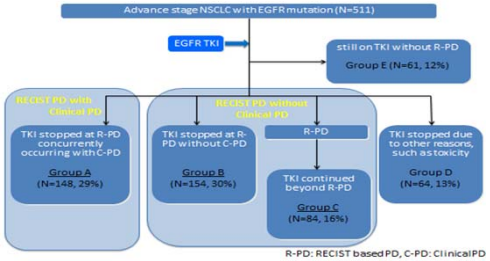
Patient accrual status as of Mar.31/2014

- Participating Institutions, which registered at least 1 patient : 31
- Registered patients : 579
- Initial CRF received : 511

Patient characteristics

Characteristics	No. of patients (n = 579)	%
TKI agent Gefitinib/Erlotinib	530/49	91.5/8.5
Registration for clinical studies Yes/No	31/548	5.4/94.6
Gender Male/Female	178/401	30.7/69.3
Age median(min-max)	69(27-93)	
ECOG PS 0/1/2/3-4/unknown	190/246/85/55/3	32.8/42.5/14.7/9.5/0.5
EGFR mutation Ex19Del/Ex21 L858R/Other	283/275/21	48.9/47.5/3.6
Smoking history Never/Current/Past/unknown	383/152/42/2	66.1/26.3/7.3/0.3

Treatment outline



35% (84/238) of the patients without clinical deterioration at R-PD were continued on TKI

Time from RECIST-based radiological PD to clinical PD

Group	No. of patients	Median time from R-PD to C-PD (range)
Group C	84	162 (37-1479) days

More than 6 months	33 patients	39.3%
More than 1 year	16 patients	19.0%

Progression free survival

	Median survival (days)	95%CI (days)
RECIST PD free survival	264	244-295
Clinical PD free survival	461	384-523

The cases that were discontinued without PD, were censored cases

Post-TKI systemic therapy

	No. of Patients
No systemic therapy given	**120**
Deterioration of PS	71
Death	28
Patient refusal	21
Not determined	**23**
Lost to follow-up/ others	9
Not reported	14
Systemic therapy given	**294**

Disease flare after discontinuation : 6 (1.3%)
Median time from the stopping initial TKI therapy to the start of 2nd line therapy (days) : 11.5 (0-645)

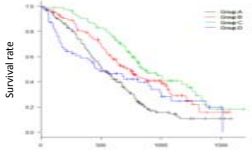
Re-administration of EGFR-TKI in later line

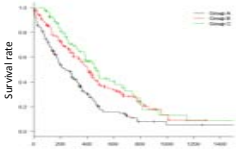
Group	No. of patients	%	Median re-administration period (days; range)
Group A	51	34.5%	77 (2-348)
Group B	53	34.4%	77.5 (8-385)
Group C	21	25.0%	77.5 (6-1013)
Group D	19	29.7%	77 (7-1039)

N.S.

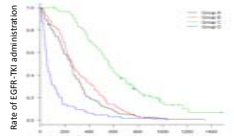
Survival of each group

Group	No. of patients	Median survival from the start of EGFR-TKI (months; 95%CI)
Group A	148	16.7 (14.4-19.6)
Group B	154	24.4 (19.7-28.8)
Group C	84	28.6 (24.6-40.1)
Group D	64	15.9 (8.4-24.3)





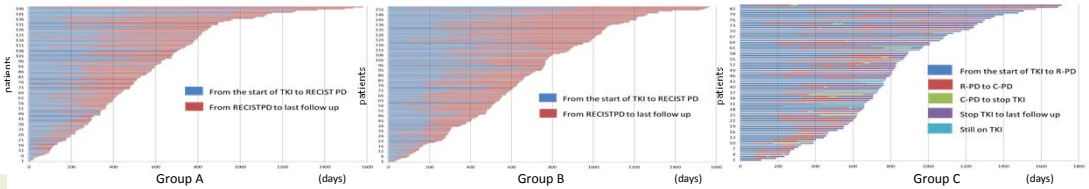
Initial* EGFR-TKI treatment period of each group



* start of therapy up to end of therapy

Group	Median days (95%CI)
Group A	247 (205-268)
Group B	264 (224-307)
Group C	557 (496-644)
Group D	55 (44-82)

Clinical course of each group



Conclusions

- Pattern of care for the patients who got radiological PD after first-line EGFR-TKI therapy was surveyed.
- About 35% 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 162 days. About 40% of them received TKI therapy and were clinically stable for 6 months or more after radiological PD.
- "Disease flare" rate after discontinuation of EGFR-TKI appears to be lower than previously reported.
- The prognosis of the patients who received initial EGFR-TKI treatment until clinical progression (Group C) were numerically better in this population.
- Re-administration of EGFR-TKI were carried out in one third of case.

Acknowledgement

This study was conducted by Comprehensive Support Project For Oncology Research(CSPOR) of Public Health Research Foundation. The study fund was provided to CSPOR with Support from an investigator Sponsored Study Programme of AstraZeneca.
We would like to thank patients, their families, and following institutions;
Hokkaido University Hospital, KKR Sapporo Medical Center, Iwate Prefectural Central Hospital, Tohoku University Hospital, Ibaraki Prefectural Central Hospital, Tochigi Cancer Center, Gunma Prefectural Cancer Center, Nishigunma National Hospital, Saitama Cancer Center, The Cancer Institute Hospital Of JFCR, Japanese Red Cross Medical Center,T oranomon Hospital, Teikyo University School of Medicine, Tokyo Teishin Hospital, Kitasato University Hospital, Kanagawa Cardiovascular and Respiratory Center, Fujisawa City Hospital, Shinshu University Hospital, Nagoya University Graduate School Of Medicine, Hiroshima Prefectural Hospital, Kurume University School of Medicine, Nagasaki University Hospital, Tosei General Hospital, Hamamatsu University School of Medicine, Kanazawa University Hospital, Graduate School of Medicine and Faculty of Medicine Kyoto University, NTT Medical Center Tokyo, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, National Cancer Center Hospital East, University of Tokyo Hospital, Mitsui Memorial Hospital