ABSTRACT

PROTOCOL NO.: NIS-OTW-XXX-2013/1 ACTIVE INGREDIENT: Not applicable.
SPONSOR: AstraZeneca

TITLE	A Retrospective, Non-interventional Study to Evaluate EGFR-Tyrosine Kinase Inhibitor Retreatment in Patients with Locally Advanced or Metastatic EGFR Mutated NSCLC who Previously Treated with EGFR TKI as First-line Therapy and Chemotherapy as Second-line Therapy – SEQUENCE study
DEVELOPMENT PHASE	Phase IV
STUDY PERIOD	Date of first enrollment: Dec-13-2013 Date of last completed: Aug-22-2014
OBJECTIVES	**Primary objective** To describe the treatment duration of EGFR TKI re-administration in patients who had ever received EGFR TKI and subsequently followed by chemotherapy. **Secondary objectives** ▪ Describe the progression-free survival (PFS), response rate (RR) and disease control rate (DCR) in different sequences of treatment: (1) initial and re-administration of EGFR-TKI therapy, (2) first time chemotherapy ever used (second-line treatment) after initial EGFR-TKI treatment. ▪ Record treatment duration in the initial EGFR-TKI therapy and first time chemotherapy. ▪ Record the reason(s) for treatment change for initial and re-administration of EGFR-TKI therapy and first time chemotherapy (second-line treatment). ▪ Explore relationships between efficacy of EGFR-TKI initial and re-administration and patient characteristics (including demographics, histology, disease stage, sites of metastasis, ECOG PS) or EGFR TKI treatment characteristics (including EGFR

mutation pattern, response to initial EGFR TKI or not, length of duration between first and second EGFR-TKI treatment).

- Explore overall survival (OS), plasma CEA level and chemotherapy regimens ever used between first time chemotherapy and EGFR-TKI re-administration (including the types and number of chemotherapy regimens, and treatment duration) for those patients who have the above data available.
- If the images are available, conduct image peer review to evaluate tumour size retrospectively in different sequences of treatment: (1) initial and re-administration of EGFR-TKI therapy, (2) first time chemotherapy ever used (second-line treatment) after initial EGFR-TKI treatment. Peer review time point includes baseline, best response and progression of last image while stopping treatment at each treatment mentioned above.
- Evaluate the reason(s) for the treatment change for initial and re-administration of EGFR-TKI therapy and first time chemotherapy (second-line treatment) after peer review and compare the difference of reason(s) for the treatment change between initial evaluation and after peer review.

METHODOLOGY	Retrospective, non-interventional, multicenter, observational chart review study
NUMBER OF PATIENTS	Approximately 200 subjects were planned to be enrolled. Eventually, 218 subjects were enrolled and analyzed.
INVESTIGATIONAL PRODUCT	Not applicable
REFERENCE THERAPY	None.

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DURATION OF TREATMENT	Not applicable for this observational chart review study.
ELIGIBILITY CRITERIA	**Inclusion Criteria** 1. Patients diagnosed with locally advanced or metastatic adenocarcinoma or positive result of thyroid transcription factor 1 (TTF1) NSCLC 2. Positive EGFR mutation result with at least one sensitizing mutation, such as exon 19 deletions or exon 21 point mutation. 3. Female or male aged ≧20 years 4. Patients treated with EGFR-TKI and subsequently treated with chemotherapy before re-administration of EGFR-TKI **Exclusion Criteria** 1. Patients with EGFR mutation status of positive exon 20 T790M mutation only. 2. Patients who were confirmed of squamous type NSCLC
ENDPOINTS	**Primary Endpoint:** The treatment duration of EGFR-TKI re-administration **Secondary Endpoints:** 1. The PFS, OS, RR and DCR of (1) initial and re-administration of EGFR-TKI therapy, (2) first time chemotherapy ever used (second-line treatment) after initial EGFR-TKI treatment. 2. The correlation between clinical efficacy of EGFR TKI retreatment and demographics or treatment characteristics. 3. OS and plasma CEA level as exploratory objectives. 4. Re-evaluation of tumor size retrospectively.

STATISTICAL METHODS

For analyses of demographic variables and clinical response, summary statistics including the number of subjects and percentage for each of the categorical variables.

For continuous variables, summary statistics including the number of observations, means, standard deviations, median, minimum, and maximum values.

For the primary endpoint, the median duration of re-administration of EGFR-TKI was summarized by days or months, if applicable. The range of this treatment duration was also presented. All analyses were performed on all eligible patients in this study. The outcome related to survival (such as PFS, OS) was presented with median values and associated 95% CIs by Kaplan-Meier curve. The outcome about response rate, the proportion of RR and DCR were estimated by all evaluable patients. The 95% exact confidence interval was constructed around the rates.

To explore the relationship between demographics or EGFR-TKI information and time to event (PFS, OS) data, Cox regression model were performed to analyse the correlation. The logistic regression model was used for evaluating the correlation between these factors and disease control rate, if applicable.

RESULTS

Demographic and baseline characteristics

A total of 218 patients were assessable for study analysis, with more females included (females vs. males: 65.1% vs. 34.9%). The mean age was 64.8 ± 12.1 years. Most patients were in NSCLC stage of IV (89.4%), stage T4 for primary tumor,

Regarding the TNM staging, more than half of patients

(52.1%) were in T4 stage. Around 80% of patients had regional lymph node metastasis, with 36.4% of patients in N3 stage and 35.5% of patients in N2 stage. Up to 89.4% of patients had tumor cells spreading to distant organs (M1).

The medication was different among the initial and re-administered EGFR-TKI. Most patients (92.7%) received Gefitnib and only 6.4% of patients received Erlotinib in the first-line EGFR-TKI treatment. Up to 92.4% of patients received Erlotinib, while only 4.8% of patients received Gefitnib in the EGFR-TKI retreatment.

Primary Endpoint

The duration of EGFR-TKI re-administration was approximately 3 months, with 105.4 ± 95.5 days on average (range: 7 days to 573 days).

Secondary Endpoints

- The mean duration from initial EGFR-TKI treatment to the second-line chemotherapy was 426.4 ± 201.4 days, ranging from 68 days to 1109 days.
- The median OS from the first-line EGFR-TKI therapy to the third-line EGFR-TKI re-administration was 1096 days. The median OS after the start of EGFR-TKI re-administration was 377 days.
- The median PFS from initial EGFR-TKI to EGFR-TKI re-administration was over 1169 days; after the start of EGFR-TKI re-administration was 426 days.
- The disease control rate (DCR) was 93.6% for the first-line EGFR-TKI treatment, 67.2% for the second-line chemotherapy, and 55.8% for the third-line EGFR-TKI re-administration.

- The response rate (RR) in the first-line EGFR-TKI treatment was 51.0% (CR: 0.5%, PR: 50.5%), in the second-line chemotherapy was 15.0% (CR: 0.0%, PR: 15.0%), and in the third-line EGFR-TKI retreatment was 6.2% (CR: 0.0%, PR: 6.2%).

- In the initial EGFR-TKI administration, 65.3% of patients showed best response for PR, and 24.2% for SD. In the second-line chemotherapy, 38.0% of patients showed best response for SD, and 17.1% for PR. In the EGFR-TKI re-administration, 34.2% of patients showed best response for SD, and 11.6% for PR.

- Analysis of responses in ECOG cohorts demonstrated statistical significance at P=0.0114 during the EGFR-TKI retreatment. The response rate was higher in the ECOG 0 cohort (40.0%) (ECOG 1: 9.1%, ECOG 2: 0.0%).

- In the multivariate predictor analysis for evaluating the duration of EGFR-TKI re-administration (≤ 180 days) in multiple parameters, the statistical significance was only detected in the comparison of first EGFR_TKI treatment duration (≤ 1 vs. >1 year, P=0.01) with odds ratio of 7.986, suggesting that long-term first-line EGFR-TKI treatment (more than 1 year) seemed to be associated with a reduced EGFR-TKI retreatment duration.

- CEA levels were apparently elevated in the second-line chemotherapy (mean change: 22.2 ± 171.3 ng/ml), as compared with the first- and third-line EGFR-TKI treatment (mean change: 7.0 ± 155.1 ng/ml and 5.7 ± 45.2 ng/ml, respectively).

- The first EGFR-TKI administration showed the largest reduction in tumor size by -25.5 ± 21.9 mm from

baseline to best response and by -15.6 ± 21.1 mm from baseline to stop treatment, as compared with the second-line chemotherapy (from best response to stop treatment: + 6.8 ± 13.5 mm) and EGFR-TKI re-administration (from baseline to best response: + 0.5 ± 18.4 mm, from baseline to stop treatment: + 9.5 ± 25.3 mm).