Background: This study was designed to analyze the efficacy of gefitinib as a second-line therapy, according to the clinical characteristics in Korean patients with non-small-cell lung cancer (NSCLC).

Methods: In this Phase IV observational study, we recruited patients, previously failed first-line chemotherapy, who had locally advanced or metastatic NSCLC, and who were found to be either epidermal growth factor receptor (EGFR) mutation-positive or satisfied 2 or more of the 3 characteristics: adenocarcinoma, female, and non-smoker. These patients were administered with gefitinib 250 mg/day, orally. The primary endpoints were to evaluate the objective response rate (ORR) and to determine the relationship of ORRs, depending on each patient’s characteristics of modified intent-to-treat population.

Results: A total of 138 patients participated in this study. One subject achieved complete response, and 42 subjects achieved partial response (ORR, 31.2%). The subgroup analysis demonstrated that the ORR was significantly higher in patients with EGFR mutation-positive, compared to that of EGFR mutation-negative (45.8% vs. 14.0%, p=0.0004). In a secondary efficacy variable, the median progression-free survival (PFS) was 5.7 months (95% confidence interval, 3.9~8.4 months) and the 6-month PFS and overall survival were 49.6% and 87.9%, respectively. The most common reported adverse events were rash (34.4%), diarrhea (26.6%), pruritus (17.5%), and cough (15.6%).

Conclusion: Gefitinib was observed in anti-tumor activity with favorable tolerability profile as a second-line therapy in these selected patients. When looking at EGFR mutation status, EGFR mutation-positive showed strong association with gefitinib by greater response and prolonged PFS, compared with that of EGFR mutation-negative.

Key Words: Gefitinib; Receptor, Epidermal Growth Factor; Mutation; Carcinoma, Non-Small-Cell Lung; Disease-Free Survival
normal activation of epidermal growth factor receptor (EGFR) signaling is implicated in the growth of many solid tumors including NSCLC.

Gefitinib is a potent and selective inhibitor of the EGFR tyrosine kinase, thus it hinders mitogenic and anti-apoptotic signals such as cell hyperplasia, growth metastasis, neovascularization, which work in the course of cancer progress. Gefitinib has shown anti-tumor activity in various solid tumors, most notable in NSCLC.

In patients with NSCLC, the characteristics of adenocarcinoma, female, non-smoking, and Asian ethnicity have all been shown to increase the response of gefitinib. As molecular predictive markers of outcome with gefitinib have been investigated, activating mutations of the EGFR have been shown to have a significant association with response to gefitinib.

In a retrospective study, the patients who had received gefitinib with advanced NSCLC in Korea were participated. The result of the objective response rate (ORR) was 64.7% (11/17 patients) with EGFR mutation-positive and 13.7% (10/73 patients) with EGFR mutation-negative.

Recently, the Phase III IRESSA Pan Asia Study (IPASS) compared gefitinib with carboplatin/paclitaxel as first-line treatment to non/light exsmokers who had lung adenocarcinoma in East Asia. In the study, progression-free survival (PFS) demonstrated significant and longer response in EGFR mutation-positive subgroup among the gefitinib group, and EGFR mutation-negative subgroup among the carboplatin/paclitaxel group.

The Phase III IRESSA NSCLC Trial Evaluating Response and Survival against Taxotere (INTEREST) study has shown overall survival (OS) rate between gefitinib and docetaxel. The result was observed to be non-inferior with the patients who were unselect, previously treated with local advanced or metastatic NSCLC.

Compared to above studies, this Phase IV, multicenter, non-randomized, open-label observational study (Second-Line IRESSA Phase IV observational study in NSCLC patient [SELINe]; NCT00608868) was conducted to analyze the efficacy of gefitinib as a second-line therapy according to the clinical characteristics in selected Korean patients with advanced NSCLC.

Materials and Methods

The study was approved by each Institutional Review Board (IRB) before initiation and was conducted in accordance with International Conference on Harmonisation (ICH) guidelines and applicable regulations. All patients signed written informed consent forms prior to participation of this study.

1. Eligibility criteria

This study recruited advanced or metastatic NSCLC patients with histologic or cytologic-confirmed in Korea. Patients, who had progressive or recurrent disease with 19 to 80 years old following first-line chemotherapy, and who had either a positive EGFR mutation result or met 2 or more of the 3 characteristics: adenocarcinoma, female, and non-smoker, were participated in this study. Patients were also required to have a measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, a World Health Organization (WHO) performance status 0~1, and a life expectancy of at least 12 weeks.

Exclusion criteria included patients with any evidence of clinically active interstitial lung disease, malignancies, severe/uncontrolled systemic disease, treatment with a non-approved or investigational drug within 30 days prior to the study treatment, and those who have history of EGFR inhibitor treatment.

2. Screening and study procedure

Before the start of treatment, all patients underwent the screening procedure, which included a physical examination, medical history, vital signs, WHO performance status, laboratory parameters, tumor assessment (RECIST), Quality of Life (QoL) assessment (by Functional Assessment of Cancer Therapy-Lung [FACT-L] Korean version 4), and EGFR mutation analysis. Determination of EGFR mutation was performed at a central laboratory (Isu Abxis Co., Ltd., 6th Yonsei University Medical Center, Seoul, Korea) or at 2 local laboratories (Konkuk...