Clinical Study Report Drug Substance: IRESSA(Gefitinib) Study Code: D7913L00056 Edition Number: 1 Date: 02 December 2008	**SYNOPSIS**	

An open-label, multi-centre study to evaluate efficacy and safety of Gefitinib as the first-line treatment for locally advanced (IIIB), metastatic (IV) or recurrent pulmonary adenocarcinoma patients with EGFR mutation.

Publications

None at the time of writing this report.

Study Dates		**Phase of development**
First patient enrolled	**13 March 2006**	**Therapeutic exploratory (II)**
Last patient enrolled	**2 May 2007**	
Date of data cut-off	**31 December 2007**	

Objectives

The primary objective of this study was to evaluate the overall objective tumour response rate (ORR) of Gefitinib.

Secondary objectives were:

To evaluate progression free survival of Gefitinib

To evaluate overall survival of Gefitinib

To describe Gefitinib in terms of safety profile

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Study design

This was an open-label, multi-centre, single arm and phase II study. 147 patients were screened for EGFR mutation and 46 patients were enrolled in this study.

Target patient population

The target population was locally advanced (IIIB), metastatic (IV) or recurrent pulmonary adenocarcinoma patients with EGFR mutation

Investigational product: dosage, mode of administration and batch numbers

The investigational product was gefitinib(Iressa^{TM}) 250mg tablet once oral daily dose(one 250mg tablet per dose). Gefitinib was supplied by AstraZeneca. The Formulation (batch) numbers for the tablets used in this study were POE03294-021L01, 007L02, 009L01, 010L01, 012L02, 013L01 and 015L04.

Duration of treatment

Patients received gefitinib until clinical or objective progression, unacceptable toxicity or patient refusal (whichever is sooner). After discontinuation, the patients were treated according to clinical practice at the discretion of the investigator. Data Cut-off date was 31th Dec 2007. After data cut-off date, patients could continue to receive gefitinib if they were delivering clinical benefit.

Primary outcome variable

Objective response rate (ORR) based on RECIST criteria

Secondary outcome variables:

Progression free survival

Overall survival

Safety profile (type, frequency and severity of adverse events; laboratory parameters and vital signs) according to NCI CTCAE version 3.0

Exploratory outcome variables:

Biomarkers – as below and/or other related analyses to be determined in the future

- Somatic mutations (non-inheritable) analyses of genes in the ErbB family, in the EGFR signalling pathway, or other genes for receptors thought to be influenced by gefitinib in tumour cells

- EGFR signalling pathway markers

Subject to additional patient consent, optional germline genetic factors (polymorphisms of pre-specified inheritable genes)

Statistical methods

All the efficacy analyses were performed using the intent-to-treat (ITT) population which included all patients who received Gefitinib.

Primary endpoint, overall objective tumour response rate (ORR) was estimated by population proportion test and 95% confidence interval was reported supportively. For secondary endpoints, median of overall survival was calculated by Kaplan-Meier Product Limit, and effect of significant factors which affected secondary endpoints (survival, etc.) was analyzed using Cox proportional Hazard model.

For the safety analysis, all adverse events were listed with detail explanation by system organ, and frequencies of adverse events related and not related to the study drug were listed by system organ. For the incidence of adverse events and the percentage of the patients who experienced at least one adverse event, 90% confidence interval was calculated, and the adverse events related to the study drug were analyzed in a same way compared with existing study drug data by cases.

For the laboratory data, continuous data like hematologic and chemistry laboratory results were analysed by paired t test or wilcoxon signed rank sum test for difference between baseline data and the final data. Categorical data was analyzed by GEE method. And statistically significant variables among two laboratory results and urinalysis were divided into normal and abnormal and analysed by GEE method considering effect by each center.

Subject population

In total, 147 patients were consented and received screening tests in 7 centres. Out of 147 patients, 46 patients were EGFR mutation positive and treated with Gefitinib, and 101 patients were EGFR mutation negative and not treated. Among 46 enrolled and treated patients, 21 patients (45.65%) discontinued treatment by data-cut off, leaving 25 patients (54.35%) continuing treatment.

The mean age of 46 patients in the ITT population was 60.57±12.70 and there were 11 males (23.91%) and 35 females (76.09%). For the performance status at the baseline, the most frequently reported status was ‘1’, reported in 32 patients (69.57%), followed by ‘0’ (11 patients (23.91%)), ‘Not done’ (2 patients (4.35%)) and ‘2’ (1 patient (2.17%)). Regarding smoking history, there were 37 patients (80.43%) who never smoked, 8 patients (17.39%) who were ex-smoker, and 1 patient (2.17%) who was a regular smoker.

For disease stage at screening, 6 patients (13.04%) were ‘IIIB’ and 40 patients (86.96%) were ‘IV’. For metastatic sites, the frequently observed sites were lung (18 patients (39.13%)), bone (16 patients (34.78%)), and other (11 patients (23.91%)). Out of 46 patients in ITT population,

12 patients (26.09%) had 'not-related NSCLC' surgical history, and 6 patients (13.04%) had 'related NSCLC' surgical history. 3 patients (6.52%) have taken an adjuvant therapy as a previous anticancer treatment. The number of major protocol deviations was low (4 patients (8.7%)), suggesting that the study was conducted to high quality.

Summary of efficacy results

The analyses were based on a data cut-off date of 31 December 2007. The results are as follows:

Objective Response Rate was 52.17% (24 out of 46, 95% CI: [37.74, 66.61]). P value is shown to be 0.1640. Also, 95% confidence interval for population proportion lies between 37.74% and 66.61% which including 45%.

Disease Control Rate (DCR) was 84.78% (39 out of 46, 95% CI: [74.40, 95.16]).

Progression free survival calculated using Kaplan-Meier Product Limit was shown to be below 50% at the end of follow-up period, so the median was not able to calculate. However, PFS rates were 86.25% (95% CI: [71.91, 93.58]) at 4 months and 74.59% (95% CI: [58.81, 85.05]) at 6 months.

Overall survival calculated using Kaplan-Meier Product Limit was shown to be below 50% at the end of follow-up period, so the median was not able to calculate. However, OS rates were 95.50% (95% CI: [83.19, 98.86]) at 6 months and 82.26% (95% CI: [63.31, 92.00]) at 12 months.

For the result of Cox proportional hazard model which covariates were sex, age, performance status at baseline and smoking status, there was no statistically significant factor which affects PFS or OS.

Summary of safety results

The mean treatment exposure was 264.61±128.72 days, and the median was 254 days. The duration of treatment in months was calculated by dividing total days by 30.4 (=365/12).

The AEs experienced patients were 44 patients (95.65%, 90% exact CI: [90.71, 100]) out of 46 patients in EFS population. Among these, 43 patients (93.48%) experienced treatment-related AEs (ADR). Regarding the ADR, 'Rash' (33 subjects (71.74%, 37 events)) was the highest, followed by 'Pruritus' (22 subjects (47.83%, 26 events)), 'Anorexia' (17 subjects (36.96%, 19 events)), 'Diarrhoea' (13 subjects(28.26%, 18 events)) 'Skin exfoliation' (11 subjects (23.91%), 13 events) and 'Nausea' (10 subjects (21.74%), 10 events).

The number of patients who had experienced grade 3 or 4 AEs was 6 (13.04%) and 3 patients (6.52%) experienced grade 3 or 4 ADRs. The ADRs of grade 3 were 'Rash' and 'Pruritus' (1

subjects 2 events)) and ‘Anorexia’ (1 subjects (2.17%, 1 events)). ALT/AST increased (1 subjects 2 events)). No grade 4 AEs was reported.

In addition, 4 patients (8.70%, 90% exact CI: [1.86, 15.53]) experienced serious adverse events and 1 patient (2.17%) died due to SAE with ‘Pneumonia’, but none of these SAEs were considered to be related to the study drug.

Two patients (4.35%) discontinued treatment due to AE. Among them, 1 patient (2.17%) discontinued due to ADR with AST/ALT increasing, and 1 patient (2.17%) discontinued due to SAE with Pneumonia.

Regarding the clinical laboratory results, no new safety concerns were identified. No clinically relevant changes in vital signs and physical findings were evident.

Date of the report

02 December 2008