Clinical Study Report Synopsis	
Drug Substance	Gefitinib
Study Code	D7913L00067
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A Phase IV, multicenter, non-randomized, open-labeled study to evaluate the efficacy of gefitinib (IRESSA®) as a second-line therapy in NSCLC patients

Study dates: First subject enrolled: 17 Jan 2007
Last patient enrolled: 02 Jul 2008
Cut off: 02 Jan 2009

Phase of development: Phase IV

Study centre(s)

Yeungnam University Medical Center and other 10 trial sites.

Publications

13th World Conference on Lung Cancer, San Francisco, CA, USA, Jul 31–Aug 4, 2009

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate ORR (Objective Response Rate) of gefitinib as a second-line therapy for Non-Small-Cell Lung Cancer (NSCLC) patients based on the Response Evaluation Criteria in Solid Tumors Group (RECIST) and to assess ORR difference according to Epidermal Growth Factor Receptor (EGFR) mutation, gender, smoking history, and type of tumor.	The proportion of subjects indicating PR (partial response) or CR (complete response) among the best overall response.	Efficacy
Secondary	**Secondary**	
To evaluate the following about gefitinib in NSCLC patients		
1) PFS (Progression-Free Survival)	1) PFS (Progression-Free Survival)	Efficacy
2) Assessment of symptom improvement and QoL(Quality of Life) by FACT-L(the Functional Assessment of Cancer Therapy-Lung)	2) Symptom improvement by FACT-L and QoL based on FACT-L	Efficacy
3) Overall Survival (OS)	3) Overall Survival	Efficacy
4) Safety	4) Adverse event	Safety

Study design

A multicenter, non-randomized, open-label study to evaluate the efficacy of gefitinib (IRESSA®) as a second-line therapy in patients who have failed in the first cancer chemotherapy on NSCLC.

Target subject population and sample size

Subjects were male or female who were at least 19 years old and younger than 80 years old, and pathologically diagnosed as locally advanced/metastatic NSCLC who had failed in the first-line chemotherapy, and who had the WHO Performance Status of 0 to 2.

The subjects were able to provide tumour sample for EGFR mutation testing Was this mandatory? As we do not have testing for all patients it will be good to make this point clear. . And the subjects who had positive EGFR results or satisfy more than two condition of adenocarcinoma, female or non smoker were eligible.

The sample size calculation in this study was done to evaluate ORR (Objective Response Rate) of gefitinib as a second-line therapy for NSCLC patients based on the RECIST (Response Evaluation Criteria in Solid Tumors Group) criteria. The appropriate sample size was attained by assuming 21.5% of ORR as a second-line therapy in the targeted NSCLC patients who treated gefitinib.

21.5% of response rate was established based on the result of Expanded Access Program. For a two sided test at a 5% of significance level , a planned sample size of 197 evaluable subjects were required to ensure 80% power and total 219 subjects were planned to recruit considering withdrawal rate 10%. However, 156 subjects were enrolled due to the difficulty in recruitment even though the recruitment period was extended 6 months.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

1) Test Article(s):

Gefitinib tablet 250mg

2) Dosage and Administration:

Gefitinib 250mg/day was administered orally according to investigator's prescription.

Duration of treatment

This section tells about the follow-up and procedures done at the follow-up. It does not tell the duration of treatment. Suggestion: either change the title, or give the relevant information.

Subject visited every 4 weeks for follow-up, physical examination, vital signs, WHO performance status, laboratory test, adverse events, concomitant medication, chest X-ray, drug compliance until disease progression was confirmed. Tumor assessment and FACT-L were assessed every 8 weeks during treatment period.

After disease progression was confirmed, only survival was assessed every 12 weeks.

Statistical methods

All subjects who had received at least one dose of the investigational product and had at least one safety follow up was considered as an EFS (Evaluable for Safety) set and the subjects who have received at least one dose of the investigational product among all registered subjects and had at least one tumour assessment were included in the ITT (Intent-to-treat) set. Among the ITT set, the subjects who was considered serious protocol violation which may affect the efficacy evaluation or the subjects whose efficacy evaluation was not obtained were excluded from PP population.

1) Efficacy analysis:

Primary efficacy endpoint ORR was the proportion of subjects showing PR (partial response) or CR (complete response) as best response until final tumor assessment. Additional subanalysis was done based on the subgroup of EGFR mutation, gender, smoking history, and type of tumor using chi-square test.

Median of PFS was presented and comparison between different subgroups was performed by using the Kaplan-Meier method. Multivariate analysis by the Cox regression model was carried out.

The proportion of subjects whose symptoms improved was calculated by obtaining each score change from baseline. The QoL improvement rate defined as change of ≥6 points in overall FACT-L from baseline and that the rate of patients who regarded as showing symptom improvement the change of points ≥2 in lung cancer subscale (LCS) of FACT-L..

Each descriptive statistical value was presented for QoL using FACT-L.

2) Safety analysis:

Safety analysis was performed based on the safety set, and safety data were new AEs arisen after the administration of study medication and the results of laboratory test implemented at each visit.

AE coding complied with MedDRA(version 12.0) and was reported and categorized by severity of symptoms based on NCI CTC(version 3.0). The number of cases that occurred and occurrence rate were calculated and presented. Also, the occurrence rate of AEs was calculated in accordance with their relationship to the study medication and severity of the event.

Subject population

From January 2007 to July 2008, 156 subjects were enrolled from 11 centers in Korea. Among them, 154 subjects were included in the EFS population (two subjects who did not receive study treatment were excluded from the EFS population) and 138 subjects were included in ITT population (eight subjects who had no target lesion at baseline and eight subjects who had no tumor assessment after baseline were excluded from the ITT population) (data cut-off January 2009).Total 121 subjects were considered as PP population.

Subject demographics are summarised in Table S2. The overall mean age of the 138 subjects in the ITT was 64 years and over half of the subjects were <65 years (52.5%). Among the 138 subjects, female were 87.0 % (120/138 subjects) and male 13.0 % (18/138 subjects) and all of the study subjects were Asians. For the tumour type, the most subjects had Adenocarcinoma (87.7 %, 121/138 subjects). 9.4 % (13/138 subjects) were Squamous carcinoma, 2.2% (3/138 subjects) were Non small cell carcinoma, and 0.7 % (1/138 subjects) was Adenosquamous carcinoma. Regarding the EGFR mutation status of subjects, 42.8 % (59/138 subjects) were positive, 36.2 % (50/138 subjects) were negative and 21.0% (29/138) were NA.

Table S2 Subject demographics and disease characteristics at baseline (ITT population)

Characteristic	Gefitinib (n=138)		Characteristic	Gefitinib (n=138)	
Gender,	n	(%)	Tumor histology,	n	(%)
Male	18	(13.0)	Adenocarcinoma	121	(87.7)
Female	120	(87.0)	Squamous carcinoma	13	(9.4)

Age	n	(%)	Other	4	(2.9)
≥65 years,	66	(47.8)			
Median, years	64				
WHO PS	,n	(%)	Smoking history,	n	(%)
0	50	(36.2)	Never-smoker	117	(84.8)
1	73	(52.9)	Ex-smoker	17	(12.3)
2	15	(10.9)	Regular smoker	4	(2.9)
Disease stage at screening	,n	(%)	EGFR mutation status,	n	(%)
I	1	(0.7)	Positive	59	(42.8)
IIIA	4	(2.9)	Negative	50	(36.2)
IIIB	20	(14.5)	Unknown	29	(21.0)
IV	113	(81.9)			

Summary of efficacy results

In the ITT set, a total of 138 patients have had tumour evaluation. One subject had a complete response, and 42 subjects experienced a partial response, giving an ORR of 31.2% (95% CI 23.6, 39.6). %). In the PP set, a total of 121 patients were evaluated and ORR was 34.7 % (42/121 patients, 95 % CI 26.3 %~43.9%). Respectively 53 subjects (38.4%) and 52 subjects (43%) were achieved stable disease.

Subgroup analysis was only performed in the ITT set. The ORR was significantly higher in subjects whose tumors were EGFR mutation-positive compared with subjects whose tumors were EGFR mutation-negative (45.8% versus 14.0%, p=0.0004 [Chi squares test]).

There were no statistically significant differences in ORR between male versus female (33.3% versus 30.8%, p=0.8309 [Chi-squares test]), between never-smokers versus ever-smokers (31.6% versus 28.6%, p=0.7809 [Chi-squares test]), and between adenocarcinoma versus other histology subtypes (33.1% versus 17.6%, p=0.1989 [Chi-squares test]). However, the small numbers of males, ever-smokers and subjects with non-adenocarcinoma histology limits the inferences that can be drawn from these comparisons.

Median PFS was 5.7 months (95% CI 3.9, 8.4) for the overall study population. EGFR mutation-positive status was associated with longer PFS than EGFR mutation-negative status (p=0.0009 [log-rank test] for difference in PFS, with medians of 9.3 versus 2.2 months).

Median OS was not reached at data cut-off. There was no significant difference in OS by EGFR mutation status.

As for the results of QoL, the rate of improvement with the change of points ≥ 6 in overall FACT-L score was 43.6% (41/94 patients) in ITT and 45.1% (41/91 patients) in PP set. Overall LCS improvement rate was changed with points ≥ 2 in 51.6% (49/95 patients) in ITT and 53.3% (49/92 patients) in PP set.

Summary of safety results

In total, serious adverse events (SAEs) were reported by 25 subjects (16.2%) and were considered treatment-related in 5 subjects (3.2%). Discontinuation due to AEs occurred in

15 subjects (9.7%) and 5 of these were considered treatment-related (3.2%). SAEs leading to death occurred in 10 subjects (6.5%) and were considered treatment-related in 2 subjects (1.3%; both due to interstitial lung disease).

The most common reported AEs by MedDRA, in order of decreasing frequency, were rash (34.4%), diarrhea (26.6%), Pruritus (17.5%), and cough (15.6%). These events are consistent with the known toxicity profile of gefitinib from previously conducted studies, and were mostly CTC grade 1 (mild) of 2 (moderate).