Drug product:	IRESSA	**SYNOPSIS**	
Drug substance(s):	Gefitinib		
Study code:	V-15-32 (D791AL00001)		
Edition No.:	1		
Date:	15 January 2008		

A multicentre, randomised, open-label, parallel-group, Phase III post-marketing clinical study to compare the overall survival between gefitinib and docetaxel in patients with advanced or metastatic (Stage IIIB/IV), or recurrent non-small cell lung cancer, who have failed one or two chemotherapy regimens

Study centre(s)

This study was conducted at 50 centres in Japan

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First subject enrolled	19 September 2003	Post-marketing clinical study (III)
Last subject completed	31 October 2006 (data cut-off date)	

Objectives

The primary objective of this study was to compare the overall survival between gefitinib and docetaxel and to show the non-inferiority of gefitinib to docetaxel in the overall survival in patients with advanced or metastatic (Stage IIIB/IV), or recurrent non-small cell lung cancer (NSCLC), who had failed one or two chemotherapy regimens (at least one having contained platinum).

Secondary objectives of this study were:

- To compare progression-free survival between gefitinib and docetaxel

- To compare time to treatment failure between gefitinib and docetaxel
- To compare changes in disease-related symptoms between gefitinib and docetaxel based on the assessment of lung-cancer subscale (LCS)
- To compare changes in quality of life between gefitinib and docetaxel based on the assessment of the QOL questionnaire (FACT-L)
- To compare response rate (CR + PR)/disease control rate (CR + PR + SD [≥12 weeks] between gefitinib and docetaxel by evaluating objective tumour response based on the RECIST guidelines
- To compare the overall safety between gefitinib and docetaxel based on the frequency and severity of adverse events (AEs)

Exploratory objective of this study was:

- To investigate the correlation of the expression of biomarkers in tumour tissue, pleural effusion, cytological samples, and serum, whenever obtainable with the response to gefitinib or docetaxel and to determine a set of biomarkers that are predictive of the response to gefitinib therapy in non-small cell lung cancer patients (The results on biomarkers are presented in Appendix 12.1.13.)

Study design

This was a multicentre, randomised, open-label, parallel-group, Phase III, post-marketing clinical study to compare overall survival between gefitinib and docetaxel in Japanese patients with advanced or metastatic (Stage IIIB/IV) or recurrent NSCLC who had failed one or two chemotherapy regimens (at least one having contained platinum).

Target subject population and sample size

The target population was Japanese patients with advanced or metastatic (Stage IIIB/IV), or recurrent NSCLC, who had failed one or two chemotherapy regimens (at least one having contained platinum).

A total of 296 deaths were needed for 90% power to show non-inferiority with a one-sided 2.5% significance level under the assumption that the median survival time is 12 months for docetaxel and 14 months for gefitinib. In a planned recruitment period of 12 months (at a constant rate) and with a minimum follow-up period of 12 months, a total of 484 patients (242 patients per group) were required.

More recent data from post market experience in Japan, the SIGN study (Study D791AC00009), and the high level of switching to subsequent anticancer therapies in this study suggested that, in truth, gefitinib and docetaxel have similar overall survival. If that is the case then the power of the study to demonstrate non-inferiority is less than 50%.

Investigational product : dosage, mode of administration and batch numbers

Gefitinib (IRESSA® Tablets 250) 250 mg in oral tablet form.

Docetaxel (TAXOTERE® Injection) 60 mg/m^2 every 3 weeks, intravenously over 1 hour once a day.

Duration of treatment

Subjects continued their assigned treatment until disease progression, intolerable toxicity, subject's will or discontinuation from the study for any other reason.

Criteria for evaluation (main variables)

Efficacy

- Primary outcome variable:
  - Overall survival
- Secondary outcome variables:
  - Progression-free survival (PFS)
  - Time to treatment failure (TTF)
  - Objective tumour response (CR + PR) and the disease control rate (CR + PR + SD [≥12 weeks]) based on the RECIST guidelines

Safety

- Secondary outcome variables:
  - Frequency and severity of AEs

Patient reported outcomes (PROs)

- Secondary outcome variables:
  - Lung cancer subscale (LCS)
  - QOL according to FACT-L questionnaire (Trial Outcome Index [TOI], FACT-L total score)

Biomarker

- Exploratory outcome variables:

- Biomarkers related to expression, activation and dimerisation of EGFR and other ErbB family receptors and associated pathways including downstream signalling pathways

- Biomarkers related to somatic (non-inheritable) mutation analyses of genes of the ErbB family, their signalling pathways and associated pathways which are thought to be influenced by gefitinib in tumour cells
(Biomarkers evaluated were EGFR gene copy number, EGFR mutation and EGFR expression. The results on biomarkers are presented in Appendix 12.1.13.)

Statistical methods

The primary analysis population for the overall survival was the Intention-to treat (ITT) population. The overall survival was also assessed in the Per-Protocol (PP) population to assess the sensitivity of the conclusion to the choice of the analysis set.

The primary analysis of overall survival estimated the gefitinib: docetaxel hazard ratio and associated 95.24% two-sided confidence interval (CI, CI adjusted for the interim analysis) and p-value from a Cox proportional hazards model without covariate adjustment in the ITT population. Non-inferiority was to be concluded if the upper limit of this CI was less than 1.25. Robustness of the primary conclusion was assessed by comparison with results in the PP population and via supportive Cox regression analyses with covariate adjustment for sex (male versus female), histology (adenocarcinoma versus other), performance status (0 or 1 versus 2), smoking history (ever versus never), prior chemotherapy regimens (1 versus 2), age at randomisation (<65 versus ≥65 years), time from diagnosis to randomisation (<6 versus 6 to 12 versus >12 months), and best response to prior chemotherapy (CR/PR versus SD versus PD/NE/unknown).

Several subgroup analyses based on the covariates included in the Cox regression analyses were pre-planned. In order to claim a significant survival benefit in a subgroup, the following had to be achieved as pre-defined in the analysis plan:

- $p<0.05$ for the individual treatment by covariate interaction test, to assess if the subgroups are behaving differently to each other and therefore if it is reasonable to consider the treatment comparison within the subgroup itself, and then

- $p<0.05$ for the comparison of gefitinib versus docetaxel within the subgroup itself

The primary analysis population for secondary outcome variables was the evaluable-for-response population. The hazard ratio (gefitinib/docetaxel) for progression-free survival and time to treatment failure was calculated together with its associated 95% confidence interval using the proportional hazard model without covariates. The difference in response rate and disease control rate between gefitinib and docetaxel was calculated together with its associated 95% confidence interval. The Newcombe-Wilson score method without continuity

correction was used to calculate the confidence interval. A logistic regression model including covariates was used to explore factors that might affect the response rate.

The primary focus for assessment of QOL was on the LCS, trial outcome index (TOI) and FACT-L total scores. The analyses of LCS were performed in the analysis set of evaluable-for-LCS. Analyses of other scores were performed in the evaluable-for-QOL analysis set.

Adverse events were summarised by System Organ Class and preferred term, using MedDRA 9.1 Vital sign and clinical laboratory data were summarised using descriptive statistics.

Patient population

A total of 490 patients with an advanced or metastatic, or recurrent pre-treated NSCLC were randomised to treatment (245 patients to gefitinib and 245 patients to docetaxel). One randomised patient was excluded from the ITT analysis set due to GCP violation. The patient population was representative of an advanced pre-treated NSCLC population suitable for chemotherapy in a clinical trial setting in Japan, with good WHO performance status (PS) (approximately 96% of patients showed WHO PS 0 or 1). The number of patients with major protocol deviations was low (30 patients [6.1%]) with no imbalance across the treatment groups. Only 7 patients were excluded from the PP population due to major deviation. The treatment groups were generally well balanced at baseline with respect to demography and disease characteristics, except for some small imbalance in smoking status (Table S 1).

Table S 1 Patient population (ITT population) and disposition

Characteristic		Number (%) of patients			
		Gefitinib 250 mg (N=245)		Docetaxel 60 mg/m2 (N=244)	
Demography					
Sex	Male	151	(61.6)	151	(61.9)
	Female	94	(38.4)	93	(38.1)
Age (years) [mean (SD)]		62.7	(9.6)	63.5	(9.0)
WHO performance status	0	85	(34.7)	93	(38.1)
	1	149	(60.8)	141	(57.8)
Smoking history	Never-smoker	71	(29.0)	87	(35.7)
	Ex-smoker	159	(64.9)	134	(54.9)
	Regular smoker	14	(5.7)	23	(9.4)
Disease characteristics					
Histology	Adenocarcinoma	192	(78.4)	188	(77.0)
	Squamous carcinoma	37	(15.1)	41	(16.8)
Time from diagnosis to randomisation	<6 months	70	(28.6)	60	(24.6)
	6 to 12 months	99	(40.4)	96	(39.3)
	>12 months	76	(31.0)	87	(35.7)

Table S 1 Patient population (ITT population) and disposition

Characteristic		Number (%) of patients			
		Gefitinib 250 mg (N=245)		Docetaxel 60 mg/m2 (N=244)	
Stage at diagnosis	IIIB	47	(19.2)	50	(20.5)
	IV	159	(64.9)	150	(61.5)
	Recurrence	39	(15.9)	44	(18.0)
Prior cancer therapy					
Previous chemotherapy	One regimen	212	(86.5)	201	(82.4)
	Two regimen	33	(13.5)	42	(17.2)
	Three regimen	0	(0.0)	1	(0.4)
Best response to any previous chemotherapy	CR/PR	113	(46.1)	106	(43.4)
	SD	91	(37.1)	101	(41.4)
	PD/NE/unknown	41	(16.7)	37	(15.2)

CR Complete response
NE Not evaluable
PD Progressive disease
PR Partial response
SD Stable disease
WHO World Health Organization

Efficacy

(a) Primary outcome variable: overall survival

The analyses of overall survival are based on a data cut-off of 31 October 2006, by which time 306 deaths had accrued, median follow-up was 10.7 months, and total mortality was 62.6%.

Statistical non-inferiority of gefitinib relative to docetaxel in terms of overall survival was not achieved according to the protocol-specified criterion (confidence interval includes non-inferiority limit of 1.25). However, no evidence of a statistical difference in overall survival between treatments was apparent (p=0.330).

Both gefitinib and docetaxel showed good signs of efficacy in this study (gefitinib 250 mg median survival 11.5 months versus docetaxel 60 mg/m^2 median survival 14.0 months).

A supportive Cox regression analysis, accounting for pre-defined prognostic factors, narrowly missed the pre-defined non-inferiority margin, suggesting a small imbalance in demography may be having some impact on the primary unadjusted overall survival result. The supportive per-protocol analyses, excluding major protocol deviations, showed similar results (Table S 2, Figure S 1).

Differences in post progression treatments complicated the interpretation of the overall survival result. In line with routine clinical practice in Japan for this population, a large proportion of patients received additional anti-cancer therapy following discontinuation of randomised study treatment. 59.6% of gefitinib patients and 73.8% of docetaxel patients received additional therapy that differed to their randomised treatment. Specifically, 35.5% of gefitinib patients switched to docetaxel, and 53.3% of docetaxel patients switched to gefitinib at some point after discontinuation of randomised treatment.

Table S 2 Summary and analysis of overall survival

	Gefitinib 250 mg (N=245)	**Docetaxel 60 mg/m^2 (N=244)**	**Hazard ratio[a]**	**95.24% CI[b]**	**p-value**
Primary ITT population					
Number (%) who died	156 (63.7)	150 (61.5)			
Primary unadjusted analysis[c]			1.12	0.89 to 1.40	0.330
Supportive adjusted analysis[d]			1.01	0.80 to 1.27	0.914
Median survival (95% CI [months])	11.5 (9.8 to 14.0)	14.0 (11.7 to 16.5)			
One-year survival rate (%)	47.8	53.7			
Supportive PP population					
Primary unadjusted analysis[c]			1.12	0.89 to 1.41	0.310

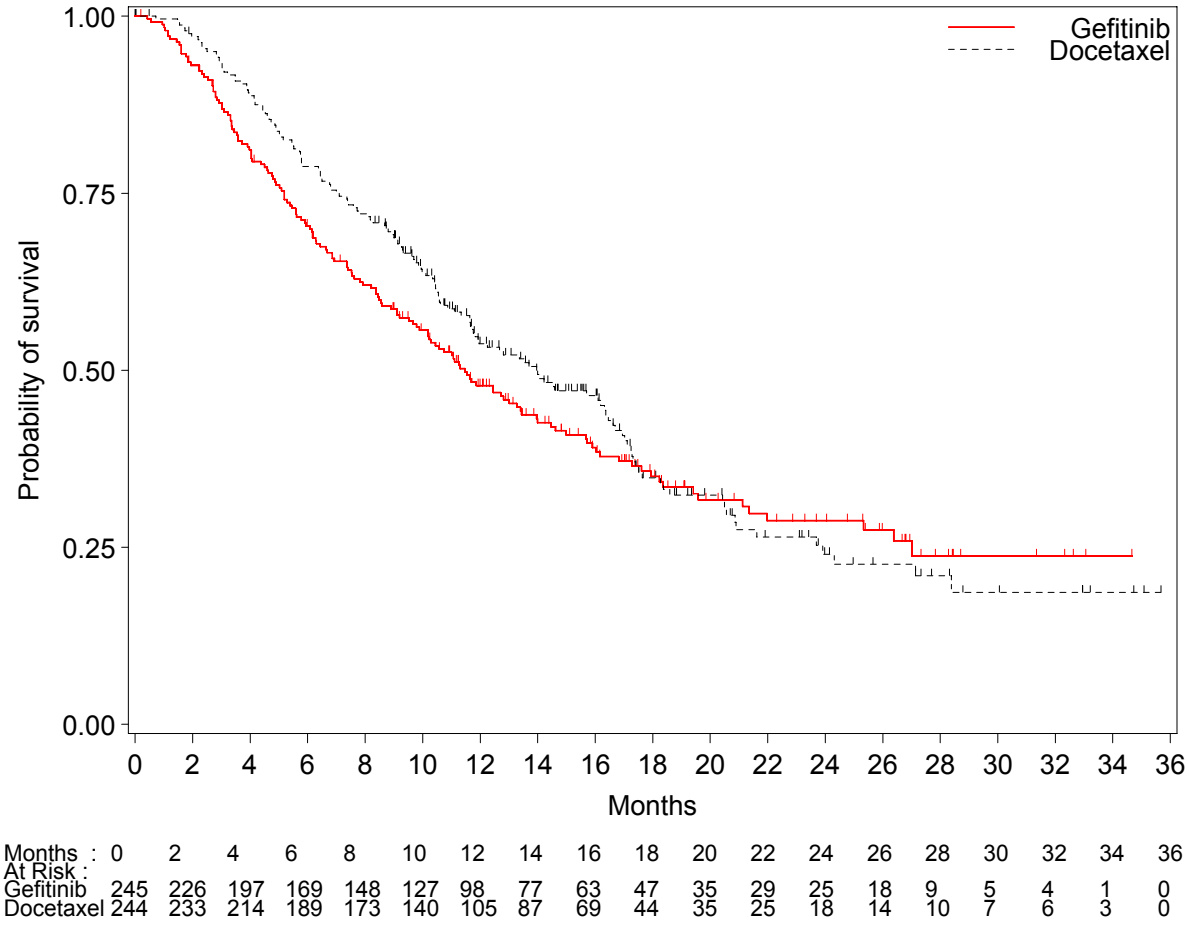
[a] Hazard ratios <1.00 indicate that treatment with gefitinib 250 mg is associated with a longer survival time than docetaxel.

[b] 95.24% confidence interval presented for primary ITT analysis to account for interim analysis. Other confidence intervals are 95%.

[c] From log-rank test.

[d] Cox proportional hazards model included terms for sex (male versus female), histology (adenocarcinoma versus other), performance status (0 or 1 versus 2), smoking history (ever versus never), prior chemotherapy regimens (1 versus 2), age at randomisation (<65 versus ≥65 years), time from diagnosis to randomisation (<6 versus 6 to 12 versus >12 months), and best response to prior chemotherapy (CR/PR versus SD versus PD/NE/unknown).

Figure S 1 Overall survival probability for the ITT population



Months :	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
At Risk :																			
Gefitinib	245	226	197	169	148	127	98	77	63	47	35	29	25	18	9	5	4	1	0
Docetaxel	244	233	214	189	173	140	105	87	69	44	35	25	18	14	10	7	6	3	0

(b) Secondary outcome variables: progression-free survival, time to treatment failure, objective tumour response and disease control rate

For secondary endpoints, that are largely unaffected by subsequent therapy, gefitinib showed similar or superior efficacy compared to docetaxel (Table S 3).

No evidence of a difference between treatments in terms of progression-free survival or disease control rate was evident; gefitinib was similar to docetaxel.

Gefitinib was superior to docetaxel in terms of time to treatment failure ($p<0.001$) and objective response rate ($p=0.009$).

The supportive Cox regression analyses and the ITT analyses of PFS and TTF showed similar results. Furthermore, objective response rate and disease control rate using the Response Evaluation Committee (REC) judgement of response confirmed the primary results for these endpoints based on the investigators' judgement.

Table S 3 Summary of secondary efficacy results: progression-free survival, time to treatment failure, objective response rate and disease control rates: Evaluable for response population

Outcome variable/analysis[a]	Gefitinib 250 mg (N=200)	Docetaxel 60 mg/m^2 (N=187)	HR/OR[b]	95% CI	p-value
Progression-free survival					
Number (%) progressed	180 (90.0)	158 (84.5)			
Median PFS (95% CI [months])	2.0 (1.8 to 2.3)	2.0 (1.9 to 2.8)			
6-month progression-free rate (%)	21.6	20.0			
Primary unadjusted analysis			0.90	0.72 to 1.12	0.335
Supportive adjusted analysis			0.81	0.65 to 1.02	0.077
Time to treatment failure					
Number (%) failed	187 (93.5)	182 (97.3)			
Median TTF (95% CI [months])	1.8 (1.3 to 2.0)	1.4 (1.0 to 1.6)			
6-month time to treatment failure rate (%)	18.5	5.0			
Primary unadjusted analysis			0.63	0.51 to 0.77	<0.001
Supportive adjusted analysis			0.54	0.44 to 0.68	<0.001
Objective response rate					
Number (%) CR+PR					
[Investigator assessment]	45 (22.5)	24 (12.8)			
[REC judgement]	41 (20.8)	20 (10.8)			
Primary adjusted analysis[c]			2.14	1.21 to 3.78	0.009
Supportive unadjusted analysis[c]			1.97	1.15 to 3.39	0.014
Disease control rate[d]					
Number (%) CR+PR+SD>12weeks					
[Investigator assessment]	68 (34.0)	62 (33.2)			
[REC judgement]	58 (29.4)	56 (30.3)			
Primary adjusted analysis[c]			1.08	0.69 to 1.68	0.735
Supportive unadjusted analysis[c]			1.04	0.68 to 1.58	0.860

a Results of secondary ITT analyses were consistent with the primary EFR analyses presented in the table.
b Hazard ratios for PFS and TTF <1.00 indicate treatment with gefitinib 250 mg was associated with a more favourable outcome compared with docetaxel 60 mg/m^2; odds ratios for ORR and disease control rate>1.00 indicate treatment with gefitinib 250 mg was associated with a more favourable outcome compared with docetaxel 60 mg/m^2.
c The analysis were performed by use of the data from the investigator assessment.
d Criterion for SD was SD>12 weeks rather than 8 weeks.
CI Confidence interval

Patient reported outcomes (PROs)

Overall compliance for completion of the FACT-L questionnaire was high in both treatment groups during the first 12 weeks of the study.

No evidence of a difference between gefitinib 250 mg and docetaxel 60 mg/m^2 in terms of disease-related symptoms, as measured by LCS, was evident.

Statistically significant differences in mean change from baseline QOL score over the first 12 weeks of the study, as measured by TOI and total FACT-L, were observed between gefitinib and docetaxel, but the differences were not considered clinically relevant (based on pre-defined criteria of ≥6 points for the evaluation of these endpoints).

Significantly more gefitinib treated patients experienced clinically relevant improvements in quality of life compared to docetaxel (TOI improvement rate 20.5% versus 8.7%, p=0.002, FACT-L improvement rate 23.4% versus 13.9%, p=0.023).

Safety results

The tolerability profiles of gefitinib and docetaxel were consistent with previous experience in Japan.

The majority of patients treated with gefitinib or docetaxel experienced one or more AEs. No clinically relevant differences in the frequencies of patients with serious AEs or AEs leading to discontinuations were observed between gefitinib and docetaxel. Fewer patients with CTC grade 3 or 4 AEs were reported with gefitinib (40.6%) than with docetaxel (81.6%). There were 4 AEs leading to death with gefitinib (3 interstitial lung disease considered by the investigator to be possibly treatment related, the other was pneumonia and not considered to be treatment-related) while no patients died due to AEs with docetaxel (Table S 4).

Table S 4 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events: Evaluable for safety population)

Category[a]	Number (%) of patients	
	Gefitinib 250 mg (N=244)	Docetaxel 60 mg/m^2 (N=239)
Patients with an adverse event (AE)	242 (99.2)	236 (98.7)
Serious AEs	42 (17.2)	34 (14.2)
SAE leading to death	4 (1.6)	0
AE leading to discontinuation	33 (13.5)	42 (17.6)
CTC grade 3 or 4 AEs	99 (40.6)	195 (81.6)
Treatment-related AEs	233 (95.5)	233 (97.5)

[a] Patients with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

N Number of patients

The most commonly reported AEs were rash (67.2%) and diarrhoea (51.6%) for gefitinib group. For docetaxel group the most commonly reported AEs were neutropenia (79.5%), alopecia (59.4%), leukopenia (56.9%), anorexia (49.8%) and fatigue (44.8%).

Fourteen patients (5.7%) treated with gefitinib developed interstitial lung disease (ILD)-type events in comparison to 7 patients (2.9%) on docetaxel.