Drug product:	IRESSA™	**SYNOPSIS**	
Drug substance(s):	Gefitinib		
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Date:	05 September 2007		

A nested case-control study to determine the relative risk of and risk factors for interstitial lung disease in a cohort of NSCLC patients treated with and without gefitinib

Study centre(s)

The patients were recruited from 51 centres (54 medical units) in Japan.

Publications

None at the time of writing this report.

Study dates   **Phase of development**

First subject enrolled   12 November 2003   Therapeutic use (IV)

Last subject completed   22 February 2006

This study was started in November 2003 and was completed in February 2006 with 4473 registrations. During the study period, 155 Interstitial lung Disease (ILD) cases were reported by the treating physicians, and of those 122 cases were confirmed by Case Review board (CRB). The study was completed as the required number of ILD cases had been accumulated to assess the relative risk of ILD development which is the primary objective of this study.

Objectives

Primary objectives:

- to estimate the relative risk of ILD in advanced/recurrent NSCLC patients treated with gefitinib as compared to other chemotherapy treatment, and to assess the risk factors for ILD in advanced/recurrent NSCLC patients undergoing treatment
- to provide an estimate of the incidence of ILD in a group of advanced/recurrent NSCLC patients undergoing treatment

Secondary objective:

A secondary objective of this study was to assess the pharmacokinetic characteristics of gefitinib and the potential association with occurrence of ILD in advanced/recurrent NSCLC patients treated with gefitinib.

Exploratory objectives:

- to identify differences in single nucleotide polymorphisms (SNPs) between patients who have developed ILD and those who have not developed ILD in advanced/recurrent NSCLC patients treated with gefitinib and construct a scoring system for the risk of ILD. For this objective, to identify differences in SNPs between patients who have developed ILD and those who have not developed ILD also in non-gefitinib treated patients and to compare the results with those from gefitinib-treated patients.
- to identify protein expression patterns that may indicate susceptibility to ILD in advanced/recurrent NSCLC patients treated with gefitinib

Study design

This was an observational study in advanced/recurrent NSCLC patients with ILD and randomly extracted patients without ILD from a defined cohort of advanced/recurrent NSCLC patients (hereafter referred to as "a nested case-control study").

Target subject population and sample size

Target subject population:

Patients to be included in the cohort: advanced/recurrent NSCLC patients who have had one or more chemotherapy regimens who were to receive gefitinib or other chemotherapy treatments.

Of those patients, patients treated with gefitinib, as well as all patients who develop ILD (cases) and selected patients who did not develop ILD (controls) were subject to the Good Clinical Practice (GCP) and Good Post-Marketing Surveillance Practice (GPMSP).

Sample size:

Approximately 6000 patients with advanced/recurrent NSCLC (hereinafter "advanced/recurrent NSCLC" were planned to be enrolled in the cohort, among whom 110 to 140 were expected to develop ILD (cases) for inclusion in the case-control study; for each of those cases 4 times that number without ILD (control) were also included in the case-control study.

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

Gefitinib and other chemotherapy regimens used for the treatment of NSCLC, as decided by the investigator(s) and patient. Commonly used dosage and administration in clinical practice (including gefitinib 250 mg tablet given once daily)

Batch number: Not applicable

Duration of treatment

The duration of treatment was not specified. It was to be that considered most appropriate by the investigator(s) for the patient's treatment and well-being.

Follow-up period: Follow-up period was up to 12 weeks after the start of treatment or until the patient meets the discontinuation criteria. If a new anti-cancer treatment regimen started for a patient during the follow-up period or after the end of follow-up period, the patient was allowed to be re-enrolled in the study.

Criteria for evaluation (outcome variables)

       Efficacy: Not applicable

       Patient reported outcomes: Not applicable

       Health economics: Not applicable

       Pharmacokinetic:

       –   Secondary outcome variable:

Exposure (AUC, C_{max}, and C_{min}) estimated for individual advanced/recurrent NSCLC patients treated with gefitinib, using population pharmacokinetic analysis and Bayesian estimation. Plasma concentrations of gefitinib at the occurrence of ILD, if possible.

Pharmacodynamic: Not applicable

Safety:

– Primary outcome variables:
  · Risk factors for ILD
  · Occurrence of ILD

Proteins possibly involved in the occurrence of ILD in gefitinib-treated patients (to be explored by proteomics), and single nucleotide polymorphisms (SNPs) possibly involved in the occurrence of ILD in patients treated with gefitinib or other non-gefitinib treatments were additional exploratory variables. These results will be presented separately to this report.

Statistical methods

Data were analysed with tabular and regression type methods. Standard model-searching strategies used in epidemiological research were used to analyse the risk factors for ILD. An independent Epidemiology Advisory Board (EAB) monitored study design, conduct and analysis.

Estimates of relative risk measured as incidence rate ratios for ILD were obtained by means of odds ratios (OR) with 95% confidence intervals (CI) estimated by logistic regression from the case-control data. Crude (observed) incidence rates and risks were calculated from the cohort data.

Subject population

This nested case-control study is an observational research design using epidemiological methodology where a case-control study is performed within a defined cohort of individuals followed over time (Figure S 1). Patients received the most appropriate treatment regimen for treatment of advanced/recurrent NSCLC and improvement of conditions as judged by the investigator(s).

Advanced/recurrent NSCLC patients who have received at least one chemotherapy regimen and consented to participate in the cohort study at the study sites (51 hospitals) were enrolled. Each patient was enrolled in the cohort and followed-up for up to 12 weeks from the start of the treatment. If a new treatment was started, the patient could be re-registered to the cohort for a new 12-week follow-up period.

The patients who developed ILD in the cohort and provided informed consent to participate in the case-control study were registered as "case"(Figure S 2). For each patient with ILD ("case") , four patients were randomly selected among the patients without ILD in the cohort

("control") (Figure S 2). Detailed data on suspected risk factors for ILD were collected for all provisional cases and controls (Figure S 3).

Figure S 1   Schematic illustration of study groups in the nested case-control study
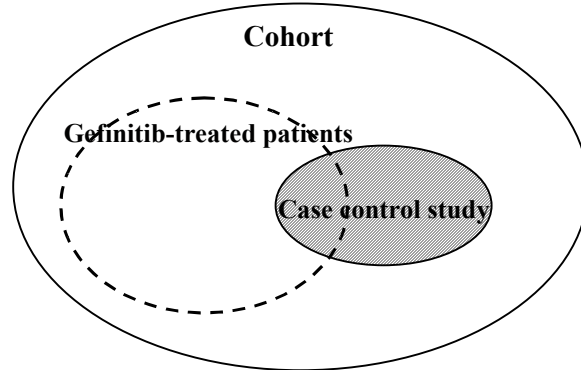

Figure S 2   Sampling of cases and 4 controls per case from the cohort
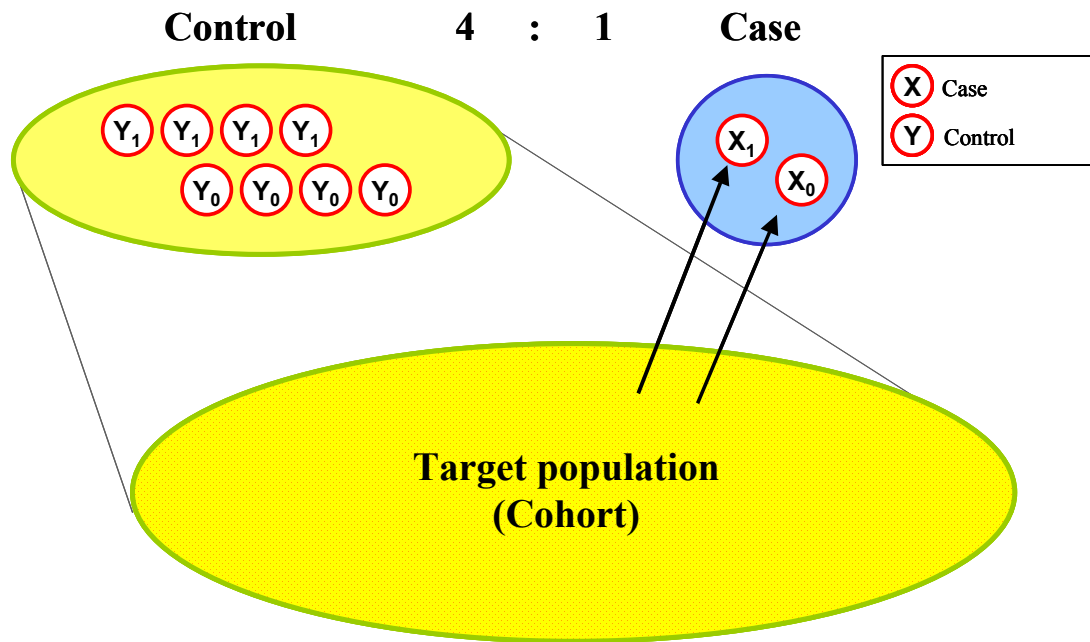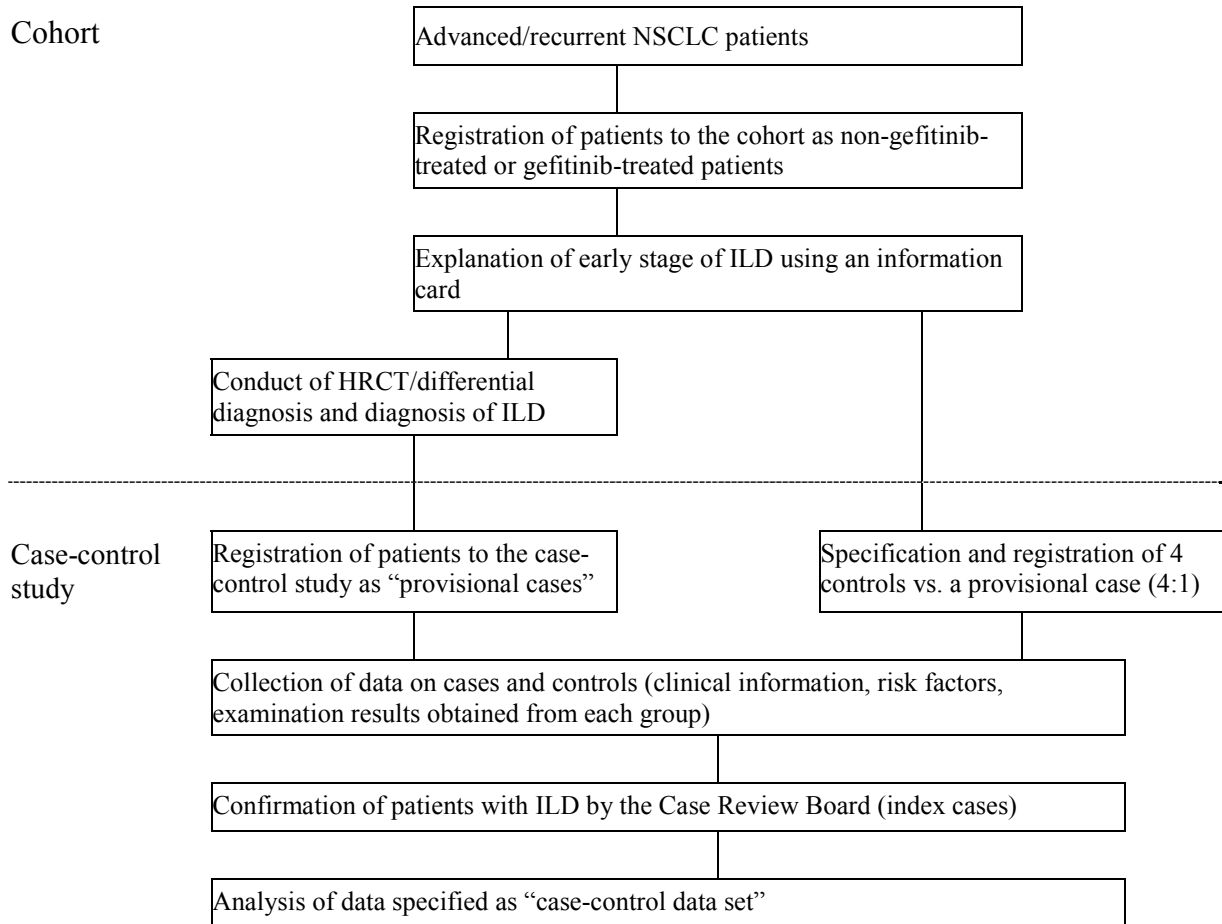
Figure S 3   Flow Chart of the Study

Cohort

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                    ┌─────────────────────────────────────────────┐
                    │ Advanced/recurrent NSCLC patients           │
                    └─────────────────────────────────────────────┘
                                        │
                    ┌─────────────────────────────────────────────┐
                    │ Registration of patients to the cohort as   │
                    │ non-gefitinib-treated or gefitinib-treated  │
                    │ patients                                     │
                    └─────────────────────────────────────────────┘
                                        │
                    ┌─────────────────────────────────────────────┐
                    │ Explanation of early stage of ILD using an  │
                    │ information card                            │
                    └─────────────────────────────────────────────┘
                                        │
                ┌─────────────────────────────────┐
                │ Conduct of HRCT/differential    │
                │ diagnosis and diagnosis of ILD  │
                └─────────────────────────────────┘
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Case-control study

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    ┌──────────────────────────────────┐        ┌──────────────────────────────────┐
    │ Registration of patients to the  │        │ Specification and registration   │
    │ case-control study as            │        │ of 4 controls vs. a provisional  │
    │ "provisional cases"              │        │ case (4:1)                       │
    └──────────────────────────────────┘        └──────────────────────────────────┘
                        │
    ┌────────────────────────────────────────────────────────────────┐
    │ Collection of data on cases and controls (clinical information, │
    │ risk factors, examination results obtained from each group)    │
    └────────────────────────────────────────────────────────────────┘
                        │
    ┌────────────────────────────────────────────────────────────────┐
    │ Confirmation of patients with ILD by the Case Review Board      │
    │ (index cases)                                                   │
    └────────────────────────────────────────────────────────────────┘
                        │
    ┌────────────────────────────────────────────────────────────────┐
    │ Analysis of data specified as "case-control data set"          │
    └────────────────────────────────────────────────────────────────┘
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All patients were Japanese. A total of 4437 registrations were allocated to the cohort set (gefitinib;1886, non-gefitinib; 2551). A total of 4423 registrations were included in cohort analysis set (gefitinib;1872, non-gefitinib; 2551). A total of 729 registrations were included in case-control analysis set (gefitinib;355, non-gefitinib; 374), 33 of which were not confirmed as cases by the CRB and were therefore excluded from most analyses. As expected in a non-randomised study where treatment assignment was at the choice of the investigator, some imbalances in demographic characteristics between treatment groups were found in the cohort and control data. The proportion of smokers (past + present) in the gefitinib-treated contorols was lower than the non-gefitinib-treated controls (55.2% vs.75.5%). Similarly, the proportion of patients with pre-existing interstitial pneumonia (IP) in gefitinib-treated controls was lower than non-gefitinib-treated controls (3.8% vs 13.6%).

Regarding to age, sex, histological type and WHO performance, the proportions in the controls were similar to those in the cohort. This suggests that the random sampling of controls from the cohort was successful. The distribution of some demographic and baseline variables between the gefitinib and non-gefitinib control groups sampled from the cohort is

shown in Table S1, along with the observed distribution of those variables in the corresponding case groups.

Table S1 **Descriptive statistics of registrations by demographic and other baseline variables for the cases and controls (per protocol case-control analysis set)**

		Case			Control			Total
		Gefitinib	Non-gefitinib	Total	Gefitinib	Non-gefitinib	Total	
Total		79	43	122	252	322	574	696
Age (years)	<65	33 (41.8)	14 (32.6)	47 (38.5)	113 (44.8)	161 (50.0)	274 (47.7)	321 (46.1)
	>=65	46 (58.2)	29 (67.4)	75 (61.5)	139 (55.2)	161 (50.0)	300 (52.3)	375 (53.9)
	<55	8 (10.1)	3 (7.0)	11 (9.0)	43 (17.1)	52 (16.1)	95 (16.6)	106 (15.2)
	>=55	71 (89.9)	40 (93.0)	111 (91.0)	209 (82.9)	270 (83.9)	479 (83.4)	590 (84.8)
Sex	Male	54 (68.4)	38 (88.4)	92 (75.4)	126 (50.0)	234 (72.7)	360 (62.7)	452 (64.9)
	Female	25 (31.6)	5 (11.6)	30 (24.6)	126 (50.0)	88 (27.3)	214 (37.3)	244 (35.1)
Duration of NSCLC from the first diagnosis (years)	<0.5	32 (40.5)	17 (39.5)	49 (40.2)	65 (25.8)	88 (27.3)	153 (26.7)	202 (29.0)
	0.5 - <1	25 (31.6)	11 (25.6)	36 (29.5)	67 (26.6)	87 (27.0)	154 (26.8)	190 (27.3)
	>=1	22 (27.8)	15 (34.9)	37 (30.3)	120 (47.6)	147 (45.7)	267 (46.5)	304 (43.7)
Histological type	Squamous carcinoma	15 (19.0)	14 (32.6)	29 (23.8)	27 (10.7)	76 (23.6)	103 (17.9)	132 (19.0)
	Adenocarcinoma	57 (72.2)	23 (53.5)	80 (65.6)	207 (82.1)	207 (64.3)	414 (72.1)	494 (71.0)
	Others	7 (8.9)	6 (14.0)	13 (10.7)	18 (7.1)	39 (12.1)	57 (9.9)	70 (10.1)
WHO PS	0	13 (16.5)	5 (11.6)	18 (14.8)	68 (27.0)	86 (26.7)	154 (26.8)	172 (24.7)
	1	38 (48.1)	31 (72.1)	69 (56.6)	148 (58.7)	210 (65.2)	358 (62.4)	427 (61.4)
	2-3	28 (35.4)	7 (16.3)	35 (28.7)	36 (14.3)	26 (8.1)	62 (10.8)	97 (13.9)
Smoking history	No	17 (21.5)	4 (9.3)	21 (17.2)	113 (44.8)	79 (24.5)	192 (33.4)	213 (30.6)
	Past+ Present	61 (77.2)	39 (90.7)	100 (82.0)	139 (55.2)	243 (75.5)	382 (66.6)	482 (69.3)
	Unknown	1 (1.3)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Table S1 **Descriptive statistics of registrations by demographic and other baseline variables for the cases and controls (per protocol case-control analysis set)**

		Case			Control			Total
		Gefitinib	Non-gefitinib	Total	Gefitinib	Non-gefitinib	Total	
Previous gefitinib	No	77 (97.5)	36 (83.7)	113 (92.6)	241 (95.6)	224 (69.6)	465 (81.0)	578 (83.0)
	Yes	2 (2.5)	7 (16.3)	9 (7.4)	11 (4.4)	98 (30.4)	109 (19.0)	118 (17.0)
Previous chemotherapy	No	0 (0.0)	1 (2.3)	1 (0.8)	0 (0.0)	7 (2.2)	7 (1.2)	8 (1.1)
	Yes	79 (100)	42 (97.7)	121 (99.2)	252 (100)	315 (97.8)	567 (98.8)	688 (98.9)
Previous radiotherapy	No	42 (53.2)	25 (58.1)	67 (54.9)	137 (54.4)	153 (47.5)	290 (50.5)	357 (51.3)
	Yes	37 (46.8)	18 (41.9)	55 (45.1)	115 (45.6)	169 (52.5)	284 (49.5)	339 (48.7)

( ): %

Pharmacokinetic results

In the Population Pharmacokinetic (hereafter, PPK) analysis, 336 patients were evaluable including 51 cases, 116 controls and 169 other patients, enrolled in the cohort by around April of 2004. All subjects with exception of cases (n = 51) were categorised as non-case subjects (n = 285). In total, 1891 plasma concentrations were obtained from 336 evaluable patients based on the sparse sampling method predefined in Clinical Study Protocol. Blood samples were taken at the following 6 time points; 1-3 hours, 3-8 hours and 24 hours post the first dosing and after achieving steady state, pre-dose and 1-3 hours and 3-8 hours post dose. In addition, a blood sample was taken from a case if possible at ILD occurrence. The blood sample was available at ILD occurrence from 27 patients within 51 cases. These available concentration data (1891) were used for the PPK analysis.

The plasma concentrations of gefitinib were well described by means of 1-compartment model with first order absorption process and absorption lag time. It was shown that α_1-acid glycoprotein (α_1-AGP), age, body weight and concomitant use of CYP3A4 inducers were factors which could affect CL/f of gefitinib. It was also shown that CL/f was lower at ILD occurrence compared with the period without ILD occurrence. α_1-AGP and body weight were identified as factors which could affect V/f of gefitinib.

Using the PPK model (final model) incorporating the covariates described above, PK parameters (CL/f, V/f, absorption rate constant [k_a] and absorption lag time [t_{lag}]) were estimated for each individual patient by means of Bayesian method. Then the exposure (area under the plasma concentration – time curve from 0 – 24 hours post dose [AUC_{0-24}], maximum plasma concentration [C_{max}] and trough plasma concentration [C_{min}]) in each individual was calculated using those estimated PK parameters. Comparison of calculated

exposures did not show any marked difference between cases and non-cases and essentially completely overlapping ranges of predicted values for the two groups. On the other hand, when the exposure at ILD occurrence was evaluated for ILD cases where such blood samples were available and compared to average exposure in the period without ILD in non-cases, the average exposure of gefitinib at ILD occurrence in cases tended to be higher.

Safety results

Primary results

The study showed an increased risk of ILD associated with gefitinib compared to non-gefitinib. The overall adjusted OR over the 12 weeks after initiation of treatment was 3.23 (95% confidence interval [CI] 1.94-5.40).

The increased risk of ILD on gefitinib relative to non-gefitinib was mainly seen during the first 4-weeks after start of treatment. During that interval, the adjusted OR was 3.80 (95% CI 1.88-7.66); after this, the relative risk was lower (OR 2.51 95% CI 1.08-5.80).

Some risk factors other than treatment were confirmed and further defined that determined patients at increased risk of ILD on both treatments

- Smoking, pre-existing IP, Short duration of initial diagnosis of NSCLC to the onset of ILD (<6 months), high age (≥55yr), poor PS (≥2), low normal lung coverage on CT scan (≤50%), concurrent cardiac disease

The naive observed cumulative incidence (frequency) of ILD was 3.0% in the cohort of NSCLC patients undergoing treatment (4.0% for gefitinib, 2.1% for non-gefitinib, unadjusted for imbalances in risk factors between treatments).

Additional results

Based on the risk factor profiles of patients in the study, it appeared that physicians had selected for gefitinib treatment NSCLC patients that had a lower risk of ILD. Thus, gefitinib treated patients were more likely to be female, non-smokers, adenocarcinoma, without pre-existing IP and some other pre-existing lung condition and concurrent diseases.

Some other risk factors were just as important or more important than treatment in determining the relative chance of a patient developing ILD (on either treatment), e.g. poor PS vs. good PS OR 4.0

No treatment specific risk factor was found. Hence, for a particular patient, the risk of ILD is higher when treated with gefitinib compared to non-gefitinib, irrespective of other patient characteristics. However, patients with multiple risk factors for ILD will have a higher baseline risk to start with and so caution should be exercised when making a treatment decision and consideration should be given to the overall benefit-risk assessment for the individual.

Of the ILD cases, the proportion with a fatal outcome were 31.6% for gefitinib (25/79) and 27.9% for non-gefitinib (12/43).