European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT

FOR

IRESSA

International Nonproprietary Name: gefitinib

Procedure No. EMEA/H/C/001016

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant AstraZeneca AB submitted on 06 May 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for IRESSA, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on18 December 2007.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies

The applicant applied for the following indication: IRESSA is indicated for the treatment of adults with locally advanced or metastases Non Small Cell Lung Cancer (NSCLC) eligible for further chemotherapy after receiving prior platinum based chemotherapy.

Scientific Advice:
The applicant received Scientific Advice from the CHMP on the 26 October 1999, 1st June 2006 and 18 October 2006. A clarification letter was also received on 27th July 2006. The Scientific Advice pertained to the clinical aspects of the product development.

Licensing status:
IRESSA has been given a Marketing Authorisation in the following countries:

Country:	Date of authorisation:
Japan	05.07.2002
Australia	28.04.2003
USA	05.05.2003
Singapore	22.05.2003
Argentina	30.05.2003
South Korea	14.06.2003
Taiwan	27.08.2003
Malaysia	29.08.2003
Mexico	12.09.2003
Philippines	23.09.2003
Nicaragua	15.12.2003
Canada	17.12.2003
Curacao	18.12.2003
Dominican Republic	19.12.2003
Hong Kong	31.12.2003
Israel	07.01.2004
Honduras	08.01.2004
New Zealand	22.01.2004
Guatemala	04.02.2004
United Arab Emirates	17.02.2004
Thailand	24.02.2004
Indonesia	05.03.2004
India	11.03.2004
Peru	22.03.2004
El Salvador	28.04.2004

Bahrain	04.05.2004
Panama	05.05.2004
Venezuela	26.07.2004
Chile	30.07.2004
Serbia and Montenegro	10.09.2004
Uruguay	29.09.2004
Qatar	13.10.2004
Russia	30.11.2004
China	06.12.2004
Sri Lanka	12.02.2007

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Tomas P Salmonson** Co-Rapporteur: **Eva Skovlund**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 06 May 2008.
- The procedure started on 28 May 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2008.
- During the meeting on 22-25 September 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 September 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 November 2008.
- A GCP inspection was carried out at three investigator sites in P.R. of China, between 20-31 October 2008, in relation to the conduct of trial D791GC00001. The final integrated inspection report was issued on 20 November 2008.
- On 15 December 2008 a clarification meeting was held with the applicant and the Rapporteurs.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 December 2008.
- During the CHMP meeting on 19-22 January 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 16 February 2009.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the CHMP list of outstanding issues on 02 March 2009.
- During a SAG Oncology meeting on 06 March 2009, experts were convened to address questions raised by the CHMP.
- The applicant submitted further responses to the CHMP list of outstanding issues on 13 March 2009.
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the CHMP list of outstanding issues on 13 March 2009.
- During the CHMP meeting on 16-19 March 2009, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- The Rapporteurs circulated a further updated Joint Assessment Report to the CHMP on 17 April 2009.
- During the meeting on 20-23 April 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to IRESSA on 23 April 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on date 22 April 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Lung cancer is the most common form of cancer with the highest incidence worldwide. The mortality rates are highest in males and second highest in females, after breast cancer[1]. In Europe, an estimated 386300 cases of lung cancer were diagnosed in 2006; with 334800 deaths (20% of all cancer-related deaths) attributed to the disease[2].

The genetic predisposition to NSCLC is still under intensive investigation, however, studies have shown that the epidermal growth factor receptor (EGFR), a receptor tyrosine kinase (TK) and member of the erbB family, is frequently over-expressed and activated to a phosphorylated state in NSCLC. The activity of EGFR in cancer cells results in the phosphorylation of downstream proteins that promote cell proliferation, invasion, metastasis, and inhibition of apoptosis[3]. Targeting the EGFR pathway therefore constitutes a relevant strategy for cancer therapy.

The vast majority of advanced or metastatic NSCLC patients will subsequently progress after treatment with first line chemotherapy and the prognosis of these patients is poor, frequently suffering from symptomatic disease and a median survival of 4 to 5 months, if left untreated.

Currently commonly used treatments in the EU for advanced or metastatic NSCLC include bevacizumab in addition to platinum-based chemotherapy (1st line treatment), docetaxel (2nd line treatment) and docetaxel in combination with cisplatin (1st line treatment), pemetrexed (1st and 2nd line treatment) and erlotinib (2nd and 3rd line treatment).

In the initial application, AstraZeneca had submitted a marketing authorisation application (MAA) for the following indication:

- IRESSA (gefitinib) for the treatment of adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) eligible for further chemotherapy after receiving prior platinum based chemotherapy.

However, following the assessment and objections raised by the CHMP, a new indication was proposed:

- IRESSA is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK (see section 5.1).

The recommended posology of IRESSA is one 250 mg tablet once a day. If a dose of IRESSA is missed, it should be taken as soon as the patient remembers. If it is less than 12 hours to the next dose, the patient should not take the missed dose. Patients should not take a double dose (two doses at the same time) to make up for a forgotten dose.

2.2 Quality aspects

Introduction

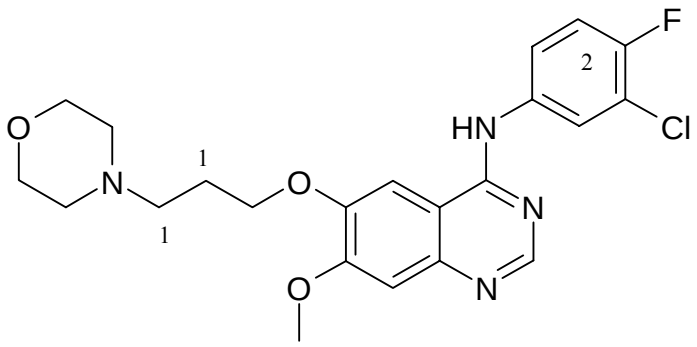
[1] Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94:153-6.
[2] Ferlay J, Autier P, Bioniol M, Heanue M, Colombet M, and Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007;18:581-92.
[3] Ranson M, Hammond LA, Ferry D, Kris M, Tullo A, Murray PI, et al. ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a Phase I trial. J Clin Oncol 2002;20:2240-50.

The medicinal product IRESSA is presented as brown, round, biconvex, film-coated tablets which are impressed with “IRESSA 250” on one side and plain on the other side. Each film-coated tablet contains 250 mg gefitinib. Other ingredients include (tablet core): lactose monohydrate, microcrystalline cellulose E460, croscarmellose sodium, povidone E1201, sodium laurilsulfate, magnesium stearate, (tablet coating): hypromellose E464, macrogol 300, titanium dioxide E171, yellow iron oxide E172 and red iron oxide E172. The tablets are packaged in PVC/Aluminium-blisters over-wrapped and sealed with aluminium foil laminate flow-wraps.

Active Substance

The chemical name for gefitinib is N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine.

Structure of the active substance:



Gefitinib is a white, crystalline, non-hygroscopic powder. The processing conditions have been chosen to ensure that gefitinib is always produced as a single crystalline morphological form.
Gefitinib doesn’t contain asymmetric carbon atoms. The drug substance exhibits basic properties, with two pKa values of 5.42 and 7.24, respectively.
The solubility of gefitinib in aqueous solution is pH dependent. At pH 3 it is sparingly soluble, while it is practically insoluble at pH 7. Gefitinib is freely soluble in glacial acetic acid and in dimethylsulfoxide, soluble in pyridine, sparingly soluble in tetrahydrofuran and slightly soluble in methanol, ethanol (99.5%), ethyl acetate, propan-2-ol and acetonitrile. Based on permeability/absorption data and results from solubility studies, gefitinib has been classified as a low solubility, high permeability drug (class 2) according to the Biopharmaceutical Classification System (BCS System).
The chemical structure of gefitinib has been confirmed using analytical data by elemental microanalysis, UV and IR spectroscopy, nuclear magnetic resonance spectroscopy, mass spectrometry and X-ray crystallography. All data are consistent with the proposed structure.

- Manufacture

Gefitinib is synthesised in a number of steps via an intermediate.
Detailed information about the manufacturing, validation and analytical controls of the active substance has been provided. The starting materials have been adequately characterized and the manufacturing process has been adequately validated.
All relevant impurities have been appropriately discussed and characterized. The levels of the impurities are considered acceptable and appropriate specifications have been set.

- Specification

The active substance specification includes appropriate tests for appearance, identifications (IR spectra), assay and organic impurities (HPLC), residual solvents, particle size distribution, water content and residue on ignition/sulphated ash.
The impurity limits are acceptable and there is no concern in relation with safety or efficacy.

The batch analysis data support the proposed acceptance limits.

- Stability

Stability studies have been performed in accordance with the ICH requirements. Data from 3 production scale batches covering 5 years at 25°C/60% RH, 12 months at 30°C/60% RH and 6 months at 40°C/75% RH have been provided. In addition, data for 3 pilot scale batches packed in similar material as that proposed for routine storage covering 5 years at the long term conditions, 12 months at the intermediate conditions and 6 months at the accelerated conditions have been evaluated.
The test parameters evaluated in these studies were description, assay and organic impurities by HPLC, particle size distribution and water content, and morphology. The stability data provided justify the proposed retest period at the proposed storage conditions.

Medicinal Product

- Pharmaceutical Development

The Marketing Authorisation Holder satisfactory describes the formulations used in clinical trials, the choice of the excipients and their amounts, the development of the dissolution test and evaluation of its discriminatory ability, the overages applied, the evaluation and optimisation of the manufacturing process, bioequivalence, and the choice of packaging material.
The excipients were chosen based on the results from compatibility studies and consideration of the physico-mechanical properties of the drug substance together with those of the excipients. Investigations have been carried out regarding the possibilities for minimising tablet size by increased drug loading, and to omit microcrystalline cellulose as a second diluent. The levels of binder, disintegrant and lubricant have also been optimised.

- Adventitious Agents

All excipients except lactose monohydrate are produced from non-animal sources. The lactose is derived from milk fit for human consumption and a satisfactory statement from the lactose monohydrate manufacturer has been submitted.

- Manufacture of the Product

IRESSA 250 mg film-coated tablets are manufactured using a conventional wet granulation, compression and film coating processes consisting of the following steps: dry mixing, wet granulation, drying, tableting and coating. All critical process parameters have been identified and controlled by appropriate in-process controls. The manufacturing process demonstrates to be reproducible and provides a finished product that complies with the finished product specifications.

- Product Specification

Appropriate drug product specifications have been set. All excipients used in the formulation comply with the monographs of the current Ph.Eur., except for yellow and red iron oxide which are referenced to USP/NF and JP.
The specifications for the finished product at release and shelf life are the same and are classical for this pharmaceutical form. They include tests for appearance, identity, assay, degradation products, dissolution, content uniformity, and microbial content.

All tests included in the specification have been satisfactorily described and validated, according to the state of the art. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. Batch analysis data are presented for 42 production scale batches manufactured at the commercial site during 2000-2007. All batches complied with the finished product specification.

- Stability of the Product

Stability studies have been carried out according to the ICH requirements on 3 production scale batches of drug product packaged in the commercial package and on one pilot batch packaged in the bulk package. All batches were manufactured by the commercial manufacturer. The batches in the commercial package were stored at 25 °C/60 %RH and 30 °C/75 %RH for 48 months and at 40 °C/75 %RH for 6 months, while the bulk batches were stored at 25 °C/60 %RH and 30 °C/75 %RH for 24 months) and at 40 °C/75 %RH for 6 months. The parameters tested and analytical methods used were identical to those used for the release specifications. In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SmPC.
In use stability study results for one production batch packaged in PVC/Aluminium blisters with the foil wrap removed and stored for one month at 40 °C/75 %RH are also presented. The only change observed during storage was a slight increase in water content, confirming that the drug product is stable for at least 30 days after opening of the foil-wrap.

Discussion on chemical, pharmaceutical and biological aspects

The quality of IRESSA is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation. There are no major deviations from EU requirements.

The active substance is well characterised and documented. The manufacturing process of IRESSA is under control and ensures both batch-to-batch reproducibility and compliance with standard procedures and specifications. The analytical methods have been validated and ensure consistent quality of the active substance and the finished product, the synthetic pathway is presented and the structure and impurity profile are well characterised and in line with current ICH guidelines. The stability data on the active substance supports the proposed re-testing period.
The stability data of the finished product in the proposed package support the shelf life stated in the SmPC.
At the time of the CHMP opinion there were no unresolved quality issues.

2.3 Non-clinical aspects

Introduction
All pivotal safety pharmacology and toxicology studies have been conducted in accordance with GLP regulations. GLP status has been confirmed for the majority of the pharmacokinetic studies.

Pharmacology

- Primary pharmacodynamics

Inhibition of kinase activity
Gefitinib inhibited tyrosine phosphorylation of a synthetic peptide substrate by EGFR prepared from A431 human squamous carcinoma cells (IC_{50}=0.033 μM) or by the isolated kinase domain of EGFR expressed in a baculovirus expression system (IC_{50}=0.027 μM). Gefitinib acted as a competitive inhibitor of ATP and a non-competitive inhibitor of peptide binding to EGFR TK .

Inhibition of cell proliferation and EGFR autophosphorylation
Cell growth was measured in the human KB cell line (derived from a vulval squamous tumour) using the MTT assay, and by cell counting and inhibition of EGF, FGF, and VEGF induced stimulation of HUVEC cells (isolated from umbilical cords) was measured using [^{3}H]thymidine incorporation. Gefitinib inhibited EGF-stimulated growth with IC_{50}=0.054 μM, more than 100-fold less than the inhibition of basal growth (IC_{50}=8.8 μM). EGF-stimulated growth of human umbilical vein endothelial cells (HUVEC) was inhibited by gefitinib (IC_{50}=0.03-0.1 μM), but FGF- and VEGF-stimulated growth

was relatively unaffected (IC_{50}=1-3 μM). The effect of gefitinib was mainly cytostatic, but higher doses increased apoptotic cell death.

The effect of gefitinib on EGF induced EGFR autophosphorylation was measured in lysates of different tumour-derived cell lines by electrophoresis and Western blotting with an antibody against tyrosine phosphorylated proteins. Phosphorylation was reduced to control levels in the presence of 0.16 – 0.8 μM gefitinib and reduced EGF-induced EGFR autophosphorylation in a concentration-dependent manner in all tested cell types.

Inhibition of downstream signalling
The effects on EGFR autophosphorylation downstream signalling molecules (p-ERK and p-AKT), cell cycle progression (p27, a negative regulator of G1 to S transition; and BrdU incorporation, a measure of DNA synthesis) and apoptotic cell death (caspase 3) were assessed. *In vitro* studies were therefore conducted to clarify the effect of gefitinib on EGFR downstream signalling in wild type (WT) EGFR-expressing lung tumour cell lines with different sensitivities to gefitinib (resistant Calu-6, sensitive Calu-3 and hypersensitive NCIH322 cell lines) and the PC-9 cell line, which expresses a somatic activating mutation in the kinase domain of EGFR (delE746-A750)17 and is hypersensitive to gefitinib, was also examined. Treatment of cells with gefitinib showed a decreased viability and decreased auto-phosphorylation of EGFR and the effects correlated well with decreased p-ERK, p-AKT and BrdU incorporation and an increase in p27 protein expression. Caspase-3 expression remained mostly unchanged in cells Calu-6, Calu-3 and NCIH322. Therefore, it appears that the cell line with mutated EGFR is more dependent on apoptosis than the cells with wild-type EGFR.

***In vivo* anti-tumour activity**
The *in vivo* activity on tumour growth was studied in xenograft models. Gefitinib inhibited the growth of different tumours to a variable degree. Effective dose-dependent growth inhibition was seen with A431 (vulval squamous carcinoma), A546 (lung tumour) and Du145 (prostate tumour) where gefitinib inhibited tumour growth in a dose-dependent manner. The susceptibility to growth inhibition did not correlate with EGFR expression in the different cell types. Gefitinib had a cytostatic effect on tumour growth. The importance of continuous drug treatment to maintain tumour activity was examined in studies where gefitinib therapy (200 mg/kg) was withdrawn after 50 or more consecutive days of administration. Results demonstrated a persistent tumour inhibitory effect, which was reversible upon cessation of treatment even after a long period of treatment (> 100 days).

Metabolites
The pharmacological activity of metabolites and potential metabolites of gefitinib was evaluated using *in vitro* kinase assay and the MTT assay in the human KB cell line. Five metabolites identified in humans were studied for pharmacological activity. All metabolites demonstrated potent and selective EGFR TK inhibition, similar to that of gefitinib. The activity of the major human metabolite, M523595, was further studied in an in vivo xenograft model (LoVo tumour bearing nude female mice). Comparing gefitinib at 75 mg/kg and M523595 at 150 mg/kg, gefitinib showed significant inhibition of tumour growth while M523595 had no effect on tumour growth. While plasma exposures of the two compounds were comparable, tumour concentrations of M523595 were approximately 7-times lower than those of gefitinib. The metabolites are unlikely to contribute in a significant manner to the pharmacological activity of gefitinib.

- Secondary pharmacodynamics

Affinity of gefitinib to various secondary enzymes and receptors has been screened, using enzyme and radioligand binding assays (TSY276, non-GLP). Activity against the structurally closely related HER-family member erbB2 was 100-fold less than that against EGFR TK and, had little or no activity against the receptors for vascular endothelial cell growth factor (VEGF), KDR and c-flt. Gefitinib did not inhibit the activity of any of the serine/threonine kinases raf, MEK-1 and ERK-2 (MAPK).

- Safety pharmacology programme

Studies were performed to evaluate the effect of gefitinib on gastrointestinal (rat, GI transit), respiratory (rat, plethysmography), central nervous system (rat, Functional Observation Battery and

locomotor activity) and cardiovascular (dog, telemetry) functions. *In vitro* studies were performed to evaluate effects on cardiac action potential (dog Purkinje fibres and hERG expressing cells). In the rat studies, gefitinib was administered orally at single doses of 5, 50 and 500 mg/kg. In the dog study, gefitinib was administered orally at single doses of 5 and 50 mg/kg

No effects were seen on the gastro-intestinal function. Minimal effects were seen on the respiratory system at 50 and 500 mg/kg (decreases in peak inspiratory flow, peak expiratory flow, tidal volume and minute volume. Minor effects were seen on the central nervous system at 50 and 500 mg/kg (slight reduction in motor activity). Minor effects were seen on the cardiovascular system at 50 mg/kg (slight hypotension).

Gefitinib was active in the hERG assay with an IC_{50} of 1 μM (446 ng/ml). Gefitinib induced a statistical significant prolongation of the action potential duration at 90% of repolarisation (APD90) in a dog Purkinje fibre preparation at 3462 ng/ml (protein free levels). At a low stimulation frequency (0.33 Hz) the degree of prolongation was increased only at the higher concentrations of gefitinib. At exposure levels of gefitinib in clinical use, however, the conditions do not suggest an increased risk of action potential prolongation. In a QT interval assessment in conscious telemetered dogs, there were no statistical significant increases of QT or QTc intervals in dogs treated with gefitinib at either 5 or 50 mg/kg. However, examination of the individual data shows that at 2 hours post-dose, 1 out of 6 dogs at 5 mg/kg and 2 out of 6 dogs at 50 mg/kg experienced a greater than 10% QTc prolongation in comparison to baseline values. No dogs receiving the vehicle showed such a change.

- Pharmacodynamic drug interactions

A number of interaction studies were submitted to explore the effects of gefitinib and certain cytotoxic drugs *in vitro* and *in vivo* on tumour cell growth (data not shown).

Pharmacokinetics

The majority of the pharmacokinetic studies in rats and dogs were conducted at dose levels of 5 mg/kg, which was the intermediate dose level in the 6-month oral toxicity studies in these species. Some studies were however performed with higher dose levels (20-50 mg/kg), in order to facilitate metabolite identification.

- Methods of analysis

A high performance liquid chromatography method with ultraviolet detection (HPLC-UV) assay was developed for determination of concentrations of gefitinib in rat and dog plasma. A more sensitive method with HPLC with tandem mass spectrometric detection (HPLC-MS-MS) was developed for clinical analysis of gefitinib and for measurement of known metabolites (M537194, M527301, M295820, M523595 and M387783) in plasma from rat, dog and man. For radiochemical analysis, gefitinib was [14C]labelled either in the propoxy chain (KML002, KML032, KML039, KML042) or in the chlorofluorophenyl ring. Radiochemical purity >98% was determined by TLC and HPLC.

- Absorption

Assessment of oral absorption by comparison of urinary excretion of radioactivity following administration of single oral and/or intravenous doses of [^{14}C]-gefitinib was considered inappropriate since recovery from urine was low. Bioavailability was estimated from plasma pharmacokinetic data.

Pharmacokinetic parameters after single oral and intravenous administrations to rats and dogs are summarised in Table 1. Data from single dose studies in humans are included.

Table 1: A summary of the pharmacokinetic parameters after oral or intravenous administration of gefitinib

study	species	n	dose	route	T_{max}	C_{max}	AUC	$T_{1/2}$	F

			(mg/kg)		(h)	(ng/ml)	(ng·h/ml)	(h)	(%)
KKR008	Rat	36M	5	oral	6	127	620*	NC	NC
		36F	5	oral	4	230	1780	4.1	50
		36M	12.5	oral	5	381	3520	4.7	77
		36F	12.5	oral	3	590	7160	5.7	88
		36M	5	i.v.	0.03	1820	1990	3.2	NA
		36F	5	i.v.	0.03	1650	3540	5.3	NA
KPR055	Rat	21M	5	oral	2	164	1440	6.8	44
		21F	5	oral	2	216	2050	6.7	39
		21M	20	oral	2	836	7830	10.1	59
		21F	20	oral	3	1220	13800	9.7	66
		21M	20	i.v.	0.03	9550	13200	13.8	NA
		21F	20	i.v.	0.03	10000	20900	8.2	NA
KKD009	Dog	3M	5	oral	4	357	3882	4.5	49
		3M	5	i.v	0.08	6163	7851	3.4	NA
KPD025	Dog	6M	100mg	oral (fed)	2-8	1190	7436	5.0	NA
		6M	100mg	oral (fasted)	2-8	919	8380	6.6	NA
KPD050	Dog	3M	5	oral	2	510	3380	7.0	64
		3M	5	i.v.	0.08	2280	5781	7.8	NA
0031	Human volunteers	4	50 mg	i.v.	1[a]	115[a]	1202	40.3	
		4	100 mg	i.v.	1[a]	233[a]	1646	27.9	
0035	Human patients	19	50 mg	i.v.	NA	2231[b]	1621	48.3	
0002, 0003, 0027, 0033 and 0034	Human volunteers	45	50 mg	oral	5	14.3	434	30.1	
		29	100 mg	oral	5	35.3	940	26.5	
		122	250 mg	oral	5	101	2583	30.0	
		55	500 mg	oral	3	200	5768	33.8	

***: 0-8H**

a: C_{inf}, infusion time 1 h
b: C_{inf}, infusion time 5 min
NC: not calculable
NA: not applicable
F: bioavailability

Two studies on single dose kinetics have been performed in rats (KKR008 and KPR055), with intravenous and peroral doses in the range 5-20 mg/kg and two more studies on single dose kinetics were performed with 3 male dogs, both with 5 mg/kg gefitinib administered orally or intravenously (KKD009 and KPD050) (Table 1). Both studies in rats demonstrated higher levels of exposure in females than in males, with female AUC levels 1.4-2 times male AUC levels. AUC levels were shown to increase in a non-proportional manner and bioavailability of gefitinib increased with increasing dose, indicating increased absorption or saturation of first pass metabolism. There was gender difference in rats, with female rats showing an exposure approximately double that in male rats. Gefitinib was extensively distributed in both sexes, with apparent volumes of distribution calculated to 8-10.4 l/kg. Mean terminal half-life in dogs was 3-8 hours. Apparent volume of distribution was found to be smaller than in rats, 2.1-6.3 l/kg. Gefitinib was cleared from dog plasma at 10-16 ml/min/kg.

The effect of food on the pharmacokinetics of gefitinib was examined in male dogs dosed with a single 100 mg gefitinib tablet (KPD025, Table 1). Peak plasma concentrations were greater when gefitinib was administered after feeding, and inter individual variability decreased. However, no evidence of a food effect on the pharmacokinetics of gefitinib in dogs was found.

Studies of repeat dose kinetics were conducted during repeat-dose toxicity studies in mice, rats and dogs as part of the toxicokinetics programme. Exposure in male rats was lower than in females, but no obvious sex difference was observed in dogs.

Following oral and intravenous administration of [14C]-gefitinib, elimination of radioactivity into urine was low (<7.5%) in all species. However, high levels of radioactivity were recovered in faeces of rats (96-98%), dogs (72-86%), and rabbits (94%).

- Distribution

Tissue distribution, plasma protein binding, tumour xenograft distribution, transplacental distribution, and distribution in blood have been examined *in vitro* and *in vivo* after oral dosing of radiolabelled gefitinib. Except for KPJ013, KMR010, KMR051 and KMR016 none of the studies were GLP compliant. Radiolabelled material was rapidly absorbed and widely distributed into the tissues following administration of a 5 mg/kg single oral dose of [^{14}C]-gefitinib to albino and pigmented male rats, with readily detectable levels of radioactivity still present 96 h after dosing. Peak concentrations of radioactivity were achieved at 2 h after dosing and were highest in the organs of metabolism and excretion (liver, kidney, lung, GI tract) and in glandular tissue (lachrymal gland, salivary gland, adrenal glands), low levels of radioactivity distributed within the central nervous system and the testis. Radioactivity was extensively distributed into tumours and normal tissues of nude mice bearing subcutaneous human tumour (LoVo - colorectal; A549 and Calu-6 - lung) with the mean peak tumour concentration being achieved 2-8 h after dosing. Most of the tumour radioactivity was accounted for by unchanged gefitinib. The apparent elimination half-life of ZD1839 was 3.1 to 3.3 h in plasma and in the range of 4.7 to 5.8 h in tumour xenografts. Concentrations of gefitinib in blood was evaluated in the rat and dog following administration of single oral and intravenous doses of [^{14}C]-gefitinib. The blood:plasma concentration ratio was approximately 1:0.8 in both males and females and across all dose groups (oral: 5 and 12.5 mg/kg; i.v: 5 mg/kg). In contrast, the blood:plasma concentration ratio in the dog was approximately 1:1.6 following both oral and intravenous doses at 5 mg/kg, indicating a minimal distribution of gefitinib and its metabolites to the cellular components of blood.

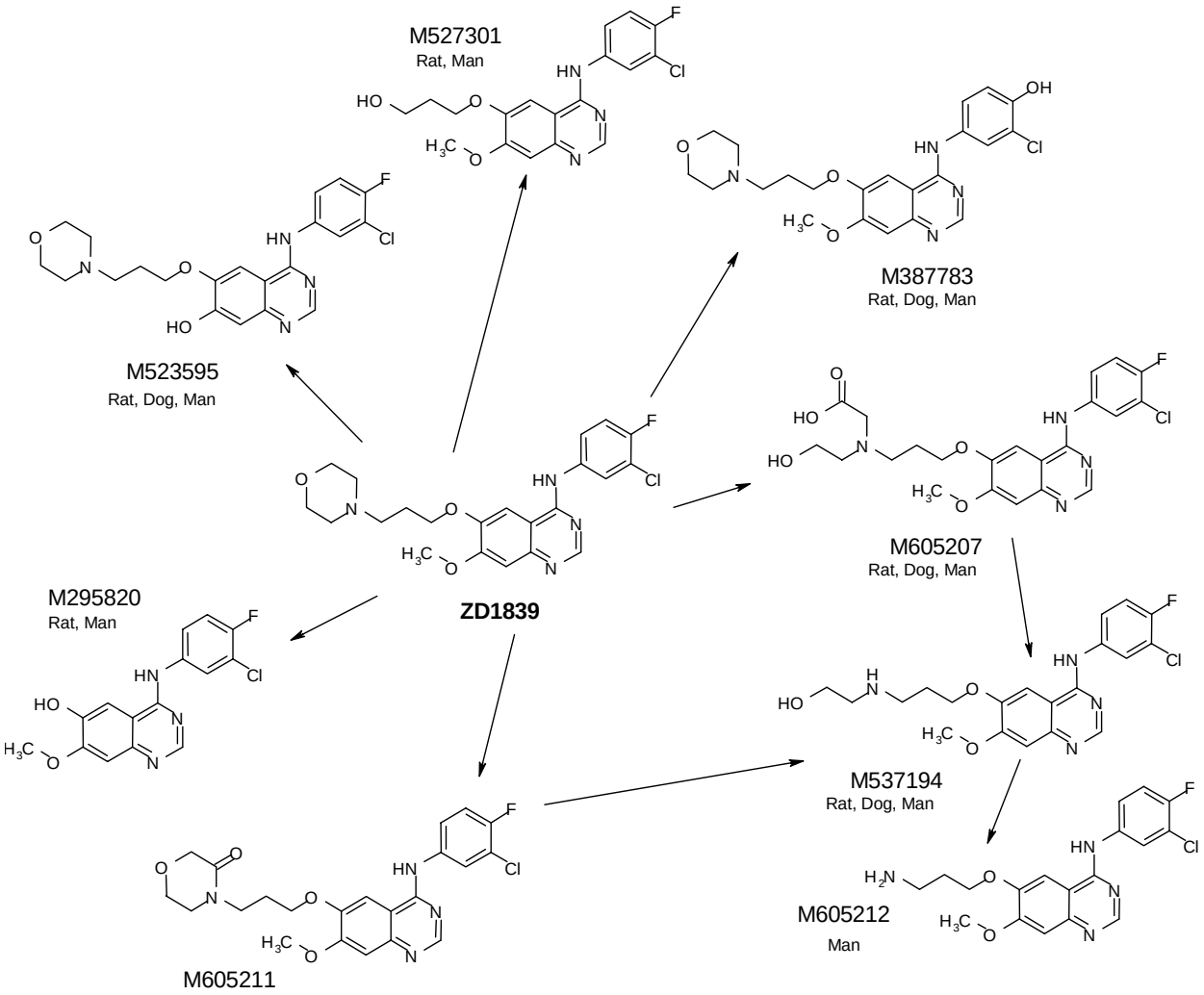
Using the MDR1-MDCK cell monolayer system, gefitinib was shown to be a good substrate for Pgp-dependent transport, although it had no obvious potency as an inhibitor of Pgp-mediated efflux. The *in vivo* effects of this property were assessed in an *in situ* rat brain penetration model, which showed that gefitinib at 0.5 μM exhibited low brain permeation due to Pgp-mediated efflux. However, brain penetration was increased 3-fold by cyclosporin A (10 μM). Gefitinib has been shown to be a substrate and inhibitor of the BCRP (ABCG2) transporter, both *in vitro* and *in vivo*, with an inhibition of BCRP that is 10-fold higher than that for Pgp.

Transplacental transfer of radioactivity was investigated following administration of single oral doses (5 mg/kg) of [^{14}C]-gefitinib to pregnant rats and rabbits. It was shown that placental transfer of drug-related material readily occurs in both rat and rabbit.

- Metabolism

The *in vitro* metabolism of gefitinib was investigated by incubating [^{14}C]-gefitinib with rat, dog or human hepatocytes. There was extensive metabolism to a large number of components, with unchanged gefitinib accounting for 55% (rat), 28% (dog) or 34-81% (human) after a 3 hr incubation. The main metabolites detected *in vivo* are shown in figure 1. The chromatographic pattern of the metabolites suggested that the major metabolites were similar in the three species.

Figure 1: Proposed *in vivo* metabolism pathway for gefitinib in rat, dog and human



ZD1839=gefitinib

Three distinct metabolites were formed after incubation with human hepatic microsomes and two were identified as M537194 and M387783. These were isolated and analysed by mass spectrometry and nuclear magnetic resonance spectroscopy. A further study on the metabolism of gefitinib and M387783, M537194 and M52395 (the main metabolites found in man) led to the identification of 14 more metabolites. *In vivo* metabolism studies were performed in rats, dogs and humans. Circulating levels of metabolites were low and the major route of excretion was into faeces. Metabolite profiling from faecal extracts showed that in rat, gefitinib and M537194 were the major components identified in faeces. In dog, a number of components were identified including gefitinib, M537194, M523595 and M387783, together with hydroxylated, dihydroxylated and carboxypropyl metabolites of gefitinib.

P450 enzymes involved in the metabolism of gefitinib were identified by the use of selective inhibitors and *in vitro* studies using microsomal fractions from cells expressing individual P450 enzymes. These studies showed that gefitinib was metabolised through the action of CYP3A4 and CYP2D6. Metabolism was also observed with CYP3A5, but to a lesser extent. In the presence of CYP2D6, there was rapid metabolism of gefitinib with M523595 as the predominant metabolite.

The effect of selective inhibitors on the metabolism of [^{14}C]-gefitinib is summarised in Table 2. The formation of metabolites M387783 and M537194 were markedly reduced by ketoconazole, a selective inhibitor of CYP3A4. The inhibition of CYP2C19 by omeprazole reduced the formation of M537194. Inhibition of CYP2D6 by quinidine resulted in a significant reduction of M523595, confirming that M523595 is catalysed almost exclusively by CYP2D6.

Table 2: Effect of P450-selective inhibitors on [^{14}C]-gefitinib metabolism by human liver microsomes (KMX024 and KMX065)

			% of Compound in Sample				
			Study KMX024			Study KMX065	
P450	*Inhibitor*	*Conc (μM)*	*gefitinib*	*M387783*	*M537194*	*gefitinib*	*M523595*
	Control		30.3	9.0	32.1	50.8	4.1
CYP1A2	Furafylline	25	26.1	13.2	33.7	47.7	3.9
CYP2C9	Sulfaphenazole	25	34.2	9.3	29.1	50.1	3.5
CYP2C19	Omeprazole	20	55.5	8.6	23.1	58.8	3.8
CYP2D6	Quinidine	1	25.3	11.7	39.5	52.2	1.4
CYP3A4	Ketoconazole	1	92.1	1.3	3.5	85.4	5.1

The potential of gefitinib to inhibit the activity of the major human P450 enzymes was studied in human hepatic microsomes *in vitro*. Gefitinib produced little inhibition (< 10%) of CYP1A2, 2C9 and 3A4 enzyme activity. Inhibition of CYP2C19 and 2D6 was more pronounced, with enzyme activity decreased to 76% and 57% of control at maximum gefitinib concentration (5 μg/ml), respectively.

- Excretion

Excretion was primarily via the faeces (>90% of recovered dose) after oral and intravenous dosing in rats, rabbits and dogs. Elimination was relatively slow. The proportion of the dose being recovered in the first 24 hours was 70% in rats, 51% in rabbits and 40% in dogs.

Following administration of a single oral dose (5 mg/kg) of ^{14}C-gefitinib to lactating rats, drug-related material was excreted in milk with peak concentrations observed at 4 hours post-dose. The major component in the milk was gefitinib with concentrations of 11 to 19 fold higher than in blood.

Toxicology

All pivotal toxicity studies were conducted in accordance with GLP criteria. The toxicity of gefitinib was assessed in a standard program of non-clinical safety evaluation with repeat-dose toxicity studies in rats and dogs up to 12 months in duration, standard reproductive toxicity studies in rats and rabbits, genotoxicity studies and studies of antigenic potential.

- Single dose toxicity

The single dose toxicity of gefitinib was assessed in mice and rats in oral and IV administration routes and dogs in oral administration route only. Studies in rats showed that an oral dose of 2000 mg/kg led to severe adverse effects 5 days after treatment related to a perforated duodenal ulcer, which lead to premature deaths in females. There were other major findings, including damage to kidneys, liver, skin and upper gastro-intestinal tract. Both mice and rats tolerated 20 mg/kg IV administration without signs of toxicity. In studies of single oral toxicity in dogs, doses of up to 1000 mg/kg did not induce death but caused adverse effects which were rapid at onset but reversible. These effects include emesis, diarrhoea, loss of skin tone, reduced blood pressure, reduced appetite, loss of body weight and increased plasma ALT, AST and ALP activities.

- Repeat dose toxicity (with toxicokinetics)

The repeat-dose toxicity studies of gefitinib was evaluated in rats (daily dosing for 2 to 4 weeks and 6 months) and in dogs (daily dosing for 2 weeks and 1, 6, 12 months) following oral administration and by intravenous administration (daily dosing for 14 days and 7 to 14 days, respectively). For rats studies, oral doses from 0-125 mg/kg/d for the 2week repeat study, 0-40 mg/kg/d for the 1 month repeat study and 0-25 mg/kg/d for the 6 month repeat study demonstrated severe toxicity at high doses and a NOAEL of 10 mg/kg/d whereas for IV administration, high and intermediate doses showed similar lesions as the oral studies, with a NOAEL of 1 mg/kg/d. For dog toxicity studies, oral doses from 0-75 mg/kg/d for the 2 week repeat study and 0-40 mg/kg/d for the 1 repeat month study and 0-25 mg/kg/d for the 6 month repeat study showed severe toxicity at high doses and a NOAEL of 1-10 mg/kg/d. In the 6 months studies, the high-dose of 25 mg/kg/day had to be reduced to 15 mg/kg/day

from day 11 in dogs and from week 9 in rats. In addition, repeat-dose studies were performed in mice for a carcinogenicity study. The toxicity findings in a number of target organs were mostly attributed to the pharmacological effects of gefitinib. The target organs affected were:

Ovary
While the effect was reversible, there was a reduction in the weight of ovaries and an increase in the number of corpora lutea seen at higher doses in rats in the one month and six month oral toxicity studies. There was also reduced female fertility in rats at 20 mg/kg.

Eye
There was reversible corneal epithelial atrophy observed in the one month studies in rats and dogs. In studies in dogs, residual corneal translucency remained even after the recovery period. The histopathological changes observed were corneal epithelial atrophies without ulceration, inflammation and epidermal microabscesses of the eyelids with folliculitis and degeneration of hair follicles. Similar changes were found in the 6/12 month studies for both rat and dog. However, in the dog studies, the corneal translucencies progressed to corneal opacities which did not reverse.

Skin
There were skin changes observed in studies of rats and dogs. The changes were partly or fully reversible after recovery.

Haematologic parameters
There was an observed increase in white blood cell counts and decrease red cell parameters were considered to be secondary to the skin lesions.

Kidney
In the kidneys, renal papillary necrosis was observed in studies with high-doses of gefitinib in both rats and dogs. These changes were partially reversible in rats.

Liver
In the liver, in addition to increases in plasma liver enzymes (ALP, AST and AST), hepatocellular necrosis and eosinophilic sinusoidal macrophage infiltration were observed in the rat studies at 6 months at doses of 5 and 25 mg/kg (reduced to 15 mg/kg at 9 weeks). In dog studies, there was no increase in liver enzymes.

Gastro-intestinal tract
There was villous stunting and ulceration of the gastrointestinal tract observed in rats after a single 2000 mg/kg dose. In a rat 14 day study, villous atrophy was observed at 50 and 125 mg/kg. There were no salient findings in the GI tract in rats in the 1 and 6 month studies. In oral toxicity studies in dog, no salient findings were reported with a histopathological correlate.

Heart
There were observation of lengthened PR intervals and one case of second degree heart block in the 1 month oral toxicity study in dogs. In the 6 month study, one dog in the 25 mg/kg (reduced to 15 mg/kg at 9 weeks) dose group showed a PR interval prolongation.

- Genotoxicity

There was no evidence for a genotoxic potential of gefitinib when studied in a standard battery of genotoxicity assays. Gefitinib containing 1% of the impurity gefitinib 4-isomer showed no effects in *in vitro* assays for mutagenicity and clastogenicity.

- Carcinogenicity

Carcinogenicity studies have been performed in mice and rats. There was a small increase in the incidence of hepatic adenoma in male mice at the mid and high dose and in female mice at the high dose. An increase in hepatic adenoma was also observed in male and female rats at the high dose. An increased incidence in haemangiosarcoma of the mesenteric lymph node was observed in female rats at the high dose (10mg/kg/day) only. At no-effect levels there was no margin to clinical exposure.

- Reproduction Toxicity

There was no evidence of teratogenicity in the rat and rabbit in developmental studies below maternally toxic doses.

- Toxicokinetic data

Toxicokinetics data were reported from most of the repeat-dose toxicity studies. There was gender differences observed after a single dose with higher exposure observed in female rats. There was accumulation of toxicity observed after repeated oral dosing in most studies (3 to 4 fold in rat, 1.3 to 1.7 fold in dogs). The exposure levels (AUC) were relatively similar between rats and dogs at the same doses. There were no clear safety margins as most of the toxicity findings in the animal studies occurred at exposures under the expected clinical exposure

- Local tolerance

Phototoxicity studies were performed to evaluate the phototoxicity of gefitinib. Gefitinib was phototoxic to Balb/c 3T3 fibroblasts with a Photo Irritation Factor (PIF) of 11.62. Gefitinib showed no photoallergenic potential in guinea pig. There were no photogenotoxic studies performed.

- Other toxicity studies

Ecotoxicity/environmental risk assessment

An environmental risk assessment has been performed, and there are no indications that gefitinib pose a significant risk to the environment.

Discussion on the non-clinical aspects

The results from non-clinical studies support the oral formulation of the dose administered once daily.

The PD studies submitted suggest that gefitinib may have a cytostatic effect on tumour cell growth, and highlight the importance of continuous treatment to maintain antitumour activity. Complete inhibition of tumour growth was only observed at doses approximately 40 times the human therapeutic dose (5 mg/kg). The antitumour effect was not observed in all *in vivo* xenograft models, in spite of the excessive doses of gefitinib administered. The inhibition of tumour growth was small or absent in xenografts derived from pancreatic, bronco-epithelial, gastric, or breast tissue. It is suggested that other members of the ErbB family, who heterodimerise with ErbB1, may play a role in determining gefitinib sensitivity and resistance. There were several cell lines with either mutated or WT EGFR displaying different sensitivities to gefitinib. There was no clear difference between any of the factors related to cellular proliferation and inhibition of cell cycle progression that could account for the resistant phenotype. However, cell lines with WT EGFR displayed differences in factors associated with apoptosis when treated with gefitinib. Therefore, the results indicate that gefitinib may affect several intracellular signalling cascades and impact on tumour growth.

Based on the studies with the radiotracer gefitinib, the major organs affected for toxicity are the liver, kidney, bone marrow, spleen, as well as glandular tissue. Distribution of gefitinib and its metabolites into tumour xenografts were extensively studied and results showed that the level of radioactivity were higher in tumours than plasma and was significantly lower in other tissues (liver, kidney and lung). The role of gefitinib in P-gp transport was assessed both in an *in vitro* cell monolayer study and in an *in situ* brain penetration study. Gefitinib was shown to be a substrate for P-gp dependent transport, and results from the *in situ* study indicate that gefitinib limit P-gp mediated efflux.

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to the clinical exposure levels and with possible relevance to clinical use were as follows (See SmPC section 5.3):

- Corneal epithelia atrophy and corneal translucencies
- Renal papillary necrosis
- Hepatocellular necrosis and eosinophilic sinusoidal macrophage infiltration

Data from *in vitro* studies indicate that gefitinib has the potential to inhibit cardiac repolarization (e.g. QT interval). There was an observation that gefitinib could lengthen PR intervals, and consequently

affect heart function. Three non-clinical assays were performed to investigate the potential for QT prolongation. The dog Purkinje fibre assessments and the hERG assay showed a clear dose response relationship with increasing gefitinib concentrations. Although the dog telemetry study showed no statistically significant effects on QTc, a proportion of individual dogs receiving gefitinib showed some evidence of prolonged QTc. The clinical significance of these findings is unknown (See SmPC section 5.3)

A reduction in female fertility was observed in the rat at a dose of 20 mg/kg/day (See SmPC section 5.3).

Published studies have shown that genetically modified mice, lacking expression of EGFR, exhibit developmental defects, related to epithelial immaturity in a variety of organs including the skin, gastrointestinal tract and lung. When gefitinib was administered to rats during organogenesis, there were no effects on embryofoetal development at the highest dose (30 mg/kg/day). However, in the rabbit, there were reduced foetal weights at 20 mg/kg/day and above. There were no compound-induced malformations in either species. When administered to the rat throughout gestation and parturition, there was a reduction in pup survival at a dose of 20 mg/kg/day (See SmPC section 5.3).

Following oral administration of C-14 labelled gefitinib to lactating rats 14 days post partum, concentrations of radioactivity in milk were 11-19 fold higher than in blood (See SmPC section 5.3).

It is not known whether gefitinib is secreted in human milk. Gefitinib and metabolites of gefitinib accumulated in milk of lactating rats (see SmPC section 5.3). IRESSA is contraindicated during breast-feeding and therefore breast-feeding must be discontinued while receiving IRESSA therapy (see SmPC sections 4.3 and 4.6).

IRESSA is contraindicated for patients that are hypersensitive to the active substance or to any of the excipients (see SmPC section 4.3).

The toxicity of gefitinib was assessed in all major organs. In repeat dose studies, toxicity was mainly observed in the ovaries, eyes, skin, kidney, liver and the gastro-intestinal tract. There was some toxicity observed in the liver. The effects of gefitinib may be linked to the role of EGF in the regulation of normal function in these organs. For example, it is known that EGFR is involved in the regulation of ovarian function, lachrymal gland function, ocular homeostasis, gastrointestinal function, keratinocyte and hair follicle development and the integrity of the skin structure. EGF is also produced in the kidney as a growth factor for the regulation of epithelial cells in the kidney and urinary tract.

There was a lack of teratogenicity and no genotoxic potential was found in mice with gefitinib (see SmPC section 5.3). Given the known importance of EGFR in embryonic development this was unexpected since mice lacking EGFR exhibit developmental defects. Therefore, because of mechanistic considerations it is suggested that a potential for teratogenicity still exists and gefitinib should not be used during pregnancy unless necessary. Furthermore, studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. IRESSA should not be used during pregnancy unless clearly necessary, and women of childbearing potential must be advised not to get pregnant during therapy (see SmPC sections 4.6 and 5.3).

Gefitinib showed no genotoxic potential.

A 2-year carcinogenicity study in rats resulted in a small but statistically significant increased incidence of hepatocellular adenomas in both male and female rats and mesenteric lymph node haemangiosarcomas in female rats at the highest dose (10mg/kg/day) only. The hepatocellular adenomas were also seen in a 2-year carcinogenicity study in mice, which demonstrated a small increased incidence of this finding in male mice at the mid dose, and in both male and female mice at the highest dose. The effects reached statistical significance for the female mice, but not for the males. At no-effect levels in both mice and rats there was no margin in clinical exposure. The clinical relevance of these findings is unknown (See SmPC sedction 5.3).

The results of an *in vitro* phototoxicity study demonstrated that gefitinib may have phototoxicity potential (See SmPC sedction 5.3).

In conclusion, a number of target organs have been identified. There are no safety margins and these toxic events can therefore be expected to occur in the clinical situation. The safety evaluation must be based on clinical safety documentation and a well-performed monitoring of toxicity to those organs, which have been identified as potential target organs for toxicity. The toxicity studies were performed at doses up to maximal tolerated dose.

2.4 Clinical aspects

Introduction
The applicant originally sought a MAA in Europe in February 2003 for the indication "treatment of patients with locally or advanced metastatic Non-Small Cell Lung Cancer (NSCLC) who are refractory to both platinum-containing and docetaxel chemotherapy" but withdrew the application in January 2005.

For the current MAA, the applicant has submitted a pivotal Phase III study (INTEREST) and a Phase III study in a selected patient population in first line treatment (IPASS). The applicant has also submitted three supportive studies; V-15-32 – a Phase III study, SIGN – a Phase II symptom control study, and ISTANA – a Phase III study.

There is no paediatric development programme for gefitinib. There is no relevant indication for use of IRESSA in children and adolescents.

The tablet may be taken with or without food, at about the same time each day. The tablet can be swallowed whole with some water or if dosing of whole tablets is not possible, tablets may be administered as a dispersion in water (non-carbonated). No other liquids should be used. Without crushing it, the tablet should be dropped in half a glass of drinking water. The glass should be swirled occasionally, until the tablet is dispersed (this may take up to 20 minutes). The dispersion should be drunk immediately after dispersion is complete (i.e. within 60 minutes). The glass should be rinsed with half a glass of water, which should also be drunk. The dispersion can also be administered through a naso-gastric or gastrostomy tube (see SmPC section 4.2).

The INTEREST study was reviewed as part of a European Scientific Advice in the context of the follow-on study IDENTIFY, concerning parts of the development plan for gefitinib in early 2006 (Ref: EMEA/H/SA/137/4/2006/11). The CHMP advised the applicant that a large unrestricted indication in all patients would be of concern if the positive benefit would be limited in relation to EGFR FISH+ status, thus, it would be necessary that efficacy be demonstrated in the overall population.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A GCP inspection was carried out at 3 investigator sites in China involved in the INTEREST study. The final report of the GCP inspection concluded that there were no critical findings but noted 3 major deviations on the quality of the sponsors monitoring, the incomplete and inaccurate drug accountability and the inadequate process for updating informed consent during the study. However, the findings were found not have any detrimental impact on the well-being of the patients or the quality of the data. The data presented were accurately described and could be accepted for evaluation.
Pharmacokinetics

- Absorption

Gefitinib was slowly absorbed after an oral administration of tablets and capsules under fasting conditions. In the majority of the individuals the maximum plasma concentrations were observed between 3-7 h post-dose. Following oral administration of gefitinib, absorption is moderately slow and peak plasma concentrations of gefitinib typically occur at 3 to 7 hours after administration. The mean AUC values (ng.h/mL) in healthy volunteers were 434, 940, 2631 and 5768 ng.h/mL for 50, 100, 250 and 500 mg, respectively. The trapezoidal area under the curve $AUC_{(0-t)}$ accounted for more than 80% of the total AUC for the majority of the plasma concentration-time profiles, indicating that the profiles had been well defined. The mean C_{max} values in the healthy volunteers were 14.3, 35.3, 104.5 and 199.9 ng/ml for 50, 100, 250 and 500 mg, respectively. The data from cancer patients, which received the same dose, showed that AUC and C_{max} achieved was generally higher than that achieved in healthy volunteers.

The absolute bioavailability of the 250 mg oral dose of gefitinib was assessed in two Phase I clinical studies, 0031 and 0035. Study 0031 was performed in healthy volunteers and study 0035 was performed in patients with advanced solid tumours. In both studies, subjects received i.v. and oral doses of gefitinib. The bioavailability data from study 0031 are limited because the study design was amended following reports of adverse events at the infusion site (thrombophlebitis and rash). The calculation of the absolute bioavailability in both studies was based on the individual AUC data for the oral and i.v. doses. For the six volunteers in study 0031, the gmean absolute bioavailability was 57.2% with a 90% confidence interval of 48.5 to 67.5%. The absolute bioavailability in cancer patients was approximately 59.1%, with a 90% CI of 50.8 to 68.7%. In study 0229, the relative bioavailability of gefitinib 250 mg when administered as a tablet or as a tablet dispersion preparation (drink and tube administered) was determined in 18 healthy male volunteers. The pharmacokinetic parameters (AUC, C_{max}, t_{max} and t½) were similar following each method of administration of a single 250 mg tablet.

The influence of food on the relative bioavailability of gefitinib tablets was assessed in healthy volunteers in study 0002 and study 0036. The study 002 was performed using a dose of 50 mg and 0036 was performed using the relevant clinical dose of 250 mg. In both studies, volunteers were given a high-fat breakfast within 30 minutes before receiving the dose. In study 0036 the effect of a sustained elevation of gastric pH >5 on the relative bioavailability of gefitinib tablets was investigated since this study used the clinical relevant dose. Results from the two studies showed some disparity as the t_{max} was slightly higher in the fed group compared to fasted in the 002 study and no difference in the 036 study, the AUC and C_{max} in study 0002 decreased (by 14% and 34 %, respectively) after a fat-rich meal, while the AUC and C_{max} in study 0036 increased (by 37 % and 32 %, respectively) after a fat-rich meal. The overall effect of the sustained elevation in gastric pH (greater than 5) was a reduction in the relative bioavailability of the gefitinib tablet by 47% and is therefore of clinical relevance.

The study 0036 had two groups of volunteers with a crossover design. Group 1 consisted of 26 volunteers, who received either 250 mg gefitinib under fasted conditions or 250 mg gefitinib following a high fat breakfast (1262 kcal). Group 2 consisted of 26 volunteers, who received either two oral doses of 450 mg ranitidine (13 h and 1 h before the gefitinib dose) followed by a 250 mg dose of gefitinib, or only a single dose of 250 mg gefitinib, under fasted conditions. Ranitidine is a rapid-acting H2-receptor antagonist that should elevate the gastric pH to a value higher than five for at least four hours. Sodium bicarbonate was applied if a pH of ≥ 5 was not achieved. A summary of the results for study 0036 are shown in Table 3.

Table 3 PK parameters of a single oral dose 250 mg of gefitinib for group 1 and group 2 in healthy volunteers – Study 0036

Parameters	**Summary statistic**	**Group 1 [250 mg gefitinib]**		**Group 2 [250 mg gefitinib]**	
		Fasted	**Fed**	**Alone**	**+ raniditine**
AUC(ng.h/mL)	gmean CV(%)	2272(65.43)	3102(63.44)	2794(71.91)	1441(83.42)
$AUC_{(0-t)}$(ng.h/mL)	gmean CV(%)	2239(65.17)	3050(64.01)	2748(72.93)	1370(93.27)

$AUC_{(0-24)}$(ng.h/mL)	gmean CV(%)	1218(44.16)	1719(37.85)	1550(48.27)	544(48.59)
C_{max} (ng/mL)	gmean CV(%)	104.0(39.91)	137.4(31.39)	121.7(46.29)	35.54(47.03)
t_{max} (h)	median (range)	5.0(2.0-23.9)	5.0(2.0-8.0)	5.0 (2.0-7.0)	6.0(5.0-47.5)
$t_{1/2}$ (h)	mean (SD)	25.0(12.8)	26.9(15)	26.6(12.9)	29.4(18.5)

- Distribution

In the studies 0031 and 0035, the mean steady-state volume of distribution (given as V_{ss}) for gefitinib after an iv dose was estimated to be approximately 1600 L for healthy volunteers and 1400 L for cancer patients.

In vitro data indicate that gefitinib is a substrate to the P-glycoprotein transporter.

Distribution in blood:
There were two studies with oral administration of [^{14}C]-gefitinib (studies 0003, 0719) submitted. The concentrations of radioactivity in blood were lower compared to plasma at all times examined. The ratio of blood to plasma radioactivity was approximately 0.7 in study 0003 and 0.8 in study 0719. This indicated that a larger proportion of the drug-related radioactivity was associated with plasma than with the cellular components of the blood.

Plasma protein binding:
In study KPJ013, the binding to plasma proteins was found to be approximately 90%. The binding was independent of gefitinib concentration and there were no evidence of any gender difference in humans. Studies with purified human serum albumin and purified α-1 acid glycoprotein showed that gefitinib was bound to both proteins and that α-1 acid glycoprotein binding, appeared to be saturable at higher concentrations of gefitinib.

- Elimination and Excretion

Elimination of gefitinib was evaluated in healthy volunteers and cancer patients after an i.v. administration of gefitinib. The mean single-dose terminal half-life in volunteers ranged from 6.5 to 74.5 h (mean 30.5 h) and in cancer patients from 15.6 to 111 h (mean 41.0 h).

Single ascending oral doses of 1, 3, 10, 25, 50 and 75 mg of gefitinib were administered. After 24 hours, there was less than 0.5 % of the initial dose recovered in the urine, indicating that the renal route is not a major route of elimination for gefitinib in humans.

In studies where [^{14}C]-gefitinib was administered to healthy volunteers, approximately 84 % of the radioactivity was recovered in urine and faeces over 7 days and 90 % over 10 days. The majority of the dose, approximately 81-86 %, was eliminated in the faeces. Urinary excretion accounted for less than 4 % of the dose.

- Metabolism

The metabolism of [^{14}C]-gefitinib was explored *in vitro* using pooled human microsomes. Two principal *in vitro* metabolites (M537194 and M387783) were formed. These metabolites were the products of oxidative cleavage of the propoxymorpholine ring and defluorination of the chlorofluorophenyl ring and it was shown that their formation was mainly catalysed by CYP3A4. In total, 17 metabolites of gefitinib were identified from *in vitro* systems. The major metabolite found in human plasma, O-desmethyl gefitinib, M523595, was detected only in minor quantities.

The use of selective chemical inhibitors and heterologous expressed human P450 enzymes showed that the oxidative metabolism of gefitinib in human hepatic microsomes was catalysed mainly by CYP3A4. The quantitatively most important routes of [^{14}C]-gefitinib metabolism were mediated by CYP3A4, while CYP3A5 was a minor contributor. However, formation of M523595, the major human metabolite, was catalysed almost exclusively by CYP2D6.

The metabolism of gefitinib *in vivo* was also explored. Gefitinib accounted for up to 20% of the plasma radioactivity in healthy volunteers, and although M523595 accounted for some of the other 80%, there are other components present that were not measured by the metabolite assay. In human, the major single metabolite in faeces was M523595, which accounted for 13.7% of the dose. A large number of other components (including M387783, M605207, M537194, M605212 and gefitinib), each accounting for between 1.6-13.2% of the dose, were also detected in human faeces. Unchanged gefitinib accounted for only 3.9% of the dose, indicating that gefitinib was extensively metabolised in man.

In humans, the major metabolite M523595 represented ~12% of circulating radioactivity between 3 and 5 h, then rising to around 17% at 8 h onwards.

- Dose proportionality and time dependencies

The dose proportionality has been taken into consideration in both single- and multiple dose studies. Three single-dose studies of gefitinib evaluating the dose proportionality in healthy male volunteers were submitted. It was not possible to conclude the dose proportionality in the terms of AUC and C_{max} for gefitinib over the range 50 to 500 mg. The terminal half-life of gefitinib appeared to be independent of dose, although there was a considerable variability between volunteers. There was a 19.2 fold and a 16.7 fold difference of exposure at the 250 mg and at the 500 mg level, respectively. To assess the degree of non-proportionality, pair-wise comparisons of dose-normalised AUC and C_{max} for each dose level were made. The estimated dose effect on the dose–normalised AUC and C_{max} after 50 and 100 mg, 50 and 250 mg and 100 and 250 mg, appeared to indicate proportionality, since the p-values were not significant. The opposite was shown by comparisons of the estimated dose effect on the dose-normalised AUC or C_{max} after 50, 100 and 250 mg, all compared with 500 mg. All results gave significant p-values. The conclusion was that dose proportionality was not shown over the entire dose range, and the degree of non-proportionality was highest in the largest administered doses, both in cancer patients and healthy volunteers.

For multiple dose studies, patients received one of six gefitinib doses ranging from 50 mg/day to 700 mg/day. $AUC_{(0-24)}$ following multiple dosing for 14 days. The results show that proportionality was observed up to the recommended therapeutic dose. Non-proportionality was observed for doses exceeding 250-400 mg.

Time dependency was evaluated in two studies with healthy volunteers and two studies with cancer patients. Steady-state plasma concentrations were achieved after 3 to 7 days in healthy volunteers and after 6 to 10 days in patients with solid tumours.

Relationship between exposure/concentration and efficacy and adverse events was not established. However there is a trend with adverse events and increasing dose. There is no data on decreasing dose or halving the dose for patients who have increased toxicity and therefore, it is not known if plasma concentrations would still be therapeutic.

- Special populations

No study was conducted to assess the effect of renal impairment on the pharmacokinetics of gefitinib. From analyses of population pharmacokinetic data in cancer patients, no relationships were identified between predicted steady state trough concentration and patient age, body weight, gender, ethnicity or creatinine clearance (above 20 ml/min).No dose adjustment is required in patients with impaired renal function at creatinine clearance >20 ml/min. Only limited data are available in patients with creatinine clearance ≤ 20 ml/min and caution is advised in these patients (see SmPC section 4.2 and 5.2).

Gefitinib has been evaluated in a clinical trial conducted in 41 patients with solid tumours and normal hepatic function, or moderate or severe hepatic impairment (classified according to baseline Common Toxicity Criteria grades for AST, alkaline phosphatase and bilirubine) due to liver metastases. It was shown that following daily administration of 250 mg gefitinib, time to steady state, total plasma clearance ($C_{maxSS)}$ and steady-state exposure (AUC_{24SS}) were similar for the groups with normal and moderately impaired hepatic function. Data from 4 patients with severe hepatic impairment due to

liver metastases suggested that steady-state exposures in these patients are also similar to those in patients with normal hepatic function.

In a phase I open-label study of single dose gefitinib 250 mg in patients with mild, moderate or severe hepatic impairment due to cirrhosis (according to Child-Pugh classification), there was an increase in exposure in all groups compared with healthy controls. An average 3.1-fold increase in exposure to gefitinib in patients with moderate and severe hepatic impairment was observed. None of the patients had cancer, all had cirrhosis and some had hepatitis. This increase in exposure may be of clinical relevance since adverse experiences are related to dose and exposure to gefitinib.Patients with moderate to severe hepatic impairment (Child Pugh B or C) due to cirrhosis have increased plasma concentrations of gefitinib. These patients should be closely monitored for adverse events. Plasma concentrations were not increased in patients with elevated aspartate transaminase (AST), alkaline phosphatase or bilirubin due to liver metastases (see SmPC section 4.2 and 5.2).

No dose adjustment is required on the basis of patient age (see SmPC section 4.2 and 5.2).

There was no evidence of any relevant differences in renal impairment, gender, ethnicity, weight, age in the pharmacokinetics of gefitinib.

- Pharmacokinetic interaction studies

In vitro and *in vivo* studies indicate that gefitinib is metabolised mainly by CYP3A4 and CYP2D6.

Ketoconazole, an inhibitor of CYP3A4, markedly reduced formation of some of the metabolites of gefitinib *in vitro*. Clinical drug-drug-interaction studies were performed to explore the inhibition and induction of CYP3A4 by other drugs and influence on the plasma exposure to gefitinib. In studies in healthy volunteers, inhibition of CYP3A4 with itraconazole increased the exposure to gefitinib by 60-80% while induction of CYP3A4 with rifampicin reduced the exposure to gefitinib by about 80%.

There were no *in vivo* studies exploring the effect of drugs inhibiting CYP2D6 on gefitinib pharmacokinetics. However, in subjects with a poor CYP2D6 activity, intake of gefitinib resulted in a mean 2-fold higher exposure to the drug compared to extensive CYP2D6 metabolisers, and it would be expected that strong CYP2D6 inhibitors (e.g. fluoxetine, paroxetine) increased gefitinib exposure to the same extent. This increase is considered clinically relevant and has been included in the SmPC. No specific dose adjustment is recommended in patients with known CYP2D6 poor metaboliser genotype, but these patients should be closely monitored for adverse events (see SmPC section 4.2 and 5.2).

In vitro studies indicate that gefitinib may have the potential to inhibit CYP2D6. A drug-drug interaction study was also performed to explore whether gefitinib could inhibit CYP2D6. A modest inhibition of CYP2D6 by gefitinib, by measuring the metabolism of metoprolol, was found.
There were no *in vivo* interaction studies in humans to explore induction of CYP1A and inhibition of CYP2C19, CYP3A4 and UGT1A1 by gefitinib.

Pharmacodynamics

- Mechanism of action

No clinical studies have been submitted. The epidermal growth factor (EGF) and its receptor (EGFR [HER1; ErbB1]) have been identified as key drivers in the process of cell growth and proliferation for normal and cancer cells. EGFR activating mutation within a cancer cell is an important factor in promotion of tumour cell growth, blocking of apoptosis, increasing the production of angiogenic factors and facilitating the processes of metastasis.

Gefitinib is a selective small molecule inhibitor of the epidermal growth factor receptor tyrosine kinase and is an effective treatment for patients with tumours with activating mutations of the EGFR tyrosine kinase domain regardless of line of therapy. No clinically relevant activity has been shown in patients with known EGFR mutation-negative tumours.

- Primary and Secondary pharmacology

No clinical studies exploring the primary pharmacology of gefitinib have been submitted. In studies investigating biomarkers of EGF receptor tyrosine kinase in skin biopsies taken before and on-trial changes reflective of EGF receptor inhibition (i.e. activated mitogen-activated protein kinase, p27, Ki 67, cell cycle Gi arrest, and apoptosis) were present at all dose levels tested. Gefitinib has been shown to inhibit tyrosine phosphorylation by acting as a competitive inhibitor of ATP. In contrast to data from tumour cell-line and anti-tumour activity, mainly cytostatic, has been demonstrated in a conventional, based non-clinical development programme. However, in clinical trials, tumour shrinkage was observed in only a small proportion of patients, was in many cases rather dramatic and occurred early, median time to response about 4 weeks.

Clinical efficacy

This application is based on three Phase III studies (ISEL, INTEREST and IPASS), supported by 3 additional studies (V-15-32, SIGN and ISTANA). In addition, to the pivotal and supportive studies shown in table 20, the Phase II IDEAL I and IDEAL II studies were submitted as dose-finding studies. Furthermore, a number of other studies have been submitted with gefitinib in NSCLC but in other patient populations. Data from these studies are included in the evaluation of safety.

The table below provides an overview of studies of relevance for this submission

Study	Phase	Line-therapy	Dosages	Gefitinib (n)	Control (n)
IDEAL I & II	II	2nd and later	250 mg vs. 500 mg od	424	
ISEL	III	2nd and later	250 mg od vs. placebo	1129	563
INSTEP	II	1st	250 mg od vs. placebo	100	101
INTEREST	III	2nd and later	250 mg od vs. docetaxel 75 mg/m2	733	733
V-15-32	III	2nd and later	250 mg od vs. docetaxel 60 mg/m2	245	244
SIGN	II	2nd	250 mg od vs. docetaxel 75 mg/m2	71	70
ISTANA	II	2nd	250 mg od vs. docetaxel 75 mg/m2	78	83
IPASS	III	1st	250 mg od vs carboplatin/paclitaxel	609	608

- Dose response study(ies)

In several phase I studies, including the studies D7913C0005, D7913C00011, D7913C00012 and V-15-11, up to nine dose levels of gefitinib was tested, ranging from 50 mg to 1000 mg. MTD was established at 750 mg and 1000 mg. Clear dose-dependency was seen with respect to tolerability. Doses below 600 mg were accompanied by mild and readily reversible side effects, while 600 mg or higher doses yielded toxicity leading to treatment interruption and dose reductions. Tumour response was seen across a wide range of doses between 150 and 800 mg.
Two randomised, dose-comparative studies in patients with advanced NSCLC have been performed in the US (0039, IDEAL II) and across Europe, South Africa, Australia and Japan (0016, IDEAL I). Study 0039 focused on patients previously treated with cisplatin-based regimens and docetaxel. The regimen for both studies was 250 mg or 500 mg daily oral dose of gefitinib.

The Phase II IDEAL studies, evaluated the efficacy and safety of the 250 mg and 500 mg doses of gefitinib for the treatment of patients with pre-treated NSCLC. The trials were similar in design (multicentre, double-blind and parallel-group) and both recruited patients with relapsed disease. IDEAL I was conducted primarily in Europe and Japan and IDEAL II was conducted in the US. Patients were randomised to receive either 250 mg or 500 mg of gefitinib per day. Objective tumour response was a primary efficacy endpoint for both studies. IDEAL II had an additional primary endpoint of disease-related symptom improvement rate, measured using LCS, the 7-symptom Lung Cancer Subscale of the Functional Assessment of Cancer Therapy-Lung (FACT-L).The key efficacy findings are presented in Table 4. No significant differences between the two dose groups of 250 mg and 500 mg were evident for any efficacy endpoints. These efficacy results, together with an evaluation of the adverse events associated with the two doses, led to the choice of gefitinib 250 mg as the optimum biological effective dose.

Table 4 Key efficacy results from the Phase II IDEAL studies: ITT population for IDEAL II; EFR or LCS population for IDEAL I

Efficacy parameter	IDEAL I[a]		IDEAL II	
	250 mg (N = 103)	500 mg (N = 105)	250 mg (N = 102)	500 mg (N = 114)
Objective tumour response rate (%) (95% confidence interval)	18.4 (11.5 to 27.3)	19.0 (12.1 to 27.9)	11.8 (6.2 to 19.7)	8.8 (4.3 to 15.5)
Symptom improvement rate (%) (95% confidence interval)	40.3 (28.5 to 53.0)	37.0 (26.0 to 49.1)	43.1 (33.4 to 53.3)	35.1 (26.4 to 44.6)
Disease control rate (%) (95% confidence interval)	54.4 (44.3 to 64.2)	51.4 (41.5 to 61.3)	42.2 (32.4 to 52.3)	36.0 (27.2 to 45.5)
Median PFS (months) (95% confidence interval)	2.7 (2.0 to 2.8)	2.8 (1.9 to 3.8)	1.9 (1.8 to 2.8)	2.0 (1.6 to 2.2)
Median survival (months)[b] (95% confidence interval)	7.6 (5.3 to 10.1)	8.0 (6.7 to 9.9)	6.1 (4.8 to 7.7)	6.0 (4.3 to 7.2)
FACT-L improvement rate (%) (95% confidence interval)	23.9 (14.3 to 35.9)	21.9 (13.1 to 33.1)	34.3 (25.2 to 44.4)	22.8 (15.5 to 31.6)
TOI improvement rate (%) (95% confidence interval)	20.9 (11.9 to 32.6)	17.8 (9.8 to 28.5)	33.3 (24.3 to 43.4)	20.2 (13.2 to 28.7)

[a]Evaluable-for-symptom-improvement population (applicable to symptom improvement rate) consisted of 140 patients (250 mg, n = 67; 500 mg, n = 73).
[b]Median survivals in IDEAL I not calculable at time of completion of the CSR due to insufficient events; subsequently reported in Fukuoka et al 2003.

- Main study(ies)

IPASS (D791AC00007): *An Open Label, Randomised, Parallel Group, Multicentre, Phase III Study to Assess Efficacy, Safety and Tolerability of Gefitinib (IRESSA) (250mg tablet) Versus Carboplatin / Paclitaxel Doublet Chemotherapy as First-Line Treatment in Selected Patients with Advanced (Stage IIIB or IV) Non-Small Cell Lung Cancer (NSCLC) in Asia*

METHODS

Study Participants
Patients had to fill the following inclusion criteria:
1. Male or female aged 18 years and over
2. Histologically or cytologically confirmed NSCLC with adenocarcinoma histology (including bronchoalveolar). Note: adeno-squamous histology was not allowed. Sputum cytology alone was not acceptable. Cytological specimens obtained by brushing, washing, or needle aspiration of a defined lesion were acceptable.
3. Locally advanced Stage IIIB not amenable to local therapy (eg, pleural effusion) or Stage IV (metastatic) disease.
4. Never smokers (defined as having smoked less than 100 cigarettes in their lifetime [as detailed in protocol amendment 01]) or light ex-smokers (defined as having ceased smoking at least 15 years before Day 1 of study treatment and having smoked 10 pack-years or fewer)
5. No prior chemotherapy, biological (including targeted therapies such as EGFR and vascular epidermal growth factor [VEGF] inhibitors) or immunological therapy. Previous adjuvant chemotherapy was permitted if treatment was not platinum-based and was completed more than 6 months before Day 1 of study treatment. Prior surgery or radical radiotherapy had to be completed more than 6 months before Day 1. Palliative radiotherapy to a metastatic site was permitted, but palliative wide field radiotherapy to the lung had to be completed at least 4 weeks before Day 1, with no persistence of any radiotherapy-related toxicity.
6. Measurable disease according to RECIST criteria with at least 1 measurable lesion not previously irradiated

7. World Health Organization (WHO) performance status (PS) of 0 to 2
8. Willing to complete the FACT-L questionnaire

Patients who had any of the following were excluded from the study:
9. Known severe hypersensitivity to gefitinib or any of the excipients of this product
10. Known severe hypersensitivity to carboplatin, paclitaxel or any of the excipients of these products
11. Known severe hypersensitivity to pre-medications required for treatment with carboplatin / paclitaxel doublet chemotherapy
12. Newly diagnosed Central Nervous System (CNS) metastases that had not yet been definitively treated with surgery and/or radiation. Patients with previously diagnosed and treated CNS metastases or spinal cord compression could be considered if they were clinically stable and had been discontinued from steroid therapy for at least 4 weeks prior to first dose of study medication.
13. Other co-existing malignancies or malignancies diagnosed within the last 5 years (as detailed in protocol amendment 01) with the exception of basal cell carcinoma or cervical cancer in situ
14. Past medical history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis which required steroid treatment or any evidence of clinically active interstitial lung disease
15. Pre-existing idiopathic pulmonary fibrosis evidence by computerised tomography (CT) scan at baseline
16. Any unresolved chronic toxicity greater than Common Toxicity Criteria (CTC) AE Grade 2 from previous anticancer therapy
17. Absolute neutrophil counts (ANC) less than 2.0 x 10^9/l (2,000/mm^3), platelets less than 100 x 10^9/l (100,000/mm3) or haemoglobin less than 10 g/dl
18. Serum bilirubin greater than 1.5 times the upper limit of reference range (ULRR).
19. Serum creatinine greater than 1.5 times the ULRR or creatinine clearance less than or equal to 60 ml/min
20. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 2.5 times the ULRR if no demonstrable liver metastases or greater than 5 times the ULRR in the presence of liver metastases.
21. Unable to tolerate carboplatin / paclitaxel doublet chemotherapy, as judged by the investigator.
22. Life expectancy of less than 12 weeks
23. Insufficient lung function as determined by either clinical examination or an arterial oxygen tension (PaO_2) of < 70 Torr
24. Concomitant use of phenytoin, carbamazepine, rifampicin, barbiturates, or St. John's Wort
25. Treatment with a non-approved or investigational drug within 30 days before Day 1 of study treatment
26. Known biomarker status of 1 or more of the following: tumour EGFR gene copy number, tumour EGFR gene mutation status, tumour EGFR protein expression (as detailed in protocol amendment 01).

Treatments
For the gefitinib arm, patients received oral dose of 250 mg tablet once a day. For the carboplatin/paclitaxel arm, patients received intravenous (i.v.) 200 mg/m^2 paclitaxel over 3 hours followed by i.v. carboplatin AUC 5.0 or 6.0 for 15-60 minutes, every 3 weeks for a maximum of 6 cycles. Dose modifications of carboplatin and paclitaxel for toxicity were allowed. After progression, patients randomised to the gefitinib treatment arm could receive carboplatin / paclitaxel for a maximum of 6 cycles. Investigators could decide to treat with another approved therapy if carboplatin / paclitaxel therapy was considered unsuitable. Subsequent treatment following discontinuation of carboplatin / paclitaxel in both treatment arms was at the investigator's discretion.

Objectives
The primary objective was to compare gefitinib with carboplatin / paclitaxel doublet chemotherapy given as first-line treatment in terms of PFS in selected NSCLC patients (non-inferiority).

Outcomes/endpoints
Primary efficacy analyses

The primary efficacy outcome was PFS, defined as the interval from the date of randomisation to the date of objective disease progression per RECIST criteria, or the date of death from any cause. Patients were censored for progression at their last evaluable objective tumour assessment only if they had neither progressed nor died. Patients censored at their last evaluable objective tumour assessment include those who were lost to follow up or who had withdrawn their consent to continue in the study. Progression information continued to be collected for patients discontinuing study therapy prior to disease progression, irrespective of whether the patient subsequently took anti-cancer therapy after study therapy discontinuation.

Secondary efficacy outcome variables

The secondary efficacy outcomes were OS, ORR, QoL (as measured by FACT-L and TOI) and symptom improvement (as measured by LCS). QOL and symptoms were assessed using the FACT-L questionnaire, which comprised 5 domains: 4 that evaluated physical (PWB), social-familial (SWB), emotional (EWB), and functional well-being (FWB) and 1 that evaluated additional QOL aspects specifically related to lung cancer (LCS).

Exploratory efficacy outcome variables

Tumour samples were analysed to determine biomarker status in the following priority order; 1) EGFR mutation status, 2) EGFR gene copy number (FISH status) and 3) EGFR protein expression status.

Sample size

The calculation of the number of patients required for this study was based upon the assessment in the overall patient population for PFS with a non-inferiority limit HR of 1.2, which translates to up to 1 month shortfall on gefitinib if the PFS on carboplatin / paclitaxel is 6 months. With a recruitment period of 20 months and 1212 patients randomised (606 per treatment arm), a follow up period of 6 months would be sufficient to see 944 progression events (80% power and 5% (2-sided) significance level).

Randomisation

Randomisation was stratified with respect to World Health Organisation (WHO) performance status (PS) (0 or 1 versus 2), smoking history (never versus light ex-smokers), gender and centre.

Blinding (masking)

The study was open label.

Statistical methods

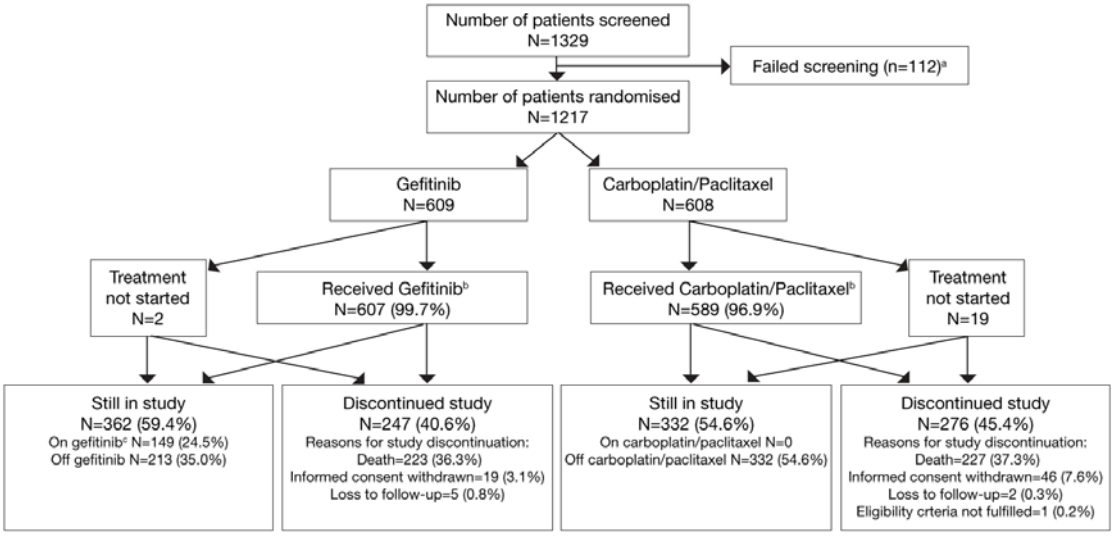
The primary analysis was performed by Cox proportional hazards model with covariates for randomised treatment, sex, WHO performance status and smoking history. All statistical tests were performed at a 2-sided 5% significance level unless otherwise stated.

Interim analyses

There was one interim analysis planned to detect inferiority of gefitinib to carboplatin / paclitaxel for PFS. Termination of the study early was considered if PFS for gefitinib was inferior to carboplatin / paclitaxel at a 2-sided 10% significance level. That is, if the lower 90% CI for the HR was >1.0. There was no adjustment of significance level for the primary analysis of PFS as there was no opportunity in the interim analysis to accept the hypothesis of non-inferiority for PFS.

RESULTS

Participant flow



[a] Main reasons were: serum creatinine greater than 1.5 x upper limit of reference range or creatinine clearance less than or equal to 60 mL/min; newly diagnosed CNS metastases that had not yet been definitively treated with surgery and/or radiation; ANC less than 2.0 x 109/L, platelets less than 100 x 109/L or haemoglobin less than 10 g/dl.
[b] The safety analysis, conducted according to treatment received, was performed on this population.
[c] 63 (10.3%) patients that were treated with gefitinib and had disease progression received gefitinib after progression as the investigator considered it was providing benefit and 1 (0.2%) patient that was treated with carboplatin / paclitaxel and had disease progression continued received carboplatin / paclitaxel after progression as the investigator considered it was providing benefit.
AE=adverse event; DCO=Data cut-off date (14 April 2008); N=Number of patients.

Recruitment
A total of 1329 patients were screened for the study and 1217 subsequently randomised. All patients were recruited from 87 centres from several countries in Asia.

Conduct of the study
Few patients in either treatment group had major deviations: 12 (2%) in the gefitinib arm and 28 (4.6%) in the carboplatin / paclitaxel arm. Protocol deviations were generally balanced between treatment groups with the exception of the number of patients that failed to receive randomised treatment: 19 patients in the carboplatin / paclitaxel group compared with 2 patients in the gefitinib group (reason for treatment discontinuation was 'subject not willing to continue treatment),

Treatment compliance
Patients self-administered gefitinib and compliance was assessed by tablet count. Treatment compliance with gefitinib was high (98.3%). Carboplatin and paclitaxel administration were documented. The mean (median) dose intensity of chemotherapy (total carboplatin / paclitaxel received per week divided by that planned) was 92% (96%) for both carboplatin and paclitaxel.

Concomitant medication
More gefitinib-treated patients received different types of topical corticosteroids to mainly treat skin toxicity events. Carboplatin / paclitaxel patients received premedication with dexamethasone, diphenhydramine, H2-blockers, and 5-HT3 antagonists. In addition, patients received propulsives, colony stimulating factors, benzodiazepine derivates, antihistamines such as chlorphenamine and contact laxatives, which were more commonly given to patients in the carboplatin/paclitaxel. Concomitant medications reflected toxicity management, which were consistent with the safety profile of all drugs.

Baseline data
Demographic and baseline characteristics are summarised in Table 5.

Table 5 Demographic and baseline characteristics (ITT Population) - IPASS

Demographic or baseline characteristic		Gefitinib (N=609)		Carboplatin / Paclitaxel (N=608)		Total (N=1217)	
Sex, n (%)	Male	125	(20.5)	127	(20.9)	252	(20.7)
	Female	484	(79.5)	481	(79.1)	965	(79.3)
Age (years)	Mean (SD)	56.5	(11.4)	56.8	(11.1)	56.7	(11.2)
	Median	57.0		57.0		57.0	
	Range	24.0 to 84.0		25.0 to 84.0		24.0 to 84.0	
Age distribution, n(%)	<45 years	98.0	(16.1)	84.0	(13.8)	182.0	(15.0)
	45 to 64 years	349.0	(57.3)	368.0	(60.5)	717.0	(58.9)
	65 to 74 years	138.0	(22.7)	128.0	(21.1)	266.0	(21.9)
	≥75 years	24.0	(3.9)	28.0	(4.6)	52.0	(4.3)
Race, n (%)	Caucasian	3	(0.5)	1	(0.2)	4	(0.3)
	Oriental	603	(99.0)	606	(99.7)	1209	(99.3)
	Other	3	(0.5)	1	(0.2)	4	(0.3)
Ethnic group, n, (%)	Asian[a]	179	(29.4)	184	(30.3)	363	(29.8)
	Chinese	314	(51.6)	304	(50.0)	618	(50.8)
	Japanese	114	(18.7)	119	(19.6)	233	(19.1)
	Other[b]	2	(0.3)	1	(0.2)	3	(0.2)
Smoking history, n (%)	Never smoked	571	(93.8)	569	(93.6)	1140	(93.7)
	Light ex-smoker	37	(6.1)	38	(6.3)	75	(6.2)
	Ex-smoker (non-light)	1	(0.2)	1	(0.2)	2	(0.2)

[a] Patients belonging to Asian ethnic groups other than Chinese and Japanese.
[b] Indian (2 patients) and Punjabi (1 patient).
ITT=Intention-to-treat; N=Number of patients; SD=standard deviation

Primary endpoint: Progression free survival

The randomised phase III first line IPASS study was conducted in patients in Asia with advanced (stage IIIB or IV) NSCLC of adenocarcinoma histology who were ex-light smokers (ceased smoking ≥ 15 years ago and smoked ≤ 10 pack years) or never smokers. The primary efficacy analysis on PFS is summarised in Table 6 and Figure 2.

Table 6 PFS for the overall population – IPASS

Analysis	N	Number (%) Progressed		Hazard ratio[a]	95% CI	p-value
Primary ITT analysis[b]						
Gefitinib	609	**453**	**(74.4)**	**0.741**	0.651, 0.845	<0.0001
Carboplatin/ paclitaxel	608	**497**	**(81.7)**			
Supportive PP analysis[b]						
Gefitinib	597	446	(74.7)	0.743	0.652, 0.848	<0.0001
Carboplatin/ paclitaxel	580	489	(84.3)			
Supportive ITT analysis: Unadjusted for covariates						
Gefitinib	609	453	(74.4)	0.735	0.645, 0.838	<0.0001
Carboplatin/ paclitaxel	608	497	(81.7)			

Table 6 PFS for the overall population – IPASS

Analysis	N	Number (%) Progressed		Hazard ratio[a]	95% CI	p-value
Supportive ITT analysis: Censoring events occurring >12 weeks after previous adequate RECIST assessment[c]						
Gefitinib	609	444	(72.9)	0.745	0.653, 0.850	<0.0001
Carboplatin/ paclitaxel	608	484	(79.6)			
Supportive ITT analysis: Censored before the start of additional anti-cancer therapy[d]						
Gefitinib	609	442	(72.6)	0.737	0.645, 0.843	<0.0001
Carboplatin/ paclitaxel	608	467	(76.8)			

[a] Hazard ratios derived from Cox proportional hazards model with covariates for randomised treatment, sex, WHO performance status and smoking history: a HR <1 implies a lower risk of progression/death over a given period with gefitinib compared with carboplatin / paclitaxel. The non-inferiority margin was HR 1.2.

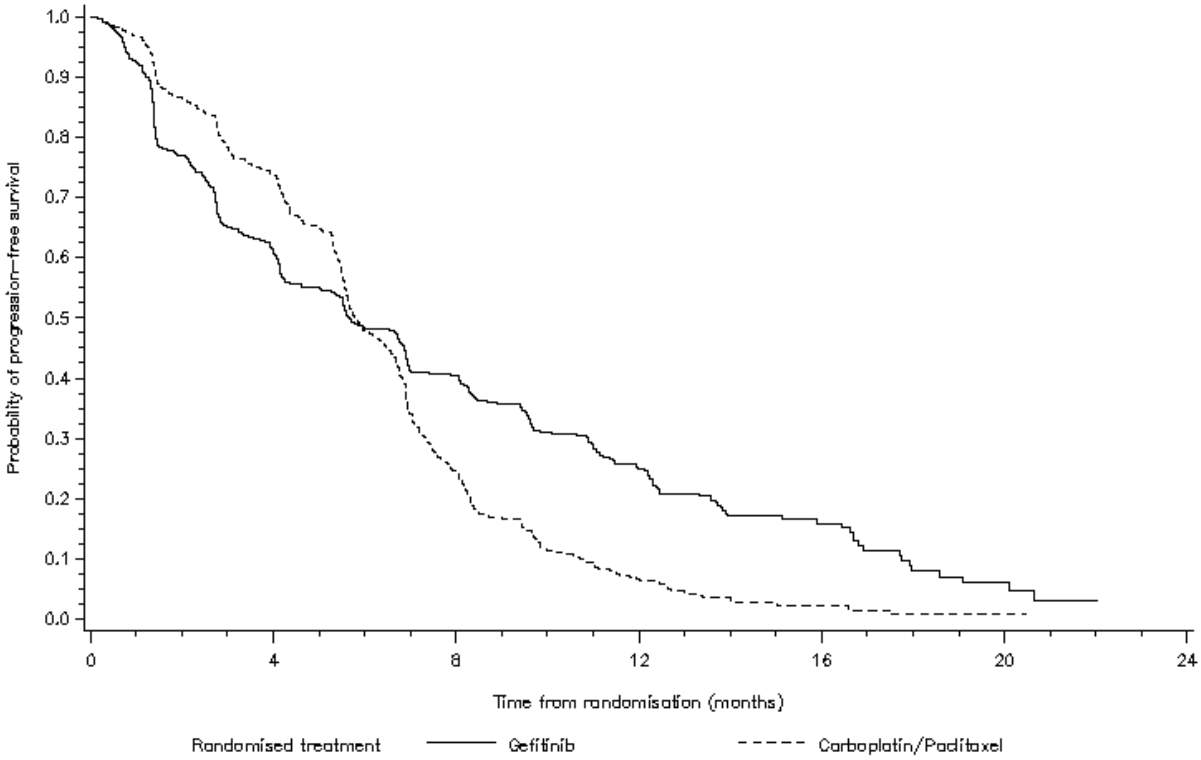
[b] The primary ITT and the PP analyses includes all progression events, or deaths in the absence of progression, regardless of when they occurred.

[c] The secondary ITT analysis does not include progression events, or deaths in the absence of progression which occur more than 12 weeks after the last evaluable RECIST assessment.

[d] The secondary ITT analysis does not include progression events, or deaths in the absence of progression that occurred after the start of additional anti-cancer therapy.

CI=Confidence interval; ITT=Intention-to-treat; PFS=progression free survival; PP=Per-protocol; RECIST=Response Evaluation Criteria in Solid Tumours

Figure 2 Kaplan-Meier curves for the primary analysis of PFS (ITT Population) - IPASS



Number of patients at risk

Months	0	4	8	12	16	20	24
Gefitinib	609	363	212	76	24	5	0
Carboplatin/Paclitaxel	608	412	118	22	3	1	0

At the data cut off (14 April 2008) for the primary analysis, OS data had not reached maturity as 450 deaths had occurred (450/1217, 37% maturity) and the final analysis is planned when 944 deaths will

have occurred. The OS in the ITT at the data cut off was similar in both treatment groups (HR 0.91; 95%CI 0.76-1.10) where the median survival was 18.6 months in the gefitinib arm and 17.3 months in the carboplatin / paclitaxel arm (Table 7 and Figure 3).

Table 7 Summary and analysis of overall survival (ITT population) - IPASS

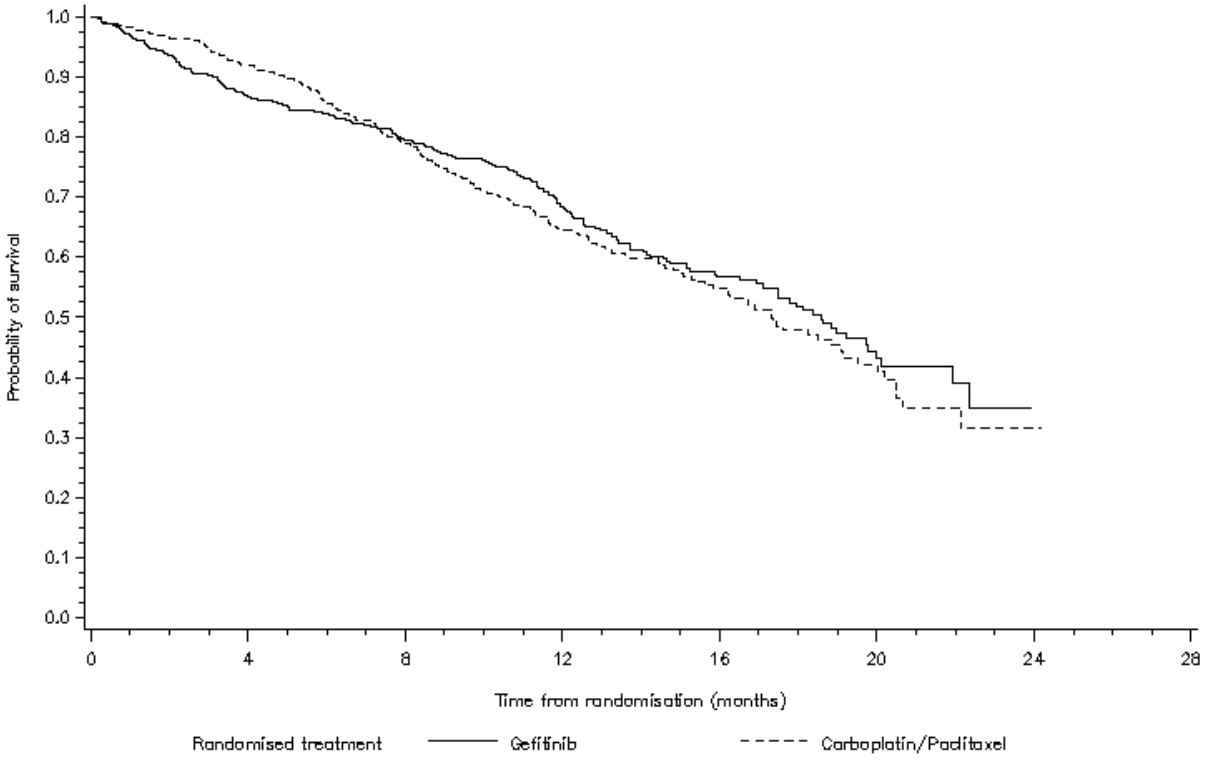
	Gefitinib (N=609)	Carboplatin / Paclitaxel (N=608)
Analysis of overall survival		
HR[a] (95% CI)	**0.911 (0.757, 1.097)**	
Summary of overall survival		
Number (%) died	223 (36.6)	227 (37.3)
Median survival (months)[b]	**18.6**	**17.3**
6-month survival rate (%)[b]	84.0	85.5
9-month survival rate (%)[b]	77.1	74.7
1 year survival rate (%)[b]	68.3	64.4

[a] HRs derived from Cox proportional hazards model: a HR <1 implies a lower risk of death over a given period on gefitinib compared with carboplatin / paclitaxel.

[b] Calculated using Kaplan-Meier technique.

CI=confidence interval; HR=hazard ratio; ITT=Intention-to-treat; N=Number of patients

Figure 3 Kaplan-Meier curves for overall survival (ITT Population) - IPASS



Number of patients at risk

Months	0	4	8	12	16	20	24	28
Gefitinib	609	514	423	239	118	38	0	0
Carboplatin/Paclitaxel	608	524	401	212	104	32	1	0

The secondary endpoint objective tumour response is summarised in Table 8. The ORR was higher with gefitinib compared to carboplatin / paclitaxel (43% compared 32%, respectively).

Table 8 Summary of best overall response (ITT population) - IPASS

	Gefitinib (N=609)		Carboplatin / Paclitaxel (N=608)	
Best overall response, n (%)				
Complete response (CR)	5	(0.8)	1	(0.2)
Partial response (PR)	257	(42.2)	195	(32.1)
Stable disease (SD)	182	(29.9)	286	(47.0)
Progression	129	(21.2)	70	(11.5)
Objective tumour response (CR+PR)	**262**	**(43.0)**	**196**	**(32.2)**
Disease control (CR+PR+SD)	444	(72.9)	482	(79.3)
Not evaluable	36	(5.9)	56	(9.2)
Incomplete post-baseline data	2	(0.3)	9	(1.5)
No post-baseline scans	34	(5.6)	47	(7.7)
Analysis of objective tumour response				
Odds ratio (95% CI)	1.587 (1.254, 2.008)			
p-value	0.0001			

Exploratory biomarkers

683 patients out of the 1217 patients randomised in the study provided a sample for exploratory biomarker analysis. The total number of patients with evaluable data was 437 (36%) for EGFR mutation analyses, 365 (30%) for EGFR protein expression analyses and 406 (33%) for EGFR FISH status analyses. There were 60% (261/437) of patients that were positive for EGFR mutation status, 61% (249/406) for EGFR FISH status and 73% (266/365) for EGFR protein expression status.

The PFS results from analysis of patients with EGFR mutation status are shown in Table 9 and Figure 4. The results show that PFS was significantly longer with gefitinib than carboplatin / paclitaxel treatment in patients who were EGFR mutation positive (HR 0.48; 95%CI 0.36-0.64; p<0.0001) while PFS was significantly shorter with gefitinib than carboplatin / paclitaxel treatment in patients who were EGFR mutation negative (HR 2.85; 95%CI 2.05-3.98; p<0.0001). Results in the mutation unknown group (HR 0.68; 95%CI 0.58-0.81; p<0.0001) were similar to that for the ITT population. The ORR results by EGFR mutation status were consistent with the PFS results by EGFR mutation status.

Table 9 Analysis of clinical outcomes according to EGFR mutation status (ITT Population) – IPASS

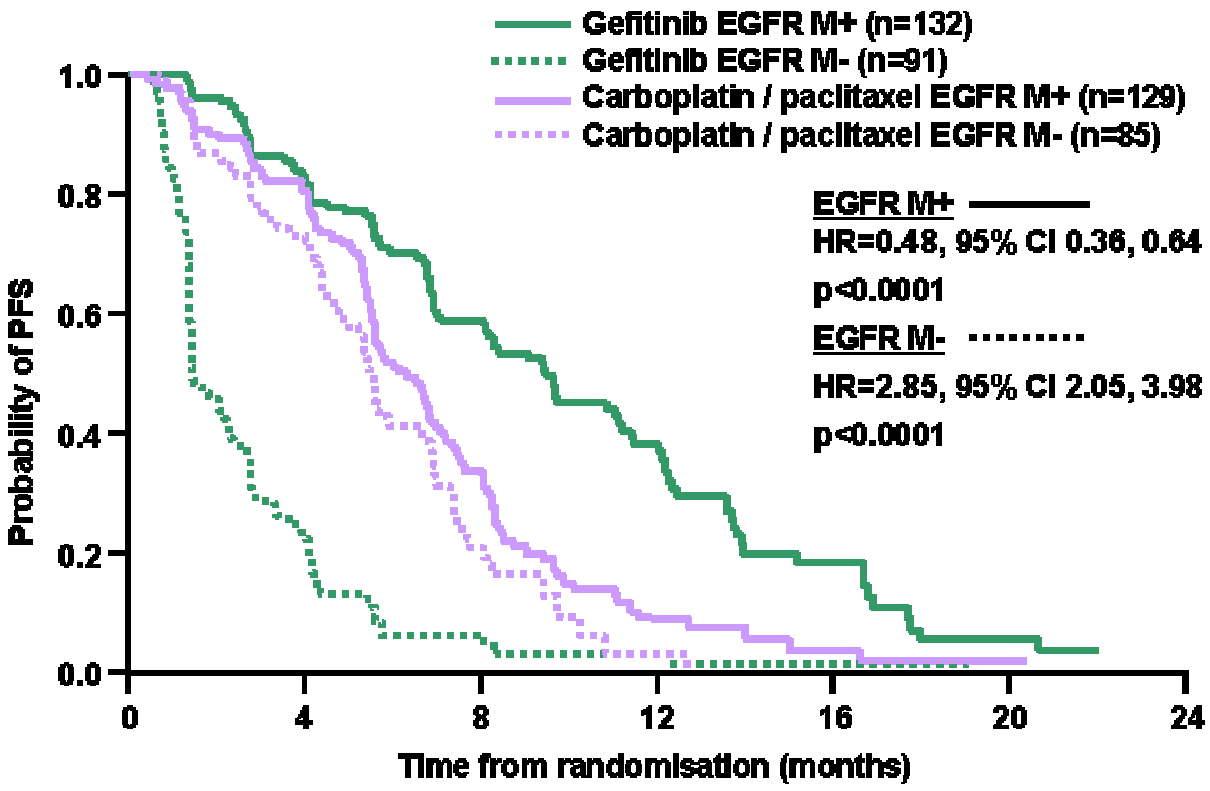
EGFR mutation	Gefitinib		Carboplatin / paclitaxel			Hazard ratio/ Odds ratio[a]	2-sided 95% CI	p-value
	N	Number (%) events	N	Number (%) events				
Progression-free survival								
M+	**132**	**97 (73.5)**	**129**	**111**	**(86.0)**	**0.482**	**0.362 to 0.642**	**<0.0001**
M-	**91**	**88 (96.7)**	**85**	**70**	**(82.4)**	**2.853**	**2.048 to 3.975**	**<0.0001**
Known	223	185 (83.0)	214	181	(84.6)	0.853	0.690 to 1.055	0.1426
Unknown	386	268 (69.4)	394	316	(80.2)	0.684	0.579 to 0.808	<0.0001
Objective response rate[b]								
M+	**132**	**94 (71.2)**	**129**	**61**	**(47.3)**	**2.751**	**1.646 to 4.596**	**0.0001**
M-	**91**	**1 (1.1)**	**85**	**20**	**(23.5)**	**0.036**	**0.005 to 0.273**	**0.0013**
Known	223	95 (42.6)	214	81	(37.9)	1.212	0.825 to 1.780	0.3268
Unknown	386	167 (43.3)	394	115	(29.2)	1.877	1.390 to 2.534	<0.0001

[a] HRs derived from Cox proportional hazards model; a HR <1 implies a lower risk of progression/death over a given period with gefitinib compared with carboplatin / paclitaxel. Odds ratios derived from logistic regression model; odds ratios >1 indicate a greater chance of response with gefitinib than carboplatin / paclitaxel.

[b] Objective tumour response defined as CR+PR.

CI=Confidence interval; EGFR=epidermal growth factor receptor; M+=EGFR mutation positive; M-=EGFR mutation negative; N=Number of evaluable patients.

Figure 4 Comparison of gefitinib and carboplatin/paclitaxel treatment arms for PFS based on their EGFR mutations status – IPASS study



An exploration of OS by mutation status was also performed (Table 10 and Figure 5). There were no differences observed between EGFR M+ and M- in the overall population and, no effect on OS was observed according to treatment.

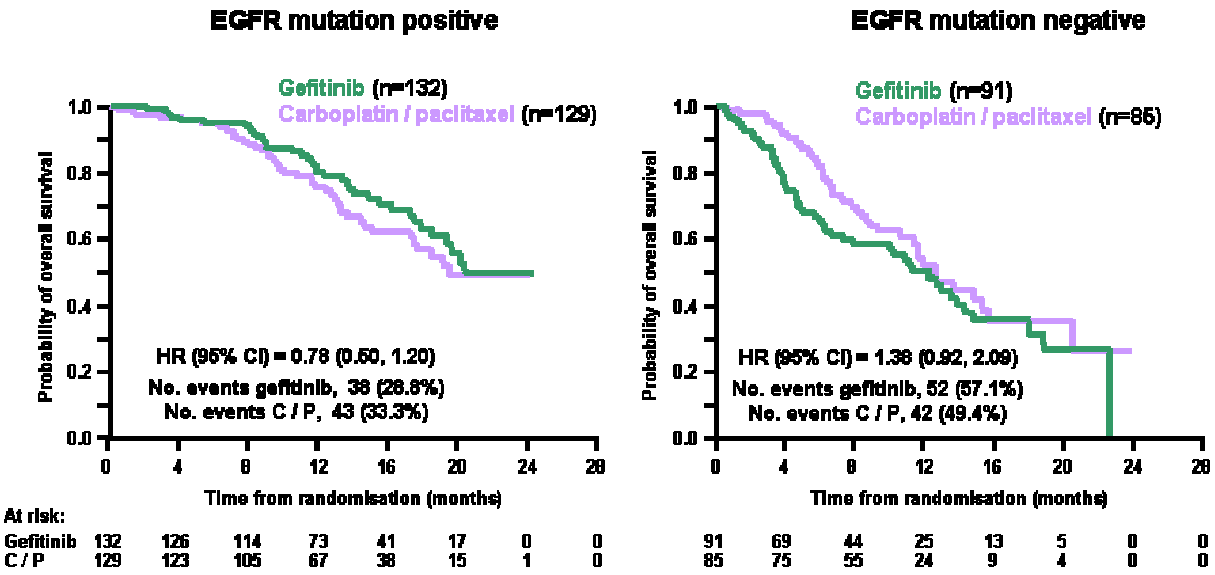
Table 10 Post-hoc analysis of overall survival according to EGFR mutation status (ITT Population) - IPASS

EGFR mutation	Gefitinib		Carboplatin / paclitaxel		Hazard ratio[a]	
	N	Number (%) events	N	Number (%) events		2-sided 95% CI
M+	**132**	**38 (28.8)**	**129**	**43 (33.3)**	**0.776**	**0.500 to 1.202**
M-	**91**	**52 (57.1)**	**85**	**42 (49.4)**	**1.384**	**0.915 to 2.092**
Known	223	90 (40.4)	214	85 (39.7)	0.996	0.740 to 1.341
Unknown	386	133 (34.5)	394	142 (36.0)	0.858	0.677 to 1.089

[a] HRs derived from Cox proportional hazards model; a HR <1 implies a lower risk of death over a given period with gefitinib compared with carboplatin / paclitaxel.

CI=Confidence interval; EGFR=epidermal growth factor receptor; M+=EGFR mutation positive; M-=EGFR mutation negative; N=Number of evaluable patients

Figure 5 Comparison in OS between the gefitinib and carboplatin/paclitaxel treatment arms based on the EGFR mutation status – IPASS study



A relationship between EGFR FISH status and PFS was observed where PFS was significantly longer with gefitinib than carboplatin / paclitaxel treatment in patients who had FISH positive tumours (HR 0.66; 95%CI 0.50-0.88; p=0.0050). In contrast, in FISH negative tumours PFS was numerically shorter with gefitinib than carboplatin / paclitaxel treatment in patients although this was not statistically significant (HR 1.24; 95%CI 0.87-1.76; p=0.2368). A post-hoc analysis was performed to investigate whether the effect in PFS in the patients with EGFR FISH positive tumours was related to EGFR mutation status. Of the 245 patients with EGFR FISH positive tumours whose EGFR mutation status was also known, 190 patients also had a positive EGFR mutation status. The results from this post-hoc analysis showed that PFS was significantly longer with gefitinib than carboplatin / paclitaxel treatment in patients who had EGFR FISH positive and EGFR mutation positive tumours (HR 0.48, 95% CI 0.34 to 0.67) but was significantly shorter in patients who had EGFR FISH positive tumours with no EGFR mutation detected (HR 3.85, 95% CI 2.09 to 7.09). This result suggests that the PFS

benefit seen in the subgroup of patients with FISH positive tumours may be driven by the overlap with positive mutation status. The ORR results by EGFR FISH status were consistent with the PFS results by EGFR FISH status. There was no evidence that EGFR protein expression status influenced PFS or ORR outcomes.

QoL and disease-related symptoms

Quality of life outcomes differed according to EGFR mutation status. In a post-hoc analysis in EGFR mutation-positive patients, significantly more IRESSA-treated patients experienced an improvement in quality of life and lung cancer symptoms vs carboplatin/paclitaxel. QoL data are shown in Table 11.

Table 11 Improvement rates for QOL and disease-related symptoms (EFQ population) – IPASS

Population	N	FACT-L QoL improvement rate [a] %	LCS symptom improvement rate [a] %
Overall	1151	(48.0 % vs 40.8 %) p=0.0148	(51.5 % vs 48.5 %) p=0.3037
EGFR mutation-positive	259	(70.2 % vs 44.5 %) p<0.0001	(75.6 % vs 53.9 %) p=0.0003
EGFR mutation-negative	169	(14.6 % vs 36.3 %) p=0.0021	(20.2 % vs 47.5 %) p=0.0002

Trial outcome index results were supportive of FACT-L and LCS results
[a] Values presented are for IRESSA versus carboplatin/paclitaxel.
N=Number of patients evaluable for quality of life analyses; QoL=Quality of life; FACT-L=Functional assessment of cancer therapy-lung; LCS=Lung cancer subscale

The times to worsening in QoL and disease-related symptoms were longer in the gefitinib arm (7.1 to 9.7 months) compared with the carboplatin / paclitaxel arm (2.5 to 3.1 months).

In patients with EGFR mutation positive status, improvement rates for QoL and in lung cancer symptoms favoured gefitinib compared with carboplatin / paclitaxel. In patients with EGFR mutation negative status by contrast, improvement rates for QoL and in lung cancer symptoms favoured carboplatin / paclitaxel compared with gefitinib.

The time to worsening in QoL and disease-related symptoms were longer in the gefitinib arm (11.3 to 16.6 months) compared with the carboplatin / paclitaxel arm (2.9 to 3.0 months) in patients with EGFR mutation positive status. In contrast, in patients with EGFR mutation negative status, time to worsening in QoL and disease-related symptoms were similar or shorter in the gefitinib arm (1.4 months) compared with the carboplatin / paclitaxel arm (1.4 to 4.2 months).

INTEREST (D791GC0001): *A Randomised, Open-label, Parallel-group, International, Multicentre, Phase III Study of Oral ZD1839 (IRESSA) versus Intravenous Docetaxel (TAXOTERE) in Patients with Locally Advanced or Metastatic Recurrent Non-small Cell Lung Cancer who have Previously Received Platinum-based Chemotherapy.*

METHODS

Study Participants

The main inclusion criteria were as follows:

1. Histological or cytological confirmation of NSCLC (from initial diagnosis of NSCLC or subsequent biopsy). (Note: sputum cytology alone was not acceptable. Cytological specimens obtained by brushing, washing or needle aspiration of a defined lesion were acceptable.)
2. Locally advanced or metastatic NSCLC that was not amenable to curative surgery or radiotherapy
3. One or two prior chemotherapy regimens, at least one of which must have been platinum-based
4. Measurable (unidimensional) disease by RECIST criteria in a lesion not previously irradiated, or non-measurable disease (i.e., the patient was to have at least one lesion at baseline - either target lesion or non-target lesion)
5. World Health Organization (WHO) performance status (PS) of 0, 1, or 2
6. Absolute neutrophil count (ANC) $>1.5x10^9$/l and platelets $>100x10^9$/l
7. Adequate hepatic function, defined as BOTH a bilirubin less than or equal to the upper limit of the reference range (ULRR) AND an 'eligible' combination of transaminases (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) and alkaline phosphatase (ALP) as defined in Table 12
8. Recovery from all acute toxicities of prior therapies
9. Life expectancy of at least 8 weeks

Table 12 Hepatic function eligibility criteria

ALP	**AST or ALT**			
	≤ULRR	**>1x but ≤1.5x**	**>1.5x but ≤5x**	**>5x ULRR**
≤ULRR	Eligible	Eligible	Eligible	Ineligible
>1x but ≤2.5x	Eligible	Eligible	Ineligible	Ineligible
>2.5x but ≤5x	Eligible	Ineligible	Ineligible	Ineligible
>5x ULRR	Ineligible	Ineligible	Ineligible	Ineligible

The main exclusion criteria were as follows:

1. Prior gefitinib therapy or prior therapy with an experimental agent whose primary mechanism of action was inhibition of EGFR or its associated tyrosine kinase
2. Prior docetaxel treatment for NSCLC
3. Newly diagnosed CNS metastases that had not yet been treated with surgery and/or radiation. Patients with previously diagnosed and treated CNS metastases or spinal cord compression could be considered if they had evidence of clinically stable disease (no steroid therapy or steroid dose being tapered) for at least 28 days.
4. Less than 14 days since the completion of prior radiotherapy or persistence of any radiotherapy related toxicity
5. Less than 21 days since prior chemotherapy, immunotherapy, or biological systemic anticancer therapy
6. Known, severe hypersensitivity to gefitinib or any of the excipients of this product
7. Known hypersensitivity to docetaxel, polysorbate 80 or other drugs formulated with polysorbate 80, or any of the excipients of docetaxel
8. Other co-existing malignancies or malignancies diagnosed within the last 5 years, with the exception of basal cell carcinoma or cervical cancer in situ
9. Any evidence of clinically active interstitial lung disease (ILD) (patients with chronic, stable, radiographic changes who were asymptomatic or patients with uncomplicated progressive lymphangitic carcinomatosis need not be excluded)
10. Signs of neurological symptoms consistent with new onset spinal cord compression
11. Patients with pre-existing peripheral neuropathy ≥Grade 2 (National Cancer Institute common toxicity criteria [NCI CTC])
12. Concomitant use of phenytoin, carbamazepine, rifampicin, barbiturates, or St John's Wort

Treatments
Gefitinib was given as a 250 mg tablet on a 4-cycle supply (3 months). On Day 1 of the first cycle, gefitinib was administered during the clinic visit. Subsequently, gefitinib therapy was taken once daily, at about the same time. Treatment could be taken with or without food. Patients receiving gefitinib were to maintain visits according to the 21-day schedule

Docetaxel 75 mg/m^2 was administered intravenously over 1 hour, every 3 weeks (1 cycle equalled 21 days). If excessive toxicity or side effects were observed at this dose, patients were recommended to undergo a dose reduction to 60 mg/m^2 for subsequent cycles. Docetaxel doses were calculated using the patient's actual height and weight to determine the patient's body surface area (BSA) using the DuBois and DuBois formula: BSA = 0.007184 x weight (kg) 0.425 x height (cm) 0.725.

Patients continued to receive treatment with either gefitinib or docetaxel until disease progression, unacceptable toxicity, severe non-compliance, patient lost to follow-up and death.

Objectives
Primary objective
The primary objective was to compare overall survival for gefitinib and docetaxel, using the following pre-defined co-primary analyses:

- An assessment of non-inferiority in the overall per protocol (PP) population, and if accepted, an assessment of superiority in the overall intention to treat (ITT) population
- An assessment of superiority in the ITT EGFR FISH+ population

Outcomes/endpoints
The primary efficacy endpoint was OS as measured from the date of randomisation to the date of patient death due to any cause, or to the last date the patient was known to be alive.

Secondary endpoint
The secondary efficacy endpoint were PFS, ORR and PRO. PFS was defined as the interval from the date of randomisation to the date of objective disease progression (per RECIST criteria) or death from any cause. Patients who had not progressed or died at the time of analysis were censored at the time of their last full adequate objective tumour assessment. This included patients lost to follow-up or who had withdrawn consent. PFS for patients without post-baseline tumour assessment was censored at zero days. For patients who died in the absence of objective progression more than 12 weeks after their last RECIST assessment, PFS was censored at the time of their last RECIST assessment. For patients who had objective progression more than 12 weeks after the previous RECIST assessment, PFS was censored at the time of last RECIST assessment immediately prior to the gap of 12 weeks or more. PFS analyses were conducted in the overall EFR population and the EFR population of patients found to be EGFR FISH+.

For PRO outcomes, the overall improvement was measured in patient-reported functionality (measured by TOI), quality of life (measured by total FACT-L) and disease-related symptoms (measured by LCS) questionnaires.

Exploratory efficacy endpoints
The exploratory efficacy endpoints included biomarker analysis of EGFR FISH, EGFR mutation status, EGFR protein expression and K-Ras mutation status. Tumour tissue samples for EGFR/biomarker analysis were taken at baseline. Urine and plasma samples for biomarker analysis were taken at baseline and at day 43 (visit 4).

Sample size
The calculation for the number of patients required for this study was based upon the assessment in the overall PP patient population of overall survival for non-inferiority, to be interpreted using 95%

confidence intervals. Based on the TAX-317 study[4], the median overall survival was 7.5 months for docetaxel 75 mg/m^2 and 4.6 months for BSC. There were approximately 45 and 77 deaths in the docetaxel and BSC arms, respectively. From these data, the estimated log hazard ratio (active-control effect size) for docetaxel to BSC was approximately 0.49 (-log [4.6/7.5]) with a standard error of 0.18 (2 / sqrt [45 + 77]).

The null hypothesis to be tested was that gefitinib 250 mg would retain less than 50% of the active-control effect on survival. The relative difference between the treatment arms would be analyzed by estimating a hazard ratio (gefitinib to docetaxel) and its 95% CI from an unadjusted proportional hazards model in the PP population. The null hypothesis was to be rejected if the upper 95% CI limit for the log HR was less than k, where k is a constant derived using the methodology of Rothmann et al[5] (dependent on the number of observed events and alpha used, the active-control effect size and its standard error).

If the null hypothesis of survival inferiority was rejected, then superior survival for gefitinib was to be declared relative to docetaxel if the upper 2-sided 95% CL was below 1.0 (estimated in the ITT population)[6].

The sample size goal was to have at least 85% power to reject the survival inferiority null hypothesis at a 2-sided 5% significance level versus the alternative hypothesis that the HR is 0.975. This required about 1150 observed deaths. Approximately 1440 patients were to be randomized.

Randomisation
Patients had to begin study therapy within 72 hours of the date of randomisation. Patients were randomised on a 1:1 basis using dynamic balancing[7] with respect to tumour histology (adenocarcinoma vs other), performance status (0-1 vs 2), prior platinum therapy (refractory vs received), prior paclitaxel therapy (refractory vs received vs none), prior regimens (1 vs 2), smoking history (ever vs never), and centre.

Blinding (masking)
The study had an open-label design due to differences in the method of administration of the two treatment regimens.

Statistical methods
There were two co-primary analyses performed by unadjusted proportional hazards model: 1) test of non-inferiority in the overall PP patient population and, if accepted, a test of superiority for gefitinib over docetaxel in the overall ITT population 2) test of superiority for gefitinib over docetaxel in EGFR FISH+ patients from the ITT population. Subgroup analyses based on stratification factors derived from the final clinical database were also conducted comparing overall survival in the following subgroups of (1) the overall PP population, and (2) the EGFR FISH+ ITT population: 1) histology (adenocarcinoma; other), 2) performance status (0,1; 2), 3) prior platinum therapy (refractory; received), 4)smoking history (ever; never), 5)prior paclitaxel therapy (refractory; received; none), 6)prior regimens (1; 2), 7) sex (female; male) [an analysis covariate], 8) race (Asian; other) [an analysis covariate], 9) age at randomisation (<65 years; 65+ years), 10) time from diagnosis to randomisation (<6 months, 6 to 12 months, >12 months), 11) best response to prior chemotherapy (CR/PR; SD; PD; unknown). Patients were to be followed for survival information after discontinuation for any reason (except withdrawal of consent by the patient or patient lost to follow-

[4] Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18(10):2095-103.
[5] Rothmann M, Li N, Chen G, Chi GYH, Temple R, Tsou H-H. Design and analysis of non-inferiority mortality trials in oncology. Statist Med 2003;22:239-64.
[6] Morikawa T, Yoshida M. A useful testing strategy in Phase III Trials: Combined test of superiority and test of equivalence. Journal of Biopharmaceutical Statistics1995;5(3):297-306.
[7] Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103-15.

up). All subsequent chemotherapy, radiation, surgical or other anticancer therapy during the time until death was recorded.

Primary efficacy analyses
The tests of non-inferiority in the overall population and of superiority in the EGFR FISH+ patient population were considered to be co-primary analyses. To preserve the overall type I error rate, a modified Hochberg procedure was employed where 1% of the overall 5% type I error rate was to be spent on the test of superiority in EGFR FISH+ patients. Other than for the co-primary analyses of overall survival, all statistical tests were performed with a two-sided 5% significance level. Both co-primary analyses were performed with an unadjusted proportional hazards model and the results were presented in terms of hazard ratio, confidence interval and p-value.

Applying the Hochberg methodology in the calculation of the non-inferiority margin led to the following procedure for the co-primary analyses: If superiority in EGFR FISH+ patients in the ITT population was demonstrated, the null hypothesis of inferiority was to be rejected if the upper limit of the 95% CI for the HR in the PP population was lower than 1.1598. If superiority in EGFR FISH+ patients was not demonstrated, the null hypothesis of inferiority was to be rejected if the upper limit of the 96% CI for the HR was lower than 1.1545. If non-inferiority was concluded, superiority of gefitinib over docetaxel would be declared if the upper limit of the 95% CI for the HR in the ITT population was below 1.0.

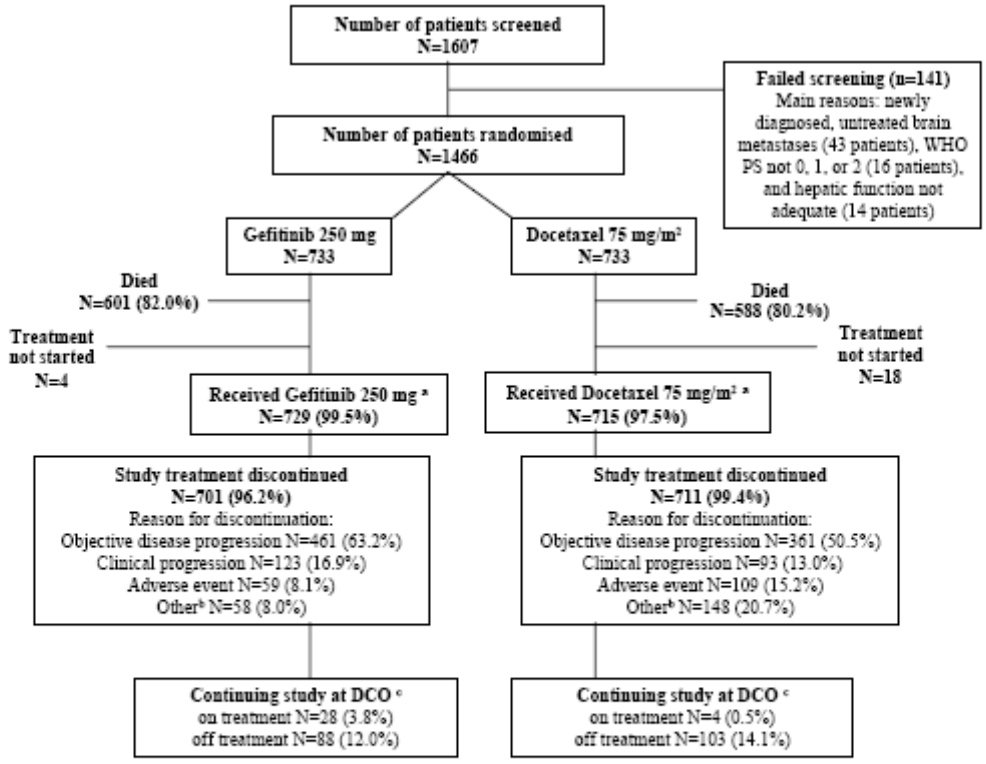
Further supportive analyses were conducted comparing overall survival in several subgroups. A global interaction test was performed to test the overall strength of evidence for consistency over all subgroups. Covariate by treatment interactions were also assessed individually.

Secondary efficacy outcome variables
Progression free survival (PFS) was analysed in the "evaluable for response" population using an adjusted proportional hazards model. Objective tumour response and QoL and symptom improvement was analysed by multiple logistic regression models. Time to worsening was analysed by a proportional hazards model.

Interim analyses
One pre-planned interim analysis for overall survival was conducted following 346 deaths. The purpose of this analysis was to detect inferiority relating to overall survival for gefitinib relative to docetaxel. No alpha-adjustment for the type I (false positive) error rate was applied to the final analysis since there was no opportunity at the interim analysis to accept the hypothesis of non-inferiority for overall survival.

RESULTS

Participant flow: Status of all patients as of data cut-off of 06 March 2007



a The safety analysis, conducted according to treatment received, was performed on this population.
b Other reasons include lost to follow-up, withdrawal of consent, non-compliance, and completing the planned number of docetaxel cycles.
c Continuing study at DCO refers to patients who were still being followed-up for survival at the DCO.
DCO Data cut-off date (06 March 2007).
N Number of patients.

Recruitment
The first patient was enrolled 01 March 2004 and the last patient was enrolled 17 February 2006. The data cut-off date was 06 March 2007.

Conduct of the study
The original protocol was dated 17 October 2003. There were four amendments to the study protocol, all of which were made after the start of patient recruitment. One amendment introduced the co-primary analyses in the subgroup of EGFR FISH+ patients and included amendments to the statistical considerations to ensure the overall type-I error was not inflated by having these two co-primary analyses. The majority of other changes were clarifications and are expected to have had no impact for the primary endpoint.

Treatment compliance

A very small proportion of patients discontinued study treatment permanently due to severe non-compliance (0.3% and 0.4% in the gefitinib and docetaxel groups, respectively). Overall, 82.2% of all docetaxel cycles were given at full dose. A total of 289 patients (20.0%) had interruptions to their gefitinib or docetaxel therapy; these interruptions were generally of short duration.

Concomitant medication
In gefitinib-treated patients, anti-infective treatments used more frequently to manage skin toxicities, while for docetaxel-treated patients, there were more antihistamines, corticosteroids, 5-HT_3 antagonists, H_2-blockers, G-CSFs, erythropoietin, propulsives, blood and related products that were used.

Baseline data

Disease characteristics and history at entry: ITT population

The patient demographics and baseline characteristics are shown in Table 13 and disease characteristics are shown in Table 14. For previous cancer treatments, 1229 patients (83.8%) had received at least one previous chemotherapy regimen and 31.0% of patients had experienced a best response of PD/unknown to their last chemotherapy. All patients in the overall study population had received a platinum compound, with 18.5% of all patients also receiving paclitaxel at some stage in their treatment.

Table 13 Summary of demographic and baseline characteristics: ITT population –INTEREST

Demographic or baseline characteristic		Gefitinib 250 mg (N=733)		Docetaxel 75 mg/m^2 (N=733)	
Age (years)	Median	61		60	
	Range	27 to 84		20 to 84	
Gender (n [%])	Male	466	(63.6)	488	(66.6)
	Female	267	(36.4)	245	(33.4)
Racial origin (n [%])[a]	Caucasian	550	(75.0)	540	(73.7)
	Asian[b]	154	(21.0)	169	(23.1)
	Black	10	(1.4)	12	(1.6)
	Other	19	(2.6)	12	(1.6)
Smoking history (n [%])	Regular smoker	110	(15.0)	117	(16.0)
	Occasional smoker	6	(0.8)	7	(1.0)
	Ex-smoker	469	(64.0)	459	(62.6)
	Never-smoker	148	(20.2)	150	(20.5)
WHO performance status	0 (normal activity)	218	(29.7)	181	(24.7)
	1 (restricted activity)	428	(58.4)	463	(63.2)
	2 (in bed ≤50% of the time)	86	(11.7)	84	(11.5)
	3 (in bed >50% of the time)	0		0	
	Not recorded	1	(0.1)	5	(0.7)

[a] Racial origin refers to the racial origin of a patient's group which is not necessarily their place of birth. For example, a person of Japanese origin even if second or third generation American, still belongs to the Asian category.
[b] Asian (this definition excludes those of Indian origin) and corresponds to the Oriental race category.
ITT=Intention to treat; N= Number of patients.

Table 14 Disease characteristics and history at entry: ITT population – INTEREST

Characteristic	Number (%) of patients			
	Gefitinib 250 mg (N=733)		Docetaxel 75 mg/m^2 (N=733)	
WHO performance status				
0 (normal activity)	218	(29.7)	181	(24.7)
1 (restricted activity)	428	(58.4)	463	(63.2)
2 (in bed ≤50% of the time)	86	(11.7)	84	(11.5)
3 (in bed >50% of the time)	0		0	
Not recorded	1	(0.1)	5	(0.7)
Tumour histology type				
Adenocarcinoma	395	(53.9)	402	(54.8)
Bronchoalveolar[a]	17	(2.3)	16	(2.2)
Squamous	185	(25.2)	176	(24.0)

Table 14 Disease characteristics and history at entry: ITT population – INTEREST

Characteristic	Number (%) of patients			
	Gefitinib 250 mg (N=733)		Docetaxel 75 mg/m^2 (N=733)	
Large cell	35	(4.8)	30	(4.1)
Mixed	13	(1.8)	14	(1.9)
Undifferentiated	41	(5.6)	52	(7.1)
Other	46	(6.3)	43	(5.9)
Not recorded	1	(0.1)	0	
Metastatic sites				
Lung	461	(62.9)	456	(62.2)
Bone	162	(22.1)	189	(25.8)
Liver	124	(16.9)	138	(18.8)
Adrenal	86	(11.7)	105	(14.3)
Brain	42	(5.7)	59	(8.0)
Skin/soft tissue	32	(4.4)	21	(2.9)
Other[b]	160	(21.8)	151	(20.6)
Not recorded	17	(2.3)	13	(1.8)
Disease status (at baseline)				
Metastatic	633	(86.4)	638	(87.0)
Locally advanced	99	(13.5)	95	(13.0)
Not recorded	1	(0.1)	0	
Stage classification (at diagnosis)				
0/I	44	(6.0)	44	(6.0)
IIa/IIb	27	(3.7)	27	(3.7)
IIIa	89	(12.1)	68	(9.3)
IIIb	183	(25.0)	211	(28.8)
IV	388	(52.9)	383	(52.3)
Not recorded	2	(0.3)	0	
Lesions present[c]				
Measurable	667	(91.0)	676	(92.2)
Target lesions only	171	(23.3)	152	(20.7)
Target and non-target lesions	496	(67.7)	524	(71.5)
Non-measurable only (ie, non-target lesions only)	61	(8.3)	53	(7.2)
No evaluable lesions	5	(0.7)	4	(0.5)

[a] Patients with bronchoalveolar histology were included in the adenocarcinoma subgroup.
[b] The most common other metastatic sites were pleura, pericardium, and kidney.
[c] Patients may have both measurable and non-measurable lesions present.
ITT=Intention to treat;N=Number of patients; WHO=World Health Organisation.

Numbers analysed

This study included six populations: intention-to-treat (ITT), evaluable-for-safety (EFS), per-protocol, evaluable-for-response (EFR), evaluable-for-pulmonary-symptom-improvement, and evaluable-for-QOL. In addition, the co-primary EGFR FISH+ population was evaluated throughout.

Of the 1466 patients randomised, 150 (10.2%) were excluded from the EFR population due to protocol deviation or non-measurable disease at baseline. Therefore, the EFR population consisted of 1316 patients.

Of the 1466 patients randomised, 500 (34.1%) were excluded from the EFQ population. Therefore, a total of 966 patients were included in the QoL analyses. Technical problems with the use of the electronic diary for collection of the QoL data accounted for the proportion of missing data being somewhat higher than some other gefitinib studies.

Outcomes and estimation

The randomised phase III INTEREST study was conducted in patients with locally advanced or metastatic NSCLC who had previously received platinum-based chemotherapy. The analyses of overall survival were based on a data cut-off of 06 March 2007, by which time 1169 deaths had occurred in the primary PP population (Table 16 and Figure 6). In the PP population, the median overall survival was 7.6 months for gefitinib treated patients and 8.0 months for docetaxel treated patients (HR 1.020; 96% CI 0.905-1.150) (Table 15). The CI for the HR fell below the non-inferiority limit of 1.154. When adjusting the PP analyses using a Cox proportional hazards model, with covariate adjustment for histology (adenocarcinoma versus other), performance status (0 or 1 versus 2), prior platinum therapy (refractory versus received), smoking history (ever versus never), prior paclitaxel therapy (refractory versus received versus none), prior regimens (1 versus 2), sex, and racial origin (Asian versus other), the HR was 1.044; 96% CI 0.925-1.178.

In the EGFR FISH+ population the median overall survival was 8.4 versus 7.5 months for gefitinib and docetaxel treated patients, respectively (HR 1.087; 95%CI 0.782-1.510; p=0.6199). No association between EGFR FISH status and survival outcome was observed.

Table 15 Analysis of overall survival: overall PP population and EGFR FISH+ population

Analysis	Hazard ratio[a]	2-sided CI[b]	p-value
Overall population			
Primary unadjusted PP analysis	1.020	0.905 to 1.150	0.7332
Secondary adjusted PP analysis[c]	1.044	0.925 to 1.178	0.4693
Secondary unadjusted ITT analysis	1.015	0.901 to 1.143	0.7985
EGFR FISH+ population			
Primary unadjusted ITT analysis	1.087	0.782 to 1.510	0.6199
Secondary adjusted ITT analysis[c]	1.053	0.753 to 1.472	0.7634

[a] Hazard ratios <1.00 indicate that treatment with gefitinib 250 mg is associated with a longer survival time than docetaxel.
[b] 95% confidence interval presented for EGFR FISH+ population; 96% confidence interval presented for overall population, in accordance with pre-planned Hochberg procedure, since EGFR FISH+ result failed to reach statistical significance at 5% level.
[c] Cox proportional hazards model included terms for histology (adenocarcinoma versus other), performance status (0 or 1 versus 2), prior platinum therapy (refractory versus received), smoking history (ever versus never), prior paclitaxel therapy (refractory versus received versus none), prior regimens (1 versus 2), sex, and racial origin (Asian versus other)
CI=Confidence interval.

Figure 6 Overall survival probability in the PP population – INTEREST

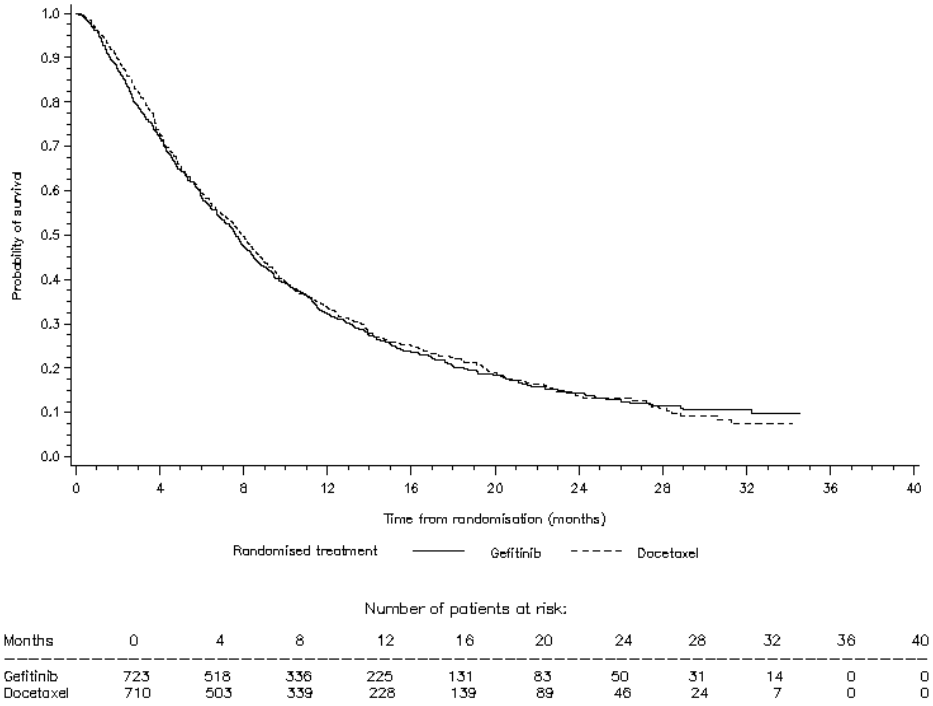
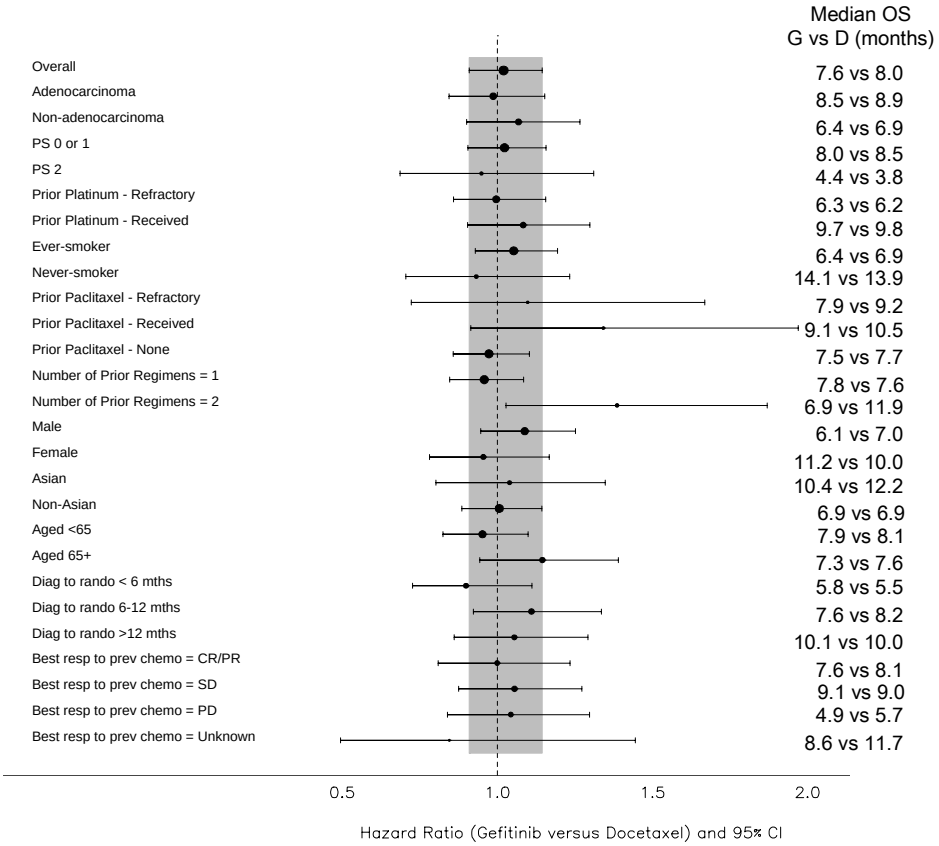


Table 16 Survival effects in subgroups in the PP population – INTEREST



Hazard ratios <1 indicate a difference in favour of gefitinib 250 mg while hazard ratios >1 favour docetaxel 75 mg/m^2.
The size of the point estimate reflects the number of deaths in a subgroup – the larger this appears the greater the number of deaths; the grey band represents the confidence interval for the overall (all patients) hazard ratio. G=gefitinib; D=docetaxel.

In the overall population, no statistically significant difference between gefitinib and docetaxel (75 mg/m^2) was observed for OS, PFS and ORR

Secondary outcomes: Progression-free Survival (PFS) and Objective response rates (ORR) (EFR population)

There was no statistically significant difference in terms of PFS between gefitinib and docetaxel in the EFR population (HR 1.04; 95%CI 0.93-1.18; p=0.4658) (Table 17 and Figure 7).

Table 17 Summary of PFS in Overall EFR population – INTEREST

Outcome variable/analysis	Gefitinib 250 mg (N=659)	Docetaxel 75 mg/m^2 (N=657)	HR[a]	95% CI	p-value
Progression-free survival[b]					
Number (%) progressed	593 (90.0)	544 (82.8)			
Median PFS (months)	**2.2**	**2.7**			
Primary adjusted analysis[c]			1.045	0.929 to 1.176	0.4658
Supportive unadjusted analysis[d]			1.020	0.907 to 1.147	0.7440

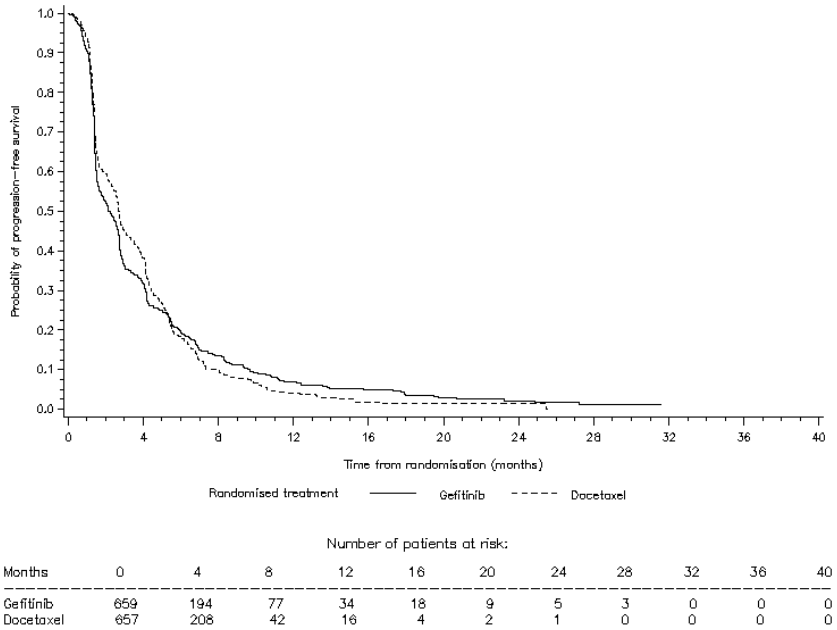
[a] Hazard ratios for PFS <1.00 indicate treatment with gefitinib 250 mg was associated with a more favourable outcome compared with docetaxel 75 mg/m^2.

[b] Progression-free survival was calculated by AstraZeneca from target lesion measurements recorded by the investigator, the investigator's assessment of non-target lesions and new lesions, and/or the date of patient death.

[c] Adjusted models 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), prior platinum therapy (refractory versus received), prior paclitaxel therapy (refractory versus received versus none) and racial origin (Asian versus other).

[d] From unadjusted Cox proportional hazards model.

Figure 7 PFS of gefitinib compared to docetaxel in the overall EFR population – INTEREST

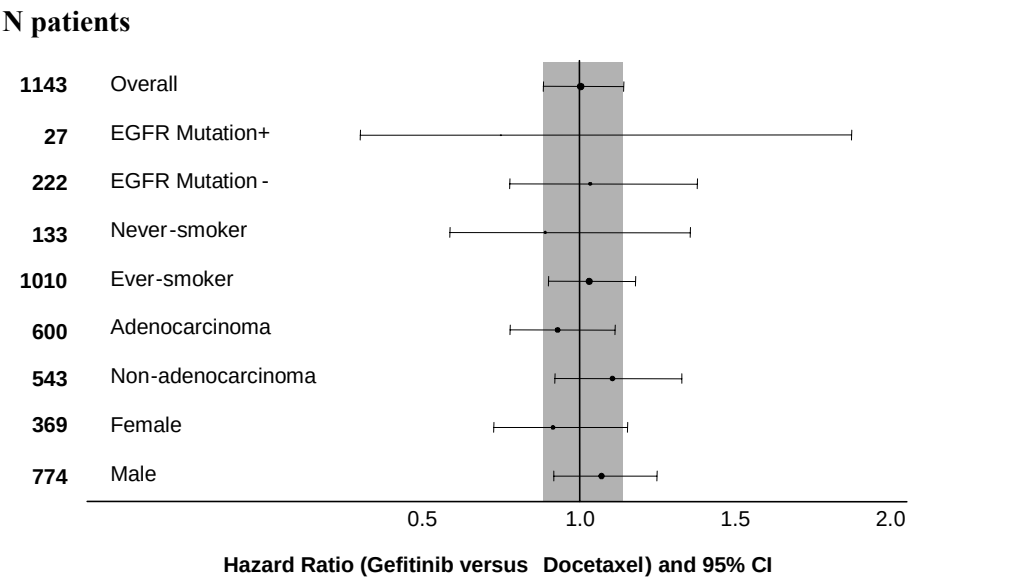


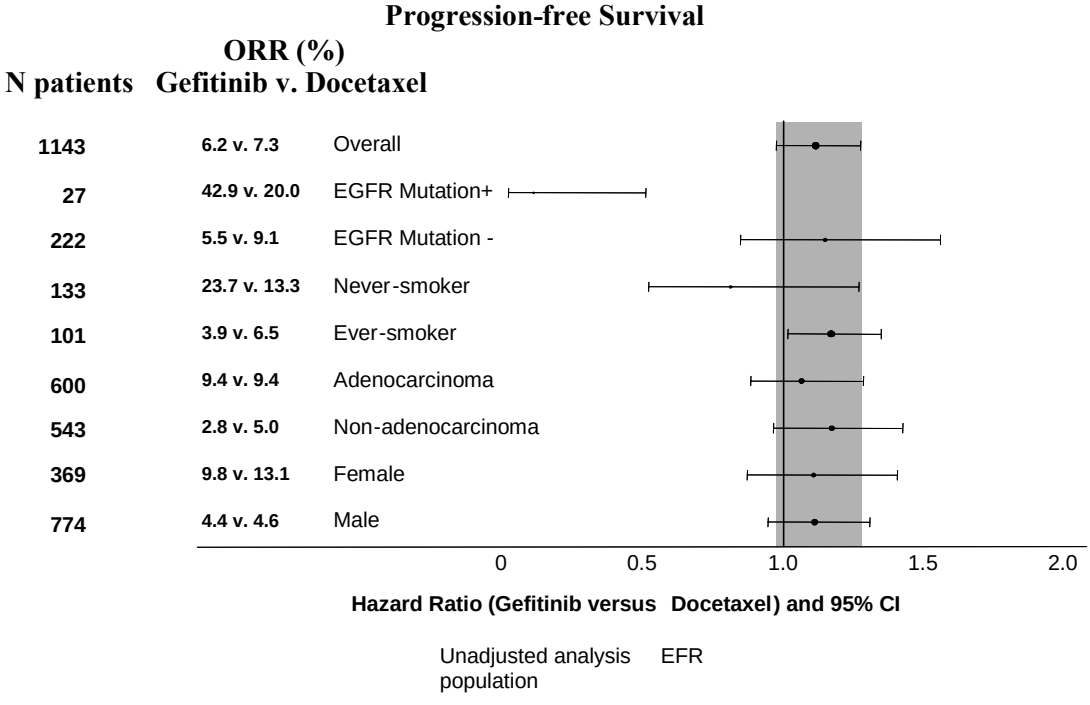
Objective response rates were similar in both treatment groups (OR 1.22; 95%CI 0.82-1.84, p=0.3257). Objective tumour responses were achieved for 9.1% and 7.6% of patients in the gefitinib

and docetaxel groups, respectively. For subgroup analysis, ORR was generally consistent across subgroups.

Subgroup analyses for the non Asian population
As the INTEREST trial had a high number of Asian patients, a subgroup analysis for OS, PFS and ORR was performed in the non-Asian population only, based on clinical characteristics on EGFR mutation, smoking and histology status. The results are presented in Figure 8. In the EGFR M+ status patients, no differences in OS were observed but, notably, the ORR were 42.9% and 20% for gefitinib and docetaxel, respectively, and PFS was in favour of gefitinib.

Figure 8 Efficacy outcomes in subgroups of non-Asian patients – INTEREST study





N patients=number of patients randomised; Hazard ratio <1 favours Iressa

Exploratory analysis results for PFS and OS according to smoking status and histology.

An exploratory analysis for the interaction between smoking and PFS was presented (Table 18 and Table 19). The results showed a statistically significant interaction between treatment and smoking status for PFS, with never smokers achieving longer progression-free survival with gefitinib. However, there was no interaction found for OS.

Table 18 Progression-free survival results according to smoking status

Subgroup/population	HR	95% CI	p-value
Overall EFR population	1.04	0.93 to 1.18	0.4658
Ever smokers	1.18	1.03 to 1.34	0.0139
Never smokers	0.60	0.45 to 0.79	0.0004

HR Hazard ratio derived from Cox proportional hazards model with the following terms: randomised treatment, histology, prior platinum therapy, prior paclitaxel therapy, number of prior chemotherapy regimens, WHO performance status, sex, race.

There was no interaction found between treatment and histology for both PFS and OS (Table 19).

Table 19: Treatment-by-histology and treatment-by-smoking status interaction tests for PFS and overall survival

Interaction	Endpoint	p-value[a]
Treatment-by-Histology[b]	PFS	0.1708
	OS	0.2746
	OS[c]	0.2116
Treatment-by-smoking status[d]	PFS	<0.0001
	OS	0.1360
	OS[c]	0.1527
Treatment-by-Histology-by-Smoking status[e]	PFS	0.9772
	OS	0.7552
	OS[c]	0.6984

[a] P-value based on comparison of subsequent models adding interaction terms versus a basic Cox proportional hazards model with the following terms: randomised treatment, histology, smoking history, prior platinum therapy, prior paclitaxel therapy, number of prior chemotherapy regimens, WHO performance status, sex, race, age, time from diagnosis to randomisation and best response to prior chemotherapy. This basic model was defined in the Statistical Analysis Plan (SAP) for evaluation of the overall survival interactions. The same model was fitted for PFS.
[b] The Cox proportional hazards model additionally fitted a term for treatment-by-histology to the basic model to compare to the basic model alone.
[c] Overall survival with censoring at the time of any additional first new post-discontinuation therapy.
[d] The Cox proportional hazards model additionally fitted a term for treatment-by-smoking history to compare to the basic model alone.
[e] The Cox proportional hazards model additionally fitted the following terms to the basic model: treatmentby-histology, treatment-by-smoking history, histology-by-smoking history, and treatment-by-histology-bysmoking history. This was compared to the same model excluding the treatment-by-histology-by smoking history interaction.

In EGFR FISH+ patients, there was no difference observed between gefitinib and docetaxel in terms of PFS (HR 0.84, 95% CI 0.59 to 1.19, p=0.3343). However, gefitinib-treated patients had a higher response rate than docetaxel in terms of ORR (13.0% vs 7.4%, p=0.0387). There was no evidence of a difference between gefitinib and docetaxel in terms of these clinical outcomes for patients with EGFR FISH-negative tumours.

In both treatment groups approximately 47% of patients received subsequent anti-cancer therapies that differed from randomised therapy post-discontinuation. Of the gefitinib-treated patients, 31% received docetaxel post-discontinuation and of docetaxel-treated patients 37% received subsequent EGFR tyrosine kinase inhibitor (TKI) therapy (15% gefitinib, 21% erlotinib).

Exploratory biomarker results for EGFR mutation status
The key demographic characteristics for patients with evaluable tissue samples for biomarker exploratory analyses were generally comparable to the demographics for the overall study population, with slightly fewer samples available from patients of Asian racial origin. In particular, only 1.8% of patients that were evaluable for K-Ras mutation status were Asian, primarily due to unavailability of the assay in China. Characteristics of patients with high EGFR gene copy number and EGFR-positive tumours were similar to the overall study population. Patients with EGFR mutations tended to be female, never-smokers, of Asian racial origin, and have adenocarcinoma histology. They also appeared less likely to have responded to their last chemotherapy. There were a high proportion of Asian patients with EGFR mutations as compared to Caucasian population. In contrast, there was a higher rate of EGFR FISH+ patients in Caucasian patients compared to Asian patients (Table 20). There was a tendency for patients with K-Ras mutations to have adenocarcinoma histology and to be smokers. The majority of patients positive for one EGFR biomarker were also positive for the other EGFR biomarkers as overlapping for more than one biomarker was high.

Table 20 Summary of EGFR FISH and mutation positive rates between Caucasian and Asian patients: Patients with known EGFR FISH and mutation status (INTEREST study)

	Randomised treatment					
	Gefitinib 250 mg		Docetaxel 75 mg/m^2		Overall	
	Caucasian (N=107)	Asian (N=23)	Caucasian (N=123)	Asian (N=21)	Caucasian (N=230)	Asian (N=44)
EGFR FISH+	55 (51.4)	8 (34.8)	60 (48.8)	8 (38.1)	115 (50.0)	16 (36.4)
EGFR M+	13 (12.1)	6 (26.1)	10 (8.1)	10 (47.6)	23 (10.0)	16 (36.4)

The results from EGFR mutation analysis from the INTEREST trial are presented in Table 21. There were differences in terms ORR and PFS. The ORR for EGFR M+ status patients were 42.1% and 21.1% (HR 25.2; 95%CI 1.23-515.53; p=0.036) for gefitinib and docetaxel, respectively. PFS had a HR 0.16, suggesting a benefit in favour of gefitinib. No significant differences were observed between gefitinib and docetaxel on OS in patients with EGFR M+

Table 21 Analysis of clinical outcomes according to EGFR mutation status – INTEREST

EGFR mutation status	Gefitinib 250 mg		Docetaxel 75 mg/m^2		Hazard ratio/ Odds ratio[a]	2-sided 95% CI	p-value
	N	Number (%) events	N	Number (%) events			
Overall survival							
M+	**22**	**15 (68.2)**	**22**	**17 (77.3)**	**0.832**	**0.414 to 1.670**	**0.6043**
M-	119	101 (84.9)	134	114 (85.1)	1.015	0.776 to 1.327	0.9131
M unknown	592	485 (81.9)	577	457 (79.2)	1.027	0.904 to 1.167	0.6808
Overall	723	593 (82.0)	710	576 (81.1)	1.020	0.910 to 1.144	0.7332
Progression-free survival							
M+	**19**	**18 (94.7)**	**19**	**17 (89.5)**	**0.163**	**0.054 to 0.488**	**0.0012**
M-	106	96 (90.6)	123	107 (87.0)	1.239	0.935 to 1.643	0.1353

EGFR mutation status	Gefitinib 250 mg			Docetaxel 75 mg/m^2			Hazard ratio/ Odds ratio[a]	2-sided 95% CI	p-value
	N	Number (%) events		N	Number (%) events				
M unknown	534	479	(89.7)	515	420	(81.6)	1.053	0.922 to 1.202	0.4488
Overall	659	593	(90.0)	657	544	(82.8)	1.045	0.929 to 1.176	0.4658
Objective response rate[b]									
M+	**19**	**8**	**(42.1)**	**19**	**4**	**(21.1)**	**25.218**	**1.234 to 515.532**	**0.0361**
M-	106	7	(6.6)	123	12	(9.8)	0.630	0.228 to 1.739	0.3720
M unknown	534	45	(8.4)	515	34	(6.6)	1.348	0.836 to 2.176	0.2208
Overall	659	60	(9.1)	657	50	(7.6)	1.225	0.817 to 1.835	0.3257

[a] Hazard ratios derived from Cox proportional hazards model: unadjusted for overall survival, and including terms for histology (adenocarcinoma versus other), performance status (0 or 1 versus 2), prior platinum therapy (refractory versus received), smoking history (ever versus never), prior paclitaxel therapy (refractory versus received versus none), prior regimens (1 versus 2), sex, and racial origin (Asian versus other) for PFS; hazard ratios <1.00 indicate that treatment with gefitinib 250 mg is associated with a longer survival/PFS time than docetaxel 75 mg/m^2. Odds ratio derived from Logistic regression model with the same covariates as for PFS; odds ratios >1.00 indicate a greater chance of response with gefitinib 250 mg.

[b] Objective tumour response defined as complete response (CR)+partial response (PR).

CI=Confidence interval; N=Number of evaluable patients; ORR and PFS based on evaluable-for-response population.

No relationship between K-Ras mutation status and relative survival outcome, PFS or ORR was observed in both treatments. The ORR was low in patients with mutated K-Ras in both study arms. The presence of mutated K-Ras and EGFR were in essence mutually exclusive.

Overall survival, PFS and ORR were similar for gefitinib and docetaxel irrespective of EGFR protein expression status, No relationship between EGFR protein expression status and survival outcome in the two treatment groups was found (EGFR protein expression status-by-treatment interaction, p=0.8713).

Disease-related symptoms and Quality of life (QoL)

The QoL was measured whilst the patient was receiving randomised treatment. Overall compliance for completion of the FACT-L questionnaire was more than 75% in both treatment groups. The results from the LCS test showed that gefitinib was similar to docetaxel in terms of disease-related symptoms (improvement rates 20% versus 17%, p=0.1329) while significantly more gefitinib-treated patients experienced clinically relevant improvements in QoL compared with docetaxel (TOI improvement rates 17% versus 10%, p=0.0026, FACT-L 25% versus 15%, p<0.0001) (Table 22).

Table 22 Improvement rates for QOL and disease-related symptoms: evaluable-for-QOL population: INTEREST

Variable	Improvement rate[a] (%) Gefitinib 250 mg (N=490)	Improvement rate[a] (%) Docetaxel 75 mg/m^2 (N=476)	Odds ratio[b]	2-sided 95% CI	p-value
FACT-L	25.1	14.7	1.989	1.417 to 2.791	<0.0001
TOI	17.3	10.3	1.824	1.234 to 2.695	0.0026
LCS	20.4	16.8	1.288	0.926 to 1.790	0.1329

[a] A clinically relevant improvement was pre-defined as a 6-point improvement for FACT-L and TOI, and a 2-point improvement for LCS, maintained for at least 21 days.

[b] From multivariate logistic regression model including terms for histology (adenocarcinoma versus other), performance status (0 or 1 versus 2), prior platinum therapy (refractory versus received), smoking history (ever versus never), prior paclitaxel therapy (refractory versus received versus none), prior regimens (1 versus 2), sex, and racial origin (Asian versus other); odds ratios >1.00 indicate that treatment with gefitinib 250 mg is associated with a higher improvement rate than docetaxel 75 mg/m^2.

FACT-L: Functional Assessment of Cancer Therapy – Lung; range 0 to 136; LCS: Lung Cancer Subscale; range 0 to 28; TOI: Trial Outcome Index; range 0 to 84.

N=Number of patients.

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

ISEL(D7913C00709): *A Double-blind, Placebo-controlled, Parallel-group, Multicentre, Randomised, Phase III Survival Study Comparing ZD1839 (IRESSA) (250 mg Tablet) plus Best Supportive Care versus Placebo plus Best Supportive Care in Patients With Advanced NSCLC who Have Received One or Two Prior Chemotherapy Regimens and are Refractory or Intolerant to Their Most Recent Regimen*

METHODS

Study Participants

This study aimed to recruit patients who had received either 1 or 2 prior chemotherapy regimens for treatment of NSCLC who were refractory or intolerant to their most recent regimen. For patients aged <70 years at initial diagnosis, at least 1 prior therapy should have included platinum-based chemotherapy; however, elderly patients (≥70 years of age at initial diagnosis) were not required to have received prior platinum therapy and may have received 1 or 2 prior non-platinum or single agent regimens. The key inclusion criteria were: locally advanced or metastatic NSCLC that was not amenable to curative surgery or radiotherapy; refractory or intolerant to most recent chemotherapy regimen; performance status (PS) of 0, 1, or 2 (patients of PS 3 were also eligible unless the investigator believed the poor PS was predominantly due to co-existing morbidity, e.g., previous cerebrovascular accident, debilitating rheumatoid arthritis or severe cardiac impairment); life expectancy of at least 8 weeks. This study was conducted in centres from different countries worldwide.

Treatments

The gefitinib dose level for this study was 250 mg with matching placebo tablets. Gefitinib or placebo was dispensed to patients in a double-blind manner on Day 1, and as required thereafter. Gefitinib or placebo treatment was taken once daily. It could be taken with or without food. If the patient forgot to take a dose (or had emesis within 30 minutes of taking that dose), they took the last missed dose as soon as they remembered, as long as it was at least 12 hours before the next dose was due. Patients continued to take gefitinib or placebo until they were no longer considered by the investigator to be deriving clinical benefit, the treatment was stopped due to toxicity, consent was withdrawn, or gefitinib or placebo was discontinued for other reasons.

Objectives

The primary objective was to compare overall survival for gefitinib plus BSC versus placebo plus BSC. The secondary objectives were to compare gefitinib plus BSC versus placebo plus BSC in terms of time to treatment failure, investigator assessed overall objective tumour response (complete response [CR] +partial response [PR]), quality of life changes, and tolerability. The study also aimed to investigate the correlation of EGFR and other related biomarker status with efficacy in those patients where such tumour material was available. The statistical hypothesis was made on the basis of increased response rates and their durability observed in an uncontrolled Phase II setting, and the study design was based on the primary hypothesis that therapy with gefitinib would result in a statistically significant improvement in survival for patients with adenocarcinoma histology. It was hypothesised that gefitinib would reduce the hazard rate by 25% relative to the placebo arm among patients with adenocarcinoma.

Outcomes/endpoints

Overall survival was the primary variable and was used as the basis for the sample size calculation. Overall survival was assessed from the date of randomisation to the date of patient death, due to any cause, or to the last date the patient was known to be alive (intention to treat population).

Time to treatment failure defined from the date of randomisation to the date at which the patient discontinued from study therapy or the last on-study therapy visit for patients still receiving study therapy prior to data cut-off (intention to treat population). Objective tumour response determined by the investigator at discontinuation of study therapy or the last visit prior to data cut-off (evaluable for response and intention to treat population). RECIST criteria were used by the investigator to assess objective tumour response. The overall best confirmed response rate was calculated as the percentage of evaluable patients with complete response (CR) or partial response (PR).

In patients where tumour tissue samples were available (paraffin embedded tissue block or sections cut from the tissue blocks), analyses of EGFR were undertaken. This included assessing total and phosphorylated EGFR protein expression, EGFR tyrosine kinase mutation status, EGFR gene copy number and receptor dimerisation patterns associated with EGFR and other HER family members (ErbB2 and ErbB3). Related signal transduction, proliferation and apoptosis markers were also to be performed at a central laboratory. Provision of a biopsy sample was not mandatory for inclusion in the study.

The quality of life outcome variables of this study were based on the Functional Assessment of Cancer Therapy-Lung [FACT-L] (evaluable for QOL population), and included mean change from baseline, best overall response, time to improvement, duration of improvement and time to worsening derived for each score. The FACT-L questionnaire comprised 5 domains, 4 that evaluated physical, social-familial, emotional, and functional well-being and one that evaluated additional QOL aspects specifically related to lung cancer. Each domain consisted of up to 10 QOL statements. For each statement, patients indicated the extent to which the statement was true, using the following 5-point Likert scale: 0 (not at all) to 4 (very much).

Sample size

The study design was based on the primary hypothesis that therapy with gefitinib would result in a statistically significant improvement in survival for patients with adenocarcinoma histology. It was hypothesised that gefitinib would reduce the hazard rate by 25% relative to the placebo arm among patients with adenocarcinoma. The sample size estimation assumed a 2:1 randomisation (gefitinib:placebo), uniform accrual over 12 months, and a minimum follow-up of 9 months.

It was anticipated that approximately 15% of patients would crossover from placebo to gefitinib after progression. Using the methodology of Porcher et al (2002)[8] to account for crossover, the final analysis required a minimum of 696 events to achieve 90% power for a 2-sided 5% significance level test. Assuming exponential survival, if the 1-year survival rate for the placebo arm was 20%, a total of 866 patients with adenocarcinoma (577:289) were to be randomised. It was estimated that 66% of patients screened would have adenocarcinoma. It was therefore estimated that to obtain 866 patients with adenocarcinoma, approximately 1299 (866:433) patients would be randomised altogether. However, the initial protocol rationale for focusing on the adenocarcinoma subset of patients was

[8] Porcher R, Levy V, Chevret S. Sample size correction for treatment crossovers in randomized clinical trials with a survival endpoint. Control Clin Trials 2002; 23:650-61.

questioned once data from the BR-21 study emerged suggesting that tumour response alone does not explain the increase in survival (Shepherd et al 2004). Assuming gefitinib 250 mg is as efficacious as erlotinib in terms of survival, and with up to 1800 patients entered, the current study would have been overpowered. Following patients through to mid-2005 as per the study protocol (see Appendix 12.1.1) would have resulted in a test with over 99% power. It was therefore calculated that the efficacy of gefitinib 250 mg could be assessed with reasonable power sooner than was anticipated in the protocol, thus minimising the time patients were exposed to trial procedures and randomised treatment. By assuming up to a 3-month delay in the separation of Kaplan-Meier curves as observed in the BR-21 study and that gefitinib 250 mg is associated with an underlying improvement in survival equal to that associated with erlotinib, it was calculated that 900 deaths would provide at least 86% power to detect this magnitude of effect at the 2.5% 1-sided significance level.

Randomisation

The actual treatment given to individual patients was determined by the Centralised Registration/Randomisation Centre, using a minimisation method[9]. Patients were categorised at randomisation with respect to tumour histology (adenocarcinoma versus other), gender (male versus female), smoking history (never smoked versus current/former smoker), reason for prior chemotherapy failure (refractory versus intolerant), and centre. Centre was used as a balancing factor but had less weighting than the 4 stratification factors.

Blinding (masking)

The study medication was supplied as round, brown film-coated tablets with a matching placebo. The active and placebo tablets were identical and presented in the same packaging to ensure blinding of the medication. The label attached to each bottle of study material had a unique material pack code that was linked to the randomisation scheme. The Centralised Registration/Randomisation Centre assigned the bottle of study material to be dispensed to each patient.

Statistical methods

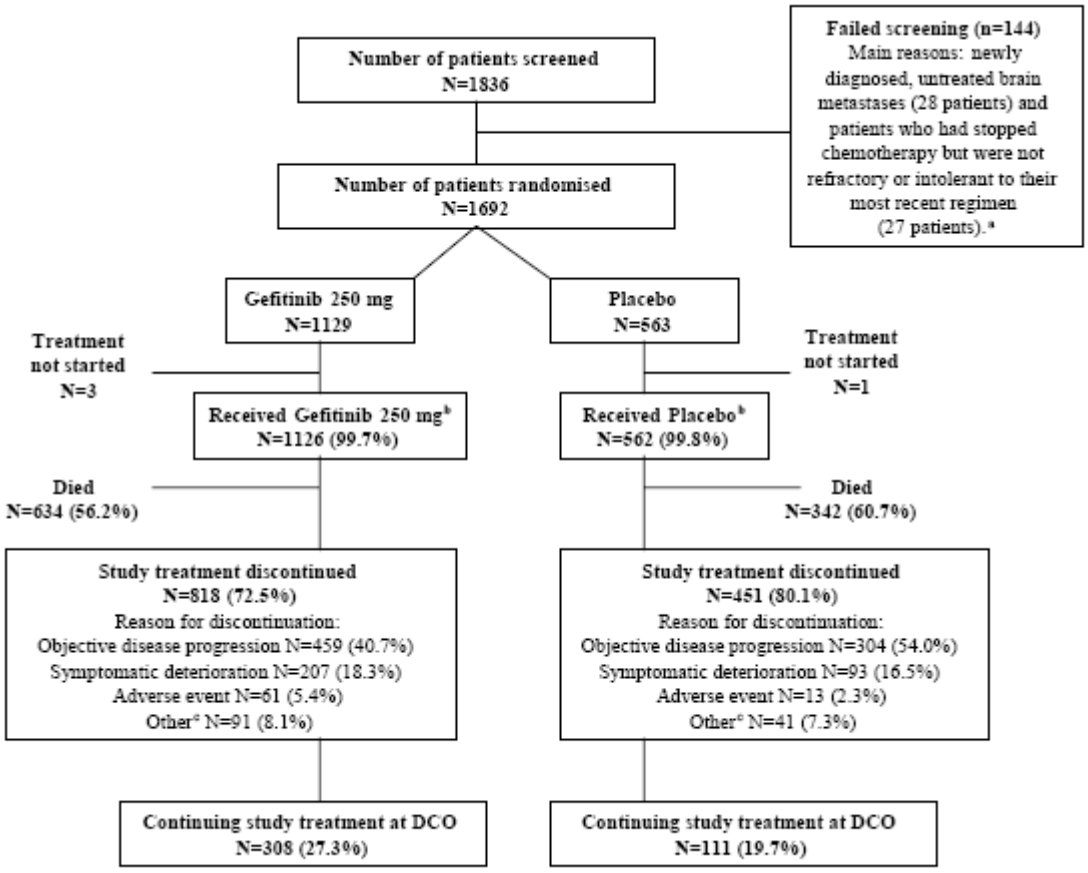
The primary analysis compared overall survival of gefitinib 250 mg to placebo. This analysis was performed on the ITT population. The treatment arms were compared with a log-rank test stratified for the following factors:

- histology (adenocarcinoma versus other)
- gender (male versus female)
- smoking history (never smoked versus current/former smoker)
- reason for prior chemotherapy failure (refractory versus intolerant)
- number of prior chemotherapy regimens (1 versus 2 regimens)
- performance status (0 or 1 versus 2 or 3).

RESULTS

Participant flow

[9] Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31:103-15.



Recruitment

A total of 1836 patients were screened for the study and 1692 patients were randomised to treatment (1129 patients to receive gefitinib 250 mg and 563 patients to receive placebo); these patients were recruited from 210 centres in 28 countries and included 812 patients (48.0%) with adenocarcinoma histology. Patients were recruited from 210 centres in 28 countries (Argentina, Australia, Brazil, Bulgaria, Canada, Estonia, Germany, Greece, Hungary, India, Ireland, Latvia, Lithuania, Malaysia, Mexico, Netherlands, Norway, Philippines, Poland, Romania, Russia, Singapore, Slovakia, Sweden, Taiwan, Thailand, Turkey, and United Kingdom). The first patient was enrolled on 15 July 2003, and the last patient was enrolled on 2 August 2004.

Conduct of the study

Table 23 Summary of demographic and baseline characteristics in ITT population – ISEL study

Demographic or baseline characteristic		Gefitinib 250 mg (N=1129)		Placebo (N=563)	
Age (years)	Mean (SD)	61	(10.3)	61	(10.3)
	Median	62		61	
	Range	28 to 90		31 to 87	
Age distribution (n [%])	<45 years	64	(5.7)	32	(5.7)
	45-64 years	618	(54.7)	321	(57.0)
	65-74 years	343	(30.4)	152	(27.0)
	≥75 years	104	(9.2)	58	(10.3)
Gender (n [%])	Male	761	(67.4)	378	(67.1)
	Female	368	(32.6)	185	(32.9)
Racial origin (n [%])[a]	Caucasian	843	(74.7)	431	(76.6)
	Asian[b]	235	(20.8)	107	(19.0)
	Black	9	(0.8)	5	(0.9)
	Other	42	(3.7)	20	(3.6)
Smoking history (n [%])	Habitual smoker	189	(16.7)	90	(16.0)
	Occasional smoker	12	(1.1)	7	(1.2)
	Ex-smoker	678	(60.1)	340	(60.4)
	Non-smoker	250	(22.1)	125	(22.2)
	Not recorded	0		1	(0.2)

[a] Racial origin refers to the racial origin of a patient's group which is not necessarily their place of birth. For example, a person of Japanese origin even if second or third generation American, still belongs to the Asian category.
[b] Asian (this definition excludes those of Indian origin) and corresponds to the Oriental race category
ITT=Intention to treat; N=Number of patients.

There were 2 amendments to the study protocol. The first amended the stratification of patients to include tumour histology (adenocarcinoma versus other) and gender (male versus female), while race (Asian versus other) and prior number of chemotherapy regimens (1 versus 2) were removed.

In addition, histology (adenocarcinoma versus other) was included as a stratification factor in the secondary analysis.

The second amendment occurred after data from the BR-21 study of erlotinib versus placebo in patients with recurrent NSCLC who had failed at least one prior chemotherapy regimen (Shepherd et al 2004) showed a significant survival advantage for erlotinib that was independent of histology. In the light of these data, the IDMC recommended that the overall population be included as a co-primary population alongside the adenocarcinoma population, and that an interim analysis should be conducted at the close of recruitment and the final analysis should be performed once 900 deaths had accrued in the overall population.

For the interim analysis of overall survival, an extreme p-value was applied ($p<0.001$) to ensure the trial was only unblinded in the event of a highly convincing result and to preserve the overall type-I error at 5% in the final analysis.

Baseline data

Table 24 Disease characteristics and history at entry in ITT population – ISEL study

Characteristic	Number (%) of patients			
	Gefitinib 250 mg (N=1129)		Placebo (N=563)	
WHO performance status				
0 (normal activity)	140	(12.4)	70	(12.4)
1 (restricted activity)	598	(53.0)	318	(56.5)
2 (in bed ≤50% of the time)	332	(29.4)	145	(25.8)
3 (in bed >50% of the time)	55	(4.9)	29	(5.2)
Not recorded	4	(0.4)	1	(0.2)
Tumour histology type				
Adenocarcinoma	512	(45.3)	255	(45.3)
Bronchoalveolar[a]	29	(2.6)	16	(2.8)
Squamous	399	(35.3)	187	(33.2)
Large cell	58	(5.1)	33	(5.9)
Mixed	21	(1.9)	13	(2.3)
Undifferentiated	106	(9.4)	58	(10.3)
Not recorded	4	(0.4)	1	(0.2)
Metastatic sites				
Lung	533	(47.2)	281	(49.9)
Lymph nodes	310	(27.5)	162	(28.8)
Bone	275	(24.4)	129	(22.9)
Liver	182	(16.1)	74	(13.1)
Adrenal	121	(10.7)	65	(11.5)
Brain	93	(8.2)	51	(9.1)
Skin/soft tissue	36	(3.2)	23	(4.1)
Other[b]	126	(11.2)	67	(11.9)

[a] Patients with bronchoalveolar histology were included in the adenocarcinoma subgroup.
[b] The most common other metastatic sites were pleura, pericardium, and kidney.
N=Number of patients;WHO=World Health Organisation.

Table 25 Disease characteristics and history at entry in ITT population – ISEL study

Characteristic	Number (%) of patients			
	Gefitinib 250 mg (N=1129)		Placebo (N=563)	
Current disease status				
Metastatic	896	(79.4)	450	(79.9)
Locally advanced	233	(20.6)	113	(20.1)
Stage classification (at diagnosis)				
I	52	(4.6)	33	(5.9)
II	45	(4.0)	25	(4.4)
IIIa	109	(9.7)	51	(9.1)
IIIb	385	(34.1)	170	(30.2)
IV	536	(47.5)	282	(50.1)
Not recorded	2	(0.2)	2	(0.4)
Lesions present[c]				
Measurable	999	(88.5)	503	(89.3)
Non-measurable	893	(79.1)	402	(71.4)

[a] Patients with bronchoalveolar histology were included in the adenocarcinoma subgroup.
[b] The most common other metastatic sites were pleura, pericardium, and kidney.
[c] Patients may have both measurable and non-measurable lesions present.
ITT Intention to treat.
N Number of patients.
WHOWorld Health Organisation.

Table 26 Previous cancer treatment in ITT population – ISEL study

Characteristic	Number (%) of patients			
	Gefitinib 250 mg (N=1129)		Placebo (N=563)	
Previous lines of chemotherapy				
None	1	(0.1)	1	(0.2)
1	549	(48.6)	274	(48.7)
2	566	(50.1)	281	(49.9)
≥3	13	(1.2)	7	(1.2)
Time from diagnosis of NSCLC[a]				
<6 months	293	(26.0)	140	(24.9)
6 to 12 months	419	(37.1)	222	(39.4)
>12 months	417	(36.9)	201	(35.7)
Previous chemotherapy				
Platinum compound	1085	(96.1)	538	(95.6)
Both platinum compound and docetaxel	304	(26.9)	158	(28.1)
Reason for discontinuation of last chemotherapy				
Refractory[b]	1011	(89.5)	512	(90.9)
Intolerant[c]	114	(10.1)	48	(8.5)
Unknown	4	(0.4)	3	(0.5)

[a] Time from diagnosis of NSCLC refers to the time interval between first diagnosis of NSCLC and randomisation to this study.

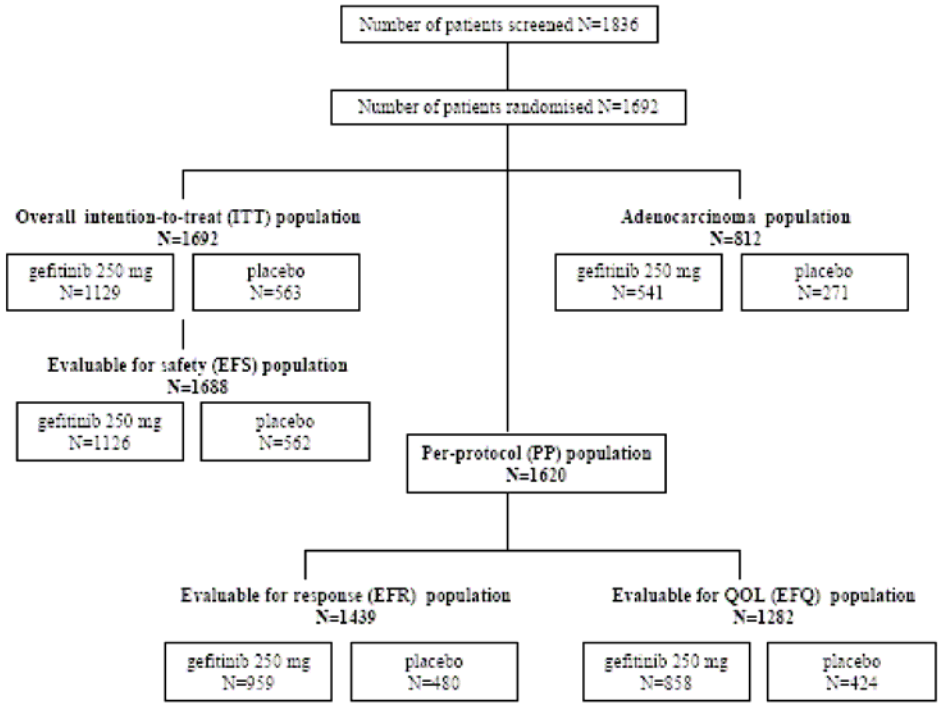
[b] Refractory defined as recurrent or progressive disease [clinical or radiological] while receiving or within 90 days of last dose of chemotherapy.
[c] Intolerant defined as in Section 5.3.1 of the CSR.
ITT=Intention to treat; N=Number of patients.

Table 27 Previous cancer treatment in ITT population – ISEL study

Characteristic	Number (%) of patients	
	Gefitinib 250 mg (N=1129)	Placebo (N=563)
Best response to last chemotherapy[d]		
Complete response	6 (0.5)	2 (0.4)
Partial response	194 (17.2)	104 (18.5)
Stable disease	416 (36.8)	207 (36.8)
Progression/Non-evaluable	510 (45.2)	249 (44.2)
Not recorded	3 (0.3)	1 (0.2)

[a] Time from diagnosis of NSCLC refers to the time interval between first diagnosis of NSCLC and randomisation to this study.
[b] Refractory defined as recurrent or progressive disease [clinical or radiological] while receiving or within 90 days of last dose of chemotherapy.
[c] Intolerant defined as in Section 5.3.1.
[d] Last chemotherapy refers to the most recent chemotherapy regimen prior to entering this study.
ITT Intention to treat.
N Number of patients.

Numbers analysed



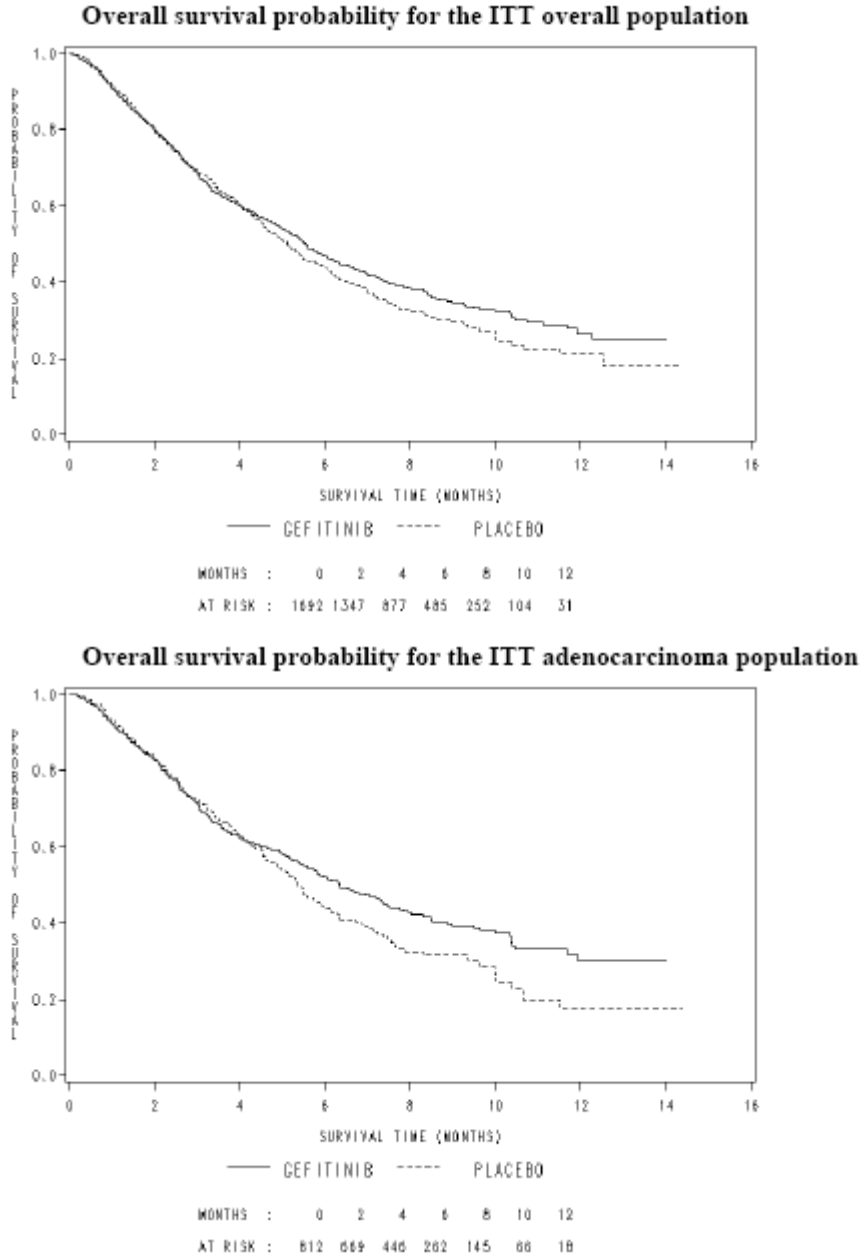
N Number of patients.
QOL Quality of life.

Outcomes and estimation

The randomised phase III ISEL study, was conducted in patients with advanced NSCLC who had received 1 or 2 prior chemotherapy regimens and were refractory or intolerant to their most recent regimen. The analyses was based on a data cut-off of 29 October 2004, by which time 976 deaths had accrued, median follow-up was 7.2 months. No statistically significant difference for the primary

stratified log-rank test was observed. For the overall population the HR was 0.89, (95% CI 0.77 to 1.02, p=0.0871. A hazard ratio < 1 implies a lower risk of death on gefitinib).

Figure 9 Overall survival of the ITT overall population and adenocarcinoma population – ISEL study



Gefitinib plus best supportive care was compared to placebo plus best supportive care. IRESSA did not prolong survival in the overall population. Survival outcomes differed by smoking status and ethnicity

Secondary endpoints:

For the adenocarcinoma population the HR for overall survival was 0.84, (95% CI 0.68 to 1.03, p=0.0885). Gefitinib 250 mg was associated with an 18% reduction in the risk of treatment failure compared with placebo (ITT population: HR 0.82, 95% CI 0.73 to 0.92, p=0.0006). Objective responses were achieved for 77 (8.0%, 1 complete response and 76 partial responses) patients in the gefitinib 250-mg group compared with 6 (1.3%) patients in the placebo group. No significant differences were observed in terms of survival outcomes in relation to EGFR expression status

although patients with EGFR-positive tumours achieve better outcomes when treated with gefitinib as opposed to placebo than patients with EGFR-negative tumours (EGFR expression status-by-treatment interaction, p=0.0488).

Quality of life including disease-related symptoms during treatment with gefitinib 250 mg was similar to placebo. Gefitinib provided more symptomatic control than placebo; the difference was not considered clinically relevant according to the pre-defined criteria of ≥2-point difference in LCS score (Evaluable for QOL population: mean change from baseline in LCS score [gefitinibplacebo] 0.51 points, 95% CI 0.08 to 0.94, p=0.0192). The overall compliance for completion of the FACT-L questionnaire was 86% and 85% for gefitinib and placebo, respectively. No clinically relevant changes in mean QOL or symptom scores were observed over the course of the study.

Ancillary analyses

Several subgroup analyses were planned in advance of unblinding the study data. Increased response rates were observed with gefitinib therapy in all subgroups with the largest differences among patients who had never smoked, were female, of Asian racial origin, or had adenocarcinoma histology.

Figure 10 Survival effect in subgroup analyses in the ITT population – ISEL study

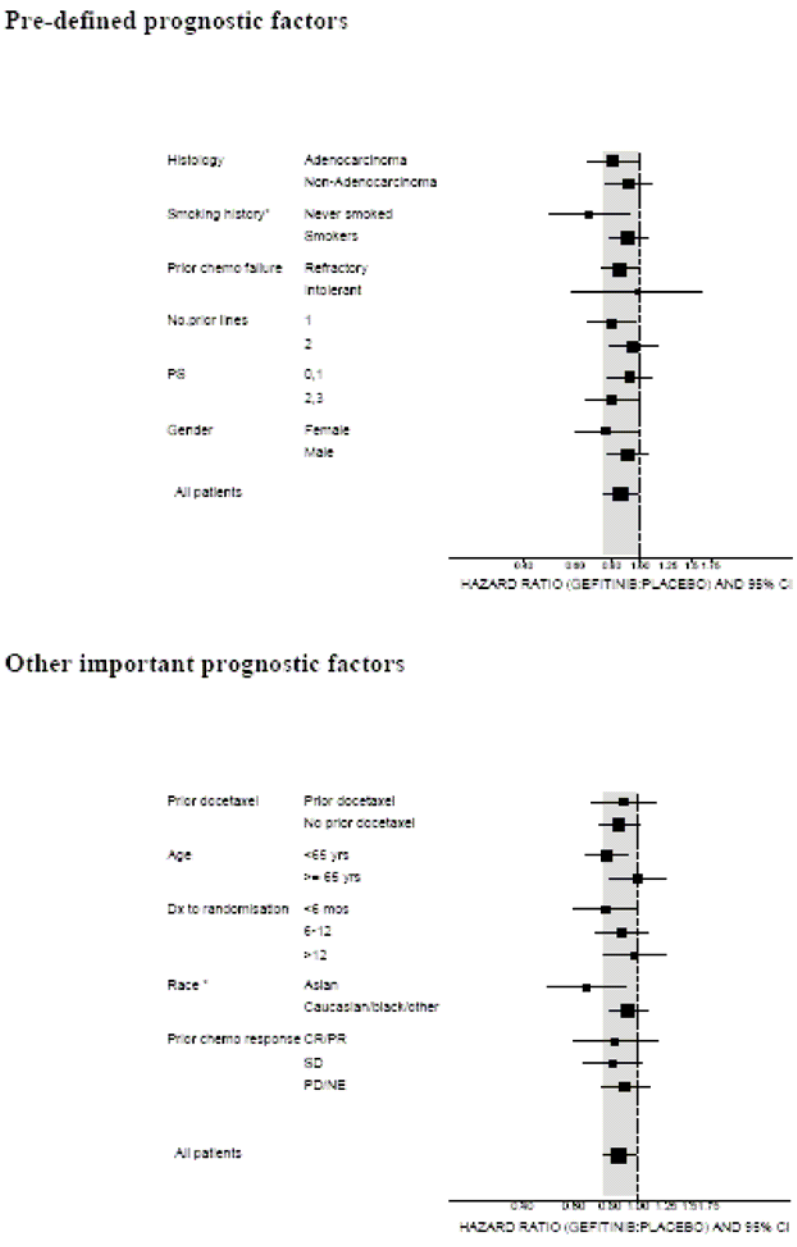
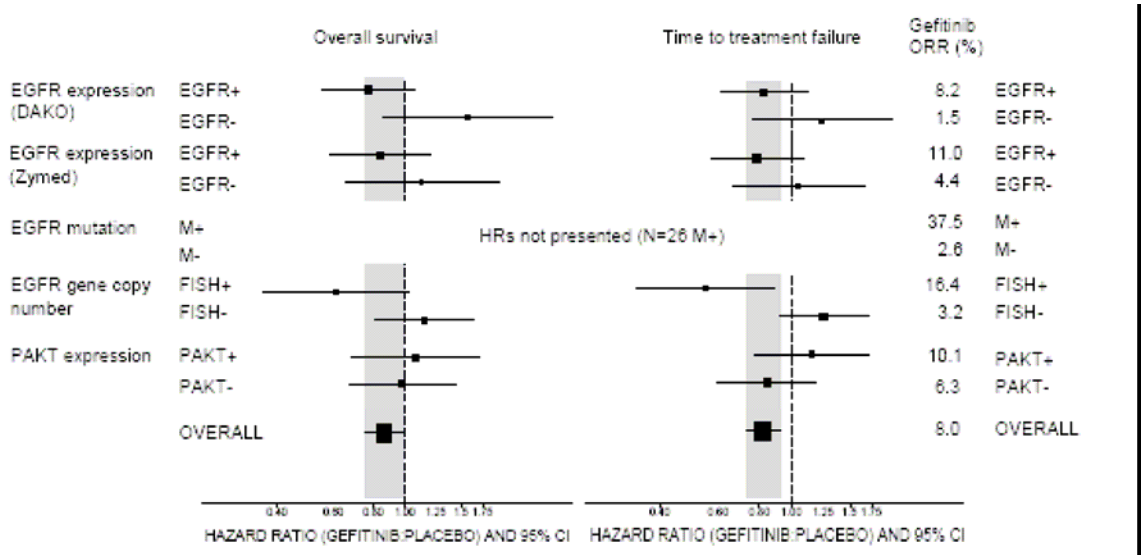


Figure 11 Overall survival and time to failure effect in subgroup analyses based on tumour EGFR expression, EGFR mutation, EGFR FISH and PAKT expression



Hazard ratios <1 indicate a difference in favour of gefitinib 250 mg while hazard ratios >1 favour placebo.
The size of the point estimate reflects the number of events in a subgroup – the larger this appears the greater the number of events; the grey band represents the confidence interval for the overall (all patients) hazard ratio.
M+ (EGFR mutation-positive), M- (EGFR mutation-negative); FISH+ (high EGFR gene copy number), FISH- (low EGFR gene copy number); PAKT+ (P-Akt expression-positive), PAKT- (P-Akt expression-negative).
No summaries for K-Ras or B-Raf mutations presented due to insufficient data.

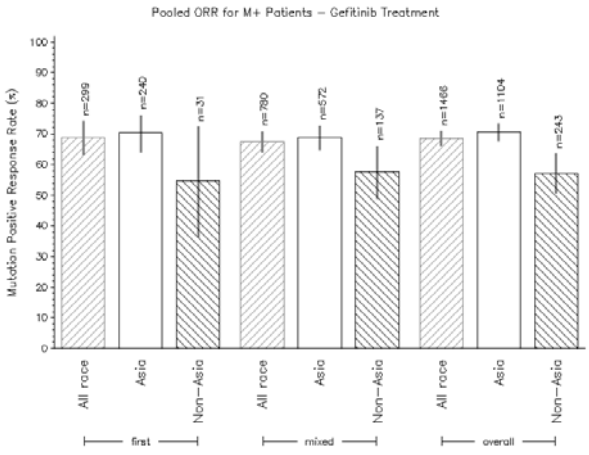
Ancillary analyses

- Analysis performed across trials (pooled analyses)

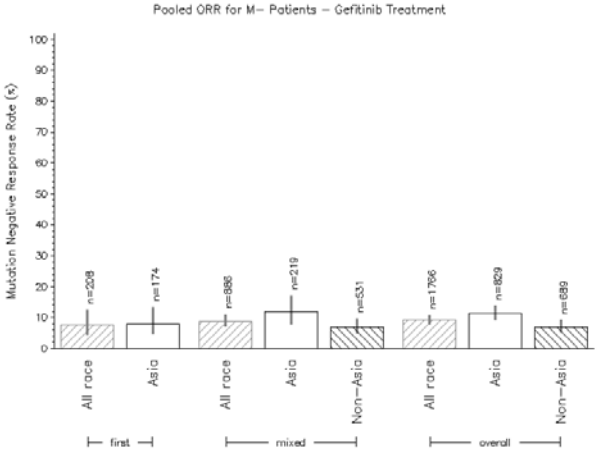
The applicant performed a pooled analysis for ORR by EGFR mutation status and subdivided by ethnicity and line of treatment from all available data with gefitinib (Figure 12).

Figure 12 Pooled analyses of data from clinical trials and literature review for ORR by EGFR mutation assessing gefitinib treatment and chemotherapy in Asian and Non-Asian patient populations

Gefitinib M+

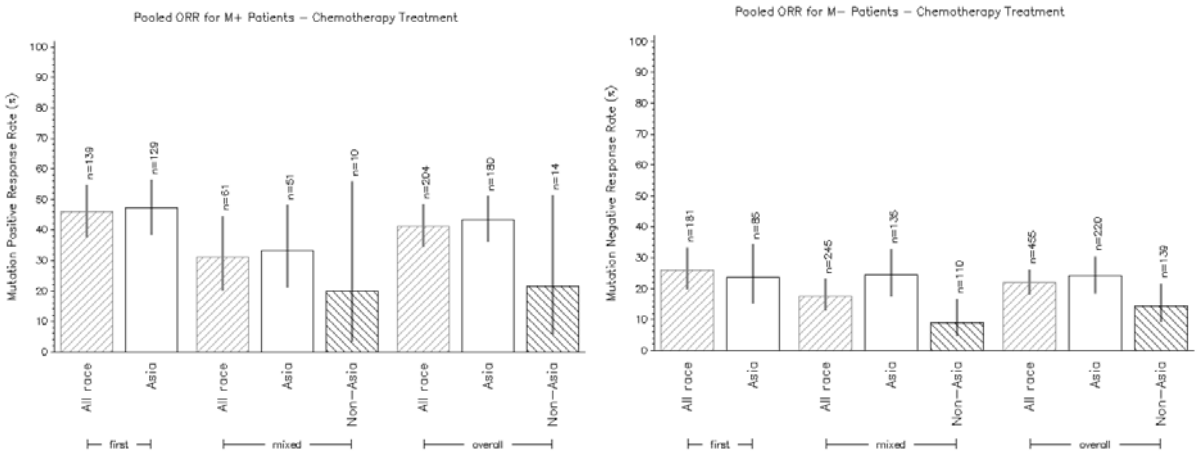


Gefitinib M-



Chemotherapy M+

Chemotherapy M-



Note that bars are grouped according to line of therapy, and the overall summaries presented in these figures include a number of studies for which line of therapy was not given.

The applicant performed a pooled multivariate logistic regression model analysis from patients in the INTEREST, INVITE, ISEL, INTACT I and II and IDEAL I and II trials (786 Caucasian patients) to identify clinical factors that may predict EGFR mutation status. Clinical characteristics of never smoker, adenocarcinoma histology, and female gender have been shown to be independent predictors of positive EGFR mutation status in a multivariate analysis Caucasian patients from gefitinib studies (Table 28). Asian patients also have a higher incidence of EGFR mutation-positive tumours.

Table 28 Summary of multivariate logistic regression analysis to identify factors which independently predicted for the presence of EGFR mutations in Caucasian patients

Factors that predicted for presence of EGFR mutation[a]	p-value	Odds of EGFR mutation	
Smoking status	<0.0001	6.5 times higher in never smokers than ever-smokers	28/70 (40%) of never smokers are M+ 47/716 (7%) of ever smokers are M+
Histology	<0.0001	4.4 times higher in adenocarcinoma than in non-adenocarcinoma	63/396 (16%) of patients with adenocarcinoma histology are M+ 12/390 (3%) of patients with non-adenocarcinoma histology are M+
Gender	0.0397	1.7 times higher in females than males	40/235 (17%) of females are M+ 35/551 (6%) of males are M+

Analysis based 786 Caucasian patients evaluable for EGFR mutation status in the INTEREST, INVITE, ISEL, INTACT I and II and IDEAL I and II studies.

[a] Age and WHO PS were not found to be significant predictors.

A pooled analysis from studies INTEREST, ISEL and INVITE for ORR for gefitinib in FISH positive but mutation negative tumours was investigated. The ORR for FISH- and M- was 5/69 versus 7/155 in response rate for FISH+ and M-.

- Clinical studies in special populations

There were no studies in special population that were conducted.

- Supportive study(ies)

The two pivotal studies are supported by three additional studies of gefitinib versus docetaxel in the same clinical setting as INTEREST - the Japanese Phase III V-15-32 study (490 patients), the Phase II SIGN study (141 patients), and the Korean post-marketing ISTANA study (161 patients), that collectively with INTEREST provide efficacy and safety results from over 2200 patients.

V-15-32
The trial V-15-32 failed to meet its non-inferiority objective. Survival point estimates overall and in most reasonably large subgroups tended to favour docetaxel despite that this study was conducted in a Japanese population and at a relatively low dose of docetaxel (60 mg/m^2).

SIGN
This Phase II study recruited patients from 25 centres in 12 countries (non-Asian), and were representative of an advanced NSCLC population who had failed previous chemotherapy and were eligible for second-line treatment. Mean change from baseline scores for symptom improvement (assessed by LCS) and QoL (FACT-L) were similar for gefitinib and docetaxel treated patients. Improvement rates were numerically higher for gefitinib compared with docetaxel, but the differences were not statistically significant.

ISTANA
The trial ISTANA enrolled a high percentage of never-smokers (41%) and all patients were Asian. A high response rate was reported in the gefitinib arm (28%) and PFS tended to be longer HR: 0.7, p=0.09. The survival data are immature to draw any meaningful conclusions.

- Discussion on clinical efficacy

The IPASS study recruited an enriched patient population who had biological factors that had been previously identified in the ISEL and IDEAL studies as conferring greater clinical benefit derived from gefitinib treatment. The ISEL study had identified a subgroup of patients who were never smokers and of Asian origin which benefited the most and the two Phase II studies IDEAL I and II had identified patients with adenocarcinoma who had a high rate of response to gefitinib. Overall, disease characteristics at entry were well balanced across the two treatment groups. The trial met its primary endpoint in the overall population where PFS was considered improved in the gefitinib arm compared to the doublet chemotherapy [HR 0.74; 95%CI 0.65-0.85; p<0.0001]. The subgroup analysis (male, female, never smokers, ex-smokers, age and whether it is locally advance or metastatic) showed that there were no major differences between the subgroups. At the time of submission, the OS data was not mature. Preliminary data on OS showed that both treatment arms were comparable (HR 0.91; 95%CI 0.76-1.10). However, the data on OS is difficult to interpret because of the cross-over design of the trial which may confound the survival data. The median survival was 18.6 months with gefitinib compared to 17.3 months for the doublet chemotherapy. Patients treated with gefitinib experienced an improvement in QoL compared to the doublet chemotherapy.

A significant interaction was observed between treatment with gefitinib and EGFR mutation in terms of PFS. PFS was significantly longer with gefitinib than carboplatin/paclitaxel treatment in patients who were EGFR M+ with a HR of 0.48 (95%CI 0.36-0.64; p<0.0001) while PFS was significantly shorter with gefitinib than carboplatin/paclitaxel treatment in patients who were EGFR M- with a HR of 2.85 (95%CI 2.05-3.98; p<0.0001). No relevant activity was observed for gefitinib in patients with EGFR FISH+ and EGFR M- tumours. Similar results were observed in a pooled analysis of ORR from studies INTEREST, ISEL and INVITE where in patients that were EGFR FISH- and EGFR M- the ORR was 5/69 (7.2%) versus 7/155 (4.5%) in patients with EGFR FISH+ and EGFR M- tumours. Therefore, using EGFR FISH status as a marker to predict patient benefit with gefitinib is not considered appropriate.

Two exploratory post-hoc analyses were presented in the IPASS study, an analysis of OS by EGFR mutation status and QoL by mutation status. OS appeared more favourable in patients that were EGFR M+ and treated with gefitinib rather than doublet chemotherapy (HR 0.776; 95%CI 0.500-1.202). A greater improvement in QoL as measured by FACT-L and TOI was shown in EGFR M+ patients. The opposite was observed in EGFR M- patients, where there was an improvement in favour of the doublet chemotherapy. When analysing time to worsening and disease-related symptoms as measured by FACT-L and TOI, the results obtained were consistent and comparable to that observed for QoL. The very low activity of gefitinib in terms of response rate in EGFR M- tumours, 1.1%, is worth highlighting. It is important to note that the mutation detection methodology used in IPASS differed from those employed in previous studies with gefitinib. While previous studies used Sanger Sequencing technology, the method of choice for IPASS was ARMS using the EGFR 29 Mutation

Test Kit (DxS). This assay has shown improved sensitivity. Thus the number of false negative samples is likely to be smaller in IPASS and because of the very high activity of EGFR in EGFR M+ tumours, a small percentage of false negative samples would affect the apparent activity of gefitinib in a "mutation negative" tumours.

The INTEREST trial was a randomised, open label, multicentre, Phase III double arm trial, comparing once-daily oral gefitinib 250 mg with 3-weekly intravenous docetaxel 75 mg/m2 in 1466 patients with locally advanced or metastatic NSCLC who had previously received platinum-based chemotherapy and were eligible for further chemotherapy (second-line therapy). The primary analysis met the non-inferiority criterion (1.154) with a confidence interval upper limit of 1.150. However, the per protocol, co-variate adjusted analysis, did not fall within the predefined acceptance limits and a median difference in survival , in the worst case scenario, of about 1.2 months in favour of docetaxel could be a possibility. In the overall population, the OS was 7.6 versus 8.0 months (HR 1.020; 96%CI 0.905-1.150) for gefitinib and docetaxel-treated patients, respectively. In the EGFR M+ status patients, no differences in OS were observed but, notably, the ORR were 42.1% and 21.1% (OR 25.2; 95%CI 1.23-515.53; p=0.036) for gefitinib and docetaxel, respectively. For PFS, the median was 7.0 vs 4.1 months (HR 0.16, 95%CI 0.05-0.49; p=0.0012] for gefitinib and docetaxel, respectively. For patients that were never smokers, PFS had HR 0.60 (95%CI 0.45-0.79, p=0.0004), the ORR was 23.7% vs 13.3% for gefitinib compared to docetaxel.

The ISEL study was a randomised, double-blind, Phase III study comparing overall survival of gefitinib 250mg plus BSC versus placebo plus BSC in pre-treated patients with locally advanced or metastatic NSCLC who were not suitable for further chemotherapy. The survival difference did not reach statistical significance in the primary stratified log-rank test; OS for gefitinib was 5.6 months and 5.1 months for BSC (HR 0.89; 95%CI 0.77-1.02; p=0.0871). Improved TTF of 3.0 months compared to 2.6 months for gefitinib and placebo (HR 0.82; 95%CI 0.73-0.92; p=0.0006) and ORR 8.0% versus 1.3% (OR 7.3, 95%CI 3.1-16.9) were observed for gefitinib and placebo, respectively. Exploratory biomarker analyses revealed EGFR FISH+ was a strong predictive factor for response. Higher response rates were observed in gefitinib-treated patients harbouring EGFR M+ (37.5% vs 0% for gefitinib and placebo, respectively) than for EGFR M- (2.6% vs 0% for gefitinib and placebo, respectively).

The CHMP noted the heterogeneity in tumour responses in relation to PFS and ORR in different subgroups analysed in the INTEREST trial as well as in the other supportive studies, where some subgroups faired better with gefitinib while other did better with docetaxel treatment. Amongst the subgroups identified were patients who are female, of Asian racial origin, those with adenocarcinoma histology, never/light smokers (analyses in a proportional hazards model showed a statistically significant interaction between gefitinib treatment and never smokers for PFS), EGFR FISH+ but the data was in particular stronger for patients with EGFR activating mutation (M+). As the INTEREST trial had included many Asian patients, a subgroup analysis was performed to ascertain the validity of the results in the overall population to the Caucasian only population. The results of the subgroup analyses in the Caucasian population for OS, PFS and ORR were consistent with the results in the overall population which showed that ORR performed better in the subgroups of never/ever smokers and patients presenting EGFR FISH+ tumours and PFS in the subgroup of never smokers was favourable to gefitinib. Therefore, the CHMP considered that the data from the overall population could be extrapolated to the Caucasian population.

There was higher response rate in Asians than in non-Asian in EGFR M+ tumours from a pooled analysis of data from clinical trials and the literature. The reason for this is unexpected and may be an issue related to the methodology used for testing as the prevalence of mutation positive tumours is much higher in Asians. A moderately lower but relevant activity is observed in pre-treated patients. Although the activity observed in non-Asians is lower than in Asians (ORR, PFS and OS in the Asian population tended to be longer than for the non-Asian population), the CHMP acknowledged that the activity is still high at 56% ORR (n=243, pooled lines of therapy). Nonetheless, the low number of first-line non-Asian patients with EGFR M+ tumours is of concern and the applicant has committed to perform a trial in the Caucasian population in EGFR M+ to further confirm the results.

The difference in OS and ORR between gefitinib-treated Asians and gefitinib-treated Caucasians could partly be accounted for by the mutation status of EGFR, but not by EGFR FISH status. EGFR mutations occur more frequently in Asians (40% vs 10%) and therefore these higher rates translate into better efficacy with gefitinib. When assessing the EGFR mutation status of a patient, it is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations.

The CHMP consulted the Scientific Advisory Group (SAG) in Oncology to provide guidance on the significance of the clinical benefit observed in the context of the trials conducted in a predominantly Asian patient population with a defined genetic criteria of tumours harbouring EGFR activating mutations and the applicability of defining and treating a patient population based on their EGFR mutation status in a clinical practice.

The SAG expressed concerns about the results submitted, in particular about the large amount of missing data with respect to EGFR mutation status which should have been controlled by design and conduct of the clinical studies. In this respect, the clinical studies presented were considered to be inadequate in view of the vast amount of data available in the literature and available regulatory guidance about the importance of tumour material for identifying a population more likely to respond with this type of agents. A more careful design and conduct of the clinical studies would have established the benefits of gefitinib more efficiently and convincingly, and would have identified populations more likely to respond in a more reliable way leading to better patient selection. According to the SAG, the applicant should commit to conduct further postmarketing studies to explore ways to further improve patient selection based on tumour biology data.

Despite the fact that the design and conduct of the studies presented was considered to be inadequate, the SAG unanimously agreed that across all studies gefitinib shows a consistent pattern of activity in EGFR mutation status positive patients. Although the issue could have been addressed more efficiently and convincingly with well designed and conducted studies based on adequate tumour tissue availability for all patients, the evidence across trials is consistent and supported by clinical and non-clinical pharmacodynamic data from numerous independent sources in the literature.

The SAG unanimously agreed that a strong recommendation to limit treatment with gefitinib to patients with documented evidence of activating EGFR mutation based on reliable assays is supported by the data presented. Adequate warnings should be included in the product information about the fact that clinical predictors such as smoking history, histology or sex are unreliable predictors of response to gefitinib and should not be used to replace EGFR mutation status based on reliable assays, whenever it is possible to use such assays. However, there should be no absolute restriction of the indication or absolute contraindication in case of unavailability of such assays.

The SAG unanimously agreed that a restriction to patients with activating EGFR mutation positive tumours is feasible from a clinical perspective because in current clinical practice a diagnosis should be established based on biopsy data, so that EGFR mutation status should be available for the majority of patients. Where this is for some reason not possible, treatment with gefitinib should still be possible but strong warnings should be provided in the product information that clinical predictors of response can be used to select patients but they are poor predictors of the population most likely to respond, and that patient selection based on clinical characteristics alone may result in unnecessary under and over-exposure to gefitinib.

The SAG unanimously agreed that a restriction by line of therapy is not supported by the data presented.

The SAG unanimously agreed that there is no need to conduct a confirmatory first-line study in Caucasian patients, although further data from e.g., single-arm studies to be conducted post-marketing looking at response rate in a well defined Caucasian population with documented EGFR mutation status should be conducted to better define the level of activity and further explore predictors of response.

Having received and discussed the SAG recommendations, the CHMP concluded that EGFR mutation status may account for the benefit observed in patients treated with gefitinib. Thus, based on the data and the views of the SAG Oncology, the CHMP considered that the indication should be restricted to

patients harbouring activating mutations as this subgroup of patients appeared to derive the most clinically meaningful benefit from gefitinib therapy.

During the procedure the applicant addressed other issues which pertained to the statistical analysis of the primary endpoints and the presentation of a number of subgroup analyses (smokers versus never-smokers, adenocarcinoma histology versus non-adenocarcinoma histology, Asian versus non-Asian, male versus females, EGFR FISH+ versus FISH-, k-Ras+ versus k-Ras-) from the different submitted trials with respect to the efficacy of gefitinib in terms of OS, PFS and ORR. The "never smoker" group were found to have the highest predictive value for EGFR M+ tumours, followed by histology of adenocarcinoma and gender where females appear to have a higher probability to have EGFR M+ tumours.

Gefitinib has a mean steady state volume of distribution of 1400 l indicating extensive distribution into tissue. Plasma protein binding is approximately 90 %. Gefitinib binds to serum albumin and alpha 1-acid glycoprotein. Following oral administration of gefitinib, absorption is moderately slow and peak plasma concentrations of gefitinib typically occur at 3 to 7 hours after administration. Mean absolute bioavailability is 59 % in cancer patients. Studies pertinent to the evaluating the effect of substances that elevate gastric pH demonstrated an impaired bioavailability of gefitinib which could potentially decrease the efficacy of the treatment. Exposure to gefitinib is not significantly altered by food. In a trial in healthy volunteers where gastric pH was maintained above pH 5, gefitinib exposure was reduced by 47 %, likely due to impaired solubility of gefitinib in the stomach (see SmPC sections 4.4 and 4.5). *In vitro* data indicate that CYP3A4 and CYP2D6 are the major P450 isozyme involved in the oxidative metabolism of gefitinib. *In vitro* studies have shown that gefitinib has limited potential to inhibit CYP2D6. Gefitinib shows no enzyme induction effects in animal studies and no significant inhibition (*in vitro*) of any other cytochrome P450 enzyme.

Gefitinib is extensively metabolised in humans. Five metabolites have been fully identified in excreta and 8 metabolites in plasma. The major metabolite identified was O-desmethyl gefitinib, which is 14-fold less potent than gefitinib at inhibiting EGFR stimulated cell growth and has no inhibitory effect on tumour cell growth in mice. It is therefore considered unlikely that it contributes to the clinical activity of gefitinib.The formation of O-desmethyl gefitinib has been shown, *in vitro*, to be via CYP2D6. The role of CYP2D6 in the metabolic clearance of gefitinib has been evaluated in a clinical trial in healthy volunteers genotyped for CYP2D6 status. In poor metabolisers no measurable levels of O-desmethyl gefitinib were produced. The levels of exposure to gefitinib achieved in both the extensive and the poor metaboliser groups were wide and overlapping but the mean exposure to gefitinib was 2-fold higher in the poor metaboliser group. The higher average exposures that could be achieved by individuals with no active CYP2D6 may be clinically relevant since adverse effects are related to dose and exposure.

Concomitant use of CYP3A4 inhibitors or inducers showed an altered effect on gefitinib pharmacokinetics which could lead to clinical significant effect, as CYP2D6 is a metaboliser for gefitinib; the effect of an inhibitor on gefitinib bioavailability might be especially important (see section 4.5 in SmPC). The observed CYP3A4 interactions with itraconazole and rifampicin were described. Pre-treatment with itraconazole resulted in an 80% increase in the mean AUC of gefitinib whereas pre-treatment with rifampicin reduced the mean AUC by 83% of gefitinib (see section 4.5 in SmPC). In addition, published literature indicates that gefitinib might be a potent inhibitor of BCRP (see section 4.5 in the SmPC). The applicant justified the lack of *in vivo* data on interaction between gefitinib and substrates for CYP2C19, CYP3A4 and UGT1A1 as it was unlikely that an interaction could be observed because of the low inhibition observed *in vitro* at very high concentration of gefitinib and an no changes in AUC of an active metabolite cleared by UGT1A1 were observed in animal models with gefitinib. *In vitro* data indicate that gefitinib is a substrate for the membrane transport protein Pgp.

Gefitinib is excreted mainly as metabolites via the faeces, with renal elimination of gefitinib and metabolites accounting for less than 4 % of the administered dose.

Gefitinib total plasma clearance is approximately 500 ml/min and the mean terminal half-life is 41 hours in cancer patients. Administration of gefitinib once daily results in 2 to 8-fold accumulation, with steady state exposures achieved after 7 to 10 doses. At steady state, circulating plasma concentrations are typically maintained within a 2- to 3-fold range over the 24-hour dosing interval.

Clinical safety

The total estimated exposure to gefitinib as of January 2008 was greater than 275 000 patients. The majority of patients (98%) received a 250 mg daily dose and the majority of patient exposure (71%) was in patients receiving gefitinib during the marketed use. An estimated 80 000 patients (approximately 29% of total exposure) were exposed to gefitinib in clinical studies, of which approximately 58 000 received gefitinib treatment as part of the Expanded Access Programme.

- Patient exposure

The majority of patients in clinical studies (90%) received gefitinib for the treatment of advanced NSCLC, with the remaining exposure to gefitinib being distributed across a range of investigational tumour indications (mainly breast, head and neck, colorectal, central nervous system, gastrointestinal and ovarian cancers). Approximately 2 800 patients received gefitinib 250 mg monotherapy in key clinical studies in advanced NSCLC.

The duration of treatment in the INTEREST study was at least one dose of gefitinib in 729 patients and at least one dose of docetaxel in 715 patients. The overall median exposure to study treatment was 2.4 months for gefitinib and 2.8 months for docetaxel. Docetaxel was administered for a median number of 4 cycles (range 1 to 24 with 82.2% of all cycles given at the full dose). More gefitinib treated patients received treatment for longer than 6 months. In the IPASS study, overall exposure to first-line study treatment was longer with gefitinib than carboplatin/paclitaxel treatment (medians of 5.6 months and 4.1 months, respectively). A high percentage of gefitinib-treated patients received treatment for longer than 6 months (47.6%) compared with none in the carboplatin / paclitaxel group. The median and mean number of chemotherapy cycles administered were 6.0 and 4.6, respectively. Dose modifications (interruptions, delays and reductions) because of toxicity were less common in patients treated with gefitinib (16.1%) compared with carboplatin / paclitaxel (35.2%/37.5%)

- Adverse events

In the ISEL study, the overall incidence of AEs was higher for gefitinib than for placebo (Table 29). The incidence of AEs leading to discontinuation or AEs leading to death were low in both treatment groups, but were slightly higher for the gefitinib group. No clinically relevant differences in the frequency of SAEs or CTC grade 3 or 4 AEs were evident between the treatment groups.

Table 29 Overview of the number (%) of patients who had an AE in any category – ISEL (EFS population)

Category [a]	Number (%) of patients			
	Gefitinib 250 mg (N=1126)		Placebo (N=562)	
All adverse events (AEs)	**927**	**(82.3)**	**397**	**(70.6)**
Treatment-related [b] AEs	658	(58.4)	161	(28.6)
All serious adverse events (SAEs)	**216**	**(19.2)**	**98**	**(17.4)**
Treatment-related [b] SAEs	27	(2.4)	8	(1.4)
Non-fatal SAEs	180	(16.0)	83	(14.8)
Deaths due to SAEs	55	(4.9)	22	(3.9)
Deaths due to treatment-related [b] SAE	5	(0.4)	1	(0.2)
Discontinuations from study treatment due to AEs	**61**	**(5.4)**	**13**	**(2.3)**
Due to treatment-related [b] AE	31	(2.8)	3	(0.5)
Due to SAE	33	(2.9)	10	(1.8)

Table 29 Overview of the number (%) of patients who had an AE in any category – ISEL (EFS population)

Category [a]	Number (%) of patients			
	Gefitinib 250 mg (N=1126)		Placebo (N=562)	
Due to treatment-related [b] SAE	10	(0.9)	3	(0.5)
CTC [c] Grade 3 or 4 AEs	**341**	**(30.3)**	**151**	**(26.9)**
Treatment-related[b] CTC [c] Grade 3 or 4 AEs	90	(8.0)	16	(2.8)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] Treatment-related adverse events were those events that the investigator considered to be possibly related to study treatment.
[c] CTC Grade NCI version 2.0.
EFS=Evaluable for safety; N =Number of patients

In the INTEREST study, the majority of patients experienced one or more AE during the course of the study. Fewer SAEs (22.1% vs 29.4%), CTC grade 3 or 4 AEs (37.3% vs 55.9%), and AEs leading to discontinuation (8.1% vs 14.3%) were reported with gefitinib compared with docetaxel. The frequency of SAEs leading to death (4.3% vs 3.9%) was similar for both treatments, Table 30.

Table 30 Number (%) of patients who had an AE in any category – INTEREST (EFS population)

Category[a]	N (%) of patients			
	Gefitinib 250 mg (N=729)		Docetaxel 75 mg/m^2 (N=715)	
All adverse events (AEs)	687	(94.2)	668	(93.4)
Treatment-related[b] AEs	527	(72.3)	588	(82.2)
All serious adverse events (SAEs)	161	(22.1)	210	(29.4)
Treatment-related[b] SAEs	28	(3.8)	130	(18.2)
Non-fatal SAEs	141	(19.3)	194	(27.1)
SAEs leading to death	31	(4.3)	28	(3.9)
Treatment-related[b] SAEs leading to death	6	(0.8)	15	(2.1)
AEs leading to discontinuation from study treatment	59	(8.1)	102	(14.3)
Due to treatment-related[b] AEs	30	(4.1)	78	(10.9)
Due to SAEs	42	(5.8)	42	(5.9)
Due to treatment-related[b] SAEs	17	(2.3)	25	(3.5)
CTC[c] Grade 3 or 4 AEs	272	(37.3)	400	(55.9)
Treatment-related[b] CTC[c] grade 3 or 4 AEs	62	(8.5)	291	(40.7)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] Treatment-related adverse events were those events that the investigator considered to be possibly related to study treatment.
[c] CTC Grade NCI version 2.0.
EFS=Evaluable-for-safety; N =Number of patients

In the INTEREST study, the most commonly reported AEs for gefitinib were rash/acne, diarrhoea, vomiting, asthenic conditions, anorexia, nausea, dry skin, cough and dyspnoea (Table 31). These events were mostly CTC grade 1 or 2. Patients with poorly tolerated diarrhoea or skin adverse reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg dose (see section 4.8). For patients unable to tolerate treatment after a therapy interruption, IRESSA should be discontinued and an alternative treatment should be considered (see SmPC section 4.2). A pooled dataset for adverse reactions from the ISEL, INTEREST and IPASS clinical trials is presented in Table 32. The safety profile is based on the

gefitinib clinical development programme and postmarketed experience but adverse reactions were assigned frequency categories based on the incidence in the pooled dataset.

Docetaxel was most commonly associated with haematological toxicity (derived from the haematological laboratory data), and AE reports of asthenic conditions, alopecia, nausea, diarrhoea and neurotoxicity. Most AEs for docetaxel were CTC grade 1 or 2, with the exception of AE reports of neutropenia and leukopenia, where the majority of AEs were CTC grade 3 or 4.

Table 31 Most common AEs (occurring in at least 5% of patients in either treatment group), irrespective of causality – INTEREST (EFS population)

System organ class and preferred term	Number (%) of patients[a]			
	Gefitinib 250 mg (N=729)		Docetaxel 75 mg/m^2 (N=715)	
Blood and lymphatic system disorders				
Neutropenia[b]	8	(1.1)	126	(17.6)
Anaemia	34	(4.7)	84	(11.7)
Febrile neutropenia	9	(1.2)	72	(10.1)
Leukopenia[b]	1	(0.1)	51	(7.1)
Gastrointestinal disorders				
Diarrhoea	255	(35.0)	177	(24.8)
Nausea	148	(20.3)	187	(26.2)
Vomiting	109	(15.0)	123	(17.2)
Constipation	79	(10.8)	121	(16.9)
Stomatitis[c]	67	(9.2)	93	(13.0)
Abdominal pain	38	(5.2)	37	(5.2)
General disorders				
Asthenic conditions[c]	182	(25.0)	334	(46.7)
Pyrexia	69	(9.5)	118	(16.5)
Fluid retention[c]	48	(6.6)	112	(15.7)
Infections and infestations				
Lower respiratory tract and lung infections[c]	71	(9.7)	74	(10.3)
Nasopharyngitis	48	(6.6)	37	(5.2)
Metabolism and nutrition disorders				
Anorexia[c]	159	(21.8)	151	(21.1)
Musculoskeletal and connective tissue disorders				
Myalgia	24	(3.3)	113	(15.8)
Arthralgia	23	(3.2)	68	(9.5)
Nervous system disorders				
Neurotoxicity[c]	49	(6.7)	171	(23.9)
Headache	46	(6.3)	52	(7.3)
Dizziness	31	(4.3)	45	(6.3)
Dysgeusia	17	(2.3)	37	(5.2)
Psychiatric disorders				
Insomnia	30	(4.1)	56	(7.8)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	120	(16.5)	117	(16.4)

Table 31 Most common AEs (occurring in at least 5% of patients in either treatment group), irrespective of causality – INTEREST (EFS population)

System organ class and preferred term	Number (%) of patients[a]			
	Gefitinib 250 mg (N=729)		Docetaxel 75 mg/m^2 (N=715)	
Cough	108	(14.8)	102	(14.3)
Epistaxis	39	(5.3)	25	(3.5)
Haemoptysis	37	(5.1)	26	(3.6)
Skin and subcutaneous disorders				
Rash/Acne [c]	360	(49.4)	73	(10.2)
Alopecia	23	(3.2)	254	(35.5)
Dry skin	111	(15.2)	10	(1.4)
Pruritus[c]	68	(9.3)	28	(3.9)
Nail disorder	13	(1.8)	46	(6.4)

[a] Percentages are of total patients in each treatment group in decreasing order of incidence within the System Organ Class across both treatment groups. Patients are counted once within any preferred term.

[b] Clinically significant laboratory findings were only reported as adverse events if a criterion for a serious adverse event was fulfilled, the abnormality caused study treatment to be discontinued, or the investigator insisted the abnormality was to be reported as an adverse event. Therefore, laboratory findings worsening from baseline to CTC grade 3 or 4should be referred to for the primary assessment of haematological toxicity.

[c] Grouped terms were specified as follows. Stomatitis (aphthous stomatitis, mouth ulceration, oral mucosal eruption, and stomatitis); Asthenic conditions (asthenia, fatigue, malaise, and prostration); Fluid retention (fluid retention, oedema, oedema peripheral, generalised oedema, localised oedema, and pitting oedema); Lower respiratory tract and lung infections (bronchitis, bronchopneumonia, lobar pneumonia, lower respiratory tract infection, lung infection, pneumonia, and post procedural pneumonia); Anorexia (anorexia and decreased appetite); Neurotoxicity (dysaesthesia, hypoaesthesia, hypoaesthesia oral, neuropathy, neuropathy peripheral, neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy); Rash/Acne (High level term (HLT) 'rashes, eruptions and exanthems', HLT 'acnes' and preferred terms rash pustular, dermatitis, dermatitis exfoliative, exfoliative rash, rash erythematous, and rash popular); Pruritis (pruritus, pruritus generalised, and rash pruritic).

EFS=Evaluable-for-safety; N =Number of patients.

The safety profile presented in Table 32 is based on the gefitinib clinical development programme and postmarketed experience. Adverse reactions have been assigned to the frequency categories in Table 32 based on the incidence of comparable adverse event reports in a pooled dataset from the ISEL, INTEREST and IPASS phase III clinical trials (2462 IRESSA-treated patients). Frequencies of occurrence of undesirable effects are defined as: very common (≥ 1/10); common (> 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 32 Adverse reactions

Adverse reactions by system organ class and frequency			**Number of patients reporting AEs in IRESSA arms of ISEL, INTEREST and IPASS (Total N=2462)**
Metabolism and nutrition disorders	Very Common	Anorexia mild or moderate (CTC grade 1 or 2).	19.7% (484 patients)

Adverse reactions by system organ class and frequency			**Number of patients reporting AEs in IRESSA arms of ISEL, INTEREST and IPASS (Total N=2462)**
Eye disorders	Common	Conjunctivitis, blepharitis, and dry eye[1], mainly mild (CTC grade 1).	6.7% (164 patients)
	Uncommon	Corneal erosion, reversible and sometimes in association with aberrant eyelash growth.	0.3% (8 patients)
Vascular disorders	Common	Haemorrhage, such as epistaxis and haematuria.	4.3% (105 patients)
Respiratory, thoracic and mediastinal disorders	Common	Interstitial lung disease (1.3 %), often severe (CTC grade 3-4). Cases with fatal outcomes have been reported.	1.3% (33 patients)
Gastrointestinal disorders	Very Common	Diarrhoea, mainly mild or moderate (CTC grade 1 or 2).	34.9% (860 patients)
		Vomiting, mainly mild or moderate (CTC grade 1 or 2).	13.8% (339 patients)
		Nausea, mainly mild (CTC grade 1).	17.8% (439 patients)
		Stomatitis, predominantly mild in nature (CTC grade 1).	11.0% (272 patients)
	Common	Dehydration, secondary to diarrhoea, nausea, vomiting or anorexia.	1.8% (45 patients)
		Dry mouth[1], predominantly mild (CTC grade 1).	2.0% (49 patients)
	Uncommon	Pancreatitis	0.1% (3 patients)
Hepatobiliary disorders	Very Common	Elevations in alanine aminotransferase[2], mainly mild to moderate.	10.1% (225/2236 patients)
	Common	Elevations in aspartate aminotransferase[2], mainly mild to moderate.	7.9% (174/2204 patients)
		Elevations in total bilirubin[2], mainly mild to moderate.	2.7% (61/2223 patients)
	Rare	Hepatitis	0.08% (2 patients)

Adverse reactions by system organ class and frequency			Number of patients reporting AEs in IRESSA arms of ISEL, INTEREST and IPASS (Total N=2462)
Skin and subcutaneous tissue disorders	Very Common	Skin reactions, mainly a mild or moderate (CTC grade 1 or 2) pustular rash, sometimes itchy with dry skin, on an erythematous base.	57.9% (1426 patients)
	Common	Nail disorder	7.9% (194 patients)
		Alopecia	4.7% (115 patients)
	Uncommon	Allergic reactions[3], including angioedema and urticaria	0.9% (22 patients)
	Rare	Toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme	0.04% (1 patient)
Renal and urinary disorders	Common	Asymptomatic laboratory elevations in blood creatinine[2]	1.5% (33/2253 patients)
		Proteinuria[4]	7.7% (106/1370 patients)
General disorders	Very Common	Asthenia, predominantly mild (CTC grade 1).	17.7% (435 patients)
	Common	Pyrexia	8.7% (213 patients)

1 This event can occur in association with other dry conditions (mainly skin reactions) seen with IRESSA.

2 These frequencies were calculated based on patients with a change from baseline of 2 or more CTC grades in the relevant laboratory parameters. As these calculations were based on laboratory data rather than adverse event data, the denominator for the calculation was the number of patients with a baseline laboratory value and at least one post-baseline value for each relevant parameter, rather than the number of patients evaluable for safety.

3 The overall incidence of Adverse Events (AEs) of allergic reaction reported in the pooled analysis of the ISEL, INTEREST and IPASS trials was 1.5% (36 patients). Fourteen of the 36 patients were excluded from the reported frequency as their reports contained evidence of either a non allergic aetiology or that the allergic reaction was the result of treatment with another medicine

4 The proteinuria frequency descriptor was calculated based on the number of patients in ISEL and INTEREST with deterioration from baseline of 3 or more categories of proteinuria as measured by urinalysis. IPASS data was not included in the calculation as urinalysis data was not routinely collected in the study and only a limited amount of data was available.

CTC grade 3 or 4 adverse events

In the INTEREST study, 272 patients (37.3%), and 400 patients (55.9%) in the gefitinib and docetaxel treatment groups, respectively, had at least one AE of CTC grade 3 or 4. Fewer CTC grade 3 or 4 AEs and fewer treatment-related CTC grades 3 or 4 AEs were reported with gefitinib than with docetaxel. The only CTC grade 3 or 4 AE commonly reported with gefitinib (≥5%) was dyspnoea. This was reported at a slightly higher incidence on the docetaxel arm and is probably indicative of the underlying disease. AEs commonly reported for gefitinib, diarrhoea, nausea, vomiting and asthenic conditions, were more frequently reported as CTC grade 3 or 4 AEs with docetaxel than gefitinib.

In the IPASS study, a total of 192 patients (31.6%) in the gefitinib arm and 368 patients (62.5%) in the carboplatin / paclitaxel arm had at least 1 AE of CTC grade 3, 4 or 5. Fewer CTC grade 3, 4 or 5 AEs and fewer treatment-related CTC grade 3, 4 or 5 AEs were reported with gefitinib than with carboplatin / paclitaxel. The most commonly reported CTC grade 3, 4 or 5 AEs (≥3%) were ALT increased, diarrhoea and hepatic function abnormal with gefitinib, and neutropenia, leukopenia, anaemia, neutrophil count decreased, and white blood cell decreased with carboplatin / paclitaxel. The CTC grade 3, 4 or 5 AEs reported on each treatment arm were generally consistent with the known safety profiles of the two treatments and the underlying disease. The majority of AEs of haematological toxicity reported on the gefitinib arm (neutropenia, leukopenia, febrile neutropenia and bone marrow failure) were reported during the 28-day follow up period, when patients were receiving 2nd line chemotherapy.

- Serious adverse event/deaths/other significant events

In the INTEREST study, the incidence of SAEs was lower for gefitinib than for docetaxel; 161 (22.1%) and 210 (29.4%), respectively. The most frequently reported SAE in the gefitinib treatment group was pneumonia (2.5%) which was reported at a similar rate in the docetaxel treatment group (2.9%). More of the docetaxel treated patients experienced at least one SAE, particularly febrile neutropenia (1.1% vs 7.6%, gefitinib and docetaxel, respectively) and other haematological toxicities such as neutropenia (2.4%), anemia (0.7%), granulocytopenia (0.6%) and leucopenia (0.6%). The SAEs of febrile neutropenia or neutropenia in the gefitinib treatment group occurred after discontinuation of gefitinib and while the patient was receiving post treatment chemotherapy.

Fewer gefitinib treated patients experienced SAEs that were considered to be treatment related; 3.8% versus 18.2% of docetaxel treated patients. The most commonly reported treatment-related SAEs for the gefitinib and docetaxel treated patients were: febrile neutropenia (0.1% versus 7.6%), neutropenia (0 versus 2.4%), pyrexia (0 versus 1.1%), pneumonia (0.3% versus 1.5%), and diarrhoea (1.0% versus 0.4%).

Interstitial lung disease (ILD)
The majority of data on ILD has come from post-marketing use in the Japanese population, in particular from a post-marketing surveillance (PMS) study, and a pharmacoepidemiological nested case-control study (V-15-33). The incidence of ILD-type events was comparable in both treatment groups in the INTEREST trial and IPASS (Table 33). This incidence of ILD-type events is consistent with that reported in the ISEL study. The reporting rate in the pooled data from INTEREST and ISEL is 1.1%.

Table 33 ILD type events – INTEREST and IPASS (EFS population)

Interstitial lung disease type events	**Number (%) of patients**			
INTEREST [a]	**Gefitinib 250 mg (N=729)**		**Docetaxel 75 mg/m^2 (N=715)**	
All events	10	(1.4)	8	(1.1)
CTC grade 3 or 4	5	(0.7)	5	(0.7)
IPASS[b]	Gefitinib 250 mg		Carboplatin / Paclitaxel	

Table 33 ILD type events – INTEREST and IPASS (EFS population)

Interstitial lung disease type events	Number (%) of patients			
INTEREST [a]	**Gefitinib 250 mg (N=729)**		**Docetaxel 75 mg/m^2 (N=715)**	
	(N=607)		(N=589)	
All events	16	(2.6)	8	(1.4)
CTC grade 3, 4 or 5	8	(1.3)	1	(0.2)
Outcome of death	3	(0.5)	1	(0.2)
Events with a preferred term of ILD	7	(1.2)	0	

[a] Events reported in this study representing ILD-type events (by MedDRA preferred term) were: pneumonitis (4 patients), lung infiltration (5 patients), interstitial lung disease (6 patients), pulmonary fibrosis (2 patients), and chest x-ray abnormal (1 patient).

[b] Events reported in this study representing ILD-type events (by MedDRA preferred term) were: acute respiratory distress syndrome, interstitial lung disease, pneumonitis, radiation pneumonitis.

EFS=Evaluable for safety.; N=Number of patients.

Based on available data received as of January 2008, from worldwide clinical studies, expanded access/compassionate use and post marketing use, the estimated reporting rate of ILD-type events overall is estimated to be 0.8% (approximately 0.2% outside of Japan and approximately 3% in Japan). Of the reported ILD-type events, approximately 36% have a fatal outcome (32% outside of Japan and 37% in Japan). A special warning has been introduced in the SmPC in relation to the risk of ILD.

Ophthalmological event

Based on animal toxicology studies demonstrating dose and duration related corneal translucencies and opacities (see non-clinical section), a comprehensive ophthalmology monitoring was conducted in the Phase I and II studies. The 246 healthy volunteers from the Phase I studies underwent ophthalmological assessments and there were no observations related to the non-clinical findings but corneal ulcer occurring at higher doses of gefitinib which healed rapidly. In the Phase II studies IDEAL I and II studies no evidence of any consistent or drug-related ophthalmological toxicity were demonstrated. There were more events in the Eye Disorders SOC reported in the INTEREST study by patients in the gefitinib arm (9.2%) than in the docetaxel arm (6.9%). Individual event terms were reported by small numbers of patients, with the exception of conjunctivitis (2.9% for gefitinib and 1.4% for docetaxel) and dry eye (1.8% for gefitinib and 0.4% for docetaxel).

ECG abnormalities

Cardiovascular monitoring was performed in the Phase I and Phase II studies. Cardiovascular monitoring of 246 healthy volunteers revealed no clinically significant abnormalities in these subjects. Comparable results were obtained in other studies included the INTEREST study.

Hepatoxicity

In the INTEREST study the incidence of AEs from the hepatobiliary SOC was low in both the gefitinib and docetaxel treatment arms (12 patients (1.6%) and 8 patients (1.1%), respectively). The frequency of transaminase changes were higher with gefitinib than with docetaxel, although the majority of transaminase changes observed were mild to moderate. Although liver function test abnormalities (including increases in alanine aminotransferase, aspartate aminotransferase and bilirubin) were common, they were rarely observed as hepatitis (see SmPC section 4.4 and 4.8). Therefore, periodic liver function testing is recommended. Gefitinib should be used cautiously in the presence of mild to moderate changes in liver function. Discontinuation should be considered if changes are severe. Impaired liver function due to cirrhosis has been shown to lead to increased plasma concentrations of gefitinib (see SmPC section 5.2).

Renal disorders

There was low incidence of AEs from the renal and urinary disorder SOC in the INTEREST trial (34 patients (4.7%) and 30 patients (4.2%) respectively in the gefitinib and docetaxel treatment arm). The results from other studies were consistent with the INTEREST study.

Deaths
Of the 1444 patients in the safety population of the INTEREST study, 1180 (81.7%) had died by the data cut-off date of 06 March 2007 (82.2% of gefitinib-treated patients and 81.3% of docetaxel-treated patients). The incidence of SAE leading to death was 4.3% and 3.9% in the gefitinib and docetaxel groups, respectively. The most common SAE leading to death in both treatment arms was pneumonia. The incidence of individual SAEs leading to death were similar across the two treatment groups except for a slightly higher incidence of dyspnoea and haemoptysis in the gefitinib-treatment group (0.4% each), and a slightly higher incidence of febrile neutropenia and septic shock in the docetaxel-treatment group 0.6% and 0.4%, respectively. The treatment-related SAEs that led to death in the gefitinib treated patients were: ILD, pneumonia, hepatitis, dyspnoea and renal failure/diarrhoea.

- Laboratory findings

There was a difference observed between the gefitinib and docetaxel treatment in the INTEREST study in terms of the laboratory findings for white blood cell count and absolute neutrophils. The number of patients worsening from baseline to CTC grade 3/4 leukopenia in the docetaxel arm was more pronounced than in the gefitinib arm (42.3% vs 1.8%, for WBC and 58.2% vs 2.2%, for ANC, respectively). The frequency of clinically relevant deteriorations of haemoglobin and platelet count was low for both docetaxel and gefitinib treatments (8,6% vs 2.1% for haemoglobin and 2.9% vs 1.4% for platelet count, respectively) but more docetaxel-treated patients experienced deterioration of haemoglobin levels. The laboratory results from the IPASS were comparable and are consistent with the expected higher toxicity of carboplatin/paclitaxel chemotherapy therapy.

The deteriorations of two or more CTC grades from baseline in creatinine levels were higher in gefitinib-treated patients (2.2%) and than docetaxel-treated patients (1.2%) in the INTEREST study. Similar results were observed for the IPASS study.

In the INTEREST study, an increased frequency of haematuria and proteinuria was observed among gefitinib-treated patients (7.2% and 9.9%, respectively) as compared to docetaxel treated patients (4.4% and 2.1%, respectively)

- Safety in special populations

The evaluation of safety in special populations is derived predominantly from the INTEREST study. There were no differences in gender, ethnicity, histology, hypertension, renal impaired patients and smoking status on the reporting of SAE. There was an increase in worsening of the SAE, CTC grade 3 and 4 and AE leading to death with worsening of baseline performance status, increased weight of the patient and patients with chronic obstructive pulmonary disease (COPD) for gefitinib and docetaxel.

The review of AEs by age range (i.e., <45 years; 45 to 64 years; 65 to 74 years; ≥75 years) was conducted using data from the INTEREST study. There was a general tendency for increases in reporting of SAEs, grade 3/4 AEs, and AEs leading to discontinuation in the two older age groups on both treatments. In both treatment groups, there were similar incidences with increased age in the reporting of event terms in most system organ classes (SOCs). This may reflect the underlying morbidity with increasing with age where these events are more commonly associated with elderly patients, e.g. asthenia, fatigue, weight decrease, anorexia. In the nervous system SOC, there was a notable increase in CTC grade 3 or 4 events with age, mostly consisting of cerebrovascular accident cases in those over 75 years. Similarly, the respiratory SOC appeared to show an increase in CTC grade 3 or 4 events with age, primarily due to an increase in dyspnoea. For the risk of developing ILD, the Japanese Pharmacoepidemiological Case Control study showed that older age (≥55 years) was identified as a risk factor for developing ILD irrespective of the treatment received. The Japanese pharmacoepidemiological case control study in 3159 patients with NSCLC receiving gefitinib or chemotherapy who were followed up for 12 weeks, the following risk factors for developing ILD (irrespective of whether the patient received gefitinib or chemotherapy) were identified: smoking, poor performance status (PS≥ 2), CT scan evidence of reduced normal lung (≤ 50 %), recent diagnosis of NSCLC (< 6 months), pre-existing ILD, older age (≥ 55 years old) and concurrent cardiac disease. An increased risk of ILD on gefitinib relative to chemotherapy was seen predominantly during the first 4

weeks of treatment (adjusted OR 3.8; 95 % CI 1.9 to 7.7); thereafter the relative risk was lower (adjusted OR 2.5; 95 % CI 1.1 to 5.8). Risk of mortality among patients who developed ILD on gefitinib or chemotherapy was higher in patients with the following risk factors: smoking, CT scan evidence of reduced normal lung (≤ 50 %), pre-existing ILD, older age (≥ 65 years old), and extensive areas adherent to pleura (≥ 50 %). However, in the INTEREST trial, the number of ILD-type events was very small and no apparent trend on either treatment group related to age at study entry was found. ILD, which may be acute in onset, has been observed in 1.3 % of patients receiving gefitinib, and some cases have been fatal (see section 4.8). If patients experience worsening of respiratory symptoms such as dyspnoea, cough and fever, gefitinib should be interrupted and the patient should be promptly investigated. If ILD is confirmed, gefitinib should be discontinued and the patient treated appropriately.

In a phase I/II trial studying the use of gefitinib and radiation in paediatric patients, with newly diagnosed brain stem glioma or incompletely resected supratentorial malignant glioma, 4 cases (1 fatal) of Central Nervous System (CNS) haemorrhages were reported from 45 patients enrolled. A further case of CNS haemorrhage has been reported in a child with an ependymoma from a trial with gefitinib alone. An increased risk of cerebral haemorrhage in adult patients with NSCLC receiving gefitinib has not been established.

In patients that have moderate or severe hepatic impairment as a result of liver metastases, results showed that there was no increase in exposure to gefitinib and frequency and severity of AEs (study D7913C00032). Another study with patients with moderate or severe hepatic impairment due to cirrhosis showed an average of 3.1-fold increased exposure to gefitinib which may be of clinical relevance (study D7913C00718). This is reflected as a warning in the SmPC.

- Safety related to drug-drug interactions and other interactions

CYP3A4 Inhibitors
An interaction between gefitinib and itraconazole was shown in *in vitro* and in clinical drug interaction studies (0027 and 0051). The concomitant use of gefitinib and itraconazole (200mg single daily dose for 12 days) resulted in an increase of gefitinib exposure (60%-80% of AUC). Therefore concurrent use of CYP3A4 inhibitors in patients taking gefitinib may result in increased plasma levels of gefitinib. This is reflected in the SmPC as a potential drug interaction.

CYP3A4 Inducers
An interaction between gefitinib and rifampicin was shown in a clinical interaction study (0030). The concomitant use of gefitinib and rifampicin (300 mg b.i.d.) resulted in decreased gefitinib exposure (83% of AUC). This may in turn decrease gefitinib plasma concentrations and reduce efficacy. CYP3A4 inducers may increase metabolism of gefitinib and decrease gefitinib plasma concentrations. Therefore, concomitant administration of CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, barbiturates or herbal preparations containing St John's wort/*Hypericum perforatum*) may reduce efficacy of the treatment and should be avoided (see SmPC section 4.5).

CYP2D6 inhibitors
There were no studies performed exploring the effect of concomitant use of gefitinib and a CYP2D6 inhibitor. However, in poor metabolisers for CYP2D6, it would be expected that strong CYP2D6 inhibitors (e.g. fluoxetine and paroxetine) will increase exposure to gefitinib by 2-fold. In individual patients with CYP2D6 poor metaboliser genotype, treatment with a potent CYP3A4 inhibitor might lead to increased plasma levels of gefitinib. At initiation of treatment with a CYP3A4 inhibitor, patients should be closely monitored for gefitinib adverse reactions (see SmPC section 4.5).

No clinical studies have been performed exploring the interaction between gefitinib and substrates for CYP2C19, CYP3A4 and UGT1A1.
Gastric pH
The effect of food and the effect of increased gastric pH (≥5) were investigated in a clinical study (0036). The results showed that food had increased bioavailability of gefitinib by 37%. In addition, sustained elevation of gastric pH (using 2x450mg ranitidine) resulted in 47% decreased bioavailability

of gefitinib. Medicinal products that cause significant sustained elevation in gastric pH, such as proton-pump inhibitors and h_2-antagonists may reduce bioavailability and plasma concentrations of gefitinib and, therefore, may reduce efficacy. Antacids if taken regularly close in time to administration of gefitinib may have a similar effect (see SmPC sections 4.5 and 5.2).

Vitamin K antagonists
International normalised ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin together with gefitinib (see SmPC section 4.5). Patients taking warfarin and gefitinib concomitantly should be monitored regularly for changes in prothrombin time (PT) or INR.

P-glycoprotein (Pgp) inhibitors
No Pk studies were performed to study interaction of Pgp inhibitors with gefitinib. *In vitro* studies have shown that gefitinib is a substrate of p-glycoprotein (Pgp). Available data do not suggest any clinical consequences to this *in vitro* finding.

Lactose
Gefitinib contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicinal product.
Other medicinal products
Data from phase II clinical trials, where gefitinib and vinorelbine have been used concomitantly, indicate that gefitinib may exacerbate the neutropenic effect of vinorelbine.

- Discontinuation due to adverse events

In the IPASS study, fewer AEs leading to discontinuation were reported for patients in the gefitinib arm (6.9%) compared with the carboplatin / paclitaxel arm (13.6%). Commonly reported AEs leading to discontinuation of gefitinib included abnormal hepatic function (1.5%), increased AST (1.0%), increased ALT (0.8%) and ILD (0.8%). Commonly reported AEs leading to discontinuation of carboplatin / paclitaxel included neutropenia (3.1%), drug hypersensitivity (1.5%), hypoaesthesia (1.4%), peripheral neuropathy (1.0%) and peripheral sensory neuropathy (0.8%). ILD, which may be acute in onset, has been observed in 1.3 % of patients receiving gefitinib, and some cases have been fatal (see SmPC section 4.8). If patients experience worsening of respiratory symptoms such as dyspnoea, cough and fever, gefitinib should be interrupted and the patient should be promptly investigated. If ILD is confirmed, gefitinib should be discontinued and the patient treated appropriately.

In the INTEREST study, the number of patients and incidence of patients with AEs leading to discontinuation was lower for gefitinib than for docetaxel (8.1%) compared to docetaxel (14.3%). In addition, treatment-related AEs leading to discontinuation were slightly lower in the gefitinib group than for docetaxel (2.3% compared to 3.5%). Commonly reported (>0.5%) AEs leading to discontinuation of gefitinib treatment included skin events (0.8%), ILD (0.5%), and dyspnoea (0.8%). Commonly reported AEs (>0.5%) leading to discontinuation of docetaxel were haematological toxicities (including febrile neutropenia and neutropenia), nervous system disorders (including neuropathies), asthenic conditions, and septic shock.

- Post marketing experience

Gefitinib is currently approved in 36 countries worldwide as a monotherapy for the treatment of patients with locally advanced or metastatic NSCLC at a daily dose of 250 mg. The majority of patient exposure (71%; >195000 patients) is in patients receiving gefitinib during marketed use. The following safety signals have been raised from post-marketing adverse event reports and as a result have been incorporated into the proposed SmPC for gefitinib:

- Interstitial lung disease
- Pancreatitis
- Allergic reactions, including angioedema and urticaria
- Hepatitis
- Pyrexia

- **Discussion on clinical safety**

In the INTEREST study, the most commonly reported AEs for gefitinib were skin reactions, diarrhoea, vomiting, nausea, anorexia, asthenic conditions, cough and dyspnoea while for docetaxel most commonly reported AEs were haematological toxicity, neurotoxicity, myalgia, asthenic conditions, and alopecia. Overall, the AEs reported in the V-15-32 and SIGN studies were the same as for the INTEREST study. In the dose-finding studies, IDEAL I and II and the ISEL study, the most common AEs seen were consistent with INTEREST study. Some AEs, most notably diarrhoea, rash, acne, and dry skin, occurred more frequently in patients receiving gefitinib 500 mg than patients receiving 250 mg. In the pooled dataset from the ISEL, INTEREST and IPASS phase III clinical trials (2462 gefitinib-treated patients), the most frequently reported adverse drug reactions (ADRs), occurring in more than 20 % of the patients, are diarrhoea and skin reactions (including rash, acne, dry skin and pruritus). ADRs usually occur within the first month of therapy and are generally reversible. Approximately 8 % of patients had a severe ADR (common toxicity criteria, (CTC) grade 3 or 4). Approximately 3 % of patients stopped therapy due to an ADR. Interstitial lung disease (ILD) has occurred in 1.3 % of patients, often severe (CTC grade 3-4). Cases with fatal outcomes have been reported.

Generally, most of the reported AEs for gefitinib were CTC grade 1 or 2. The reported rash and diarrhoea as CTC grade 3 or 4 AEs were at a low frequency, 1.6% and 2.5%, and 1.1%, and 2.8%, in the INTEREST and ISEL studies, respectively. The frequency of patients with CTC grade 3 and 4 increased with the gefitinib dose. The incidences of SAEs and treatment related SAEs were higher for docetaxel than for gefitinib. Across the studies, the most commonly reported gefitinib related SAE was diarrhoea, with a frequency of ≤2%. Furthermore, the incidences of gefitinib related SAEs leading to death were ≤ 0.8%. In V-15-32, the most frequently reported SAE in gefitinib treated patients was ILD which is known to be more common in the Japanese population. In the INTEREST trial, the incidence of ILD type events was 1.4 % (10) patients in the gefitinib group *vs.* 1.1 % (8) patients in the docetaxel group. One ILD-type event was fatal, and this occurred in a patient receiving gefitinib.

In the ISEL trial, the incidence of ILD-type events in the overall population was approximately 1 % in both treatment arms. The majority of ILD-type events reported was from patients of Asian ethnicity and the ILD incidence among patients of Asian ethnicity receiving gefitinib therapy and placebo was approximately 3 % and 4 % respectively. One ILD-type event was fatal, and this occurred in a patient receiving placebo.

In a post-marketing surveillance study in Japan (3350 patients) the reported rate of ILD-type events in patients receiving gefitinib was 5.8 %. The proportion of ILD-type events with a fatal outcome was 38.6 %.

In a phase III open-label clinical trial (IPASS) in 1217 patients comparing gefitinib to carboplatin/paclitaxel doublet chemotherapy as first-line treatment in selected patients with advanced NSCLC in Asia, the incidence of ILD-type events was 2.6 % on the gefitinib treatment arm versus 1.4 % on the carboplatin/paclitaxel treatment arm.

Overall, in the INTEREST study discontinuation due to AEs was less frequent in the gefitinib treated patients compared to the docetaxel treated patients. Discontinuation due to AEs was higher for patients receiving gefitinib than for patients receiving placebo (5.4% vs 2.3% in the ISEL study). The most common AE leading to discontinuation included diarrhoea, skin events, gastrointestinal events and ILD. The incidence of ILD-type events with gefitinib in the Japanese studies was higher than that in the Caucasian populations (4-6% vs 1%).

Assessment of the adverse event profile of gefitinib in special populations does not raise safety concerns based on gender, racial origin, age, body mass index, performance status, smoking status, or tumour histology. Gefitinib was generally well tolerated in all patient populations assessed. Toxicity with respect to EGFR M+ and EGFR M- status was not analysed.

There were no clinically relevant ECG abnormalities or any suggestion of arrhythmogenic potential across the gefitinib study programme. Among the ophthalmological AEs observed, conjunctivitis, blepharitis, corneal erosion and dry eyes were the most common. Furthermore, the studies did not reveal any clinically relevant differences between gefitinib treated and either docetaxel or placebo treated patients in terms of renal disorders (e.g., renal failure) or hepatic dysfunction other than mild to moderate elevations in transaminases. For Japanese patients there seemed to be a higher incidence of abnormal hepatic function.

In patients with mild or moderate renal impairment at baseline, AE in gefitinib treated patients was similar to patients with normal renal function at study entry. The number of patients with severe renal impairment was too small to evaluate the safety profile of gefitinib in this population of patients. In patients with hepatic impairment due to cirrhosis, a 3.1-fold increase in exposure to gefitinib was shown. This increase in exposure may be of clinical relevance since adverse experiences are related to dose and exposure to gefitinib. However, patients with hepatic impairment due to liver metastases did not show an apparent increase in exposure to gefitinib and frequency and severity of AEs. In the INTEREST study, no specific safety concerns were identified for patients who received gefitinib and had concurrent diabetes mellitus, COPD or hypertension.

There was no association of gefitinib with haematological toxicity. However, increases in liver transaminases and a slightly greater incidence of increased creatinine were observed for patients treated with gefitinib compared to placebo and docetaxel. Furthermore, there was a slightly increased frequency of haematuria and, to a lesser extent, proteinuria, among gefitinib treated patients compared to patients treated with docetaxel or placebo.

There are no data from the use of gefitinib in pregnant women. Studies in animals have shown reproductive toxicity (see SmPC section 5.3). The potential risk for humans is unknown. Gefitinib should not be used during pregnancy unless clearly necessary, and women of childbearing potential must be advised not to get pregnant during therapy.

It is not known whether gefitinib is secreted in human milk. Gefitinib and metabolites of gefitinib accumulated in milk of lactating rats (see SmPC section 5.3). Gefitinib is contraindicated during breast-feeding and therefore breast-feeding must be discontinued while receiving gefitinib therapy (see SmPC section 4.3).

There were several drug-drug interactions that might affect the safety of gefitinib administration. The metabolism of gefitinib is via the cytochrome P450 isoenzyme CYP3A4 (predominantly) and via CYP2D6. Substances that inhibit CYP3A4 may decrease the clearance of gefitinib. Concomitant administration with potent inhibitors of CYP3A4 activity (e.g. ketoconazole, posaconazole, voriconazole, protease inhibitors, clarithromycin, telithromycin) may increase gefitinib plasma concentrations. The increase may be clinically relevant since adverse reactions are related to dose and exposure. The increase might be higher in individual patients with CYP2D6 poor metaboliser genotype. Pre-treatment with itraconazole (a potent CYP3A4 inhibitor) resulted in an 80 % increase in the mean AUC of gefitinib in healthy volunteers. In situations of concomitant treatment with potent inhibitors of CYP3A4 the patient should be closely monitored for gefitinib adverse reactions. An interaction between gefitinib and rifampicin, a potent inducers of CYP3A4, was shown in a clinical interaction study (0030). The concomitant use of gefitinib and rifampicin resulted in decreased gefitinib exposure and a potential decrease in gefitinib plasma concentrations. Substances that are inducers of CYP3A4 activity may increase metabolism and decrease gefitinib plasma concentrations and thereby reduce the efficacy of gefitinib. Concomitant medicinal products that induce CYP3A4 (e.g. phenytoin, carbamazepine, rifampicin, barbiturates or St John's wort (*Hypericum perforatum*)), should be avoided. Pre-treatment with rifampicin (a potent CYP3A4 inducer) in healthy volunteers reduced mean gefitinib AUC by 83 % (see SmPC section 4.4). In poor metabolisers for CYP2D6, it would be expected that strong CYP2D6 inhibitors (e.g. fluoxetine and paroxetine) will increase exposure to gefitinib by 2-fold. There are no data on concomitant treatment with an inhibitor of CYP2D6 but potent inhibitors of this enzyme might cause increased plasma concentrations of gefitinib in CYP2D6 extensive metabolisers by about 2-fold (see SmPC section 5.2). If concomitant treatment with a potent CYP2D6 inhibitor is initiated, the patient should be closely monitored for adverse

reactions. *In vitro* studies have shown that gefitinib has limited potential to inhibit CYP2D6. In a clinical trial in patients, gefitinib was co-administered with metoprolol (a CYP2D6 substrate). This resulted in a 35 % increase in exposure to metoprolol. Such an increase might potentially be relevant for CYP2D6 substrates with narrow therapeutic index. When the use of CYP2D6 substrates are considered in combination with gefitinib, a dose modification of the CYP2D6 substrate should be considered especially for products with a narrow therapeutic window (see SmPC section 4.5).

The effect of food and the effect of increased gastric pH (≥5) showed that food had increased bioavailability of gefitinib by 37%. And sustained elevation of gastric pH (using 2x450mg ranitidine) resulted in 47% decreased bioavailability of gefitinib. Substances that cause significant sustained elevation in gastric pH may reduce gefitinib plasma concentrations and thereby reduce the efficacy of gefitinib. High doses of short-acting antacids may have a similar effect if taken regularly close in time to administration of gefitinib. Concomitant administration of gefitinib with ranitidine at a dose that caused sustained elevations in gastric pH ≥5, resulted in a reduced mean gefitinib AUC by 47 % in healthy volunteers (see SmPC section 4.4 and 5.2).

Gefitinib inhibits the transporter protein BCRP *in vitro*, but the clinical relevance of this finding is unknown.
INR elevations and/or bleeding events have been reported in some patients concomitantly taking warfarin (see SmPC section 4.4).

Patients should be advised to seek medical advice immediately if they experience:
- any eye symptoms.
- severe or persistent diarrhoea, nausea, vomiting or anorexia as these may indirectly lead to dehydration.

These symptoms should be managed as clinically indicated (see SmPC section 4.8).

Gefitinib has no or negligible influence on the ability to drive and use machines. However, during treatment with gefitinib, asthenia has been reported. Therefore, patients who experience this symptom should be cautious when driving or using machines.

There is no specific treatment in the event of overdose of gefitinib, and possible symptoms of overdose are not established. However, in phase I clinical trials, a limited number of patients were treated with daily doses of up to 1000 mg. An increase of frequency and severity of some adverse reactions was observed, mainly diarrhoea and skin rash. Adverse reactions associated with overdose should be treated symptomatically; in particular severe diarrhoea should be managed appropriately.

Therefore, the overall safety profile for gefitinib in the proposed dose for marketing was considered acceptable and relatively well tolerated.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan

Table 34 Summary of the risk management plan

Safety concern/missing information	Proposed pharmacovigilance activities (routine)	Proposed risk minimisation activities (routine)
General Activities that apply to all safety concerns	**Routine pharmacovigilance**	**Routine Risk Minimising Activities**
Interstitial lung disease	Routine pharmacovigilance. Targeted follow-up questionnaire for reports of ILD and review on a bi-annual basis. Regular updates on ILD reporting and review of reports of ILD in those receiving the drug for indications other than NSCLC. Exploratory Single Nucleotide Polymorphism Analysis of nested case control study in Japan.	Warning in section 4.4 of the SmPC states that ILD may be acute in onset, has been observed in 1.3% of patients receiving IRESSA, and that some cases have been fatal. Advises interrupting IRESSA and initiating prompt investigation if patients experience worsening of respiratory symptoms such as dyspnoea, cough and fever. If ILD is confirmed, IRESSA should be discontinued and the patient treated appropriately. Risk factors for development of ILD (irrespective of treatment) include smoking, poor performance status (PS≥ 2), CT scan evidence of reduced normal lung (≤ 50%), recent diagnosis of NSCLC (< 6 months), pre-existing ILD, older age (≥ 55 years old) and concurrent cardiac disease. An increased risk of ILD on gefitinib relative to chemotherapy was seen predominantly during the first 4 weeks of treatment. Risk of mortality with ILD is higher in patients with the following risk factors: smoking, CT scan evidence of reduced normal lung (≤ 50%), pre-existing ILD, older age (≥ 65 years old), and extensive areas adherent to pleura (≥ 50%). Included in section 4.8 of the SmPC 'Undesirable effects' Frequency for interstitial lung disease is given in this section.
Hepatitis	Routine pharmacovigilance. Possible reports of hepatitis and other serious hepatic dysfunction, to be followed-up using a targeted follow-up questionnaire for liver toxicity, and reviewed on a bi-annual basis.	Section 4.4 'Special warnings and special precautions for use' of the SmPC states Although liver function test abnormalities (including increases in alanine aminotransferase, aspartate aminotransferase, bilirubin) were common, they were rarely observed as hepatitis (see section 4.8). Therefore, periodic liver function testing is recommended. IRESSA should be used cautiously in the presence of mild to moderate changes in liver function. Discontinuation should be considered if changes are severe. Hepatitis and increases in alanine aminotransferase, asparate aminotransferase and bilirubin are included in section 4.8 of the SmPC 'Undesirable effects'
Haemorrhagic events	Routine pharmacovigilance. Reports of haemorrhagic events to be followed-up using a targeted follow-up questionnaire and reviewed on a bi-annual basis.	Section 4.8 of the SmPC 'Undesirable effects' discusses haemorrhage, such as epistaxis and haematuria. Currently available data contains insufficient information to establish a causal relationship with gefitinib and haemorrhagic events other than epistaxis and haematuria. Therefore, no risk minimising activities, other than those above, are proposed.

Safety concern/missing information	Proposed pharmacovigilance activities (routine)	Proposed risk minimisation activities (routine)
Leukaemia-type events	Routine pharmacovigilance.	Currently available data contains insufficient information to establish a causal relationship with gefitinib. Therefore, no risk minimising activities are proposed.
	Reports of leukaemia-type events to be followed-up using a targeted follow-up questionnaire and reviewed on a bi-annual basis.	
Cerebrovascular events	Routine pharmacovigilance	Currently available data contains insufficient information to establish a causal relationship with gefitinib. Therefore, no risk minimising activities are proposed.
	Reports of cerebrovascular events to be followed-up using a targeted follow-up questionnaire and reviewed on a bi-annual basis.	
Tumour haemorrhage	Routine pharmacovigilance	Currently available data contains insufficient information to establish a causal relationship with gefitinib. Therefore, no risk minimising activities are proposed.
	Possible reports of tumour haemorrhage to be followed-up using a targeted follow-up questionnaire, and reviewed on a bi-annual basis.	

Safety concern/missing information	Proposed pharmacovigilance activities (routine)	Proposed risk minimisation activities (routine)
Drug interactions	Routine pharmacovigilance	Section 4.4 'Special warnings and special precautions for use' of the SmPC states: CYP3A4 inducers may increase metabolism of gefitinib and decrease gefitinib plasma concentrations. Therefore, concomitant administration of CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, barbiturates or herbal preparations containing St John's Wort/Hypericum perforatum) may reduce efficacy of the treatment and should be avoided, (see Section 4.5). In individual patients with CYP2D6 poor metaboliser genotype, treatment with a potent CYP3A4 inhibitor might lead to increased plasma levels of gefitinib. At initiation of treatment with a CYP3A4 inhibitor, patients should be closely monitored for gefitinib adverse reactions (see section 4.5). International Normalised Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin together with gefitinib (see Section 4.5). Patients taking warfarin and gefitinib concomitantly should be monitored regularly for changes in Prothrombin Time (PT) or INR. Medicinal products that cause significant sustained elevation in gastric pH, such as proton-pump inhibitors and H2-antagonists may reduce bioavailability and plasma concentrations of gefitinib, and therefore, may reduce efficacy. Antacids if taken regularly close in time to administration of gefitinib may have a similar effect (see sections 4.5 and 5.2). Section 4.5 'Interaction with other medicinal products and other forms of interaction' outlines the metabolism of gefitinib (via the cytochrome P450 isoenzyme CYP3A4 predominantly, and via CYP2D6), and discusses substances that affect the absorption or clearance of gefitinib, the limited potential of gefitinib to inhibit CYP2D6 in vitro, the in vitro inhibition of BCRP by gefitinib, and INR changes in some patients taking warfarin. Advice to monitor for adverse events in patients with known CYP2D6 poor metaboliser genotype included in section 4.2 of the SmPC.

Safety concern/missing information	Proposed pharmacovigilance activities (routine)	Proposed risk minimisation activities (routine)
Pregnant or lactating women	Routine pharmacovigilance	Contraindication in section 4.3 of the SmPC for lactation. Section 4.6 'Pregnancy and lactation' of the SmPC states: There are no data from the use of gefitinib in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3). The potential risk for humans is unknown. Gefitinib should not be used during pregnancy unless clearly necessary, and women of childbearing potential must be advised not to get pregnant during therapy. It is not know whether gefitinib is secreted in human milk. Gefitinib and metabolites of gefitinib accumulated in milk of lactating rats (see section 5.3). Breast-feeding is contraindicated, therefore breast-feeding must be discontinued while receiving gefitinib therapy (see section 4.3).
Severe renal impairment	Routine pharmacovigilance	Advice in section 4.2 'Posology and method of administration' of SmPC to use caution in patients with creatinine clearance ≤ 20 ml/min

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality
The quality of the medicinal product IRESSA is considered to be acceptable when used in accordance with the conditions defined in the SmPC.
Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
At the time of the CHMP opinion there were no unresolved quality issues.

Non-clinical pharmacology and toxicology

Gefitinib was shown in *in vitro* and *in vivo* studies to inhibit EGF-stimulated tumour cell growth and auto-phosphorylation of EGFR in a number of human tumour cell lines. The *in vivo* activity of gefitinib was shown to completely block the growth of tumour xenographs at a daily oral dose of 200 mg/kg of gefitinib. A lack of correlation between anti-tumour activity and EGFR expression was seen both in the animal models and in the clinic.

Safety pharmacology studies addressed the influence of gefitinib on respiratory, CNS and cardiovascular functions. The only safety concern was a potential for QT prolongation. Data from *in vitro* studies indicate that gefitinib has the potential to inhibit cardiac repolarization (e.g. QT interval). The clinical significance of these findings is unknown.

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to the clinical exposure levels and with possible relevance to clinical use were corneal epithelia atrophy and corneal translucencies, renal papillary necrosis, hepatocellular necrosis and eosinophilic sinusoidal macrophage infiltration

A reduction in female fertility was observed in the rat at a dose of 20 mg/kg/day. Published studies have shown that genetically modified mice, lacking expression of EGFR, exhibit developmental defects, related to epithelial immaturity in a variety of organs including the skin, gastrointestinal tract

and lung. When gefitinib was administered to rats during organogenesis, there were no effects on embryofoetal development at the highest dose (30 mg/kg/day). However, in the rabbit, there were reduced foetal weights at 20 mg/kg/day and above. There were no compound-induced malformations in either species. When administered to the rat throughout gestation and parturition, there was a reduction in pup survival at a dose of 20 mg/kg/day.

Following oral administration of C-14 labelled gefitinib to lactating rats 14 days post partum, concentrations of radioactivity in milk were 11-19 fold higher than in blood.

Gefitinib showed no genotoxic potential. A 2-year carcinogenicity study in rats resulted in a small but statistically significant increased incidence of hepatocellular adenomas in both male and female rats and mesenteric lymph node haemangiosarcomas in female rats at the highest dose (10mg/kg/day) only. The hepatocellular adenomas were also seen in a 2-year carcinogenicity study in mice, which demonstrated a small increased incidence of this finding in male mice at the mid dose, and in both male and female mice at the highest dose. The effects reached statistical significance for the female mice, but not for the males. At no-effect levels in both mice and rats there was no margin in clinical exposure. The clinical relevance of these findings is unknown.

The results of an *in vitro* phototoxicity study demonstrated that gefitinib may have phototoxicity potential.

Efficacy

In support of the indication, the applicant submitted three pivotal trials (IPASS, INTEREST and ISEL) and 3 additional supportive studies (v-15-32,SIGN and ISTANA). The INTEREST trial was a randomised, open label, multicentre, Phase III double arm trial, comparing once-daily oral gefitinib 250 mg with 3-weekly intravenous docetaxel 75 mg/m^2 in 1466 patients with locally advanced or metastatic NSCLC who had previously received platinum-based chemotherapy and were eligible for further chemotherapy (second or thirdline therapy). The primary endpoint was OS. The trial was designed to demonstrate non-inferiority in terms OS of gefitinib to docetaxel and superiority of gefitinib in the EGFR FISH+ patients, the co-primary analysis evaluating EGFR gene copy number as measured by fluorescence in situ hybridisation (FISH). The median OS was 7.6 versus 8.0 months (HR 1.020; 96%CI 0.905-1.150) for gefitinib and docetaxel-treated patients, respectively. The primary unadjusted analysis had a confidence interval upper limit of 1.150 which was very close to the pre-specified 1.154 non-inferiority limit. However, the secondary adjusted analysis did not meet the pre-specified limit of 1.154 and the upper limit of 1.178 would correspond to an estimated possible median difference of 1.2 months in favour of docetaxel. In the EGFR FISH+ population, the median overall survival was 8.4 versus 7.5 months for gefitinib and docetaxel treated patients, respectively (HR 1.087; 95%CI 0.782-1.510; p=0.6199) and the PFS and ORR was comparable in both treatment groups. In the EGFR M+ status patients, no differences in OS were observed but, notably, the ORR were 42.1% and 21.1% (OR 25.2; 95%CI 1.23-515.53; p=0.036) for gefitinib and docetaxel, respectively, and PFS had a HR 0.16 in favour of docetaxel. A subgroup analysis for the non-Asian population was performed and demonstrated consistent results with the overall patient population.

There were two placebo controlled, add-on studies to BSC that were submitted as part of the application. The ISEL study, a last-line study in patients not suitable for further chemotherapy and the INSTEP study, a first line study in patients not considered suitable for chemotherapy. In both of these studies, patients with FISH- tumours benefited less from treatment with gefitinib. In the ISEL study, the point estimates for survival and time to treatment failure actually indicated that benefit was confined to patients with FISH+ tumours. Of importance in the interpretation of study data is the overlap between FISH positivity and activating mutations. The IPASS study was the first study to demonstrate that the gefitinib activity in EGFR FISH+ but EGFR M- tumours was low, indicating that EGFR FISH status was not predictive of response of tumours for gefitinib.

The IPASS was a randomised, open label, multicentre, Phase III double arm trial, comparing once-daily oral gefitinib 250 mg with carboplatin / paclitaxel doublet chemotherapy (paclitaxel 200 mg/m^2 iv over 3 hours followed by carboplatin AUC 5.0 or 6.0 iv over 15 minutes to 60 minutes, every 3 weeks, for a total of 6 cycles) in selected Asian patients with advanced NSCLC in first line therapy.

The trial recruited 1217 patients exclusively in Asia with adenocarcinoma histology, which had not smoked or were ex-light smokers. This was an enriched Asian patient population who had biological factors that had been previously identified in the ISEL and IDEAL studies as conferring greater clinical benefit derived from gefitinib treatment. The ISEL study had identified a subgroup of patients who were never smokers and of Asian origin which benefited the most and the two Phase II studies IDEAL I and II had identified patients with adenocarcinoma who had a high rate of response to gefitinib. The trial met its primary endpoint in the overall population where PFS was considered improved in the gefitinib arm compared to the doublet chemotherapy [HR 0.74; 95%CI 0.65-0.85; p<0.0001] where the risk of progression was reduced by 26%. Analysis of PFS by biomarker status showed a strong association between EGFR mutation status and PFS. In patients who were EGFR M+, PFS was significantly longer in the gefitinib arm compared to the doublet chemotherapy (HR 0.48; 95%CI 0.36-0.64; p<0.0001). In patients who were EGFR M-, PFS was significantly shorter than with the doublet chemotherapy (HR 2.85; 95%CI 2.05-3.98, p<0.0001). The ORR was 71.2% and 47.3% in EGFR M+ patients and 1.1% and 23.5% for EGFR M- patients, for gefitinib and doublet chemotherapy, respectively. Post-hoc analyses of OS according to EGFR mutation status was more favourable in patients that are EGFR M+ and treated with gefitinib rather than doublet chemotherapy.

Therefore, these results confirmed the finding that patients that receive greatest benefit from gefitinib treatment are patients with the activating mutation of EGFR.

Safety
There were fewer grades 3 to 5 AE in the gefitinib arm (31.6% compared to 62.5% in the doublet chemotherapy) and fewer AE leading to discontinuation (6.9% compared to 13.6%). Treatment related deaths were similar for both arms (0.7% for gefitinib and 0.5% for doublet chemotherapy). ILD adverse events were reported in both arms with slightly higher frequency in the gefitinib arm (2.6%) than in the doublet chemotherapy (1.4%).

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these concerns

- User consultation

The user testing of the PL was performed and judged as acceptable. No further amendments to the method or result presentation are required.

Risk-benefit assessment
The IPASS study provided the opportunity to evaluate, in a selected Asian patient population, the EGFR status in tumours and test the hypothesis for activity of gefitinib against this pre-defined genetic marker in a first line treatment. In EGFR mutation positive patients, gefitinib was associated with an increase of ORR by 23.9% (95% CI: [12.0 %, 34.9 %]) and a HR for PFS of 0.48 (95% CI: [0.36, 0.64], p<0.0001, median 9.5 months vs 6.3 months for gefitinib vs chemotherapy). The results were consistent across trials for ORR. ORR was influenced to a certain extent by line of therapy and by ethnicity, where response rate in the non-Asian population was lower than Asian population. The CHMP acknowledged that this could be due to the prevalence of the EGFR mutation in the Asian population and/or the test that was used to analyse mutation status. These results were supported by exploratory analyses from the INTEREST trial, where an effect in terms of PFS and ORR was observed in patients with EGFR M+ tumours but not EGFR M- tumours. Comparable results were also observed in never-smoking patients. Therefore, the CHMP noted that the data presented support the therapeutic indication and patients who derive the most benefit from gefitinib are patients that harbour an EGFR activating mutation.

The CHMP expressed some concern over the OS data in the full study population in the INTEREST trial where a difference of up to 1.2 months in favour of docetaxel could not be convincingly ruled out. However, the CHMP considered that any possible differences in efficacy between gefitinib and docetaxel are likely to be marginal in the restricted indication. The estimated treatment effect of

gefitinib compared to docetaxel in the 2nd/3rd line treatment in EGFR+ patients in terms of PFS are: HR 0.16 95%CI [0.05, 0.49], median PFS 7 months vs 4.1 months for gefitinib and docetaxel, respectively. For OS, the treatment effects are: HR 0.83 95%CI [0.41, 1.67], median OS 14.2 months vs 16.6 months for gefitinib and docetaxel, respectively. Thus from the limited data presented, there seems to be minor benefit in terms of OS. The results may have to some extent been confounded by cross-over. The estimated treatment effect of gefitinib in the ISEL study, a last line treatment, compared to placebo in EGFR+ patients in terms of PFS are: HR not calculated, due to insufficient events, median PFS 10.8 months vs 3.8 months for gefitinib and placebo, respectively. These results were supported by ORR data and data in never-smokers.

The applicant, at an oral explanation, presented further data claiming that EGFR M+ was an overall predictive factor for response rate and efficacy in patients treated with gefitinib and never-smoking could be used as a surrogate marker for EGFR M+ status as 40% of never- smokers were found to have EGFR activating mutations. In the INSTEP study, the patient benefit seemed to be related to never-smoking status.

There are no clinical or pharmacodynamic data to compare directly the clinical efficacy and safety of gefitinib versus erlotinib in patients with EGFR M+ tumours. Therefore, whether or not there are any relevant differences between gefitinib and erlotinib in terms of activity in patients with EGFR M+ tumours is unknown. No clinically relevant activity has been shown in patients with known EGFR mutation-negative tumours. Gefitinib should not be used in patients with tumours known to be EGFR M-.

The CHMP also had concerns over the extrapolation of the IPASS data and INTEREST data for a Caucasian population. The conclusion of efficacy of gefitinib in EGFR+ patients is mainly based on the results of the IPASS study as the number of EGFR+ patients in INTEREST and ISEL was rather limited. The CHMP members expressed different positions with regards to the limited data in the INTEREST and ISEL study and extrapolation of the Asian population in the IPASS study to a Caucasian population. The applicant provided subgroup analysis based to patients characteristics and risk factors which showed that the data in the overall population in the INTEREST trial could be extrapolated to the Caucasian population. The applicant described further subgroup analyses across the trials included in the application and literature references to support the indication in the Caucasian population. The CHMP accepted the relevance of EGFR mutations on the efficacy data in gefitinib-treated patients in relation to the indication. The CHMP noted that although the INTEREST trial showed efficacy in the Caucasian population comparable to the overall population studies, there was still a need to confirm the efficacy of gefitinib in the selected population with EGFR M+ tumours conducted in a prospective study in a Caucasian population. The issue over extrapolation of data to the Caucasian population was resolved by the applicant's commitment to submit data from a trial designed to assess tumour response in selected patients for EGFR mutation conducted in a Caucasian population. The applicant has committed to further discuss the appropriate trial design for the Caucasian population.

Tumours with co-mutations (KRAS and EGFR) are uncommon and thus, at this time the CHMP is of the opinion that there are no major concerns regarding the status of KRAS mutation.

The CHMP noted the well characterised safety profile and better tolerability of gefitinib as compared to chemotherapeutic agents (docetaxel, carboplatin/paclitaxel) used for treatment of NSCLC. The main AE for gefitinib were gastrointestinal disorders (diarrhoea) and skin and subcutaneous disorders (rash, dry skin and pruritis). The CHMP noted that there was an increased risk for interstitial lung disorders (ILD), both in Asian and in Caucasian patients treated with gefitinib and that the outcome was fatal in about 1 in every 3 affected. However, the CHMP considered the risk of ILD to be minimal with respect with the overall safety profile of gefitinib. The CHMP noted the improved QoL data in favour of gefitinib as shown in the IPASS (open label).

In light of the overall positive results from the well conducted and appropriately designed pivotal trials and supportive data from other trials and the views of the SAG Oncology, the CHMP supported the

recommendation of the restricted therapeutic indication in patients with tumours harbouring activating EGFR mutations.

Treatment with gefitinib should be initiated and supervised by a physician experienced in the use of anticancer therapies.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of IRESSA in the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK (see SPC section 5.1) was favourable and therefore recommended the granting of the marketing authorisation.