Drug Product	IRESSA 250-mg tablet	**SYNOPSIS**	
Drug Substance	IRESSA (gefitinib, ZD1839)		
Study Code	D791GC00001 (1839IL/0721)		
Edition Number	1		
Date	13 December 2007		

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

Study centre(s)

This study was conducted in 149 centres from 24 countries worldwide: Argentina (12), Belgium (7), Brazil (5), Canada (15), China (5), Croatia (1), Denmark (6), Spain (10), Estonia (2), France (8), Germany (12), Hong Kong (1), Indonesia (2), Italy (14), Latvia (2), Malaysia (2), Mexico (3), Philippines (3), Slovenia (1), Sweden (9), Switzerland (3), Thailand (1), Turkey (3), and United States (22).

Publications

Douillard J-Y, Kim ES, Hirsh V, Mok T, Socinski M, Gervais R, et al. Gefitinib (IRESSA) versus docetaxel in patients with locally advanced or metastatic non-small-cell lung cancer pre-treated with platinum-based chemotherapy: a randomized, open-label Phase III study (INTEREST). J Thorac Oncol 2007; 2(8) Suppl 4: S305-S306.

Douillard J-Y, Kim ES, Hirsh V, Mok T, Socinski M, Gervais R, et al. Phase III, randomized, open-label, parallel-group study of oral gefitinib (IRESSA) versus intravenous docetaxel in patients with locally advanced or metastatic non-small-cell lung cancer who have previously received platinum-based chemotherapy (INTEREST). Eur J Cancer Suppl 2007; 5(6): 2, abs 2LB.

Study dates		**Phase of development**
First patient enrolled	01 March 2004	Therapeutic confirmatory (III)
Last patient enrolled	17 February 2006	
Data cut-off date	06 March 2007	

Objectives

The primary objective of this study was to compare overall survival between 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 population of patients with high epidermal growth factor receptor (EGFR) gene copy number (hereafter referred to as EGFR FISH+)

The secondary objectives of the study were to compare:

- time to progression (TTP) between gefitinib and docetaxel [Hereafter this will be described as progression-free survival (PFS)]
- progression-free rates at 4 months and 6 months between gefitinib and docetaxel
- the overall objective tumour response rate (ORR) between gefitinib and docetaxel
- patient-reported functionality (PRF) and quality of life (QOL) between gefitinib and docetaxel
- safety and tolerability of gefitinib and docetaxel

The exploratory objectives of the study were:

- to investigate the correlation of EGFR and other related biomarker status with efficacy of gefitinib in those patients where such tumour material is available
- to correlate baseline profiles and modulation of biomarkers in serum, plasma and urine (including plasma and urine proteomics, serum cytokines [US sites only] and metabonomics) evaluated at baseline and during therapy with measures of patient outcome (such as response rate or QOL measures)[a]
- to evaluate pulmonary symptom changes (in symptomatic US and Latin American patient population only) between gefitinib and docetaxel

- to investigate the potential correlation between spirometry and pulmonary symptoms[b]
- to evaluate patient-reported perceptions of treatment side effects between gefitinib and docetaxel
- to evaluate changes in pain and fatigue (in symptomatic US and Latin American patient population only) between gefitinib and docetaxel
- to evaluate a patient-reported global assessment of change in pulmonary symptoms between gefitinib and docetaxel, which will potentially provide an anchoring of the pulmonary symptoms endpoint to patient-perceived clinical benefit (in symptomatic US and Latin American patient population only)[b]
- to evaluate the health care resource use by patients between gefitinib and docetaxel.[a]

[a] These exploratory objectives are not addressed within this report.
[b] There were insufficient data available to evaluate these endpoints.

Study design

This was a randomised, open-label, parallel-group, international, multicentre, phase III study, designed to compare gefitinib (250 mg daily) with intravenous docetaxel (75 mg/m^2 3-weekly) in terms of overall survival outcome for patients with locally advanced or metastatic recurrent non-small cell lung cancer who have previously received platinum-based chemotherapy, with co-primary analyses of (1) the overall study population and (2) EGFR FISH+ patients.

Target patient population and sample size

The target population was patients with locally advanced or metastatic NSCLC who had received prior platinum-based chemotherapy, had progressive or recurrent disease, and were now considered candidates for further chemotherapy with docetaxel.

The total number of patients expected to be exposed to study procedures was approximately 1440 in order 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 hazard ratio for the relative treatment difference (gefitinib to docetaxel) estimated from the overall per protocol (PP) population is 0.975. Approximately 1150 death events were required for analysis.

Patients were recruited by investigational sites throughout the world with expertise in treating patients with NSCLC.

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

Gefitinib 250 mg, once daily in oral tablet form (one 250-mg tablet per dose), or docetaxel at 75 mg/m^2 every 3 weeks, intravenously over 1 hour. The gefitinib formulation, (batch) numbers were [redacted] Commercially-available docetaxel (manufactured by Sanofi-Aventis) was supplied by either AstraZeneca or the investigators' pharmacies. The batch numbers are listed in Appendix 12.1.6.

Duration of treatment

Patients continued to receive treatment with either gefitinib or docetaxel until disease progression, unacceptable toxicity, or other specific criteria were reached. Patients were able to continue their assigned study treatment following disease progression if deemed to be deriving clinical benefit.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: overall survival
- Secondary variables: PFS, ORR

Patient-reported outcomes (PROs)

- Secondary variables: improvement in PRF as measured by Trial Outcome Index (TOI), and Quality of Life (QOL) as measured by FACT-L total score. Disease-related symptoms were also to be evaluated by the Lung Cancer Subscale (LCS).

Safety

- Secondary variables: frequency and severity of adverse events (AEs) and laboratory parameters

Statistical methods

The primary aim of this study was to compare overall survival between gefitinib and docetaxel.

The 2 analyses of overall survival (non-inferiority in the overall population and superiority in the EGFR FISH+ population) were considered co-primary. To ensure that the overall type-I error rate was not inflated by having these 2 co-primary analyses, a modified Hochberg procedure was employed (Hochberg 1998). In applying this methodology to the co-primary analyses of overall survival:

- Overall non-inferiority was to be assessed at the 4% level if superiority was not demonstrated in EGFR FISH+ patients at the 5% level

- Superiority in EGFR FISH+ patients was to be assessed at the 1% level if non-inferiority was not demonstrated in the overall population at the 5% level

- Otherwise both overall non-inferiority and superiority in EGFR FISH+ patients were to be assessed at the 5% level

The null hypothesis to be tested in the overall population was that gefitinib retains less than 50% of the active control effect (docetaxel versus best supportive care [BSC]) on survival. The relative difference between the treatment arms was analysed by estimating a hazard ratio (gefitinib to docetaxel) and its 95% (or 96% dependent on EGFR FISH+ result) confidence interval (CI) from an unadjusted proportional hazards model in the PP population. The null hypothesis was to be rejected if the upper 2-sided confidence limit (CL) for the hazard ratio (HR) was less than k, where k was a constant (dependent on the number of observed events and alpha used, the active control effect size and its standard error) given by equation (10) in Rothmann et al 2003. For 1169 death events in the primary Per-Protocol (PP) population observed at the data cut-off (DCO) of 06 March 2007, and using a 4% significance level, k=1.1539. The historical docetaxel survival effect and its standard error used in the calculation of k were estimated from the TAX-317 study of docetaxel versus BSC (HR 0.61, standard error $\sqrt{(4/122)}$=0.181, based on the ratio of medians for overall survival and 122 deaths in the 75mg/m^2 and BSC groups, Shepherd et al 2000).

The test of superiority in EGFR FISH+ patients was also conducted using an unadjusted proportional hazards model.

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. Therefore, no alpha-adjustment for the type I (false positive) error rate was applied to the planned final analysis since there was no opportunity to stop the study at the interim analysis due to early achievement of non-inferiority for overall survival. The interim analysis was conducted independently and AstraZeneca remained blind to the results. The Independent Data Monitoring Committee (IDMC) recommended the study should continue as planned to completion.

Patient population

Consistent with the population intended by the protocol, patients who participated in this study were representative of an advanced pre-treated NSCLC population. A total of 1466 patients were randomised to treatment (733 patients to receive gefitinib 250 mg and 733 patients to receive docetaxel); these patients were recruited from 149 centres in 24 countries and all had received at least one prior platinum-based chemotherapy. Overall, 1229 patients (83.8%) were second-line, ie, had received one previous chemotherapy regimen and 31.0% of patients had experienced a best response to their last chemotherapy of disease progression [PD]/unknown; 1290 patients (88.0%) had WHO performance status 0, 1 and 830 patients (56.6%) had adenocarcinoma histology. In addition, 34.9% of patients were female, 20.3%

were never smokers, and 22.0% were of Asian racial origin. The median age of the patients was 61 years (ranging from 20 to 84 years).

The co-primary EGFR FISH+ population consisted of 174 EGFR FISH+ patients (85 gefitinib-treated patients and 89 docetaxel-treated patients), which was 12% of the overall study population, and 47% of patients with an evaluable FISH sample.

As would be expected in a large study with stratified randomisation, the two treatment groups were well balanced at baseline with respect to all important prognostic factors, thus enabling valid conclusions to be drawn from the efficacy, QOL, and safety analyses.

The study was conducted to high quality and in accordance with GCP. The number of major protocol deviations was low in both treatment groups (gefitinib 10 patients [1.4%] versus docetaxel 23 patients [3.1%]), with the main reason for major deviation being failure to start docetaxel treatment.

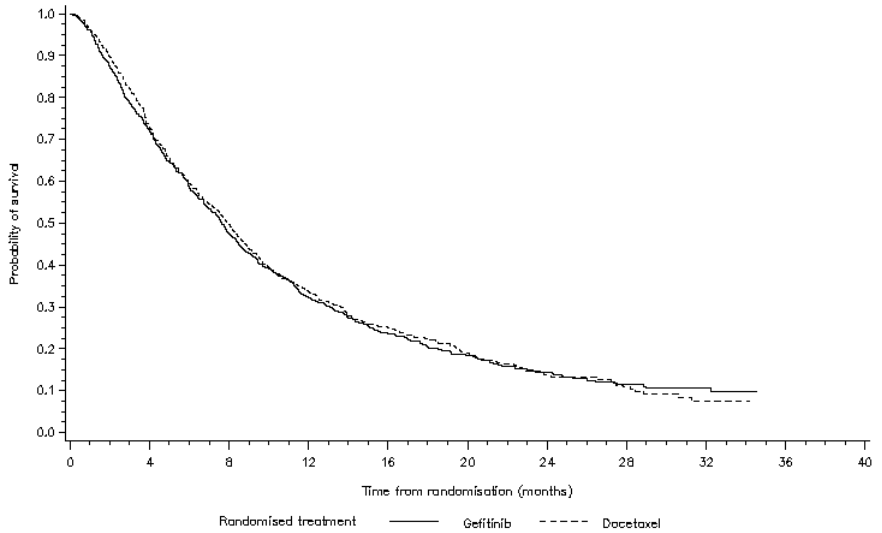
Efficacy results

Primary variable: overall survival

The analyses of overall survival based on a data cut-off of 06 March 2007, by which time 1169 deaths had accrued (total mortality 81.6%) in the primary PP population indicate:

- The study met the primary objective of demonstrating non-inferiority of gefitinib relative to docetaxel in terms of overall survival in the overall study population according to the protocol-specified criterion:
  - Hazard ratio [HR] 1.020, 96% confidence interval [CI] 0.905 to 1.150 in the per-protocol (PP) population. This CI for the HR fell entirely below the non-inferiority limit in HR terms of 1.154 (Median survival 7.6 months with gefitinib versus 8.0 months with docetaxel), with the Kaplan-Meier curves overlapping (Figure S1).
  - This equates to 96% of the historical docetaxel advantage over best supportive care being retained by gefitinib (96% CI 52% to 129%, which lies entirely above the pre-defined non-inferiority limit in effect retention terms of 50%).

Figure S1 Overall survival probability for the PP population



Number of patients at risk:

Months	0	4	8	12	16	20	24	28	32	36	40
Gefitinib	723	518	336	225	131	83	50	31	14	0	0
Docetaxel	710	503	339	228	139	89	46	24	7	0	0

- The co-primary analysis evaluating overall survival for EGFR FISH+ patients did not demonstrate superiority of gefitinib over docetaxel. Survival outcomes in EGFR FISH+ patients were similar for both treatments and similar to the overall population (HR 1.087, 95% CI 0.782 to 1.510, p=0.6199, median 8.4 versus 7.5 months).

Secondary efficacy variables: Progression-free survival, objective response rate , and patient-reported outcomes:

- PFS and ORR were similar for gefitinib and docetaxel (PFS HR 1.04, 95% CI 0.93 to 1.18, p=0.4658; ORR 9.1% vs 7.6%, odds ratio [OR] 1.22, 95% CI 0.82 to 1.84, p=0.3257).

- Significantly more gefitinib-treated patients experienced clinically important improvements in quality of life compared with docetaxel (TOI: 17% vs 10%, p=0.0026; FACT-L total score: 25% vs 15%, p<0.0001).

- Similar proportions of patients on both treatments experienced an improvement in lung cancer symptoms as measured by LCS (20% vs 17%, p=0.1329).

Subgroup findings

- Survival outcomes were generally consistent across subgroups. The subgroups commonly associated with a clinical benefit of gefitinib 250 mg relative to placebo (observed during the gefitinib development programme to date, including the Phase III ISEL study of gefitinib 250 mg versus placebo, and the extensive published data for gefitinib) also appeared to benefit from docetaxel. In the overall study population never smokers lived longer than ever smokers, females lived longer than males, Asians lived longer than non-Asians, patients with adenocarcinoma histology lived longer than other histologies, and PS 0,1 lived longer than PS 2. This was the case for both treatments.

  - No strong differentiation in overall survival outcomes between the two treatments was observed for any sub-group (including biomarkers) apart from the number of prior chemotherapy regimens

  - Subgroups defined by the number of prior chemotherapy regimens appear to be behaving differently to one another (treatment-by-covariate interaction p=0.0311). In second-line patients (N=1229) survival was similar for both groups (HR 0.96, 95% CI 0.85 to 1.08, p=0.4973; median 7.8 months [gefitinib] and 7.6 months [docetaxel]), whereas third-line patients (N=237) achieved better survival outcomes with docetaxel (HR 1.39, 95% CI 1.03 to 1.87, p=0.0326; median 6.9 months [gefitinib] and 11.9 months [docetaxel]).

Exploratory efficacy variables: Additional biomarker results

- For overall survival, no strong differentiation between the two treatments was observed for any biomarker subgroup (including EGFR FISH+), ie, no biomarker subgroup had better overall survival with one treatment compared with the other:

  - Survival outcomes for 44 EGFR mutation positive (M+) patients (32 deaths) were improved compared with the overall study population for both treatments (Median 14.2 months [gefitinib] and 16.6 months [docetaxel]).

  - Compared to the overall study population, survival outcomes were similar for gefitinib and docetaxel irrespective of FISH, EGFR protein expression or K-Ras mutation status.

Biomarker results for secondary efficacy endpoints indicated:

- Compared with the overall study population, PFS was similar for gefitinib and docetaxel irrespective of FISH, EGFR protein expression, or K-Ras mutation status.

- Among 38 M+ patients in the evaluable-for-response (EFR) population, gefitinib was superior to docetaxel in terms of PFS (35 events, HR 0.16, 95% CI 0.05 to 0.49, p=0.0012)

- Objective response rate was significantly higher for gefitinib-treated EGFR FISH+ patients (13.0% vs 7.4%, p=0.0387) and gefitinib-treated M+ patients (42.1% vs 21.1%, p=0.0361) compared with docetaxel.

Safety

The safety data indicate that gefitinib 250 mg in advanced NSCLC has a favourable tolerability profile compared to docetaxel 75 mg/m^2 in terms of the type, frequency and severity of events.

Median time on treatment was 2.4 months (mean 4.4 months, range 0 to 33.3 months) for gefitinib 250 mg and 2.8 months (mean 3.0 months, range 1 to 18.1 months) for docetaxel 75 mg/m^2. The median number of docetaxel cycles was 4 (range 1 to 24), with 82.2% of all cycles given at the full dose.

Fewer dose modifications due to toxicity occurred with gefitinib (7.5% interruption) than with docetaxel (24.2% reduction/delay).

The key safety findings were:

- Gefitinib had a more favourable tolerability profile than docetaxel:
  - Fewer SAEs, CTC grade 3 or 4 AEs, and AEs leading to discontinuation were reported with gefitinib compared with docetaxel (Table S1).
- Numbers of SAEs leading to death were similar for both treatments (Table S1). Six SAEs leading to death with gefitinib (0.8%)and 15 SAEs leading to death with docetaxel (2.1%) were considered by the investigator to be treatment-related.

Table S1 Categories of adverse events: Number (%) of patients who had at least 1 adverse event in any category (Evaluable for safety population)

Category[a]	Percentage of patients			
	Gefitinib 250 mg (N=729)		Docetaxel 75 mg/m^2 (N=715)	
Patients with an adverse event (AE)	687	(94.2)	668	(93.4)
CTC grade 3 or 4 AEs	272	(37.3)	400	(55.9)
Serious AEs	161	(22.1)	210	(29.4)
AE leading to discontinuation	59	(8.1)	102	(14.3)
SAE leading to death	31	(4.3)	28	(3.9)
Treatment-related[b] SAE leading to death	6	(0.8)	15	(2.1)

[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.

- AEs reported with gefitinib were generally consistent with the known safety profile and previous gefitinib monotherapy studies (Table S2):

  – Gefitinib was most commonly associated with diarrhoea (gefitinib 35.0% vs docetaxel 24.8%), rashes/acnes (gefitinib 49.4% vs docetaxel 10.2%), and other skin events (Table S2); the majority of these events were CTC grade 1 (mild) or 2 (moderate).

- AEs reported with docetaxel were generally consistent with the known safety profile of docetaxel (Table S2):

  – Docetaxel was most commonly associated with haematological toxicity, alopecia, and asthenic conditions (including fatigue); the majority of these events were CTC grade 1 (mild) or 2 (moderate), but haematological toxicities of neutropenia, leukopenia, febrile neutropenia were mainly CTC grade 3 (severe) or 4 (life threatening):

  – Docetaxel patients experienced more CTC grade 3 or 4 neutropenia and leukopenia (absolute neutrophil count worsening from baseline to CTC grade 3 or 4 [gefitinib 2.2% vs docetaxel 58.2%], and white blood cell count worsening from baseline to CTC grade 3 or 4 [gefitinib 1.8% vs docetaxel 42.3%]

  – AE reports of febrile neutropenia were more common with docetaxel (gefitinib 1.2% vs docetaxel 10.1%)

  – Asthenic conditions were more common with docetaxel (including fatigue, gefitinib 25.0% vs docetaxel 46.7%)

  – Alopecia was more frequently reported with docetaxel (gefitinib 3.2% vs docetaxel 35.5%)

  – Docetaxel was also associated with neurotoxicity (gefitinib 6.7% vs docetaxel 23.9%) and fluid retention (gefitinib 6.6% vs docetaxel 15.7%).

- ILD-type AEs were reported for both treatments (gefitinib 10 patients [1.4%] vs docetaxel 8 patients [1.1%]); 1 SAE leading to death in a gefitinib-treated patient was reported due to ILD (considered by the investigator to be treatment-related).

Table S2 Most common adverse events (those occurring in at least 5% of patients in either treatment group): Evaluable for safety population

System organ class and preferred term	Number (%) of patients[a]			
	Gefitinib 250 mg (N=729)		Docetaxel 75 mg/m^2 (N=715)	
	All CTC grades	CTC grade 3/4	All CTC grades	CTC grade 3/4
Blood and lymphatic system disorders				
Neutropenia[b]	8 (1.1)	6 (0.8)	126 (17.6)	112 (15.7)
Leukopenia[b]	1 (0.1)	1 (0.1)	51 (7.1)	36 (5.0)
Anaemia	34 (4.7)	11 (1.5)	84 (11.7)	15 (2.1)
Febrile neutropenia[c]	9 (1.2)	7 (1.0)	72 (10.1)	70 (9.8)
Gastrointestinal disorders				
Diarrhoea	255 (35.0)	18 (2.5)	177 (24.8)	22 (3.1)
Nausea	148 (20.3)	3 (0.4)	187 (26.2)	9 (1.3)
Vomiting	109 (15.0)	4 (0.5)	123 (17.2)	8 (1.1)
Constipation	79 (10.8)	6 (0.8)	121 (16.9)	13 (1.8)
Stomatitis[d]	67 (9.2)	0	93 (13.0)	3 (0.4)
Abdominal pain	38 (5.2)	3 (0.4)	37 (5.2)	4 (0.6)
General disorders				
Asthenic conditions[e]	182 (25.0)	32 (4.4)	334 (46.7)	64 (9.0)
Fluid retention[f]	48 (6.6)	0	112 (15.7)	5 (0.7)
Pyrexia	69 (9.5)	2 (0.3)	118 (16.5)	4 (0.6)
Infections and infestations				
Nasopharyngitis	48 (6.6)	0	37 (5.2)	0
Lower respiratory tract and lung infections[g]	71 (9.7)	23 (3.2)	74 (10.3)	25 (3.5)
Metabolism and nutrition disorders				
Anorexia[h]	159 (21.8)	11 (1.5)	151 (21.1)	7 (1.0)
Musculoskeletal and connective tissue disorders				
Myalgia	24 (3.3)	1 (0.1)	113 (15.8)	4 (0.6)
Arthralgia	23 (3.2)	3 (0.4)	68 (9.5)	3 (0.4)
Nervous system disorders				
Neurotoxicity[i]	49 (6.7)	1 (0.1)	171 (23.9)	17 (2.4)
Headache	46 (6.3)	7 (1.0)	52 (7.3)	3 (0.4)
Dizziness	31 (4.3)	0	45 (6.3)	5 (0.7)
Dysgeusia	17 (2.3)	0	37 (5.2)	0
Psychiatric disorders				
Insomnia	30 (4.1)	0	56 (7.8)	1 (0.1)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	120 (16.5)	45 (6.2)	117 (16.4)	55 (7.7)
Cough	108 (14.8)	6 (0.8)	102 (14.3)	5 (0.7)
Epistaxis	39 (5.3)	0	25 (3.5)	0
Haemoptysis	37 (5.1)	7 (1.0)	26 (3.6)	1 (0.1)

Table S2 Most common adverse events (those occurring in at least 5% of patients in either treatment group): Evaluable for safety population

System organ class and preferred term	Number (%) of patients[a]			
	Gefitinib 250 mg (N=729)		Docetaxel 75 mg/m^2 (N=715)	
	All CTC grades	CTC grade 3/4	All CTC grades	CTC grade 3/4
Skin and subcutaneous disorders				
Rashes/Acnes[j]	360 (49.4)	15 (2.1)	73 (10.2)	4 (0.6)
Alopecia	23 (3.2)	0	254 (35.5)	3[k] (0.4)
Dry skin	111 (15.2)	0	10 (1.4)	0
Pruritus[l]	68 (9.3)	2 (0.3)	28 (3.9)	0
Nail and nail bed conditions[m]	24 (3.3)	0	64 (9.0)	1[k] (0.1)

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

[b] As defined in the protocol, clinically significant laboratory findings were only reported as AEs if a criterion for a SAE was fulfilled, the abnormality caused study treatment to be discontinued, or the investigator insisted the abnormality was to be reported as an AE. Therefore, laboratory findings worsening from baseline to CTC grade 3 or 4 have been used for the primary assessment of haematological toxicity: CTC grade 3/4 neutropenia [gefitinib 2.2% vs docetaxel 58.2%], and leukopenia [gefitinib 1.8% vs docetaxel 42.3%].

[c] CTC grade 3 or 4 frequencies for febrile neutropenia should be gefitinib 9 (1.2%) and docetaxel 72 (10.1%). A total of 4 AEs of febrile neutropenia were not correctly recorded as CTC grade 3 or 4 (2 gefitinib AEs of febrile neutropenia were recorded as CTC grade 2; 1 docetaxel AE of febrile neutropenia was recorded as CTC grade 1, the CTC grade for the other docetaxel febrile neutropenia AE was not recorded).

[d] Includes MedDRA preferred terms of aphthous stomatitis, mouth ulceration, oral mucosal eruption, and stomatitis.

[e] Includes MedDRA preferred terms of asthenia, fatigue, malaise, and prostration.

[f] Includes MedDRA preferred terms of fluid retention, oedema, oedema peripheral, generalised oedema, localised oedema, and pitting oedema.

[g] Includes MedDRA preferred terms of bronchitis, bronchopneumonia, lobar pneumonia, lower respiratory tract infection, lung infection, pneumonia, and post procedural pneumonia.

[h] Includes MedDRA preferred terms of anorexia and decreased appetite.

[i] Includes MedDRA preferred terms of dysaesthesia, hypoaesthesia, hypoaesthesia oral, neuropathy, neuropathy peripheral, neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy.

[j] Includes MedDRA high level term (HLT) 'rashes, eruptions and exanthems', HLT 'acnes' and preferred terms rash pustular, dermatitis, dermatitis exfoliative, exfoliative rash, rash erythematous, and rash papular.

[k] These events have been recorded in error with an unacceptable CTC grade – they should not have been recorded with a CTC grade greater than 2.

[l] Includes MedDRA preferred terms of pruritus, pruritus generalised, and rash pruritic.

[m] Includes MedDRA preferred terms of hangnail, ingrowing nail, nail bed inflammation, nail bed tenderness, nail discolouration, nail disorder, nail dystrophy, nail growth abnormal, nail hypertrophy, nail pigmentation, nail toxicity, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia.