Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial

Edward S Kim, Vera Hirsh, Tony Mok, Mark A Socinski, Radj Gervais, Yi-Long Wu, Long-Yun Li, Claire L Watkins, Mark V Sellers, Elizabeth S Lowe, Yan Sun, Mei-Lin Liao, Kell Østerlind, Martin Reck, Alison A Armour, Frances A Shepherd, Scott M Lippman, Jean-Yves Douillard

Summary

Background **Two phase II trials in patients with previously-treated advanced non-small-cell lung cancer suggested that gefitinib was efficacious and less toxic than was chemotherapy. We compared gefitinib with docetaxel in patients with locally advanced or metastatic non-small-cell lung cancer who had been pretreated with platinum-based chemotherapy.**

Methods **We undertook an open-label phase III study with recruitment between March 1, 2004, and Feb 17, 2006, at 149 centres in 24 countries. 1466 patients with pretreated (≥one platinum-based regimen) advanced non-small-cell lung cancer were randomly assigned with dynamic balancing to receive gefitinib (250 mg per day orally; n=733) or docetaxel (75 mg/m² intravenously in 1-h infusion every 3 weeks; n=733). The primary objective was to compare overall survival between the groups with co-primary analyses to assess non-inferiority in the overall per-protocol population and superiority in patients with high epidermal growth factor receptor (EGFR)-gene-copy number in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT00076388.**

Findings **1433 patients were analysed per protocol (723 in gefitinib group and 710 in docetaxel group). Non-inferiority of gefitinib compared with docetaxel was confirmed for overall survival (593 *vs* 576 events; hazard ratio [HR] 1·020, 96% CI 0·905–1·150, meeting the predefined non-inferiority criterion; median survival 7·6 *vs* 8·0 months). Superiority of gefitinib in patients with high EGFR-gene-copy number (85 *vs* 89 patients) was not proven (72 *vs* 71 events; HR 1·09, 95% CI 0·78–1·51; p=0·62; median survival 8·4 *vs* 7·5 months). In the gefitinib group, the most common adverse events were rash or acne (360 [49%] *vs* 73 [10%]) and diarrhoea (255 [35%] *vs* 177 [25%]); whereas in the docetaxel group, neutropenia (35 [5%] *vs* 514 [74%]), asthenic disorders (182 [25%] *vs* 334 [47%]), and alopecia (23 [3%] *vs* 254 [36%]) were most common.**

Interpretation **INTEREST established non-inferior survival of gefitinib compared with docetaxel, suggesting that gefitinib is a valid treatment for pretreated patients with advanced non-small-cell lung cancer.**

Funding **AstraZeneca.**

Introduction

Lung cancer, including non-small-cell lung cancer, is a major cause of death due to cancer worldwide,[1,2] largely because most patients are diagnosed with advanced-stage disease. Treatment for these patients consists of chemotherapy and supportive care, but response rates are modest and recurrence eventually occurs for most patients after standard first-line platinum-based doublet therapy. Docetaxel (75 mg/m²) was approved for second-line treatment of advanced non-small-cell lung cancer after findings from two phase III trials TAX 317 and TAX 320 showed improved outcomes.[3,4] Docetaxel improved survival and quality of life compared with best supportive care (median survival 7·5 *vs* 4·6 months)[3] and compared with vinorelbine or ifosfamide chemotherapy (median survival 5·7 *vs* 5·6 months; 1-year survival 32% *vs* 19%).[4] The side-effects with docetaxel include diarrhoea, neuropathy, and frequent grade 3 and 4 neutropenia.[3–6]

Other cytotoxic agents[5] and molecular-targeted agents such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors[7] have been investigated as potential alternatives to increase efficacy or reduce toxic effects in this disease setting. In the JMEI trial, pemetrexed has shown similar efficacy to docetaxel and lower overall toxic effects,[5] whereas the BR.21 trial reported a significant survival advantage for erlotinib compared with placebo in patients who were not required to be refractory to their previous treatment.[8]

Furthermore, results from two randomised phase II trials (IDEAL 1 and 2)[9,10] suggested that gefitinib—an EGFR tyrosine kinase inhibitor given orally—was efficacious and less toxic, compared with previous results, than was chemotherapy in patients with previously-treated non-small-cell lung cancer. Two studies have compared gefitinib with docetaxel in pretreated non-small-cell lung cancer: the SIGN trial[6] and the Japanese phase III V-15-32 trial.[11] Both studies showed no significant difference between gefitinib and docetaxel in terms of overall survival or progression-free survival. These studies also noted similar or improved response rates, improved quality of life, and a more favourable toxicity profile for gefitinib.

Two phase III trials of gefitinib in advanced non-small-cell lung cancer followed on from the IDEAL phase II

Lancet 2008; 372: 1809–18

See **Comment** page 1785

The University of Texas MD Anderson Cancer Center, Houston, TX, USA (E S Kim MD, Prof S M Lippman MD); **McGill University Health Centre, Montreal, Canada** (V Hirsh MD); **State Key Laboratory in Oncology in South China, Sir YK Pao Centre for Cancer, Department of Clinical Oncology, Hong Kong Cancer Institute, The Chinese University of Hong Kong, Hong Kong, China** (Prof T Mok MD); **Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, NC, USA** (Prof M A Socinski MD); **Centre Regional de Lutte Contre le Cancer Baclesse, Caen, France** (R Gervais MD); **Lung Cancer Research Institute and Cancer Center, Guangdong Provincial People's Hospital, Guangzhou, China** (Prof Y-L Wu MD); **Peking Union Medical College Hospital, Beijing, China** (Prof L-Y Li MD); **AstraZeneca, Macclesfield, UK** (C L Watkins MSc, M V Sellers MSc, A A Armour FRCR); **AstraZeneca, Wilmington, Delaware, USA** (E S Lowe MD); **Cancer Hospital, Beijing, China** (Y Sun MD); **Shanghai Chest Hospital, Shanghai, China** (Prof M-L Liao MD); **Herlev Hospital, Herlev, Denmark** (K Østerlind MD); **Hospital Grosshansdorf, Grosshansdorf, Germany** (M Reck MD); **Princess Margaret Hospital, University of Toronto, Toronto, Canada** (Prof F A Shepherd MD); **and Centre René Gauducheau, Nantes, France** (Prof J-Y Douillard MD)

Correspondence to:
Edward Kim, MD Anderson Cancer Center, Thoracic/Head and Neck Medical Oncology-Box 432, 1515 Holcombe Blvd, Houston, TX 77401, USA
edkim@mdanderson.org

studies: Iressa Survival Evaluation in Lung Cancer (ISEL)[12] and Iressa NSCLC Trial Evaluating REsponse and Survival versus Taxotere (INTEREST), which we report here. The INTEREST study compared an EGFR tyrosine kinase inhibitor with chemotherapy in pretreated advanced non-small-cell lung cancer. Additionally, INTEREST aimed to investigate the relations between widely studied clinical patient characteristics and EGFR-related biomarkers and clinical outcome.

Methods

Study design and patients

INTEREST was a multicentre, randomised, open-label, phase III trial of gefitinib (Iressa, AstraZeneca, Macclesfield, UK) versus docetaxel (Taxotere, Sanofi-Aventis, Paris, France) in patients who were pretreated with platinum with locally advanced or metastatic non-small-cell lung cancer. We recruited patients from 149 centres in 24 countries from Europe; Asia; and North, Central, and South America between March 1, 2004, and Feb 17, 2006. The primary objective was to compare overall survival for gefitinib and docetaxel with co-primary analyses of (1) non-inferiority in the overall population, and (2) superiority in patients with high EGFR-gene-copy number (measured by fluorescence in-situ hybridisation [FISH]). Secondary endpoints included progression-free survival, objective response rate, quality of life, safety, and tolerability. Exploratory analyses included efficacy outcomes in patient subgroups by EGFR protein expression, EGFR, and K-Ras gene mutation status.

Eligible patients were aged 18 years or older, had histologically or cytologically confirmed locally advanced or metastatic non-small-cell lung cancer that progressed or recurred after at least one previous platinum-based chemotherapy regimen (up to two regimens allowed), had WHO performance status 0–2, had measurable or non-measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST),[13] had no previous therapy with an EGFR tyrosine kinase inhibitor, had absolute neutrophil count more than $1 \cdot 5 \times 10^9$/L, and had adequate hepatic function.

All patients provided written informed consent; we obtained separate consent for assessments of EGFR and K-Ras gene mutation. Study approval was obtained from independent ethics committees at every institution. The study was undertaken in accordance with the Declaration of Helsinki, the International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements, and AstraZeneca's policy on bioethics.

Procedures

We randomly assigned patients on a 1:1 basis to receive either gefitinib (250 mg per day orally) or docetaxel (75 mg/m² in a 1-h infusion every 3 weeks) with standard premedication (corticosteroids, antiemetics, and antihistamines) until disease progression, unacceptable toxic effects, or patient or physician request to discontinue treatment. The docetaxel dose could be reduced to 60 mg/m² to reduce toxic effects. We used a centralised registration and randomisation centre, contacted by telephone, to assign patients to a specific treatment group. Patients were randomly assigned with dynamic balancing[14] with respect to histology (adenocarcinoma *vs* other), performance status (0–1 *vs* 2), previous platinum chemotherapy (refractory *vs* non-refractory), previous paclitaxel chemotherapy (refractory *vs* non-refractory *vs* none), number of previous regimens (one *vs* two), smoking history (ever *vs* never), and study site. We defined refractory as tumour progression during treatment or within 3 months of chemotherapy completion.

We assessed overall survival from the date of randomisation to the date of death due to any cause or last date that the patient was known to be alive. We assessed tumour response by RECIST[13] every 6 weeks. Progression-free survival was defined as the time from randomisation to the earliest occurrence of disease progression or death from any cause. Quality of life was assessed with the Functional Assessment of Cancer Therapy-Lung (FACT-L) every 3 weeks (until treatment discontinuation),[15,16] and we calculated the FACT-L total score, Trial Outcome Index (TOI; sum of the physical plus functional wellbeing and Lung Cancer Subscale [LCS] scores of the FACT-L), and LCS score. We predefined clinically relevant improvement as 6-point improvement for FACT-L and TOI and 2-point improvement for LCS, maintained for at least 21 days.[17] We assessed toxic effects according to common toxicity criteria (CTC) of the National Cancer Institute (version 2.0).[18]

When paraffin-embedded archival diagnostic tumour tissue was available (tissue collection was not mandatory), FISH was undertaken to analyse EGFR-gene-copy number (tissue was available from patients recruited in Argentina [n=16], Belgium [21], Brazil [15], Canada [43], China [43], Denmark [10], Estonia [10], France [60], Germany [60], Italy [37], Latvia [5], Mexico [2], Malaysia [4], Philippines [1], Slovenia [7], Spain [22], Switzerland [1], and the USA [17]).[19] EGFR-gene-copy number was established with the Vysis LSI EGFR SpectrumOrange/CEP 7 SpectrumGreen probe FISH assay (Abbott Molecular, Illinois, USA). We defined high EGFR-gene-copy number as high polysomy (≥four copies in ≥40% of cells) or gene amplification (presence of tight gene clusters; a gene:chromosome ratio per cell of ≥2; or ≥15 copies of EGFR per cell in ≥10% of cells analysed). EGFR protein expression status was assessed by immunohistochemistry with the DAKO EGFR pharmDx kit (DAKO, Glostrup, Denmark). We classified patients as having a high EGFR protein expression if more than 10% of cells stained. EGFR gene mutations were investigated by direct gene sequencing of exons 18–21 of

chromosome seven. Patients were positive if we detected a mutation in the EGFR gene in both the forward and reverse directions in at least one of the three independent PCR products derived from the tumour DNA. K-Ras gene mutation status was assessed via the amplification refractory mutation system to detect known mutations in codons 12 and 13 of this gene. Patients were positive if any K-Ras gene mutation was detected. We did all EGFR and K-Ras gene mutation assessments in approved commercial laboratories with appropriate quality control measures.

Statistical analysis

The co-primary analysis of overall survival in patients with high EGFR-gene-copy number was introduced in August, 2006, via protocol amendment after data emerged to suggest that high EGFR-gene-copy number was a strong predictor of gefitinib survival benefit compared with placebo.[20] These co-primary analyses used a modified Hochberg procedure to ensure non-inflation of the overall 5% type-I error rate.[21] A 5% significance level would be used for each co-primary analysis unless either the superiority analysis for the high EGFR-gene-copy number was not successful, in which case a 4% significance level would be used for the overall non-inferiority analysis, or the overall non-inferiority analysis was not successful, in which case a 1% significance level would be used for the high EGFR-gene-copy number superiority analysis. With the results obtained, the final significance levels that we used were 4% for the overall analysis and 5% for the high EGFR-gene-copy number analysis.

We predefined the overall survival non-inferiority margin according to the effect-retention method.[22] Non-inferiority would be established if the lower CI limit for the percentage of the historical docetaxel advantage compared with best supportive care from the TAX 317 study[3] retained by gefitinib was greater than 50% in the per-protocol population. On the basis of previous data for docetaxel (hazard ratio [HR] 0·61 based on ratio of median survivals, standard error of log HR 0·18), a 4% significance level, and the 1169 death events in the per-protocol population resulting from INTEREST, a non-inferiority margin in HR terms would be 1·154. Therefore, non-inferiority would be established if the upper limit of the 96% CI for the HR of gefitinib versus docetaxel was less than 1·154.

We used an unadjusted Cox proportional hazards model to estimate the overall survival HR and CI in the per-protocol population (defined as patients without substantial deviations from the inclusion or exclusion criteria or the protocol) for the overall non-inferiority analysis and in the patients with high EGFR-gene-copy number from the intention-to-treat population for the superiority analysis for the high EGFR-gene-copy number. The most conservative population is per-protocol for non-inferiority analyses (since this analysis tends to increase differences between the study treatments) and intention to treat for superiority analyses (since this analysis tends to decrease differences between the study treatments), as recommended in the E9 guideline of the International Conference on Harmonisation.[23] A Cox proportional hazards model with adjustment for the effects of sex, racial origin, histology, performance status, smoking history, previous regimens, previous platinum, and previous paclitaxel was used to estimate the HR for progression-free survival in the evaluable-for-response population (patients in the per-protocol population with

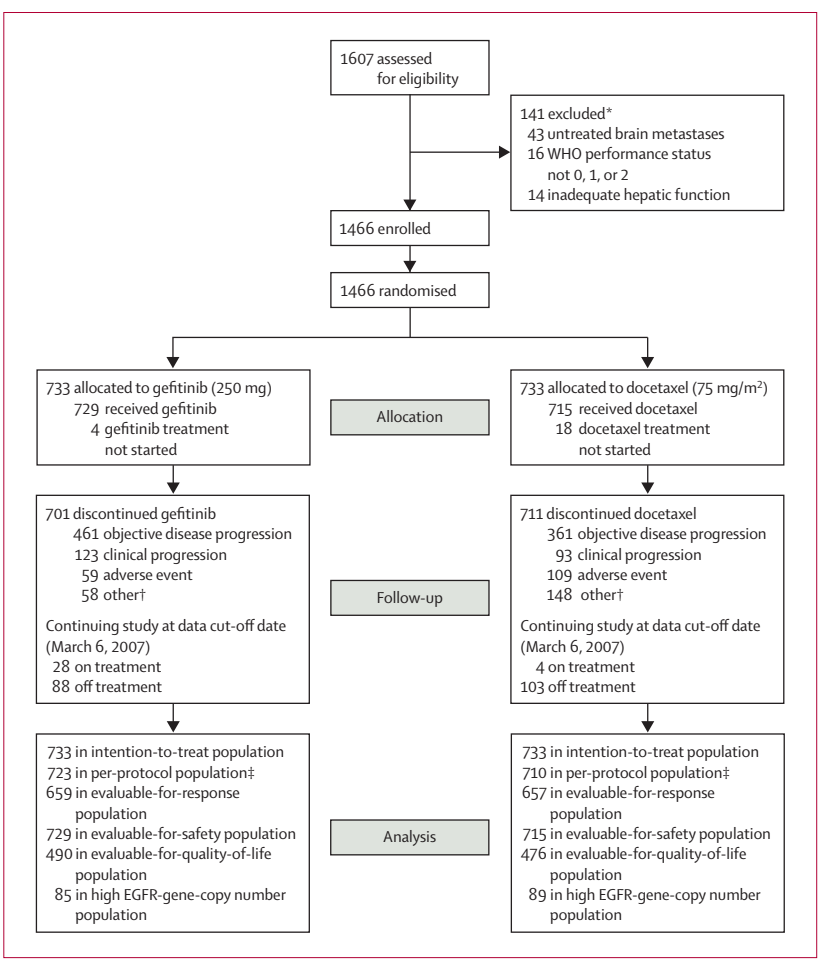

Figure 1: **Trial profile**

ITT population=all randomised patients; per-protocol population=patients who did not significantly deviate from the inclusion or exclusion criteria at entry or significantly deviate from the protocol; evaluable-for-response population=patients in the per-protocol population with unidimensional measurable disease as per the Response Evaluation Criteria In Solid Tumors (RECIST) criteria; evaluable-for-safety population=all patients who received one or more dose of study treatment; evaluable-for-quality of life population=patients in the per-protocol population with an evaluable baseline and one or more evaluable post-baseline quality-of-life assessment. ITT=intention to treat. EGFR=epidermal growth factor receptor. *Reasons for exclusion were not mutually exclusive. Patients were also excluded for several other reasons, including evidence of significant clinical disorder and withdrawal of informed consent. †Other reasons for discontinuation include loss to follow-up, withdrawal of consent, non-compliance, and completing the planned number of docetaxel cycles (docetaxel group). ‡Reasons for exclusion from per-protocol population include failure to start study treatment, newly diagnosed CNS metastases not yet treated with surgery or radiation, clinical evidence of other coexisting malignancies, previous docetaxel treatment, no histological or cytological confirmation of non-small-cell lung cancer, and non-small-cell lung cancer not locally advanced or metastatic or amenable to curative surgery or radiotherapy.

unidimensional disease according to RECIST). We assessed the objective response rate (in the evaluable-for-response population) and quality-of-life improvement rates (in the population who were evaluable for quality of life—ie, patients in the per-protocol population with an evaluable baseline and ≥one evaluable quality-of-life assessment after baseline) with a multivariate logistic regression model with the same covariates to calculate odds ratios (ORs) and 95% CIs. We also did preplanned subgroup analyses of efficacy in prespecified patient subgroups that were defined by demographic characteristics and exploratory qualitative and quantitative analyses to identify potential correlations between biomarker expressions and efficacy. We assessed safety and tolerability in the evaluable-for-safety population (ie, patients who received ≥one dose of study treatment).

We undertook a preplanned interim analysis after the occurrence of 346 deaths to assess for the possible inferiority of gefitinib compared with docetaxel in terms of overall survival. The analysis was done independently, and the independent data monitoring committee recommended that the study should continue as planned. We made no adjustment for the type-I error rate in the final analysis since we had no opportunity in the interim analysis to accept the hypothesis of non-inferiority for overall survival.

This study is registered with ClinicalTrials.gov, number NCT00076388.

	Gefitinib (n=733)	Docetaxel (n=733)
Age (years)	61 (27–84)	60 (20–84)
Sex		
Men	466 (63·6%)	488 (66·6%)
Women	267 (36·4%)	245 (33·4%)
Racial origin*		
White	550 (75·0%)	540 (73·7%)
Asian†	154 (21·0%)	169 (23·1%)
Black	10 (1·4%)	12 (1·6%)
Other	19 (2·6%)	12 (1·6%)
Smoking history		
Ever-smoker‡	585 (79·8%)	583 (79·6%)
Never-smoker‡	148 (20·2%)	150 (20·5%)
WHO performance status		
0	218 (29·7%)	181 (24·7%)
1	428 (58·4%)	463 (63·2%)
2	86 (11·7%)	84 (11·5%)
3	0	0
Not recorded	1 (0·1%)	5 (0·7%)
Tumour histology		
Adenocarcinoma	395 (53·9%)	402 (54·8%)
Bronchoalveolar§	17 (2·3%)	16 (2·2%)
Squamous	185 (25·2%)	176 (24·0%)
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
Disease stage 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
Time from diagnosis to randomisation (months)		
<6	191 (26·1%)	201 (27·4%)
6–12	280 (38·2%)	274 (37·4%)
>12	260 (35·5%)	258 (35·2%)
Unknown	2 (0·3%)	0
(Continues in next column)		
(Continued from previous column)		
Number of previous chemotherapy regimens		
1	619 (84·4%)	610 (83·2%)
2	112 (15·3%)	123 (16·8%)
3	2 (0·3%)	0
Previous chemotherapy		
Platinum compound	733 (100·0%)	733 (100·0%)
Paclitaxel	141 (19·2%)	130 (17·7%)
Refractory to previous platinum-based chemotherapy¶		
Refractory	394 (53·8%)	413 (56·3%)
Received (not refractory)	327 (44·6%)	309 (42·2%)
Unknown	12 (1·6%)	11 (1·5%)
Refractory to previous paclitaxel-based therapy¶		
Refractory	68 (9·3%)	57 (7·8%)
Received (not refractory)	67 (9·1%)	63 (8·6%)
None	592 (80·8%)	603 (82·3%)
Unknown	6 (0·8%)	10 (1·4%)
Refractory to most recent chemotherapy‖	416 (56·8%)	437 (59·6%)
Best response to most recent chemotherapy		
Complete response	12 (1·6%)	6 (0·8%)
Partial response	188 (25·6%)	222 (30·3%)
Stable disease	303 (41·3%)	282 (38·5%)
Progressive disease	192 (26·2%)	184 (25·1%)
Non-evaluable	35 (4·8%)	31 (4·2%)
Not recorded	3 (0·4%)	8 (1·1%)

Data are median (range) or number of patients (%). *Racial origin does not necessarily refer to the patient's place of birth. †This definition excludes people of Indian origin. ‡Smoking history was determined at screening. Ever-smoker refers to regular (smokes every day), occasional (smokes, but not every day), and ex-smokers (no longer smokes). Never-smoker refers to patients who had never smoked in their lifetime. §Patients with bronchoalveolar histology were included in the adenocarcinoma subgroup. ¶Refractory to platinum or paclitaxel defined as progression (clinical or radiological) on, or within, 3 months of completing last platinum or paclitaxel therapy. ‖Refractory defined as recurrent or progressive disease (clinical or radiological) while receiving chemotherapy or within 3 months of last dose.

Table 1: **Baseline patient demographics and characteristics (in the intention-to-treat population)**

Role of the funding source
The principal investigators designed the trial in collaboration with the study sponsor, AstraZeneca, and the steering committee supervised the conduct of the study. The sponsor provided funding and organisational support, collected the data, and undertook the analyses. The report was written by the principal investigators, who had unrestricted access to the study data and gave assurance for the accuracy and completeness of the reported analyses. The principal investigators had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 1466 patients were randomly assigned at 149 centres in 24 countries (803 [55%] Europe, 308 [21%] Asia, 223 [15%] North America, and 132 [9%] Central and South America). Patient demographics and baseline characteristics were much the same between treatment groups (table 1). 1433 patients were included in the per-protocol population; ten patients assigned to gefitinib and 23 assigned to docetaxel were excluded, mainly because of failure to start study treatment (figure 1). Overall mortality was 81·6%; median follow-up for survival was 7·6 months. The mean duration of treatment was 4·4 months (median 2·4; range 0–33·3) for gefitinib and 3·0 months (2·8; 1–18·1) for docetaxel. The median number of docetaxel cycles was four (range one–24).

Subsequent therapies received after discontinuing randomised study treatment were well balanced between the groups. Of the patients given gefitinib, 396 (54%) received no systemic therapy apart from further EGFR tyrosine kinase inhibitor (28 [4%] gefitinib, ten [1%] erlotinib), 225 (31%) received docetaxel, and 112 (15%) received other chemotherapy only. For patients given docetaxel, 391 (53%) received no systemic therapy apart from further docetaxel (four [1%] docetaxel), 268 (37%) received an EGFR tyrosine kinase inhibitor (111 [15%] gefitinib, 157 [21%] erlotinib), and 74 (10%) received other chemotherapy only.

Figure 2 shows the non-inferiority of gefitinib in terms of overall survival in the per-protocol population. The overall survival HR (gefitinib *vs* docetaxel) was 1·020 (96% CI 0·905–1·150), with the upper confidence limit less than the non-inferiority limit of 1·154 (593 [82·0%] *vs* 576 [81·1%] death events). Median overall survival was 7·6 months in the gefitinib group and 8·0 months in the docetaxel group, and 1-year survival was 32% and 34%, respectively. Gefitinib retained 96% (96% CI 52–129) of the historical docetaxel advantage compared with best supportive care,[3] which was above the predefined non-inferiority limit in effect-retention terms of 50%. A supportive analysis in the intention-to-treat population showed similar results (HR 1·015, 96% CI 0·901–1·143). We did not prove superior overall survival for gefitinib compared with docetaxel in the subgroup of

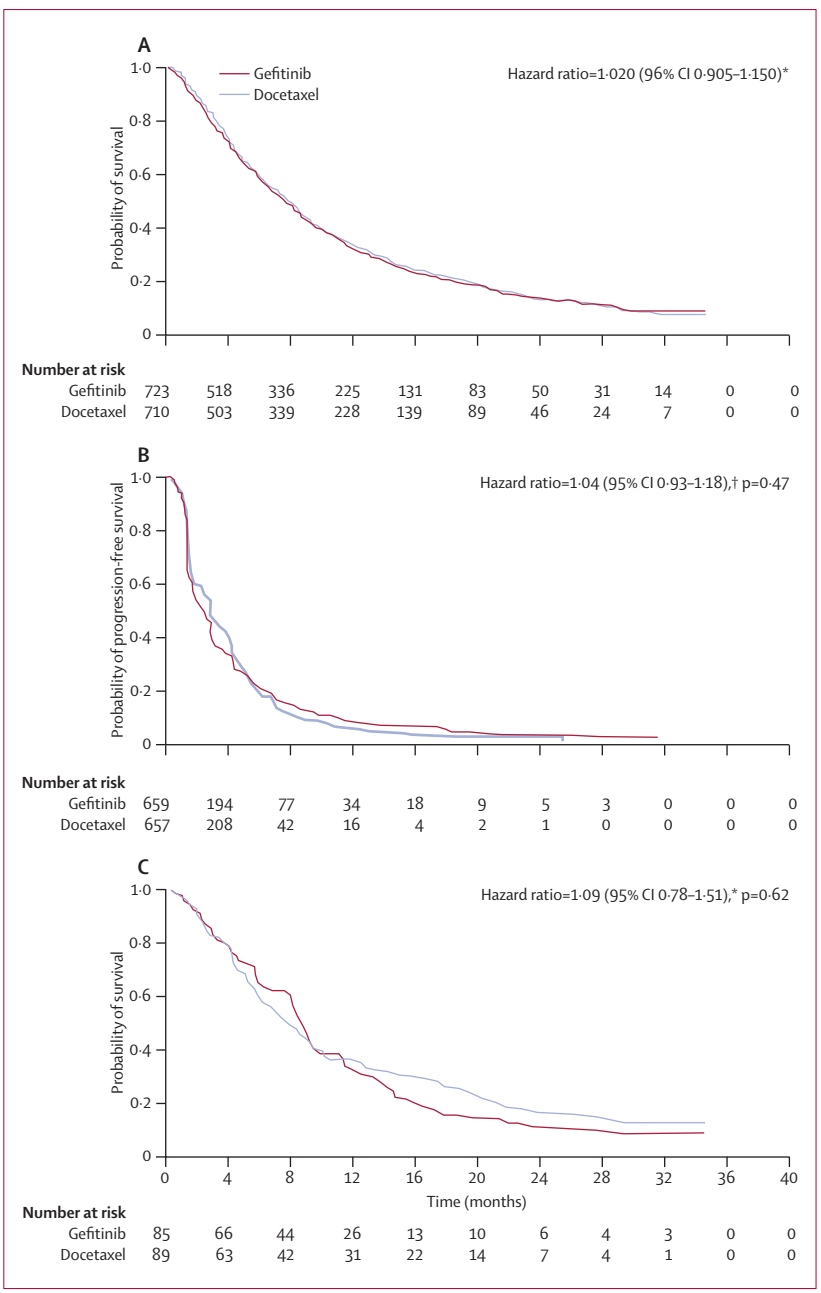

***Figure 2*: Overall survival in overall per-protocol population (A), progression-free survival in overall evaluable-for-response population (B), and overall survival in patients with high EGFR-gene-copy number in intention-to-treat population (C)**
High epidermal growth factor receptor (EGFR)-gene-copy number was defined as high polysomy (≥four copies in ≥40% of cells) or gene amplification (presence of tight gene clusters; a gene:chromosome ratio per cell of ≥2; or ≥15 copies of EGFR per cell in ≥10% of cells analysed). *Primary Cox analysis without covariates. †Primary Cox analysis with covariates (histology [adenocarcinoma *vs* other], performance status [0 or 1 *vs* 2], previous platinum therapy [refractory *vs* received], smoking history [ever *vs* never], previous paclitaxel therapy [refractory *vs* received *vs* none], previous regimens [one *vs* two], sex [men *vs* women], and racial origin [Asian *vs* other]).

174 patients with high EGFR-gene-copy number of 374 patients with evaluable results (72 [84·7%] *vs* 71 [79·8%] events; HR 1·09, 95% CI 0·78–1·51; p=0·62; figure 2). In this subgroup, median overall survival was

8·4 months in the gefitinib group and 7·5 months in the docetaxel group, and 1-year survival was 32% and 35%, respectively. We noted consistent results in an analysis adjusted for patient covariates (data not shown).

Survival results were consistent across preplanned subgroups, apart from those defined by the number of previous chemotherapy regimens (figure 3). Patients who received third-line treatment had significantly longer survival with docetaxel than with gefitinib (HR 1·39, 95% CI 1·03–1·87; p=0·0326; median survival 6·9 months for gefitinib and 11·9 months for docetaxel). In the second-line subgroup, survival was similar for both groups (0·96, 0·85–1·08; p=0·50; median survival 7·8 months for gefitinib and 7·6 months for docetaxel). Subgroups such as never-smokers, women, Asian patients, and those with adenocarcinoma had longer survival than did smokers, men, non-Asian patients, and those without adenocarcinoma, respectively, but had similarly long survival with both gefitinib and docetaxel treatment (figure 3). Survival was also similar for gefitinib and docetaxel in smokers, men, non-Asian patients, and patients without adenocarcinoma (figure 3).

Progression-free survival was similar for gefitinib and docetaxel (593 [90·0%] *vs* 544 [82·8%] events; HR 1·04, 95% CI 0·93–1·18; p=0·47; median progression-free survival 2·2 *vs* 2·7 months; progression-free survival at 4 months 32% *vs* 38%; progression-free survival at 6 months 19% *vs* 18%; figure 2). Objective response rates were similar in both treatment groups (9·1% *vs* 7·6%; OR 1·22, 95% CI 0·82–1·84; p=0·33).

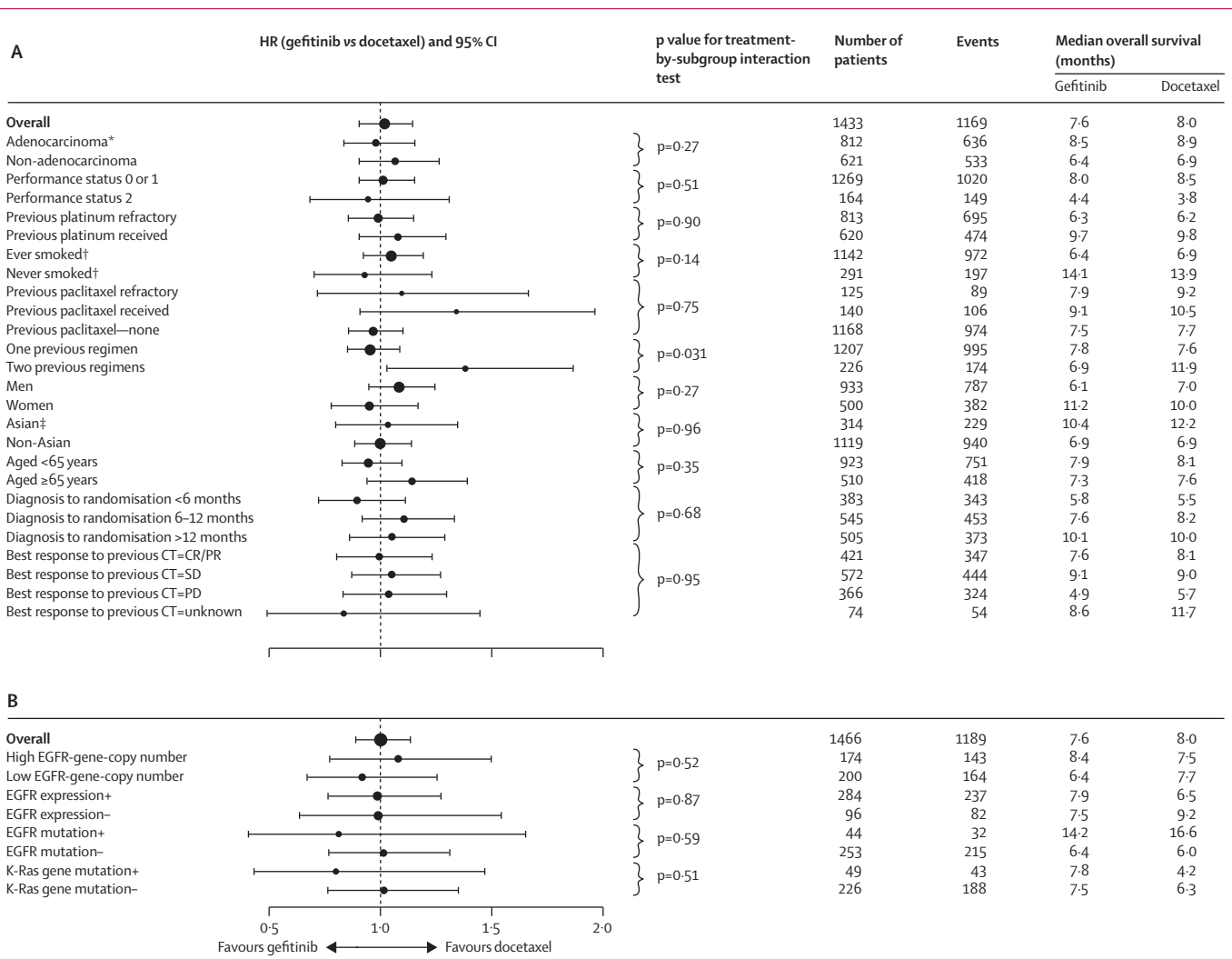

Figure 3: **Forest plot of overall survival by subgroup in per-protocol population (A) and overall survival by biomarkers in the intention-to-treat population (B)**
Cox analysis without covariates. CT=chemotherapy. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease. HR=hazard ratio. EGFR=epidermal growth factor receptor. *Patients with bronchoalveolar history were included in the adenocarcinoma subgroup. †Smoking history was determined at screening. Ever-smoker refers to regular (smokes every day), occasional (smokes, but not every day) and ex-smokers (no longer smokes). Never-smoker refers to patients who had never smoked in their lifetime. ‡Ethnic origin does not necessarily refer to the patient's place of birth. This definition excludes those of Indian origin.

Tissue samples were available from 553 patients and were evaluable for at least one biomarker from 453 patients (31% of the intention-to-treat population); we were unable to assess samples from 100 patients because of failure of quality assessment at the pathology review, which was undertaken to assess whether tissue samples were adequate for biomarker analyses. These patients were generally representative of the overall study population (with the exception of a slightly smaller proportion of Asian patients). For example, women represented 35% of the overall population, and proportions for each specific biomarker group were very similar (EGFR-gene-copy number 31% [n=116], EGFR immunohistochemistry 33% [124], EGFR mutation 31% [93], and K-Ras gene mutation 31% [84]). Histology with adenocarcinoma represented 57% (830) of the overall population, and proportions for each specific biomarker group were similar (EGFR-gene-copy number 55% [207], EGFR immunohistochemistry 54% [206], EGFR mutation 57% [169], and K-Ras mutation 52% [144]).

We detected no difference in overall survival between gefitinib and docetaxel irrespective of a patient's EGFR protein expression, EGFR gene mutation, or K-Ras gene mutation status (treatment by biomarker-interaction test was not significant for any biomarker; figure 3).

The most common adverse events were rash or acne and diarrhoea with gefitinib, and haematological toxic effects, asthenic disorders, and alopecia with docetaxel (table 2). Grades 3–4 neutropenia and febrile neutropenia were substantially higher with docetaxel than with gefitinib. Docetaxel was also associated with more neurotoxicity and fluid retention (table 2). Events from interstitial lung disease were reported for ten (1%) patients assigned to gefitinib and eight (1%) assigned to docetaxel. Serious adverse events were reported in 161 (22%) of patients receiving gefitinib and 210 (29%) receiving docetaxel; adverse events led to drug discontinuation for 59 (8%) and 102 (14%) of patients, respectively, and adverse events leading to death occurred in 31 (4%) and 28 (4%) patients, respectively.

Gefitinib was associated with lower rates of treatment-related adverse events than was docetaxel: overall (527 [72%] *vs* 588 [82%]); serious adverse events (28 [4%] *vs* 130 [18%]); adverse events leading to discontinuation of therapy (30 [4%] *vs* 78 [11%]); common toxicity criteria grades 3–4 adverse events (62 [9%] *vs* 291 [41%]); and adverse events leading to death (6 [1%] *vs* 15 [2%]).

Significantly more patients had sustained and clinically relevant improvement in quality of life with gefitinib than with docetaxel, as assessed by FACT-L total score (OR 1·99, 95% CI 1·42–2·79; p<0·0001) and the FACT-L TOI (1·82, 1·23–2·69; p=0·0026) (figure 4). Similar proportions of patients had improvements in lung cancer symptoms (FACT-L LCS) with gefitinib and docetaxel (1·29, 0·93–1·79; p=0·13) (figure 4).

	All adverse events		p value*	Grade 3–4 adverse events	
	Gefitinib (n=729)	Docetaxel (n=715)		Gefitinib (n=729)	Docetaxel (n=715)
Neutropenia†	35 (5·0%)‡	514 (73·7%)‡	<0·0001	15 (2·2%)§	406 (58·2%)§
Febrile neutropenia	9 (1·2%)	72 (10·1%)	<0·0001	9 (1·2%)	72 (10·1%)
Rash/acne¶	360 (49·4%)	73 (10·2%)	<0·0001	15 (2·1%)	4 (0·6%)
Asthenic disorders¶	182 (25·0%)	334 (46·7%)	<0·0001	32 (4·4%)	64 (9·0%)
Diarrhoea	255 (35·0%)	177 (24·8%)	<0·0001	18 (2·5%)	22 (3·1%)
Nausea	148 (20·3%)	187 (26·2%)	0·0088	3 (0·4%)	9 (1·3%)
Anorexia¶	159 (21·8%)	151 (21·1%)	0·80	11 (1·5%)	7 (1·0%)
Alopecia	23 (3·2%)	254 (35·5%)	<0·0001	0	0
Dyspnoea	120 (16·5%)	117 (16·4%)	1·0	45 (6·2%)	55 (7·7%)
Vomiting	109 (15·0%)	123 (17·2%)	0·25	4 (0·5%)	8 (1·1%)
Neurotoxicity¶	49 (6·7%)	171 (23·9%)	<0·0001	1 (0·1%)	17 (2·4%)
Cough	108 (14·8%)	102 (14·3%)	0·82	6 (0·8%)	5 (0·7%)
Constipation	79 (10·8%)	121 (16·9%)	0·0010	6 (0·8%)	13 (1·8%)
Pyrexia	69 (9·5%)	118 (16·5%)	<0·0001	2 (0·3%)	4 (0·6%)
Fluid retention¶	48 (6·6%)	112 (15·7%)	<0·0001	0	5 (0·7%)
Stomatitis¶	67 (9·2%)	93 (13·0%)	0·024	0	3 (0·4%)
Lower RTI and lung infections¶	71 (9·7%)	74 (10·3%)	0·73	23 (3·2%)	25 (3·5%)
Myalgia	24 (3·3%)	113 (15·8%)	<0·0001	1 (0·1%)	4 (0·6%)
Dry skin	111 (15·2%)	10 (1·4%)	<0·0001	0	0
Anaemia	34 (4·7%)	84 (11·7%)	<0·0001	11 (1·5%)	15 (2·1%)

Data are number of patients (%), unless otherwise stated. RTI=respiratory tract infection. *A post-hoc analysis assessed individual adverse events with a Fisher exact test. †Data from laboratory reports. Calculations include only patients with a baseline and at least one value after baseline. ‡Worsening in laboratory value from baseline. §Worsening in laboratory value from baseline to common toxicity criteria grade 3–4. n=697 for neutropenia with gefitinib and docetaxel. ¶Grouped term (sum of preferred terms).

Table 2: **Adverse events (of more than 10% frequency)**

Discussion

Although several agents including docetaxel, pemetrexed, erlotinib and, in some countries, gefitinib are approved for second-line treatment of non-small-cell lung cancer, few phase III clinical trials have compared these treatments directly for efficacy. INTEREST has established equivalent efficacy between a molecularly-targeted agent and a cytotoxic chemotherapy in advanced non-small-cell lung cancer, showing gefitinib to be non-inferior in overall survival and similar in tumour response and progression-free survival to docetaxel.

Median survival with gefitinib and docetaxel in INTEREST are comparable with previous results, suggesting that both treatment groups did as expected.[3–6,11] Non-inferior survival of gefitinib to docetaxel was not statistically proven in the Japanese phase III V-15-32 trial;[11] however, this study was fairly small (306 events in 489 patients), and imbalances in subsequent therapies after discontinuation of the study treatment complicate the interpretation of the survival data. By contrast, subsequent therapies in INTEREST were well balanced between the treatment groups.

The patient population in INTEREST was generally representative of a pretreated population with advanced non-small-cell lung cancer, with most being second-line

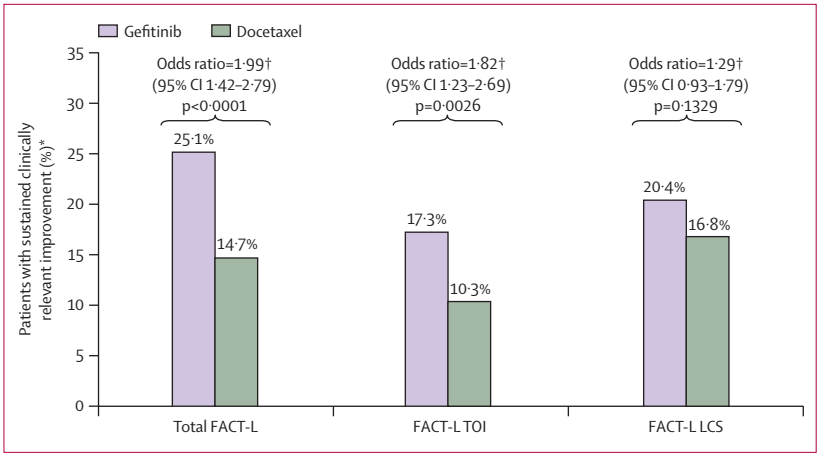

Figure 4: **Improvement rates for quality of life and disease-related symptoms in population who were evaluable for quality of life**

FACT-L=Functional Assessment of Cancer Therapy-Lung; TOI=Trial Outcome Index. LCS=Lung Cancer Subscale. *Clinically relevant improvement predefined as 6-point improvement for FACT-L and TOI; and 2-point improvement for LCS, maintained for at least 21 days. †From multivariate logistic regression model including terms for histology (adenocarcinoma *vs* other), performance status (0 or 1 *vs* 2), previous platinum therapy (refractory *vs* received), smoking history (ever *vs* never), previous paclitaxel therapy (refractory *vs* received *vs* none), previous regimens (one *vs* two), sex (men *vs* women), and racial origin (Asian *vs* other).

therapy patients. INTEREST was a global study with a population predominantly from non-Asian countries, that compared gefitinib with docetaxel, which is the standard of care treatment in this setting and a commonly used comparator in other phase III studies. The docetaxel dose and administration used in this study was consistent with standard practice. The study eligibility criteria resulted in a study population that was largely typical of patients in this stage of non-small-cell lung cancer, and we applied an appropriate recruitment period and follow-up.

The INTEREST results and its particular patient population should be considered in the context of other phase III trials in pretreated advanced non-small-cell lung cancer. The ISEL study[12] compared gefitinib and placebo in predominantly refractory patients unsuitable for further chemotherapy and showed some improvement in overall survival, which did not reach statistically significant superiority in the primary analysis of the overall study population (HR 0·89, 95% CI 0·77–1·02, p=0·087; median survival 5·6 *vs* 5·1 months). The large number of patients refractory to chemotherapy in the ISEL study (90% *vs* 58% in INTEREST) might partly explain why ISEL did not show a significant improvement in overall survival with gefitinib compared with placebo, since these patients represent a population who are difficult to treat and have a poor prognosis.[12] The BR.21 trial[8] with erlotinib reported a significant survival advantage for erlotinib compared with placebo for patients who were not required to be refractory to their previous treatment (HR 0·70, 95% CI 0·58–0·85, p<0·001; median survival 6·7 *vs* 4·7 months).[8] Only 20·8% of patients in the BR.21 trial had progressive disease as best response to previous chemotherapy treatment, compared with 38·4% in ISEL and 25·6% in INTEREST. This difference in previous response could also explain the differing outcomes. There are no comparative data for erlotinib versus chemotherapy at present, although studies are in progress.

The JMEI trial[5] showed that pemetrexed was clinically equivalent in efficacy outcomes and lower in overall toxic effects than was docetaxel (HR 0·99, 95% CI 0·82–1·20, non-inferiority p=0·226; median survival 8·3 *vs* 7·9 months). However, this trial did not prove that survival of pemetrexed was statistically non-inferior to that of docetaxel according to the original specified non-inferiority margin (upper bound of 95% CI for HR<1·11), although non-inferiority was achieved with a subsequently defined 50% effect retention margin (upper bound of 95% CI for HR<1·21). Median survival in JMEI was consistent with that in INTEREST for both gefitinib and docetaxel. Despite reported lower toxic effects, pemetrexed did not improve quality of life compared with docetaxel in JMEI,[5] whereas docetaxel did show improved quality of life compared with best supportive care in TAX 317.[3] Gefitinib is the first agent in a study of clinical lung cancer to report improved quality of life against a chemotherapy agent (docetaxel). The profiles of adverse events of gefitinib and docetaxel in INTEREST were consistent with previously reported data.[3,5,9,10]

Biomarker data in lung cancer continue to emerge as clinical trials begin to integrate these markers as important endpoints. Lung cancer sensitivity to EGFR tyrosine kinase inhibitors has previously been associated with EGFR mutations[24] and high EGFR-gene-copy number,[25] whereas K-Ras gene mutations have been associated with resistance to EGFR tyrosine kinase inhibitors[26] or chemotherapy.[27] The co-primary analysis in INTEREST produced the unexpected result that, in patients with high EGFR-gene-copy number, survival was not longer with gefitinib than with docetaxel. We acknowledge that, because of the small number of samples, a large effect was needed for statistical significance; however, since the HR for gefitinib showed no advantage, more samples would have been unlikely to change the overall result.

EGFR-gene-copy number was identified in the primary tumour from archived diagnostic samples, and whether EGFR-gene-copy number status changed upon progression or after exposure to first-line chemotherapy is unknown. Other studies that have reported data with EGFR-gene-copy number in the second-line treatment setting have used similar diagnostic tissue specimens as in INTEREST. Patients with high EGFR-gene-copy number (a poor prognostic factor in the absence of treatment)[20,28] seem to do similarly with either gefitinib or docetaxel. Previous biomarker studies that suggested better survival for patients with high rather than low EGFR-gene-copy number either compared gefitinib or

erlotinib with placebo or were single-group trials. INTEREST also investigated the efficacy of chemotherapy (docetaxel) according to biomarker status. Planned studies or those in progress are also integrating prospective biomarker validation (ie EGFR-gene-copy number) for non-small-cell lung cancer. The INTEREST results draw attention to the importance of studying biomarkers in a prospective, randomised, broad manner, with both molecular-targeted agents and chemotherapy drugs.

Clinical factors (never-smoker, Asian origin, female sex, and adenocarcinoma histology) have also been reported to predict sensitivity to EGFR tyrosine kinase inhibitors and overall improved patient outcome. In our study, these factors were associated with observed longer survival, with the benefit occurring in patients given both gefitinib and docetaxel. This finding was also unexpected since previous work has suggested that chemotherapy (docetaxel) produces similar survival in all patients.

The clinical management of advanced non-small-cell lung cancer remains challenging, but an oral agent that has similar efficacy, has a more favourable tolerability profile, and results in better quality of life than intravenous chemotherapy is an important shift in the treatment paradigm for this disease and presents an alternative option for patients. On the basis of these data, gefitinib is a valid treatment option for patients with pretreated advanced non-small-cell lung cancer.

Contributors

ESK, VH, MAS, TM, ESL, AAA, and J-YD were involved in the conception and design of the study. ESK, VH, TM, MAS, CLW, ESL, AAA, and J-YD were involved in the supervision of the study (as a part of the steering committee). ESK, VH, TM, MAS, RG, Y-LW, L-YL, YS, M-LL, KØ, MR, FAS, and J-YD were involved in the provision of study material or patients and/or data acquisition. ESK, VH, MAS, CLW, MVS, ESL, MR, AAA, FAS, SML, and J-YD were involved in data analysis and interpretation. All authors were involved in writing the report and approved the final version.

INTEREST trial organisation

Steering committee: E S Kim, J-Y Douillard, M A Socinski, V Hirsh, T Mok, A A Armour, C L Watkins, E S Lowe.
Independent data monitoring committee: J Boyett, P D Bonomi, P Harper.
Study personnel: A A Armour, Medical Science Director; J Ryan, Study Delivery Leader; E S Lowe, Study Physician; I Tchakov, Study Physician; M V Sellers, Biostatistician; C L Watkins, Biostatistician.
Investigators: Argentina—C Blajman, R H Bordenave, B B Ibarguren, L E Fein, W Batagelj, N G Pilnik, R J J di Giovanni, K Leonardo, E P Korbenfeld, G Lerzo, M Tatangelo, M Astegiano, J J Zarbá, G López; *Belgium*—L Bosque, F Bustin, J-L Canon, J Vansteenkiste, F Duplaquet, P Germonpre, M Thomeer, K Van Oortegem, A Haerems; *Brazil*—C Barrios, J Pereira, H Tadokoro, M Zukin, C Ferreira, M Federico, S J de Azevedo; *Canada*—J Wilson, L Zibdawi, J Mercharand, N Blais, N Aucoin, J Noble, B Findlay, F Shepherd, R Burkes, W Mortzycki, F Laberge, C Lee, A Arnold, S Rubin, V Hirsh, A Reiman; *China*—Y San, L Li, M Liao, G L Jaing, Y L Wu; *Croatia*—M Samarzija, E Vrdoljak; *Denmark*—O Hansen, T Palshof, H Frank, J B Sørensen, K E Østerlind, A Mellemgaard, N Gyldenkerne, C Rytter, B Sorensen; *Estonia*—P Padrik, T Vanakesa; *France*—D Debieuvre, J-Y Douillard, D Moro-Sibilot, R Gervais, P Laplaige, D Spaeth, C Roemer-Becuwe, L Uwer, G Ganem, J-J Latiffe, T Chinet, G Dabouis, M D'Arlhac; *Germany*—U Gatzemeier, H Bischoff, J Fischer, A Chemaissani, C Korstik, R Loddenkemper, M Serke, N Nierderle, H Schweisfurth, K Possinger, Y-D Ko, N Frickhofen, M Hetzel, C Schumann, C Peschel, C Manegold; *Hong Kong*—T Mok; *Indonesia*—J Kurnianda, H Reksodiputro; *Italy*—D Amadori, A R Bianco, A Brandes, F Cappuzzo, L Crino, M Rinaldi, G Numico, G Carteni, S Cascinu, A Ceribelli, F Ciardiello, P Conte, V Franciosi, G Gasparini, R Labianca, V Lorusso, F de Marinis, A Santoro, H Soto-Parra; *Latvia*—I Kudaba, G Purkalne; *Malaysia*—N Abdullah, M R Haron, K Ratnavelu; *Mexico*—F M M Loperana, A L R Mariscal, J M A Melchor, T S Sahui, F G Salazar, J A Silva, M T Velazquez; *Philippines*—P Caguioa, V Chan, G Cornelio; *Singapore*—T Eng-Huat; *Slovenia*—M Zwitter; *Spain*—C Camps, D I Casado, R Colomer, S Dominguez, M D Gómez, A Izquierdo, A C Mena, L P-A Rodriguez, J M Trigo, N Vinolas, J A Virizuela; *Sweden*—L Beckman, P Bergström, B Bergman, T Brezicka, L Hetta, H Koyi, J Lofvenberg, T Månsson, L Steinholtz, L Thaning; *Switzerland*—D Betticher, M Borner, G D'Addario, D Rauch, R Morant, C Sessa, R A Stahel; *Thailand*—S Thongprasert; *Turkey*—T Çelikel, A Demirkazik, E Göker, İ Savaş; *USA*—W Akerley, I C Anderson, F P Arena, C P Belani, D S Brantley, C M Broome, P Bushunow, P J Byrne, J E Cantrell Jr, N P Christiansen, J Crawford, T W Dobbs, R Gallardo, S Graziano, M J Guarino, H Jhangiani, R O Kerr, E Kim, R E Lamar, R Martins, A S Mehdi, T Mekhail, R B Natale, R N Odders, I A Oliff, S Perkins, K J Philip, R Reiling, H Ross, M Saleh, A Sandler, F Schnell, D E Slater, M A Socinski, J Stocks, W J Tester, J E Tseng, I Wiznitzer.

Conflict of interest statement

ESK has served on advisory boards and received consultancy and lecturing funding from AstraZeneca and Sanofi-Aventis. VH has served on advisory boards and received consultancy funding from AstraZeneca. TM has received honorarium from AstraZeneca. MAS has received research funding and served on speakers' bureaus for AstraZeneca and Sanofi-Aventis. Y-LW has received consultancy funding from AstraZeneca. FAS has served on advisory boards and received honorarium from Eli Lilly, Sanofi-Aventis, AstraZeneca, OSIP, and Roche. J-YD has served on advisory boards and received consultancy and lecturing funding from AstraZeneca and Sanofi-Aventis. CLW, MVS, ESL, and AAA are salaried employees of AstraZeneca. RG, L-YL, YS, M-LL, KØ, SML, and MR declare that they have no conflict of interest.

Acknowledgments

This study was supported by AstraZeneca. We thank the patients and their families for their support and participation in INTEREST; and Muhammed Karolia from Complete Medical Group who provided editorial assistance funded by AstraZeneca.

References

1 Parkin M, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55:** 74–108.
2 Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin* 2007; **57:** 43–66.
3 Shepherd FA, Dancey J, Ramlau R, 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:** 2095–103.
4 Fossella FV, Devore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. *J Clin Oncol* 2000; **18:** 2354–62.
5 Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004; **22:** 1589–97.
6 Cufer T, Vrdoljak E, Gaafar R, Erensoy I, Pemberton K. Phase II, open-label, randomized study (SIGN) of single-agent gefitinib (IRESSA) or docetaxel as second-line therapy in patients with advanced (stage IIIb or IV) non-small-cell lung cancer. *Anticancer Drugs* 2006; **17:** 401–09.
7 Herbst RS, Fukuoka M, Baselga J. Gefitinib—a novel targeted approach to treating cancer. *Nat Rev Cancer* 2004; **4:** 956–65.
8 Shepherd FA, Rodrigues PJ, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; **353:** 123–32.
9 Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2003; **21:** 2237–46.

10 Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small-cell lung cancer. A randomized trial. *JAMA* 2003; **290:** 2149–58.

11 Maruyama R, Nishiwaki Y, Tamura T, et al. Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. *J Clin Oncol* 2008; **26:** 4244–52.

12 Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005; **366:** 1527–37.

13 Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000; **92:** 205–16.

14 Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975; **31:** 103–15.

15 Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy Scale: development and validation of the general measure. *J Clin Oncol* 1993; **11:** 570–79.

16 Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer* 1995; **12:** 199–220.

17 Cella D, Eton DT, Fairclough DL, et al. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy-Lung (FACT-L) Questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) Study 5592. *J Clin Epidemiol* 2002; **55:** 285–95.

18 Cancer Therapy Evaluation Program. Common Toxicity Criteria, 1999. http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf (accessed Dec 10, 2007).

19 Cappuzzo F, Varella-Garcia M, Shigematsu H, et al. Increased HER2 gene copy number is associated with response to gefitinib therapy in epidermal growth factor receptor-positive non-small-cell lung cancer patients. *J Clin Oncol* 2005; **23:** 5007–18.

20 Hirsch FR, Varella-Garcia M, Bunn PA Jr, et al. Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol* 2006; **24:** 5034–42.

21 Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika* 1988; **75:** 800–02.

22 Rothmann M, Li N, Chen G, Chi GY, Temple R, Tsou HH. Design and analysis of non-inferiority mortality trials in oncology. *Stat Med* 2003; **22:** 239–64.

23 The International Conference on Harmonisation (ICH) guidelines. Statistical principles for clinical trials. The International Conference on Harmonisation (ICH), 1998. http://www.ich.org/LOB/media/MEDIA485.pdf (accessed Nov 29, 2007).

24 Lynch TJ, Bell DW, Sordell R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004; **350:** 2129–39.

25 Tsao M-S, Sakurada A, Cutz J-C, et al. Erlotinib in lung cancer—molecular and clinical predictors of outcome. *N Engl J Med* 2005; **353:** 133–44.

26 Pao W, Wang TY, Riely GJ, et al. KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. *PLoS Med* 2005: e17.

27 Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol* 2005; **23:** 5856–58.

28 Hirsch FR, Varella-Garcia M, Bunn PA Jr, et al. Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis. *J Clin Oncol* 2003; **21:** 3798–807.