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)

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Summary

Background This placebo-controlled phase III study investigated the effect on survival of gefitinib as second-line or third-line treatment for patients with locally advanced or metastatic non-small-cell lung cancer.

Methods 1692 patients who were refractory to or intolerant of their latest chemotherapy regimen were randomly assigned in a ratio of two to one either gefitinib (250 mg/day) or placebo, plus best supportive care. The primary endpoint was survival in the overall population of patients and those with adenocarcinoma. The primary analysis of the population for survival was by intention to treat. This study has been submitted for registration with ClinicalTrials.gov, number 1839IL/709.

Findings 1129 patients were assigned gefitinib and 563 placebo. At median follow-up of 7·2 months, median survival did not differ significantly between the groups in the overall population (5·6 months for gefitinib and 5·1 months for placebo; hazard ratio 0·89 [95% CI 0·77–1·02], p=0·087) or among the 812 patients with adenocarcinoma (6·3 months *vs* 5·4 months; 0·84 [0·68–1·03], p=0·089). Preplanned subgroup analyses showed significantly longer survival in the gefitinib group than the placebo group for never-smokers (n=375; 0·67 [0·49–0·92], p=0·012; median survival 8·9 *vs* 6·1 months) and patients of Asian origin (n=342; 0·66 [0·48–0·91], p=0·01; median survival 9·5 *vs* 5·5 months). Gefitinib was well tolerated, as in previous studies.

Interpretation Treatment with gefitinib was not associated with significant improvement in survival in either coprimary population. There was pronounced heterogeneity in survival outcomes between groups of patients, with some evidence of benefit among never-smokers and patients of Asian origin.

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Introduction

Lung cancer causes more than 1 million cancer-related deaths each year worldwide;[1] non-small-cell lung cancer (NSCLC) accounts for about 80% of all cases of lung cancer. With current first-line platinum-based chemotherapy regimens, median survival is 7–10 months.[2–4] With docetaxel, the only second-line treatment option available until lately, median survival is 5·7–7·5 months compared with 4·6–5·6 months for best supportive care alone.[5] Current third-line chemotherapy regimens provide little benefit, as shown in a retrospective analysis by Massarelli and colleagues, who reported median survival from the start of last treatment of 4 months.[6] The small survival benefits obtained with these treatment regimens are commonly offset by their substantial toxic effects. For patients who are refractory to or intolerant of the current chemotherapy regimens, treatment options are limited and new therapies are needed.

The epidermal-growth-factor receptor (EGFR) forms part of a signalling pathway that regulates tumour-cell proliferation, invasion, angiogenesis, metastasis, and apoptosis. EGFR is commonly overexpressed in NSCLC, so novel agents that inhibit the EGFR have been developed as potential treatments in this disorder. When this study was planned, clinical phase II data for two inhibitors of EGFR tyrosine kinase, gefitinib and erlotinib, were available. Gefitinib (250 mg/day) was the first molecularly targeted agent to be approved for the treatment of advanced NSCLC, on the basis of data from two large phase II trials of gefitinib monotherapy (250 *vs* 500 mg/day) in previously treated patients with advanced NSCLC.[7,8] In these trials, response rates and survival were the same for 250 mg/day and 500 mg/day gefitinib, but the frequency and severity of adverse events were greater at the higher dose. At the lower dose, the objective response rate was 12–18%, and higher objective response rates were observed in women, never-smokers, and patients with adenocarcinoma (in both trials[7,8]) and in Japanese patients (in the trial by Fukuoka and colleagues[8] only).[7–9] Encouraging survival data (median survival 7–8 months; 1-year survival 27–35%) have been supported by data from more than 21 000 patients treated as part of an Expanded Access Programme, among whom 1-year survival was 30%.[10] In a phase II trial of erlotinib in previously treated patients with NSCLC, the results were similar: the response rate was 12·3%, median survival was 8 months, and 1-year survival was 40%.[11]

The ISEL (Iressa Survival Evaluation in Lung Cancer) study was one of the post-marketing trials requested by the US Food and Drug Administration. It was a randomised, placebo-controlled, phase III study designed to assess the survival advantage of gefitinib plus best supportive care in patients with advanced NSCLC who were refractory to or intolerant of their latest chemotherapy regimen.

Methods

Trial design and participants

ISEL, a double-blind, placebo-controlled, parallel-group, multicentre, randomised, phase III survival study was undertaken in 210 centres in 28 countries across Europe, Asia, Central and South America, Australia, and Canada. All patients provided written informed consent, and trial approval was obtained from the ethics committee at each trial centre. The study followed the Declaration of Helsinki[12] and Good Clinical Practice guidelines. The primary endpoint was survival in the overall population of patients and those with adenocarcinoma. Secondary endpoints were time to treatment failure, objective-response rate, quality of life, and tolerability.

The study included patients aged 18 years or older with histologically or cytologically proven, locally advanced or metastatic NSCLC that was not curable with surgery or radiotherapy, who had received one or two previous chemotherapy regimens and who were refractory to (defined as recurrent or progressive disease within 90 days of the last chemotherapy dose) or intolerant of their latest chemotherapy regimen. Patients younger than 70 years, but not those aged 70 years or older, at initial diagnosis had to have received at least one previous platinum-based chemotherapy regimen. The patients had WHO performance status of 0–2 (those with performance status 3 were also eligible if the investigator believed that poor performance status was not predominantly due to comorbidity) and a life expectancy of at least 8 weeks.

Exclusion criteria were: presence of small-cell lung cancer alone or with NSCLC; administration of the last dose of single-agent chemotherapy within the previous 14 days or combination chemotherapy within the previous 21 days; untreated or clinically unstable newly diagnosed metastases in the central nervous system; less than 1 week since completion of previous radiotherapy or persistence of any radiotherapy-related toxic effects; unresolved chronic toxic effects from previous anticancer therapy; known severe hypersensitivity to gefitinib or any of the tablet excipients; inability to swallow tablets; other coexisting malignant disease (apart from basal-cell carcinoma); absolute neutrophil count less than $1{\cdot}0\times10^9$/L or platelet count less than 100×10^9/L, serum bilirubin concentration more than three times the upper limit of the reference range (at the local laboratory for the study centre); and alanine or aspartate aminotransferase concentration more than five times the upper limit of the reference range; more than two previous chemotherapy regimens for NSCLC; previous treatment with an experimental agent of which the main mechanism of action is inhibition of epidermal growth factor receptor or its associated tyrosine kinase; concomitant use of phenytoin, carbamazepine, rifampicin, barbiturates, or St John's wort; severe or uncontrolled systemic disease; clinically active interstitial lung disease (except uncomplicated lymphangitic carcinomatosis) pregnancy; and breastfeeding.

Patients were randomly assigned gefitinib (250 mg/day) or placebo tablets (double-dummy technique) in a ratio of two to one; randomisation was done by a minimisation method.[13] Physically identical tablets and packaging, assigned by the central registration and randomisation centre (Clinphone Ltd, UK), were used to ensure masking of both patients and investigators. In medical emergencies, unmasking was allowed (through the central registration and randomisation centre), after discussion with the study sponsors and after a decision to discontinue treatment had been made. All patients received the best supportive care according to the local practice of the individual institutions and centres. Patients continued to receive study medication until unacceptable toxic effects occurred, consent was withdrawn, or the patient was no longer deriving clinical benefit. Repeated dose interruptions to manage toxic effects were allowed for up to 14 days on each occasion.

Procedures

Overall survival was assessed from the date of randomisation to the date of a patient's death; participants alive at data cutoff were censored in the analysis at the last time they were known to be alive. Time to treatment failure was calculated as the time from the date of randomisation to the date at which the patient discontinued therapy owing to unacceptable toxic effects, no further clinical benefit (assessed by an investigator), the patient's choice, or death from any cause. Tumour progression (as defined by RECIST criteria) was not necessarily classed as treatment failure; patients could continue to receive treatment as long as they continued to derive clinical benefit. Patients in whom treatment had not failed at data cut-off were censored for time to treatment failure at the time of their last on-study visit. Tumours were assessed at baseline; the specific imaging modality was at the discretion of the investigator. The protocol recommended that subsequent imaging was undertaken at least every 8 weeks. The rate of objective responses (defined as all patients with complete responses plus those with partial responses) was calculated according to standard criteria.[14] Changes in quality of life (assessed with the functional assessment of cancer therapy, lung questionnaire[15]) and disease-related symptoms (assessed with the seven-item lung-cancer subscale of the

questionnaire) were assessed every 4 weeks. For changes in disease-related symptoms to be classed as clinically relevant, the score on the lung-cancer subscale had to increase by at least 2 points.[15] Adverse events were monitored and graded by the National Cancer Institute common toxicity criteria version 2.0[16] and coded according to the Medical Dictionary for Regulatory Activities terminology.[17] Routine laboratory monitoring (including biochemistry, haematology, and urine analysis) was done.

Statistical analysis

Originally, although patients with any histology were recruited, the primary objective was to find out whether gefitinib conferred a survival advantage among patients with adenocarcinoma. The protocol required a total of 696 adenocarcinoma deaths for a 33% improvement in survival to be detected with 90% power, with allowance for up to 15% crossover to gefitinib in the placebo group. The postulated 33% improvement in survival for gefitinib-treated patients was relative and assumed a median survival with best supportive care of 5·2 months (directly equivalent to 1-year survival of 20%). A similar placebo-controlled phase III study (BR21[18]) of another inhibitor of EGFR tyrosine kinase (erlotinib) showed an overall survival benefit independent of histological subtype. In the light of this finding and the fact that a substantial proportion (about 50%) of patients with non-adenocarcinoma histology had been recruited into ISEL, the independent data-monitoring committee recommended the addition of the overall population of patients as a coprimary population for analysis. To provide 90% power for a survival advantage to be detected in the overall population similar to that seen for erlotinib, we calculated that at least 900 deaths would be needed. On the basis of the accrual pattern experienced in ISEL, data cutoff (the date by which we expected that the necessary number of events would have been reached, enabling statistical analysis of the data) was set for the end of October, 2004.

The primary analysis of survival used a stratified log-rank test. The strata were histology, smoking history, reason for previous chemotherapy failure, number of previous regimens, performance status, and sex. As defined in the protocol, a supportive Cox's regression analysis was also done, with covariate adjustment for the same factors as the log-rank test. In addition to the subgroup analyses in these strata, the statistical-analysis plan prospectively allowed for the analysis of other clinically relevant subsets. On the basis of the data from the two phase II trials[7,8] and the US package label for erlotinib,[8,19] the following additional prognostic factors and groups of patients were identified for analysis before unmasking: previous docetaxel therapy, age at randomisation, time from diagnosis to randomisation, best response to previous chemotherapy, and racial origin (the ethnic origin of a patient, which is not necessarily their place of birth; for example, individuals of Japanese racial origin were classed in the Asian race category even if they were second-generation or third-generation Australian). To limit the risk of false-positive findings in subsets, a rigorous statistical approach was used. Subsets were first assessed for evidence of randomised treatment effect by subset interactions, to ensure that outcomes between subsets were very likely to be different, then the subsets for which such evidence existed were examined further. For subsets in which there was little evidence of an interaction with randomised treatment, the play of chance alone could not be ruled out. These analyses were by intention to treat. This study has been submitted for registration with ClinicalTrials.gov, number 1839IL/709.

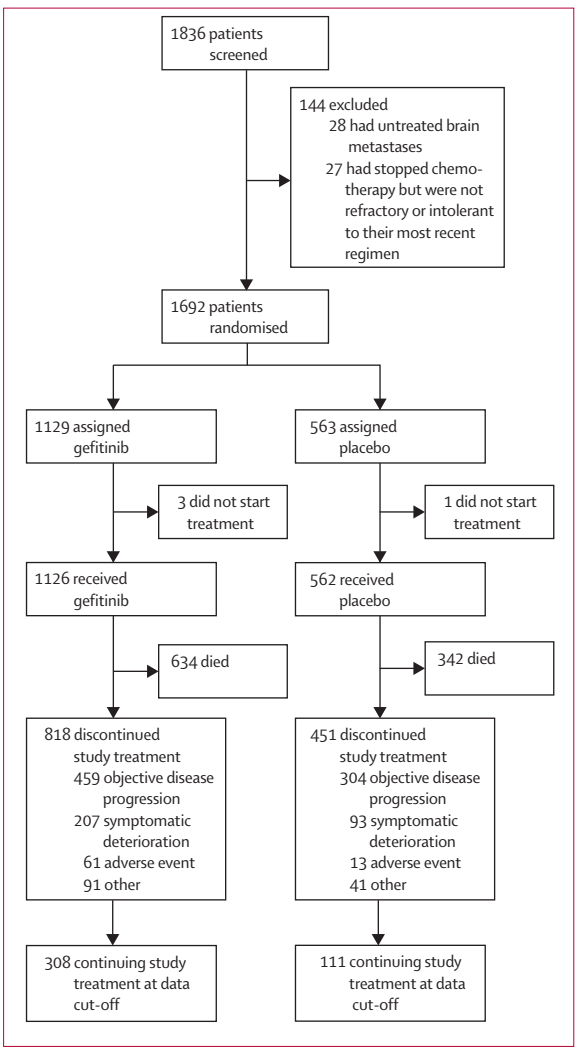

Figure 1: **Trial profile**
Intention-to-treat population=1692 randomised patients. The safety assessment was in the 1126 patients who received gefitinib and the 562 who received placebo.

Role of the funding source

This trial was coordinated and supervised by the steering committee (principal investigators plus AstraZeneca personnel) and the independent data-monitoring

committee (lung cancer and statistical experts independent of AstraZeneca), with funding and organisational support from the trial sponsor AstraZeneca. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The trial profile is shown in figure 1. 1692 patients were randomised (average eight patients per centre); 1129 were assigned gefitinib and 563 placebo. Baseline characteristics were well balanced between the two treatment groups (table 1). 36% of patients were recruited from central and eastern Europe, 24% from Asia, 16% from northern Europe, 14% from Central and South America, 7% from southern Europe, 2% from Australia, and 1% from Canada. In each treatment group, 48% of patients had adenocarcinoma histology (including bronchioalveolar carcinoma), 22% had never smoked, and about 20% were of Asian racial origin. 90% of patients had disease refractory to treatment, and in 45% the best response to the last chemotherapy regimen was progressive disease or non-evaluable response.

At data cutoff (Oct 29, 2004), median follow-up was 7·2 months and median exposure (including dose interruptions) to gefitinib was 2·9 months and to placebo was 2·7 months. Slightly more patients had received gefitinib for 6 months than had received placebo for that time (17·9% *vs* 13·2%). There was a low rate of cross-over, with about 3% of patients assigned placebo subsequently receiving gefitinib. All subsequent treatments for NSCLC were well balanced between the treatment groups.

In both the overall population and the patients with adenocarcinoma, the survival curves separated at about 4 months (figure 2), but the differences between the gefitinib and placebo groups did not reach significance in the primary log-rank test in either the overall population (hazard ratio 0·89 [95% CI 0·77–1·02], p=0·087) or the adenocarcinoma population (0·84 [0·68–1·03], p=0·089). In the overall population, median survival in the gefitinib and placebo groups, respectively, was 5·6 months and 5·1 months and the estimated 1-year survival 27% versus 21%. In the adenocarcinoma population, in the gefitinib and placebo groups, median survival was 6·3 months versus 5·4 months and the estimated 1-year survival 30% versus 18%. The supportive Cox's analysis suggested significance in favour of gefitinib for both the overall (p=0·03) and adenocarcinoma (p=0·033) populations.

On the recommendation of the independent data-monitoring committee, an additional analysis was done with an extra 3 months of follow-up, by which time 70% of patients had died and about 9% of those assigned placebo were receiving gefitinib. The survival results were similar to those of the primary analysis in both the overall population (0·89 [0·79–1·01], p=0·074) and the adenocarcinoma population (0·84 [0·70–1·02], p=0·072).

See Lancet Online for webtables 1 and 2

	Gefitinib (n=1129)	Placebo (n=563)
Median age (range), years	62 (28–90)	61 (31–87)
Sex		
Male	761 (67%)	378 (67%)
Female	368 (33%)	185 (33%)
Racial origin		
White	843 (75%)	431 (77%)
Asian*	235 (21%)	107 (19%)
Black	9 (1%)	5 (1%)
Other	42 (4%)	20 (4%)
Smoking history		
Habitual smoker	189 (17%)	90 (16%)
Occasional smoker	12 (1%)	7 (1%)
Ex-smoker	678 (60%)	340 (60%)
Never smoker	250 (22%)	125 (22%)
WHO performance status		
0	140 (12%)	70 (12%)
1	598 (53%)	318 (56%)
2	332 (29%)	145 (26%)
⩾3	55 (5%)	29 (5%)
Tumour histology		
Adenocarcinoma	512 (45%)	255 (45%)
Bronchioalveolar†	29 (3%)	16 (3%)
Squamous cell	399 (35%)	187 (33%)
Large cell	58 (5%)	33 (6%)
Mixed	21 (2%)	13 (2%)
Undifferentiated	106 (9%)	58 (10%)
Disease stage at diagnosis		
I	52 (5%)	33 (6%)
II	45 (4%)	25 (4%)
IIIa	109 (10%)	51 (9%)
IIIb	385 (34%)	170 (30%)
IV	536 (47%)	282 (50%)
Time from diagnosis		
<6 months	293 (26%)	140 (25%)
6–12 months	419 (37%)	222 (39%)
>12 months	417 (37%)	201 (36%)
Current disease status		
Locally advanced	233 (21%)	113 (20%)
Metastatic	896 (79%)	450 (80%)
Number of previous chemotherapy regimens		
0	1	1
1	549 (49%)	274 (49%)
2	566 (50%)	281 (50%)
⩾3	13 (1%)	7 (1%)
Previous therapy		
Platinum based	1085 (96%)	538 (96%)
Both platinum based and docetaxel	304 (27%)	158 (28%)
Reason for failure of last chemotherapy		
Refractory‡	1011 (90%)	512 (91%)
Intolerant	114 (10%)	48 (9%)
Unknown	4	3
Best response to most recent chemotherapy		
Complete or partial response	200 (18%)	106 (19%)
Stable disease	416 (37%)	207 (37%)
Progressive disease	427 (38%)	223 (40%)
Not evaluable	83 (7%)	26 (5%)

Unless otherwise stated, data are number of participants. *Corresponds to the oriental category of the case-record forms and refers to racial origin rather than the place of birth, but excludes people of Indian origin. †Patients with bronchioalveolar carcinoma were included in the adenocarcinoma group for analysis. ‡Recurrent or progressive disease while receiving or within 90 days of last dose of chemotherapy.
Webtables 1 and 2 show the baseline characteristics for patients of Asian origin and for non-smokers, respectively.

Table 1: **Demographic and baseline characteristics**

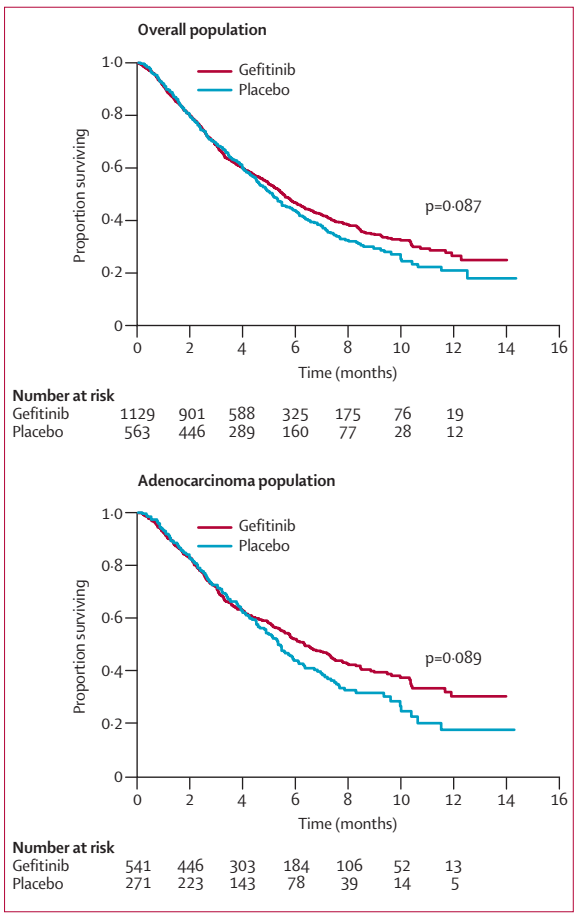

Figure 2: **Survival in the overall population and in patients with adenocarcinoma**

p values are for log-rank test. Corresponding p values for Cox's analysis were p=0·03 for the overall population and 0·033 for the adenocarcinoma population.

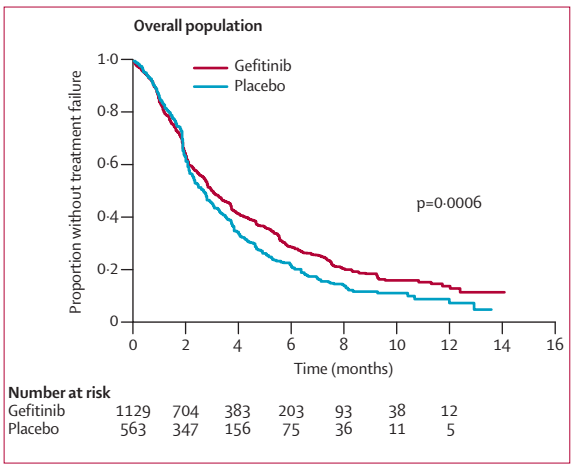

Figure 3: **Time to treatment failure in the overall population**

In the overall population, at a median follow-up of 7·2 months, median time to treatment failure was 3·0 months for patients assigned gefitinib and 2·6 months for those assigned placebo (0·82 [0·73–0·92], p=0·0006; figure 3). Disease progression (symptomatic and objective progression) was the main reason for treatment failure for most patients (59·0% for gefitinib and 70·5% for placebo).

Preplanned subgroup analyses showed heterogeneity in survival outcome among subgroups. For smoking status and racial origin, there were significant interactions with randomised treatment for survival (figure 4). Survival was better in the gefitinib group than in the placebo group among never smokers (median 8·9 *vs* 6·1 months; hazard ratio 0·67 [0·49–0·92], p=0·012), whereas survival was much the same in both treatment groups for smokers (0·92 [0·79–1·06], p=0·242). Similarly, survival was better in the gefitinib group than in the placebo group among patients of Asian origin (median 9·5 *vs* 5·5 months; 0·66 [0·48–0·91], p=0·01) but was much the same in both treatment groups for patients of non-Asian origin (0·92 [0·80–1·07], p=0·294). On the basis of the significant interactions observed in survival for smoking history and racial origin, we judged that exploratory subgroup analyses in the secondary endpoints would be appropriate to ascertain whether the trial was internally consistent with respect to the findings on survival in subsets. In subgroup analyses, the results for time to treatment failure were much the same as those for survival. There was a greater treatment effect among never-smokers (median time to treatment failure 5·6 months for gefitinib and 2·8 months for placebo; hazard ratio 0·55 [0·42–0·72], p<0·0001) than among former and current smokers (0·89 [0·78–1·01], p=0·0707), and among patients of Asian origin (median time to treatment failure 4·4 months for gefitinib and 2·2 months for placebo; 0·69 [0·52–0·91], p=0·0084) than among those of non-Asian origin (0·86 [0·76–0·98]; p=0·0197).

In total, tumour response was evaluable at baseline in 1439 patients (table 2). The objective-response rate in the overall population was significantly higher in the gefitinib group than in the placebo group (8·0% *vs* 1·3%; odds ratio 7·28 [95% CI 3·1–16·9], p<0·0001). Exploratory subgroup analyses showed a higher objective-response rate for gefitinib than for placebo in all subgroups, with the largest differences among never-smokers, women, patients with adenocarcinoma, and patients of Asian origin (figure 4).

About 85% of participants completed the functional assessment of cancer therapy lung questionnaire; the median baseline scores were 87·5 out of 136 for the full questionnaire and 17·7 out of 28 for the lung-cancer subscale, showing that quality of life was compromised and that most patients were symptomatic. In the overall population, changes in quality of life were similar in the gefitinib and placebo groups (mean change from baseline –3·66 *vs* –5·20; p=0·068; improvement rates 25·5% and 17·9%). Gefitinib was

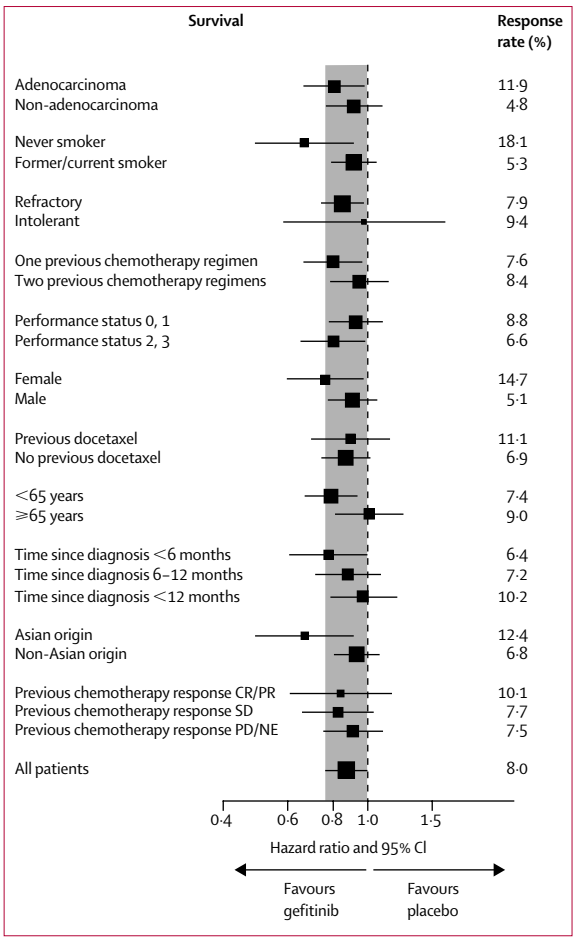

Figure 4: **Survival and response rates by subgroup analysis in the overall population**

CR=complete response; PR=partial response; SD=stable disease; NE=not evaluable. The shaded band represents the 95% CI of the hazard ratio for the overall population of patients.

associated with significant improvement in symptom score compared with placebo (mean change in score on the lung-cancer subscale from baseline –0·86 *vs* –1·38; p=0·019), although the magnitude of difference did not meet the predefined criteria for clinical relevance. Disease-related symptoms improved in 27% of patients assigned gefitinib and 22% assigned placebo.

Table 3 shows data from the exploratory post-hoc analyses of quality of life and disease-related symptoms in never-smokers and patients of Asian origin.

Overall, 1688 patients were evaluable for tolerability (table 4). Most patients experienced at least one adverse event (82% for gefitinib and 71% for placebo). The most common adverse events in the gefitinib group were rashes and diarrhoea (table 4); most were grade 1 or 2 in severity. The frequency of events of interstitial lung disease type was similar in the two treatment groups (1%). The overall frequency of grade 3 or 4 adverse events was similar for gefitinib and placebo (30% and 27% of patients, respectively). Dose interruptions due to

	Number of patients	
	Gefitinib (n=959)	Placebo (n=480)
Objective response	77 (8%)	6 (1%)
Complete response	1	0
Partial response	76 (8%)	6 (1%)
Stable disease	304 (32%)	148 (31%)
Progressive disease	360 (37%)	232 (48%)
Non-evaluable	218 (23%)	94 (20%)
Unmeasurable disease	9 (1%)	3
No follow-up scans	180 (19%)	81 (17%)
Other	26 (3%)	8 (2%)
Unknown	3	2

In each group, about 10% of patients had unmeasurable disease and about 4% had protocol deviations.

Table 2: **Best overall tumour response in patients with evaluable lesions at baseline**

adverse events were necessary in 11% of patients assigned gefitinib and 5% of those assigned placebo. Few patients experienced adverse events necessitating withdrawal (5% in the gefitinib group and 2% in the placebo group), and few patients died as a result of adverse events (5% in the gefitinib group and 4% in the placebo group). Monthly haematological and biochemical assessment showed no clinically relevant changes in haematological variables. Changes in alanine and aspartate aminotransferases were generally asymptomatic and mild to moderate in severity, consistent with previous studies.[7,8] Raised blood creatinine concentrations, mostly mild, were observed in a small number of patients.

The types of adverse events experienced by patients of Asian origin were similar to those reported for the overall population. Compared with the overall population, more patients of Asian origin experienced at least one adverse event (97% *vs* 82% for gefitinib and 86% *vs* 71% for placebo) and the frequency of grade 3 or 4 adverse events was also slightly higher (43% *vs* 30% for gefitinib; 36% *vs* 27% for placebo). In addition, the number of patients experiencing events of interstitial lung disease type was also higher in the Asian population than in the overall population; however, no difference was observed between the gefitinib and placebo groups (3% *vs* 4%).

	Gefitinib	Placebo	p
Never-smokers			
FACT-L	1·75	–3·68	0·004
LCS	0·35	–1·45	0·0002
Patients of Asian origin			
FACT-L	–0·13	–2·90	0·1623
LCS	0·39	–1·30	0·0009

Note that these analyses were post hoc; the two subgroups were identified on the basis of the global interaction tests for survival. FACT-L=functional assessment of cancer therapy lung questionnaire; LCS=lung-cancer subscale.

Table 3: **Mean change from baseline for quality of life and disease-related symptoms in never-smokers and patients of Asian origin**

Discussion

The results of ISEL show that treatment with gefitinib was not associated with a significant increase in overall survival in either the overall or adenocarcinoma coprimary population. This result is disappointing given the degree of tumour shrinkage seen in the phase II trials of gefitinib[7,8] and the finding of the phase III erlotinib study (BR21) of a 2-month increase in survival in previously treated patients with NSCLC (similar to that achieved with docetaxel in the second-line setting).[5,20] The reasons why no significant survival benefit was found are unclear, and there are several possible explanations.

The first possibility is that gefitinib has no efficacy in the setting of refractory NSCLC and there was no significant survival benefit in ISEL simply because the drug did not work. However, other studies have shown that gefitinib is active in NSCLC, with confirmed objective-response rates of 12–18%.[7,8] The significant improvements in time to treatment failure and objective-response rate seen with gefitinib in ISEL are consistent with these previous studies. Although the difference in survival between the treatment groups in ISEL did not reach significance, the chance that longer survival in the gefitinib group was due to a true effect of the drug was 95·6%, calculated as $([1-p]/2)\times100$, in both the overall and adenocarcinoma populations; the regulatory standard for proof of efficacy is 97·5% certainty (ie, $p<0·05$).

We are unable to undertake a meta-analysis of our findings and previous data, because to date, the only other phase III survival trial to compare an inhibitor of EGFR tyrosine kinase with placebo in patients with refractory NSCLC is BR21, a similarly designed study to ISEL, with erlotinib rather than gefitinib.[20] The objective-response rate reported with erlotinib in that study is similar to that reported here for gefitinib (8% *vs* 9%). However, the overall survival benefit for erlotinib in BR21 was significant (adjusted hazard ratio 0·70 [95% CI 0·58–0·85], $p<0·001$).[20] Although the point estimates differ for the two trials (hazard ratio 0·89 for ISEL and 0·70 for BR21), there is some overlap in the 95% CI (figure 5), with the small 95% CI for ISEL reflecting the larger trial size.

The second possible explanation for the lack of significant survival benefit in ISEL might be suboptimum dosing, and a higher dose (nearer the maximum tolerated dose) might have achieved a better result. In BR21, the maximum tolerated dose of erlotinib (150 mg/day) was used.[20] However, data from the phase I and II trial programme for gefitinib suggest that higher doses of gefitinib are unlikely to be more effective.[7,8,21–24] In the phase II trials,[7,8] about 400 patients were assigned either 250 mg/day or 500 mg/day gefitinib and there was no difference in survival between the dose groups, although the higher dose was associated with greater frequency and severity of adverse events. Although gefitinib doses higher than 500 mg/day have not been explored beyond phase I studies, we doubt that the dose of gefitinib in ISEL was too low.

Adverse event*	Number of evaluable patients			
	Gefitinib (n=1126)		Placebo (n=562)	
	All CTC grades	CTC grade 3–4	All CTC grades	CTC grade 3–4
Rash†	413 (37%)	18 (2%)	56 (10%)	1
Diarrhoea	309 (27%)	31 (3%)	52 (9%)	5 (1%)
Nausea	190 (17%)	9 (1%)	90 (16%)	2
Anorexia‡	193 (17%)	26 (2%)	77 (14%)	11 (2%)
Vomiting	152 (14%)	13 (1%)	56 (10%)	2
Dry skin	128 (11%)	0	20 (4%)	0
Constipation	108 (10%)	13 (1%)	71 (13%)	10 (2%)
Pruritus§	93 (8%)	4	27 (5%)	1
Pyrexia	79 (7%)	7	27 (5%)	2
Asthenic conditions¶	141 (13%)	36 (3%)	71 (13%)	15 (3%)
Cough	75 (7%)	2	45 (8%)	4
Dyspnoea	75 (7%)	35 (3%)	44 (8%)	21 (4%)
Stomatitis	68 (6%)	3	22 (4%)	1
Haemoptysis	59 (5%)	5	24 (4%)	2
Pneumonia	48 (4%)	30 (3%)	30 (5%)	15 (3%)
Cancer pain	39 (4%)	7	36 (6%)	3
Oedema peripheral	39 (4%)	1	33 (6%)	5 (1%)
Paronychia	35 (3%)	1	0	0

CTC=Common Toxicity Criteria. *MedDRA system preferred term. †Includes MedDRA high-level terms rashes, eruptions, and exanthems, plus the high-level term of acne, plus the preferred terms rash pustular, dermatitis, and dermatitis exfoliative. ‡Includes MedDRA preferred terms of anorexia, decreased appetite, and malnutrition. §Includes MedDRA preferred terms pruritus, rash pruritic, and pruritus generalised. ¶Includes MedDRA preferred terms of asthenia, fatigue, malaise, and prostration.

Table 4: **Adverse events occurring in more than 5% of either treatment group or with a difference of at least 3% between treatment groups**

A third possibility is that methodological issues affected the ISEL survival findings. In particular, the population of patients with highly refractory disease who took part in ISEL could have been inherently non-responsive to any further therapy, therefore the lack of survival benefit might have been inevitable from the outset. With the intention of recruiting a population with highly refractory disease, the inclusion criteria for ISEL defined refractory as recurrence or progressive disease during treatment or within 90 days of the last dose of chemotherapy (90% of the participants had refractory disease). The BR21 trial had no such entry criterion.[20] Furthermore, only 18% of patients in ISEL had responded to their last chemotherapy regimen compared with 38% of patients in BR21, and 45% had

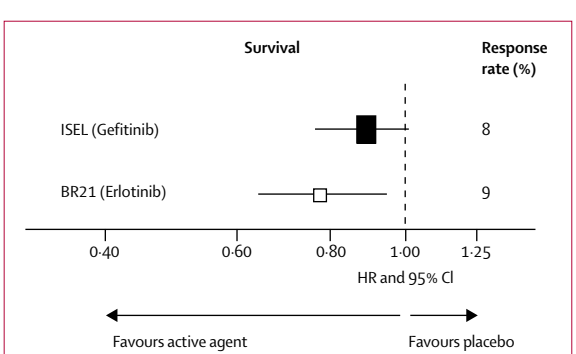

Figure 5: **Comparison of hazard ratios from ISEL and BR21**

progressive disease (or were not evaluable) compared with 28% in BR21.[20] The geographical locations of study sites in ISEL and BR21 also differed and could have influenced the trial results, through environmental factors such as exposure to smoking.

The divergence of the Kaplan-Meier survival curve for gefitinib from that for placebo after about 4 months in ISEL raises the question of whether a larger treatment effect might have been observed with longer follow-up. Therefore, on the recommendation of the independent data-monitoring committee, an additional analysis was done with an extra 3 months of follow-up (median follow-up 10·2 months rather than 7·2 months), by which time 70% of patients had died and 80% actuarial mortality had been reached. This further analysis showed no change in survival results either for the overall population or for patients with adenocarcinoma, so the results of the study seem highly unlikely to change with further follow-up. As such, we are confident that the results of ISEL are not a function of the length of follow-up.

Subset analyses in ISEL identified significant survival benefits with gefitinib for never-smokers and patients of Asian origin. However, since the primary endpoint did not reach significance, are these subgroup findings credible? The subset analyses were preplanned with a rigorous statistical approach that included statistical tests of interaction.[25] With this approach, the chance of one or more false-positive findings among the subsets analysed is very low. By contrast, a more conventional, less rigorous approach would have found many more subsets to have significant differences, and the chance of at least one of these being a false-positive finding would have been higher. As a result of the statistical approach we used, the significant survival benefits observed in never-smokers and patients of Asian origin are therefore unlikely to be due to chance, and we conclude that these effects are probably due to a real effect of gefitinib treatment. This conclusion is supported by internal consistency within the exploratory subgroup analyses of the secondary endpoint data, which show that never-smokers and patients of Asian origin also gained more benefit from gefitinib in time to treatment failure, objective response rate, quality of life, and improvement in disease-related symptoms. These results are also consistent with the subset analyses carried out on response data from the phase II studies.[7,8] Furthermore, the BR21 study also found a larger effect on survival with erlotinib in never-smokers than in smokers (multivariate hazard ratio 0·8 [0·6–1·0], p=0·048) and in Asian patients than in patients of other origins (0·7 [0·5–0·9], p=0·01).[20]

Recently published data for gefitinib and erlotinib suggest that there is an underlying biological basis for the heterogeneity in clinical outcomes seen with inhibitors of EGFR tyrosine kinase between groups of patients.[7–9,20] Translational research has identified several potential predictive biomarkers, of which two have attracted much interest—EGFR mutations and EGFR expression. Somatic mutations within the EGFR tyrosine kinase domain have been associated with striking responses to both gefitinib and erlotinib,[26–28] and the frequency of these mutations is high in never-smokers, patients of Asian origin, women, and patients with adenocarcinoma histology.[27–31] However, the association between EGFR mutation status and survival is less clear. Although Mitsudomi and colleagues found that EGFR mutations were a good predictor of survival with gefitinib in patients with refractory NSCLC,[32] the phase II gefitinib trials and BR21 found no such relation.[28,31,33] EGFR expression was not significantly related to response in the phase II trials (which were not placebo controlled),[34] but in BR21 EGFR expression was associated with response to erlotinib (p=0·03) but not survival.[28] EGFR expression is commonly associated with amplification or high polysomy of the *EGFR* gene. In contrast to the BR21 study, which reported no influence of *EGFR* copy number on survival after erlotinib treatment, Cappuzzo and co-workers reported that the number of copies of *EGFR* was significantly related to survival in patients treated with gefitinib.[33] Differences between studies could be due to inconsistent techniques and methods of analysis. Prospective studies are therefore required to clarify the relation between biomarkers such as *EGFR* gene amplification and response or survival. Further investigations are needed to identify demographic and biological predictors of response and survival to inhibitors of EGFR tyrosine kinase, and techniques and analysis methods need to be standardised. Biomarker data from ISEL (EGFR, K-Ras and B-Raf mutations, *EGFR* gene amplification, receptor dimerisation patterns, and expression of EGFR and signal transduction molecules such as p-Akt) are being analysed and will be published elsewhere.

Consistent with previously reported studies of 250 mg gefitinib monotherapy,[7,8,35] the drug was well tolerated. Although adverse events tended to be reported more frequently by patients of Asian origin, the nature of the adverse events was consistent with those reported by the overall population. Of particular note, in the overall population the frequency of events of interstitial lung disease type reported by patients assigned gefitinib was similar to that in the placebo group.

Phase III survival studies (trial 721 [INTEREST] and the Japanese trial V 15-32) comparing gefitinib with single-agent docetaxel in the second-line and third-line setting are under way and will help to elucidate the efficacy profile of inhibitors of EGFR tyrosine kinase. Prospective tissue collection from INTEREST and INVITE (a phase II study comparing gefitinib with vinorelbine in the first-line setting) should help define more clearly the population of patients most likely to benefit from an inhibitor of EGFR tyrosine kinase, which is essential for the future drug development of these agents.

Contributors

The study was designed by the sponsor and the steering committee. The data were collected by the sponsor's monitors and by the investigators listed below. The corresponding author had full access to the study data, and the analyses in this paper were interpreted by the corresponding author in consultation with the steering committee. All other authors have reviewed and provided comments on the report.

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Conflict of interest statement

NT has acted as a consultant, been a member of speakers' bureaus, taken part in formal advisory activities, and received grant support and honoraria from AstraZeneca, Lilly, and Roche. AC has received honoraria and consultancy fees from AstraZeneca. PP has been a member of the steering committee for ISEL and an investigator for AstraZeneca-sponsored clinical trials. JRP has no conflict of interest to disclose. TC has no stock holdings or research funding to disclose and is not acting as a paid consultant or advisory-board member but has received an honorarium from Roche for an invited lecture. JvP has no conflict of interest to disclose. ST is an investigator for an AstraZeneca-sponsored clinical trial. EHT is conducting research sponsored by AstraZeneca. KP and KC are employees of AstraZeneca. VA was an employee of AstraZeneca at the time of the trial.

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