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

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Our objective was to evaluate gefitinib (IRESSA), an epidermal growth factor receptor tyrosine kinase inhibitor, versus docetaxel as second-line monotherapy for advanced non-small-cell lung cancer (NSCLC). SIGN (Second-line Indication of Gefitinib in NSCLC; code 1839IL/0503) was a multicenter, randomized, parallel-group, open-label, phase II trial that investigated oral gefitinib (250 mg/day) or i.v. docetaxel (75 mg/m^2 every 3 weeks) in patients with advanced NSCLC who had previously received one chemotherapy regimen. The primary objective was assessment of symptom improvement (using the FACT-L Lung Cancer Subscale). Secondary objectives included quality of life (FACT-L total score), response rate (using RECIST), overall survival and safety. This trial recruited 141 patients (68 to gefitinib and 73 to docetaxel) who received treatment for a median duration of 3.0 (gefitinib) and 2.8 (docetaxel) months. Similar efficacy was observed with gefitinib and docetaxel, 36.8 and 26.0% symptom improvement rates, 33.8 and 26.0% quality-of-life improvement rates, 13.2 and 13.7% objective response rates, and 7.5 and 7.1 months median overall survival, respectively. Fewer drug-related adverse events were observed with gefitinib compared with docetaxel (all grades: 51.5 versus 78.9%; Common Toxicity Criteria grade 3/4: 8.8 versus 25.4%). There were no withdrawals or deaths due to drug-related adverse events with gefitinib, while three patients withdrew and three died due to adverse events in the docetaxel group that were possibly drug related. We conclude efficacy with gefitinib was similar to docetaxel, but with a more favorable tolerability profile, in the second-line treatment of advanced NSCLC. These results support further investigation of gefitinib in this disease setting.
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Introduction

Lung cancer is the most common cancer worldwide and has the highest mortality, causing 1.18 million deaths in 2002 (17.6% of the world total) [1]. Advanced non-small-cell lung cancer (NSCLC) is still an incurable disease and palliation of symptoms is an important aim of treatment [2]. Standard first-line treatment currently consists of platinum-based chemotherapy. In the second-line setting, docetaxel has demonstrated efficacy, with significantly improved median survival compared with best supportive care (7.5 versus 4.6 months) [3], and was the first agent to be approved for this indication. However, docetaxel has been associated with toxicity, particularly grade 3/4 neutropenia, which was observed in 54 [4] and 67.3% [3] of patients in two phase III trials at 75 mg/m^2. Toxicity was further increased with docetaxel 100 mg/m^2; the incidence of grade 3/4 neutropenia reached 77 and 85.7% [4]. Another agent, pemetrexed, has shown clinically equivalent efficacy to second-line docetaxel for advanced NSCLC in a phase III trial [5] and is also now approved for this indication. Although pemetrexed is associated with fewer side-effects than docetaxel, it is still a cytotoxic agent [5]. There remains a need for better-tolerated second-line therapies for advanced NSCLC.

Gefitinib (Iressa) is an orally active epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) approved for second-/third-line treatment of advanced NSCLC in many countries. In phase II studies [IDEAL

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(IRESSA Dose Evaluation in Advanced Lung cancer) 1 and 2] in pre-treated patients with advanced NSCLC, gefitinib 250 mg/day produced objective response rates of 11.8–18.4%, improved disease-related symptoms in 40.3–43.1% of patients and was generally well tolerated [6,7].

SIGN (Second-line Indication of Gefitinib in NSCLC; code 1839IL/0503) was an international, randomized, phase II study to assess second-line monotherapy for advanced NSCLC with either gefitinib or docetaxel, the only agent that had shown consistent second-line activity at the time when this trial was initiated. The primary objective was assessment of NSCLC-related symptom improvement.

Methods

Trial design

In this multicenter, randomized, parallel-group, open-label, phase II study, patients with advanced (stage IIIb or IV) NSCLC who were eligible for second-line chemotherapy were randomized 1 : 1 to one of two treatment groups: oral gefitinib 250 mg/day or docetaxel 75 mg/m^2 i.v. every 3 weeks.

The primary objective was to evaluate symptom improvement using the Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy–Lung (FACT-L) questionnaire. Secondary objectives were to estimate quality of life according to the total FACT-L score, objective response rate (complete response and partial response) using Response Evaluation Criteria In Solid Tumors (RECIST) and overall survival. The safety objective of the study was to evaluate safety and tolerability. Progression-free survival was not defined as a study variable in the protocol, but as tumor assessments were performed consistently for both treatment arms, it was also estimated.

The trial was not formally powered to test statistical differences between the treatment arms on any endpoint; however, as the treatments were randomized, bias-free comparisons could be made. The randomization was performed at the site using sealed randomization envelopes which were allocated sequentially to patients.

Patients

Eligible patients had histologically or cytologically confirmed advanced (stage IIIb or IV) NSCLC that had progressed on or after one previous chemotherapy regimen. In addition, patients were required to have one or more measurable lesion according to RECIST, WHO performance status 0–2, life expectancy $\geq$ 12 weeks, age $\geq$ 18 years, and be symptomatic (LCS score $\leq$ 24) and capable of understanding the FACT-L questionnaire.

Exclusion criteria included previous taxane treatment; treatment with any chemotherapeutic within 30 days prior to the study; radiotherapy within 3 weeks prior to the study; known cerebral metastasis; any evidence of ongoing interstitial lung disease (ILD); coexisting malignancies; malignancies diagnosed within the past 5 years, with the exception of basal cell carcinoma or cervical cancer *in situ*; any unresolved chronic toxicity above grade 2 National Cancer Institute Common Toxicity Criteria (NCI-CTC) from previous anti-cancer therapy; laboratory values outside requested limits; and psychiatric disorders that may affect completion of the FACT-L questionnaire.

All eligible patients had to provide written, informed consent and approval for the study was obtained from a recognized ethics committee. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki [8], as well as local ethical and legal requirements.

Treatment

Patients randomized to gefitinib received an oral dose of 250 mg/day. Patients randomized to docetaxel received 75 mg/m^2 i.v. every 3 weeks with a standard glucocorticoid pre-medication. In both arms, treatment continued until disease progression, unacceptable toxicity or withdrawal of consent.

Gefitinib dose interruptions of 14 or less days were the first approach to managing toxicity. These could be repeated, but no dose reduction was allowed. With docetaxel, toxicities were managed symptomatically, if possible. A dose delay was permitted, but if it was more than 2 weeks the patient was withdrawn from the study. In the case of severe toxicity as defined in the protocol, or with two postponements due to toxicity, docetaxel was reduced to 60 mg/m^2 with no dose re-escalation permitted.

Assessments

Symptom improvement and quality of life

Symptom improvement was assessed by the LCS of FACT-L, and quality of life was assessed by the FACT-L questionnaire at baseline, every 3 weeks during treatment and at withdrawal. The LCS monitors the severity of seven lung cancer symptoms (shortness of breath, cough, tightness in chest, difficulty breathing, appetite loss, weight loss and lack of clear thinking), which are rated by the patient on a 0–4 Likert scale [maximum (asymptomatic) score = 28] (Table 1). FACT-L encompasses social, functional, and physical and emotional well-being, as well as symptom improvement [9,10]. As described above with the LCS, the other four sections of the FACT-L questionnaire consist of statements that are rated by the patient on a 0–4 Likert scale. The maximum

Table 1 Scoring guide for the LCS

Item		Not at all	A little bit	Some-what	Quite a bit	Very much
1	I have been short of breath	4	3	2	1	0
2	I am losing weight	4	3	2	1	0
3	My thinking is clear	0	1	2	3	4
4	I have been coughing	4	3	2	1	0
5	I have a good appetite	0	1	2	3	4
6	I feel tightness in my chest	4	3	2	1	0
7	Breathing is easy for me	0	1	2	3	4

To obtain the LCS score, the seven statements (LCS items) in the table are rated by the patient on a five-point Likert scale: 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit and 4=very much. The scores for items 1, 2, 4 and 6 are then effectively reversed as indicated in the scoring guide to ensure that higher scores are consistently favorable. The sum of the item scores is multiplied by 7 then divided by the number of items answered (at least four items must be answered to generate a score).

(best) score attainable for the complete FACT-L questionnaire is 136. FACT-L was chosen as it is widely used in lung cancer clinical trials and provides validated clinically meaningful score changes (a + 2-point or higher LCS and a + 6-point or higher FACT-L change prospectively define 'improved' symptom and quality of life, respectively, whereas a –2-point or lower LCS and a -6–point or lower FACT-L change prospectively define 'worsened' symptom and quality of life, respectively [10,11]).

LCS and FACT-L improvement rates were the percentage of patients with a best overall response of 'improved' (consisting of two 'improved' visit responses more than 21 days apart, according to the criteria above, without an intervening visit response of 'worsened'). For patients with symptom improvement, time to improvement was defined as the interval from randomization to the first visit response of 'improved' in the sequence of visits that qualified for the best overall response. Duration of symptom improvement was defined as the time from the first visit response of 'improved' to a subsequent visit response of 'worsened'.

Tumor response

Objective tumor assessments were performed in accordance with RECIST [12] at baseline, 3 weeks after the first treatment and then every 6 weeks. For patients who responded, time to response, was defined as the time from randomization until the confirmed response and duration of response was defined as the time from response to progression.

Survival

Overall survival was defined as the period from randomization to death, from any cause, or to the last date the patient was known to be alive. Progression-free survival was defined as the interval between randomization and the earlier date of observation of objective disease progression or death due to any cause in the absence of progression.

Safety

The nature, incidence and severity of adverse events were recorded prior to, during and up to 30 days post-cessation of study treatment, using the NCI-CTC version 2.0 grading system. Clinical chemistry and hematologic laboratory parameters were analyzed at baseline, at weekly intervals for 3 weeks and at 3-weekly intervals thereafter.

Statistics

The following covariates were included in the statistical models described below: performance status (0, 1 versus 2), sex (male versus female) and smoking history (never smoked versus ever smoked).

The average LCS score during treatment was compared with baseline scores in the gefitinib and docetaxel treatment arms to calculate mean within-group changes in LCS score while on the trial. The difference and 95% confidence interval (CI) were derived by fitting a standard analysis of covariance model, allowing for the effects of the treatment group, the covariates listed above and the baseline score. Time to, and duration of, symptom improvement were calculated using Kaplan–Meier methodology.

The objective response rate was analyzed using a logistic regression model, allowing for the effect of treatment and including the covariates above. From this model, the odds ratio for treatment and the associated 95% CI were estimated. Median duration of response was estimated using the Kaplan–Meier method.

Overall and progression-free survival were analyzed using a proportional hazards model that allowed for the effect of treatment and the covariates above. The hazard ratio (HR; gefitinib:docetaxel) was estimated together with the 95% CI and *P* value. Survival was displayed graphically using a Kaplan–Meier plot.

Although this study was originally termed non-comparative and was not powered to test statistical differences between the treatment arms on any endpoint, it was decided, prior to finalizing the statistical analysis plan, that the most appropriate method of interpreting the data was to summarize the difference between the treatment arms to be able to put the effects of gefitinib into context with docetaxel. It is recognized, however, that this study was not designed to make any formal decisions based on this comparison.

Results

Patient demography

Between October 2003 and June 2004, 141 patients were randomized (68 to gefitinib and 73 to docetaxel) from 25 centers in 12 European, South American and Middle-

Eastern countries (see Appendix). Two patients randomized to docetaxel did not receive treatment due to non-compliance with the inclusion/exclusion criteria; therefore, 139 patients were evaluable for safety (68 for gefitinib and 71 for docetaxel). Across both treatment arms, almost all patients (97.9%) had received only one previous chemotherapy regimen and most (93.6%) had received prior platinum-based chemotherapy. The two treatment arms had similar demographics (Table 2).

Symptom improvement

Compliance with completing the FACT-L questionnaire was very good: 85 and 87% in the gefitinib and docetaxel groups, respectively. All randomized patients were symptomatic at trial entry (LCS score ≤ 24), with mean baseline LCS scores of 16.8 (gefitinib) and 17.2 (docetaxel). Symptom improvement rates were 36.8 and 26.0% with gefitinib and docetaxel, respectively (Fig. 1). For patients with symptom improvement, median time to improvement was 22.0 days (range 21–259 days) with gefitinib and 27.0 days (range 11–313 days) with docetaxel. Median duration of LCS improvement could not be calculated because the majority of improvements were ongoing at data cut-off; however, durations ranged from 21 to 215 days with gefitinib and from 21 to 243 days with docetaxel. Analysis of improvement in specific LCS items indicated similar benefit in both treatment arms (Fig. 2). The mean LCS score change from baseline to endpoint was 0.69 (95% CI –0.26 to 1.64) with gefitinib and 1.33 (95% CI 0.33 to 2.34) with docetaxel, which was similar ($P = 0.30$), but not clinically significant (2-point or higher change criteria). In addition to the planned analysis, mean changes in LCS scores from baseline at each time point were examined according to treatment arm and to response to treatment (Fig. 3).

Table 2 Demographic characteristics (intent-to-treat population)

	Gefitinib 250 mg/day	Docetaxel 75 mg/m^2
No. patients randomized	68	73[a]
Age (years) [median (range)]	63.0 (34–85)	59.5 (29–83)
Male:female [*n* (%)]	47:21 (69:31)	51:22 (70:30)
Race [*n* (%)]		
Caucasian	28 (41.2)	32 (43.8)
Black	0 (0)	2 (2.7)
Asian	0 (0)	0 (0)
Hispanic	33 (48.5)	29 (39.7)
Oriental	3 (4.4)	4 (5.5)
other	4 (5.9)	6 (8.2)
Performance status [*n* (%)]		
0	13 (19.1)	11 (15.1)
1	30 (44.1)	41 (56.2)
2	25 (36.8)	21 (28.8)
Ever smoked [*n* (%)]		
yes	46 (67.6)	49 (67.1)
no	18 (26.5)	18 (24.7)
unknown	4 (5.9)	6 (8.2)
Metastatic disease [*n* (%)]	41 (60.3)	41 (56.2)
Previous cancer treatment [*n* (%)]		
one previous chemotherapy regimen	66 (97.1)	72 (98.6)
prior platinum-based chemotherapy	62 (91.2)	70 (95.9)
radiotherapy	27 (39.7)	25 (34.2)
surgery	14 (20.6)	14 (19.2)

[a]Two patients randomized to docetaxel did not receive treatment due to non-compliance with inclusion/exclusion criteria.

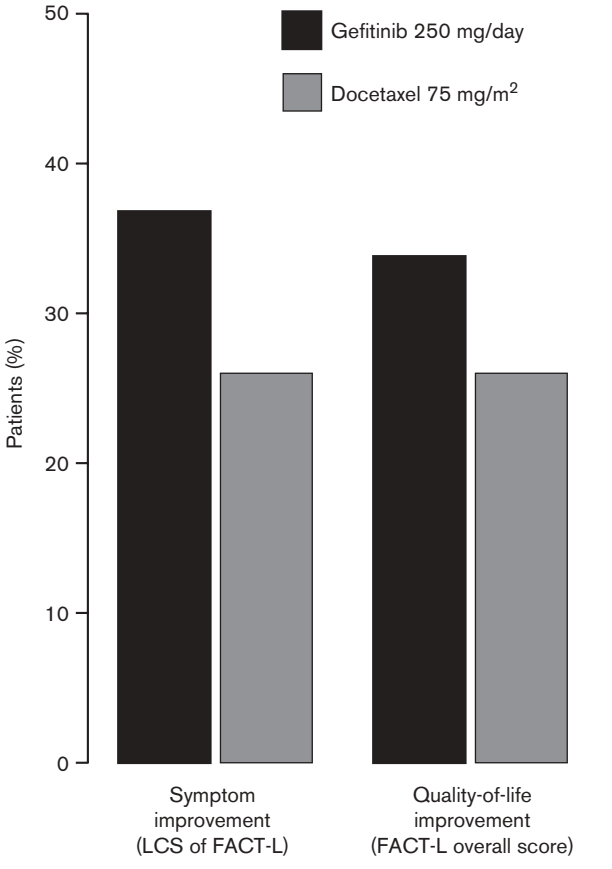
Quality of life

The patient population had compromised quality of life [mean FACT-L baseline scores: 83.8 (gefitinib) and 86.2 (docetaxel)]. Quality-of-life improvement rates were 33.8 (gefitinib) and 26.0% (docetaxel) (Fig. 1). The mean FACT-L score change from baseline to endpoint was 1.55 (95% CI –2.07 to 5.17) with gefitinib and 0.39 (95% CI –3.45 to 4.23) with docetaxel, which were similar ($P = 0.63$), but not clinically significant (6-point or higher change criteria).

Tumor response

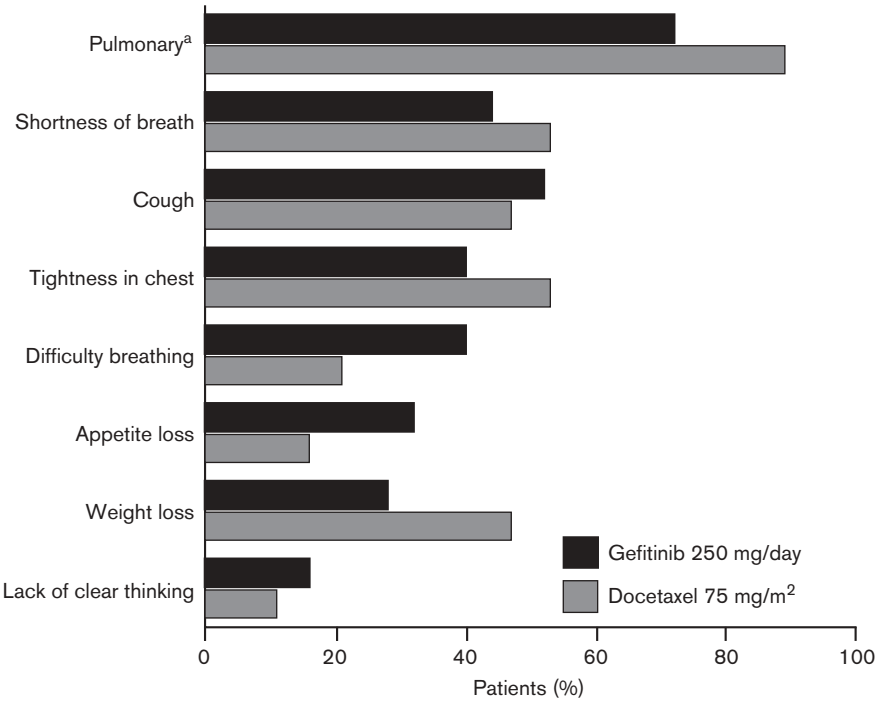
Objective response rates were 13.2 and 13.7% with gefitinib and docetaxel, respectively (Table 3). Median time to response was 23.0 days (range 22–72 days) with gefitinib and 41.5 days (range 23–110 days) with docetaxel. Durable responses were seen: with some patients still responding at data cut-off, the median

Fig. 1



Improvement in symptoms and quality of life from baseline.

Fig. 2



Improvement in specific LCS symptoms. [a]'Pulmonary' is a composite of at least one of the following: 'shortness of breath','cough','tightness in chest' and 'difficulty breathing'. Improvement in specific symptom items was defined as improvement of at least 2 points in the symptom at any time.

durations of response were 7.1 months (gefitinib) and 10.7 months (docetaxel).

Survival

After median follow-up times of 9.2 (gefitinib) and 9.4 months (docetaxel), there was no difference in overall survival between the two groups (Fig. 4). In the gefitinib and docetaxel arms, respectively, median overall survival was 7.5 and 7.1 months, and median progression-free survival was 3.0 and 3.4 months (Fig. 5) (intent-to-treat population). The 6-month survival rates were 65.6% with gefitinib and 56.1% with docetaxel.

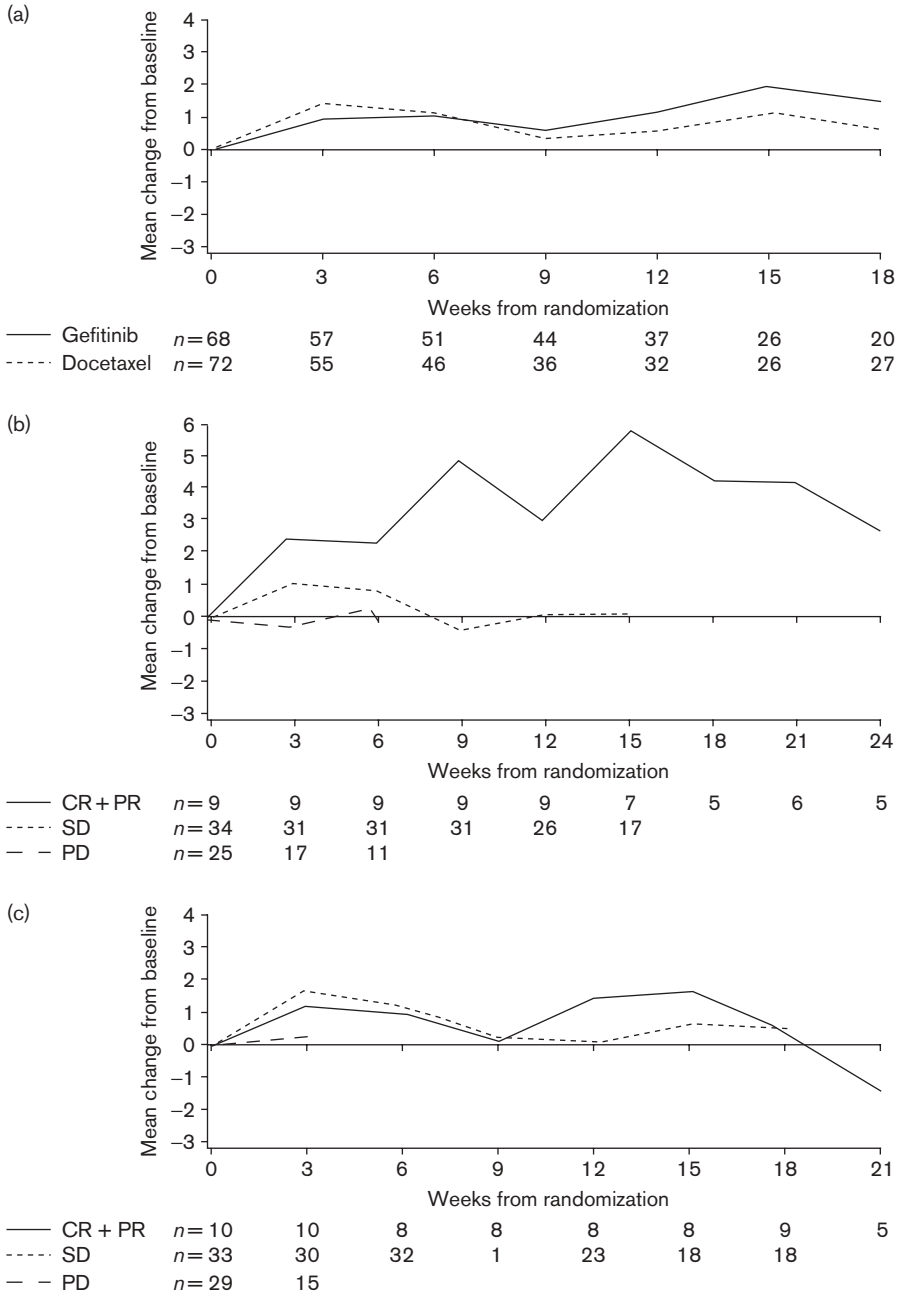
Safety

There were 139 patients evaluable for safety: 68 and 71 patients were treated with gefitinib and docetaxel, respectively. The mean number of 21-day gefitinib treatment periods received was 5.3 (SD = 4.2) and the mean number of docetaxel treatment cycles received was 4.3 (SD = 3.1). The median duration of treatment was 3.0 and 2.8 months in the gefitinib and docetaxel arms, respectively. Ten out of 68 (14.7%) patients receiving gefitinib had one or more dose interruptions due to toxicity. With docetaxel, 11 out of 71 (15.5%) patients had one or more dose delays or reductions due to toxicity. The mean cumulative docetaxel dose was 318.8 mg/m^2 and the mean dose intensity was 96.4%.

The most common adverse events are listed in Table 4. No Interstitial Lung Disease (ILD) type events were observed with gefitinib, while two patients receiving docetaxel experienced ILD-type events. Laboratory assessment of hematologic parameters showed that a grade 3/4 neutrophil count was more common with docetaxel (46.0%) than gefitinib (1.6%) (Table 5). Two cases of febrile neutropenia were seen with docetaxel. There were no clinically significant differences between the two arms for the other hematology laboratory parameters assessed. A small number of transaminases and blood creatinine elevations that were generally mild were observed in both groups.

Fewer drug-related adverse events were observed with gefitinib (51.5%) compared with docetaxel (78.9%), and CTC grade 3/4 drug-related adverse events were 8.8 and 25.4%, respectively. No withdrawals or deaths due to drug-related adverse events were recorded in the gefitinib arm, while in the docetaxel arm there were three withdrawals due to drug-related adverse events (superficial thrombophlebitis, peripheral neuropathy and abnormal hepatic function) and three deaths due to adverse events considered to be possibly drug related (acute respiratory distress syndrome, cardiorespiratory arrest and febrile neutropenia associated with septic shock).

Fig. 3



Mean change in LCS score from baseline over time for (a) the overall population (as results can only be interpreted with ease towards the beginning of the study, due to the decrease in patient numbers over time), data are plotted for the first 18 weeks when more than two-thirds of patients remained on trial) and for the two treatment arms according to best objective response: (b) gefitinib and (c) docetaxel (data are plotted until there were <50% of patients in a particular subgroup). CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Discussion

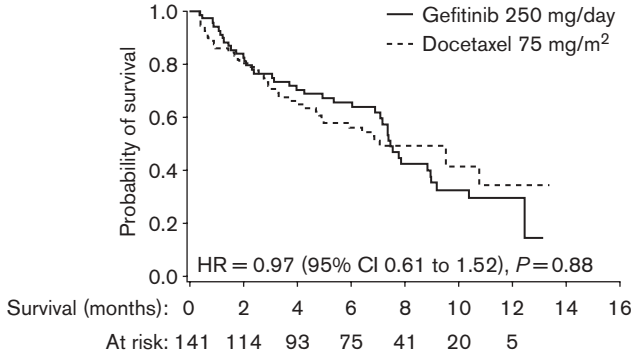
This was the first trial to investigate a targeted agent, gefitinib, versus a cytotoxic agent, docetaxel, as second-line monotherapy for advanced NSCLC. Substantial numbers of patients in both treatment groups had clinically meaningful symptom improvement (36.8 and 26.0% with gefitinib and docetaxel, respectively), exceeding the proportions showing objective responses. A comparable LCS improvement rate of 40.3% was reported for gefitinib 250 mg/day in IDEAL 1 [6]. Docetaxel has also previously demonstrated symptom relief in advanced NSCLC, such as statistically significant improvements in pain, compared with best supportive care [13], and a symptom improvement rate of 21.5% in a

Table 3 Best objective tumor responses (intent-to-treat population)

	Gefitinib 250 mg/day ($n=68$)	Docetaxel 75 mg/m^2 ($n=73$)
Complete response [*n* (%)]	2 (2.9)	0 (0)
Partial response [*n* (%)]	7 (10.3)	10 (13.7)
Stable disease [*n* (%)]	34 (50.0)	33 (45.2)
Progressive disease [*n* (%)]	13 (19.1)	11 (15.1)
Missing/non-evaluable [*n* (%)]	12 (17.6)	19 (26.0)
Response rate (%)[a]	13.2	13.7

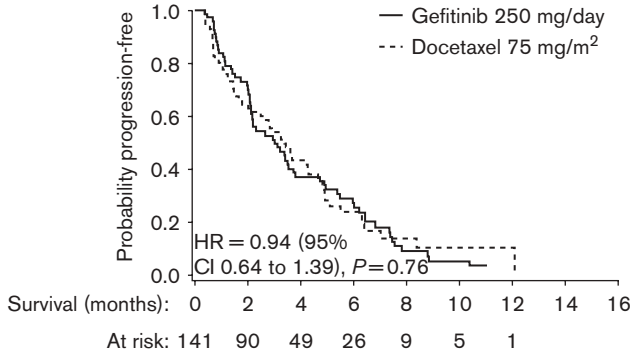
[a]Odds ratio = 0.98 (95% CI 0.47 to 2.03).

Fig. 4



Kaplan–Meier graph of overall survival.

Fig. 5



Kaplan–Meier graph of progression-free survival.

phase III second-line setting [5]. This is comparable with our data, although a different symptom-assessment tool was used. Mean LCS score changes over time were similar in both arms. With gefitinib, however, objective response was associated with substantial improvement in LCS mean scores, which was not the case with docetaxel.

Certain clinical characteristics may be associated with response to gefitinib: adenocarcinoma histology, never having smoked, female sex and Asian origin [6,7,14]. Activating EGFR mutations have been identified in patients who experienced objective responses to gefitinib [15,16], leading to the hypothesis that higher response rates may be achieved if patients are selected according to mutations or other factors that influence response. Without selecting patients for inclusion in the SIGN trial, we saw similar objective responses with gefitinib (13.2%) as with docetaxel (13.7%). It is possible that the benefit of gefitinib may have been even higher in our study if patients had been selected on the basis of biomarkers, such as EGFR mutations, although currently no validated biomarker test is available. Survival outcomes for gefitinib and docetaxel were also similar in our study and comparable with published clinical trial data for both agents in this second-/third-line setting [3–6]. Median overall survival was 7.5 months with gefitinib in SIGN, consistent with the 7.6 months seen in IDEAL 1 [6]. Two phase III survival trials in pre-treated NSCLC have compared EGFR-TKIs with placebo. ISEL (IRESSA Survival Evaluation in Lung cancer) reported some increase in median survival with gefitinib in the overall population that did not reach statistical significance; 5.6 versus 5.1 months for gefitinib and placebo, respectively [17]. The ISEL patient population was more heavily pre-treated than in SIGN, with approximately 50% of patients having received two or more prior chemotherapy regimens. Furthermore, 90% of patients in ISEL were refractory (defined as recurrent or progressive disease within 90 days of their last chemotherapy dose). In the BR21 trial, which did not stipulate that patients should be refractory, median survival was 6.7 months for erlotinib compared with 4.7 months for placebo [18]. The docetaxel arm of SIGN had a median of 7.1 months survival, while other docetaxel clinical trials reported median survivals of 5.7 [4], 7.5 [3] and 7.9 (second-line only) [5] months.

Consistent with the established tolerability profile for gefitinib [19], in our study gefitinib 250 mg/day was well tolerated in advanced, pre-treated NSCLC. The drug-related adverse events for docetaxel seen in this trial are also consistent with its reported safety profile [3–5]. The SIGN safety data suggest that gefitinib was better tolerated than docetaxel in this setting. Gefitinib was associated with fewer adverse events than docetaxel despite greater exposure to the treatment (mean treatment periods/cycles were 5.3 with gefitinib and 4.3 with docetaxel). Notably, CTC grade 3/4 neutropenia was higher with docetaxel (46.0%) compared with gefitinib (1.6%) and the two cases of febrile neutropenia occurred in the docetaxel group. Phase III studies of docetaxel have reported neutropenia at incidences of 67.3 (grade 3/4) [3], 54 (grade 4 only) [4] and 40.2% (grade 3/4) [5]. The levels of neutropenia and leukopenia in the SIGN docetaxel group may have been even higher if blood counts had been checked on a weekly basis (after the first 3 weeks, blood counts were taken every 3 weeks). There

Table 4 Number (%) of patients with adverse events that occurred in more than 10% of patients in either dose group (evaluable for safety population)

MedDRA preferred term	Gefitinib 250 mg/day ($n=68$)		Docetaxel 75 mg/m^2 ($n=71$)	
	All grades	CTC grade 3/4	All grades	CTC grade 3/4
Diarrhea	18 (26.5)	2 (2.9)	29 (40.8)	3 (4.2)
Rash-type events[a]	18 (26.5)	2 (2.9)	7 (9.9)	2 (2.8)
Pruritus	13 (19.1)	2 (2.9)	2 (2.8)	0 (0)
Asthenic conditions[b]	12 (17.6)	4 (5.9)	18 (25.4)	3 (4.2)
Dyspnea	11 (16.2)	6 (8.8)	11 (15.5)	4 (5.6)
General musculoskeletal disorders[c]	11 (16.2)	0 (0)	13 (18.3)	0 (0)
Cough	10 (14.7)	0 (0)	11 (15.5)	0 (0)
Pyrexia	10 (14.7)	0 (0)	10 (14.1)	0 (0)
Vomiting	8 (11.8)	1 (1.5)	7 (9.9)	1 (1.4)
Nausea	7 (10.3)	1 (1.5)	12 (16.9)	1 (1.4)
Mucositis[d]	6 (8.8)	1 (1.5)	11 (15.5)	1 (1.4)
Sensory neuropathy[e]	4 (5.9)	1 (1.5)	10 (14.1)	2 (2.8)
Alopecia	0 (0)	0 (0)	8 (11.3)	0 (0)

[a]Rash-type events includes the MedDRA High Level Term (HLT) 'rashes, eruptions and exanthems', plus the HLT 'acnes', plus preferred terms of 'dermatitis', 'dermatitis exfoliative' and 'dermatitis exfoliative generalized'.
[b]Asthenic conditions includes fatigue, malaise and asthenia.
[c]General musculoskeletal disorders includes general pain-related events of arthralgia, myalgia and bone pain.
[d]Mucositis includes stomatitis and mucosal inflammation.
[e]Sensory neuropathy includes neuropathy, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, neurotoxicity and hypoesthesia.

Table 5 CTC Grade 3/4 laboratory hematologic parameters (evaluable for safety population)[a]

	Gefitinib 250 mg/day ($n=67$)	Docetaxel 75 mg/m^2 ($n=67$)
Neutrophil count [n (%)][b]	1 (1.6)	29 (46.0)
White blood cell count [n (%)]	0 (0)	25 (37.3)
Hemoglobin [n (%)]	3 (4.5)	1 (1.5)
Platelet count [n (%)]	1 (1.5)	0 (0)
Febrile neutropenia [n (%)][b]	0 (0)	2 (3.2)

[a]Patient numbers for these laboratory parameters use the denominator of the number of patients who had the assessment done at baseline.
[b]$n=63$ for both treatment arms.

were no drug-related withdrawals or deaths with gefitinib; in the docetaxel group, there were three deaths due to adverse events that were possibly drug related.

Docetaxel has proven activity in second-line NSCLC compared with placebo or other chemotherapeutics in phase III trials [3–5] and is widely used for this indication. In our study, gefitinib 250 mg/day is the first EGFR-TKI to show similar efficacy to docetaxel as second-line therapy for advanced NSCLC in terms of symptom and quality-of-life improvement, objective response rate, and overall and progression-free survival. Furthermore, this trial indicated that gefitinib had a more favorable tolerability profile than docetaxel. Although SIGN was a small phase II study, the results indicate that gefitinib is worthy of further investigation in this disease setting. Two large phase III trials comparing second-line gefitinib and docetaxel in advanced NSCLC are already underway: INTEREST (IRESSA NSCLC Trial Evaluating REsponse and Survival against Taxotere) and V-15-32 in Japan. INTEREST will investigate clinical and molecular characteristics of the patient population, and these trials should provide further clarification of the role of gefitinib in this second-line setting.

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Appendix

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